Regular, low-dose, sustained-release oral morphine for chronic breathlessness – Building the evidence

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ABSTRACT

Chronic breathlessness is a devastating syndrome affecting a large proportion of people with chronic diseases. Despite receiving multiple disease-targeting and non-pharmacological treatments for chronic breathlessness, many people do not achieve adequate symptom control. Opioids are the only recommended pharmacological treatment to reduce breathlessness in these circumstances. In particular, regular, low-dose, sustained-release morphine reduces chronic breathlessness, with an acceptable safety profile. However, interindividual response to this medication is variable and questions remain about its safety in the broader context of daily life. This multi-method research project includes six discrete sub-studies focused on aspects related with the safety and effectiveness of regular, low-dose, sustained-release morphine for chronic breathlessness.

Sub-study 1 qualitatively explores patients' and carers' experiences with severe chronic breathlessness associated with chronic obstructive pulmonary disease (COPD) and their perceptions of regular, low-dose, sustained-release morphine. Results revealed dyads manage chronic breathlessness together to achieve maximal function for both. Functional improvement is the major driver for wanting to continue long-term treatment. Driving emerged as an important activity, contributing to increase dyad's physical and social space. Based on their perceptions, breathlessness at rest impairs driving, while sustained-release morphine does not.

Sub-study 2 is a systematic review of the impact of therapeutic opioid-agonists on driving-related skills. Included studies suggest that stable doses of therapeutic opioid agonists do not seem to impact driving-related skills of people with chronic conditions. No studies evaluated regular, low-dose, sustained-release morphine.

Sub-studies 3 to 5 were quantitative, hypothesis-generating, prospective sub-studies embedded in a randomised controlled trial (RCT) of regular, low-dose, sustained-release morphine for COPD-associated severe chronic breathlessness. Sub-study 3 explores this medication impact on simulated

driving. A signal for worsening driving-simulator performance was registered after 48 hours of morphine therapy, which dissipated after one week on stable doses. Sub-study 4 explored genetic differences contributing to explain interindividual variability in response to morphine. Results suggest specific genotypes may influence both breathlessness intensity and response to this medication. Sub-study 5 explores whether sustained-release morphine modulates hypothalamic–pituitary–adrenal (HPA) axis activity. Results suggest that age, performance status, perceived sleep quality and breathlessness intensity may influence the degree of HPA dysfunction associated with chronic breathlessness; people deriving more "net benefit" with sustained-release morphine may also improve HPA axis function.

Sub-study 6 is a crossover RCT of regular, low-dose, sustained-release morphine for a different aetiology of chronic breathlessness – pulmonary arterial hypertension (PAH). Although this study did not recruit to target, it suggests this medication may not reduce chronic breathlessness in people with PAH and may generate more harms.

Hypotheses generated by this research project contribute to inform future research in this field and provide important insights to improve clinical practice. From a safety perspective, this work highlights the need to exercise caution when providing driving advice to people with chronic breathlessness, particularly when initiating regular, low-dose, sustained-release morphine. From an effectiveness perspective, this work suggests that genetic factors and disease aetiology may contribute to influence response to morphine. HPA axis modulation may be one of the mechanisms by which people derive benefit from this medication.

DECLARATION

I certify that this thesis does not incorporate without acknowledgment any material previously submitted for a degree or diploma in any university; and that to the best of my knowledge and belief it does not contain any material previously published or written by another person except where due reference is made in the text.

Diana Ferreira

8 November 2021

ABBREVIATIONS

ACTH: Adrenocorticotropic Hormone

AKPS: Australian-modified Karnofsky performance score

ANZCTR: Australian New Zealand Clinical Trials Registry

ATS: American Thoracic Society

AUC: Area Under the Curve

AUCg: Area Under the Curve with respect to ground

AVP: Arginine Vasopressin

BEAMS: Breathlessness, Exertion and Morphine Sulfate

BMI: Body mass index

CAR: Cortisol Awakening Response

CCI: Charlson Comorbidity Index

CDC: Centres for Disease Control and Prevention

CI: Confidence Interval

C_{max}: Maximum serum concentration

C_{min}: Minimum serum concentration

CONSORT: Consolidated Standards of Reporting Trials

COPD: Chronic Obstructive Pulmonary Disease

COREQ: Consolidated criteria for Reporting Qualitative research

CRH: Corticotrophin Releasing Hormone

CRQ: Chronic Respiratory Questionnaire

DLCO: Diffusion capacity of the lungs for carbon monoxide

DNA: Deoxyribonucleic acid

EDTA: Ethylenediaminetetraacetic acid

EMCDDA: European Monitoring Centre for Drugs and Drug Addiction

ESAS-r: Edmonton Symptom Assessment System – revised version

$ETCO_2$: End-tidal carbon dioxide

FEV1: Forced Expiratory Volume in one second

FVC: Forced Vital Capacity

GOLD: Global Initiative for Chronic Obstructive Lung Disease

HADS: Hospital Anxiety and Depression Scale

HPA: Hypothalamic–pituitary–adrenal (axis)

IQR: Interquartile range

LTOT: Long-Term Oxygen Therapy

MDP: Multidimensional Dyspnoea Profile

MDRD: Modification of Diet in Renal Disease

MEDD: Morphine Equivalent Daily Dose

mMRC: modified Medical Research Council scale

NHMRC: National Health and Medical Research Council

NIH: National Institutes of Health

NMDA: N-methyl-D aspartate

NRS: Numerical Rating Scale

NYHA: New York Heart Association

$PaCO_2$: Partial pressure of carbon dioxide in arterial blood

PAH: Pulmonary Arterial Hypertension

PaO_2: Partial pressure of oxygen in arterial blood

PCO_2: Partial pressure of carbon dioxide

PCR: Polymerase Chain Reaction

PRISMA: Preferred Reporting Items for Systematic Review and Meta-analysis

PRN: *pro re nata*

RARs: Rapid-adapting stretch receptors

RCT: Randomised controlled trial

RTMN: Mean Reaction Time

RT-PCR: Real-time Polymerase Chain Reaction

SA: South Australia

SaO_2: Oxygen saturation as measured by blood analysis

SAPS: Southern Adelaide Palliative Services

SARs: Slow-adapting stretch receptors

SLUMS: St Louis University Mental Status Examination

SNPs: Single Nucleotide Polymorphisms

SPDEV: Mean Velocity Deviation

SR: Sustained release

SSRIs: Selective serotonin reuptake inhibitors

STDVM: Mean Steering Deviation from the Median lane position

TGA: Therapeutic Goods Administration

Tmax: Time to reach maximum serum concentration

UK: United Kingdom

VAS: 100-mm Visual Analogue Scale

WHO: World Health Organization

DEDICATION

To Carlos and Vera. May you be smiling from above.

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ANTHOLOGY OF PUBLICATIONS

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“Until death, it is all life.”

Miguel de Cervantes

CHAPTER 1 - CHRONIC BREATHLESSNESS

1.1 Chapter preface

Chronic diseases such as cardiovascular diseases, cancer and chronic respiratory diseases are currently responsible for approximately 70% of all deaths worldwide (World Health Organization [WHO], 2021). These diseases are often prolonged in time and progressive, contributing to high morbidity rates and health-related burden, which is expected to increase in the coming years (WHO, 2021). For chronic, life-limiting conditions, the focus of health care approaches needs to include easing the progression of the disease, symptom control and improvement of people's perceived quality of life. In this context, new disciplines like palliative medicine emerged to improve the quality of care provided to patients with chronic, life-limiting diseases, shifting the treatment focus from cure to wellbeing.

Palliative care is defined by the WHO as "an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual" (WHO, 2020, para. 1). Controlling physical symptoms is one of the hallmarks of palliative care, with important consequences for both patients and their carers (Stromgren et al., 2006). Symptom reduction has not only a positive impact on people's physical wellbeing, but also reduces psychological distress, and allows people to engage with life more fully until the very end (Rummans et al., 2000).

Chronic breathlessness is a particularly prevalent and debilitating symptom affecting people with chronic and life-limiting illnesses (Johnson et al., 2012b). Disease-specific treatments are often insufficient to provide relief and, in such cases, interventions targeting breathlessness reduction need to be considered. Regular, low-dose, sustained-release oral morphine is the only

pharmacological treatment approved to reduce chronic breathlessness in Australia. However, there are still questions surrounding its safety and effectiveness in the context of everyday life (Johnson et al., 2012a). These are the focus of this work.

This doctoral thesis starts with a review of chronic breathlessness, including its definition, epidemiology, individual and clinical significance, underlying mechanisms and measurement. This review aims to highlight the importance of identifying and understanding the complexity and impact of chronic breathlessness, so that people can be offered treatment strategies that are as effective as possible.

1.2 Breathlessness: acute, chronic and acute-on-chronic

Breathlessness was defined by the American Thoracic Society as "a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity" (1999, p.322). This definition is now widely accepted and introduces two important aspects of breathlessness, namely that it:

- is always unpleasant; and
- shows considerable inter- and intra-individual variation in both intensity and quality.

As such, breathlessness is both a universal and a highly individual experience. One of the aspects contributing to inter-individual variation in the experience of breathlessness is its temporal presentation. Breathlessness can present acutely, chronically or as an acute worsening of chronic breathlessness (i.e., acute-on-chronic), with distinct consequences for people who experience it. While acute breathlessness develops quickly and is usually reversible or has an obvious precipitant, chronic breathlessness is often progressive and largely irreversible. Over time, it may become deeply incapacitating, slowly encroaching every aspect of the person's life (Hutchinson et al., 2018). As severe chronic breathlessness develops, people are forced to give up their daily

activities, social relationships and autonomy, resulting in a profound disengagement with life (Gysels et al., 2007). The consequences of severe chronic breathlessness are far reaching, affecting not only those who experience it, but also those required to respond to the needs of people with severe chronic breathlessness and provide continuous support, such as families, clinicians and the health care system.

1.2.1 Chronic breathlessness as a distinct clinical syndrome

Chronic breathlessness is characterised by a constellation of clinical findings, that includes persisting breathlessness leading to significant and reproducible negative consequences from a physical, psychosocial and/or spiritual perspective. Thus, chronic breathlessness needs to be distinguished from the symptom of breathlessness (i.e., the subjective sensation of breathing discomfort) that may occur in isolation and have variable impact on people's lives. In this context, chronic breathlessness was recently identified as a *distinct clinical syndrome* defined as "breathlessness that persists despite optimal treatment of the underlying pathophysiology and that results in disability" (Johnson et al., 2017, p. 5). A specific aetiology, duration and level of breathlessness is not required to reach definition(Johnson et al., 2017).

The syndrome of chronic breathlessness can present in different ways. People may experience continuous breathlessness (i.e., breathlessness all the time), periods of breathlessness alternating with periods without breathlessness, or a combination of both (Reddy et al., 2009; Simon et al., 2013). In this context, the term *episodic breathlessness* was proposed by an international Delphi Survey to describe "a severe worsening of breathlessness intensity or unpleasantness beyond usual fluctuations in the patient's perception" (Simon et al., 2014). The original definition divided episodic breathlessness in two categories: *predictable* (e.g., triggered by exertion, emotions, temperature) and *unpredictable* (i.e., with no obvious cause) (Simon et al., 2014). While predictable episodes of breathlessness are frequent (i.e., up to multiple times a day),

unpredictable episodes have been recently shown to be rarer and particularly distressing (i.e., up to multiple times a week) (Linde et al., 2018). Importantly, new findings from a qualitative study suggest that, in retrospect, people can identify a cause for unpredictable episodes, which is frequently emotional (Linde et al., 2018). These findings can be of value to prevent further episodes associated with specific triggers (Linde et al., 2018).

Importantly, the term *episodic* may suggest that breathlessness in not in fact chronic, but rather intermittent with occasional impact on people's lives. This is most often not the case. Episodic breathlessness attempts to describe frequent aggravations in breathlessness but presumes an underlying diagnosis of chronic breathlessness. Most frequently, people with chronic breathlessness avoid activities and situations that trigger or aggravate their breathlessness (Gysels et al., 2007), which gives the impression they only experience breathlessness occasionally. However, a thorough anamnesis would identify the chronic breathlessness syndrome that is often cloaked under extreme daily adaptation and trigger avoidance. Instead of episodic breathlessness, the term *acute-on-chronic breathlessness* (Hutchinson et al., 2019) has been proposed. The concept of acute-on-chronic breathlessness builds on the definition of chronic breathlessness and may be more appropriate to describe periods of chronic breathlessness worsening (i.e., all types of episodic breathlessness), including for people who do not have significant breathlessness at rest.

1.3 Epidemiology

In recent years, population-level studies have investigated the prevalence of breathlessness in the community. An urban population survey in Norway reported an 18% prevalence of moderate to severe breathlessness on exertion, in the population aged 15 or older (Frostad et al., 2006). In the Health Survey for England 2010, 15% of the men and 23% of the women reported an intensity of breathlessness of at least 2 on the modified Medical Research Council (mMRC) scale, corresponding to shortness of breath "when hurrying on the level or walking up a slight hill", at

some point in the previous year (Craig & Mindell, 2011). Additionally, the South Australian Health Omnibus Survey 2007-08 reported that 9% of all adults and 18% of people older than 65 experience persistent breathlessness, classified as breathlessness most days for more than three months over the previous six months (Currow et al., 2009). The South Australian study was conducted before the classification of chronic breathlessness as clinical syndrome, whose definition is not limited by a minimum duration as noted above. As this was a population survey, the operational definition of chronic breathlessness needed to be clearly explained for respondents. The way the survey question was framed, if anything, may have underestimated the real proportion of people with chronic breathlessness, because, as noted above, people adapt their lifestyle to avoid breathlessness.

The most recent data on breathlessness prevalence comes from a very recent online survey conducted by the British Lung Foundation (British Lung Foundation Breath Test) that included 365 043 respondents (Elbehairy et al., 2019). This UK study reported that 20% of the respondents had an mMRC breathlessness score of at least 2. Importantly, although this survey was available to the general public, it is likely that people who were experiencing breathlessness had more interest in responding to questions and getting guidance about this symptom (Elbehairy et al., 2019). Thus, results from this study are likely to have overestimated the prevalence of breathlessness in the general population. Nevertheless, all studies investigating the prevalence of breathlessness in the general population report that this condition is frequent, possibly compromising the life of a large proportion of people worldwide.

Importantly, most prevalence studies have been conducted in high-income countries, where public health measures targeting smoking, air pollution and occupational exposure have started to have a positive impact on reducing the incidence of chronic respiratory diseases. Likely, there is a higher prevalence of chronic breathlessness in low- and middle-income countries, as a result of

less stringent public health preventative actions. As a result, the prevalence of illnesses known to cause chronic breathlessness is also likely to be higher than in high-income countries. Additionally, people affected by chronic breathlessness in low-middle income countries are also more likely to have more limited access to health services and treatments.

1.4 Clinical Significance

Chronic breathlessness poses unique challenges in the clinical setting because it is (i) prevalent; (ii) extremely impactful on people's lives; (iii) complex because it encompasses different sensations and temporal patterns; (iv) associated with worse health outcomes; and (v) associated with increased health service utilisation. These challenges are detailed below.

1.4.1 Frequency in the clinical setting

A relatively recent systematic review described that breathlessness affects 90-95% of the people with chronic obstructive pulmonary disease (COPD), 60-88% of people with congestive heart failure and 10-70% of people with cancer, among other advanced conditions (Moens et al., 2014). The wide prevalence ranges reported in this review are likely to result from different definitions of breathlessness, collection timepoints in relation to the disease trajectories of the underlying aetiologies, sample sizes and outcome measures in the included studies. Importantly, breathlessness tends to worsen in both prevalence and severity as people get closer to death. In the last year of life, one in two people will experience breathlessness, irrespective of the underlying condition (McCarthy et al., 1996; Reuben & Mor, 1986). In the last three months of life, 25% of the people receiving palliative care report severe breathlessness despite adequate treatment (Currow et al., 2010). Although breathlessness is more prevalent and intense in people who have cardio-respiratory diseases, people with undocumented cardio-respiratory diseases also report this symptom that increases in intensity in the three months before death (Currow et al., 2010; Currow et al., 2018). Moreover, in one Italian case series, breathlessness was the second

most common refractory symptom requiring palliative sedation (Maltoni et al., 2012), which highlights the challenges underlying its treatment in the last days or hours of life.

1.4.2 Extensive impact in people's lives – *Total breathlessness*

Chronic breathlessness often starts insidiously leading people to believe they are experiencing declines associated with age, poor fitness, the effects of obesity, the consequences of years of smoking or all of these. As a result, people adapt to breathlessness by progressively limiting or avoiding daily activities triggering the symptom. Presentation to health care services may occur late in the course of the underlying disease, when chronic breathlessness becomes highly limiting and distressing, and little or nothing can be done to modify the underlying cause(s). Alternatively, people may have breathlessness-related complains that are normalised by clinicians as an expected and unavoidable consequence of their underlying disease (Johnson et al., 2012b; Tod & Joanne, 2010). As a result, chronic breathlessness is underidentified and undertreated, and tends to evolve to become so restrictive that all aspects of life are affected including physical wellbeing, personal relationships, social life, and sense of self. In this context, the biopsychosocial model of breathlessness, also known as *total breathlessness* (Abernethy & Wheeler, 2008; Kamal et al., 2011), was developed to help clinicians identify how chronic breathlessness impacts every domain of life. This model recognises four essential domains that inform the experience of chronic breathlessness in more detail. The physical domain focuses on the symptom of breathlessness itself and its physical consequences; the psychological domain provides information about the emotions that the symptom triggers in each person; the social domain informs the impact breathlessness has on relationships and social life; and the existential domain focuses on the senses of hope and meaning (Kamal et al., 2011).

1.4.2.1 Physical domain

People describe chronic breathlessness as a "constant struggle" that "takes one's strength" and leads to "exhaustion" (Barnett, 2005; Nicholls, 2003). Multiple every-day life occurrences can trigger or worsen breathlessness to a degree that is unbearable for people. These include exertion, changes in position (e.g., bending forward), the weather (e.g., too hot or too cold, humidity), time of the day and strong smells (Barnett, 2005). Thus, people with chronic breathlessness are forced to adapt to their condition by avoiding or minimising any potential triggers that may worsen their breathlessness. Physical exertion is a major factor contributing to the experience of breathlessness in people with chronic breathlessness, and one over which people have some control. Thus, avoidance of daily activities that would otherwise lead to acute worsening of breathlessness is a hallmark of living with chronic breathlessness (Ahmadi et al., 2014; Gysels et al., 2007; Paap et al., 2014). In advanced stages of chronic breathlessness, basic activities such as having a shower, getting dressed or leaving the house are major challenges (Lowey et al., 2013). The relationship between chronic breathlessness and impaired functional capacity has been previously detailed in the context of COPD. Expiratory airflow limitation is a hallmark of COPD, which is associated with the development of dynamic hyperinflation (i.e., inspiration occurs prior to full exhalation of the previous breath). As a result, there is an increase in the end-expiratory lung volume and a decrease in inspiratory capacity (O'Donnell & Laveneziana, 2006). These physiopathological changes predispose to COPD exacerbations and to the development of a vicious circle of chronic breathlessness, decreased physical activity and reduced exercise capacity, which further enhance breathlessness (Ramon et al., 2018).

Chronic breathlessness is particularly hard on carers, who are frequently isolated in their role because of the need to provide around-the-clock care for these people (Gysels & Higginson, 2009). Many carers are elderly, struggle with advanced diseases themselves and feel unable or under-prepared to deal with the limitations imposed by the care recipient's chronic breathlessness

(Bergs, 2002; Gysels & Higginson, 2009; Simpson et al., 2010). Therefore, the physical domain of breathlessness encompasses more than the symptom itself and includes assessment of the impact in function, activities of daily living, aids to mobility and availability of someone who is physically able to help with care.

1.4.2.2 Psychological/Emotional domain

Chronic breathlessness is associated with psychological/emotional burdens for people who experience it and their carers. Comorbidities such as anxiety and depression are highly prevalent in populations with chronic breathlessness and associated with further functional decline, increase of healthcare utilisation and mortality (Ng et al., 2007; Yohannes et al., 2010). Recently, increasing severity of breathlessness has been associated with worse physical and mental health-related quality of life (Currow et al., 2017). Additionally, longer duration of chronic breathlessness and poorer functional status were predictors of depression, anxiety and coexistence of depression and anxiety in a recent population study (n=2977) (Currow et al., 2020). Although a cause-and-effect relationship between chronic breathlessness and anxiety/depression cannot be established from these studies, people with chronic breathlessness are unquestionably more susceptible to these conditions. “Anxiety”, “fear”, “frustration” are words often used by people with symptomatic chronic breathlessness to describe what it is like to experience breathlessness (Barnett, 2005). Qualitative research has evidenced the importance of the breathlessness-anxiety-breathlessness cycle which describes the interconnectedness between the two conditions (Barnett, 2005). Furthermore, some people (e.g., those with COPD) also express guilt, anger and regret for having a disease that is often perceived as self-inflicted through tobacco smoking (Elofsson & Öhlén, 2004; Nicholls, 2003).

Carers also experience the emotional burden of breathlessness. In many cases, carers are close family members who see their loved ones deteriorate inexorably over time, which makes them

feel fearful and helpless (Bergs, 2002). Carers describe that they live in a state of hypervigilance, even during the night, because they fear patients might die suddenly (Bergs, 2002). Thus, it is unsurprising that anxiety and depression are also prevalent in carers (Bernabeu-Mora et al., 2016; Jácome et al., 2014), who are also permanently impacted by breathlessness.

1.4.2.3 Social domain

The relevance of developing and maintaining meaningful relationships has been explored in other fields of knowledge such as psychology and social science research. It is now known that the quantity and quality of one's relationships is closely associated with health and wellbeing (Cohen, 2004; Gurung et al., 1997), and that loneliness and social isolation are independently associated with premature mortality (Holt-Lunstad et al., 2015). People with chronic breathlessness experience increasing restrictions in their social lives as a result of their functional limitations and many become housebound, particularly late in the course of their illness (Currow et al., 2009). Consequently, they become increasingly isolated, with fewer opportunities to engage with other people such as extended family, friends or colleagues. In addition, chronic breathlessness affects relationship dynamics, particularly with close relatives (Bergs, 2002; Boyle, 2009). Couples are the most affected by these changes in relationship patterns (Bergs, 2002). Partners of people with chronic breathlessness are usually forced to assume the role of the carer whether they are prepared for it or not. Consequently, their relationship patterns change to accommodate the limitations of chronic breathlessness (Simpson et al., 2010). Additionally, chronic breathlessness is associated with increased prevalence and duration of sexual inactivity, which may also contribute to decreased intimacy in relationships (Ekstrom et al., 2018). Apart from relationships, chronic breathlessness affects people's ability to engage with the physical world outside the limits of their own homes. When chronic breathlessness becomes more severe, travelling and other pleasurable activities become challenging. Thus, chronic breathlessness shrinks people's worlds both physically and socially (Ek et al., 2011).

1.4.2.4 Spiritual/Existential domain

Chronic breathlessness changes the way people perceive themselves (Nicolson & Anderson, 2003) and their role in the world (Gysels et al., 2007). Restrictions imposed by chronic breathlessness affect people's self-image and their sense of freedom and independence (Gysels et al., 2007; Seamark et al., 2004). However, people experiencing chronic breathlessness may try to act as if they had no limitations at all, mostly because they perceive chronic breathlessness as a weakness (Jonsdottir, 1998). Some people describe their lives as being so affected by breathlessness that they develop a sense of "existing" rather than "living" (Nicholls, 2003). Many people describe how they hate to feel a burden to the people surrounding them, particularly family members (Nicholls, 2003). Many people with chronic breathlessness reflect on their own death and they worry about dying from intense breathlessness or suffocating (Gardiner et al., 2009). However, despite all the challenges imposed, many people with chronic breathlessness remain hopeful in living life to the full, with the best quality of life. Factors such as spirituality and faith may help to withstand a life with chronic breathlessness and help to find meaning beyond the syndrome with which they live (Gysels et al., 2007).

1.4.3 Complexity

While the model of total breathlessness is useful to understand the extent to which chronic breathlessness affects people's lives, it does not explore possible interactions between different domains and their role in generating or aggravating symptomatic breathlessness. However, the contribution of some of these interactions has been previously described. As detailed in section 1.4.2.2, the sensation of breathlessness (physical domain) can trigger anxiety (psychological/emotional domain), while increased anxiety can contribute to aggravating breathlessness (breathlessness-anxiety-breathlessness cycle) (Barnett, 2005). Similarly, it is recognised that chronic breathlessness can lead to functional impairment (physical domain), and that such impairment promotes social isolation (social domain) (Ek et al., 2011; Gysels et al.,

2007). Interventions targeting different breathlessness domains are particularly effective for chronic breathlessness, highlighting the importance of multiple-domain contributions. Recently, the *breathing-thinking-functioning model* has been proposed both to explain how breathlessness is perpetuated and aggravated and to facilitate implementing management strategies targeting multiple domains (Spathis et al., 2017). This model is described below.

1.4.3.1 Breathing-thinking-functioning model of breathlessness

According to breathing-thinking-functioning model, breathlessness activates immediate cognitive and behavioural responses, triggering three vicious cycles (breathing, thinking and functioning), which contribute to aggravating and sustaining the symptom (Spathis et al., 2017) (Figure 1.1). The *breathing cycle* is associated with the physical domain of *total breathlessness*. Pathological changes produced by certain illnesses (e.g., lung hyperinflation in COPD, metastatic infiltration of the lung with cancer) may alter normal respiratory physiology, and trigger breathlessness. Frequently, people experience breathlessness as a sense of "not getting enough air" (Williams et al., 2008), leading to changes in breathing patterns, such as increased respiratory rate and changes in the inspiration/expiration ratio (Gorini et al., 1996). Dysfunctional breathing patterns increase the workload on accessory muscles of respiration, which can fatigue relatively quickly and hence aggravate breathlessness (Dempsey et al., 2006).

The *thinking cycle* is associated with the psychological/emotional domain described in the *total breathlessness* model and highlights the importance of the breathlessness-anxiety-breathlessness cycle to perpetuate and aggravate breathlessness (Barnett, 2005). However, the thinking cycle is broader than the psychological/emotional domain of *total breathlessness*, covering the contribution of other cognitive factors, such as previous experiences of breathlessness and breathlessness that they have seen in other people. The use of distracting auditory stimuli has been shown to reduce the sensation of breathlessness in people with chronic breathlessness,

highlighting that attention modulates the way people experience the symptom (von Leupoldt et al., 2007b). Additionally, expectation plays a role in triggering and perpetuating breathlessness, given that breathlessness-related cues can produce the symptom in people with asthma, in the absence of other triggers (Marlow et al., 2019; Rietveld et al., 1997). The thinking cycle of the breathing-thinking-functioning model also touches on the existential domain of total breathlessness, by acknowledging the contribution of thoughts about death and dying to trigger distress and aggravate breathlessness. Similar to the breathing cycle, the *functioning cycle* is linked with the physical domain of the *total breathlessness* model. However, the functioning cycle is predominantly focused on function, describing how people with chronic breathlessness tend to adjust their activity levels in order to avoid or reduce breathlessness to a minimum. Importantly, lower activity levels promote muscle deconditioning (including respiratory muscle weakness), contributing to perpetuate or aggravate breathlessness. At the same time, as people become less active, there is a tendency to disengage from social relationships and participation in the workforce, which were previously part of the motivation to leave the house (social domain of *total breathlessness*) (Ek et al., 2011; Gysels et al., 2007). As a result, social isolation may also contribute to aggravating breathlessness.

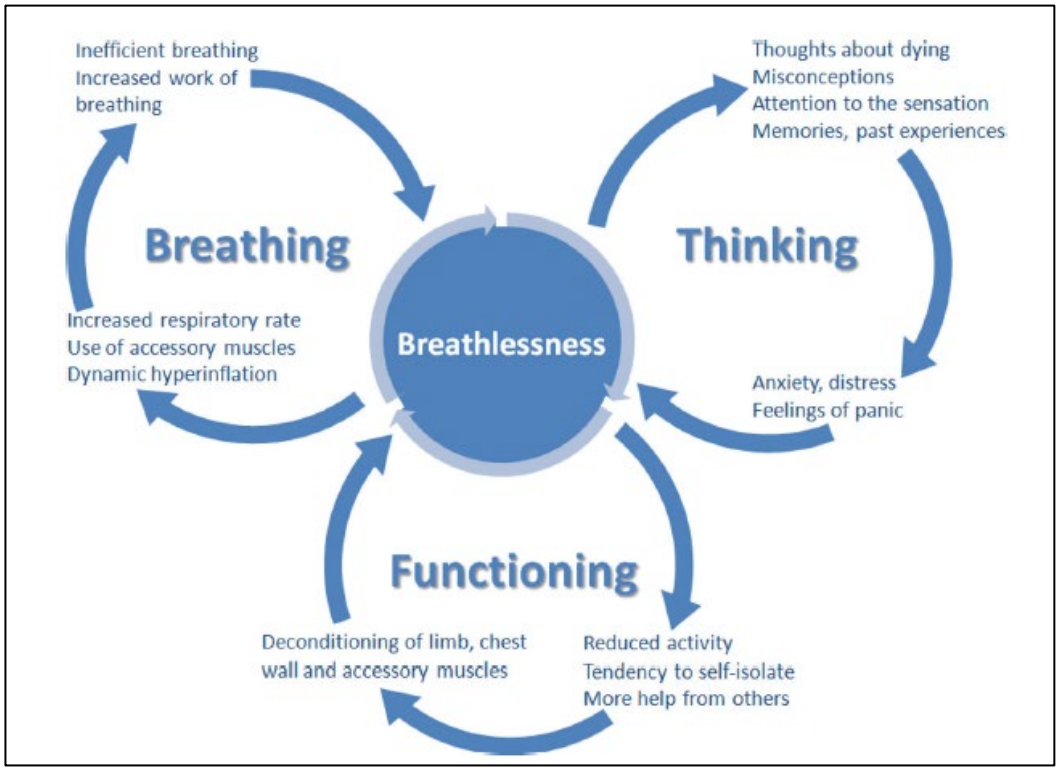

Figure 1.1 - The breathing-thinking-functioning model of breathlessness
Copied from Spathis et al. (2017) with permission from Springer Nature© (Appendix 1).

1.4.3.2 Perceived aspects of breathlessness

Within the same experience of breathlessness, people are able to perceive different aspects that can be linked to the breathing, thinking and functioning cycles. These are (Lansing et al., 2009):

- sensory-perceptual aspect (associated with the *breathing cycle*);
- affective aspect (associated with the *thinking cycle*); and
- its symptom burden (associated with the *functioning cycle*).

The distinction between the sensory-perceptual and the affective domains was demonstrated by experimental studies in which both healthy people and people with chronic breathlessness were able to distinguish between *intensity* and *unpleasantness* of breathlessness, when acute breathlessness was artificially induced (Banzett et al., 2008; Carrieri-Kohlman et al., 1996). Subsequently, a different experimental study has demonstrated that while healthy subjects give

similar scores to intensity and unpleasantness of breathlessness before experimentally induced breathlessness, there is a steeper increase in unpleasantness ratings for higher scores of breathlessness (von Leupoldt & Dahme, 2005). Under normal daily activities, people with chronic breathlessness are less likely to attribute different scores to intensity and unpleasantness of breathlessness. A recent longitudinal study of 265 people with chronic breathlessness, which provided 3630 paired observations of intensity-unpleasantness dyads of breathlessness across eight days, revealed that intensity and unpleasantness scores were highly correlated (mean intensity-unpleasantness difference of 2.1 mm on 0-100 mm visual analogue scales) (Ekström et al., 2019). In regular everyday life, people living with chronic breathlessness are likely to avoid situations triggering extreme breathlessness, which may have concealed the differences between intensity and unpleasantness of breathlessness observed for higher scores in laboratory studies. In summary, these findings suggest that intensity and unpleasantness of breathlessness are likely different constructs, which are highly interconnected, but whose trajectories may diverge for more severe breathlessness.

Within the sensory-perceptual domain, people can classify breathlessness both quantitatively and qualitatively. Quantitative classifications may rely on something as simple as a single score to reflect breathlessness intensity/severity. The score can be interpreted within the context of each scale range. Qualitative classifications are based on the different types of sensation that one can experience while being breathless. For example, some people describe themselves as having “air hunger” while others state that their breathing “requires effort” and/or that their “chest is tight” (Simon et al., 1990). While no definite conclusions have been reached, some studies suggest different physiologic mechanisms seem to be associated with different descriptors (Banzett et al., 2008). In this context, a previous study with a parallel-group design has shown that people with COPD tend to report a higher number of descriptors that are different from the ones reported by

matching healthy controls (Williams et al., 2008). These findings suggest that the mechanisms of breathlessness in COPD may differ from those found in people with no respiratory disease. Interestingly, when comparing different breathlessness aetiologies, others have found no clear association with different descriptors (Chowienczyk et al., 2016; Wilcock et al., 2002). This lack of association may be due to overlapping mechanisms of breathlessness amongst different medical conditions.

The affective domain of breathlessness includes both the unpleasantness and the emotional reaction to the stimulus (Lansing et al., 2009). The feeling of unpleasantness usually occurs immediately after the physical sensation and is not necessarily associated with symptom intensity (von Leupoldt et al., 2006). However, different degrees of unpleasantness seem to be associated with different descriptors (Banzett et al., 2008). Conversely, emotional reactions to breathlessness emerge from intricate processes that involve central processing of perceptual breathlessness and attitude / behaviour adjustments to the condition (Lansing et al., 2009). They are also dependent on the perceived burden inflicted by breathlessness and how easily people are able to cope, depending on their individual characteristics. For instance, depending on personality, life-experience and social conditions, some people may experience distress as they become increasingly more dependent on others, while other people may find it easier (or more necessary) to ask for help.

In summary, this section highlights that breathlessness is a product of different sensations, interacting in the individual context of each person, resulting in complex cognitive and behavioural adaptations. Understanding this complexity is key to develop effective, multi-domain interventions.

1.4.4 Breathlessness as a predictor of mortality

A recent population-based study of community-dwelling individuals aged 70 and older reported that breathlessness was associated with 60% increased risk of death over a 5-year follow up period (Smith et al., 2016). In people with COPD, who often experience chronic breathlessness, breathlessness was shown to be an independent predictor of mortality. For this population, breathlessness was shown to be a better predictor of mortality than the forced expiratory volume in 1 second (FEV_1), and the correlation between breathlessness and FEV_1 was poor (Nishimura et al., 2002). For other aetiologies of chronic breathlessness, studies show similar findings (Pesola & Ahsan, 2014). For people with advanced cancer, breathlessness alone increases the likelihood of dying by 28% (Vigano et al., 2004). In the setting of heart failure, the New York Heart Association (NYHA) functional classification (New York Heart Association, 1994), a tool strongly relying on the level of function someone can undertake without being breathless, has been shown to be a key predictor of mortality, second only to age (Barlera et al., 2013). In the palliative care population, worsening breathlessness is associated with increased mortality even in people with reasonable performance status (Currow et al., 2018). Given the strong association between chronic breathlessness and mortality, early diagnosis of this syndrome may enhance identification of people who have increased risk of dying in the short term, as well as timely implementation of strategies to reduce breathlessness and perhaps mortality.

1.4.5 Impact on health care services

People with chronic breathlessness have complex health care needs but their contact with health services is often narrowed to situations of acute exacerbations (Skilbeck et al., 1998). For people with advanced disease, acute-on-chronic breathlessness is one of the most frequent reasons to present to emergency departments, with such presentations carrying a high likelihood of proceeding to an admission to hospital (Langlo et al., 2014; Wallace et al., 2013). The higher the intensity of breathlessness experienced, the higher the chances of being admitted (Parshall &

Doherty, 2006; Parshall et al., 2001). Episodic presentations to health care services driven by acute-on-chronic breathlessness reflect the health-systems inability to adequately identify people with chronic breathlessness and provide them with appropriate support and care plans in order to better manage any subsequent exacerbations.

There are multiple factors contributing to the invisibility of chronic breathlessness (Gysels & Higginson, 2008). As stated before, chronic breathlessness presents insidiously and people tend to make progressive adjustments to their daily activities, which limit the likelihood of severe exacerbations of breathlessness on exertion. There is also shame around chronic breathlessness that is frequently perceived as self-inflicted (i.e., smoking). Thus, chronic breathlessness is systematically under-reported unless clinicians actively enquire about it (Ahmadi et al., 2016). As chronic breathlessness progresses, people experience increasing difficulties in leaving their homes to attend clinical appointments, and clinical encounters are frequently not tailored to these people's needs (Gysels & Higginson, 2008). As a result, there is a pressing need to find a way to identify community-dwelling people with chronic breathlessness as early as possible in order to provide them with continuous support and prevent clinical exacerbations and further deterioration.

1.5 Mechanisms of breathlessness

The experience of breathlessness results from the integration of respiratory afferents input, respiratory drive, emotional state, attention and previous experiences (O'Donnell et al., 2007). It has been hypothesised that at any given moment, the combined product of these factors is measured by a gated-comparator mechanism and, if a certain threshold is reached, the sensation of breathlessness is perceived (O'Donnell et al., 2007). Two mechanisms are responsible for the sensation of breathlessness:

- sensory input; and
- central processing.

Importantly, chronic breathlessness is a systemic condition affecting multiple body systems and requiring continuous emotional, attitudinal and behavioural adaptations. As a result, the mechanisms underlying chronic breathlessness are necessarily vaster and more complex than those associated with acute breathlessness, but this field of knowledge is still largely unexplored. The sections below describe the current understanding on the mechanisms of breathlessness and highlight their significance in the context of chronic breathlessness. Mechanisms specific to chronic breathlessness are also introduced.

1.5.1 Sensory input

Every sensation of breathlessness starts with the activation of peripheral and central receptors that send afferent signals to the brainstem respiratory centres and higher brain structures. These receptors include chest-wall and pulmonary receptors, metaboreceptors, and central and peripheral chemoreceptors. Their functions are detailed below.

1.5.1.1 Chest wall receptors

It was initially believed the sensation of breathlessness was generated by afferent signals produced by compromised/fatigued respiratory muscles. This idea was supported by breath-holding experiments showing that complete neuromuscular block decreased the sensation of breathlessness in healthy volunteers (Campbell et al., 1967; Campbell et al., 1969). This theory was later refuted after observing that people with high-level quadriplegia (with diaphragm and intercostal-muscles paralysed), and those subjected to complete neuromuscular block had an intact capacity of detecting both changes in lung-volume and partial pressure of carbon dioxide (PCO_2) (Banzett et al., 1987; Banzett et al., 1990; Banzett et al., 1989). Importantly, chest-wall vibration modulates the perception of breathlessness in people with COPD, which is thought to be

mediated by chest-wall receptors (Sibuya et al., 1994). There is also some evidence that phrenic afferents arising from the diaphragm generate and modulate breathlessness (Nishino, 2011). Together, these findings suggest that chest-wall receptors are not a sole source of generating the sensation of breathlessness, but they are important modulators and, in some circumstances, able to produce breathlessness.

1.5.1.2 Pulmonary Receptors

Pulmonary receptors are connected with the *vagus nerve*, which can induce or inhibit breathlessness, depending on the type of fibres activated (Fukushi et al., 2021). Pulmonary receptors include:

- *cold receptors*, which are located in the upper airway and respond to temperature changes (Schwartzstein et al., 1987). While it is unclear whether cold receptors are involved in the genesis of breathlessness, they seem to play a role in breathlessness modulation. Cold air directed to the nose and face reduces breathlessness in people with chronic breathlessness, by a mechanism believed to be mediated by these cold receptors (Galbraith et al., 2010; Puspawati et al., 2017).
- *slow-adapting stretch receptors (SARs)*, which are located within the smooth muscle in the tracheobronchial tree (Widdicombe & Glogowska, 1973) and are stimulated by sustained lung distension (Chou et al., 2008). Interestingly, if lung distension is sustained for long enough, they gradually return to their basal activity rate. Because this adaptation occurs slowly, they are classified as slow-adapting receptors (Schelegle & Green, 2001). In the context of chronic breathlessness, this reflex may be relevant in the genesis of breathlessness associated with COPD, particularly during exertion where there is an increase in lung volumes in already hyper-inflated lungs (O'Donnell et al., 2001). SARs are inhibited by carbon dioxide (CO_2), which may contribute to increased breathlessness in

conditions associated with hypercapnia (e.g., COPD) (Manning et al., 1992; Matsumoto et al., 1999). Conversely, furosemide sensitises SARs and has been shown to reduce experimentally induced breathlessness in healthy volunteers (Moosavi et al., 2007; Nishino et al., 2000). This medication is discussed in detail in Chapter 2.

- *rapid-adapting stretch receptors (RARs)* are mostly activated by bronchoconstriction and decreased pulmonary compliance (Chou et al., 2008). RARs are also not thought to be essential for breathlessness generation, but they may contribute to its modulation. RARs adapt quickly to continued inflation or deflation of the lungs and are sensitive to a range of different stimuli (e.g., mechanical, chemical, inflammatory, immunological) and pathological changes within the airways and lungs. Given their response pattern, RARs may potentially have a role in aggravating breathlessness associated with structural lung changes, which occurs in conditions associated with chronic breathlessness, such as COPD and interstitial lung disease (Chou et al., 2008; Nishino, 2011). Importantly, a study in rats has shown that inhaled furosemide can inhibit RARs, which is another potential mechanism by which furosemide could reduce breathlessness (Sudo et al., 2000).
- *C-fibre receptors:* Animal experiments suggest that C-fibres are responsible for conducting more than 75% of the afferent information passing through the *vagus* nerves (Jammes et al., 1982). C-fibre receptors have been classified in two groups: pulmonary and bronchial, based on their most direct accessibility through the pulmonary or bronchial circulation (Coleridge & Coleridge, 1977; Paintal, 1973). Pulmonary C-fibre receptors are also designated J (from juxtacapillary) receptors due to their intimate relationship with alveolar capillaries (Paintal, 1969). C-fibre receptors are activated by a range of different mechanical, chemical, inflammatory and immunological stimuli (Nishino, 2011). They are not only implicated in breathlessness but also in other respiratory responses such as cough and bronchoconstriction (Adriaensen & Timmermans, 2011). There is little question that C-

fibres are important to generate the sensation of breathlessness, particularly when sensitised by airway inflammation (Lin et al., 2005). This mechanism may be particularly relevant for chronic breathlessness associated with COPD and interstitial lung disease, which usually involve extensive airway inflammation. C-fibre receptors are also strongly activated by pulmonary congestion, associated with congestive heart failure (Paintal, 1969). This mechanism may contribute to chronic breathlessness in these people.

1.5.1.3 Metaboreceptors

Metaboreceptors are found in the skeletal muscle. They are responsible for the metaboreflex, which influences the respiratory drive and is triggered by an increase in the concentration of metabolites in situations of high metabolic demand (Houssiere et al., 2005). These receptors may be responsible for the genesis of breathlessness associated with early stages of exercise when hypercapnia, hypoxaemia and metabolic acidosis have not yet developed (Nishino, 2011). Interestingly, skeletal-muscle dysfunction is one of the hallmarks of chronic conditions associated with chronic breathlessness such as cancer, COPD and congestive heart failure (Currow et al., 2013; Volterrani et al., 1994) that contributes to reduced exercise tolerance (Saey et al., 2003). In advanced disease, people may develop cachexia, characterised by an underlying catabolic state, leading to further muscle atrophy (Deans & Wigmore, 2005; Johnson & Clark, 2016). Such abnormalities are further aggravated by a reduction in the proportion of type I (oxidative) versus type II (glycolytic) muscle fibres, which results in reduced production of adenosine triphosphate (ATP) (and consequent decrease in muscular endurance) and higher production of lactic acid (Currow et al., 2013). The increase in metabolism together with the increase in metabolic waste result in increased stimulation of metaboreceptors, particularly during exercise when the metabolic rate is higher (Piepoli et al., 2008). Stimulation of metaboreceptors triggers an increase in the sympathetic response, resulting in additional increase in ventilation and decreased $PaCO_2$ (Vinogradova et al., 2012).

1.5.2 Chemoreceptors

Chemoreceptors are specialised cell conglomerates that can sense fluctuations in partial pressure of carbon dioxide and oxygen in arterial blood ($PaCO_2$ and PaO_2 respectively), as well as arterial blood pH. Central chemoreceptors are located in the brainstem medulla and predominantly detect changes in $PaCO_2$ and pH; peripheral chemoreceptors are located in the carotid and aortic bodies and are mostly able to detect changes in PaO_2 (Buchanan & Richerson, 2009; Gonzalez et al., 1994). Hypercapnia is one of the most powerful breathlessness-inducing stimuli (Chonan et al., 1990), a process that is mediated by activation of chemoreceptors.

Breathlessness associated with chemoreceptor stimulation is mostly triggered by an increase in respiratory motor output and the subsequent increase in afferent signals (American Thoracic Society, 1999). However, hypercapnia can trigger breathlessness, *regardless* of respiratory motor output (Banzett et al., 1990; Banzett et al., 1989; Chonan et al., 1990). This is because chemoreceptors send direct afferent projections to the sensory cortex , signalling the level of respiratory activity (Shea et al., 1993). They also send afferent projections to the limbic system, which has been consistently implicated in the central perception of breathlessness (Pattinson & Johnson, 2014). Chronic hypoxemic and hypercapnic states are frequently associated with conditions leading to chronic breathlessness. Understanding these mechanisms of breathlessness may contribute to developing effective therapeutic agents for chronic breathlessness.

1.5.3 Central processing

Information coming from the multiple respiratory afferents converge in a gate-keeping mechanism which controls the afferent information reaching the cerebral cortex (Davenport & Vovk, 2009). If the signalling from afferent receptors is kept within the normal range, there is no transmission of information to higher cortical structures and breathing does not reach consciousness. However, if signalling from afferent receptors reaches a certain threshold, this information is transmitted to

higher brain centres, signalising a potential homeostatic threat and inducing the appropriate behavioural responses (Cromwell et al., 2008). Two pathways were proposed to describe how afferent information of a respiratory imbalance is received and processed by supra-thalamic structures (Davenport & Vovk, 2009). The first pathway results from activation of the somatosensory cortex and is responsible for the sensory or discriminative aspects of breathlessness (e.g., intensity, temporal aspects). The second pathway involves structures of the limbic system and insula, which are responsible for the affective aspects of breathlessness (i.e., emotional response to the stimuli) (Davenport & Vovk, 2009). While intensity of breathlessness seems to be a product of the first pathway, immediate unpleasantness seems to be produced by a combination of discriminative and affective processes. Additionally, the long-term emotional response to breathlessness leading to consistent behaviour seems to be more closely associated with the second pathway (Davenport & Vovk, 2009). Different pathways of breathlessness contribute to explaining why people can differentiate between intensity and unpleasantness of breathlessness (von Leupoldt & Dahme, 2005). Understanding these pathways is crucial not only to develop appropriate tools to measure the symptom, but also to develop treatments that target different pathways of breathlessness.

While the somatosensory cortex and sub-cortical structures receive respiratory afferent information, they also send projections to the motor cortex where the efferent signal is initiated and transmitted in order to increase ventilation (von Leupoldt & Dahme, 2005). Once the efferent signal is generated, a copy of this descending information is sent to perceptual areas, a mechanism designated corollary discharge (Campbell & Howell, 1963). The most accepted theory proposed to explain the genesis of breathlessness – *the mismatch theory* – suggests that breathlessness occurs when there is a mismatch between afferent information arising from the respiratory system and efferent information perceived by the corollary discharge (Campbell &

Howell, 1963; Schwartzstein et al., 1989) (Figure 1.2). Thus, the sensation of breathlessness is the result of conscious awareness of a respiratory imbalance, which involves the complex participation of cortical centres and subcortical structures.

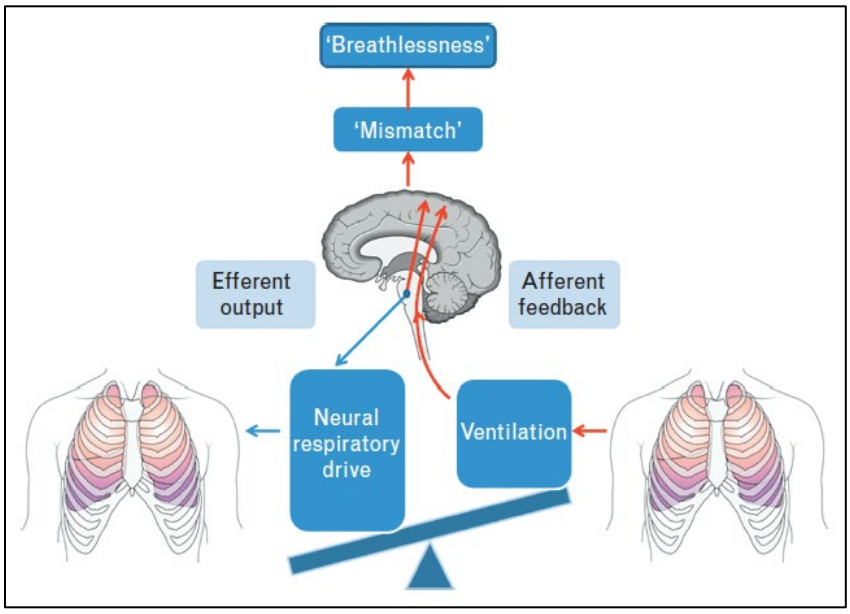

Figure 1.2 – Schematic representation of the 'mismatch theory'.
Breathlessness is perceived when, at the cortical level, there is a 'mismatch' between efferent and afferent information. Copied from Ryan et al. (2014) with permission from Wolters Kluwer Health© (Appendix 2).

Recent neuroimaging studies have provided important insights about the brain regions involved in breathlessness pathways. Although these studies differ in design and methodology, activation of the anterior insula, cingulate cortex, cerebellum and amygdala has been consistently reported (Banzett et al., 2000; Evans et al., 2002; Liotti et al., 2001; von Leupoldt et al., 2008). These brain structures correspond to the affective areas of the brain, which are also important for interoception. Such areas are also activated by other unpleasant sensations signalling homeostatic disruption (e.g., thirst, nausea, pain) (Denton et al., 1999; Miller et al., 1996; von Leupoldt et al., 2009). Importantly, most neuroimaging studies conducted so far focused on experimentally induced breathlessness rather than chronic breathlessness. The only neuroimaging study with a specific focus on chronic breathlessness had a feasibility design and verified that magnetoencephalography is well tolerated by people with chronic breathlessness and may be a

potential technique for future studies (Johnson et al., 2015). Importantly, this technique does not allow people to move freely and may limit evaluation during activity periods. High-resolution electroencephalography may be a good alternative to study brain activity patterns while people perform daily activities.

In addition to investigating patterns of brain activation, some studies have been focusing on structural brain changes associated with chronic breathlessness. A recent study using magnetic resonance imaging reported that people with COPD have decreased grey matter in the several brain structures associated with interoception and emotional processing of breathlessness, which may be a result of long-term adaptation to chronic breathlessness (Esser et al., 2016). These findings are extraordinarily important because they suggest that chronic breathlessness may contribute to lasting structural brain changes. Alternatively, it is possible that people with such structural brain changes from other causes (e.g., genetic, environmental factors) are more vulnerable to experiencing more severe chronic breathlessness, which may also be more resistant to different interventions. Importantly, similar structural changes are seen in chronic conditions associated with chronic stress (i.e., a long-lasting state of perceived threat to homeostasis), and may be involved in the mechanisms leading to more anxiety and depression in the population with chronic breathlessness (Grieve et al., 2013; Li et al., 2014). Recently, it has been suggested that chronic breathlessness contributes to a state of chronic stress, with deregulation of multiple body systems, including the hypothalamic-pituitary-adrenal HPA axis (Ryan et al., 2017). Given the overlap between the central pathways of stress and breathlessness, it is also possible that systemic deregulation associated with chronic stress may aggravate or modulate the experience of chronic breathlessness. Importantly, the mechanisms linking chronic stress with chronic breathlessness are not fully elucidated.

1.6 Measures of Breathlessness

1.6.1 Can breathlessness be measured?

Measuring chronic breathlessness is challenging because it is an attempt to standardise an experience that is highly individual, multidimensional and subjective. In a way, all tools to measure breathlessness are insufficient to describe the dimensions and experience of chronic breathlessness and its impact on daily life. In the clinical setting, tools may assist in identifying people with chronic breathlessness and assess the overall impact of the symptom on the person and their life. However, they need to be followed by a deeper discussion on the severity, consequences and meaning of breathlessness for the person in question.

Considering that chronic breathlessness is highly individual and subjective, self-reporting is the best strategy to measure it (Parshall et al., 2012). Breathlessness is frequently accompanied by objective indicators of dysfunctional breathing, such as an increase in respiratory rate, use of breathing accessory muscles, or decreased oxyhaemoglobin saturation, which may be interpreted as reflections of breathlessness and its severity. While such signs can inform about the severity of the underlying disease, they do not reflect the *experience* of breathlessness. Perhaps due to these disparities between what is *seen* and what is *felt*, ratings of breathlessness tend to vary widely between clinicians and people who experience breathlessness (Iyer et al., 2014; Miravitlles et al., 2013). In a cross-sectional study with 450 people with lung cancer and their oncologists, the patient-physician agreement in breathlessness ratings was less than 50% (Iyer et al., 2014). A second study with a similar design, explored the agreement in breathlessness ratings between people with COPD and their respiratory physicians, which was shown to be minimal (Miravitlles et al., 2013).

1.6.2 Differentiating breathlessness from objective signs of disease

In populations with chronic breathlessness, the difference between the *subjective* experience of breathlessness and *objective* signs of disease is particularly relevant. Traditionally, objective measures such as lung volumes and standardised exercise-capacity tests (e.g., 6-minute walk test, sit-to-stand test, isometric arm exercises and reading numbers aloud) were used to provide an indication of breathlessness severity and its impact on physical function and exercise capacity. However, there are some problems raised by such instruments in the context of chronic breathlessness. Firstly, the concordance between objective measures and subjective breathlessness is surprisingly low, and self-reported measures of breathlessness have been shown to be a better predictor of health-related outcomes in this population (Nishimura et al., 2002). Secondly, for people suffering from severe chronic breathlessness, rates of completion of even relatively low impact exercise tests are low (White et al., 2019). In people with advanced cancer and mMRC 3 or 4 ("stops for breath after walking about 100 metres or stops after a few minutes walking on the level" and "too breathlessness to leave the house or breathlessness when dressing or undressing"), rates of completion of the 6 minute-walk test are 50% and 20% for mMRC 3 and 4, respectively (White et al., 2019). Rates of completion of the arm exercise test and reading numbers aloud were also significantly lower in this population with severe breathlessness (White et al., 2019). The most frequent reasons for not completing these exercise tests were reduced mobility, fatigue and breathlessness.

Even when people can complete measures of exercise capacity, these may not reflect the true limitations associated with chronic breathlessness, especially in day-to-day activities. Exercise-capacity tests are conducted under intense clinical observation and people may tend to overexert to perform as well as possible, because they know they are being observed (i.e., Hawthorne effect). However, under daily circumstances, people may avoid similar effort in order to avoid

feeling breathless. Thus, their daily limitations may be greater than clinical exercise tests indicate. Additionally, exercise-capacity tests may be of questionable relevance for people who struggle to walk from the living-room to the bathroom or make their own meals independently (White et al., 2019). This last point also highlights the importance of applying/developing measures of breathlessness that are *relevant* to people with chronic breathlessness. Such measures must account for extreme physical limitations and mobility experienced by people with breathlessness, but also for what is relevant for this population.

1.6.3 Additional challenges of measuring breathlessness

There are other challenges in measuring breathlessness in populations with chronic breathlessness. These people, who are often of older age, may have difficulties understanding and completing complex assessment tools (Wade et al., 2017). Thus, breathlessness tools for this population are required to balance simplicity and comprehensiveness. Lastly, people with chronic breathlessness may introduce systematic adaptations to their lives to avoid breathing discomfort. Often, people report not feeling breathlessness, but further investigation may reveal complete avoidance of simple regular daily activities in order to prevent breathlessness (Kochovska et al., 2020). These challenges need to be considered to select effective ways of identifying and treating chronic breathlessness.

1.6.4 Breathlessness tools used in the clinical and research settings

Current guidelines divide breathlessness tools in three groups according to the domain they evaluate:

- sensory-perceptual experience;
- affective distress; or
- impact / burden.

There are multiple tools available for each domain and many tools evaluate multiple domains. Bausewein and colleagues systematically reviewed the literature to gather all the measures of breathlessness used in advanced disease, and therefore likely to include people with chronic breathlessness (2007). They identified 33 measures of breathlessness that were valid, reliable, responsive and appropriate. Four were unidimensional and evaluated the severity of breathlessness. Twenty-nine were multidimensional evaluating multiple domains of breathlessness and their impact on people's lives. From all the multidimensional tools available, 11 were breathlessness-specific and 18 were disease-specific. The disease-specific tools were mainly designed for COPD (Bausewein et al., 2007).

Another systematic review published by Dorman and colleagues focused on breathlessness scales available for the palliative care setting (Dorman et al., 2007). Their work focused primarily on construct validity and responsiveness. They identified six scales measuring breathlessness severity, four scales evaluating breathlessness quality, and 19 scales assessing breathlessness-associated functional impairment (Dorman et al., 2007).

A third systematic review looking at tools assessing severity of breathlessness in clinical trials in people with chronic heart failure has identified 6 unidimensional and 17 multidimensional breathlessness tools for this setting (Johnson et al., 2010). Following these publications, other tools have been proposed to assess breathlessness (Banzett et al., 2015; Leidy et al., 2014; Wilcox et al., 2013; Yorke et al., 2011) but none has been shown to be sufficient to evaluate all breathlessness domains.

In order to overcome this limitation, some authors recommend the use of a combination of tools to assess breathlessness in a more comprehensive way (Bausewein et al., 2008). More importantly, although there is a wide range of tools available, there are obvious time-constrains to

apply them, particularly in the clinical setting, which limits the utility of long, complex scales (Glaab et al., 2010). Thus, a single unidimensional scale measuring the severity of breathlessness may be appropriate *for screening* in the clinical setting, if followed by a detailed discussion when breathlessness is detected.

The Numerical Rating Scale (NRS) for breathlessness stands out as the most robust measuring tool in the clinical and research settings (Wilcock et al., 1999). The NRS is a quick and simple measure of intensity of breathlessness, graded from 0 to 10 and anchored on the descriptors 0 ("Not breathlessness at all") and 10 ("Worst possible breathlessness") (Gift & Narsavage, 1998; Wilcock et al., 1999). For acute breathlessness, the minimal clinically important difference defined as "the smallest benefit that is of value for patients" (McGlothlin & Lewis, 2014), is equivalent to a two-point difference in the NRS (Ander et al., 2004; Karras et al., 2000; Ries, 2005). For chronic breathlessness, the minimal clinically important difference is smaller, corresponding to a one-point difference in the NRS (Johnson et al., 2013). This means that even apparently small reductions in breathlessness are important for people who live with chronic breathlessness. The NRS is versatile and can be applied using different timeframes including *breathlessness right now*, *breathlessness at rest*, *average* and *worst breathlessness in the previous 24 hours* (Johnson et al., 2016; Wade et al., 2017). From all possible questions, *worst* and *average breathlessness in the previous 24 hours* seem to describe peoples' experience of breathlessness more accurately (Johnson et al., 2016). Importantly, the NRS can also be used to score *unpleasantness* of breathlessness, which provides an indication of the affective domain of the symptom. This might be particularly interesting in the research setting to discriminate the physical from the affective domain of the symptom. However, given that scores of intensity and unpleasantness tend to correlate very highly for people with chronic breathlessness (Ekström et al., 2019), measuring unpleasantness in this population may bring little additional value in the clinical setting.

There are other unidimensional scales available to measure breathlessness that are quick and easy to use, which include the 100-mm Visual Analogue Scale (VAS) for breathlessness (Gift, 1989) and the modified Borg Scale (Borg, 1982). Compared with the VAS scale, the NRS has been shown to be more reproducible than VAS with less variance (Wilcock et al., 1999), although this might be related to the lower number of levels in the NRS (11 for NRS versus 101 for VAS). Additionally, people seem to prefer the NRS over the VAS (Morris et al., 2007). The modified Borg scale is a 12-point scale with ratio properties that presents number-associated descriptors for all values except 6 and 8. Its greatest limitation compared with the NRS is that people tend to discard the values with no associated descriptors (Johnson et al., 2016). Importantly, these are still valid measures of breathlessness in the clinical setting if the NRS cannot be used for any reason.

The modified Medical Research Council (mMRC) scale for breathlessness is a simple tool that measures the degree of functional impairment because of limits imposed by breathlessness. Respondents are asked to classify their breathlessness from 0 ("not troubled by breathlessness except on strenuous exercise") to 4 ("too breathless to leave the house or breathlessness dressing or undressing") (Bestall et al., 1999; Stenton, 2008). This is simple tool that captures the overall tolerance to daily exertion before breathlessness limits further exertion, but it is not particularly sensitive to detect changes in breathlessness after an intervention (Bausewein et al., 2007; Sorenson, 2000). Its major applications are in establishing a baseline level of disability and use in population surveys for which it was designed.

Multidimensional measures of breathlessness are mostly used in the research setting to determine the impact of chronic breathlessness in different domains of life. However, they are more comprehensive and lengthy, constituting a major disadvantage in the clinical setting. There are multiple multidimensional measures of breathlessness, but the Chronic Respiratory Questionnaire (Guyatt et al., 1987; Schünemann et al., 2005), the St George Respiratory

Questionnaire (Jones et al., 1991), the Baseline/Transition Dyspnea Indices (Mahler et al., 1984), the Dyspnoea 12 (Yorke et al., 2010), and the Multidimensional Dyspnea Profile (Banzett et al., 2015) are some of the most relevant tools to capture the current understanding of breathlessness.

One of the most widely used self-administered tools to evaluate the functional impact of breathlessness on people's quality of life is the Chronic Respiratory Questionnaire (CRQ) (Guyatt et al., 1987; Schünemann et al., 2005). The CRQ includes four domains (breathlessness, fatigue, emotional functioning and mastery), which provide a broad assessment of breathlessness and its impact on a person's life. Each question is scored on a 7-item Likert scale. The minimum clinically important difference was established as a 0.5-point difference on each Likert scale (Jaeschke et al., 1989).

The Baseline/Transition Dyspnea Indices measures the severity of breathlessness evoked by different activities (e.g., job, housework, leisure activities, social activities). Each activity is scored based on the degree of functional impairment experienced, the magnitude or extent of task performed, and the magnitude of effort required to accomplish that task (Mahler et al., 1984). The tool is usually applied at baseline and after an intervention to detect change over time. The Baseline/Transition Dyspnea Index was demonstrated to have high test-retest reproducibility, internal consistency and validity (Mahler et al., 2007; Mahler et al., 1984; Witek Jr & Mahler, 2003). The minimal clinical important difference is change of one unit in the Transition Dyspnea Index (Mahler & Witek Jr, 2005).

The Dyspnoea-12 and the Multidimensional Dyspnea Profile were developed more recently and are based on the current understanding of the multidimensionality of breathlessness (Banzett & Moosavi, 2017). The Dyspnoea-12 consists of 12 items describing different intensity or/and qualities of breathlessness which relate to intensity, unpleasantness and affective response to the

symptom (Yorke et al., 2010). Evaluating the affective qualities of breathlessness is important because different qualities seem to correlate with different breathlessness severity (von Leupoldt et al., 2007a). Each item of the Dyspneoa-12 requires scoring in a 4-point Likert scale (none, mild, moderate, severe), and the scale provides a summary score reflecting the severity of breathlessness in the days leading up to assessment (Yorke et al., 2010). The Dyspnea-12 has high internal consistency, reliability and was shown to be valid for different populations with chronic breathlessness (e.g., COPD, heart failure, interstitial lung disease). Additionally, this scale is relatively quick to apply, which is particularly relevant for the clinical setting.

Similar to the Dyspnoea-12, the Multidimensional Dyspnoea Profile (MDP) was designed to capture both the discriminative and affective aspects of breathlessness (Banzett et al., 2015). However, there are a few differences between these scales. The MDP exhibits a clear separation between items that evaluate the sensory and the affective dimensions. Only one question involves both dimensions, describing the immediate discomfort (or unpleasantness) caused by the symptom (Banzett et al., 2015). This separation of items makes this scale particularly interesting for the research setting, where there may be more interest in studying the effects of interventions in each dimension of breathlessness. Another characteristic that sets the MDP apart from the Dyspnoea-12 is that the MDP is applied to specific focal periods (e.g., *right now*, "after having a shower", "after one minute on the treadmill"), which is also particularly useful to evaluate the specific effects of an intervention. Additionally, each item under the affective domain is used to describe a negative emotion (i.e., depression, anxiety, frustration, fear, anger) that is relevant in the context of breathlessness. Thus, compared with the Dyspnoea-12, the MDP is clearly more discriminative between different domains and qualities of breathlessness.

Both the Dyspnoea-12 and MDP are valid, reliable and quick to complete, which represent advantages in both clinical and research settings (Yorke et al., 2011). However, the minimum

clinically important difference for each scale is not yet established which constitutes a limitation for their uses, in the clinical and research settings.

1.6.5 Evaluating chronic breathlessness – practical considerations

In clinical practice, the NRS for breathlessness is a good measure of breathlessness, which is simple, quick to use and suitable for regular use because it is responsive to change after introducing new interventions (Ekstrom et al., 2015). However, it is important to consider that this tool does not account for within-subject variation in physical activity, which frequently triggers more intense breathlessness in people with chronic disease. Alternatively, the use of multi-dimensional tools may be of interest in the research setting to distinguish between different breathlessness domains, but may be limited by time constraints in clinical practice. As a result, it has been suggested that, in addition to the NRS, the question "What have you had to give up in your life because of breathlessness?" could be a quick and simple way of opening potential avenues of discussion between people experiencing breathlessness and their clinicians, in order to expose the true impact of breathlessness on a person's life (Currow & Ferreira, 2019). However, this question has not been formally investigated. It is an issue that needs to be addressed in future studies.

Lastly, there are people with chronic breathlessness that are unable to self-report or complete scales. In these challenging cases, asking carers about their perception of the person's breathlessness may be appropriate (Currow & Ferreira, 2019). Alternatively, for people who do not have a proxy (or who are inpatients), the Respiratory Distress Observation Scale evaluates breathlessness based on objective signs such as vital signs, breathing pattern and facial expression (Campbell et al., 2010). Although using an external observer to evaluate breathlessness is far from optimal, it is important to ensure these people have their breathlessness assessed and treated as well as possible.

1.7 Conclusion

This chapter introduced chronic breathlessness as a prevalent clinical syndrome, which has a significant impact on patients, carers and health systems. Despite the existence of multiple tools designed to capture different breathlessness domains, measuring breathlessness is challenging because this experience is highly subjective, encompassing different physiopathological mechanisms, sensations and temporal patterns. These findings highlight the need to have an in-depth understanding of chronic breathlessness in order to implement or develop therapies that are more likely to be effective. In this context, Chapter 2 will detail current recommended therapies for chronic breathlessness, with a particular emphasis on the role of regular, low-dose opioids, which must be acknowledged as the leitmotif of this doctoral work.

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CHAPTER 2 - TREATMENT OF CHRONIC BREATHLESSNESS

2.1 Chapter preface

Chapter 1 reviewed chronic breathlessness as a clinical syndrome, highlighting its clinical relevance, mechanisms and complexity. This chapter reviews the role of opioids for chronic breathlessness. It also reviews other proposed/recommended therapeutic options for this syndrome, which, despite not being themselves the main focus of this work, are of utmost importance to contextualise the relevance of opioids.

2.2 A three-step approach to chronic breathlessness

The treatment of chronic breathlessness involves up to three hierarchical steps (Marciniuk et al., 2011):

i. optimisation of disease-specific treatment;
ii. non-pharmacological treatment; and
iii. pharmacological treatment.

2.2.1 Optimisation of disease-specific treatment

Ensuring the underlying condition is optimally treated is the first step in treating chronic breathlessness (Rocker et al., 2007). This may include several approaches depending on the cause(s) of breathlessness and its complications. Importantly, many people will have more than one contributing cause to chronic breathlessness, which requires combined therapy with different approaches. Optimisation of the underlying condition is important because it may be sufficient to control the sensation of breathlessness in some people. If that is the case, the following treatment steps are not necessary.

2.2.2 Non-pharmacological treatment

For some people, optimising the treatment for the underlying condition(s) does not sufficiently reduce chronic breathlessness. In this case, there is a range of evidence-based non-pharmacological treatments available that have been shown to be effective in many cases. These include:

- integrated models of care and psychosocial support;
- pulmonary rehabilitation;
- chest-wall vibration;
- neuromuscular electrical stimulation;
- oxygen supplementation;
- walking aids;
- physiotherapy-based interventions;
- oxygen supplementation;
- hand-held battery, battery powered fan directed to the face;
- olfactory stimulation with L-menthol;
- non-invasive ventilation; and
- other non-pharmacological therapies.

Such treatments options are discussed below.

2.2.2.1 Integrated models of care & psychosocial support

The benefit of integrated models of care in the context of chronic breathlessness has been extensively investigated. In a European single-blinded randomised-controlled trial, participants with advanced disease and chronic breathlessness were randomised to receive either usual care or care from a multidisciplinary breathlessness service (Higginson et al., 2014). The multidisciplinary breathlessness service included palliative care, respiratory care, physiotherapy

and occupational therapy. After 6 weeks of treatment, mastery over breathlessness measured using the CRQ was significantly better in the group treated by the multidisciplinary breathlessness service. After 6 months, survival rate and overall survival was also better in this group (Higginson et al., 2014). A second study used a survey to investigate the same participants' experiences with a breathlessness support service after a 6-week intervention period (Reilly et al., 2016). Eighty-four percent of the respondents considered that this integrated model of care was helpful in improving their breathlessness. In addition, participants also felt improvement in other symptoms (e.g., cough, fatigue, pain), as well as mood and mobility (Reilly et al., 2016). Participants highlighted that the breathlessness integrated service was especially beneficial because the breathlessness interventions were effective and also because they had access to personalised care provided by attentive staff, which made them feel more empowered (Reilly et al., 2016). A more recent cohort study evaluated the impact of an integrated palliative and respiratory service for chronic breathlessness management in people with advanced, non-malignant lung disease. After integrated care initiation, there was a 52.4% reduction in mean number of hospital admissions due to respiratory problems ($p=0.007$) (Smallwood et al., 2018).

Overall, integrated models of care ensure that multiple domains of breathlessness are approached. These include symptomatic treatment of breathlessness and other symptoms (physical domain), psychosocial support, a sense of being taken care of, and education about chronic breathlessness (psychological domain), and social interaction with people from different specialities (social domain). Additionally, once people are included in an integrated model of care, the chances of further referral to other support services (including psychosocial and counselling services) are higher, which may also contribute greatly to their general wellbeing, sense of empowerment, and better health-related outcomes. Thus, integrated models of care form a

cornerstone of chronic breathlessness treatment, preventing further deterioration and promoting a sense of wellbeing for those receiving care.

2.2.2.2 Pulmonary Rehabilitation

Pulmonary rehabilitation is a complex approach that aims to improve the "*physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence to health-enhancing behaviours*" (Spruit et al., 2013, p. e14). Pulmonary rehabilitation is tailored to each person's needs and prioritises their function and independence (Ries et al., 2007). It is usually characterised by a range of different approaches including exercise training, health education, smoking cessation, nutritional advice, and psychosocial support (Ries et al., 2007). Although there is no agreement on the ideal time length of a pulmonary rehabilitation intervention, most guidelines recommend programs of at least 8 weeks (Alison et al., 2017).

There is a large body of evidence showing the benefits of pulmonary rehabilitation in people with COPD. A recent Cochrane review of 65 randomised-controlled trials that included 3822 participants with COPD, pulmonary rehabilitation has been shown to significantly improve breathlessness, functional exercise capacity and maximal exercise capacity compared with usual care (McCarthy et al., 2015). A second Cochrane review of nine randomised-controlled trials involving 432 participants studied the effects of pulmonary rehabilitation up to four weeks after COPD exacerbations. Pulmonary rehabilitation reduced hospital admissions and mortality, but also the breathlessness domain of the CRQ (Puhan et al., 2016). Importantly, people with COPD tend to have a positive view of pulmonary rehabilitation, which is perceived as an effective way of improving physical performance, increasing knowledge about their condition and promoting social interaction with other people in similar circumstances (Gysels & Higginson, 2009).

Not all the mechanisms by which pulmonary rehabilitation improves breathlessness in COPD are clear, but improvements in physical conditioning, effort management, and reduction of

breathlessness-associated distress may play a role in this process (Parshall et al., 2012). Importantly, pulmonary rehabilitation is one of the most cost-effective health interventions that has proven to be beneficial even in people with chronic respiratory failure (Carone et al., 2007). As such, its implementation early in the course of chronic breathlessness associated with COPD is of paramount importance.

There is some evidence suggesting that pulmonary rehabilitation may be helpful to improve breathlessness in other respiratory conditions such as interstitial lung disease (Dowman et al., 2021) and lung cancer (Shannon, 2010). However, the quality of studies available and the effect sizes achieved are insufficient to reach definitive conclusions about its effectiveness in these populations.

2.2.2.3 Chest-wall vibration

Chest-wall vibration consists of manual or mechanically-induced vibration of the chest wall. *In-phase* vibration refers to selective chest-wall vibration during inspiration, which has been shown to be effective to reduce breathlessness in people with COPD, in three crossover trials (Cristiano & Schwartzstein, 1997; Nakayama et al., 1998; Sibuya et al., 1994). Thus, chest-wall vibration is recommended in this population (high level of evidence). There is also one randomised-controlled trial supporting the use of this intervention to reduce breathlessness in people with motor neuron disease (Lange et al., 2006). However, this study did not use in-phase chest-vibration but rather *high-frequency chest-wall oscillation* produced by a vest that was worn for 10 to 15 minutes twice a day. The mechanisms by which chest-wall vibration reduces breathlessness are presumed to be different in COPD and motor neuron disease. In COPD, vibration during the inspiratory phase is believed to stimulate and activate mechanoreceptors which trigger an afferent signal that is able to produce breathlessness reduction centrally. In motor neuron disease, *continuous* chest-wall oscillation is believed to facilitate mucus clearance (Rubin et al., 1989). Such differences are

essential to understand why positive results in one population cannot be generalised for all causes of chronic breathlessness.

2.2.2.4 Neuromuscular electrical stimulation

Physical deconditioning is a concerning problem associated with chronic breathlessness. Some people who experience severe chronic breathlessness have reduced mobility, which prevents them from engaging in exercise programs. At the same time, physical deconditioning contributes to aggravating breathlessness in this population, which perpetuates a cycle of physical and symptomatic decline. Neuromuscular electrical stimulation, consisting of the passive stimulation of skeletal muscle contraction using a low-voltage transcutaneous electric current, offers an alternative to exercise programs for people severely disabled by chronic breathlessness. Two systematic reviews reported that this treatment modality is well tolerated by people with advanced disease and has been shown to reduce chronic breathlessness, while improving muscle mass and strength (Bausewein et al., 2008; Jones et al., 2016). Additionally, a recent double blind RCT reported that neuromuscular electrical stimulation significantly increases exercise capacity, after six weeks of therapy, in people with severe chronic breathlessness associated with COPD (Maddocks et al., 2016). Importantly, the benefit waned six weeks after ceasing the intervention, which suggests that people with debilitating breathlessness may require therapy on a continuous basis.

2.2.2.5 Walking Aids

There is moderate level of evidence suggesting that walking aids are helpful to reduce breathlessness associated with COPD (Bausewein et al., 2008). There is a range of walking aids available, but in the context of chronic breathlessness, wheeled walking frames seem to allow people to lean forward, while providing support to the shoulder girdle and facilitating the work of accessory respiratory muscles (Probst et al., 2004). Wheeled walking frames were shown to

consistently decrease breathlessness measured with a modified Borg scale and increase performance in the 6-minute walk test (Dalton et al., 1995; Honeyman et al., 1996; Probst et al., 2004). Interestingly, only one study evaluated the use of wheeled walking frames to reduce breathlessness in the regular, daily-life setting (Gupta et al., 2006). Over an 8-week period, there were no significant differences in CRQ domains between the group that was given the rollator and the group where no intervention was used (Gupta et al., 2006). However, most participants who used a wheeled walking frame reported that this device was helpful to improve breathlessness (71%) and to make them feel safer (100%) (Gupta et al., 2006). Thus, despite some questions about the effectiveness of this intervention to reduce symptomatic breathlessness, evidence suggests it may contribute to improving exercise capacity and quality of life in people with COPD. Although there is a lack of evidence supporting the role of walking aids in other causes of breathlessness, they may produce similar benefits to non-COPD populations with chronic breathlessness, who experience similar functional and quality-of-life limitations.

2.2.2.6 Physiotherapy-based interventions

Physiotherapy-based interventions includes breathing retraining methods consisting of a range of interventions, including breathing techniques, activity pacing, positioning strategies, and panic management. These interventions may already be part of pulmonary rehabilitation programs, but they can also be offered separately by specialised physiotherapists or nurses (Bausewein et al., 2008). Breathing training has been shown to be effective to reduce breathlessness in people with cardiopulmonary diseases (Hochstetter et al., 2005; Wu et al., 2006). However, studies in this area are heterogeneous and often combine multiple interventions (Bausewein et al., 2008). Thus, it is difficult to assess the value of each intervention individually. Some of the breathing training techniques explored in previous studies include pursed lip and diaphragmatic breathing, yoga breathing, Buteyko breathing and avoidance of deep breaths (Bausewein et al., 2008; Behera, 1998; Bruton & Lewith, 2005). Breathing training programs are easy to implement, beneficial for

some people, cost-effective and have low potential to cause harm. Thus, it is advisable to include them in routine breathlessness management plans.

2.2.2.7 Oxygen Supplementation

The use of supplemental oxygen is recommended in people with advanced cardio-respiratory disease, who have hypoxemia at rest or with minimal exertion (GOLD, 2021; Parshall et al., 2012). In COPD associated with chronic hypoxemia, the use of supplemental oxygen is associated with decreased mortality (GOLD, 2021; Parshall et al., 2012). However, current evidence suggests that oxygen may not improve the subjective sensation of breathlessness, particularly in people with no hypoxemia at rest or on minimal exertion.

A systematic review and meta-analysis evaluating the effects of supplemental oxygen in people with cancer and mild or no hypoxemia failed to demonstrate any improvement in breathlessness scores with this therapy (Uronis et al., 2008). However, the number of studies included was small (n=5) and some showed contradictory results (Uronis et al., 2008). A second systematic review and meta-analysis included 18 studies with 427 people with mild to no hypoxemia due to COPD. This study showed that supplemental oxygen reduced breathlessness in this population compared with medical air, but 41% of the people who derived benefit for breathlessness declined to continue therapy citing poor tolerability or inconvenience (Uronis et al., 2015). An important aspect of these two systematic reviews is that participants' breathlessness scores were secondary outcomes in all the included studies collected during standardised exercise tests (e.g., 6-minute walk test). While these participants exhibit mild to no hypoxemia at rest, it is unclear if supplemental oxygen reduced breathlessness by reducing hypoxaemia during desaturation related to exertion. However, in the daily-life setting, people may avoid reaching equivalent degrees of exertion, potentially experiencing less hypoxemia, which would possibly reduce this effect.

The largest randomised double-blind controlled trial conducted so far in this field (n=239), compared supplemental oxygen to medical air for the reduction of chronic breathlessness from different aetiologies in people with mild to no hypoxemia. Importantly this was a study conducted under regular, daily-life conditions in the home setting (Abernethy et al., 2010). Supplemental oxygen did not show any symptomatic benefit compared to medical air (Abernethy et al., 2010). A second double-blind randomised controlled trial conducted in a similar setting, compared supplemental oxygen with supplemental air for chronic breathlessness associated with COPD in a 12-week intervention for people without resting hypoxemia (Moore et al., 2011). Supplemental oxygen did not show any symptomatic benefit for breathlessness compared to supplemental air (Moore et al., 2011). More recently, a pilot, crossover study evaluated the effect of high flow nasal oxygen compared low-flow oxygen, high-flow air, and low-flow air for the reduction of breathlessness in hospitalised people with advanced cancer (Hui et al., 2021). Clinically significant improvements in breathlessness were seen with high-low oxygen and high-flow air. A second early phase study compared high-flow oxygen with bi-level positive airways pressure (BiPAP) and high-flow air for the reduction of breathlessness in the same population (Hui et al., 2013). Both high-flow oxygen and BiPAP improved breathlessness. The benefit and acceptability of these interventions needs to be evaluated in adequately powered clinical trials.

A more recent randomised controlled trial evaluated the effects of oxygen compared to medical air (both via nasal prongs at 5 litres per minute) on exercise capacity and health-related quality of life of people with COPD who presented oxygen desaturation in the 6-min walk test (Alison et al., 2019). The intervention was administered during multiple sessions of exercise training occurring three times per week, during eight weeks. At the end of the 8-week exercise programme, there were no differences in exercise capacity and health related quality of life between groups. There were also no significant differences in breathlessness scores between groups, although there were

some within-subject improvements in the oxygen group. These results require further investigation in future randomised controlled trials of oxygen for chronic breathlessness, particularly during daily activities requiring more effort.

Importantly, qualitative studies investigating people's experiences with the use of supplemental oxygen to reduce breathlessness reveal that although oxygen is regarded as an essential therapy to sustain life (Jaturapatporn et al., 2010), it comes at a high cost. Oxygen has an impact on people's self-image, mobility and is seen as a point of no return associated with increasing disease severity, a constant reminder of infirmity and the likelihood that the person is approaching the end-of-life (Kelly & Maden, 2014; Lai et al., 2007; Landers et al., 2015). Additionally, oxygen may be associated with the risk of self-immolation, particularly in people who smoke (Tanash et al., 2017). Given the inconclusive results from quantitative studies, the use of oxygen for symptomatic benefit in people who do not have hypoxemia at rest needs to be considered on an individual basis, after assessing potential benefits and burdens (Kochovska et al., 2021).

2.2.2.8 Hand-held, battery powered fan

A randomised controlled crossover trial evaluated the efficacy of the hand-held fan directed to their face and nose for the reduction of breathlessness in people with chronic breathlessness. Fifty participants with advanced disease were randomised to use the fan directed to their face or leg for 5 minutes. Participants were then allocated to the treatment they had not received in the first place. The fan directed to the mouth and nose reduced breathlessness measured with the VAS score compared to the fan directed to the leg (Galbraith et al., 2010). The use of a hand-held fan directed to the mouth and nose has been shown to reduce the sensation of breathlessness in some studies (Swan & Booth, 2015). A qualitative study pooled interview data collected in three separate clinical trials conducted with people with advanced malignant and non-malignant diseases (Luckett et al., 2017). From 111 participants who provided data, 72% perceived some

benefit and 10% perceived very substantial benefit with the use of the fan for the reduction of breathlessness (Luckett et al., 2017). Two additional studies explored the feasibility of effectiveness trials evaluating the use of the hand-held fan to reduce breathlessness (Bausewein et al., 2010; Johnson et al., 2016). These studies showed that the fan was well tolerated by most participants and had an extremely low potential to cause harms. Results also indicate the fan may have a role in improving recovery times after exertion (Johnson et al., 2016). A more recent study also suggests that people who use the fan also perceive an increase in physical activity (Barnes-Harris et al., 2019). It is believed that the fan may reduce breathlessness by activating temperature receptors in the face and upper airways, as well as branches of the trigeminal and olfactory nerves, which would ultimately modulate the central perception of breathlessness (Swan & Booth, 2015). However, this subject has not been thoroughly explored. Despite this, the fan is affordable, harmless and helpful for most people, and its use is recommended to help reduce chronic breathlessness (Barnes-Harris et al., 2019).

2.2.2.9 Olfactory stimulation with L-menthol

Olfactory stimulation with L-menthol is a promising therapy for the reduction of breathlessness associated with COPD. A recent randomised, placebo-controlled, crossover study has shown that L-menthol induced a cooling sensation in the upper airway compared with a strawberry-scented patch (placebo), which was associated with a clinically significant reduction in the intensity of breathlessness in participants with COPD (Kanezaki et al., 2020). Similar to the hand-held fan, L-menthol stimulates temperature receptors in the upper airway that are responsible for producing a cognitive illusion of enhanced inspiratory flow (Kanezaki et al., 2021). One particular receptor detected in nasal trigeminal and vagal afferents – the Transient Receptor Potential Melastatin 8 – has been implicated in this mechanism (Eccles et al., 1988; Plevkova et al., 2013). Considering the mechanism by which L-menthol may reduce the sensation of breathlessness, it is possible that this

new therapy offers benefit to people with multiple aetiologies of chronic breathlessness, which needs to be investigated in future studies.

2.2.2.10 Non-invasive ventilation

Non-invasive ventilation is an effective therapy for people with COPD and acute type II respiratory failure, characterised by hypercapnia (Lightowler et al., 2003). Similarly, non-invasive ventilation has been shown to be effective to treat acute breathlessness induced by cardiopulmonary oedema (Winck et al., 2006). In people with advanced cancer, non-invasive ventilation may be helpful to improve breathlessness associated with acute conditions (Cuomo et al., 2004). However, there is limited evidence of the benefits of long-term non-invasive ventilation for the treatment of chronic breathlessness. Additionally, masks used for non-invasive ventilation are usually a source of discomfort for those using them (Winck et al., 2006). Thus, there is no recommendation for the use of non-invasive ventilation to improve chronic breathlessness (Bausewein et al., 2008). Importantly, a recent randomised study investigated the long-term effects of oxygen-enriched high-flow nasal cannula treatment in people with COPD who had type I respiratory failure (hypoxemia) (Storgaard et al., 2018). The flow rate was set at 20 litres and the average daily use was 6 hours per day. Compared with regular long-term oxygen therapy, treatment with the oxygen-enriched high-flow nasal cannula was associated with fewer COPD exacerbations, improvement in the mMRC scores after three months, significant improvement in the St. George's Respiratory Questionnaire scores after six months and significantly improved $PaCO_2$ and exercise capacity after a year (Storgaard et al., 2018). Only five participants withdrew due to non-compliance with the active treatment (Storgaard et al., 2018). Further research is warranted to identify ideal doses, treatment duration and applicability to clinical practice but these results are promising for this population.

2.2.2.11 Other non-pharmacological therapies

Other non-pharmacological therapies have been explored for the reduction of breathlessness in people with chronic breathlessness. The most recent systematic review on this topic identified some studies exploring the role of acupuncture/acupressure, distractive auditory stimuli and relaxation techniques for the reduction of breathlessness (Bausewein et al., 2008). Studies using acupuncture/acupressure showed contradictory results and the level of evidence for this intervention is considered low. Most studies conducted with distractive auditory stimuli did not show any significant effect on breathlessness, so current evidence does not support its use. Studies with relaxation techniques are too heterogeneous, which prevents drawing any conclusions about such interventions (Bausewein et al., 2008). Importantly, with the exception of acupuncture that is minimally invasive, the other therapies discussed above are unlikely to harm people and may in fact contribute to increasing people's wellbeing. Thus, its use may be of interest for some people with chronic breathlessness.

2.2.3 Pharmacological treatment

Despite the multiple disease-specific treatments and non-pharmacological approaches available for chronic breathlessness, many people continue to have their lives severely limited by this symptom (Johnson et al., 2012b). Thus, there is a pressing need to develop or test pharmacological therapies that can reduce these people's suffering and improve their wellbeing. Opioids are the only pharmacological treatment recommended for the reduction of chronic breathlessness (Marciniuk et al., 2011). Other pharmacological treatments have also been proposed but are currently not recommended in this context. Evidence for the use of opioids, the major subject of this work, and other pharmacological therapies for chronic breathlessness is discussed below.

2.2.3.1 Opioids

Over the last decades, opioids have been investigated as a potential therapy for the reduction of chronic breathlessness, particularly when gold-standard non-pharmacological therapies fail to produce additional improvement. The first systematic review and meta-analysis evaluating systemic (i.e., oral or intravenous) and nebulised opioids for the reduction of symptomatic breathlessness suggested that systemic opioids could be beneficial for reducing the sensation of breathlessness in people with advanced disease (Jennings et al., 2002). However, this systematic review included only small, under-powered studies highlighting the need for further research with higher level of evidence. The first adequately powered study to evaluate the effect of opioids in chronic breathlessness had a crossover design and included 48 participants with different causes of chronic breathlessness (COPD, cancer, motor neuron disease and restrictive lung disease) (Abernethy et al., 2003). There was a significant reduction in breathlessness scores measured with the 0 to 100 mm Visual Analogue Scale after 4 days of treatment with regular, once-daily, sustained-release oral morphine 20 mg compared with placebo (Abernethy et al., 2003). Importantly, no cases of respiratory depression were reported, and the main harm reported was constipation. Overall, 20 mg of regular, low-dose, sustained-release oral morphine was well tolerated and safe (Abernethy et al., 2003).

Following Jennings et al. (2002) systematic review, other studies explored the safety, efficacy, and effectiveness of opioids for chronic breathlessness of different aetiologies (Currow et al., 2011; Ekstrom et al., 2015; Oxberry et al., 2011). More recently, a Cochrane systematic review and meta-analysis reviewed the most recent evidence for the use of opioids in people with chronic breathlessness due to advanced illness (Barnes et al., 2016). Twenty-six studies and a total of 526 participants were included. The authors reported that opioids slightly improved breathlessness and all the studies were classified as low and very low-quality evidence (Barnes et al., 2016). However, there were major methodological problems with this review. Firstly, most of the studies

included had a crossover design, but they were analysed as parallel-arm studies, taking into account the first treatment period only (i.e., opioid or placebo). Secondly, the authors did not account for between-study heterogeneity in design and timeframes, using a fixed-effects model instead of a random effects model to analyse the data. Thirdly, studies with sample sizes < 50 were arbitrarily classified as having high risk of bias, even when adequate power calculations had been conducted, while again taking no account of crossover design. Given the problems mentioned above, these results must be interpreted with caution.

More robust data were obtained by another systematic review and meta-analysis (16 studies, 271 participants) of opioids for chronic breathlessness associated with COPD. This study reported that systemic opioids reduced the sensation of breathlessness in a clinically important way, and the quality of evidence was considered moderate (Ekstrom et al., 2015; Johnson et al., 2013a). This study included a specific sub-group analysis of people treated to steady state, who experienced additional symptomatic benefit. More recently, 284 participants with chronic breathlessness of different aetiologies were randomised to receive regular, low-dose, sustained-release oral morphine (20 mg) or placebo for one week, in the context of an effectiveness RCT (Currow et al., 2020b). There were no differences between the morphine and placebo groups, but the ethics committee overseeing the trial had required the use of PRN immediate-release oral morphine in both arms, which may have masked any benefit with the active medication (Currow et al., 2020b). Importantly, there was a signal for improvement with regular, low-dose, sustained-release oral morphine in the sub-group with an mMRC 3 or 4 and a COPD diagnosis. Based on these findings, a second RCT was planned to investigate response in this particular sub-group, whose results are not yet available (Currow et al., 2017). The latest study published in this area investigated the effectiveness of regular, low-dose, sustained-release oral morphine (10 mg – taken 2 to 3 times a day according to response) to improve health status in 111 participants with moderate to severe

chronic breathlessness and COPD (Verberkt et al., 2020). Results suggest that regular, low-dose, sustained-release oral morphine significantly improved health status measured with the COPD Assessment Test (Jones et al., 2009; Smid et al., 2017). However, there was no difference in mean breathlessness scores between treatment groups. In the sub-population with mMRC 3 and 4, the difference in mean breathlessness scores between the treatment groups was also not significant, but there was a significantly larger reduction in "worst breathlessness in the previous 24 hours" in the morphine group compared with placebo group, which is in line with the previous findings from Currow et al. (2020).

Although evidence is more compelling for chronic breathlessness associated with COPD, there is also some evidence suggesting that morphine can reduce chronic breathlessness of other aetiologies such as chronic heart failure, cancer, or interstitial lung disease. One pilot randomised, placebo-controlled crossover study investigated the efficacy of immediate-release oral morphine (5mg every 6 hours) to reduce breathlessness associated with chronic heart failure (Johnson et al., 2002). Morphine reduced breathlessness in six of the 10 participants included in the study, and this reduction was clinically significant (Johnson et al., 2013a) when compared to placebo (Johnson et al., 2002). A randomised, double-blind, crossover study in a similar population compared immediate-release morphine (5 mg, every 6 hours) with a second opioid agonist – oxycodone (2.5 mg, every 6 hours) – and placebo (Oxberry et al., 2011). This study showed no statistically significant differences between the three interventions. The most recent randomised controlled trial in this setting did not recruit to target but results suggest there is a signal for benefit that needs to be further explored (Johnson et al., 2019).

2.2.3.1.1 Which type of opioids, formulations and doses should be used for chronic breathlessness?
In the setting of pain, morphine is usually considered the first-line therapy when an opioid is required because it is widely available, extensively studied, and inexpensive globally. Based on

these facts, most studies of opioids for breathlessness focused on investigating morphine before any other opioid. Importantly, morphine is available for different routes of administration and in different formulations. In general, oral formulations are preferred unless the oral route is unavailable (Kestenbaum et al., 2014). Oral formulations are convenient and easy to take, which make them ideal for the community setting, where most of the people with chronic breathlessness reside (Currow et al., 2009; Kestenbaum et al., 2014).

Oral morphine is produced in different formulations, which have different durations of action. The immediate-release formulation is short-acting, producing a quicker increase and decrease in serum concentrations (Argoff & Silvershein, 2009). In the pain setting, they are particularly useful for acute or breakthrough pains (Dowell et al., 2016) used in addition to regular dosing, which are usually short in duration. Immediate-release formulations are also traditionally used during therapy initiation and titration, although no studies support its use over sustained-release formulations in these circumstances (Klepstad et al., 2003). In such cases, they need to be taken every four hours to maintain their analgesic effect. Controlled-release formulations are longer-acting formulations that can produce analgesic effects for longer periods. There are controlled formulations that can be taken every 12 hours and sustained-release formulations that can be taken every 24 hours. In the pain-setting, these formulations are often used to treat chronic cancer pain over longer periods of time (Dowell et al., 2016) and are likely to have increased compliance with patients taking the medication.

Compared with immediate-release formulations, sustained-release formulations are a particularly appealing option for chronic breathlessness, even during therapy initiation and dose titration. A double-dummy, parallel-arm, randomised controlled trial conducted in the cancer-pain setting compared immediate-release morphine every four hours with sustained-release morphine (i.e., 24 hour formulation) during dose initiation and titration (Klepstad et al., 2003). This study reported

that time until adequate analgesia was similar in both groups, but participants treated with immediate-release morphine were significantly more tired after the titration period (Klepstad et al., 2003). This finding may be associated with the 4-hourly regimen in the immediate-release morphine group, which required people to interrupt their sleep, in order to take the medication. A second double-dummy, randomised, placebo-controlled trial compared two formulations of modified-release morphine (12-hour and 24-hour formulations) for the relief of moderate to severe pain associated with osteoarthritis (Broomhead et al., 1997). There were no differences between the two groups in terms of analgesia, but participants' assessment was significantly more favourable for the 24-hour formulation (Broomhead et al., 1997). In addition, sustained-release formulations produce less fluctuations in plasma concentrations. They have lower maximum plasma concentrations (C_{max}) and shorter time with maximum concentrations (T_{max}) compared with immediately-release formulations (Gourlay, 1998), which could potentially lead to a lower incidence of adverse events (Portenoy et al., 1993). These findings suggest that sustained-release morphine may be the best option to improve chronic breathlessness and the reasoning supporting its use in most randomised-controlled trials in this field.

The dose range of sustained-release morphine for the reduction of chronic breathlessness was explored in an open-label, phase II study with a phase IV pharmacovigilance phase (Currow et al., 2011). The initial dose was once-daily sustained release morphine 10mg. This dose was increased weekly for non-responders, up to a maximum of 30 mg a day (Currow et al., 2011). Given that this study was published before the publication of the minimal clinically important difference for chronic breathlessness (Johnson et al., 2013a), response was defined as a 10% decrease in baseline breathlessness. Responders could enter a pharmacovigilance phase at the dose level at which they had experienced a response (Currow et al., 2011). Two thirds of the participants experienced benefit with sustained-release morphine for breathlessness, most with doses as low

as 10 or 20 mg (90% of responders) (Currow et al., 2011). After 3 months of therapy, one third of the responders maintained benefit at the same dose level (Currow et al., 2011). After the publication of the original study, a secondary analysis explored the pattern of breathlessness scores in the days following response (Currow et al., 2013). Importantly, this study found that although there is a clinically significant improvement in breathlessness in the first day of therapy (Johnson et al., 2013a), breathlessness scores kept improving for at least six days after response (Currow et al., 2013). These studies suggest that low-dose sustained-morphine (up to 30 mg/day) is effective to reduce breathlessness in a clinically relevant proportion of people with chronic breathlessness. Moreover, there is cumulative benefit in continuing sustained-release morphine after response is detected. Interestingly, it is not known if this pattern of cumulative response continues after the first six days. More importantly, it would be interesting to explore the effect of additional dose increments *beyond* clinical response, particularly in the majority of people who were kept at very low doses (10 mg daily). A phase III randomised controlled trial is currently investigating both these questions (Currow et al., 2017).

2.2.3.1.2 Are low-dose opioids safe for people with chronic breathlessness

Clinicians and researchers have been expressing great concern about the use of opioids for chronic breathlessness (Rocker et al., 2012; Vozoris, 2014). Fear of side effects, particularly respiratory depression, is often reported as an obstacle for opioid prescription in this population (Janssen et al., 2015; Rocker et al., 2012). Concerns about respiratory depression are particularly exacerbated when the person has COPD, a disease in which the central chemoreceptors become less sensitive to hypercapnia. This relative desensitisation could potentially be further aggravated by opioids, which could increase the risk of respiratory depression. These concerns have been explored in recent studies.

A systematic review and meta-analysis of 67 studies investigated respiratory harms of opioids used for the reduction of breathlessness in people with advanced disease (Verberkt et al., 2017). COPD and cancer were, by far, the two most common aetiologies of breathlessness reported in the studies included. Results from this meta-analysis indicate that opioids did not significantly change PaO_2. Conversely, opioids increased $PaCO_2$ in a statistically significant way (Verberkt et al., 2017). Importantly, only five studies reporting $PaCO_2$ were included in the meta-analysis most with small sample sizes, variable designs, types and doses of opioids. Thus, the quality of evidence was assessed as very low (Verberkt et al., 2017).

Out of more than 1000 participants, evidence of respiratory depression was reported in four people, but no definition was provided for three of these cases, whose doses were also unknown. In the fourth case, respiratory depression was defined as respiratory rate of 4-5 breaths per minute. This participant was already taking opioids for pain and the cumulative dose of opioid taken was unknown (Verberkt et al., 2017). Importantly, no cases of respiratory depression were reported in the context of randomised controlled trials, in which doses are well defined and monitored (Verberkt et al., 2017). No cases of respiratory depression were reported in people with COPD. Results from this systematic review and meta-analysis suggest regular, low-dose systemic morphine is safe for people with chronic breathlessness with no risk of respiratory depression, even in people with severe COPD.

In addition to this study, population-based studies investigated the association between opioids and some health-related outcomes. A large population study which included 2249 people with severe COPD on long-term supplemental oxygen therapy has shown that low-dose opioid therapy was not associated with higher rates of mortality (Ekström et al., 2014). Following this publication, a retrospective population study demonstrated an association of low-dose, long-acting opioid therapy with worse health-related outcomes in people with COPD, including mortality (Vozoris et

al., 2016). Although this study had a very large sample size (n=130 979), absolute differences between groups are small which reduces the probability of these findings being clinically significant. In addition, no robust clinical data were collected in this study. For example, there is no information about people's health and functional status or reason to be prescribed an opioid. It is likely that people who are prescribed opioids are sicker, which would predispose to worse health outcomes. Thus, these findings are unlikely to reflect the effects of regular, low-dose, long-acting opioids for breathlessness. Importantly, the latest RCT exploring the effectiveness of regular, low-dose, sustained-release oral morphine to improve health status in people with chronic breathlessness and COPD was also adequately powered to detect clinically significant changes in $PaCO_2$ (Verberkt et al., 2020). There were no differences between arms after four weeks of therapy, which strongly suggests that regular, low-dose, sustained-release oral morphine does not cause respiratory depression in this setting. A new trial with a 6-month extension phase is exploring the long-term effects of low-dose sustained-release morphine in people with chronic breathlessness associated with COPD (Currow et al., 2017).

Frequently encountered side effects of regular, low-dose, sustained-release morphine include constipation, nausea and sedation. While constipation can be an ongoing problem, nausea and sedation tend to disappear after a few days of stable therapy. Importantly, sustained-release morphine should be co-administered with laxatives to prevent constipation. People who experience nausea can be treated with anti-emetics for a few days during therapy initiation and dose-titration. There is no treatment for opioid-induced sedation and people may be advised to take extra precautions to avoid putting themselves and others at risk during initial stages of therapy. People are often advised not to drive for variable periods during therapy initiation and up-titration (Weir et al., 2017). However, it is not clear to what extent low-doses of sustained-release morphine impact driving, particularly when no sedation is reported. This is an important

gap in the literature since not driving has profound consequences for people's quality of life and has been associated with worse health outcomes, including mortality (Chihuri et al., 2016; Ragland et al., 2005).

Although regular low-dose opioids appear to be safe to reduce chronic breathlessness in the context of randomised controlled trials, it is important to ensure that patients are able to take these medications as prescribed in the clinical setting. In some instances, patient dosing administration errors may lead to significant harms (e.g., respiratory depression) (Politis et al., 2017). As a result, it is important that clinicians ensure that patients understand the dosing schedule prescribed or have the appropriate support to be able to take the prescribed medication safely.

2.2.3.1.3 Is response to opioid therapy associated with the underlying disease?

Many adequately powered studies evaluating opioids for chronic breathlessness included participants with different aetiologies of breathlessness (Abernethy et al., 2003; Currow et al., 2020b; Currow et al., 2011). In a pooled analysis of 3 randomised controlled trials, aetiology did not predict response to opioid therapy, which suggested that opioids could relieve breathlessness *regardless* of the underlying cause of chronic breathlessness (Johnson et al., 2013b). This finding has profound implications because it suggests that:

- chronic breathlessness may be characterised by specific underlying mechanisms that are common across different aetiologies, and that may influence response to opioid treatment; and
- studies conducted in particular populations with chronic breathlessness (e.g., COPD) may be generalisable to other aetiologies of breathlessness.

Importantly, studies included in this pooled data analysis had a large proportion of people with COPD, chronic heart failure and cancer, but very few people had other aetiologies of breathlessness such as interstitial lung disease or pulmonary hypertension (Johnson et al., 2013b). Exploring the effectiveness of regular, oral, low-dose, sustained-release morphine in these populations is therefore crucial to understand if all people with chronic breathlessness can be offered the same pharmacological therapy with regular, low-dose, sustained-release oral morphine.

2.2.3.1.4 Are there predictors of response to opioid therapy?

Younger age and higher baseline breathlessness were identified as predictors of response to opioid therapy for chronic breathlessness. Conversely, sex and functional status did not influence response to opioid therapy (Johnson et al., 2013b). Concerning age, one possible explanation is that older age may be associated with longer disease duration, which has been associated with a decrease in grey matter in different brain areas involved in chronic breathlessness processing (Esser et al., 2016). Such structural changes may reduce plasticity in breathlessness pathways and their ability to be modulated by opioids. People with higher baseline breathlessness, another predictor of response, would have more room for improvement in their breathlessness scores, and therefore respond better to opioids. However, up to this point, there are no definitive answers to these questions, which need to be confirmed and investigated with support from basic-science studies. A recent hypothesis-generating study suggested that higher negative affect may predict smaller responses to opioids for chronic breathlessness (Abdallah et al., 2019). However, this relationship needs to be further investigated in larger prospective studies. Pharmacogenetic studies could potentially provide important insights into inter-individual variations in response to opioid therapy. A recent hypothesis-generating study conducted with more than 2000 people with cancer pain treated with regular opioids revealed that one specific genetic polymorphism - *HTRB3* rs7103572 - was associated with a three-fold increase chance of having more severe

breathlessness *despite taking morphine for pain* (Currow et al., 2015). No similar effect was seen in people taking fentanyl nor oxycodone. However, although biologically plausible, it is unclear if this genetic variant influences response to opioid therapy for symptomatic breathlessness (Currow et al., 2015). The answer to this question is important because, if specific genetic variants influence clinical response, therapy can be tailored to each person in order to achieve better health outcomes.

2.2.3.1.5 Guidelines and registration

Based on results from the two most methodologically sound systematic reviews and meta-analyses of opioids for chronic breathlessness, the Canadian Thoracic Society (Marciniuk et al., 2011), the American Thoracic Society (Parshall et al., 2012), the American College of Chest Physicians (Mahler et al., 2010) and the Global Initiative for Chronic Obstructive Lung Disease (GOLD, 2021) have published guidelines recommending systemic opioids as a valid therapeutic option for chronic breathlessness. Recently, the Therapeutic Goods Administration (TGA) in Australia was the first regulatory body in the world to approve any medication for the symptomatic reduction of chronic breathlessness. The TGA registered regular, low-dose, sustained-release oral morphine for this indication: a starting dose of 10 mg / 24 hours that could be titrated up to a maximum of 30 mg, irrespective of the underlying aetiology. Data from a large phase III trials with a long-term blinded extension is awaited by regulatory agencies in North America and Europe (Currow et al., 2017).

2.2.3.1.6 Mechanism of Action

The mechanisms by which opioids reduce breathlessness in people with chronic breathlessness, are not fully understood. However, experimental studies have been highlighting the role of opioids in mechanisms that could potentially be important for breathlessness. These include:

- *decrease in respiratory drive*: The respiratory centre in the medulla is densely populated with opioid receptors and a potential target for opioid therapy. Opioids are thought to bind to these receptors, reducing the respiratory drive with an associated decrease in the respiratory motor output (Nishino, 2011). The suppression of the efferent signal to increase ventilation, reduces the mismatch between the central respiratory drive and the magnitude of ventilation produced, which may reduce the sensation of breathlessness (O'Donnell & Webb, 1993; Schwartzstein et al., 1989). Additionally, by binding to opioid receptors in the respiratory centre, opioids may reduce the input to perception centres in the sensory cortex and the central corollary discharge (Parshall et al., 2012). Although this effect seems to be particularly relevant for high doses of opioids, it seems less evident for low or moderate doses. An experimental study with healthy volunteers reported that moderate doses of IV morphine (0.07 mg/Kg) reduced the sensation of air hunger in laboratory-induced exertion, but this reduction did not significantly correlate with the decrease in ventilatory response (Banzett et al., 2011). Moreover, clinical trials using up to 30 mg of morphine equivalent daily dose report no- to very-small changes in PaO_2 and PCO_2 after opioid administration, which indicates the respiratory drive is not substantially altered (Muers, 2002). A recent randomised crossover study compared the effects of immediate-release oral morphine (maximum dose of 10mg according to body weight) with placebo during exercise testing in people with COPD and severe functional impairment due to breathlessness (Abdallah et al., 2017). Breathlessness and exercise endurance time improved with morphine compared with placebo, which was accompanied by small changes in minute ventilation (i.e., the amount of air entering the lungs per minute), but without significant changes in gas exchange (Abdallah et al., 2017). Given the large magnitude of reductions in breathlessness and improvements in exercise endurance time, it is likely that small decrements in ventilation (with a decrease in central corollary

discharge) are only partially responsible for effects experienced by participants. Instead, it is possible that the awareness of reduced corollary discharge is responsible for the changes observed.

- *change in central perception*: Brain regions involved in the perception of breathlessness and other unpleasant sensations are also filled with opioid receptors (Baumgärtner et al., 2006), which may contribute to explaining why opioids can reduce symptomatic breathlessness. In this context, early studies have shown that the plasma levels of beta-endorphin, an endogenous agonist of the μ-opioid receptor, increase during exercise in healthy people (Farrell et al., 1987; Schwarz & Kindermann, 1992). More recently, laboratory studies demonstrated that naloxone (an opioid-receptor antagonist) increased breathlessness induced by a fixed workload in people with COPD (Gifford et al., 2011; Mahler et al., 2009). These findings suggest that endogenous opioids play a role in modulating the sensation of breathlessness induced by exercise, an effect that is reversed by the administration of naloxone. However, it was still unclear which types of opioid receptors – central or peripheral – were primarily targeted by beta-endorphin. A more recent randomised, double-blind, crossover trial manipulated the levels of peripheral (but not central) beta-endorphin levels during resisting breathing in people with COPD, demonstrating that an increase in peripheral beta-endorphins did not reduce the intensity or unpleasantness of breathlessness (Mahler et al., 2013). This finding suggested that beta-endorphin could modulate the perception of breathlessness by acting centrally instead of peripherally. Importantly, a recent randomised, double-blind, placebo-controlled crossover trial comparing placebo with naltrexone (centrally acting opioid antagonist) and methylnaltrexone (peripherally acting opioid antagonist only) for exertional breathlessness in people with COPD did not show statistically significant differences in the intensity of

breathlessness, between any of the study groups (Currow et al., 2019b). However, this study used a naloxone dose adjusted to weight (0.1 mg/Kg, up to a maximum of 10 mg), while Mahler et al. (2009) used a standard dose of 10 mg for all participants. The dose used by Currow et al. (2019) is also smaller than that of a previous study demonstrating reduced exercise tolerance due to breathlessness, after the administration of 30 mg of naloxone compared with placebo in healthy volunteers (Sgherza et al., 2002). Additionally, people exercised at 75% of their maximum capacity, which could have been insufficient to produce enough endogenous opioids, so that naloxone could produce an effect. Given the available evidence, it is still more plausible that opioids reduce breathlessness by a central mechanism. This hypothesis is further supported by neuro-imaging studies showing that other opioid agonists, such as hydromorphone and remifentanil, were able to activate areas of the brain involved in the perception of breathlessness like the anterior cingulate cortex, thalamus and amygdala (Pattinson et al., 2009; Schlaepfer et al., 1998). In a recent randomised placebo-controlled crossover study using functional MRI, remifentanil was shown to reduce the unpleasantness of breathlessness induced by increased respiratory load, but not its intensity (Hayen et al., 2017). Importantly, such changes in unpleasantness were correlated with decreased activity in the medial and lateral pre-frontal cortex, which may be one of the mechanisms by which opioids regulate the central perception of breathlessness. There are no neuroimaging studies investigating the central effects of regular, low-dose, sustained-release oral morphine and its association with intensity/unpleasantness of breathlessness. This issue needs to be explored in future research.

- *peripheral action*: There are opioid receptors in different peripheral locations such as the dorsal-root ganglia, sensory nerve fibres and the myocardium. They are also located within

the trachea and bronchial tree, particularly in bronchial glands submucosa, bronchioles' smooth muscle, bronchial epithelium, pulmonary alveoli (Mahler et al., 2013) and macrophages (Krajnik et al., 2014). Although the role of opioid receptors in the tracheobronchial tree is not fully understood, there is evidence to suggest that opioids have anti-inflammatory properties, inhibit bronchoconstriction (Kamikawa & Shimo, 1990) and decrease mucus production (Krajnik et al., 2014). However, there is only low-quality evidence suggesting that inhaled opioids, by acting locally in the tracheobronchial tree, may reduce the sensation of breathlessness (Ekstrom et al., 2015). The most recent randomised controlled trial using inhaled opioids compared the effect of 100mcg of nebulised fentanyl with placebo on exercise induced breathlessness of people with interstitial lung disease (Milne et al., 2020). There were no differences between arms in breathlessness intensity or other outcome measures used in this study (i.e., breathing pattern, pulmonary gas exchange, cardiovascular parameters) (Milne et al., 2020). As detailed in the previous paragraph, the peripheral action of opioids does not seem to play a significant role in inducing or modulating breathlessness.

- *decrease in anxiety*: It was postulated that opioids might decrease breathlessness by decreasing anxiety associated with breathlessness, which would interrupt or alleviate the *thinking cycle* of breathlessness detailed by the breathing-thinking-functioning model (Spathis et al., 2017). A randomised, double-blind, crossover study with healthy volunteers has revealed that moderate doses of IV morphine sulphate produced reductions in the intensity of breathlessness *and* a marked decrease in anxiety induced by the sensation of "air hunger" (Banzett et al., 2011). However, it is unclear whether these observations would be similar in the context of chronic breathlessness. A relatively recent experimental study compared the sensations induced by the same hypercapnic stimulus in people with

chronic breathlessness and healthy volunteers (O'Donnell et al., 2013). Results suggested that both groups experienced similar levels of breathing discomfort and similar emotional reactions when exposed to the same stimuli (O'Donnell et al., 2013). Importantly, people with chronic breathlessness tend to avoid breathlessness-inducing activities, which may also reduce the levels of symptom-related anxiety. As a result, it is less likely that opioids reduce breathlessness by improving anxiety. This hypothesis is further supported by studies of anxiolytics for chronic breathlessness, including a Cochrane systematic review, which have not shown any therapeutic benefits to reduce symptomatic breathlessness in the context of daily living (Peoples et al., 2016; Simon et al., 2016). As a result, it is unlikely that opioids can reduce symptomatic chronic breathlessness by improving anxiety.

2.2.3.2 Other pharmacological agents

2.2.3.2.1 Anxiolytics

As explained in section 1.4.2.2, there is a close connexion between anxiety and breathlessness in advanced disease. Firstly, people with chronic breathlessness have reported higher rates of anxiety and depression (Currow et al., 2020a; Yohannes et al., 2010). Secondly, this same population described that breathlessness contributes to generate or aggravate anxiety and panic; as anxiety escalates, it also aggravates breathlessness, which perpetuates the breathlessness-anxiety-breathlessness cycle that is difficult to break (Bailey, 2004). In this context, some studies have been investigating different anxiolytics for the reduction of breathlessness.

A recent Cochrane systematic review and meta-analysis has shown that benzodiazepines did not reduce breathlessness in people with advanced malignant and non-malignant diseases (Simon et al., 2016). However, only small studies were included, most of them with an unclear risk of bias, which prevented the authors from reaching definite conclusions (Simon et al., 2016). Interestingly, most of the studies included in this systematic review did not enrol participants with diagnosed

anxiety disorders, for whom anxiety may be a larger contributor to breathlessness. Moreover, none of the studies included in this review evaluated situations of acute-on-chronic breathlessness (e.g., episodes of exacerbations) (Hutchinson et al., 2019). It is unclear whether results would be similar in situations of acute-on-chronic breathlessness, which have the potential to be more anxiety-provoking, especially if there is not an obvious trigger.

There are important safety concerns raised about the prescription of benzodiazepines in people with advanced disease, who are usually older and frailer. A recent population-based, longitudinal, cohort study that included 2249 people with severe COPD on long-term supplemental oxygen therapy has shown that benzodiazepines were not associated with higher rates of hospital admission, but they were associated with a modest increase in mortality, which was dose-dependent (Ekström et al., 2014). Although this study identified an association between therapy with benzodiazepines and mortality, it is impossible to establish causality in cohort studies because there are usually too many confounders. For example, sicker people are more likely to be medicated and also more likely to have worse health outcomes, which can be related to the underlying disease and not necessarily their medications. Following this publication, a second population-based study with a retrospective design investigated the relationship between incidental benzodiazepine prescription and adverse respiratory outcomes in elderly people with COPD (Vozoris, 2014). This study reported that incidental benzodiazepine prescriptions were associated with increased risk of exacerbations and emergency-department visits due to COPD exacerbations and/or pneumonia, in the 30 days following prescription. Contrary to the previous study (Ekström et al., 2014), this study did not control for potential confounders such as disease severity and functional status, which could have influenced the outcomes. Additionally, no distinction between doses was made. Thus, findings from this study are difficult to generalise.

In summary, there is a lack of evidence supporting the use of benzodiazepines to reduce chronic breathlessness in people with advanced disease. Such findings are important because clinicians still prescribe benzodiazepines routinely to people with chronic breathlessness, some of whom may not even be anxious (Smallwood et al., 2018). Differentiating situations of acute or acute-on-chronic breathlessness (for which no cause has yet been identified) and situations of chronic breathlessness is important to determine whether a person may benefit from benzodiazepines. In situations of acute or acute-on-chronic breathlessness, for which no cause has yet been identified, it is possible that benzodiazepines may still have a role in interrupting the breathlessness-anxiety-breathlessness cycle, and perhaps, improving health-related outcomes.

2.2.3.2.2 Buspirone

Buspirone is an anxiolytic that acts primarily as a serotonin 5-HT_{1A} receptor agonist and has very little affinity for GABA receptors. Compared with benzodiazepines, buspirone has the advantage of not having a sedative effect and not impairing respiration, even in higher doses. A recent phase III, randomised, placebo-controlled trial with 432 participants with cancer receiving chemotherapy has shown that buspirone did not significantly improve breathlessness or anxiety compared with placebo, after 28 days of therapy (Peoples et al., 2016). Importantly, people participating in this study had overall low anxiety scores. Thus, buspirone may not have produced a clinically significant effect in a population that has none or mild anxiety. Given the lack of effect observed in this large randomised-controlled trial, buspirone is currently not recommended for the reduction of breathlessness in people with advanced disease.

2.2.3.2.3 Antidepressants

Selective serotonin reuptake inhibitors (SSRIs) have been evaluated for the relief of breathlessness in people with advanced disease. Some small, uncontrolled studies suggested that citalopram and sertraline could improve chronic breathlessness associated with COPD, even in people who were

not depressed (Perna et al., 2004; Smoller et al., 1998). Two subsequent small randomised controlled trials suggested that paroxetine could be effective for the relief of breathlessness in people with COPD and depression (Eiser et al., 2005; Lacasse et al., 2004). These studies suggested there were at least two hypothetical mechanisms by which SSRIs could relief breathlessness. In people with depression, SSRIs could potentially improve the affective dimension of breathlessness, helping to reduce the overall symptom. In people without significant symptoms of depression, SSRIs may help to reduce breathlessness by reducing anxiety associated with breathlessness. While some studies continue to suggest that SSRIs can relief depression as well as breathlessness (Momtaz et al., 2015), the same is not verifiable for people with none or mild depression. Interestingly, the most recent adequately powered randomised, double-blind controlled trial evaluated sertraline for the relief of breathlessness in 223 participants with different aetiologies of chronic breathlessness (Currow et al., 2019a). Most participants included had none or mild depression/anxiety symptoms and people with severe depression/anxiety were excluded. This study showed that compared with placebo, sertraline did not improve breathlessness scores after 4 weeks of treatment (Currow et al., 2019a). Given the results of this last study, SSRIs are not recommended for the relief of chronic breathlessness in people with none or mild depressive symptoms. However, they may be considered to treat depression, and for some people, that potentially have a positive impact on breathlessness.

2.2.3.2.4 Furosemide

Some small experimental studies suggest that inhaled furosemide may reduce the sensation of artificially induced breathlessness (Minowa et al., 2002; Moosavi et al., 2007; Nishino et al., 2000). In the setting of chronic breathlessness, one randomised, placebo-controlled, crossover study with 20 participants who had COPD has shown that furosemide 40 mg inhaled was able to significantly reduce the sensation of breathlessness during exercise compared to placebo (Jensen et al., 2008). Another study showed similar findings and reaffirmed that furosemide was particularly effective

during constant work rate exercise (Ong et al., 2004), in which it was responsible for significant bronchodilation (or protection from bronchoconstriction) compared with placebo. Furthermore, a randomised, placebo-controlled trial with 100 participants admitted with COPD exacerbations has shown that nebulised furosemide 40 mg in addition to standard pharmacological treatment was superior to 0.9% saline plus standard pharmacological treatment for the relief of breathlessness measured with the VAS (Vahedi et al., 2013). Importantly, other objective measures such as FEV_1, arterial blood gases and vital signs also significantly improved in the furosemide group. There is less evidence to suggest that furosemide is effective in other aetiologies of chronic breathlessness. One case study in a person with chronic heart failure reported that inhaled furosemide produced an improvement in breathlessness and other objective respiratory parameters (Towers et al., 2010). Some case studies of people with advanced cancer report similar findings (Kohara et al., 2003; Shimoyama & Shimoyama, 2002). However, one small double-blind randomised controlled trial reported no significant differences between nebulised furosemide and nebulised saline for the relief of breathlessness (Wilcock et al., 2008).

Furosemide may improve breathlessness by different mechanisms which include a potential systemic diuretic mechanism (Newton et al., 2008). However, experimental studies suggest that furosemide may have a more significant role in modulating airway reactivity to different stimuli. For example, furosemide seems to protect from (or counteract) bronchoconstriction through inhibition of cholinergic and non-cholinergic receptors (Elwood et al., 1991; Lockhart & Slutsky, 1994; Verleden et al., 1994). Additionally, it sensitises pulmonary slow-adapting stretch receptors (Moosavi et al., 2007; Nishino et al., 2000) and inhibits rapid-adapting stretch receptors (Sudo et al., 2000), which respond to a range of different mechanical, chemical and inflammatory stimuli. Thus, it is possible that furosemide is more effective in relieving breathlessness associated with conditions in which airway reactivity and inflammation are the primary underlying mechanisms

(e.g., COPD). Evidence from healthy volunteers, who do not have significant airway reactivity or inflammation, support this hypothesis (Waskiw-Ford, 2018). A recent randomised double-blind placebo-controlled trial reported that furosemide did not reduce breathlessness associated with exercise in healthy people (Waskiw-Ford, 2018).

At this stage, further research is needed before reaching definite conclusions about the use and effectiveness of inhaled furosemide for chronic breathlessness. For example, it is unclear whether furosemide would show benefits in this population under regular, daily-life conditions. This is important because people with chronic breathlessness may avoid overexertion so as not to feel breathless, which would potentially reduce any efficacy of furosemide. Importantly, early studies show promising results, particularly in the population with COPD, which should be a target of future research. Such research would potentially expand the limited pharmacological therapies available for chronic breathlessness.

2.2.3.2.5 Other pharmacologic interventions

Other pharmacological interventions such as therapeutic cannabinoids and Chinese medicine compounds have been explored in the context of breathlessness, but up to this point, there is not enough evidence to recommend their use (Abdallah et al., 2018; Li et al., 2012; Pickering et al., 2011).

2.3 Research gaps shaping the direction of this work

This review has highlighted important knowledge gaps related to the use of regular, low-dose, sustained-release oral morphine in the context of chronic breathlessness. For example, although there are meta-analysis and an effectiveness study suggesting that regular, low-dose, sustained-release oral morphine may be effective for reducing chronic breathlessness, this medication is not yet registered as a pharmacological therapy for chronic breathlessness in most world regions, including North America and Europe. Part of the answer to this problem is to conduct an

effectiveness, placebo-controlled, randomised trial of regular, low-dose, sustained-release morphine for the symptomatic reduction of chronic breathlessness, specifically designed to inform registration with international regulatory bodies. People with severe chronic breathlessness associated with COPD would be a specific population of interest given previous results indicating they may derive more benefit (Currow et al., 2020b; Verberkt et al., 2020). However, there are other crucial questions to be answered concerning the use of regular, low-dose, sustained-release oral morphine for the symptomatic reduction of chronic breathlessness. These questions are aligned with those identified by Johnson et al. in a special article outlining the evidence for the use of regular, low-dose opioids for chronic breathlessness and include (Johnson et al., 2012a):

- what are the barriers and facilitators for prescription of regular, low-dose, sustained-release oral morphine in the context of chronic breathlessness?
- what is the true role of regular, low-dose, sustained-release oral morphine for the reduction of breathlessness in clinical practice, including its harms and impact on "real world" daily living?
- can we define sub-groups of people who derive more benefit?
- by which mechanism(s) does regular, low-dose, sustained-release morphine reduce the symptom of chronic breathlessness?

This doctoral program was designed to explore these questions. Its main purpose is to expand the current knowledge in a largely overlooked field and to contribute to the well-being of a highly disadvantaged population worldwide.

2.4 Project aim

This project aimed to explore aspects related to the *safety* and *effectiveness* of regular, low-dose, sustained-release oral morphine for chronic breathlessness.

2.5 Research questions and thesis overview

This doctoral program focuses on the use of regular, low-dose, sustained-release oral morphine for chronic breathlessness, which is the therapeutic opioid supported by more robust evidence in this context. It was designed to explore aspects related to its *safety* and *effectiveness*, and to contribute to a better understanding of its therapeutic profile in the context of chronic breathlessness. This doctoral thesis includes six sub-studies. Most of them focused on people with COPD, for whom there is more evidence for the use of regular, low-dose, sustained-release oral morphine. The last sub-study included a different population with chronic breathlessness (people with pulmonary arterial hypertension), in order to investigate whether regular, low-dose, sustained-release oral morphine reduces breathlessness in all populations with chronic breathlessness.

Sub-study 1 - Patients' and their carers' experiences of living with chronic breathlessness associated with COPD before and after regular, low-dose, sustained-release oral morphine: a qualitative sub-study

Area of focus: People's experiences

Research questions: What changes (benefits and harms) do people with chronic breathlessness and their carers experience after the introduction of regular, low-dose, sustained-release oral morphine for chronic breathlessness?

Summary: This qualitative sub-study investigated:

- the impact of living with chronic breathlessness for patients, carers and patient/carer dyads. This sub-study aimed to provide the context in which therapy with regular, low-dose, oral sustained-release morphine was being introduced, including daily challenges faced by patients and carers who live with chronic breathlessness associated with COPD;
- patients' and carers' perceptions and experiences with regular, low-dose, sustained-release oral morphine for chronic breathlessness, including contributing factors to the

choice of continuing (or ceasing) this medication in the longer term; and

- patients' and carers' experiences of driving with chronic breathlessness before and after initiating therapy with regular, low-dose, sustained-release oral morphine. The focus on driving provides an example of an activity of daily living that may be affected both by chronic breathlessness and its treatment with regular, low-dose, sustained-release oral morphine especially at the time the medication is initiated or titrated.

Sub-study 2 – A systematic review on the impact of therapeutic opioid agonists on driving-related psychomotor skills

Area of focus: Safety

Question: What is the current evidence on driving safety while taking therapeutic opioids for people with chronic breathlessness and other comparable conditions?

Summary: Driving is important for people with advanced disease, fostering a sense of self-worth and continued independence. Being able to drive is also associated with better health-related outcomes. However, current guidelines do not provide consistent advice on driving while taking regular, low-dose therapeutic opioids and available evidence seems conflicting. This sub-study was designed to examine and systematise the current evidence of the impact of therapeutic opioids on people's driving-related skills.

Sub-study 3 – The impact of regular, low-dose, sustained-release oral morphine on the driving-simulator skills of COPD patients with severe chronic breathlessness – an exploratory, prospective sub-study

Area of focus: Safety

Question: Is it safe to drive while on regular, low-dose, sustained-release oral morphine for chronic breathlessness associated with COPD?

Summary: This was an exploratory, prospective sub-study conducted in a randomised, double-blind fashion, exploring the impact of regular, low-dose, sustained-release oral morphine on

simulated driving compared with placebo at three time points in the first week of therapy.

Sub-study 4 – Genetics of response to regular, low-dose, sustained-release morphine for chronic breathlessness - an exploratory study

Area of focus: Response/Effectiveness

Question: Are there genetic differences that help to explain the variability in response to regular, low-dose, sustained-release oral morphine for chronic breathlessness?

Summary: Genetic variations, particularly the ones associated with opioid pathways (metabolism, receptors or signalling), may be responsible for inter-individual differences in response to regular, low-dose, sustained-release morphine. This sub-study explored associations between four candidate single nucleotide (gene) polymorphisms and symptomatic response to regular, low-dose, sustained-release, oral morphine for chronic breathlessness.

Sub-study 5 – The impact of regular, low-dose, sustained-release oral morphine on the diurnal cortisol profile of people with COPD and severe chronic breathlessness – an exploratory, prospective sub- study

Area of focus: Mechanisms of response/effectiveness

Question: Is regular, low-dose, sustained-release, oral morphine able to modulate hypothalamic–pituitary–adrenal (HPA) axis activity by reducing breathlessness in people with COPD and chronic breathlessness?

Summary: People with moderate-to-severe breathlessness have dysregulation of the normal circadian rhythm of HPA axis activity, which translates into flatter mean diurnal cortisol slopes compared with people with mild or no breathlessness. Cortisol slopes with less diurnal variation have been shown to predict a decrease in physical function, worse physical performance and higher mortality in people with chronic conditions. Regular, low-dose, sustained-release oral morphine has been shown to reduce the sensation of breathlessness in people with chronic

diseases, which may decrease physiological stress and thus potentially modify the HPA axis response over time. This sub-study is the first prospective study investigating:

- the relationship between chronic breathlessness and their diurnal cortisol profile, in people with COPD who are opioid naïve;

- whether the introduction of regular, low-dose, sustained-release oral morphine is associated with changes in diurnal cortisol profile, and whether these correlate with variations in subjective breathlessness scores.

Study 6 – Regular, low-dose, sustained-release morphine for chronic breathlessness associated with pulmonary arterial hypertension

Area of focus: Response/Effectiveness

Question: Is regular, low-dose, sustained-release, oral morphine equally effective to reduce breathlessness in people with different aetiologies of breathlessness?

Summary: Although regular, low-dose, sustained-release oral morphine has been shown to be effective in reducing breathlessness in people with COPD, it is unclear whether it has a similar effect in people with other aetiologies of breathlessness. This study was a double-blind, randomised, placebo-controlled, crossover study investigating the effectiveness of regular, low-dose, sustained-release oral morphine in a population with pulmonary arterial hypertension.

Results of these six sub-studies will contribute to the body of literature informing the use of regular, low-dose, sustained-release oral morphine for chronic breathlessness, and may be relevant to influence future research directions, clinical practice and policy.

2.6 Conclusion

This chapter reviewed current recommended therapeutic options for chronic breathlessness, with a particular focus on the role of opioids. Despite the broad range of disease-specific treatments

and non-pharmacological approaches available, many people will not achieve appropriate symptom control requiring the initiation of opioids. In particular, the use of regular, low-dose sustained-release oral morphine is supported by more robust evidence, and it is the core of this doctoral research project.

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CHAPTER 3 - GENERAL METHODS

3.1 Chapter preface

As detailed in Chapter 2, there are still important knowledge gaps concerning the use of regular, low-dose, sustained-release oral morphine to reduce chronic breathlessness, which are mainly related to its safety in the context of everyday life and its variable effectiveness (Johnson et al., 2012). Exploring these knowledge gaps requires a research program that is sufficiently broad to explore different research questions which, collectively, will contribute to better understanding how regular, low-dose, sustained-release oral morphine can be used to reduce chronic breathlessness. This chapter details the methodology chosen for this doctoral research project, including the rationale for using a multi-method approach. Given that four of the six sub-studies included in this doctoral thesis were embedded in the same RCT (i.e., BEAMS study), this chapter also provides an overview of the BEAMS study and the methodological aspects common to these four sub-studies.

3.2 Objectives

The objectives of this multi-method research project were to:

i) Understand people's experiences with regular, low-dose, sustained-release oral morphine in the context of symptomatic treatment for chronic breathlessness;

ii) Explore the impact of treatment with therapeutic opioid agonists on people's driving-related skills;

iii) Explore the impact of the introduction of regular, low-dose, sustained-release morphine on driving-related skills of people living with chronic breathlessness;

iv) Explore the impact of regular, low-dose, sustained-release oral morphine for chronic breathlessness on people's diurnal cortisol profile; and

v) Investigate response to regular, low-dose, sustained-release oral morphine in people with pulmonary arterial hypertension as the main cause of chronic breathlessness.

3.3 Research design

A multi-method design, consisting of six discrete sub-studies was selected to investigate different aspects of the safety and effectiveness of regular, low-dose, sustained-release oral morphine for chronic breathlessness, as outlined by Johnson et al. (2012):

- Sub-study 1: Semi-structured interviews with people living with chronic breathlessness and their carers (Ferreira et al., 2020a; 2020b) (reported in Chapter 4).
- Sub-study 2: A systematic review of the impact of opioid agonists on driving-related skills (Ferreira et al., 2018b) (reported in Chapter 5).
- Sub-study 3: A prospective study evaluating the impact of introducing regular, low-dose, sustained-release oral morphine on the driving-simulator skills of people with chronic breathlessness (reported in Chapter 6);
- Sub-study 4: A genetic analysis exploring the impact of a small array of genetic polymorphisms on people's response to regular, low-dose, sustained-release oral morphine for chronic breathlessness (reported in Chapter 7);
- Sub-study 5: A biochemistry analysis exploring the impact of regular, low-dose, sustained-release oral morphine for chronic breathlessness on people's diurnal cortisol profile (reported in Chapter 8); and

- Sub-study 6: A double-blind, randomised, placebo-controlled, crossover study evaluating the effectiveness of regular, low-dose, sustained-release morphine for symptomatic chronic breathlessness associated with pulmonary arterial hypertension (Ferreira et al., 2018a) (reported in Chapter 9).

Of the six sub-studies included in this doctoral program, Sub-study 2 (systematic review) did not require recruitment; four sub-studies (1, 3, 4 and 5) were embedded in an effectiveness trial of regular, low-dose, sustained-release oral morphine for chronic breathlessness associated with COPD – the BEAMS (Breathlessness, Exertion and Morphine Sulfate) study (Currow et al., 2017a). Sub-study 4 (genetic analysis) also recruited participants from a second randomised-controlled trial evaluating the effectiveness of regular, low-dose, sustained-release oral morphine for chronic breathlessness of different aetiologies. Sub-study 6 was a separate randomised, placebo-controlled, crossover trial of regular, low-dose, sustained-release oral morphine for people with chronic breathlessness associated with pulmonary arterial hypertension (Figure 3.1).

This chapter provides an overview of the BEAMS study, which includes methodological aspects that are common to sub-studies 1, 3, 4 and 5. Specific methods for each individual sub-study, are detailed in the corresponding chapters.

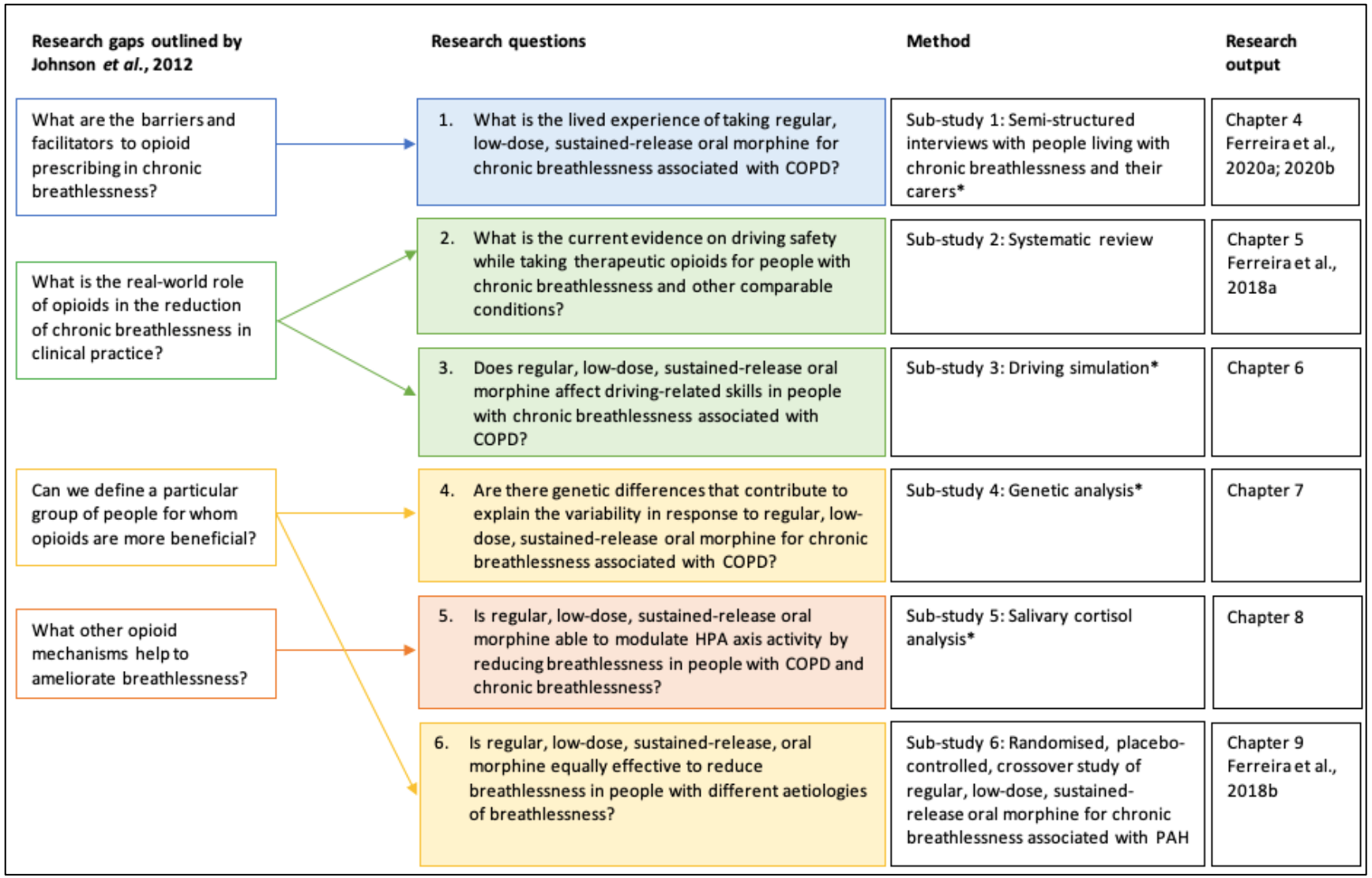

Figure 3.1 - Outline of this doctoral thesis including research gaps outlined by Johnson et al. (2012), research questions, methods, and research outputs.

*Sub-studies of the BEAMS study.
COPD = chronic obstructive pulmonary disease; PAH = pulmonary arterial hypertension

3.3.1 Rationale for the use of a multi-methods approach

This doctoral program had a broad scope, aiming to explore distinct aspects related to the same overarching theme (i.e., the safety and effectiveness of regular, low-dose, sustained-release oral morphine for the symptomatic reduction of chronic breathlessness). In this context, a multi-methods approach is useful because it uses different methods to explore *different research questions within the same research program* (Morse, 2003). Contrary to mixed-methods research, multi-methods research may not necessarily combine quantitative and qualitative methodologies, but rather include a variety of different methodologies that can be quantitative, qualitative or a combination of both (Hunter & Brewer, 2015). Importantly, multi-methods research programs do not require data integration because they aim to answer different sub-questions (Clark & Ivankova, 2015). Each sub-study included in this doctoral program was designed to investigate a distinct aspect related to the safety or effectiveness of regular, low-dose, sustained-release morphine for chronic breathlessness. Collectively, they explore factors contributing to the overall therapeutic effect (i.e., weighing benefits and harms) of regular, low-dose, sustained-release morphine for chronic breathlessness.

3.4 BEAMS study design

The BEAMS study was an effectiveness, multi-centre, parallel-arm, dose-increment, block-randomised, double-blind, placebo-controlled study designed to evaluate the effectiveness of regular, low-dose, sustained-release oral morphine for the reduction of breathlessness in people with severe chronic breathlessness associated with COPD.

3.5 Study settings

The BEAMS study recruited participants from 19 sites across Australia between August 2016 and November 2019. Sites were palliative care and respiratory services located in metropolitan areas of the Australian Capital Territory, New South Wales, Queensland, South Australia, Victoria and

Western Australia (Currow et al., 2017a). Overall, the BEAMS study included nine optional, hypothesis-generating sub-studies, four of which (Sub-studies 1, 3, 4 and 5) were part of this doctoral program. Given the large number of sub-studies included and the diversity of sites involved, only a limited number of sub-studies was implemented and/or prioritised at each site in order not to overburden participants. Sub-studies available/prioritised in each site were selected based on existing human and technical resources, local interests and services characteristics (Table 3.1). Specific considerations concerning sub-study recruitment are included in the respective chapters.

Table 3.1 - List of sites recruiting for Sub-studies 1, 3, 4 and 5 (BEAMS study)

BEAMS recruiting sites	Sub-study 1 (Patients and carers experiences)	Sub-study 3 (Driving simulation)	Sub-study 4 (Genetic analysis)	Sub-study 5 (Salivary cortisol analysis)
Australian Capital Territory				
Clare Holland House, Canberra			X	X
New South Wales				
Sacred Heart health Service, Darlinghurst		X	X	X
Calvary Healthcare, Kogarah		X	X	X
Calvary Mater, Newcastle			X	X
Concord Repatriation Hospital, Concord		X	X	X
Greenwich Hospital, Greenwich		X	X	X
Liverpool Hospital, Liverpool		X	X	X
Westmead Hospital, Westmead			X	X
Queensland				
Mater Health Service, Brisbane			X	X
Nambour Hospital, Nambour			X	X
The Prince Charles Hospital, Chermside			X	X
St Vincent's Private Hospital, Brisbane			X	X
South Australia				
Repatriation General Hospital, Daw Park	X	X	X	X
Southern Adelaide Palliative Services, Daw Park	X	X	X	X
Victoria				
Austin Hospital, Heidelberg			X	X
Barwon Health, Geelong			X	X
Royal Melbourne Hospital, Melbourne			X	X
St Vincent's Hospital, Melbourne			X	X
Western Australia				
Sir Charles Gairdner Hospital, Nedlands			X	X

3.5.1 BEAMS study participants

Participants were people with moderate to severe COPD with breathlessness scores of 3 or 4 in the mMRC scale for breathlessness corresponding to “stops for breath after walking about 100 meters or stops after a few minutes walking on the level” and “too breathlessness to leave the house or breathlessness when dressing or undressing”, respectively (Bestall et al., 1999; Stenton, 2008). This group was selected based on previous observations from a randomised controlled study, in which the group of participants with COPD who experienced more functional impairment due to breathlessness (i.e., mMRC 3 or 4) had indications of a greater improvement with regular, low-dose, sustained-release oral morphine for chronic breathlessness (Currow et al., 2020b; Verberkt et al., 2020). Additionally, potential participants needed to report a score of at least 3 on the NRS for *worst breathlessness in the previous 24 hours*, in which 0 corresponded to “no breathlessness” and 10 corresponded to “worst possible breathlessness” (Gift & Narsavage, 1998; Wilcock et al., 1999). Exclusion criteria included taking any opioid in the seven days prior to the study, not having optimally treated causes of breathlessness according with their treating specialist, and not being on stable medication for seven days before starting the study. Boxes 1 and 2 report the complete list of BEAMS inclusion and exclusion criteria (Currow et al., 2017a).

Box 3.1 - BEAMS inclusion criteria

- 18 years of age or older;
- physician diagnosed COPD (confirmed by spirometry with the most recent result available defined as a prior post-bronchodilator FEV1/FVC < 0.7 in accordance with the GOLD 2014 criteria);
- clinician-confirmed optimisation of treatment of COPD;
- on stable medication for COPD or its symptomatic management over the prior week, except routine “as needed” medications;
- breathlessness of a level 3 or four 4 on the mMRC breathlessness scale;
- *worst breathlessness* intensity in the previous 24 hours of at least 3 out of 10 on the NRS;
- English speaking with sufficient reading and writing ability demonstrated through the completion of the St Louis University Mental Status Examination (SLUMS) score of ≥23/30 or as deemed suitable by the site principal investigator; and
- able and willing to provide written informed consent.

Text Box 3.2 - BEAMS exclusion criteria

- Taking any opioid for breathlessness in the previous 7 days;
- on regularly prescribed opioid medications for other conditions, including codeine preparations at or above 8mg oral morphine equivalent daily dose (MEDD) in the previous 7 days;
- history of adverse reactions to any of the study medications or constituents in the placebo;
- Australian-modified Karnofsky Performance Status (AKPS) less than 50 at the beginning of the study;
- respiratory or cardiac event in the previous one week (excluding upper respiratory tract infections). Illness must have been resolved completely prior to baseline evaluation, as judged by the person's treating physician;
- evidence of respiratory depression with resting respiratory rate <8 cycles/min;
- documented central hypoventilation syndrome;
- current or recent history of abuse of alcohol, or recent history of substance misuse;
- uncontrolled nausea, vomiting or evidence of a gastrointestinal tract obstruction;
- renal dysfunction with creatinine clearance calculated (MDRD) less than 20 mL/minute;
- evidence of severe hepatic impairment defined as transaminases or bilirubin >4x normal (excluding Gilbert's syndrome); or
- pregnant or breastfeeding.

3.5.2 Recruitment and consent

BEAMS participants were recruited following one of three pathways:

- primary and secondary care clinicians identified and approached potential participants, who were then referred to the BEAMS research team at each participating site;
- the BEAMS research team at each participating site approached potential participants directly, after seeking consent from their treating clinicians (with Human Research Committee oversight); *or*
- participants self-referred to the study as a result of ethics-approved study advertising targeting groups of people with advanced COPD.

All potentially eligible participants were thoroughly informed about the BEAMS study and, if applicable, the optional sub-studies. Patients' information sheets were used as prompts to ensure all study participants received adequate information about the study procedures and facilitated discussions of potential questions and concerns raised by participants. Eligibility was confirmed by

the research team at each site. All participants provided written informed consent for the BEAMS study and sub-studies of choice. Consent for Sub-study 4 (genetic analysis) was obtained in the participant information and consent forms used for the main study (Appendix 3). Consent for sub-studies 1 (semi-structured interviews), 3 (driving simulation) and 5 (salivary cortisol analysis) was obtained in separate participant information and consent forms (Appendices 4 to 6, respectively).

3.5.3 Randomisation

The study sponsor developed randomisation tables for each site, which were kept by the sites pharmacies. Block randomisation (blocks of 6) ensured that for each site, allocations were evenly distributed across the study arms. This randomisation method is particularly appropriate for multi-centre studies because, at each site, participants have equal opportunities of being allocated to the active treatment, allowing inter-site comparison of outcomes. The use of block randomisation was also crucial for the sub-studies, because it increased the chances of having an even number of participants per arm, even when recruitment was restricted to a limited number of sites.

The BEAMS study included collection of baseline data across two days. Once baseline assessments were completed, participants were evenly allocated to one of three arms:

- regular, once-daily, sustained-release oral morphine 8 mg;
- regular, once-daily, sustained-release oral morphine 16 mg; *or*
- identical-looking placebo.

In addition to the study medication, all participants were prescribed offered blinded laxative (docusate and senna *or* placebo laxative) in order to prevent constipation. Participants took this medication for seven days (*week 1*). The end of week 1 corresponded to Stage 1, the study primary endpoint.

At the end of week 1, there was a second randomisation, regardless of benefits (but

independently of harms), to *an additional*:

- placebo (participants maintained the dose they were taking on week 1), *or*
- regular, once-daily, sustained-release oral morphine 8 mg (participants increased the dose they were taking on week 1 by 8 mg).

This dose was taken for seven days (*week 2*). The end of week 2 corresponded to Stage 2. Participants who were allocated to placebo in week 1 and sustained-release morphine in week 2 were provided with blinded docusate and senna (instead of placebo laxative) if they were allocated, while still double-blind, to receive active medication.

At the end of week 2, there was a third randomisation to *an additional*:

- placebo (participants maintained the dose they were taking at that time), *or*
- regular, once-daily sustained-release oral morphine 8mg (participants increased the dose they were taking at the time by another 8mg).

This dose was taken for seven days (*week 3*). The end of week 2 corresponded to Stage 3. Participants who were initiating the active medication for the first time were provided with blinded docusate and senna (instead of placebo laxative).

The completion of week 3 corresponded to the end of the randomisation period. By the end of week 3, participants could be taking five different doses of the study medication:

- placebo (1/12 chance);
- regular, once-daily, sustained-release oral morphine 8 mg (3/12 chance);
- regular, once-daily, sustained-release oral morphine 16 mg (4/12 chance);
- regular, once-daily, sustained-release oral morphine 24 mg (3/12 chance); *or*
- regular, once-daily, sustained-release oral morphine 32 mg (1/12 chance).

After completing the randomisation stage, participants were given the option of continuing taking the same dose taken on week 3 for a blinded-extension period up to 6 months (Figure 3.2). Specific randomisation procedures are described in the BEAMS study protocol publication (Currow et al., 2017a).

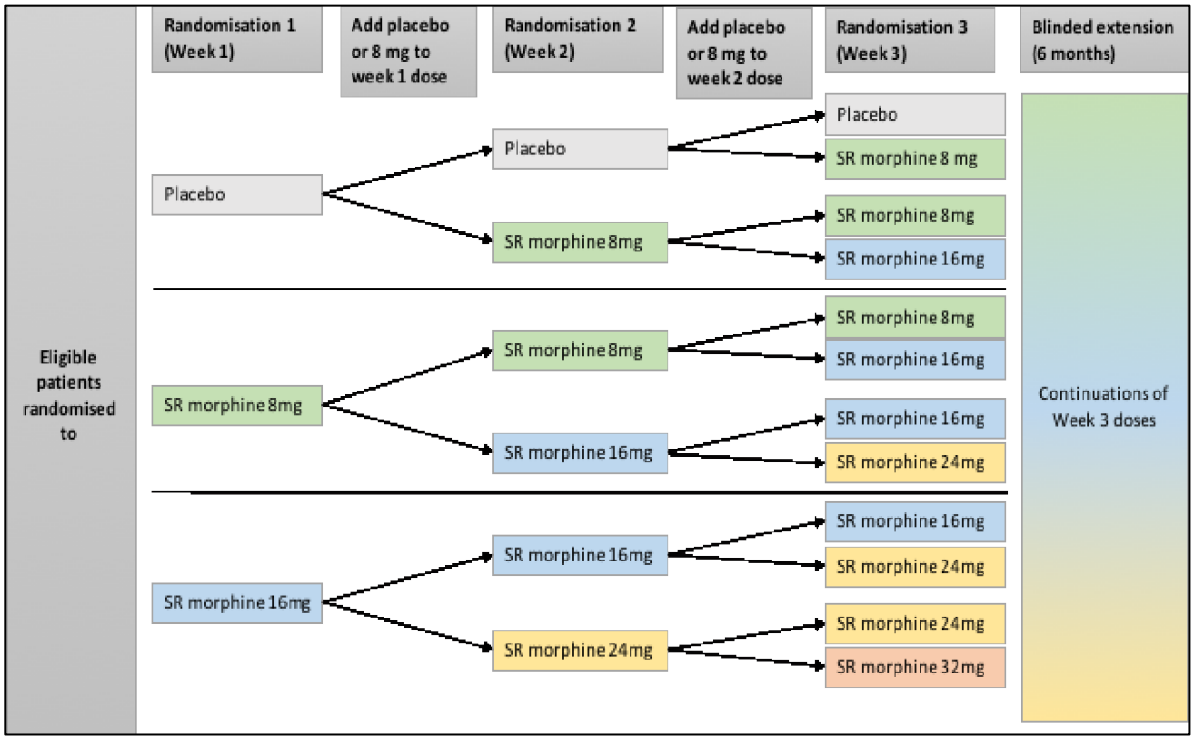

Figure 3.2 - BEAMS study design including randomisations 1, 2 and 3 and the 6-month blinded extension.

SR = Sustained release

3.5.4 Outcomes of interest

The BEAMS study had multiple outcomes of interest, but only some were selected as outcomes of interest in its sub-studies.

3.5.4.1 Demographic measures

Demographic characteristics used to describe the populations included in at least one of the sub-studies of this doctoral thesis included:

- age;

- sex;
- ethnicity;
- usual language spoken at home;
- type of residence;
- highest level of education;
- marital status; and
- carer availability.

In Sub-study 5 (salivary cortisol analysis), age, sex, and carer availability were also included in the analysis as variables of interest, due to their potential impact on the HPA axis and diurnal salivary cortisol levels (Guidi et al., 2021). All demographic characteristics were collected as part of the BEAMS study and used in the sub-studies to avoid collection of repeated data, with additional burden for participants.

3.5.4.2 Baseline clinical assessment

Specific baseline clinical information collected as part of the BEAMS study was used to describe the populations included in the sub-studies. These included:

- Body mass index (BMI);
- Charlson Comorbidity Index adjusted for age;
- Smoking status;
- Use of supplemental oxygen;
- List of relevant medical history and medication; and
- Saint Louis University Mental Status (SLUMS).

3.5.4.2.1 Body mass index (BMI)

Measuring the BMI is relevant in the context of chronic breathlessness because increasing BMI has been previously associated with increased functional impairment due to breathlessness (Currow et

al., 2017c). Obesity has multiple negative consequences on the respiratory system, which include reduced lung volumes and compliance, and increase workload of intercostal muscles (El-Gamal et al., 2005). These may contribute to aggravating chronic breathlessness and potentially decrease the efficacy of some symptomatic interventions. The BMI was reported in all quantitative sub-studies included in this doctoral program and explored as a specific variable of interest in Sub-study 5 (salivary cortisol analysis), due to its possible influence on diurnal cortisol levels (Adam et al., 2017).

3.5.4.2.2 Charlson Comorbidity Index adjusted for age

The Charlson Comorbidity Index (Charlson et al., 1994; Charlson et al., 1987) is a summary measure of multi-morbidity, which is commonly present in people with chronic breathlessness (Smith et al., 2016). Identifying the presence of co-morbidities in people with chronic breathlessness is important because such conditions may potentially contribute to aggravating breathlessness, produce disability, and influence aspects related to the safety and effectiveness of regular, low-dose, sustained-release oral morphine in this population (e.g., people's ability to drive).

3.5.4.2.3 Smoking status

Older adults who are current smokers are more likely to experience chronic breathlessness (Bowden et al., 2011), and it is unclear whether smoking affects response to regular, low-dose, sustained-release oral morphine in the setting of chronic breathlessness. As a result, smoking status *(i.e., current smoker, former smoker, never smoked)* was used as a variable of interest in the sub-studies exploring aspects related to the *effectiveness* of regular, low-dose, sustained-release oral morphine for chronic breathlessness.

3.5.4.2.4 Use of supplemental oxygen

The use of supplemental oxygen (in litres/minute) may reflect higher severity of the underlying disease, but not necessarily more severe breathlessness. The use of supplemental oxygen was used to describe baseline populations included in the sub-studies.

3.5.4.2.5 List of relevant medical history and medication

Individual medical histories and medications prescribed were collected as part of the BEAMS study to ensure participants were eligible to enrol (i.e., were not taking regular opioids) and had their medication stabilised for at least one week before initiating the study medication. Any changes in their regular medication during the study were also documented, so they could be accounted for in the analysis. Specific health conditions and medications were examined as part of sub-studies 3 (driving simulation assessments) and 5 (salivary cortisol analysis), which is detailed in the respective chapters.

3.5.4.2.6 Saint Louis University Mental Status (SLUMS) examination.

The SLUMS is an 11-question, clinician-administered assessment tool designed to identify cognitive impairment (Tariq et al., 2006). Scoring varies from 0 to 30 points according to the number of questions answered and, when applicable, the difficulty level achieved in each question. The scoring range is different for people who have completed high school education and those who have not, with the *normal range* corresponding to 27 – 30 *or* 25 – 30 points, respectively; *mild neurocognitive disorde*r corresponding to 21 – 26 *or* 20 – 24 points, respectively; and *dementia* corresponding to 1 – 20 *or* 1 – 19, respectively. The SLUMS has been validated in different populations of elderly adults, and takes approximately seven minutes to complete, which represents an advantage in frail populations (Feliciano et al., 2013; Tariq et al., 2006). Minimum clinically important differences have not been established. The SLUMS was used in the BEAMS study to assist investigators to determine whether potential participants were able to understand and complete the study procedures (Currow et al., 2017a). The SLUMS was also used in Sub-study

3 (driving simulation) to exclude participants with scores suggestive of dementia, which could potentially affect their ability to drive on the simulator (Wadley et al., 2009).

3.5.4.3 Measures of breathlessness

3.5.4.3.1 NRS measures of breathlessness

BEAMS' primary outcome was change, from baseline to days 5 to 7, in intensity of *worst breathlessness in the previous 24 hours*, measured with the NRS for breathlessness (Gift & Narsavage, 1998; Wilcock et al., 1999). As explained in section 1.6.2, the NRS is recommended in the clinical and research settings because it is easy to utilise and responsive to change (Johnson et al., 2016). *Worst breathlessness* was selected as the primary outcome because it is more responsive to change and seems to reflect peoples' experiences of breathlessness change more accurately (Johnson et al., 2016; Lovell et al., 2019). Changes in *average* and *unpleasantness* of breathlessness in the previous 24 hours were also collected at similar timepoints using the NRS. *Average breathlessness* is relevant to capture the overall intensity of breathlessness across 24 hours, but it is less responsive to change compared with *worst breathlessness* and seems to exhibit a ceiling effect for values higher than 8 (Johnson et al., 2016; Lovell et al., 2019). *Unpleasantness of breathlessness* scores were collected to complement the previous measures by capturing the affective domain of this symptom (Johnson et al., 2016). For differences in breathlessness scores, the mean scores of days 5 to 7 were used to calculate a summary value in stage 1, because people would have reached morphine plasma steady-state concentrations by then (Currow et al., 2020b). Using the mean scores of days 5 to 7 also aimed to reduce the influence of daily breathlessness fluctuations and minimise missing data in such a frail population (Currow et al., 2020b). Between-arm differences in NRS *worst*, *average* and *unpleasantness* of breathlessness, from baseline to days 5 to 7, were used as outcome measures in all BEAMS quantitative sub-studies included in this doctoral program. Breathlessness measures included in Sub-study 6 (crossover study of regular,

low-dose, sustained-release oral morphine for chronic breathlessness associated with pulmonary arterial hypertension) are discussed in Chapter 8.

3.5.4.3.2 mMRC

The sub-group of people with COPD and severe functional impairment due to breathlessness (i.e., mMRC 3 or 4) had shown the largest signal for improvement in a previous RCT of regular, low-dose, sustained-release oral morphine for the reduction of symptomatic chronic breathlessness from multiple aetiologies (Currow et al., 2020b). As a result, the BEAMS study focused on recruiting only participants with COPD and mMRC 3 or 4 (Currow et al., 2017a). Although the mMRC is not particularly sensitive to detect change in intervention-based studies (Jones et al., 2014), it was collected throughout the study and included in some of the sub-studies in order to detect large changes (i.e., improvement or worsening) in chronic breathlessness, with impact on people's overall tolerance to daily exertion (Sorenson, 2000).

3.5.4.4 Other measures

3.5.4.4.1 Australia-modified Karnofsky Performance Status (AKPS)

The Australia-modified Karnofsky Performance Status (AKPS) is an adaptation of the ordinal Karnofsky Performance Status, which has been developed to suit the needs of people in the community (Abernethy et al., 2005). Scores vary from 100 to 0 in decrements of 10 based on people's ability to perform a range of daily tasks. The AKPS is validated in people with advanced disease, has a high inter-rater reliability and is sensitive to change over time (Abernethy et al., 2005). In the context of the BEAMS study and the sub-studies included in this doctoral thesis, this tool was used to facilitate selection of participants who had better chances to complete the trial (AKPS > 40) and to measure any functional change (improvement or worsening) due to the study intervention (Currow et al., 2017a).

3.5.4.4.2 Quality of life (EQ-5D-5L)

The EQ-5D-5L instrument is one of the most used tools to measure health-related quality of life in a variety of populations and settings (Herdman et al., 2011). The tool comprises two sections: a simple descriptive profile and a summary value for overall health status. The descriptive profile (EQ-5D) consists of five questions, evaluating five different dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each question is scored in a 5-level Likert scale. The summary value (EQ-VAS) is scored on a 0-100 visual analogue scale (VAS) with 0 corresponding to "the worst" and 100 corresponding to "the best health you can imagine". The EQ-5D-5L instrument is simple and quick to complete, and also valid, reliable and responsive to change, including in populations with chronic breathlessness (Herdman et al., 2011; Nolan et al., 2016). The EQ-5D-5L instrument was used in Sub-study 5 (salivary cortisol analysis) to capture baseline health-related quality of life and possible changes after the introduction of regular, low-dose, sustained-release oral morphine.

3.5.4.4.3 Subjective sleep quality

People with chronic breathlessness are likely to have sleep problems, which may contribute to decreasing people's quality of life (Currow et al., 2021). Regular, low-dose, sustained-release oral morphine may improve perceived quality of sleep by reducing the sensation of breathlessness (Martins et al., 2016). In this context, subjective sleep quality was collected in the BEAMS study using the question "*How was your sleep last night?*", scored in a 4-point Likert scale (Martins et al., 2016). Subjective sleep quality was used as a covariate in sub-studies 5 (driving simulation) and 7 (salivary cortisol analysis), given that sleep deprivation may interfere with people's driving skills (Jongen et al., 2015; Vakulin et al., 2009) and change people's diurnal cortisol profile (Nordberg et al., 2021; Williams et al., 2013).

3.5.4.4.4 The Hospital Anxiety and Depression Scale (HADS)

The Hospital Anxiety and Depression Scale (HADs) is a 14-item questionnaire comprised of two 7-item sub-scales, one measuring depression, and another one measuring anxiety (Zigmond & Snaith, 1983). Each sub-scale is scored from 0 to 21, with scores >8 suggesting considerable symptoms of anxiety or depression. The HADS is quick to complete, valid and reliable, including for people with advanced disease (Ibbotson et al., 1994; Le Fevre et al., 1999). Minimal clinically important differences are reductions of 1.32 points in the anxiety sub-scale and of 1.4 points in the depression sub-scale (Puhan et al., 2008). There is a close association between chronic breathlessness and anxiety, depression, and coexistence of anxiety and depression (Currow et al., 2017b; Currow et al., 2020c). Thus, introducing a medication with the potential to reduce breathlessness (i.e., regular, low-dose, sustained-release oral morphine) can potentially lead to changes in anxiety and depression scores. As a result, the HADS was collected in different stages of the BEAMS study. The HADS was also included in Sub-study 5 (salivary cortisol analysis), given that anxiety and depression can be associated with changes in people's diurnal cortisol profile (Adam et al., 2006; Adam et al., 2017).

3.5.4.4.5 Karolinska Sleepiness Scale

The Karolinska Sleepiness Scale is a 9-level scale that measures perceived sleepiness at the time of administration (Åkerstedt & Gillberg, 1990; Kaida et al., 2006). The scale takes approximately 10 seconds to complete, and scores vary from 1 corresponding to "very alert" to 9 "very sleepy, great effort to keep awake, fighting sleep". This scale is validated and has been shown to correlate well with objective brain-wave activity and behavioural measures (Åkerstedt & Gillberg, 1990; Kaida et al., 2006). The Karolinska Sleepiness Scale has been widely used in driving-assessment studies to evaluate the impact of subjective sleepiness on driving related-skills (Ahlstrom et al., 2018; Sagaspe et al., 2008). Given that morphine has the potential to cause sleepiness, participants

included in Sub-study 3 (driving simulation) were asked to complete the Karolinska Sleepiness Scale before each driving assessment.

3.5.4.4.6 Edmonton Symptom Assessment System – revised version (ESAS-r)

The Edmonton Symptom Assessment System (ESAS) is a 10-item instrument designed to evaluate the presence and severity of nine core symptoms (i.e., pain, tiredness, drowsiness, nausea, lack of appetite, shortness of breath, depression, anxiety, well-being), and an optional 10th symptom defined as "other problem" (Bruera et al., 1991; Watanabe et al., 2011). Each item or symptom is rated on a 0-to-10 numerical rating scale in which 0 corresponds to "no symptom" to 10 to "the worst possible symptom". This scale reports to people's experience at the time of administration. The ESAS-r is validated for people with advanced disease and the minimal clinically important difference was defined as a 1-point difference in each numerical rating scale (Hui et al., 2015; 2016). Given that chronic breathlessness often coexists with other symptoms, the ESAS-r was used in the BEAMS study to evaluate the presence and severity of other symptoms, and any changes experienced after the introduction of regular, low-dose, sustained-release oral morphine. ESAS-r scores of pain, tiredness, drowsiness and anxiety were also examined in Sub-study 3 (driving simulation) due to their potential impact on driving-related skills (Philip et al., 2005; Vakulin et al., 2009; Veldhuijzen et al., 2006).

3.5.4.4.7 Harms

In the BEAMS study, harms were measured using the National Cancer Institute Common Criteria for Adverse Events (version 4.0) (National Cancer Institute, 2009). This tool was initially developed for the oncology setting but is now widely used in other populations with advanced disease, who are also particularly vulnerable to medication toxicity due to their overall health status and exposure to multiple medications (Currow et al., 2017b; Morrison et al., 2016). The National Cancer Institute Common Criteria for Adverse Events (version 4.0) provides a uniform

nomenclature system to classify harms and their severity in clinical trials. It covers a broad range of symptoms and signs affecting all body systems, including those commonly associated with morphine (e.g., constipation, nausea, sedation). Harms are identified and rated by clinicians using a five-point Likert scale, where 1 corresponds to "mild" and 5 corresponds to "death". In the context of the BEAMS study, study staff used this tool in each study visit to monitor toxicity experienced by participants, in order to ensure they were safe to continue taking the study medication. In addition, participants were specifically asked about symptoms commonly associated with morphine (e.g., constipation, drowsiness, nausea) in the participants' diary. Each symptom was scored using 4-point Likert scales, with 0 corresponding to "not at all" and 3 corresponding to "severe" symptoms. The presence and severity of harms was examined in sub-studies 3 (driving simulation) and 5 (salivary cortisol analysis), because harms could potentially interfere with people's performance on the driving simulator and change their diurnal cortisol profile. Considering that some sub-study assessments did not coincide with BEAMS study visits, the National Cancer Institute Common Criteria for Adverse Events (version 4.0) did not provide sufficient data to be used in the sub-studies. As a result, self-rated harms using 4-point Likert scales were prioritised in the sub-studies. Of note, Sub-study 6 (crossover study of regular, low-dose, sustained-release oral morphine for chronic breathlessness associated with pulmonary arterial hypertension) used the National Cancer Institute Common Criteria for Adverse Events (version 3.0), which was the current version at the time the sub-study was conducted (Trotti et al., 2003).

3.5.4.4.8 Global impression of change

The global impression of change consists of a 7-point Likert scale to capture participants' blinded perception of change after initiating the study medication (i.e., morphine or placebo) (Farrar et al., 2001). This tool was included as an outcome measure in Sub-study 5 (salivary cortisol analysis), to

help determine the overall clinical significance of the changes experienced with the study medication and their potential impact on people's diurnal cortisol profile.

3.5.4.4.9 Objective measures

Respiratory rate, estimated arterial blood oxygen saturation (measured with pulse oximetry) and end-tidal CO_2 (measured using a portable capnograph) were collected as part of BEAMS. Given that hypercapnia and hypoxaemia may reduce the ability to concentrate, they were used as variables of interest in Sub-study 5 (driving simulation). Additionally, Sub-study 7 (salivary cortisol analysis) also included these measures as potential factors affecting diurnal cortisol secretion (Morgan et al., 1995; Raff & Levy, 1986).

3.5.5 General ethical considerations

All outcome measures of the BEAMS study and respective sub-studies were carefully planned to minimise burden on participants. With respect to the four sub-studies included in this doctoral program, a single blood sample taken at the same time as blood samples for eligibility was the only invasive procedure included, which was collected at one point in time for Sub-study 4 (genetics analysis). Collection procedures and tools used in all sub-studies were designed to be easy and brief to complete. For the only sub-study requiring extra-travelling time to and from research facilities (Sub-study 3 – driving simulation), participants were provided with taxi funding vouchers to minimise the effort involved. Given that the target population of BEAMS was severely limited by chronic breathlessness, participants were advised they could interrupt sub-study procedures at any time if they felt unable to continue their participation. When possible, they were offered the possibility of resuming these assessments at a later stage if they so wished. Participants were also advised their participation in both the BEAMS study and the sub-studies were completely voluntary and could be terminated at any time without compromising their medical care.

3.5.6 Ethics approvals

The BEAMS study was approved by the Hunter New England Ethics Committee as well as by local Research Governance Offices at each site. Sub-studies 1, 3, 4 and 5 included in this doctoral program were approved as sub-studies of the BEAMS study (HREC no. 15/12/16/306) (Appendix 7).

3.5.7 Sponsor

The BEAMS study was sponsored by Flinders University, Adelaide, South Australia. The study sponsor was responsible for the operationalisation, management and ongoing monitoring of the study. It was also responsible for organising correspondence with the ethics committee overseeing the study. The study sponsor had no role in the study design, data collection, analysis or dissemination of the study results.

3.5.8 Funding

The BEAMS study and the associated sub-studies were fully funded by the National Health and Medical Research Council (NHMRC), Project Grant APP1065571, ClinicalTrials.gov ID NCT02720822.

3.5.9 Role of the researcher

The researcher (DF) started to work alongside the BEAMS implementation team (Adelaide, South Australia) six months before study initiation, where she had a central role in sub-study design, ethics application, development and implementation. The researcher was responsible for writing the sections of the BEAMS protocol corresponding to the sub-studies included in this doctoral thesis. She presented the BEAMS protocol and associated sub-studies at potential participating sites, creating opportunities for questions and discussions with study staff in order to promote successful study operationalisation. Following BEAMS implementation, she provided ongoing study and sub-study support, which included correspondence with the ethics committee

overseeing the trial, development of study documents, training of site staff at each location, ongoing data monitoring and safety reporting, and ongoing support to local research teams. Early engagement with the BEAMS implementation team facilitated the development of cooperative relationships with local research teams and study staff involved in the BEAMS study, who were also recruiting for the sub-studies.

Recruitment of potential participants for sub-studies 1, 3, 4 and 5 was conducted by local research teams with ongoing support from the researcher. Collection procedures for sub-studies 4 (genetic analysis) and 5 (salivary cortisol analysis) were exclusively conducted by the research teams at each site. In most cases there was no interaction between the researcher and participants.

For sub-studies 1 (semi-structured interviews) and 3 (driving simulation), the local research teams were responsible for approaching potential participants. Only those providing verbal consent were referred to the researcher, who then contacted them to provide more information about the sub-studies. Interviews for Sub-study 1 (semi-structured interviews) were conducted by the researcher. Driving simulation assessments for Sub-study 3 were conducted by DF in South Australia and by a second researcher in New South Wales (Doctor Rodrigo Martins). DF analysed all blood samples collected as part of Sub-study 4 (genetic analysis) and an external laboratory analysed all saliva samples collected as part of Sub-study 5 (salivary cortisol analysis). Data analysis for all sub-studies was conducted by DF only (Table 3.2).

In all participant-researcher interactions, the researcher introduced herself as a doctoral candidate, disclosed her professional background and motivations for conducting the sub-study in question. Sub-study procedures were explained to all potential participants, who were encouraged to ask questions and detail any concerns. These initial encounters were essential to ensure participants felt safe and confident to proceed with participation in the sub-studies. There were no

pre-existing relationships between the researcher and study participants. The fact that the researcher was not involved in the clinical care provided to participants may have enhanced the willingness to participate in the sub-studies without fear of potential consequences for their clinical care.

Table 3.2 - Researcher (DF) role in sub-studies 1 to 6

Sub-studies	Design	Ethics application	Staff training	Collection procedures	Laboratory analysis	Data analysis
Sub-study 1* (Semi-structured interviews)	X	X	X	X	N/A	X
Sub-study 2 (Systematic review – Driving)	X	N/A	N/A	X	N/A	X
Sub-study 3* (Driving simulation)	X†		X	X	N/A	X
Sub-study 4* (Genetic analysis)	X†		X	X	X	X
Sub-study 5* (Salivary cortisol analysis)	X	X	X	X		X
Sub-study 6 (Crossover study - Pulmonary arterial hypertension)					N/A	X

*BEAMS sub-studies
†contributed to the sub-study design, but idea conceived by other researchers

3.6 Conclusion

This chapter has outlined the rationale for using a multi-method design, and introduced the BEAMS study, which was the basis for four of the six sub-studies included in this doctoral research project. The following chapters report, in detail, the individual sub-studies comprising this doctoral work.

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CHAPTER 4 - PATIENTS' AND THEIR CARERS' EXPERIENCES OF LIVING WITH CHRONIC BREATHLESSNESS ASSOCIATED WITH COPD BEFORE AND AFTER REGULAR, LOW-DOSE, SUSTAINED-RELEASE MORPHINE: A QUALITATIVE SUB-STUDY

4.1 Chapter preface

As the use of regular, low-dose, sustained-release morphine in people living with chronic breathlessness is still relatively new, it raises multiple questions regarding its impact on this population's broader daily-life, including driving. One way of exploring these questions is to elicit the perspectives and experiences of those who experience it first-hand: patients and their carers. Understanding the impact of introducing regular, low-dose, sustained-release morphine on people's lives requires an in-depth exploration of the context in which regular, low-dose, sustained-release oral morphine is being introduced (i.e., the experience of living with chronic breathlessness before the introduction of this medication), and any changes experienced once therapy is initiated. It also needs to include patients' and carers' personal views on regular, low-dose, sustained-release oral morphine, including any perceived challenges associated with this medication. In the context of challenges associated with this medication, people's perspectives on driving while living with chronic breathlessness is a widely unexplored issue, both before and after initiating treatment with regular, low-dose, sustained-release oral morphine. Driving is likely to be important for people who have their mobility restricted and a daily activity potentially affected by both chronic breathlessness and its treatment. Based on these premises, this chapter explores patients' and carers' experiences of living with chronic breathlessness before and after initiating regular, low-dose, sustained-release oral morphine, with a special focus on driving.

4.2 Publication references

This sub-study has a broad scope encompassing patients' and carers' experiences of living with chronic breathlessness before the introduction of regular, low-dose, sustained-release oral

morphine; their views and experiences with this medication after it was introduced; and their perspectives on driving before and after taking regular, low-dose, sustained-release oral morphine. As a result, it was impossible to compile the totality of the results in a single publication. Instead, this sub-study generated two articles, which were published in 2020 in international peer reviewed journals.

1. Ferreira, D. H., Kochovska, S., Honson, A., Phillips, J. L., & Currow, D. C. (2020). Two faces of the same coin: a qualitative study of patients' and carers' coexistence with chronic breathlessness associated with chronic obstructive pulmonary disease (COPD). BMC palliative care, 19, 1-12.

Number of citations: 7

BMC Palliative Care: Impact factor: 2.922; Scimago Journal Ranking 2018: 413/2836 [Medicine (miscellaneous)].

2. Ferreira, D. H., Boland, J. W., Kochovska, S., Honson, A., Phillips, J. L., & Currow, D. C. (2020). Patients' and caregivers' experiences of driving with chronic breathlessness before and after regular low-dose sustained-release morphine: A qualitative study. Palliative medicine, 34(8), 1078-1087.

Number of citations: 1

Journal of Pain and Symptom Management: Impact factor: 3.249; Scimago Journal Ranking 2018: 9/122 (Anesthesiology and Pain Medicine), 53/363 (Neurology [Clinical]), 3/140 (Nursing [Miscellaneous]).

This chapter contains an edited, combined version of the two publications (Appendices 8 and 9).

4.3 Introduction

4.3.1 The lived experience of chronic breathlessness

As detailed in Chapter 1, the experience of breathlessness is highly subjective because it is modulated by complex interactions of physiological, psychological, social and environmental factors (Parshall et al., 2012). The experience of severe chronic breathlessness has an additional layer of complexity because it tends to be severely debilitating and inexorable, forcing people to permanently restructure every aspect of their daily lives, including their relationships (Hutchinson et al., 2018; Simpson et al., 2010). As breathlessness worsens, people tend to rely on others for basic daily activities such as shopping, housekeeping and personal care (Bergs, 2002; Williams et al., 2007). As breathlessness eventually confines people to their homes, they often feel like they are "existing" instead of "living" (Nicholls, 2003). Not surprisingly, as people become more restricted by chronic breathlessness, their anxiety or depression increases while their health-related quality of life worsens (Currow et al., 2020; Currow et al., 2017a). Given that chronic breathlessness permeates all aspects of life, collecting patients' experiences of living with this syndrome is particularly important to paint the full picture of what it is like to live with and respond to chronic breathlessness. This includes exploring the physical, psychological, relational and social consequences of chronic breathlessness, while focusing on what patients value the most (Kochovska et al., 2020). This approach is essential to design therapeutic approaches focused on outcomes that are relevant for people living with chronic breathlessness.

For carers, chronic breathlessness is equally challenging. As patients become more dependent due to breathlessness, carers may find themselves taking greater responsibility for the care and wellbeing of the patient. Many carers are isolated in their role as carers and report they feel they are at a breaking point due to the demands imposed by breathlessness (Gysels et al., 2007). Additionally, carers of people with chronic breathlessness are often elderly people who are forced then to balance their own health with caring for someone with severe disability (Gysels &

Higginson, 2009). These circumstances produce additional challenges that reflect on carers' wellbeing. Carers often report that they feel they have no control over their own lives, which is fully committed to patients' needs (Gabriel et al., 2014). Anxiety and depressive symptoms are frequently reported by carers of people with chronic breathlessness, at comparable rates to the ones reported by patients (Bernabeu-Mora et al., 2016; Jácome et al., 2014). Based on this, a comprehensive assessment of the lived experience of chronic breathlessness needs to include the views of carers.

Qualitative studies are critical in understanding the perspectives of people living with chronic conditions, especially as the condition progresses, and their carers. Up to this point, the patients' and carers' experience of chronic breathlessness in COPD has been explored separately (Hutchinson et al., 2018). While individual experiences are important, they do not describe how each member of a patient-carer dyad experiences the same situation. Understanding patients' and their carers' individual experiences and responses to the same circumstances of breathlessness and how they coexist could enable identification of factors that contribute to successful coping and adaptation to the symptom for both parts involved. These insights are important for informing new models of care that better meet the needs of this largely invisible palliative population (Gysels & Higginson, 2008).

4.3.2 Experiences with regular, low-dose, sustained-release oral morphine for chronic breathlessness

Exploring the experience of living with chronic breathlessness is also important to understand what may change with the introduction of a new treatment. Pharmacological treatments have the potential to improve symptoms and improve people's quality of life. However, the association between efficacy and willingness to take a particular medication is not linear. For example, regular, low-dose, sustained-release oral morphine reduces the intensity of breathlessness in two

in every three people (Currow et al., 2011). However, not all patients who experience a reduction in breathlessness choose to continue this medication long-term (Ferreira et al., 2016). This is because there are multiple factors contributing for people's adherence to a given treatment (Janz & Becker, 1984). As detailed in Chapter 1, people's demographic, physiological and psychosocial background, their experiences of breathlessness, perceived benefits and harms associated with the treatment, and cues to facilitate engagement, create an overall effect that enhances or hinders patients' adherence (Bourbeau & Bartlett, 2008; Janz & Becker, 1984). These factors need to be explored in the context of regular, low-dose, sustained-release oral morphine for the treatment of chronic breathlessness in order to fully understand the benefits and harms experienced by patients and optimise therapeutic outcomes.

Understanding causes of adherence and non-adherence in people with chronic breathlessness taking regular, low-dose, sustained-release oral morphine, necessarily means giving voice to those who experience this therapy first-hand. These include patients and their carers, who live with chronic breathlessness daily and are uniquely positioned to report on barriers and facilitators associated with this treatment (Gysels et al., 2007; Hutchinson et al., 2018). Previous qualitative work suggests that both patients and carers find opioids to be helpful for breathlessness and improve quality of life (Rocker et al., 2012; Rocker et al., 2013). However, such work included different opioids and formulations, and focused exclusively on patients who were already successfully taking regular prescribed opioids (and potentially having benefit). This highlights the need to explore people's experiences with the current recommended doses of regular, low-dose, sustained-release oral morphine for chronic breathlessness (Currow et al., 2011; Therapeutic Goods Administration, 2019). These experiences should be explored as the therapy is being introduced, in order to capture a wider range of perceptions, including of people who may not experience any benefits.

4.3.3 Driving before and after taking regular, low-dose, sustained-release oral morphine for chronic breathlessness

Driving is a prime example of one of many challenges faced by people with chronic breathlessness. This is because people's ability to drive can be potentially affected by breathlessness itself and by its treatment with regular, low-dose, sustained-release oral morphine. Although there is evidence to suggest driving is a crucial daily activity for most adults (King et al., 2011; Mezuk & Rebok, 2008), including those with advanced disease (Widman & Bergström, 2014), there is a scarcity of studies specifically exploring the relevance of driving for people with chronic breathlessness. For people with chronic breathlessness, the sensation of breathlessness is triggered or aggravated by some degree of exertion, which restricts their freedom of movement (Gysels et al., 2007). In this context, driving can expand the living space of people that are otherwise fully ready to engage with their lives (Williams et al., 2007). Conversely, people with chronic breathlessness often try to avoid situations that can potentially trigger or aggravate breathlessness, resulting in a contraction of their living space (Hanania & O'Donnell, 2019; Nicholls, 2003). If driving is one such activity, patients may progressively disengage from it. Exploring patients' and carers' reflections on driving with chronic breathlessness is therefore critical to identify the challenges that are specific to this population and create effective intervention strategies that are tailored to patients' needs.

Importantly, as previously discussed, people's behaviours are conditioned by a range of different factors, heavily influenced by their belief systems (Bourbeau & Bartlett, 2008; Janz & Becker, 1984). Thus, the willingness or unwillingness to drive is also influenced by how confident people feel driving, their expectations, and both the benefits and the risks they associate with the task. In this context, it is important to understand people's experiences of driving with chronic breathlessness, including how they believe breathlessness affects their driving. Similarly, it is critical to understand people's views of driving with regular, low-dose, sustained-release oral morphine, including their first-hand experiences after initiating this medication.

4.4 Aim

To understand COPD patients' and carers' experiences of living with chronic breathlessness before and after initiating regular, low-dose, sustained-release oral morphine, with a specific focus on their driving experiences.

4.5 Objectives

The specific objectives were:

1. To understand patients' and their carers' experiences of living with severe chronic breathlessness before taking regular, low-dose, sustained-release morphine, including its impact on physical, psychological, social and existential domains of life;
2. To explore patients' and carers' perceptions of regular, low-dose, sustained-release oral morphine for chronic breathlessness;
3. To identify factors influencing patients' decision to continue taking regular, low-dose, sustained-release morphine for chronic breathlessness;
4. To explore the experience of driving with chronic breathlessness before and after initiating regular, low-dose, sustained-release oral morphine.

4.6 Methods

4.6.1 Sub-study design

This sub-study is reported using the *consolidated criteria for reporting qualitative research* (COREQ) framework (Tong et al., 2007). This was a qualitative sub-study embedded in the BEAMS trial (Currow et al., 2017b). After ceasing the BEAMS trial by withdrawal or completion, participants were invited to be interviewed. Each interview had two sections. The first section explored patients' and carers' experiences of coexisting with and responding to chronic breathlessness associated with COPD, before the introduction of regular, low-dose, sustained-release morphine (Domain 1). The second section explored patients' and carers' views and

experiences with regular, low-dose, sustained-release oral morphine, including any changes in their lived experience of chronic breathlessness after starting this medication (Domain 2). A third domain specifically designed to explore self-reported driving before and after initiating regular, low-dose, sustained-release morphine oral was embedded in Domains 1 and 2, providing a practical example of how these two domains intersect for these patients and their carers (Domain 3, Figure 4.1).

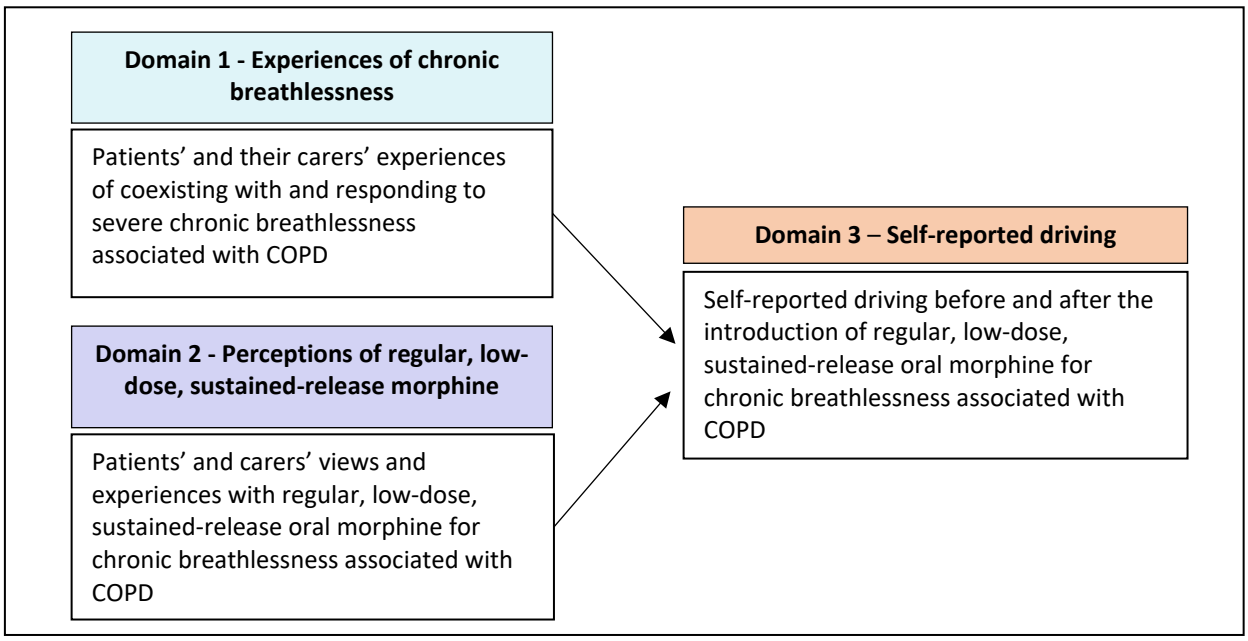

Figure 4.1 - Domains included in this sub-study

4.6.2 Sub-study setting

This sub-study was undertaken within the Southern Adelaide Palliative Services (SAPS) and the respiratory services at Flinders Medical Centre. The respiratory services at Flinders Medical Centre provide medical and nursing care to inpatients and outpatients with a wide range of respiratory diseases. The Southern Adelaide Palliative Services provide palliative care to residents in the southern region of metropolitan Adelaide, South Australia, Australia. Its clinical unit is a level 6 palliative care service providing inpatient hospice care, inpatient consultation and outpatient and community care to people with life-limiting conditions. Level 6 palliative care services are highly

specialised services which provide comprehensive care to patients with complex palliative care needs and their carers (SA Health, 2016). This service has also a long-standing interest in the palliation of respiratory diseases.

4.6.3 Sub-study participants

Participants were patients who had ceased their participation in the BEAMS trial (i.e., by completion or withdrawal), and their carers, if available. Carers were defined as "the person who knew the participant best, provided the most help at home, and could help understand any changes experienced on trial" (Burns et al., 2011; Farquhar, 2016). All carers of participating patients were eligible to participate, unless they were unavailable or unwilling to do so.

The BEAMS population was chosen because recruiting from an RCT with defined inclusion and exclusion criteria allowed transparency in selecting a sample of patients with chronic breathlessness, whose COPD was confirmed by spirometry and optimally treated. Recruiting from this trial also allowed transparency in the morphine doses taken by participants. In the early stages of this qualitative sub-study, recruitment targeted only patients with a carer, who were believed to be in sufficient numbers to provide a wide range of experiences for this qualitative sub-study. Due to slow recruitment, Domains 2 and 3 of this qualitative sub-study were later broadened to include participants who did not have a carer. Justification for this decision is provided in the sections below. In addition to BEAMS eligibility criteria, additional inclusion criteria for this sub-study included being in a sufficient state of health to be interviewed; and willing and able to provide informed consent. The only additional exclusion criterion for this sub-study was geographic location (i.e., people living more than 70 km away from the researcher or in areas of difficult access by public transport).

4.6.4 Sampling strategy

Convenience sampling was used to recruit participants for this qualitative sub-study. Convenience sampling is a widely used non-probability sampling method in qualitative research, which has the advantages of being inexpensive and allow for easy identification of potential participants (Bornstein et al., 2013). However, this type of sampling is often not representative of the overall population of interest (Etikan et al., 2016) because participants are selected based on their accessibility or proximity to the research (Jager et al., 2017). Importantly, the sample selected for this study was relatively homogeneous in terms of age (i.e., elderly adults), degree of exertion before being limited by breathlessness (e.g., mMRC 3-4), COPD-status, COPD-therapy optimisation, and previous exposure to regular, low-dose, sustained-release oral morphine for chronic breathlessness (Currow et al., 2017b). Specific sampling considerations for each domain are detailed below.

4.6.4.1 Domain 1 sampling - Experiences of chronic breathlessness

Given the large body of work investigating patients' and carers' individual experiences of chronic breathlessness, Domain 1 aimed to build on that knowledge by providing a comprehensive perspective of patients' and their carers' experiences of *coexisting* with chronic breathlessness. This perspective was adopted to provide a more in-depth look of how patients and carers belonging to the same family unit experience and *respond to the same circumstances* of chronic breathlessness, including potential roles assumed by patients and carers as they adapt to this symptom. Based on this, only patients with available carers were included in this domain.

4.6.4.2 Domain 2 sampling – Perceptions of regular, low-dose, sustained-release oral morphine

Domain 2 aimed to explore patients and carers views on regular, low-dose, sustained-release morphine for chronic breathlessness. In contrast to Domain 1, the body of literature exploring this issue was practically non-existent. As such, Domain 2 sought to include all perspectives on regular,

low-dose, sustained-release oral morphine for chronic breathlessness. Consequently, patients without a carer were included in this domain.

4.6.4.3 Domain 3 sampling – Self-reported driving

Domain 3 aimed to explore experiences with driving before and after taking regular, low-dose, sustained-release oral morphine for chronic breathlessness. Similar to Domain 2, this issue was largely unexplored in the literature and all individual perspectives (of patients and carers) would add to current knowledge. Thus, the perspectives of patients who did not have a carer were included. In addition to the selection criteria mentioned in section 4.6.3, patients needed to be: active drivers; *or* people who had recently stopped driving and were still able to recall their experiences of driving with chronic breathlessness. The latter group contributed to increase the understanding of the experience of driving with this disabling syndrome, but was not questioned about driving after initiating regular, low-dose, sustained-release oral morphine.

4.6.5 Recruitment and consent

Potential participants were identified and approached by telephone, by the BEAMS trial study nurses. If interested, they were then telephoned by the interviewer (DF). In a subsequent face-to-face meeting, the interviewer introduced herself, detailed her background, described her reasons for conducting the sub-study, explained the sub-study context and procedures, and clarified patients' and carers' questions before obtaining written informed consent. Participants chose the interview location that was more convenient to them, which could be either at home or at the hospital.

4.6.6 Specific ethical considerations

This sub-study required participants to reflect on their experiences with chronic breathlessness and its impact on all dimensions of life. Reflecting on their own vulnerability could have been distressing for patients and their carers. As such, participants were advised they would only need

to answer the questions with which they were comfortable and that they could stop the interview at any time, without any impact on their clinical care. Importantly, such reflections were welcomed by all participants, who were happy to have someone listening to their challenges.

4.6.7 Data collection

Data collection occurred from July 2017 until November 2018. From July 2017 until October 2017, only patients with a carer were recruited. From October 2017 until November 2018, Domains 2 and 3 were also open to patients without a carer. Participants' demographic information was obtained from the BEAMS case report forms (patients) and a short demographic form (carers) (Appendix 10). Single, face-to-face, in-depth, semi-structured interviews were conducted *separately* with patients and their carers. Carers were specifically asked to leave the room where the interview with the patient was taking place. Carers were then interviewed in a separate room, while patients waited in the room they were initially interviewed in. Individual interviews were chosen because they have the advantage of providing a safe and private space for each individual, which facilitates the expression of concerns and emotions (Laidsaar-Powell et al., 2013; Swetenham et al., 2015).

The topic guides were designed based on the topic guides created by Rocker et al., which had previously explored patients' and carers' perspectives on opioids for chronic breathlessness associated with COPD (Rocker et al., 2012). The first section of the topic guides (corresponding to Domain 1) was adapted to reflect the framework of "total breathlessness" (Abernethy & Wheeler, 2008; Kamal et al., 2011). Focus areas included daily activities (including driving), feelings, relationships, concerns and hope. The second section of the topic guides (corresponding to Domain 2) was modified to incorporate factors relevant for COPD patients' choices related to therapy (Bourbeau & Bartlett, 2008). Exploration of self-reported driving (Domain 3) was prompted within specific questions of Domains 1 and 2 (Appendix 11).

Patients included in this sub-study were very frail and the research team was particularly mindful about minimising any burden from their participation, without compromising the methodological integrity of the sub-study. While patients and carers were not involved in the sub-study design or recruitment, research nurses with extensive experience recruiting people with chronic breathlessness contributed to the design of the interview guides to ensure they were appropriate, applicable and relevant for the population targeted. This group of research nurses had recruited and randomised a total of more than 700 patients for chronic breathlessness trials, which had been a population of focus for the previous 15 years. They not only see patients and carers at the hospital, but they also visit them regularly at home, where they discuss the challenges patients and carers face daily. Thus, this team was uniquely positioned to provide high quality feedback, without having to overburden patients and carers.

Participants' responses were audio-recorded and transcribed verbatim (DF). Interview transcripts were not returned to participants in order to minimise burden for this very frail population. Review of interview transcripts is a common technique employed to verify accuracy and correct potential errors but there is evidence to suggest they add little value and have the potential to create complications in the analysis (Hagens et al., 2009). Potential misinterpretations were minimised by having a second researcher (A.H.) listen to each interview recording and check the transcription's accuracy. Participants were only contacted a second time if researchers who oversaw the transcription had any doubts about what participants had said.

In this qualitative sub-study, field notes were collected during each interview detailing contextual information deemed relevant for complementing participants' statements (Phillippi & Lauderdale, 2018). Field notes included descriptions of participants' body language while answering interview questions; environmental aspects (e.g., physical aids to minimise breathlessness); and observable roles assumed by patients and carers at home. The researcher also kept a reflexive journal with impressions from each participant-researcher interaction. Impressions captured in the reflexive

journal were strategically compared with data emerging from the interviews to facilitate the interpretation of the findings (Smith, 1999).

Data were collected until saturation (i.e., no new concepts were emerging), as agreed between participating researchers (DF, JP, DC).

4.6.8 Data Analysis

Data was entered into NVivo (V 11.4.0 for Mac). An inductive approach based on the principles of grounded theory was used (Boeije, 2002; Glaser et al., 1968). This included the use of the constant comparative method in an iterative process to help identify new concepts emerging from the data that could be explored in subsequent interviews (Boeije, 2002; Hallberg, 2006). This approach was chosen because it provided clear delineation of the steps involved in data analysis and enabled the emergence of themes and concepts grounded in the data and not in pre-existent theories (Chun Tie et al., 2019; Glaser et al., 1968). Inductive approaches are particularly useful when the topics of interest are relatively unexplored, which was deemed to be the case in this sub-study (Chun Tie et al., 2019).

Familiarisation with the data occurred during interview transcription and by reading the transcripts and field notes multiple times (DF). To enhance rigour, open coding of the interview transcripts was conducted independently by two researchers (DF, AH). Descriptive codes were then grouped into themes (DF) and illustrated with several quotes to confirm coding validity (DF, JP). Concepts emerging from the patients' and carers' data were further examined for any major differences between the two viewpoints (DF, JP, DC). Three matrices summarised the findings of patients and their carers for the three different domains.

4.6.9 Trustworthiness of the findings

The Consolidated Criteria for Reporting Qualitative Research (COREQ) checklist was used to guide the design and reporting of this sub-study (Tong et al., 2007). The sub-study development was

grounded on the four criteria outlined by Lincoln & Guba to achieve trustworthiness: credibility, dependability, confirmability and transferability (Lincoln & Guba, 1985).

Strategies adopted to enhance *credibility* included:

- careful design of semi-structured interviews, which ensured that a particular line of enquiry was followed, but allowed participants to express their thoughts freely, prioritising the issues that were more relevant to them;
- development of an interview guide grounded in existent models of chronic breathlessness and focused on aspects deemed relevant in previous studies with similar populations (Oxberry et al., 2012; Rocker et al., 2012);
- collaboration with nurses with expertise in chronic breathlessness, who could provide continuous feedback during the development of interview guides;
- explaining to participants that their identities would not be disclosed to people, institutions or organisations outside the research team, including in any publications resulting from the research project;
- conducting separate interviews with patients and their carers, to ensure people felt at ease to express their feelings without concern of upsetting their loved ones;
- use of different methods of data collection (i.e., interviews and field notes), which were complementary of each other, aiming to compensate for their individual limitations (Shenton, 2004); and
- use of a reflexive journal where the researcher reflected on the progress of each interview, her positioning and potential personal influence on the interview process, the relationship established with each participant, and potential new lines of enquiry; the reflexive journal was used to prompt discussions between the researcher and her supervisors in order to

explore alternative/additional approaches in subsequent researcher-participant encounters.

Transferability was enhanced by selecting participants from a phase III trial with clear inclusion and exclusion criteria, providing a detailed description of the context, setting and participants included. The trial had a pragmatic design, which ensured participants were drawn from the overall population of interest (Matsuoka et al., 2019). Moreover, the methods employed in this qualitative sub-study were clearly described and justified. Together, these strategies allow other researchers to easily determine if results from this qualitative sub-study are relevant to other contexts of interest (Braun & Clarke, 2014; Lincoln & Guba, 1985).

Dependability was facilitated by following a standardised qualitative-research methodology, which offered clear guidance regarding the steps involved in data analysis. Additionally, the sub-study design and reporting followed widely accepted reporting criteria for qualitative research (Tong et al., 2007).

Confirmability was achieved by constant reflection on the researcher's own predispositions, and its potential influence on each stage of the sub-study design, data collection and analysis. During data analysis, every new level of coding was illustrated by participants' quotes to confirm the findings and discussed with peers and supervisors to ensure data interpretation was as transparent as possible.

4.7 Findings

4.7.1 Participants' characteristics

From the 50 patients recruited to the RCT during the study period at that site, 21 had an available carer. Of those, 12 patients were excluded from the qualitative sub-study because they were residing more than 70 km away from the city, which would have required travel that was not

possible (n=5); were experiencing rapid functional deterioration and were too frail to be interviewed (n=4); declined to be interviewed citing fatigue (n=2); or were unable to be contacted (n=1). Thus, of patients with an available carer, nine were included in all domains of the qualitative sub-study (1, 2 and 3) with their respective carers (Figure 4.2).

From the 29 patients without an available carer (recruited after October 2017), 25 were excluded because their last study contact with the RCT team occurred before October 2017, when recruitment was focused exclusively on patients with a carer (n=19); were unable to be contacted by the researcher (n=2); declined participation citing fatigue or extreme breathlessness (n=2); were too frail to be interviewed (n=1); or a suitable interview time could not be arranged (n=1). Thus, of patients without an available carer, four were also included in Domain 2 of the qualitative sub-study, adding to the previous 9 patients with a carer. All patients included in Domains 2 (n=13) were current drivers or had recently stopped driving. Thus, all 13 patients and their carers (n=9) were included in Domain 3.

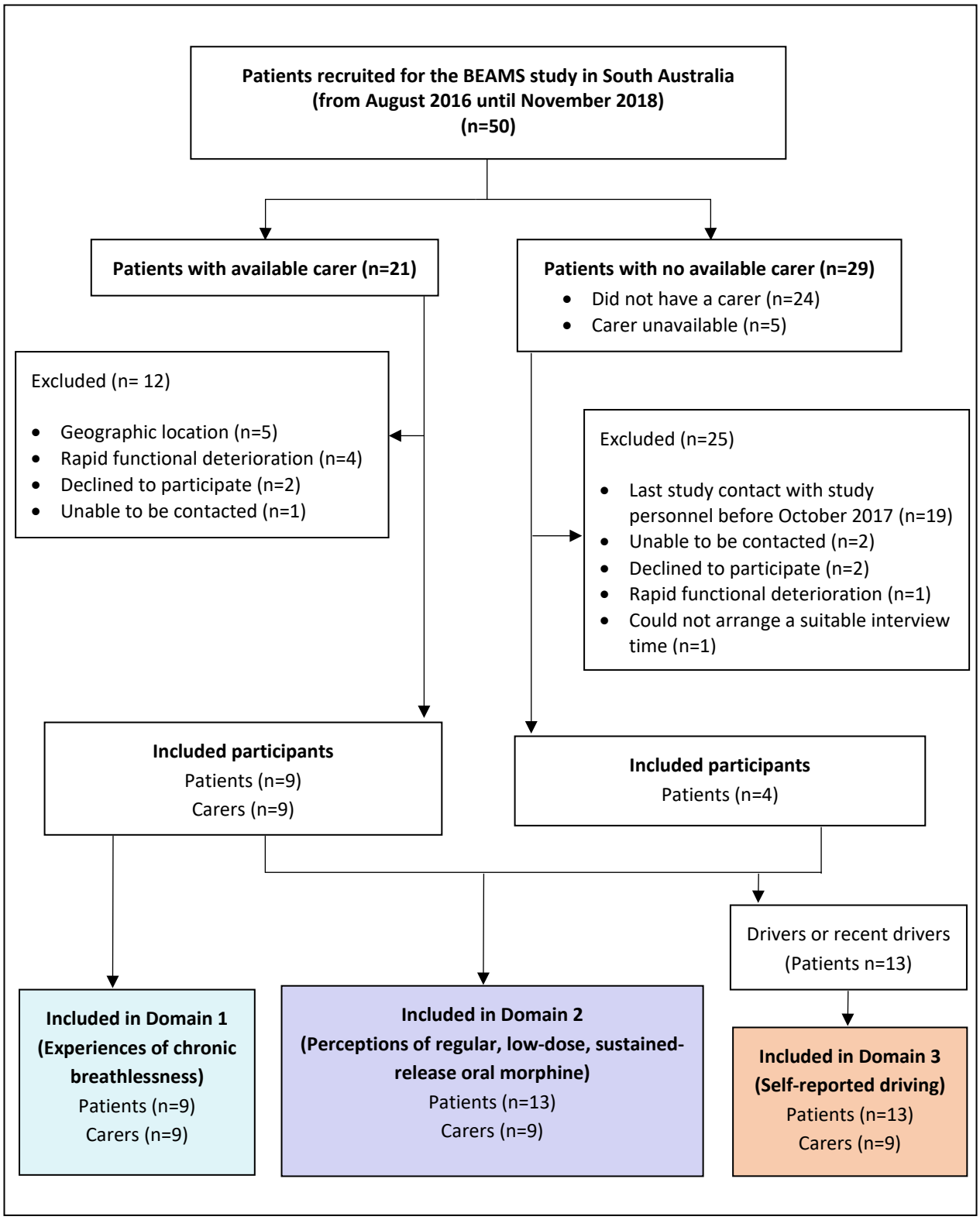

Figure 4.2 - Diagram of patients and carers recruited for Domains 1, 2 and 3 of this sub-study

All patients and their carers (if available) were interviewed separately in their homes. Each interview took 21-55 minutes to complete. Of the 13 patients included in the qualitative sub-study, nine patients were male with a median age of 76 years (interquartile range [IQR] 68-78]). All were from English-speaking backgrounds and lived in private residences. More than 50% had completed high school. All patients were severely limited by breathlessness but still able to function outside their homes [mMRC 3 (n=13)]. Most required some degree of assistance daily [AKPS≤60 (n=9)]. Table 4.1 outlines demographic and clinical characteristics of patients included in each domain.

Of the total of 13 patients included in Domain 3 (self-reported driving), eight were regularly driving and one drove occasionally. Two of nine men had recently stopped driving, while two of four women had recently stopped driving. The four participants who had stopped driving had all driven regularly until recently (Table 4.2).

Carers were mostly women (n=6), who had a median age 70 years (IQR 69-79) and were patients' wives. Most had been living with the patients for many years and were solely providing patients' care. Seven carers were providing hands-on care [median 4 years (IQR 3-5); Table 4.3].

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Table 4.1 - Summary of patients' characteristics

Characteristics	Domain 1	Domains 2 & 3
Median age (IQR)	77 (72 – 79)	76 (68 – 78)
Sex		
Female	3	4
Ethnicity		
Oceanian (Australia or New Zealand)	8	11
North-West European	1	2
Usual language spoken at home		
English	9	13
Residence		
Living in a private residence	9	13
Marital status		
Married or de facto	8	9
Widowed	1	2
Separated or divorced	-	2
Highest level of education		
Did not complete high school	4	4
Completed high school	1	4
Completed a trade certificate	2	3
University Degree	2	2
mMRC score at baseline		
3	9	13
NRS Worst breathlessness (24 hours)		
4	1	1
6	2	3
7	3	4
8	2	3
9	1	1
10	-	1
AKPS		
50	3	3
60	3	6
70	3	3
80	-	1

mMRC = 0-4 modified Medical Research Council scale (higher scores correspond to lower levels of exertion achieved before being limited by breathlessness); NRS = 0 to 10 numerical rating scale (0 = no breathlessness; 10 = worst possible breathlessness); AKPS = Australia-modified Karnofsky Performance Status (higher scores correspond to better performance status).

Table 4.2 – Relationship between patients (n=13) and their carers (n=9) and their driving status

Patient & carer identification number	Patient	Carer	Relationship with the patient	Driving status	Reasons to stop driving
1	Female	Male	Husband	Not currently driving	Deemed unfit to drive
2	Male	Female	Wife	Active driver	-
3	Male	-	-	Active driver	-
4	Female	Male	Son	Not currently driving	Sold the car after husband died
5	Male	Female	Wife	Not currently driving	Deemed unfit to drive
6	Male	Female	Wife	Active driver	-
7	Female	-	-	Active driver	-
8	Male	Female	Wife	Active driver	-
9	Male	-	-	Active driver	-
10	Male	-	-	Not currently driving	Sold the car (financial issues)
11	Male	Female	Wife	Active driver	-
12	Female	Male	Husband	Active driver	-
13	Male	Female	Wife	Active driver (occasionally)	-

Table 4.3 - Summary of carers' characteristics (n=9)

Characteristics	Domains 1, 2 & 3
Median age (IQR)	70 (69 - 79)
Sex	
Female	6
Ethnicity	
Australasian (Australia or New Zealand)	6
North-West European	3
Highest level of education	
Did not complete high school	4
Completed high school	3
University degree	2
Marital status	
Married or de facto	9
Living with the patient	
Yes	8
No	1
Median time living with the patient (years) (IQR)	45 (21 - 56)
Hands on care	
Yes	7
No	2
For how long has the carer been providing hands-on care? (median time in years) (IQR)	4 (3 - 5)
Time spent together weekly	
> 40 hours	7
20 – 40 hours	1
10 – 20 hours	1
Other people involved in providing care	
No	9
Changes to employment status due to patient's condition	
No	9

4.7.2 Themes

From the three different domains analysed, five themes emerged from Domain 1 (Experiences of chronic breathlessness); four emerged from Domain 2 (Perceptions of regular, low-dose, sustained-release oral morphine); and three emerged from Domain 3 (Self-reported driving).

4.7.2.1 Domain 1 – Experiences of chronic breathlessness

Themes describing the experience of chronic breathlessness outlined by patients and their carers included: (1) shrinking world; (2) mutual adaptation; (3) co-management; (4) emotional coping; and (5) meaning in the face of death (Table 4.4).

4.7.2.1.1 Theme 1 – Shrinking world

Most patients described that breathlessness significantly impacted their activities of daily living and social lives. Within each patient-carer unit, the level of limitation experienced by carers was highly dependent on the severity of breathlessness experienced by the patients. Carers felt responsible for patients' wellbeing and spent most of their time with them. Occasionally, carers were forced to leave patients by themselves, but they were constantly concerned and found it hard to disconnect from the carer's role.

> *"Well it takes me a long time to get from here to the bed and back. By the time I get there, I got to get on the nebulizer you know? I can get dressed by myself but I have a girl coming to shower me."* [Patient 1]

> *"I have to go shopping and I bought myself a little emergency mobile phone which I haven't told anybody anything about it. It's just simply so I can ring home to check on her… And I bought a walker for her hoping that she would use the walker."* [Carer 1]

As the patient experiences more limitations associated with breathlessness, patient and carer reduce the time they spend apart. In such cases, the carer's life becomes almost as restricted as that of the patient. At the same time, there is an attempt to find strategies that enhance patients' function, allowing the patient-carer unit to perform at a higher level.

"We went to town about a month ago, we used to do quite a bit of that, become a tourist in your own town, sort of thing. We went there and I walked maybe 50 meters in North Terrace [a street]. I could not go any further. I just could not walk any further. So, that [mobility scooter] will fix our problem. I can even walk to the shops with J. [wife]." [Patient 9]

"I would like to go and do things with him, like go to the zoo, the art gallery, places like that but that is out of the question because I couldn't get the car close enough for him to even get in the place. To be able to walk to get in places. We can't get around. I don't go to everything that I would normally go to." [Carer 9]

Independently of overall breathlessness severity, both patients and their carers described great daily variability in breathlessness intensity, using terms like "good days" and "bad days" to describe fluctuations and their impact on daily life. Occasionally, they would identify triggers (e.g., temperature, humidity) for such fluctuations, but mostly, they were unpredictable.

"I have good days and bad days. Some days, I can't get out of bed basically and other days is fine. (…) It is unexpected, and you just take it day by day." [Patient 8]

"There are good days and bad days. There are days in which she can't do much and she just sits down or lays on the bed and does not do much. And other days she has got a lot of energy and does a lot of other stuff. There are quite a few ups and downs. (…) In the end you just go with the flow, treat it from day to day, whatever comes up. Yeah." [Carer 8]

4.7.2.1.2 Theme 2 - Mutual adaptation

Within each patient-carer unit, attempts to reconcile the level of function of the patient with that of the carer were ongoing. While patients tried to be as functional as possible, carers learned how take over certain tasks so as not to allow the patient to over-exert. Both elements worked to keep each patient-carer unit as functional as possible under difficult circumstances.

"Occasionally, I try to do a bit of cooking. But I can't always do it. I can't do any cooking really when I am using this [points at the oxygen tube] because of the fire risk." [Patient 6]

"He can't do anything which is very annoying - not to me, but to him - because he quite often says… A couple of weeks ago he said "I'll cook you dinner". He was going to make a curry. He got up there and I have to switch his oxygen off - because of the gas, you see… Two minutes later he said "I am sorry, I can't…" and I said "It's ok you just sit down and relax and I'll do it". [Carer 6]

In some circumstances, carers learned how to slow down to meet the patient's level of function. This strategy seemed to allow patients to keep as much autonomy as possible.

"We have a system. T. [son] takes me shopping and I can take a trolley in. And I can do my own shopping like that." [Patient 3]

"Just be patient and let them take their time. When we go to the shops, I don't rush mum and we just go slow. Be patient." [Carer 3]

Within each patient-carer unit, patients and carers had learned to adapt to breathlessness. In most cases, patients had developed an accurate sense of their exertional capacity, learning to push themselves to be as active as possible, while managing their breathlessness, including avoiding situations that created intense or unmanageable breathlessness. In these cases, carers trust the patient's capacity to manage the degree of exertion they are able to tolerate.

"And I think you adapt to the problem. You know you have a problem, so you adapt to it. So you create a situation where you don't get that short of breath, you know? Because you don't do things." [Patient 5]

"(…) he sits a lot and plays games on the computer and all that, so he knows when he can't do things. So yeah, that doesn't concern me." [Carer 5]

In other cases, the carer played an essential role in preventing what was perceived as over-exertion causing excess breathlessness.

"I just don't want it to beat me. I know my limits and I will push myself to the limits." [Patient 7]

"The last couple of times we used the caravan, it was in the beginning of last year actually. It's an old caravan so it takes a lot of putting the annex part of it because it doesn't have a pull-out roof on it and it takes quite a while to put it up, but I have to say "Stop and sit down!" and he says "No, I want to get this done!" and I say "Well, you need to have a rest" so I say "I'll make you a coffee". So then he stops. Or we'll go and have lunch and come back and finish it, you know?" [Carer 7]

4.7.2.1.3 Theme 3 - Co-management

In all patient-carer units, both members had active roles in managing breathlessness. However, carer participation in breathlessness management was largely dependent on the degree of limitation experienced by the patient. In cases where the patient was still reasonably independent, the carer was mainly responsible for more physically demanding tasks such as shopping or cleaning. In such cases, there was still a clear separation of roles:

"My wife knows I have a problem and we just get on with it. I do most of the cooking and she does most of the cleaning." [Patient 7]

"I do a few jobs around the house, but I don't have to do anything for him, really. He can dress himself and all things like that. I used to have to cut his toenails… But now, because we have a care plan, we go to the podiatrist." [Carer 7]

In cases where the patient required considerable assistance, carers had a particularly active role. Both patients and carers had developed strategies which allowed them to work as a cohesive team to overcome the limitations imposed by breathlessness.

"Getting dressed is… hands above the head is a problem. But the rest of it is fine, it is just slow. So J. [wife] comes in and helps me and we get through it together." [Patient 9]

"Like we had our granddaughter 21st birthday in the city and it took an hour and a half for him to get dressed. He would do one little thing and then he would get out of breath. And then I would go away and try to put something on myself and come back and do some small thing." [Carer 9]

Carers were particularly important in situations of acute, uncontrolled breathlessness, that could be sudden and unpredictable. In some cases, the patient is able to reach for carer's help but is unable to take further action.

> *"When that flu hit me, I couldn't breathe at all. It was so bad all of a sudden. M. [wife] had to call the ambulance."* [Patient 4]

> *"When he had that flu, I called the ambulance, and they came pronto. I know what to do in those cases because I've done it before, but it's a bit scary."* [Carer 4]

4.7.2.1.4 Theme 4 - Emotional coping

While most patients expressed annoyance at being unable to function fully independently, the sensation of daily breathlessness with which they had lived for so long did not generate distress because they were familiar with the symptom and how to handle it. Conversely, daily breathlessness was an emotional challenge for carers who not only experienced a constant state of worry, but also felt the need to appear calm to patients.

> *"No, not scared [by daily breathlessness]. I tend to be a phlegmatic sort of guy; I have low anxiety levels. And I am used to it."* [Patient 2]

> *"Just watching him trying to get his breath… That is horrible to watch. And there is nothing you can do to help. Just keep him comfortable and be there, whatever he needs… I try not to worry too much; I try to keep calm because I don't want him to get worse."* [Carer 2]

Conversely, both patients and carers felt emotionally challenged by episodes of acute breathlessness (e.g., COPD exacerbations), which were described as "a worry", "scary" and "awful".

> *"But a couple of times, a couple of months ago, I had a real breathlessness attack, and I could not breathe. It that was quite scary, but I managed it ok, I sort of did what I had to and I was ok."* [Patient 8]

> *"It scares me [when she gets more intense breathlessness]. Very much! Especially when she has an infection or something a bit more serious, that is really scary."* [Carer 8]

While some patients expressed being annoyed with their condition, their carers experienced more intense feelings, such as frustration and resentment, by being forced to step up to the carer's role. For some, being a carer made them give up a part of their identity, which created a sensation of being trapped in the carer's role.

> *"I get up in the morning, have breakfast, shower. I don't shower every day because I get so breathless showering. But when I do shower, then M. [wife] helps me sometimes. And then I sit down, and I have my iPad, I look at all the papers from all over the world and I just keep my brain working thinking about things but physically, I don't do anything at all. (…) sometimes I get bored. Bored you know? I think "what should I do next?"".* [Patient 6]

> *"My life is boring! [laughs] I am a very outgoing person, I like the outdoors, and on a day like today you think "oh, let's get in the car and go!" But I have to think of him first because he can't walk from here to there before he gets breathlessness, so I think "well… just scrap it", and do nothing you know? So, it makes it hard on me because I want to do things, but I can't you know?"* [Carer 6]

4.7.2.1.5 Theme 5 - Meaning in the face of death

The relationship between patient and carer brought a sense of meaning to both parts and helped to withstand the limitations imposed by chronic breathlessness. For patients, their perspectives on life and death changed with the experience of chronic breathlessness. Many were aware of the severity of their condition but were not afraid to die. Unlike patients, their carers felt more concerned about the future and did not bring up the topic of death easily.

> *"No, not anymore [I don't worry about the future]. I look at it this way, if something is going to happen, it is going to happen. There is nothing you can do about it."* [Patient 4]

> *"I wonder just how bad he's going to get… What is going to be like further down the track."* [Carer 4]

Within a patient-carer unit, both patient and carer were essential to ensure the patient kept living a meaningful life. For patients, an essential part of living a good life was being close to their carers.

Carers were not only involved in dealing with the physical burdens of breathlessness, but they also felt responsible for bringing meaning and joy to patient's lives.

> *"Life is pretty good, yeah. B. [husband] does everything and we are together all the time. He is a good doctor! A very good doctor [laughing]."* [Patient 1]

> *"I buy her some flowers every fortnight and I put them in there so she can sit at the table and look at them. Just to introduce a bit of colour and a variety into the family. I am trying to make it fairly compatible being at home (and I think for the last year she has been home now) I think she said she was happy I think, yeah."* [Carer 1]

Table 4.4 – Domain 1 comparative analysis of findings from patients and carers

Patients & Carers	Patients	Carers
1. Shrinking world Breathlessness shrinks the physical and social world available to patients and carers and increases the time they spend together	• Restriction of daily activities • Restriction of independence • Good days and bad days	• Restriction of their own daily activities • Describe patients have good days and bad days • Hard to disconnect from the carer's role
2. Mutual adaptation Patient and carers work individually and together to create optimal functioning for both	• Keep as active as possible • Try to avoid over-exertion • Some push to the limit	• Take over some tasks • Slow down • Step in to prevent perceived over-exertion
3. Co-management Patient and carers have active and complementary roles in managing breathlessness	• Have an active role in managing breathlessness • Work with the carer to overcome breathlessness	• Have an active role in managing breathlessness • Degree of participation depends on each patient's limitations • Step in to help manage episodes of acute breathlessness
4. Emotional coping Emotional coping with breathlessness is difficult for patients, but harder for carers	• Annoyance • Frustration	• Frustration • Resentment • Feeling trapped • Giving up part of their identity
5. Meaning in the face of death Sense of meaning created by the relationship between patients and carers	• See death as natural (no fear) • Find meaning in their relationship with the carer	• Fear patients' death and their future • Try to bring joy and happiness to the patient

4.7.2.2 Domain 2 – Perceptions of regular, low-dose, sustained-release oral morphine

From the 13 patients interviewed, 11 took regular, low-dose, sustained-release oral morphine during the sub-study. Doses included were 8mg (n=4); 16mg (n=3); 24mg (n=3); and 32mg (n=1) (Table 4.5). The inclusion of people taking placebo provided perspective on the benefits and harms exclusively reported by those taking regular, low-dose, sustained-release oral morphine. Four themes described the combined experience of patients and carers: 1) receptivity and knowledge 2) function as a priority; 3) harmful and helpful side effects; and 4) therapy-centred aspects (Table 4.6). The concept of *net effect* emerged from the integration of these four themes, describing the interplay of different factors that contribute to patients' decisions whether or not to continue regular, low-dose, sustained-release morphine.

4.7.2.2.1 Theme 1 - Receptivity and knowledge

Before enrolling in the trial, most participants were aware that morphine was a potent pain killer but they had never heard about its potential role in breathlessness. As a result, most patients and carers reported they did not know what to expect but they were hopeful it could help reduce breathlessness.

> *"I really didn't know what to expect. (…) But I was hoping it could help me breathe better..."* [Patient 4 – Female, aged 76 years, randomised to placebo]

> *"Yes, I'd heard about morphine, but not for that reason [breathlessness]… I knew about it for pain. But I was hoping it could help with the shortness of breath."* [Carer 11 – Female, aged 69 years, patient randomised to placebo]

Few patients were concerned with addiction or associated morphine with end-of-life before participating in the trial. These patients raised these concerns with their clinicians/study staff who demystified morphine-related fears, by highlighting the small, regular doses used in the context of breathlessness.

"It got a perception that morphine was one of those interesting drugs that had both benefits and downsides (…) But also morphine was one that in some cases [was a prelude to] death. I heard about it for people who were terminal." [Patient 2 – Male, aged 77 years, maximum morphine dose 16mg]

"No really, my only concern was 'hang on a minute, is this an addictive drug?' And P. and U. [study staff] said 'addiction is not going to be a problem with these doses. It will either help you or it won't. And I trusted them." [Patient 6 – Male, aged 74 years, maximum morphine dose 24mg]

Compared with patients, carers had fewer concerns about morphine prior to trial commencement. Most expressed complete trust in the study procedures and were happy for having the opportunity to try a medication that could potentially help to reduce the symptom of chronic breathlessness.

"No, I was not concerned [about addiction]. I didn't even think about that! [laughing] I mean, I knew it was an addictive drug, but not in very small doses apparently. I think I've got quite a lot of confidence in these studies because I know they have to go through quite a rigorous approval process. They wouldn't be able to put anyone on it if there was any real danger." [Carer 13 – Female, aged 79 years, maximum morphine dose 16mg]

4.7.2.2.2 Theme 2 - Function as a priority

Some patients described symptomatic benefit with the study medication, including not only an improvement in breathlessness but also in other symptoms (e.g., pain and cough), as well as better sleep. Some patients found it difficult to pinpoint specific improvements, but explained they improved overall. All patients who described symptomatic improvement were taking sustained-release morphine 8-24mg.

"Well, when you wake up gasping… It's not a great way of waking up, I can tell you! It happens occasionally now, but not much anymore. While before it was quite frequent, once or twice every week. I get one of those, every couple of months now. I don't know how morphine does this, but I am not arguing because it works (laughing)!" [Patient 3 – Male, aged 67, randomised to morphine 8mg]

> *"Oh, [I felt] generally better in myself you know? My breathing was perhaps a little better, but I felt more alive I suppose you could say… Yeah, just felt better in myself."* [Patient 8 – Male, aged 84 years, maximum morphine dose 8mg]

In most cases, carers' perceptions of improvement/non-improvement matched patients' descriptions. However, carers attributed more importance to practical outcomes that had more impact on their own lives. For example, one carer reported that despite no symptomatic improvement in breathlessness with the study medication, the patient had stopped having breathlessness exacerbations resulting in hospital admissions. For this carer, this was the main advantage of taking morphine, which was not reported by the patient.

> *"We were on the morphine, I believe. That's only a suggestion, but she sort of didn't go backwards all the time for the 6 months (…) Everyone commented (…) she has better colour. I am confident she will hold her own now."* [Carer 1 – Male, aged 81 years, maximum morphine dose 16 mg]

Some participants reported that taking the study medication resulted in patients' function improving, which expanded both patients' and carers' "living space" (i.e., the actual physical space in which they move and have social interactions) because of easier access to the world (Ek et al., 2011a). Different patients reported different degrees of functional improvement. However, even small functional gains were important for both patients and carers. Patients experiencing functional benefit were mostly taking sustained-release morphine 16-24mg.

> *"Climbing a set of stairs was difficult. There were steps up from the Festival Theatre to King William road, three flights… I would try going up those, but it took at least three stops to get from the bottom to the top, and then I was panting… (…) About a month ago I walked up all three flights and continued walking without a pause. And that is more or less across the board. I can do things now that I haven't been able to do for a long, long time."* [Patient 2 – Male, aged 77 years, maximum morphine dose 16mg]

> *"He can walk to the letter box to get the letters (…), so he is doing that which he didn't do before. Yeah, so there was a marked improvement."* [Carer 6 – Female, aged 64 years, maximum morphine dose 24mg]

Patients' functional gains had a positive impact on carers' lives, who also saw their living space widen as well as the range of daily activities they were able to share with the patient.

> *"Going for a walk for instance was really hard work for him so I worried the whole time. So, it was not really very enjoyable. Now, we go out more, we enjoy life more, because we are not constantly worried. That's just been amazing!"* [Carer 2 – Female, aged 78, maximum morphine dose 16mg]

Participants describing no changes in breathlessness or function were almost all taking placebo or very small doses of sustained-release morphine (8mg).

> *"He's just gone on the same."* [Carer 8 – Female, aged 81 years, maximum morphine dose 8mg]

4.7.2.2.3 Theme 3 - Harmful and helpful side effects

Despite being given blinded laxatives as part of the trial, constipation was the only harm reported by participants. For some patients, additional doses of open-label laxatives helped, while others reported relief with prune juice. Some patients withdrew from the trial due to unmanageable constipation, without any significant improvement in breathlessness. Patients with unresolved constipation were more likely taking higher doses of sustained-release morphine (24-32 mg).

> *"Constipation was the downside. That was big downside! Before it all started, I could go to the toilet in the morning right after breakfast. And later in the afternoon or early evening, I had to go again. But once I started, it took me 2 to 3 days to get before I could get rid of it. And that continued all the way through. I felt very bloated."* [Patient 5 – Male, aged 79 years, maximum morphine dose 24mg]

Constipation was also distressing for carers who tried to step up and help the patients to the best of their abilities. In some cases, they were unable to improve patients' symptoms despite their best efforts. In other cases, carers were essential in the management of harms.

> *"It [constipation] was bothering him a lot... I tried to give him more roughage but his appetite is very poor so what can you do? If he says 'I don't want to take it' you can't you know? (…) It worries me sometimes."* [Carer 8 – Female, Aged 81 years, maximum morphine dose 8mg]

> *"He spoke with U. [study nurse] and she told him to take prune juice, which he has done to good effect. And that's probably the only thing that's really helped. All the medication that he had to take with the trial didn't really do much at all. So, I've been cooking prunes madly and he's been having those. And that helped a little bit and he's on the prune juice now and I believe that's working much better."* [Carer 2 – Female, aged 78 years, maximum morphine dose 16mg]

Some side effects were reported as positive and an incentive to continue the study medication. One patient and his carer reported mild-to-moderate anorexia with the study medication, which prevented him from snacking between meals (morphine 24mg). As a result, he experienced significant weight loss allowing him to move more freely. Another patient and her carer reported improvement in other symptoms (e.g., thoracic pain, cough), which motivated her to continue taking the medication (morphine 24mg).

> *"So, one of the side effects that I have with the morphine is it reduces my appetite. It changes your diet. You don't pick, you don't have a piece of cake in the middle of the day and things like that so, I lost 10 Kg in weight. And because you lose the weight, it's easier to do your shoes up so physically you just become more active."* [Patient 6 – Male, aged 74 years, maximum morphine dose 24mg]

> *"She stopped having chest pain since she was put on the medication. She used to get quite bad chest pain at times. That is better, which is good."* [Carer 12 – Male, aged 70 years, maximum morphine dose 24mg]

4.7.2.2.4 Theme 4 – Therapy-centred aspects

Both patients and carers reported that the study medication was easy to take and did not require any major changes in daily routine. This contributed to maintain people's long-term adherence to the study medication, even after study cessation.

> *"That was quite easy [taking the study medication] because he just used to take it with all his other medications. So that was no problem."* [Carer 5 – Female, aged 69 years, maximum morphine dose 24mg]

> *"Even though I didn't find it [morphine] helpful, I might have been on placebo. And it's easy enough to give it a try, you know? (…) Now, I am taking [sustained-release] morphine 10 mg a day. I will try it for 2 months and then I will have a discussion with S. [respiratory physician] and if she thinks I should continue on it, then I will."* [Patient 13 – Male, aged 79 years, maximum morphine dose 16mg]

For some people who had benefit, getting a morphine prescription after the trial was difficult, partially because sustained-release morphine was not approved by any regulatory body at that time. Patients describe some clinicians were reluctant to provide a prescription, due to lack of a registered indication for breathlessness and fear of potential harms. Thus, morphine prescribing resulted from discussions and negotiation between patients, carers, the research teams and general practitioners.

> *"Well, I think mine [general practitioner] is courageous, he's been prescribing it [morphine] based on a phone call with [the study investigator]. (…) Besides I can be very persuasive if I put my mind to it. I just said to him: 'It is very simple, do you want me suffocating quietly here and there on a regular basis, or do we use something that we now know it works?' I can understand it [the reluctance], but I am not prepared to suffer like I am suffocating here because you have got some moral idea that you don't think it's good for me. You think it's better for me to suffer than have the morphine, I am sorry but I am in here and I am gonna disagree with that argument."* [Patient 3 – Male, aged 67 years, maximum morphine dose 8mg]

Difficulties in accessing a prescription for sustained-release morphine also had implications for carers, whose distress increased as patients reverted to their previous state before initiating sustained-release morphine.

> *"Now he is sleeping like a baby again... But when he stopped [the study], he could not sleep, and I could not sleep… It was awful."* [Carer 6 – Female, aged 64 years, maximum morphine dose 24mg]

Table 4.5 - Individual patients' benefits, harms and outcomes reported by dose in Domain 2

Patient	Dose of morphine on trial				Patient-reported benefits	Patient-reported harms	Study completion and subsequent therapy
	Week 1	Week 2	Week 3	Extension			
1	Placebo	8mg	16mg	16mg (for 6 months)	• Mild improvement in overall well-being • Stable disease with less breathlessness exacerbations and less hospital admissions	• Mild constipation resolved with laxatives	Completed the study; currently taking prescribed morphine
2	16mg	16mg	16mg	16 mg (for 6 months)	• Reduced breathlessness • Reduced cough • Dramatic improvement in function • Improvement in relationships	• Severe constipation resolved with prune juice (no improvement with laxatives)	Completed the study; currently taking prescribed morphine
3	Placebo	Placebo	8mg	8 mg (for 6 months)	• Reduced episodic breathlessness during the night • Mild improvement in function	• No harms reported	Completed the study; currently taking prescribed morphine
4	Placebo	Placebo	Placebo	-	• No benefits reported	• No harms reported	Stopped the study drug after 3 weeks on trial due to lack of benefit
5	16mg	16mg	24mg	24mg (for 1 month)	• Mild improvement in breathlessness	• Constipations that did not resolve with laxatives	Stopped the study drug after 1 month on the extension phase due to lack of benefit and persistent constipation
6	8mg	16mg	24mg	24 mg (for 6 months)	• Reduced breathlessness • Clear improvement in function • Appetite loss (led to weight loss)	• Moderate constipation, which became mild with laxatives	Completed the study; currently taking prescribed morphine
7	16mg	24mg	32mg	-	• No benefits reported	• Constipation that did not resolve with laxatives	Stopped the study drug after 3 weeks on trial due to lack of benefit and persistent constipation
8	8mg	8mg	8mg	8 mg (for 6 months)	• No benefits reported	• Constipation that never resolved with laxatives	Completed the study; decided not to continue morphine due to lack of benefit and constipation that never fully resolved
9	Placebo	8mg	8mg	8 mg (for 3 months)	• No benefits reported	• No harms reported	Stopped the study drug after 3 months on the extension phase due to lack of benefits
10	8mg	8mg	8mg	8 mg	• No benefits reported	• No harms reported	Completed the study; decided not to continue morphine due to lack of benefits
11	Placebo	Placebo	Placebo	Placebo (for 1 month)	• No benefits reported	• Constipation that did not resolve with laxatives	Stopped the study drug after 1 month on the extension phase due to lack of benefit and persistent constipation
12	8mg	16mg	24mg	24 mg (for 6 months)	• Improvement in chest pain	• No harms reported	Completed the study; currently taking prescribed morphine.
13	Placebo	8mg	16mg	16 mg (for 6 months)	• No benefits reported	• No harms reported	Completed the study; currently taking prescribed morphine.

Table 4.6 – Domain 2 comparative analysis of findings from patients and carers

Patients & Carers	Patients	Carers
1. Receptivity and knowledge Both patient and carer are receptive to sustained-release morphine for breathlessness	• Morphine is a potent painkiller • Lack of knowledge of morphine for breathlessness • No expectations • Fear of addiction • Association with end-of-life • Discussion with clinicians helps resolve concerns	• Morphine is a potent painkiller • Lack of knowledge of morphine for breathlessness • No expectation • Trust in the study processes • Happy to be included in a study that could ameliorate the patient's breathlessness
2. Function as a priority Functional gains widen the "living space" of both patients and carers	• Improvements in breathlessness are important • Functional gains are important, even if small • By improving function, morphine widens patients' living space	• Attribute importance to observable benefits with impact on their own lives • By improving patients' function, morphine widens carers' living space and the number of activities they share
3. Harmful and helpful side effects Side-effects of sustained-release morphine can be harmful or helpful	• Constipation is common and the only harmful side effect reported by these patients • Anorexia and decreased pain can be helpful side effects	• Distressed with patients' constipation • Help patients overcome harmful side effects
4. Therapy-centred aspects From a practical point of view, sustained-release morphine is easy to adapt to	• Regular, low-dose, sustained-release oral morphine is easy to take • Distressed with not being able to access morphine after the study	• Therapy with oral sustained-release morphine requires no changes in their daily routine • Distressed by the return of patients' symptoms after ceasing the trial

4.7.2.2.5 Emerging concept - Net effect

In addition to the findings presented above, the concept of 'net effect' (i.e., the perceived effect experienced with the study medication after weighing benefits and harms) emerged from examining the relationship between themes, sub-themes and the decision to continue taking sustained-release morphine after study completion (Figure 4.3). People who experienced breathlessness improvement, and especially functional improvement, were more likely to continue the study medication. In contrast, people experiencing constipation were more likely to discontinue the study medication, particularly if refractory to symptomatic treatment, reflecting a narrower therapeutic window for some people (Ferreira et al., 2016). For some people reporting breathlessness improvement, severe constipation prevented them to continue the study medication. Those who experienced functional improvement were more tolerant of constipation for which they explored different therapeutic options, describing it as "a small price to pay" to get the benefits of morphine. Patients who did not experience any benefits or harms were generally open to try morphine post-trial because they were unsure if they were taking the active medication or placebo.

Of note, of the four patients living alone, only one was taking prescribed morphine after study completion. Conversely, six out of nine patients living with a carer chose to take morphine after the study; of the three who did not, two were on placebo during the trial. Carers often play an active role in managing chronic breathlessness, helping patients adjust to the drawbacks of therapy (Kochovska et al., 2021). It is also possible that patients may decide taking regular, low-dose, sustained-release oral morphine long-term to soothe carers' anxiety (i.e., provide a sense that 'something is being done' to improve their condition). This aspect of the patient-carer dynamic and its contribution for the 'net effect' experienced with this medication needs to be unpacked in future studies.

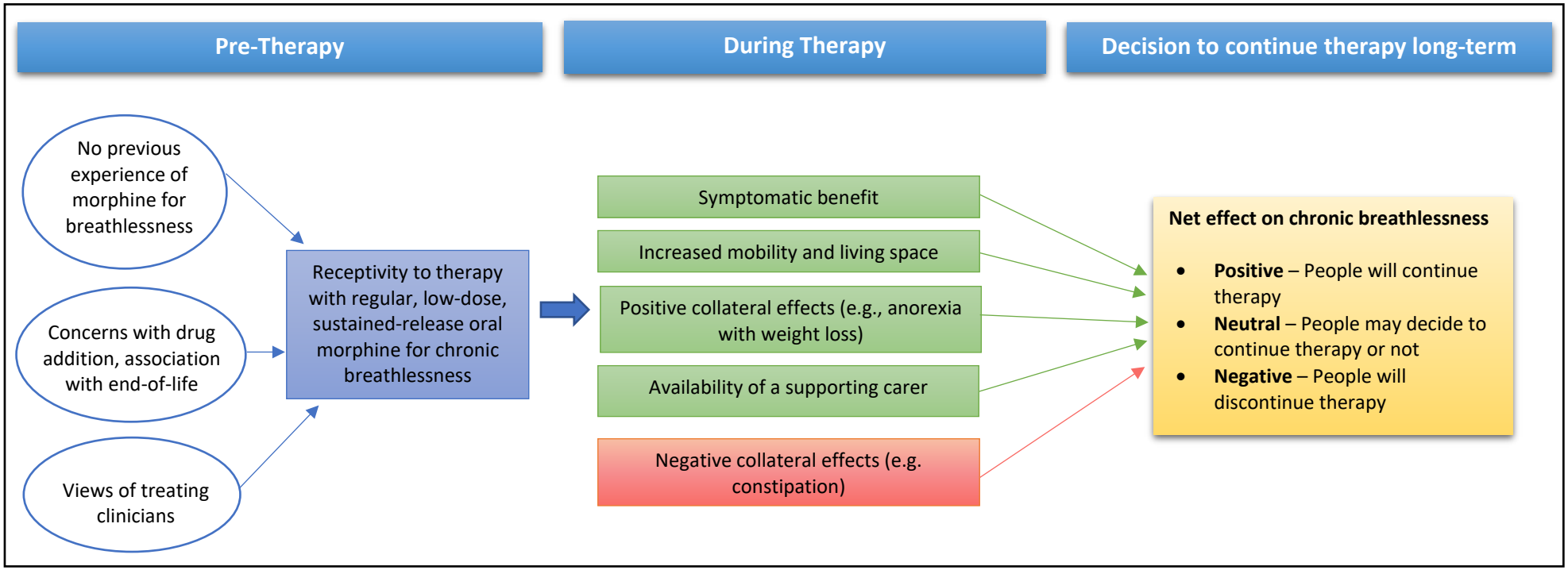

Figure 4.3 - Factors conditioning the net effect of regular, low-dose, sustained-release oral morphine for chronic breathlessness

4.7.2.3 Domain 3 – Self-reported driving

Three major themes described the experience of driving for patients with chronic breathlessness and their carers: 1) independence, 2) breathlessness impact on driving, 3) driving while taking regular low-dose sustained-release oral morphine (Table 4.6).

4.7.2.3.1 Theme 1 - Independence

Being able to drive helped patients keep their sense of self and feeling useful. This was more noticeable in patients experiencing severe functional limitations due to breathlessness.

> *"Well, I suppose it's something that I don't do every day (driving) and you know, and I am doing something! Maybe that's the reason why… Well I've always enjoyed driving actually but more so now, more so now, yeah… Probably because it's something different in my life now, you know? I can do something! Whereas usually, I am just sitting."* [Patient 8]

Most patients reported that driving was one of the few activities that brought them a sense of joy and pleasure. Even those patients not required to drive (i.e., because their carer drove), still felt the need to drive at times for pure enjoyment.

> *"We have got the van and I drive the van. I love getting out in the country and driving."* [Patient 12]

For carers, seeing their partners enjoy themselves was particularly important. They acknowledged the role of driving in widening the physical space available to both the patients and themselves, a space that had been severely reduced by breathlessness in most cases.

> *"Well, driving is important… There are certain things… When we go on holiday because he is not bothered about walking out on the streets, you know? (…) But we went to Barossa Valley last week, (…) but we went to Mengler's Hill to the look out. He got up there, well we drove up there of course, we got out of the car and we*

walked down a little bit to the picnic area there and he stayed there while I walked around and looked at it because walking down and up and down… [meaning it was tiresome for him]. So things like that you know?" [Carer 11]

For some patients, driving was their most important activity. One patient without a carer explained that driving was key to maintaining relationships and roles, whilst also providing a sense of purpose:

"I get my adult daughter every Saturday for a while, she is profoundly autistic, she just had her 26th birthday yesterday and it is very important to her. So, I have got to drive to go get her, drive to bring her back. So, it's a very important thing, making sure I can still drive. (…) And that's the main reason, apart from that, it is just to get to the shop and the doctor which are a kilometre away. That's the only big one." [Patient 3]

Another patient explained that driving was the only out-of-home activity he was still able to do independently and that losing it would be extremely disturbing.

"Well, I think the most important thing to be able to do at the moment is to be able to drive because physically there is nothing I can do, I can't do anything". [Patient 8]

Overall, people who were still driving expressed fear about not being able to drive in the future. Driving was seen as an important marker of independence and there was fear over any loss and its consequences.

"I couldn't give up driving, I couldn't do that [disturbed facial expression]. I think it's your independence, you know? And once that is taken away, you're reliant on somebody else…" [Patient 9]

For the four patients who had stopped driving, only one (male) reported that driving was important to maintain his independence. The other three patients (one male, two females) reported driving was not overly important because their carers could drive when needed.

"It gives me a lot more freedom to have the car. I don't do things that I would normally do… If I had the car and I felt like KFC for lunch, I can go and get it (laughing)… or if I wanted to go out for dinner with someone, I could just go and do it. Whereas now, for me to walk to the bus stop to get a bus somewhere, it's just too hard…" [Patient 10]

"I don't miss driving. B. (husband) does everything. We are together all the time anyway." [Patient 1]

4.7.2.3.2 Theme 2 - Chronic breathlessness impact on driving

In general, both patients and carers considered that breathlessness did not reduce patients' driving skills because it did not require over-exertion.

"Normally, I am fine. I don't get tired driving." [Patient 7]

Some patients reported they had situations in which they felt breathlessness at rest. When present, they felt their driving ability was affected. Strategies to overcome this limitation included not driving at all or using oxygen while driving. Interestingly, the use of oxygen in the car raised some concerns about its safety and legality.

"There were a couple of times in which I have been buggered a bit. I haven't had the oxygen the night before, so I will put the oxygen on the car and I will have the oxygen running while I am driving. Whether that's legal or not I don't know."[1] [Patient 11]

One patient experiencing breathlessness at rest explained that breathlessness impacted on his concentration and hence ability to drive. When he drove, he felt anxious and concerned about his and other people's safety.

"For me it is not so much driving, but the concentration level about what is going on around. Stuff I used to take for granted, so I automatically did it before. Now, I have

[1] In Australia, it is legal to drive while using oxygen, as long as the oxygen cylinder is securely stored in the vehicle (Australia New Zealand Industrial Gas Association, 2011).

to make sure I do it. And it depends on the concentration because if it is concentrating on something that could end in a disaster, is a bit different to concentrating on something that might just a non-event anyway." [Patient 13]

Overall, carers' views matched patients' views. Most carers confirmed that patients drove safely despite their breathlessness. For the only patient who stated that driving was stressful (previous quote, patient 13), the carer thought he could still drive safely.

"Yes, usually when we go stay with our son at Wallaroo, he drives there. So, he can. And he is quite good, I think. I don't notice any diminishing of his driving skills. I feel quite relaxed when he is driving." [Carer 13]

4.7.2.3.3 Theme 3 - Driving while taking regular, low-dose sustained-release oral morphine

Participants' views on driving were quite uniform, irrespectively of the drug (i.e., morphine or placebo) and dose. Most patients and carers perceived that the study drug did not have any perceived adverse impact on patients' ability to drive, irrespectively of the study drug/dose.

"No, no problems (to drive while taking the study drug)." [Patient 7 – Female, aged 79 years, maximum morphine dose 32mg]

"No, no, not at all. I don't think driving was affected (by morphine)". [Carer 2 – Female, aged 78 years, maximum morphine dose 16mg]

Despite not perceiving any impact on driving with the study drug, a small number of participants were still concerned about the potential effects of morphine on driving. Most believed that the trial dose (up to 32mg sustained-release morphine a day) could impair driving. One carer did not want the patient to continue with morphine because she believed morphine could lead to driving cessation. One patient took action to minimise any negative impact of morphine on his driving skills.

"I was concerned about… If he does take it, I think he wouldn't be able to drive (…) and I don't really want him to go on that because he loves driving and I think if he took it, that would be the end. I want him to be around for a few more years yet." [Carer 8 – Female, aged 81 years, maximum morphine dose 8mg]

"I have a friend coming here and he will sit with me (while I drive) and tells me what is going on with the driving. (…) I know they say if I am taking a quite powerful opioid drug that driving while under the immediate influence is probably not that smart. I would not be inclined to do it unless it was an emergency." [Patient 3 – Male, aged 67 years, maximum morphine dose 8mg]

Table 4.7 – Domain 3 comparative analysis of findings from patients and carers

Patients & Carers	**Patients**	**Carers**
1. Independence Driving widens the 'living-space' for both patient and carer	• Doing something • Being useful • Enjoyment and pleasure • Fear of losing their ability to drive • The most important activity	• Happy to see patients enjoy themselves • More independence if the patient is able to drive • Fear that patients lose their ability to drive
2. Breathlessness impact on driving Breathlessness does not impact on perceived driving	• Overall, breathlessness does not impact on driving • Breathlessness at rest can affect concentration and the ability to drive	• Breathlessness does not affect the patients' ability to drive safely • More confident about patients' driving skills than the patients themselves
3. Driving while taking regular, low-dose sustained-release oral morphine Regular, low-dose, sustained-release oral morphine does not impact on perceived driving	• Did not perceive any changes in driving ability with the study drug • Fears associated with low-dose morphine - putting others at risk	• Did not perceive any changes in patients' driving ability with the study drug • Fears associated with low-dose morphine – patients' decline

4.8 Discussion

This is one of the first studies exploring patients and carers coexistence with chronic breathlessness associated with COPD, their perceptions of regular, low-dose, sustained-release oral morphine for chronic breathlessness and their perceived experience of driving with chronic breathlessness before and after initiating regular, low-dose, sustained-release oral morphine. Findings suggest that chronic breathlessness is a systemic condition that permeates all aspects of the patient's and carer's lives, and that carers are particularly susceptible to emotional distress caused by patients' breathlessness. Working as a team, patients and carers manage chronic breathlessness to achieve maximal function and well-being. Functional improvement is the great driver influencing positively the decision to take sustained-release morphine long-term. However, the degree of symptom reduction, improved function, side-effects severity, and carers' availability creates a net-effect driving patients' decisions to continue or discontinue the medication. Importantly, driving emerged as a key daily activity contributing to maintain patients' sense of identity and independence. Being able to drive increased the physical and social space available to patients and carers, their social engagement and well-being. Patients reported breathlessness at rest may impair driving skills, while the introduction of sustained-release morphine seemed to have no self-reported impact on driving.

4.8.1 Domain 1 – Experiences of chronic breathlessness

This study highlights important issues for patients and carers individually, but also for the patient and carer as a group. These findings suggest that patients and carers share the experience of chronic breathlessness, working as a team to overcome the restrictions imposed by this syndrome. The breathing-thinking-functioning model of chronic breathlessness (detailed in Chapter 1) provides a framework to understand these findings

(Spathis et al., 2017). According to this model, breathlessness activates immediate cognitive and behavioural responses, triggering three vicious cycles associated with the breathing, thinking and functioning aspects of breathlessness, which contribute to aggravating and sustaining the symptom (Spathis et al., 2017). This qualitative sub-study suggests that *both the patient and the carer* are active participants in the breathing-thinking-functioning cycles of chronic breathlessness (Spathis et al., 2017), and that therapeutic approaches need necessarily to consider both elements within the patient-carer dyad.

Breathing

Both patients and carers reported that COPD-associated breathlessness took over their lives. While patients experienced breathlessness daily and had learnt how to accept and adapt to the symptom, carers were frequently distressed by watching patients trying to catch their breath. Previous evidence suggests that carers of people with COPD feel they lack understanding about the experience of breathlessness and its causes (Farquhar et al., 2017). More importantly, they are seldom involved in therapies aiming to optimise lung function and exercise tolerance (Farquhar et al., 2017). Thus, frequent distress with daily breathlessness may be a consequence of lack of education for carers in this area.

Interestingly, the terms “good / bad days” are used very consistently by both patients and carers to describe daily fluctuations in breathlessness, in which a “good day” corresponds to being as functional as possible and a “bad day” to severely restricted daily activities because of breathlessness. Fluctuations in breathlessness were previously described in a large prospective study examining breathlessness intensity in people with severe COPD, over a 6-month period, in which breathlessness was measured monthly (Bausewein et al., 2010). The current sub-study suggests that fluctuations in breathlessness are frequent, with substantial

daily variations. The concept of “good” and “bad” days has been described before in other qualitative work (Giacomini et al., 2012). However, there is no understanding of the predictors of such fluctuations and the mechanisms behind them. These findings highlight the natural history of chronic breathlessness, and the need to develop specific interventions that can target daily fluctuations in breathlessness. Moreover, the descriptions of “good” and “bad” days are consistent between patients and carers, which indicates they share a common experience and lexicon. Thus, specific interventions targeting “good” and “bad” days should target both the patient *and* the carer *together*.

Thinking

Patients and carers both reported distress due to breathlessness, but while patients’ distress is triggered by sudden and unpredictable acute-on-chronic breathlessness (Hutchinson et al., 2019), carers live in a constant state of worry, which is amplified when breathlessness worsens. Although patients feel regularly annoyed for not being able to fully function, the daily experience of breathlessness does not seem to cause them anxiety because it is predictable and manageable. However, unexpected surges of intense breathlessness (e.g., exacerbations of COPD) cause fear and anxiety because they are surprising and difficult to manage. In such situations, fear may itself contribute to aggravating breathlessness (Lansing et al., 2009). In general, the experience of breathlessness seems to be particularly distressing for carers, who are unable to disconnect from the carer’s role, live in a permanent state of hypervigilance, force themselves to keep calm in order not to disturb patients, and spend their lives feeling helpless. On top of that, carers are required to step up in situations of acute, unpredictable breathlessness, whether they feel prepared for it or not. While breathlessness-induced emotional burden has been

previously described for patients and carers (Bailey, 2001; Gysels et al., 2007), this sub-study adds to our understanding by demonstrating that within the same patient-carer unit, similar experiences of breathlessness trigger different emotional responses in patients and carers. More importantly, situations that are not distressing for patients, may be severely distressing for carers. Such findings are important not only because they highlight carers' psychological vulnerability, but also because there is a significant association between the psychological well-being of patients and their carers (Mi et al., 2017). Thus, it is imperative to implement psychological interventions that target both the patient *and* the carer. Importantly, patients and carers have specific emotional vulnerabilities that may require specific, *individual* approaches.

It is also interesting that patients' choices of words are underpinned by a sense of acceptance and adaptation to their condition. Some patients acknowledge they may deteriorate and talk easily about dying. This acceptance may be related to the often progressive nature of COPD providing time to process and adapt to new challenges and, for some, the perception of having a self-inflicted disease (i.e., believing they are just living with the consequence of their actions) (Lindqvist & Hallberg, 2010; Nicholls, 2003). Conversely, many carers find it difficult to accept their role. Many carers feel forced to give part of their identity, trapped in the carers' role and have difficulties discussing death-related themes (Bergs, 2002). Thus, coping with the long-term consequences of breathlessness may also be more challenging for carers, which may require interventions tailored to their needs.

Functioning

In this sub-study, patients and carers reported that they saw their worlds shrink physically and socially due to chronic breathlessness. This limitation of each person's "living space" (Ek

et al., 2011a) has a profound impact on patients' and carers' wellbeing. Patient and carer become confined to activities at home and increasingly isolated (Gabriel et al., 2014). This sub-study highlights the concept of "mutual adaptation" in which there is an attempt to reconcile the patient's and the carer's levels of function so they can function *together*. As breathlessness progresses, patients become more accepting of their limitations (Caress et al., 2010), but they constantly strive to be as functionally independent as possible (Morgan et al., 2017; Steinhauser et al., 2000). For people with advanced diseases, not being a burden to their families (Heyland et al., 2006) is often more important than having their symptoms under control. This helps to explain why patients are constantly working to their physical (and psychological) limits. Conversely, carers learn to either take over certain tasks or slow down to adapt to the patients' rhythm. Although a change in life rhythm has been previously reported in patients with COPD and their partners, that consisted mostly on the carer's compromise to adapt to the patient's limitations (Ek et al., 2011b). This sub-study suggests both carer and patient play an active role in this process.

Another key finding is that carers may be crucial to prevent over-exertion. It has been described that patients adapt to breathlessness by avoiding situations that may trigger unmanageable breathlessness and by carefully planning each daily activity to minimise the consequences of breathlessness (Nicholls, 2003). This sub-study supports these findings by showing that patients push to their perceived limit while avoiding a degree of exertion that would trigger uncontrollable breathlessness. However, in some relationships, there may be a mismatch between a patient's and a carer's perceptions on what constitutes the "limit". One hypothesis is that the carer's perceptions of breathlessness are inaccurate, which is supported by previous research showing only fair patient-carer agreement in breathlessness

ratings (Mi et al., 2018). Alternatively, the carer may indeed play a crucial role in preventing over-exertion. The presence of a carer may also contribute to increasing patient's confidence to push themselves because there is help available if breathlessness becomes uncontrollable. These hypotheses need to be investigated in future work. Nevertheless, given that breathlessness is managed by patient and carer *together*, it is important to reconcile patient's and carer's views on what constitutes over-exertion.

This work also shows that patients and carers are both actively involved in managing breathlessness. Initially, breathlessness is managed by sharing tasks. At this point there is still a clear definition between the patient's and the carer's roles. This sub-study shows that as breathlessness progresses, patient and carer transition to managing breathlessness as a cohesive team requires flexibility and constant adaptation by both parties. This is in line with previous work describing the lack of definition and unpredictability associated with the carer's role in severe COPD (Bove et al., 2016).

Overall, both patient and carer work (individually and together) to withstand the limitations imposed by breathlessness. Carers, and particularly family carers, are a source of physical and emotional support for patients with advanced COPD (Gardiner et al., 2010). Close relationships are essential in creating meaning in people's lives, contributing to their psycho-social well-being and, ultimately, their quality of life (Strang & Strang, 2001). Because breathlessness leads to social isolation, the carer is frequently the only person providing a sense of connectedness with another person (Lin & Bauer-Wu, 2003). Thus, the carer is not only the person providing care but also the person providing meaning and, as such, is essential in enhancing optimal coexistence with breathlessness. Given that breathlessness impacts on both patients and carers, and both elements play a role in

breathlessness management, it was suggested that the patient-carer unit should be targeted as the unit of care (Farquhar, 2017). This work supports this idea. However, it also highlights that patients and carers have specific and, at times, differing needs, which need to be addressed separately.

4.8.2 Domain 2 – Perceptions of regular, low-dose, sustained-release morphine

Patients' perception of regular, low-dose, sustained-release oral morphine seems to be determined by the experienced net effect (weighing benefits and harms). The net effect will determine whether a patient will decide to continue the study medication long-term. Benefits contributing to the net effect included breathlessness improvement, increased mobility, and positive side-effects such as improved sleep at night; constipation was the only harm reported. Carers' and patients' experiences with regular, low-dose, sustained-release oral morphine are similar, although carers tend to focus more on observable benefits which made a difference in their own lives. Importantly, many carers are critical in helping manage any harms from regular, low-dose sustained-release morphine and seem to contribute to the likelihood of continuing this medication long term. Participants' experiences seem to vary according to morphine doses. Generally, people taking placebo or sustained-release morphine 8mg were less likely to report benefits or harms. People taking 16mg and 24mg were more likely to experience benefits, but also side-effects (beneficial or harmful). The only participant taking sustained-release morphine 32mg experienced only harms.

The concept of net effect when beneficial has been used to explain people's choices of sustained-release morphine versus placebo for chronic breathlessness (Currow et al., 2017b; Ferreira et al., 2016). This sub-study saw *net effect*, with positive, negative or neutral

outcomes which, in turn, drive decisions to continue or cease the study medication. From the participants' perspective, although symptomatic improvement was essential, better function was the main driver of perceived benefit. This aligns with findings from Domain 1 and previous work describing the importance of independence and mobility for patients with COPD who become increasingly more restricted as the disease progresses (Ferreira et al., 2020; Gysels et al., 2007; Gysels & Higginson, 2010). Up until now, intensity of breathlessness measured with unidimensional breathlessness scales has been used as the preferred outcome of measure in randomised controlled trials of opioids for chronic breathlessness. Findings from this study suggest that primary outcome measures focused on function may be more relevant for participants. This hypothesis is further supported by a previous randomised controlled trial of people with COPD and chronic breathlessness, in which regular, low-dose, sustained-release oral morphine has been shown to significantly improve health status using the COPD assessment test, especially when assessing walking upstairs or hills (Verberkt et al., 2020). As a result, it is important to select primary outcome measures evaluating function in future studies evaluating opioids for chronic breathlessness.

Observable gains in function are also critical for carers not only because they see their loved-ones become more independent, but also because their own living space increases (Ek et al., 2011a) and their moment-by-moment responsibilities are diminished. In some cases, carers provide unique perspectives on the benefits and downsides of therapy, which patients alone are unable to provide. These findings contribute to solidify findings from Domain 1, by illustrating that patients and carers have both individual and shared experiences of breathlessness and both are affected by the introduction of regular, low-

dose, sustained-release oral morphine. Thus, it is important to include carers' perspectives in the assessment or re-assessment of any new therapy, in order to get a full picture of its effects (Farquhar, 2017).

This sub-study brings a new lens on side effects caused by regular, low-dose, sustained-release oral morphine. Firstly, while some side-effects were experienced as harmful, others were perceived as helpful. Importantly, clinicians' and patients' perceptions are not always aligned, particularly in symptom evaluation (Haugdahl et al., 2015; Iyer et al., 2014). This sub-study highlights that side effects typically perceived as harmful by clinicians may contribute to treatment success in some cases. Secondly, sedation and nausea were not reported in this sub-study. These are frequent opioid side-effects particularly during therapy initiation and upward titration. The use of very small doses of sustained-release oral morphine (8mg) and controlled upward titration (maximum 16mg weekly) may have contributed to these findings. However, constipation was common in this sub-study and one of the few side effects contributing to discontinuing therapy. In line with previous findings, managing constipation might be critical to influence adherence to therapy in people taking regular, low-doses, sustained-release oral morphine for chronic breathlessness (Ferreira et al., 2016). Regular, sustained-release oral morphine 8mg caused few side effects but was also unlikely to improve breathlessness. With such small doses, the amount of morphine binding to μ-opioid receptors may be insufficient to trigger any clinical effect (Fallon & Cherny, 2015). Slow upward titration allows the development of tolerance to morphine, which can reduce side effects experienced after abrupt introduction of higher doses (Fallon & Cherny, 2015).

This qualitative sub-study shows that most people are unaware of the use of sustained-release morphine for chronic breathlessness. This may represent a practical advantage in the clinical setting given that patients and carers may be intrigued about its potential effects and less focused on opioid-related concerns (e.g., addiction) (García-Toyos N, 2014). Additionally, for people who do express concerns, information about the low doses used for chronic breathlessness may be sufficient to reassure them. In any case, support from treating clinicians is critical *before* initiating the sub-study medication (Oxberry et al., 2012; Rocker et al., 2012). However, *after* experiencing net benefit, some participants may want to continue taking morphine even when they face clinicians' resistance. This requires clinicians to be well informed and prepared to deal with such challenges. Overall, carers were less concerned about side-effects and more willing to try a new medication that could improve breathlessness. This is not surprising as carers are often severely and persistently distressed by patients' breathlessness and their functional decline (Booth et al., 2003). It is likely they are receptive to any treatment aiming to reduce patients' suffering.

Overwhelmingly, participants reported that regular, low-dose, sustained-release oral morphine was easy to take and therefore not an obstacle to therapy continuation. Sustained-release formulations are often well tolerated because they require less frequent administrations and do not require interruptions to sleep when compared with immediate-release morphine (taken approximately every four hours) (Klepstad et al., 2003). For people who experienced benefit, getting a prescription of sustained-release morphine after the study was difficult and frustrating. This was partially attributed to a lack of a formal indication and registration for chronic breathlessness at that time. However, clinicians are often resistant to prescribe morphine in people with COPD due to fear of respiratory

depression and overall concerns related to opioid safety (Hadjiphilippou et al., 2014). Such fears may still persist after sustained-release morphine approval and may require interventions aiming to inform and support clinicians. Moreover, despite supportive international guidelines (GOLD, 2021; Parshall et al., 2012), regular, low-dose sustained-release oral morphine is still not registered for chronic breathlessness outside Australia. Thus, accessing this treatment is still a challenge for many patients with disabling breathlessness and their clinicians.

Similar to Domain 1, Domain 2 also highlighted the importance of carers who help managing the side effects of regular, low-dose, sustained-release oral morphine therapy. Taking into account the carer's role in facilitating coping with constipation and the proportion of patients with a carer willing to continue morphine after the trial, this work suggests that the carer may be a key player in patients' adherence to treatment with regular, low-dose, sustained-release oral morphine. The relevance of carers in facilitating patients' adherence to therapy was highlighted before (Bourbeau & Bartlett, 2008), suggesting that the carer may not only be a care recipient but also a potential co-worker with clinicians (Stajduhar et al., 2008).

4.8.3 Domain 3 – Self-reported driving

This is the first sub-study reporting patients' and carers' perspectives and experiences of driving with chronic breathlessness before and after initiating regular, low-dose, sustained-release oral morphine. Findings suggest that driving is crucial in helping patients with chronic breathlessness keep a sense of identity, purpose, independence and connection to the outside world, while also being a source of joy and comfort for both patients and carers.

According to patients, breathlessness at rest can reduce their driving skills but the study drug (i.e., morphine/placebo) had no perceived impact on their ability to drive.

Similar to healthy individuals, owning and driving a private vehicle is perceived as an amenity offering people freedom of movement (Guiver, 2007). However, participants' reflections highlight that the ability to drive is particularly important for people experiencing severe functional limitations in other aspects of life due to chronic breathlessness and their carers. For these patients, driving is associated with a sense of identity and feeling useful. Similar findings were reported by a previous qualitative sub-study of three focus groups: i) low disability/broad living space, ii) high disability/broad living space, iii) high or low disability/constricted living space. Although all groups considered driving an important activity, the third group was the most affected by driving cessation which was perceived by them as devastating (King et al., 2011). Importantly, the present sub-study also shows that driving widens both patients' and carers' living space (i.e., the physical space in which they move and socially interact) (Ek et al., 2011a; King et al., 2011). Previous evidence suggests that, as patients become more restricted by chronic breathlessness, carers tend to adjust by slowing their life rhythm, also becoming more restricted (Ek et al., 2011b). Thus, it is likely that any strategies supporting patients' function (such as driving) may also positively affect carers (Bergs, 2002). Functional decline is one of the major contributors to driving cessation in older age (Chihuri et al., 2016). Older adults who stop driving have twice the risk of depressive symptoms compared to those who continue driving (Chihuri et al., 2016). Given the association between patients' and their carers' well-being, risks and benefits for patients and carers need to be weighed carefully before advising patients not to drive (Mi et al., 2017).

Most patients considered that their chronic breathlessness did not impact on their driving primarily because driving was sedentary and did not trigger breathlessness. Patients who had experienced or were experiencing breathlessness at rest explained that breathlessness affected their concentration when driving. Previous research has highlighted potential effects of uncontrolled symptoms on people's driving skills (Nilsen et al., 2011). Worsening breathlessness scores are associated with worsening performance in neuropsychological assessments but any relationship with driving performance is unknown (Karakontaki et al., 2013). Worsening breathlessness scores are associated with increased chances of experiencing breathlessness at rest (Bestall et al., 1999). Thus, it is possible that patients with worse breathlessness are particularly at risk of having some degree of psychomotor impairment that could affect driving. Interestingly, carers did not seem to notice any changes in patients' ability to drive. This may result from patients' adaptation to breathlessness, including development of driving strategies that are not evident to carers (e.g., increased concentration required, driving slightly slower). Reportedly, the use of oxygen while driving may be one of these strategies. Using oxygen while driving is legal in most countries, but patients need to ensure oxygen tanks are adequately secured and respect specific legislative and regulatory requirements. Given that driving cessation is also emotionally challenging for carers, they may overlook changes in patients' driving ability in order to keep them driving (Liddle et al., 2016).

All participants agreed that their study drug/dose did not affect their perceived driving skills. Previous research had suggested that regular therapeutic opioid-agonists are unlikely to affect driving-related skills (Ferreira et al., 2018). This sub-study raises the hypothesis that low-doses of sustained-release morphine may have no impact on driving even during

therapy initiation and careful upward titration. This is in line with previous studies showing that uncontrolled symptoms are more likely to have an impact on driving than therapeutic opioids (Nilsen et al., 2011). Despite that, both patients and carers were still concerned about potential side effects of sustained-release morphine that could affect their driving. Concerns about opioids are common amongst patients, carers and clinicians (Janssen et al., 2015; Rocker et al., 2012). Interestingly, while patients' concerns were focused on safety for themselves and others, carers were more concerned with patients' deterioration if they were to stop driving. Chronic breathlessness and its treatments affect both patients and carers, involving both in symptom management and again reinforcing the patient-carer unit as the unit of care (Farquhar, 2017).

This sub-study suggests that initiating morphine for chronic breathlessness may raise concerns about driving for patients and carers, and those concerns need to be proactively addressed with both. Frequently, clinicians advise patients not to drive immediately after taking opioids (Weir et al., 2017). There is a need for further research to understand if patients taking regular, low-dose, sustained-release morphine are able to drive safely given the different pharmacokinetic profile they have to immediate-release oral morphine solutions (Gourlay et al., 1995). The relation between breathlessness and driving performance whilst on opioids must also be explored as current legal morphine limits for driving (where imposed) are far higher than the doses used in this study (Boland et al., 2018).

4.8.4 Strengths and Limitations

This is the first sub-study exploring how patients and carers coexist and respond to the same circumstances of chronic breathlessness and how they perceive therapy with regular, low-

dose, sustained-release oral morphine for this indication. This is also the first sub-study exploring the issue of self-reported driving with chronic breathlessness before and after initiating regular, low-dose sustained-release morphine. People had recently started this medication, and some have chosen to discontinue it. This provided a range of experiences (positive and negative) which were not captured before (Rocker et al., 2012).

A strength of this sub-study is that participants were recruited from a phase III RCT that allowed COPD-status and morphine-dose transparency. Additionally, participants and researchers were blinded to the study medication, which reduced bias while selecting and interviewing participants. Due to the main trial dose-increment design, people were more likely to be taking morphine than placebo after the randomisation period (11:12 chance). This reduced the number of perspectives from people taking placebo but increased the number of people who could provide useful information about morphine.

Although patients and carers were interviewed separately, they were aware of each other's presence in the house, which may have inhibited the expression of concerns. English was not the interviewer's first language, which could have led to misunderstandings or misinterpretations during the interview process and interview transcription. Potential misinterpretations between interviewer and interviewees were mitigated by interview and transcription checking performed by a native English-speaker researcher (A.H.). Additionally, data checking/analysis involved researchers with different backgrounds, reducing the risk of bias. This is a qualitative sub-study so its findings cannot be generalised. Importantly, the main trial was an effectiveness study as opposed to an efficacy study. Effectiveness studies in this setting have demonstrated to have high external validity for the population of interest (Matsuoka et al., 2019; Patsopoulos, 2011). This sub-study included a high

proportion of patients who had completed secondary education, which may not reflect the totality of the population seen in clinical practice. Some participants were excluded based on their geographic location, which may have excluded the perspectives of people who live in more remote areas.

As part of Domains 1 and 3, patients and carers were asked to recall their experiences of breathlessness (including driving) before the intervention was administered. The possibility of recall bias needs to be considered. All participants had agreed to be part of the trial, which could have led to selection bias of people who were willing to accept morphine. Additionally, all participants completed at least three weeks on the BEAMS trial. Perceptions from this group may not reflect the views of all people with COPD and chronic breathlessness.

Findings from Domain 3 are limited by looking at self-reported effects on driving. People tend to overestimate their own driving performance (Freund et al., 2005). Most studies conducted in this field asked participants to rate their driving ability compared with the "average driver", rather than assessing aspects of their own driving (Sundström, 2011). The latter has been shown to more accurately reflect driving performance and is closer to the approach used in this sub-study (Koppel et al., 2016; Sundström, 2011). Similarly, carers' perception is not an optimal reflection of patients' driving skills, but their assessment of specific driving aspects correlates with on-the-road performance (Hemmy et al., 2016). Opioids may affect cognitive function, which may affect self-perception (Ersek et al., 2004). However, it is less likely that would be the case with small doses of morphine (Pask et al., 2020).

4.8.5 Implications for future research

This sub-study identified that both patient and carer are active participants in the vicious cycles of breathlessness proposed in the breathing-thinking-functioning model of chronic breathlessness (Spathis et al., 2017). Framing patients' and carers' interventions in accordance with the breathing-thinking-functioning model of breathlessness facilitates the identification of factors that contribute to aggravating and ameliorating each cycle. The complete identification of such factors may ultimately aid to develop an intervention program that is appropriate for patient, carer and the patient-carer unit as a whole. This sub-study also underlines the importance of conducting future dyadic studies in the setting of chronic breathlessness, which not only examine the separate perspectives of patients and carers but also how their relationship facilitates coping with breathlessness and what type of support they require.

This sub-study shows that the choice to continue regular, low-dose, sustained-release oral morphine long-term is explained by the net effect experienced by patients. The concept of "net effect" may help to understand people's choice to continue other therapies for chronic breathlessness. This sub-study shows that carers are instrumental in alleviating harms associated with regular, low-dose, sustained-release oral morphine. It is important to investigate carers' needs in this context and understand how patient and carer can better cooperate in the management of this medication. It is also imperative to understand how to facilitate coping with therapy for patients who do not have a carer.

This sub-study highlights that driving is important for people living with chronic breathlessness and their carers, and that regular, low-dose, sustained-release morphine does not impact on patients' perceived ability to drive. Based on these findings, there is a

need to objectively evaluate the impact of chronic breathlessness on patients' driving ability. Previous studies focused on objective measures of disease severity but not on the symptom itself (Prior et al., 2015). It is also important to understand if people are safe to drive with low doses of sustained-release morphine, particularly during therapy initiation and upward titration. There is a common assumption in the clinical setting that people should refrain from driving in the first hours or days after initiating any opioid. There are no published RCTs to confirm whether this should be the case with low-dose sustained-release morphine.

4.8.6 Implications for clinical practice

This sub-study identifies crucial aspects of the patients' and their carers' experience with severe chronic breathlessness associated with COPD. Recommendations for clinical practice include:

- Functional losses due to breathlessness are devastating for patients and carers and should be proactively investigated in all stages of COPD.
- Understanding the natural history of COPD and its impact on daily fluctuations in chronic breathlessness may assist in tailoring future interventions for chronic breathlessness, especially self-management strategies involving patient and carer.
- Carers are severely affected by the experience of chronic breathlessness and their specific needs ought to be assessed in clinical practice.
- Both patient and carer are essential in the effective management of chronic breathlessness. Both need to be targeted (together and separately) to optimise clinical outcomes in breathlessness associated with COPD. From a service point of

view, the carer is both a care recipient and a co-worker with health professionals (Farquhar, 2017).

- The concept of net effect can be used in clinical practice to explore factors contributing to patients' willingness to initiate/continue therapy with regular, low-dose, sustained-release oral morphine.
- Discussing the potential role of regular, low-dose, sustained-release oral morphine to reduce chronic breathlessness and highlighting the small doses required for this indication may increase patients' and carers' acceptance of this medication in clinical practice.
- For patients taking regular, low-dose, sustained-release oral morphine, carers are active agents in ameliorating the impact of harms associated with therapy. Informing and preparing carers for potential harms of regular, low-dose, sustained-release oral morphine may reduce their anxiety and empower them to better respond to such situations.
- Due to lack of evidence to support decision making, clinicians may advise people taking low-dose sustained-release morphine to stop driving, but they need to be aware that this may have severe implications for people's wellbeing and social functioning.
- Loss of independence worries both patients and carers, often with more apprehension from the carers.

4.9 Conclusions

Patients and carers share many aspects of the experience of chronic breathlessness, which seems to permeate all aspects of their lives. Carers are particularly distressed by the

patients' breathlessness, and they continuously cooperate with patients, so that they can achieve maximal function and well-being. The hope to achieve or maintain functional improvement is the great driver influencing positively the decision to take regular, low-dose, sustained-release oral morphine long-term. The level of symptom reduction, improved function, side-effects severity and carers' availability creates a net-effect driving patients' decisions to continue or discontinue the medication. Future chronic breathlessness interventions should target the patient and the carer, both together and separately to optimise outcomes for both parts.

Driving emerged as a key daily activity for some patients contributing to a sense of identity and independence and increasing the physical and social space available to patients and carers. Patients reported that breathlessness at rest may impair driving skills, while the introduction of regular, low-dose, sustained-release oral morphine seemed to have no self-reported impact on driving. Investigating this last perception objectively, especially in terms of safety, will be the subject of Chapter 5 and 6.

4.10 References

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CHAPTER 5 - A SYSTEMATIC REVIEW OF THE IMPACT OF THERAPEUTIC OPIOID AGONISTS ON DRIVING-RELATED PSYCHOMOTOR SKILLS

5.1 Chapter preface

Chapter 4 highlighted that being able to drive is essential for some people living with chronic breathlessness. As regular, low-dose, sustained-release oral morphine becomes increasingly used as the first pharmacological treatment to reduce symptomatic breathlessness in people with chronic breathlessness, it is important to understand if this medication is safe in the broader context of daily living, which includes driving. Therapeutic opioids are centrally active medications with the potential to cause sedation in some people, and in some circumstances, cognitive, psychomotor and driving impairment. However, it is not clear whether regular, low-dose, sustained-release oral morphine produces similar effects. As detailed in Chapter 4 people living with chronic breathlessness perceived that regular, low-dose, sustained-release oral morphine did not seem to impact their ability to drive. Despite this finding, it is important to investigate if participants' perceptions match their actual driving performance.

This chapter is divided into two sections. The first section is an introduction describing the skills required for driving and presenting the rationale for framing the issue of therapeutic opioids and driving using the best clinical and pharmacological knowledge. It also provides an overview of current trends in clinical practice, clinical guidelines and national and international policy related with driving while taking therapeutic opioids. The second section of this chapter, which was designed based on the evidence presented in the first section, is a systematic review to appraise the current evidence on the safety of therapeutic opioid agonists, and in particular regular, low-dose, sustained-release oral morphine, on driving-related skills of people taking this medication for symptom reduction.

5.2 Publication reference and citations

Results of this systematic review were published in 2018 in Palliative Medicine, a highly ranked, peer reviewed journal dedicated to improving knowledge and clinical practice in palliative care.

This chapter contains an edited version of the published manuscript (Appendix 12).

> Ferreira, D. H., Boland, J. W., Phillips, J. L., Lam, L., & Currow, D. C. (2018). The impact of therapeutic opioid agonists on driving-related psychomotor skills assessed by a driving simulator or an on-road driving task: a systematic review. *Palliative Medicine*, *32*(4), 786-803.

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Palliative Medicine: Impact factor: 4.956; Scimago Journal Ranking 2018: 6/122 (Anesthesiology and Pain Medicine), 157/2836 (Medicine [Miscellaneous]).

5.3 Introduction

As described in Chapter 4, driving is important for people living with chronic breathlessness because it helps them maintain a sense of identity, purpose, independence, and connection to the outside world. Importantly, the ability to drive can also be seen as a marker of health. People who are unable to drive are twice as likely to report symptoms of depression (Chihuri et al., 2016; Ragland et al., 2005; Windsor et al., 2007), and the transition to driving cessation is also associated with accelerated cognitive decline (Choi et al., 2014). In older populations, who are more likely to experience chronic breathlessness, driving cessation contributes to social isolation (Mezuk & Rebok, 2008) and is associated with decrements in several health-related domains, higher risk of being admitted into long-term care facilities, and higher mortality (Chihuri et al., 2016; Choi et al., 2014; Marottoli et al., 2000). Given this reality, it is crucial to ensure that people living with

chronic breathlessness who are still willing and fit to drive continue driving, as this may improve their quality of life and reduce undesirable health outcomes (Chihuri et al., 2016; Marottoli et al., 2000). Importantly, people who experience chronic breathlessness are at an increased risk of being asked to cease driving, not only because they are older, frailer and have other comorbidities, but also because they are more likely to be prescribed regular, low-dose, sustained-release oral morphine (Corlateanu et al., 2016; Currow et al., 2017; Smallwood et al., 2017). Thus, it is essential to understand if this medication has the potential to impair driving.

The following sections present the current evidence on therapeutic opioids and driving, with particular focus on people with chronic breathlessness who may be prescribed regular, low-dose, sustained-release oral morphine. It also provides an overview of current clinical, policy and regulatory environments.

5.3.1 Opioids and driving – one question with multiple answers

The issue of therapeutic opioids and driving has been consistently examined from a broad-scope perspective, by asking some variation of the question "Are people safe to drive while taking therapeutic opioids?" This broad-scope approach resulted in a large body of work showing conflicting results, with some studies reporting that therapeutic opioids can cause significant driving impairment and others reporting no significant problems (Mailis-Gagnon et al., 2012). Inconsistences in the literature are also reflected in current guidelines and legislation, which vary considerably, sometimes within the same country (Austroads, 2017; Chaplin, 2015; Hedlund, 2018). In reality, the issue of opioids and driving is likely too broad to be explored by a single research question, because results are expected to change according to the *population*, *intervention*, and *driving-related outcomes* included (Mailis-Gagnon et al., 2012). Thus, producing clinically relevant evidence needs to start necessarily with rigorously designed research questions, that are grounded in the best available evidence. The following sections introduce the skills and

structures involved in driving a motor vehicle, and detail the importance of carefully selecting populations, interventions, and driving outcomes in the context of evaluating driving-related skills in people with chronic breathlessness taking regular, low-dose, sustained-release oral morphine.

5.3.2 Skills and structures required for driving

At the most basic level, driving is an activity requiring sensorial, perceptual, cognitive, and psychomotor skills. As drivers "read the road", they gather *sensorial information* in the form of visual, auditory and tactile stimuli (Anstey et al., 2005), which is continuously transmitted to the brain through afferent neural pathways. As sensory information reaches brain centres, it is processed and interpreted, which is heavily mediated by cognitive processes and largely influenced by past experiences (Groeger, 2000a; Jackson et al., 2013). Cognitive skills required for driving include attention, visual-spatial processing, processing speed, executive functioning and memory (Ortoleva et al., 2012; Schultheis & Whipple, 2014). As human beings have limited capacity to focus on multiple sensorial stimuli at once, they tend to instinctively search for key cues to monitor and predict events on the road (Hole, 2018). Identifying key cues requires placing *attention* on seemingly relevant stimuli either voluntarily or involuntarily. Intense stimuli may draw drivers' attention immediately and involuntarily (e.g., bright traffic signs, unexpected noise). Conversely, people may voluntarily draw their attention to certain stimuli, according to their internal state and previous experiences on the road. For example, drivers recently involved in nose-to-tail collisions may place extra attention in ensuring safety distances from other vehicles (Rajalin & Summala, 1997). Thus, this latter process is highly dependent on *memory*. Once key cues are identified, they are used to create *perceptual schemas*, which are abstract generalisations derived from limited sensorial information (Hole, 2018; Stuss et al., 1995). As a result, perceptual schemas are largely a brain product, triggered by external and internal stimuli. *Visual-spatial processing skills are* coordinated by the parietal cortex ensuring that schematic representations

accurately depict how objects are organised in space (Groeger, 2000a). For example, while drivers may be able to perceive their car and the road, they also need to be able to perceive the car position *in relation* to the road. In addition, sensorial stimuli need to be *processed in a reasonable timeframe* to allow for continuous adaptations to a dynamic environment. For example, drivers who see a car brake in front of them need to integrate this information quickly so they can organise the appropriate motor response (i.e., braking) in time (Groeger, 2000a; Hole, 2018).

Cognitive skills, including attention, visual-spatial processing, processing speed, and memory, are recruited as needed during driving in order to respond to circumstantial demands. This continuous selection and coordination of the appropriate cognitive abilities to plan, respond and adapt to the environment is termed *executive functioning* (Diamond, 2013; Harvey, 2019). Executive functioning is the first step involved in generating the complex motor responses required for driving (Anstey et al., 2005; Jackson et al., 2013), which is a process largely overseen by the pre-frontal cortex (Bradshaw & Mattingley, 2013). Information from the pre-frontal cortex is then transmitted to the pre-motor cortex, that *selects* specific motor systems required to perform intended actions (e.g., braking) and conveys this information to more posterior brain areas involved in their *execution*. Brain structures responsible for executing the appropriate actions include the primary motor cortex, the cerebellum and the basal ganglia (Groeger, 2000b; Roland, 1984). The primary motor cortex is responsible for activating the appropriate groups of muscles to perform specific tasks; the cerebellum fine-tunes posture and movement execution, as well as the timing of such responses; and the cerebral ganglia are responsible for complex motor tasks and movement sequencing (Groeger, 2000b; Willingham, 1998). In addition to these structures, the spinal cord, peripheral motor neurons, and the musculoskeletal system are required for the dynamic aspects of movement associated with driving (Willingham, 1998). Thus, driving is an

activity involving multiple body systems that need to work in a coordinated way to ensure people can perform on the road.

Interestingly, there are other direct influences on people's driving ability. These include emotional states and previous driving experience (Lindstrom-Forneri et al., 2010). For example, anxiety can activate limbic structures, which provide input to the pre-frontal cortex and influence executive functioning and decision-making (Groeger, 2000b). Additionally, the level of driving experience influences both knowledge about safe driving practices and people's driving skills (Lindstrom-Forneri et al., 2010). For example, more experienced drivers tend to have broader perception fields, potentially resulting from knowing "what to look for" on the road in order to keep safe (Chapman et al., 2002; Robbins & Chapman, 2019; Underwood et al., 2002). Differences in the perceptual and cognitive aspects of driving translate into increased situational awareness for more experienced drivers, who can anticipate road hazards more effectively and tend to experience less crashes (Curry et al., 2015; Jackson et al., 2009). Thus, *learning* seems to be a key aspect of driving.

Understanding the fundamental aspects of driving is important to identify factors that are potentially disruptive to carry on this task. Multiple individual and contextual factors may contribute to disrupt driving, depending on the person in question. Specific factors contributing to sensorial, cognitive and psychomotor deficits in people with chronic breathlessness are detailed below.

5.3.3 Defining the population – people with chronic breathlessness

People with chronic breathlessness are usually of advanced age, have multiple health conditions, important functional limitations, and need to take multiple medications (Milton et al., 2008; Naughton et al., 2006). These factors are likely to decrease people's sensorial, cognitive and psychomotor abilities, and are important predictors of driving cessation (Dellinger et al., 2001;

Marie Dit Asse et al., 2014). As a result, this group is much more vulnerable to stop driving than younger, healthier and fitter populations traditionally participating in studies examining the effects of therapeutic opioids on driving-related skills (e.g., healthy participants). Additionally, key factors associated with chronic breathlessness have the potential to affect alertness, perception, cognition and psychomotricity (i.e., the relation between cognitive and physical processes). For example, people who experience chronic breathlessness may have underlying diseases which predispose them to develop hypoxia and/or hypercapnia. These states, particularly when acute, may decrease alertness, attention and concentration. Additionally, breathlessness may reduce people's ability to focus their attention on the road, to a larger extent than the underlying health condition itself. In this context, a cross-sectional study of 318 elderly adults suggested that uncontrolled symptoms are more closely associated with perceived driving difficulties than health conditions alone (Tuokko et al., 2007). However, it is not clear whether these perceived driving difficulties translate to poorer outcomes on the road or to the avoidance of driving. Importantly, a previous cross-sectional study comparing driving-simulator performance of people with COPD without severe hypoxemia or hypercapnia (n=17; mean PaO_2 68.9 ± 8.5 mmHg; mean $PaCO_2$ 40.3 ± 5.8 mmHg) and age-matching healthy participants (n=10) has found that participants with COPD experienced more crashes, which were not correlated with the severity of their disease measured by spirometry results, polysomnographic parameters, and blood gas analysis (Orth et al., 2008). This study was not adequately powered, and it is possible that the absence of statistically significant associations results from a small sample size. However, this study did not report any measure of breathlessness or other symptoms, which may be a key contributor for worse outcomes on the driving-simulation task (Tuokko et al., 2007). A second cross-sectional study in this setting compared driving-simulation performance of people with COPD (FEV_1 < 50% of expected value) receiving (n=8) and not receiving long-term oxygen therapy (n=8), people with

interstitial lung disease (DLCO <50%; n=8), and age- and sex-matched controls (n=8) (Prior et al., 2015). Using road positioning parameters as outcome measures (deviation from the centre of the road; number of off-road events), people with COPD receiving LTOT performed significantly worse than all other groups. Additionally, people with COPD not receiving LTOT performed significantly worse than people with ILD (deviation from the centre of the road only) and healthy participants, and results could not be explained by hypoxemia (Prior et al., 2015). Similar to Orth et al. (2007), Prior at al. (2015) did not report any measures of breathlessness or other symptoms and their potential association with driving-simulator outcomes. However, this study was adequately powered to detect differences in driving-simulator measures between groups, suggesting that differences found in driving-simulation outcomes are likely to result from unmeasured variables, such as breathlessness or other symptoms.

It is also important to consider that chronic breathlessness is frequently associated with a cluster of other symptoms, which can impact people's perceptual, cognitive and psychomotor skills. Some of the most common ones are pain and fatigue (Bausewein et al., 2010), which may potentially affect alertness and attention, or reduce mobility (Seward et al., 2021). Although there is still a small number of studies examining the role of pain in driving (Veldhuijzen et al., 2006), fatigue has consistently been shown to impact driving-related skills in driving-simulation studies (Philip et al., 2005; Philip et al., 2003). Importantly, people with chronic breathlessness may also experience anxiety associated with breathlessness, which may affect their capacity for concentration, problem-solving and decision-making (Groeger, 2000a). Indeed, anxiety has been linked to an increased likelihood of risky driving and car crashes, but it is unclear if there is a cause-and-effect relationship between these two variables (Dula et al., 2010).

Frequently, people with chronic breathlessness take multiple medications (including therapeutic opioids), some of which can directly affect cognitive and psychomotor skills, and therefore may contribute to impaired driving. Evidence from large observational studies suggests that benzodiazepines, non-benzodiazepine sedative hypnotics, antidepressants and therapeutic opioids are associated with increased risk of car crashes (Chihuri & Li, 2017; Dassanayake et al., 2011; Ravera et al., 2011; Rudisill et al., 2016). People who take these medications are also more likely to be sicker and experience more functional limitations that can impair driving. Additionally, people with chronic breathlessness may experience cognitive decline as a result of age and comorbidities frequently associated with breathlessness. In such cases, it is unclear how psychoactive medications (such as therapeutic opioids) interact to produce driving impairment. Consequently, differentiating between the effects of long-term medications and the effects of the underlying diseases is difficult.

There is evidence from randomised, placebo-controlled studies showing that different benzodiazepines can impair driving performance (Verster et al., 2004). Experimental evidence for antidepressants is more conflicting with results differing depending on the type of antidepressant used and the treatment duration (Brunnauer et al., 2006; van der Sluiszen et al., 2021). Importantly, these medications need to be accounted for in people with chronic breathlessness because they have the potential to impact cognitive and psychomotor skills, alone or in combination with therapeutic opioids.

5.3.4 Defining intervention – Therapeutic opioid types

Besides defining the population of interest, defining the type of therapeutic opioids to be included in studies evaluating driving-related skills in people with chronic breathlessness is essential. This is because therapeutic opioids are a heterogeneous group of pharmacological agents with different pharmacological properties and often widely varying doses, which are expected to produce

variable clinical effects. For example, therapeutic opioids are divided into different *classes*, according to their mechanism of action on opioid receptors. They are also available in different formulations with distinct pharmacokinetic properties, and the therapeutic doses vary according to the person and the therapeutic time-point (i.e., initiation, steady-state, or up-titration). Pharmacological differences between different therapeutic opioids must be accounted for when evaluating their impact on people's ability to drive. Therefore, it is necessary to ensure that, in each study, there is an appropriate selection of *specific therapeutic-opioid classes, formulations, dose-levels, dose-intervals and time-points* in the population of interest and their specific context.

5.3.4.1 Classes of opioids

Opioid receptors are widely distributed in the brain. Thus, therapeutic opioids target several brain structures that are involved in perception, cognition and perceptual-motor integration (van Steenbergen et al., 2017). Sedation is one of the most common side effects reported with therapeutic opioids, which may potentially result in reduced alertness and impaired driving-related skills. This mechanism is thought to be mediated by the μ- and κ-opioid receptors, which may also be responsible for cognitive and psychomotor impairment (Ricardo Buenaventura et al., 2008; Vella-Brincat & Macleod, 2007). However, different classes of therapeutic opioids bind with different affinities to opioid receptors, which may account for different clinical effects (Trescot et al., 2008). For example, full opioid agonists have the highest affinity for opioid receptors, with a predictable dose-response relationship. This class does not have a celling effect (i.e., the recommended dose is the one that produces maximum clinical effect with manageable adverse events) (Trescot et al., 2008). Other classes of opioids, such as partial agonists and mixed agonists-antagonists, have a sub-optimal action on the opioid receptors, and a celling effect that limits dose escalation (Trescot et al., 2008). Full-opioid agonists, such as regular, low-dose, sustained-release oral morphine, may have different effects on driving when compared with different classes of

opioids. Similarly, differences between therapeutic opioid agonists should be considered from a pharmacological and clinical point of view. Methadone is an opioid agonist, with concomitant action as an N-methyl-D aspartate (NMDA) receptor antagonist (Brown et al., 2004). NMDA receptors play an important role in memory dysfunction and cognition (Newcomer et al., 2000), which means any effect observed on driving performance may result from this mechanism of action rather than from its effect on opioid receptors. These mechanisms are important differences to consider when evaluating driving performance in any setting.

5.3.4.2 Routes of administration and formulations

As detailed in Chapter 2, therapeutic opioids are preferably administered orally, because it is easy and convenient for people living in the community. Oral opioids are available in two formulations: immediate release and controlled release (Argoff & Silvershein, 2009). Immediately-release formulations are most often used to treat acute or acute-on-chronic pain. They have a relatively quick onset of action, with higher plasma concentration peaks (C_{max}), shorter times with maximum concentrations (T_{max}), and more accentuated declines of plasma concentration over time. As a result, they have a shorter duration of action (usually 3 to 6 hours). Controlled-release formulations are recommended as first-line options for long-term therapy, due to their longer duration of action, which requires less frequent administrations and is more convenient for patients (Hariharan et al., 2007; Nicholson, 2003). Their pharmacokinetic profiles show less fluctuation in plasma concentrations, with lower C_{max}, longer T_{max} and higher minimum plasma concentrations (C_{min}) (Gourlay et al., 1997). Therefore, controlled-release formulations have longer duration of action (usually 8 to 24 hours). In the context of driving, lower C_{max} may be particularly important, because it can potentially be associated with fewer harms including sedation, difficulty in concentrating and deficits in cognitive and psychomotor performance (Gourlay, 1998). Transdermal formulations are somewhat similar to oral controlled-release formulations because

they diffuse slowly into the bloodstream, enabling steady plasma concentrations over prolonged periods (Portenoy et al., 1993). Conversely, other formulations (e.g., intravenous, intranasal, buccal, sublingual, rectal) exhibit variable pharmacokinetic characteristics and are not recommended as first-line, regular therapy. Distinguishing between long-acting (i.e., controlled-release and transdermal) and short-acting (i.e., immediate-release oral) therapeutic-opioid formulations is therefore essential to evaluate the potential effects on people's ability to drive.

5.3.4.3 Opioid-agonist dose

In the context of analgesia, therapeutic opioid agonists exhibit a wide therapeutic window in healthy individuals due to genetic and acquired influences (Dumas & Pollack, 2008; Fine, 2007). As a result, there is no pre-defined therapeutic doses for chronic pain. The individualised dose is usually achieved by up titrating the dose until achieving analgesia or triggering unmanageable harms. Importantly, while pharmacokinetic characteristics contribute to inter-individual differences in response to therapeutic opioid agonists, pharmacodynamic adaptations play a crucial role in changes in response longitudinally (Dumas & Pollack, 2008). For example, the μ-opioid receptor, the most important mediator for analgesia and sedation has a highly dynamic pattern of expression (Trescot et al., 2008). This receptor is over-expressed in peripheral inflammatory states (Puehler et al., 2004), frequently associated with chronic pain and chronic breathlessness but under-expressed in other situations like chronic opioid exposure (Al-Hasani & Bruchas, 2011). As such, some specific situations, rather than the therapeutic opioid-agonist dose alone, need to be considered in the context of driving. These include:

- *Dose initiation*. Single-dose studies show that side effects of therapeutic opioid agonists are accentuated when therapy is initiated (Zacny et al., 1992; Zacny & Lichtor, 2008). As a result, most people rapidly develop tolerance to opioid-induced sedation (Benyamin et al., 2008), allowing safe driving (Fishbain et al., 2003).

- *Upwards dose titration*. People taking therapeutic doses of opioid agonists may experience increased sedation and cognitive and psychomotor impairment following an increase in their regular dose (Bruera et al., 1989).
- *High steady state*. Increments in therapeutic opioid-agonists dose produce increasing analgesia up to a certain threshold, which is variable between individuals. Increments beyond this point cause the emergence of harms with no additional benefit. In such cases, sedation, cognitive and psychomotor impairment may persist even with stable doses of therapeutic opioid agonists (Fallon & Cherny, 2015).

In relation to potential driving impairment, people with chronic breathlessness taking regular, low-dose, sustained-release oral morphine for the reduction of breathlessness constitute a particular use case. This is because it is not clear whether sustained-release oral morphine formulations in low-doses (up to 30 mg a day) (Currow et al., 2011) cause perceptual, cognitive or psychomotor deficits with the potential to impair driving, including during therapy initiation and upward dose titration. These need to be further investigated in prospective studies.

5.3.5 Defining outcomes - measures of driving performance

Currently, the best evaluation of driving skills is an on-the-road driving test, which consists of a 100-km drive on a public highway, under regular traffic conditions (Verster & Ramaekers, 2009). However, this test is time-consuming, expensive, and difficult to apply in clinical or research settings. As a result, there have been many attempts to implement alternative outcome measures that could accurately predict on-road outcomes (Verster & Roth, 2012). Based on the skills required for driving, batteries of cognitive and psychomotor tests are frequently used as quick and easy predictors of on-road driving performance (Weaver & Bédard, 2012). Importantly, despite evaluating skills required for driving, these tests or combination of tests are still poor predictors of performance on the road (Helland et al., 2016; Jongen et al., 2015; Verster & Roth, 2012). In fact, a

battery of five psychometric tests has been shown to have a total predictive value of only 33.4% to the on-the-road driving test (Verster & Roth, 2012). Because driving is a complex and dynamic task resulting from the interplay of multiple individual and environmental factors, drivers may potentially compensate for specific cognitive and sensorial deficits by adjusting their approach to driving (Lindstrom-Forneri et al., 2010). As a result, worse performance in selected cognitive and psychomotor tests may underestimate people's ability to drive safely. Importantly, driving simulators may be better alternatives to cognitive and psychomotor tests because, rather than examining isolated cognitive and psychomotor skills, they reproduce key aspects of driving requiring complex cognitive processes and perceptual-motor integration (Jackson et al., 2013; Walter et al., 2001). They have the advantage of allowing assessment of driving-related skills in a safer and more controlled environment compared to the on-the-road driving task (Gillberg et al., 1996). Additionally, there is increasing evidence that driving simulators can predict driving outcomes on the road (Galski et al., 1992; Helland et al., 2013) The predictive value of driving simulators seems to be better than what is observed for combinations of psychometric tests. For example, a study evaluating the predictive validity of a driving simulator following traumatic brain injury reported a predictive value of 82% with on-the-road performance at follow up (Lew et al., 2005). These characteristics make driving simulators particularly attractive options for evaluating driving-related skills, particularly in prospective studies requiring sequential driving assessments, which focus on detecting changes from baseline. For example, driving simulators are commonly used in studies with a pre-test and post-test design to evaluate the effect of drugs (alcohol or illicit drugs) or sleep disorders' detrimental effects on driving (Desai et al., 2007; Jongen et al., 2015; Logan & Kay, 2011; Vakulin et al., 2009).

Importantly, there are different types of simulators, which can measure specific driving-related outcomes. Different types of simulators, simulator tasks and driving outcomes may be selected

according to specific research questions (Campos et al., 2017). For example, therapeutic opioid agonists, including regular, low-dose, sustained-release morphine, are more likely to affect driving performance by causing sedation, which can affect attention and concentration. Thus, selecting a simulator designed to evaluate these deficits may be appropriate.

In general, output measures from driving simulators include kinematic data such as measures of lateral (e.g., deviation of lateral position) and longitudinal control (e.g., speed variability), as well as summary statistics such as reaction time (e.g., brake response time) and number of crashes (Caird & Horrey, 2011; Campos et al., 2017). The first ones provide more detailed information about the driving task and are usually more sensitive to impairment than summary measures (Campos et al., 2017). Importantly these measures complement each other providing a fuller picture of the aspects involved in driving.

5.3.6 Laws and regulations, guidelines, and clinical practice

The lack of robust evidence surrounding the issue of therapeutic opioids and driving is reflected in laws and regulations, clinical guidelines, and clinical practice, with major consequences for the life of millions of people worldwide. These aspects are reviewed below.

5.3.6.1 Legal and regulatory aspects

Laws and regulations for driving while taking therapeutic opioids differ depending on the country, and sometimes the state in question (Table 5.1). Most countries in the world have a national drug-driving law in place, which may or may not include therapeutic opioids (WHO, 2018). In countries where there is legislation about driving while taking therapeutic opioids, there is usually an *impairment approach*, in which people are not allowed to drive if they show any evidence of "impairment" (European Monitoring Centre for Drugs and Drug Addiction [EMCDDA], 2021; National Conference of State Legislatures [NCSL], 2014). This is the case for Australia and New

Zealand, where people who take therapeutic opioids are still able to drive, unless they are cognitively or physically impaired (WHO, 2016). Importantly, regulatory bodies encourage people taking therapeutic opioids to consult with their clinicians before operating a motor vehicle, to make sure they are safe to drive (Transport for NSW, 2021; UK Government, 2021). One of the challenges posed by these laws is that the concept of 'impairment' is usually not clearly defined, and there is no universal tool to measure it. Importantly, this legal void may negatively impact people taking therapeutic opioids, who are able to drive safely. While holding proof of opioid prescription for medical reasons can be enough to avoid road penalties in routine police checkpoints, car-crash involvement may raise additional problems for the driver taking therapeutic opioids. In such cases, it becomes challenging to prove there is no evidence of impairment, even when the driver was not responsible for the accident, or other hazards contributed for the crash (e.g., lack of attention, insufficient sleep, external factors). Identifying the cause of road crashes is important because the penalties will vary according to the driver's circumstances, and most insurance companies will not cover damages if a person is deemed to be impaired by drugs (EMCDDA, 2021; UK Government, 2021).

In addition to the standard impairment approach, sixteen states in the United States of America and countries such as Portugal and Spain adopted a *zero-tolerance* approach (EMCDDA, 2021; Hedlund, 2018), in which any driver with detectable opioid levels in their blood will be penalised, irrespective of its source, dose, purpose, or clinical effects. This approach does not distinguish therapeutic opioids from abuse substances, which negates the right to drive for people who may not be at risk of hazardous driving and may thus contribute to worsen people's quality of life and health-related outcomes, as described above.

An increasing number of European countries are adopting regulations based on morphine blood concentrations, but the legal cut-off is variable (Vindenes et al., 2012; Wolff et al., 2013). Variations in the legal limit depend on the criteria used to establish the cut-off. For example, in countries like France and the Netherlands, the cut-off was set around the laboratory limit of detection (≤ 20 ug/L) (Wolff et al., 2018; Wolff et al., 2013). However, the United Kingdom legal limit was set to distinguish drivers taking therapeutic opioids (who usually have blood concentrations below 80 ug/L), from those taking illicit drugs (who usually have higher blood concentrations) (Wolff et al., 2013). Such differences in the criteria utilized to establish the legal limit reflect the lack of evidence supporting the use of opioid blood concentrations to predict cognitive and psychomotor impairment (Jones et al., 2008).

Table 5.1 - International legislative approaches to driving while taking therapeutic opioids and maximum morphine plasma concentrations allowed.

World Region	Country	Type of Legislation	Maximum morphine plasma concentration allowed (ug/L)
Europe (EMCDDA, 2021; Marillier & Verstraete, 2019; Vindenes et al., 2012)	Belgium	Based on blood concentrations	10
	Croatia	Zero-tolerance	-
	Denmark	Based on blood concentrations	10
	Germany	Based on blood concentrations	10
	Finland	DUID (impairment)	-
	France	Based on blood concentrations	10
	Latvia	DUID (impairment)	-
	Netherlands	Based on blood concentrations	20
	Norway	Based on blood concentrations	9
	Poland	Based on blood concentrations	20
	Portugal	Zero-tolerance	-
	Spain	Zero-tolerance	-
	Sweden	DUID (impairment)	-
	UK (England and Wales)	Based on blood concentrations	80
North America (Canadian Centre on Substance Use and Addiction, 2019; Hedlund, 2018; Legislative Counsel Bureau, 2018)	Canada	Impairment	-
	USA[a]	Impairment	-
	USA[b]	Zero-Tolerance	-
	USA[c]	Based on blood concentrations	50 (Nevada) Not defined (Ohio)[d]
Oceania (WHO, 2016)	Australia	DUID (impairment)	-
	New Zealand	DUID (impairment)	-

UK = United Kingdom; USA = United States of America; DUID = Driving under the influence of drugs

[a] All states

[b] Arizona, Delaware, Georgia, Illinois, Indiana, Iowa, Kentucky, Michigan, Minnesota, North Carolina, Oklahoma, Pennsylvania, Rhode Island, South Dakota, Utah, Wisconsin

[c] Nevada and Ohio

[b] There is no legal morphine plasma concentration limit for morphine in Ohio, but they are enforced for other opioids.

The heterogeneity of legislative approaches to the issue of driving while taking therapeutic opioids results, at least in part, from the conflicting evidence available and the assumption that such evidence is generalisable for all people who drive, independent of the type of therapeutic opioids, formulations, and doses they taken (Boland et al., 2018; Mailis-Gagnon et al., 2012). Moving forward, it is extremely important to take these factors into account, both while examining previous studies, and designing new ones, so that robust legislation can be put in place to ensure road safety without restricting drivers needlessly.

5.3.6.2 Clinical guidelines

The lack of robust and consistent evidence clarifying the safety of therapeutic opioids (including regular, low-dose, sustained-release oral morphine) and driving, also translates into variations between the few existing clinical guidelines (Austroads, 2017; Drug & Alcohol Services South Australia, 2008; Hegmann et al., 2014). The most recent Australian guidelines, released by national driving regulatory agencies, state that people taking stable therapeutic opioids for chronic pain may be able to drive safely, if doses "have been stabilised over some weeks and they are not abusing other impairing drugs" (Austroads, 2017). Interestingly, there is a specific comment on short-acting formulations, suggesting they may cause higher fluctuations in blood concentrations compared with long-acting formulations, and that they require specialised assessment. This represents an important update in relation to the previous published version, which did not consider any pharmacological differences between therapeutic opioid formulations (Austroads, 2014). These guidelines also suggest that changes in opioid dose (i.e., initiation or up-titration) may cause sedation and affect driving, an effect that tends to subside quickly. However, no distinction is made between different therapeutic opioids, formulations, and doses, suggesting that even the introduction of small doses, and small increments in dose, may be perceived to represent a hazard for driving in this context (Austroads, 2017). A similar approach is suggested by the 2017 Canadian Guideline for Opioids for Chronic Non-Cancer Pain, which state that people should be advised to stop driving when initiating or up titrating any opioid (Busse et al., 2017). It is not clear whether low-dose, sustained-release oral morphine affects driving ability, even during therapy initiation and up-titration, as most prospective studies examining the effects of opioids on driving did not specifically evaluate this formulation and dose (Mailis-Gagnon et al., 2012).

Other clinical guidelines within Australia suggest different approaches, which may result both from the inconsistencies found in the literature regarding opioid safety, and the evidence available at

the time they were published. *Opioid prescription in Chronic Pain Conditions* is a set of guidelines published to aid decision-making of South Australian general practitioners (Drug & Alcohol Services South Australia, 2008). Similar to the Australian national guidelines, this document suggests that people taking stable doses of opioids may be safe to drive. One important difference is a specific recommendation suggesting that people taking morphine equivalent daily doses of 200 mg or higher should be referred for a formal driving assessment (Drug & Alcohol Services South Australia, 2008). Importantly, it is unclear how the cut-off of 200 mg of morphine equivalent daily doses was achieved and the type of driving assessment proposed. In accordance with the previous guideline, people who are initiating or up-titrating their opioid doses are advised not to drive, irrespective of the type of opioid, formulation, and dose taken. Interestingly, neither one of these guidelines provides a specific timeframe in which people should avoid driving after introducing or changing their opioid dose (Drug & Alcohol Services South Australia, 2008). Across the literature, there is considerable variation in proposed timeframes for not driving, which vary from a few hours to several weeks after a new opioid dose is introduced (Australian Drug Foundation, 2010; Parekh, 2019).

Clinical guidelines for Hong Kong and those proposed by the American Pain Society and the American Academy of Pain Medicine have a less conservative approach suggesting that studies to date failed to demonstrate that opioids can impair driving (Cheung et al., 2016), but that people should be informed about factors, related to opioid medication, that produce driving impairment (Cheung et al., 2016; Chou et al., 2009). These include changes in dose, sleep disturbances, intense pain, and concomitant use of alcohol or other psychoactive substances. According to these documents, people should only be advised not to drive if they show signs of cognitive or psychomotor impairment, including somnolence, poor coordination, or concentration impairment (Cheung et al., 2016; Chou et al., 2009). These recommendations are substantially different from

the Australian guidelines, relying on symptoms and clinical signs of impairment to direct people to the appropriate course of action. Importantly, people's individual experiences with regular, low-dose, sustained-release oral morphine may aid the decision-making process, as people taking this medication are able to report when they feel drowsy or unable to concentrate (Currow et al., 2020).

Guidelines from the American College of Occupational and Environmental Medicine propose a more conservative approach, suggesting that all people taking opioids, acutely or chronically, should be advised to cease driving for the whole duration of opioid therapy, independent of the context (i.e., introduction, up-titration, or stable therapy), type of opioid, formulation, or dose taken (Hegmann et al., 2014). These recommendations are largely based on observational studies which rely on a wide range of opioid prescriptions to predict the risk of crashes. Such studies do not account for different contexts (e.g., they do not distinguish opioid maintenance treatment for addiction from symptom management), populations and opioid type. In most cases it is unclear if people were taking opioids as prescribed. Additionally, for observational studies, it is impossible to establish a causal relationship between opioid prescription and the risk of a crash, as most people who require opioids may also be sicker and experience more risk factors for hazardous driving (e.g., comorbidities, other medication).

5.3.6.3 Clinicians providing advice about driving

Prescription of therapeutic opioids is still challenging for many clinicians, mostly due to fear of life-threatening side effects such as respiratory depression (Hadjiphilippou et al., 2014; Rocker et al., 2012). Clinicians also report feeling unprepared to deal with sedation, which may occur as opioids are introduced or up titrated (Janssen et al., 2015). These aspects may lead them to be overly cautious when providing advice about driving. A recent survey of palliative-care specialists in Australia and New Zealand has shown that the majority of these clinicians (64%) would advise

patients to temporarily refrain from driving or stop driving completely (12%) after initiating short-acting oral morphine (5 mg every 4 hours *PRN*) (Weir et al., 2017). From those who would advise temporary driving cessation, most would advise patients to stop driving for a period of four hours (36%), but responses were heterogeneous varying from “up to 3 hours” to “more than six hours”. Respondents were also asked what advice they would provide if they were to replace therapy with immediate-release oral morphine 5mg every 4 hours, with an equivalent daily dose of sustained-release oral morphine (15 mg every 12 hours). Only 10% of the respondents would advise patients to continue driving, with the majority reporting they would advise patients to stop driving for 1-2 weeks (43%) (Weir et al., 2017). Given that most respondents were aware and familiar with current guidelines, it is likely that variability in responses results from unclear guidance provided by these documents in what concerns measures after therapeutic opioid prescription (Weir et al., 2017). From a pharmacological point of view, regular, sustained-release oral morphine leads to more stable blood concentrations compared with the immediate-release formulation (Boland et al., 2018). Such differences need to be considered by future guidelines.

5.4 Context for this systematic review

This systematic review differs from previous published work by clearly defining the population of interest, differentiating and grouping the type of therapeutic opioids, routes of administration, formulations, and doses based on current pharmacological principles. The study also includes driving outcomes that could be more closely translated into people’s driving performances in real-world settings. Initially, this work aimed to include studies targeting people with chronic breathlessness who were taking regular, low-dose, sustained-release oral morphine. After a preliminary literature search, it became clear that most studies evaluating driving-related skills in people taking therapeutic opioids were conducted in people with chronic pain, who tend to use higher doses of opioids (>30 mg/day of oral morphine equivalent). Given the similarities between

populations who experience chronic pain (defined as “ongoing or recurrent pain, lasting beyond the usual course of acute illness or injury, or more than 3–6 months, and which adversely affects the individual’s well-being”) (Loeser & Treede, 2008), and those who experience chronic breathlessness, and the overlapping mechanisms of both symptoms, this systematic review was designed to include both populations. In this context, a broad research question was developed, with progressively narrower sub-questions of interest.

5.5 Aim

To appraise the current evidence on the impact of regular therapeutic opioid agonists for long-term symptom control on driving-related psychomotor skills as assessed by a driving simulator or an on-road driving task.

5.6 Objectives

To investigate if people taking *therapeutic*, *regular* opioid agonists for long-term symptom control (chronic pain, chronic breathlessness) are able to drive safely.

To define if any of these data specifically relate to either:

a) Prescribed *sustained-release* or *transdermal* formulations;
b) Prescribed *low doses* (≤30mg/day oral morphine equivalent dose) *or if there is a dose-response relationship*; or
c) *Both a) and b)*.

5.7 Methods

Design: Systematic Review.

This systematic review is reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement (Moher et al., 2009).

5.7.1 Protocol and Registration

This systematic review protocol was registered in PROSPERO – international prospective register of systematic reviews (Registration Number CRD42017055909; available in https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017055909).

5.7.2 Eligibility Criteria

English language, peer-reviewed studies were included if they reported empirical data on driving-simulation, "real-world" driving, or driving outcomes in adults taking therapeutic opioid agonists for long term symptom control (i.e., chronic pain and/or chronic breathlessness). Studies using opioid-agonists with a strong action on NMDA receptors (e.g., methadone) were excluded. By acting both on the opioid receptors and NMDA receptors, these medications have the potential to cause cognitive side effects by differing mechanisms. As such it would be difficult to generalise results to other opioid agonists. Anaesthesia and surgical settings were excluded because of single dose or short-term exposure, and the likelihood of exposure to other centrally acting medications, surgical interventions, and invasive procedures that all could influence the ability to drive (Dijkstra et al., 1999). Studies conducted with populations with severe renal or hepatic impairment were also excluded because opioid agonists are, to different extents, metabolised/excreted by these organs (Smith, 2009). The participant / intervention / control / outcome / setting (PICOS) for this systematic review is in Table 5.2.

Table 5.2 - Population, intervention, comparison, outcomes, and settings (PICOS) used in the systematic review.

P (Population)	Adults (≥ 18 years) requiring opioid agonists for pain or breathlessness control
I (Intervention)	**1.** Therapeutic regular opioid agonists for chronic pain or chronic breathlessness **2.** Sub-group examination of: a. Sustained-release or transdermal formulations b. Low doses (≤30mg/day oral morphine equivalent dose) or dose-response relationship c. Both a and b
C (Comparison)	Placebo / No intervention / Control group
O (Outcome)	Impairment of driving-related psychomotor skills as assessed by: Driving simulator On-the road driving tasks Driving outcomes (e.g., crashes)
S (Setting)	Hospital, community, ambulatory

5.7.3 Information Sources and Search Strategy

The following databases were systematically searched up until 15 January 2017: Medline (Ovid, 1946-2016), PubMed (Non-Medline subset only which includes citations not yet or never-to-be indexed for Medline), Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effect), EMBASE (Ovid, 1974-2016), Scopus and the Cumulated Index to Nursing and Allied Health Literature: CINAHL (ESBCOhost).

The final search strategy included two sets of terms. Set 1 was designed to include all literature relating to opioids, particularly the most common opioid agonists used in clinical practice. Set 2 was created to capture all terms related to driving-related psychomotor skills which included driving-simulation, driving tasks and driving outcomes (e.g., crashes). Within each set, terms were combined using the Boolean Operator 'OR'. Both sets were then combined using the Boolean Operator 'AND'. Pain and breathlessness were not included as a separate set of terms, but they were hand searched at a later stage from the list of retrieved articles.

Before running the final search strategy, a preliminary search of Medline was conducted to identify suitable Medical Subject Headings (MeSH terms) and useful TextWords included in titles and abstracts. A detailed search was then constructed in Medline (Ovid; Table 5.3) and translated for each database of interest (Appendix 13). Consultation with a specialist research librarian was undertaken to ensure that the search strategy was appropriate.

Table 5.3 - MEDLINE search strategy: conducted in December 2016

#	Searches	
1	analgesics, opioid/ or codeine/ or fentanyl/ or hydromorphone/ or morphine/ or oxycodone/	Set 1
2	(opioid* or codeine or fentanyl or hydromorphone or morphine or oxycodone).tw.	
3	or/1-2	
4	automobile driving/ or driving under the influence/ or Accidents, Traffic/	Set 2
5	((abilit* or competen* or skill* or task* or simulation* or aptitude* or perform* or capacit* or capab* or function* or risk* or safe* or unsafe or impair* or danger* or influence or fit* or unfit or impact or advice or cessation or restrict*) adj4 driv*).tw.	
6	(automobile* or car or cars or road or traffic or accident* or crash*).tw.	
7	reaction time/	
8	(react* adj2 time*).tw.	
9	or/4-8	
10	3 and 9	
11	Animals/ not (Human/ and Animals/)	
12	(Letter or comment or editorial or news or case reports).pt.	
13	10 not (11 or 12)	
14	limit 13 to English language	

Grey literature was searched using Google, Google Scholar, the Australian New Zealand Clinical Trials Registry (ANZCTR), the ClinicalTrials.gov database and the ProQuest Dissertations & Theses Database. Additionally, the reference lists of relevant articles were hand searched.

5.7.4 Study Selection

Relevant articles were managed using Endnote X7 (Thomson Reuters, Philadelphia, PA, USA). First, duplicates were removed. Subsequently, articles that did not match the eligibility criteria were excluded. Two authors (DF, JP) independently reviewed all titles and abstracts in order to assess

their relevance for inclusion. Full-text papers were retrieved for all those fulfilling the inclusion criteria or anywhere there was equivocation using title and abstract alone. Full texts of all remaining relevant studies were then assessed. Specific reasons were provided for any articles excluded at this stage. Disagreement at all stages was resolved by discussion or recourse to a third author (DC).

5.7.5 Data Extraction Process

Data from potentially relevant studies were extracted by two authors (DF, JB). A Data Extraction Form was developed to collect information from potentially relevant studies. Fields included year of publication, journal, title, first author, country, settings, study design, time period, number of subjects, % men, mean age, diagnoses, type of opioid agonist, dose, acute or chronic administration (<⩾ 7 days), route, formulation, type of driving test performed and outcomes. The data collection forms were complied with randomised controlled trials, observational studies, systematic reviews and meta-analyses.

5.7.6 Quality and risk of bias appraisal

Critical appraisal of the included studies was conducted using the quality assessment tools from the National Institutes of Health (National Institutes of Health, n.d.). The NIH tools can accommodate a range of study designs. All included studies were independently rated by two authors (DF, JB) for quality and risk of bias. Incongruences in rating were discussed in order to achieve a consensus.

5.7.7 Synthesis of results

Given the variety of study designs, a narrative synthesis was conducted based on the methods described by Popay et al. (Popay et al., 2006). This included the development of a theoretical model before initiating the synthesis, which informed the population, interventions, outcomes, and settings to include; conducting a preliminary results synthesis using tabulation; exploring

relationships within and between selected studies, including variability in population, design, outcomes, and settings; and critically reflecting on the results' robustness by comparing and contrasting with existent literature and considering their generalisability for other populations and settings.

5.8 Results

5.8.1 Study Selection

The initial systematic search retrieved a total of 6553 articles: MEDLINE (n=1179), PubMed (non-MEDLINE content only; n=221), Embase (n=2197), CINAHL (n=64), Cochrane Database of Systematic Reviews (n=3), Cochrane Central Register of Controlled Trials (n=234), Database of Abstracts of Reviews of Effect (n=5) and Scopus (n=2650). Three more articles were found by hand search. A total of 3809 articles remained after removal of duplicates. After screening title and abstract, 29 papers were full text assessed, of which 26 were excluded, leaving three articles meeting inclusion criteria (Figure 5.1).

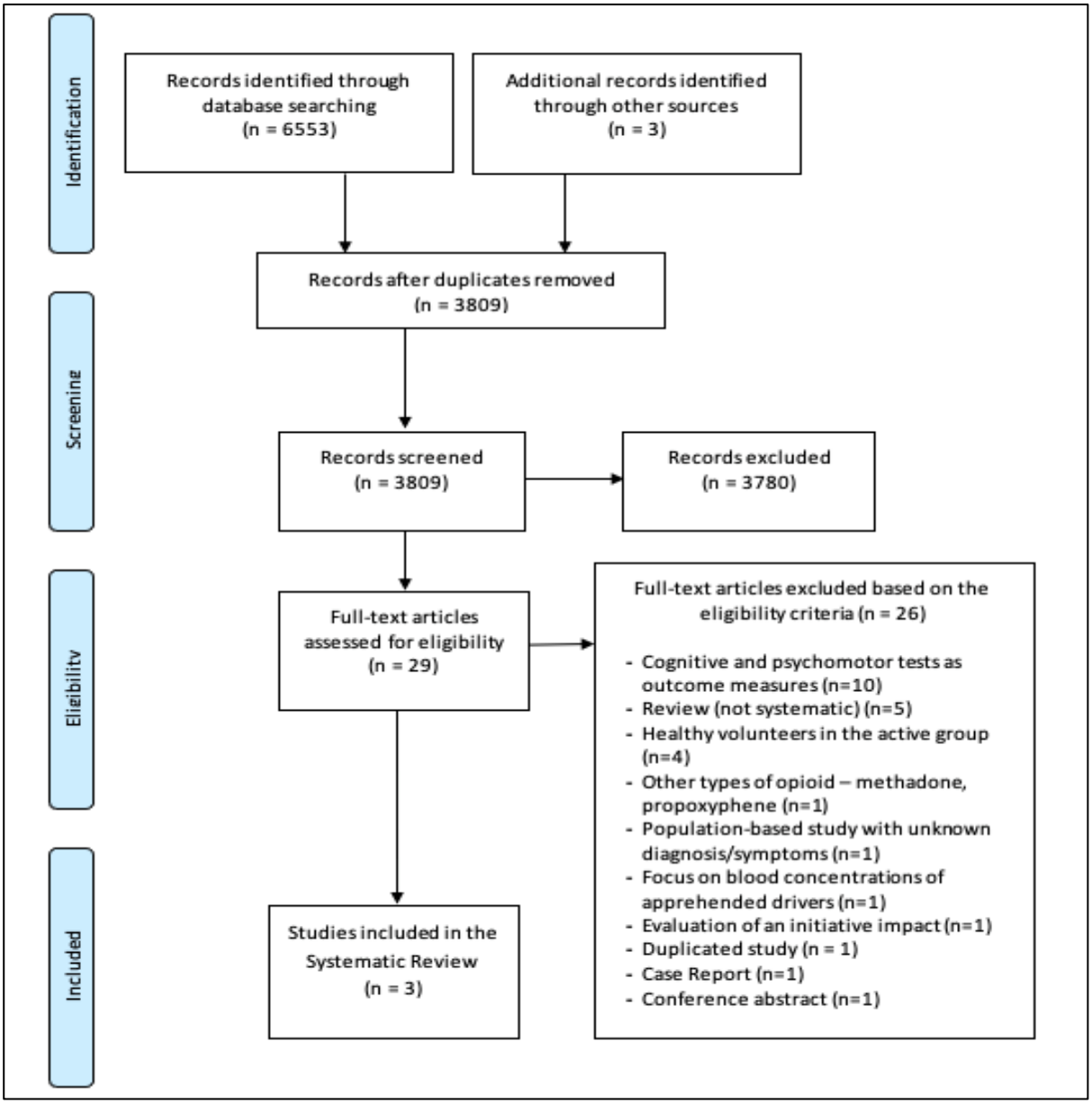

Figure 5.1 - PRISMA diagram with the studies included in this systematic review

5.8.2 Study Characteristics, Quality and Bias

Of the three included studies, one was a cross-sectional study (Nilsen et al., 2011), one had a pre- and post-test design (Menefee et al., 2004) and one was a case-control study (Galski et al., 2000) (Table 5.4). All were published between 2000 and 2011. Two studies were conducted in the United States (Galski et al., 2000; Menefee et al., 2004), and one in Norway (Nilsen et al., 2011). The quality of studies was 'good' or 'fair' according to the NIH quality assessment tools (Table 5.5). The heterogeneity in methodology and reporting made a meta-analysis impossible.

5.8.3 Population and Setting

All studies included participants with chronic non-malignant pain followed in outpatient pain clinics. The range of the mean age in the opioid group (n = 59) was 43 – 48 years (Galski et al., 2000; Menefee et al., 2004; Nilsen et al., 2011). For two of the studies, diagnosis in the opioid group (n = 43) included musculoskeletal conditions (62.8%), neuropathic pain (32.6%), abdominal pain (2.3%), and chronic headache (2.3%) (Menefee et al., 2004; Nilsen et al., 2011). The third study reported additional diagnoses of fibromyalgia and reflex sympathetic dystrophy, but distribution of participants in each diagnostic group was not reported (Galski et al., 2000). Mean pain intensity was reported in all studies using the NRS or VAS scores. Menefee et al. reported a statistically and clinically significant reduction in mean pain scores between the baseline visit and the stabilisation visit (mean VAS score at baseline = 67; mean VAS score at the stabilisation visit = 53; p = 0.02). Nilsen et al. reported no significant differences between the chronic pain group taking opioids (mean NRS score = 5.8), and the first control group of participants with chronic pain not taking opioids (mean NRS score = 5.5; p = non-significant) over the week prior to the assessment. Additionally, pain scores did not differ significantly between groups at the time of the first (NRS scores = 4.8 and 4.6, respectively; p = non-significant) and second driving assessments (NRS scores = 5.1 and 5.7, respectively; p = non-significant). However, a significant difference in the average pain score over the preceding week was reported between the chronic pain group and the second control group (healthy volunteers; NRS scores = 5.6 and 0.4, respectively; $p < 0.05$). Galski et al. reported no significant differences in pain scores between the active (mean NRS score = 3.48 ± 2.4) and the control groups (mean NRS score = 3.66 ± 2.5) at the time of the driving assessments.

5.8.4 Type of opioids, doses, formulations and routes reported

All studies included only participants on regular therapeutic opioid agonists. One study included only short-acting opioids (Nilsen et al., 2011), and two studies included only sustained-release formulations as regular therapy (Galski et al., 2000; Menefee et al., 2004). Nilsen et al. included participants taking regular oral codeine. Menefee et al. included participants taking transdermal fentanyl only, with a maximum of three *pro re nata* (PRN) tablets of combined acetaminophen 325 mg with oxycodone 5 mg/day during the titration period. Galski et al. included participants taking long-acting opioids which comprised controlled-release oral morphine and transdermal fentanyl. PRN opioids, including hydromorphone and oxycodone, were allowed. Doses utilised in this study were not reported. Fentanyl doses ranged from 25 to 75 µg/hour in the Menefee et al.'s study with a median dose of 50 ug/hour (oral morphine daily equivalent doses: 60–180 mg, median 120 mg) (Eastern Metro Palliative Care Consortium, 2016). Codeine doses ranged from 120 to 270 mg/day in the study from Nilsen et al. with a median dose of 180 mg (oral morphine daily equivalent doses: 12–27 mg, median 18 mg) (Eastern Metro Palliative Care Consortium, 2016).

5.8.5 Driving Outcomes

Overall, studies found no significant changes in driving-related outcomes with opioid agonists (Table 5.6). Nilsen et al. tested the participants twice on the same day coinciding with peak and trough codeine blood concentrations, respectively. Reaction times, steering precision and missed signs were analysed in rural and urban driving settings. No significant differences were found between participants with chronic pain taking codeine (n = 20) and participants with chronic pain free of opioids (n = 20) in any of the study measures ($p > 0.5$; confidence interval [CI] 95%). However, the chronic pain group (n = 40) performed significantly worse compared with healthy controls in all study parameters ($p < 0.036$). Menefee et al. subjected participants to four different driving tasks where simple braking reaction time, cue reaction time, destination driving, and

evasive action were evaluated. For the first three tasks, the average of errors in braking, steering, speed and signalling were calculated to achieve a final score. Evasive action was measured using the average time spent to take appropriate action in three different driving situations. This study found no significant differences in driving simulator performance parameters before and after fentanyl therapy ($p \geqslant 0.2$). Galski et al. found no significant differences in driving parameters (number of errors in braking, steering, accelerating, speed and signalling) between participants with chronic pain taking opioid agonists and cerebrally compromised participants assessed as fit to drive after an on-the-road driving test.

Table 5.4 – Summary of studies characteristics

Study	N Subjects	N (% men)	Population	Mean Age (years)	Design	Comparison	Time Period	Formulation	Type of Assessment	Outcome	Statistical Power
Nilsen, 2011	60 (20 per group)	50%	Participants with chronic non-malignant pain	43.2 codeine group; no significant differences between groups	Cross-sectional	Oral Codeine (12mg-27mg OME/day (mean 18mg OME/day) vs Matching Chronic pain participants not using codeine vs Matching Healthy Volunteers	NA	Immediate Release	Driving-Simulator	**Primary outcome:** Reaction time (seconds) to traffic-sign symbols and missed reactions. **Secondary outcome:** steering precision (pixels).	Twenty subjects per group provide over 80% power for detecting a difference with $p < 0.05$
Menefee, 2004	23	26%	Participants with non-malignant pain	47	Pre- and Post-test design	Fentanyl TD (60-180 mg OME/day, median 120mg OME/day); Participants tested before and after exposure	before initiating drug; vs after 1 month of stable dose	Slow or sustained-release	Driving-simulator	Average of errors in the following tasks: Simple braking reaction time; Cue reaction time; Destination Driving. Average of time spent to take appropriate action in 3 different driving scenarios (evasive action).	No reference
Galski, 2000	16 opioid group; 327 historical control group	NI	Participants with non-malignant pain	48.38	Case-control study	Opioid agonist in stable doses; vs Cerebral compromised participants previously cleared to drive	NA	Slow or sustained-release	Driving-simulator	Number of errors in braking, steering, accelerating, speed and signalling.	No reference

*OME: Oral morphine equivalent. NA=Not applicable; NI=no information.

Table 5.5 - NIH Quality Assessment Tools (Critical Appraisal)

	Study		
Questions	**Nilsen et al., 2011**	**Menefee et al., 2004**	**Galski et al., 2000**
	NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies	NIH Quality Assessment Tool for Before-After (Pre-Post) Studies with No Control Group	NIH Quality Assessment of Case-Control Studies
1. Research question / objectives clearly stated	Yes	Yes	Yes
2. Study population clearly identified	Yes	Yes	Yes
3. Similarity between sample and population of interest	Yes	Yes	No
4. Application of the eligibility criteria	Yes	Yes	Yes
5. High % of eligible participants enrolled or random selection of eligible participants	No	Yes	Yes
5. Sample size calculation	Yes	No	No
6. Exposure preceded outcome	Yes	Yes	Yes
7. Definition and consistent measures of exposure	Yes	Yes	Yes
8. Definition and consistent measures of outcomes	Yes	Yes	Yes
9. For exposures that vary in amount or level, measurement of different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)	Yes	NA	NA
10. Blinding of outcome assessors	NR	NR	No
11. Loss to follow up ≤ 20% (included in the analysis)	Yes	Yes	NA
12. Timeframe adequacy	Yes	NA	NA
13. Measurement of confounding variables	Yes	NA	No
14. Measurement of effects at a group level	NA	NA	NA
Classification (Good, Fair, Poor)	Good	Good	Fair

NR: Not Reported; NA: Not Applicable

Table 5.6- Driving Simulator Performance: Specific Outcomes

	Simulator Measures					
Nilsen et al., 2011		**CP* taking Codeine Group 1 Mean (SD)**	**CP* no opioids Group 2 Mean (SD)**	**Healthy Volunteers Group 3 Mean (SD)**	**P values (Group 1 *vs* 2; Groups 1+2 *vs* 3)**	**Statistical Test**
	Reaction Time Rural Test (choice reaction) [b]	0.96 (0.14)	0.93 (0.11)	0.84 (0.13)	P=0.53 ; P=0.026[c]	Multiple Regression
	Reaction Time Urban Test (simple reaction) [b]	0.87 (0.21)	0.88 (0.13)	0.76 (0.13)	P=0.98 ; P=0.035[c]	
	Missed Reactions Rural Test	Because missed reactions in the rural condition were <1% only the results for the urban condition were reported				
	Missed Reactions Urban Test [a,b]	10.20 [CI 95% (8.85-11.69)]	10.85 [CI 95% (9.45-12.39)]	6.10 [CI 95% (5.07-7.28)]	P=0.19; P=0.001	
	Steering Precision Rural Test	The steering precision results were equal				Poisson Regression
	Steering Precision Urban Test	The steering precision results were equal				
Menefee et al., 2004		**Before fentanyl Mean (SD)**	**On fentanyl Mean (SD)**	**P value**		Wilcoxon Signed Rank Test
	Simple breaking reaction time, seconds	0.90 (0.17)	0.91 (0.18)	0.74		
	Cue recognition reaction time, seconds	0.88 (0.17)	0.91 (0.23)	0.72		
	In-town driving, errors made	13.2 (4.4)	13.0 (3.6)	0.20		
	Highway destination driving, errors made	5.3 (2.4)	5.3 (2.8)	0.24		
	Evasive action reaction time, seconds	0.90 (0.03)	0.76 (0.36)	0.29		
Galski et al., 2000		**CP* taking opioids**	**CCompromised** Participants**	**P value**		Analysis of Variance (ANOVA); Tukey's honest significant differences (HSD) test: differences between CPP taking Opioids and CCompromised** Participants who passed the behind-the-wheel driving test (*post hoc* comparisons)
	Basic Acceleration % Errors	3.50 ± 6.26	7.15 ± 11.47	No significant difference		
	Basic Signalling % Errors	14.63 ± 15.01	23.30 ± 20.27	No significant difference		
	Basic Breaking % Errors	31.25 ± 26.22	37.66 ± 23.12	No significant difference		
	Basic Steering Distance	56.19 ± 24.74	70.74 ± 20.47	No significant difference		
	Evasive Action Braking Distance	39.83 ± 19.33	48.95 ± 25.95	No significant difference		
	Evasive Action Braking % Valid	73.44 ± 24.95	65.17 ± 31.55	No significant difference		
	Evasive Action Steering Distance	75.79 ± 39.36	69.46 ± 37.44	No significant difference		
	Evasive Action Steering % Valid	43.79 ± 32.09	40.86 ± 29.67	No significant difference		
	Threat Recognition Braking Distance	113.74 ± 22.13	125.95 ± 34.22	No significant difference		
	Threat Recognition Braking % Valid	82.50 ± 29.10	60.47 ± 33.63	P<0.05		
	Threat Recognition Steering Distance	102.88 ± 32.72	117.99 ± 25.10	No significant difference		
	Threat Recognition Steering % Valid	75.00 ± 28.75	78.59 ± 27.51	No significant difference		

* CP: Chronic-pain participants ** CCompromised: Cerebral compromised

a Mean numbers of long reaction times (>3.95 s) for each subject (out of 104 possible reaction times for each subject).

b No significant differences were found between high (peak) and low (trough) blood concentration levels (p>0.05).

c Age-adjusted P values and differences.

5.9 Discussion

This systematic review highlights the paucity of studies evaluating the impact of regular therapeutic opioid agonists on driving-related psychomotor skills of participants with chronic pain or chronic breathlessness, which often require the use of therapeutic opioids and other palliative interventions. All three studies included in this review report data on participants with chronic non-malignant pain demonstrating the lack of evidence available for participants with chronic cancer pain or chronic breathlessness. Additionally, only one study provided a power calculation (Nilsen et al., 2011). Nevertheless, all three studies showed no negative impact on participants' driving-related skills when compared to control groups which suggests that participants with chronic non-malignant pain on stable doses of regular therapeutic opioid agonists may be able to drive safely.

5.9.1 Research question 1 - Are participants on therapeutic, regular opioid agonists for chronic pain or chronic breathlessness able to drive safely?

All three studies met the inclusion criteria for this question. All studies reported similar results: for participants with chronic non-malignant pain, regular therapeutic opioid agonists did not significantly impair driving-related psychomotor skills (Galski et al., 2000; Menefee et al., 2004; Nilsen et al., 2011). This is in line with results from an earlier systematic review that examined the effects of opioids on opioid-dependent/tolerant participants' driving-related skills that found no association between opioids and changes in driving-related outcomes (Fishbain et al., 2003). However, studies included in this review by Fishbain et al. were excluded from this systematic review because they included populations who were opioid dependent and did not report the opioid doses taken. Results from this systematic review are also similar to those published in previous observational work showing no effect of opioids on the driving ability of participants with chronic pain (Byas-Smith et al., 2005). Byas-Smith et al. evaluated two groups of participants with

chronic pain through a community-driving task and an obstacle course task. The first group was not taking opioids, and the second group was taking stable doses of opioids for chronic pain. No significant differences were found between groups in all specific measures of driving ability, even though different types of opioids were included (Byas-Smith et al., 2005). This study was excluded from this systematic review because it included multiple types of therapeutic opioids, including methadone.

5.9.2 Research question 2a - Sustained-release or transdermal formulations

The inclusion criteria for this question encompassed participants taking regular, sustained-release oral or transdermal opioid agonists which are frequently prescribed for long-term therapy (Hariharan et al., 2007). Two studies were included in this group: one using transdermal fentanyl (Menefee et al., 2004) and another using several types of strong opioid agonists in controlled-release formulations (Galski et al., 2000). Controlled-release opioid agonists showed no significant impact on driving simulator performance even with the addition of occasional PRN opioids for incidental pain. Based on the current available evidence, it is difficult to know if the use of controlled-release opioid agonists confers any advantage compared with immediate-release preparations when considering participants' driving performances. However, one study comparing the two types of formulations has found that participants reported statistically significant more tiredness after a titration period with the immediate-release formulation (Klepstad et al., 2003), which could potentially cause a detrimental impact on participants' driving-related skills (Galski et al., 2000). Studies comparing these two types of formulations should then be developed to bring light into this issue.

5.9.3 Research question 2b - Low doses (dose-response relationship)

Nilsen et al. (2011) was the only study using low doses of opioids (median dose 18 mg / day oral morphine equivalent dose). This dose range is effective in reducing the sensation of

breathlessness in most participants with chronic breathlessness (Currow et al., 2011) and its importance should be highlighted. Importantly, these findings are similar to the ones from Menefee et al. (2004) (median oral morphine equivalent dose 120 mg) and Galski et al. (2000; unknown doses). One theory is that neuroadaptation quickly develops following exposure to an unchanged dose of an opioid agonist (Weaver & Bédard, 2012). This corroborates findings from previous studies showing that stable doses of opioids fail to produce cognitive impairment, while therapy initiation and up-titration produce significant cognitive and psychomotor impairment (Bruera et al., 1989; Weaver & Bédard, 2012). However, epidemiological data suggest that very low doses of therapeutic opioid agonists (defined in this study as doses < 20 mg of oral morphine equivalent a day) may be safer than higher doses when considering performance on the road (Gomes et al., 2013), even when controlling for potential confounders such as age, hospitalisations, other medication use and number of emergency department visits in the previous year. Further research should also take this factor into consideration.

5.9.4 Research question 2c - Prescribed sustained-release, low-dose opioid agonists

No study was available evaluating the effects of therapeutic, regular, low-dose, sustained-release oral opioid agonists for pain or breathlessness on driving-related psychomotor performance. As such, this important question remains unanswered after this systematic review, highlighting an important gap in research that needs to be investigated.

5.9.5 Impact of pain and breathlessness

Pain and breathlessness are often reported by participants suffering from chronic diseases like cancer, degenerative joint disease and chronic cardiorespiratory diseases among others (Johannes et al., 2010; Reuben & Mor, 1986). In fact, participants that are suffering from pain are more likely to report breathlessness, and participants with breathlessness have also a higher prevalence of pain (Clark et al., 2014). Additionally, pain and breathlessness commonly emerge and subside

together, which highlights the association between the two symptoms (Clark et al., 2014). One explanation is that both symptoms share common neural pathways especially in the limbic region (von Leupoldt et al., 2009). Another important idea is that both pain and breathlessness may reflect the same underlying disease process. Whatever the extent of influence of these factors may be, these symptoms commonly occur in similar populations, which motivated its inclusion together in this review.

An interesting finding from the only a priori adequately powered study in this review (Nilsen et al., 2011) is that participants with chronic pain (taking and not taking therapeutic opioids) performed significantly worse than healthy volunteers after adjusting for age, sex, education, driving experience, personality traits, emotional stability and extraversion. This corroborates previous findings suggesting that uncontrolled pain is a stronger influence on cognitive and psychomotor performance than prescribed opioids (Sjøgren et al., 2000; Veldhuijzen et al., 2006). Importantly, the difference in mean pain scores reported between the chronic non-malignant pain group and the healthy volunteer group was not only statistically significant but also clinically significant (pain NRS mean score 5.6 and 0.4, respectively) (Farrar et al., 2001). Although no studies were found for participants with breathlessness, there is evidence suggesting that an increase in the intensity of breathlessness correlates with worsening driving-related neuropsychological performance skills (Karakontaki et al., 2013). These studies highlight that symptom intensity may influence driving performance and should be considered as potential confounders when analysing the impact of opioids in populations with chronic pain or chronic breathlessness.

5.9.6 Strengths and limitations

This systematic review was conducted in line with the methodology proposed by the PRISMA Statement (Moher et al., 2009). This is the first systematic review assessing opioids and driving-related psychomotor skills with a focus on population, intervention and outcomes. The selection

criteria were carefully thought to include (i) a representative population of people with chronic conditions, (ii) the most common types of prescribed opioids selected based on current pharmacologic knowledge, (iii) the most robust outcome measures. It is also important to highlight that the simulators used in the studies included in this systematic review have been previously validated for on-road driving (Galski et al., 1992; Helland et al., 2013). This approach prevented the inclusion of a heterogeneous group of studies whose results would not be generalisable.

Only three studies were included in this review as a result of the selection criteria applied. This is regarded by the authors as both a strength and a limitation. On the one hand, the population, opioids and outcomes selected are relatively homogeneous which would allow the generalisability of results to this group of participants. On the other hand, the scarcity of studies available means the conclusions cannot be definitive. This systematic review only included articles published in English which may have increased the risk of selection bias. Also, given the heterogeneity of study designs, a meta-analysis could not be performed. Patients with chronic breathlessness are usually of older age compared with the group included in this systematic review. Increasing age is associated with higher likelihood of cognitive decline, which may impact on people's driving-related skills. Additionally, people with chronic breathlessness frequently experience other symptoms and have other comorbidities, which may affect alertness, cognition and psychomotor coordination. It is possible that these factors may worsen any potential cognitive and psychomotor effects caused by therapeutic opioids. As a result, findings from this study may not be generalisable for the population with chronic breathlessness.

5.9.7 Implications for future research

Currently there are few studies assessing the impact of therapeutic opioid agonists on people's driving-related skills. The studies included in this systematic review all selected a population of participants with chronic non-malignant pain, and the results obtained may not be generalisable

for participants with chronic malignant pain or chronic breathlessness. However, it is important to note that chronic pain is a common feature of non-malignant life-limiting diseases, and the results of this work are important for this population (Traue & Ross, 2005). Nonetheless, future research should also focus on populations with chronic malignant pain and chronic breathlessness. The impact of oral extended-release and transdermal formulations during the titration phase on cognitive and psychomotor skills is unknown, although studies in other populations suggest they may have fewer adverse events (Gourlay, 1998; Klepstad et al., 2003). Another important issue to explore in future research is the true impact of different intensities of pain / breathlessness in driving outcomes as they might be important predictors of poorer driving performances. Additionally, it is important to conduct studies in people of older age, who may experience more comorbidities which can impact on driving.

5.9.8 Implications for clinical practice

Although opioids are currently recommended as the first line treatment for moderate to severe pain, many clinicians remain reluctant to use them mostly due to fear of side effects (Hadjiphilippou et al., 2014; Rocker et al., 2012). Based on this fear, clinicians may withhold or withdraw therapeutic opioids from people who could potentially benefit from this therapy. Alternatively, some clinicians may also advise people not to drive while taking therapeutic opioids (Weir et al., 2017), with potential consequences for people's independence and wellbeing (Chihuri et al., 2016; Choi et al., 2014; Marottoli et al., 2000).

Findings from this systematic review suggest that participants with chronic non-malignant pain may be able to drive safely while taking regular, stable doses of a therapeutic opioid agonist. One important factor to consider is that uncontrolled symptoms like pain and breathlessness may contribute to worsen driving-related psychomotor skills and performance on the road, to a greater extent than opioids (Nilsen et al., 2011; Sjøgren et al., 2000).

5.10 Conclusions

This systematic review examined the literature about driving-related psychomotor performance of people with chronic pain or chronic breathlessness taking therapeutic opioid agonists. Despite the evidence supporting the use of opioids for symptom reduction in these populations, their effects on driving need further exploration. From the limited available studies for people with chronic non-malignant pain stable doses of therapeutic opioid agonists do not seem to cause any significant changes in driving-related psychomotor performance. More intense chronic pain may have a significant effect on driving skills and should be carefully monitored and controlled. Clinicians are recommended to use their best clinical judgement to advise patients to drive or not to drive based not only on the regular therapeutic opioid agonist prescribed, but also on their comorbidities, symptoms and pre-morbid driving abilities.

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Chapter 6 - The impact of regular, low-dose, sustained-release oral morphine on the driving-simulator skills of COPD patients with severe chronic breathlessness – an exploratory, prospective sub-study

6.1 Chapter preface

The qualitive sub-study presented in Chapter 4 suggested that people living with chronic breathlessness and their carers do not feel chronic breathlessness impacts people's ability to drive safely. Despite the mounting evidence for the use of regular, low-dose, sustained release oral morphine to reduce chronic breathlessness, the systematic review presented in Chapter 5 found that there is a complete absence of prospective studies evaluating the objective impact of any therapeutic opioid agonist on driving-related skills of people with chronic breathlessness. This systematic review only included participants with chronic non-malignant pain, for whom the evidence available is also limited. The review of clinical practice, clinical guidelines and policy found wide variation between countries, and frequently, within the same country.

This Chapter presents the findings of a sub-study prospectively evaluating, for the first time, the effects of regular, low-dose, sustained-release oral morphine on driving-related skills of people with COPD and severe chronic breathlessness. People with COPD and severe chronic breathlessness were selected because they are more likely to benefit from regular, low-dose, sustained-release oral morphine (Currow et al., 2017; Verberkt et al., 2020). The sub-study used the current recommended dose ranges of regular, low-dose, sustained-release oral morphine for chronic breathlessness (TGA, 2019), and focused on detecting changes from baseline in driving-simulation outcomes during therapy initiation and stabilisation.

6.2 Aim

To prospectively explore, for the first time, the effects of regular, low-dose, sustained-release oral morphine on driving-related skills of people with COPD and severe chronic breathlessness.

6.3 Objectives

To explore the effect of regular, low-dose, sustained-release oral morphine on driving-simulator outcomes of people with COPD and chronic breathlessness during:

- Therapy initiation; and
- After achieving steady state concentrations.

6.4 Methods

6.4.1 Study Design

An exploratory, prospective, observational study, embedded in the BEAMS trial (trial registration number NCT02720822), exploring the effects of regular, low-dose, oral sustained-release morphine on driving-simulator skills of people with severe chronic breathlessness associated with COPD (Currow et al., 2017).

6.4.2 Study setting

Six of the 18 Australian health-care centres participating in BEAMS were invited to participate in this sub-study. Sites were selected according to proximity to driving-simulator facilities, which were only available in Adelaide (South Australia) and Eastern Sydney (New South Wales) and included: Southern Adelaide Palliative Services (South Australia); Sacred Heart Health Service, Calvary Health Care Kogarah, Greenwich Hospital, Concord Repatriation General Hospital, Liverpool Hospital (New South Wales).

Driving-simulator facilities in South Australia were located at the Institute for Sleep Health, in the Repatriation General Hospital, Adelaide. Assessments conducted at this location were performed

by the researcher (D.F.), with the support of the resident research team, that had extensive experience with the AusEd driving simulator (Vakulin et al., 2009; Vakulin et al., 2014). Driving-simulator facilities in New South Wales were located at the Neuroscience Research Australia building, in eastern Sydney. Studies at this location were conducted by a second researcher (RM), who had previous experience with the AusEd driving simulator. Due to difficulties in recruitment during the first year, sub-study procedures were revised to enable participants to take driving-simulator tests at their homes. This required an initial assessment of their home setting to ensure laboratory-like conditions could be replicated and remained consistent between each driving-simulator test. Equipment and facilities used in the driving simulation sessions are detailed in Box 6.1.

Box 6.1 - Facilities and Equipment required for the AusEd driving-simulator assessment

Facilities - Light-controlled room
Equipment - Personal computer - Speakers - AusEd driving simulator (with steering wheel and pedals) - Recording camera - Communication system (e.g., phone, hand-held transceiver)

6.4.3 Participants

Participants recruited for the BEAMS trial were invited to participate in this sub-study if they were residents of South Australia or New South Wales and based less than 30-minutes away from the driving-simulator assessment centres. People who were required to travel more than 30 minutes by car to participate in the simulated-driving assessments were excluded to minimise the daily time requested for overall study participation and facilitate adherence to the main trial for people who were already frail. Participants also had to be considered to be fit enough to tolerate three driving-simulator assessments in one week, in addition to the BEAMS study requirements. Fitness

to participate was determined by research nurses at each site, based on their clinical and research experience with similar cohorts of participants.

Exclusion criteria for this study included evidence of dementia assessed with the Saint Louis University Mental Status (SLUMS) scale (Tariq et al., 2006), which could potentially impair understanding the study and reduce performance on the driving simulator (Matas et al., 2014; Wadley et al., 2009); motor disability impeding adaptation to the simulator, including difficulties in manoeuvring the steering wheel and pedals; history of unstable vertigo and evidence of acute confusional states, which could potentially alter behaviour and/or hinder driving-related psychomotor skills. Participants who did not have a drivers' licence were not excluded from this study. This was both because the driving simulator was sufficiently easy to operate without having learned how to drive, and because this sub-study aimed to explore *change from baseline* in driving-related psychomotor skills rather than ability to drive in a real-world setting (Table 6.1).

Table 6.1 - Selection criteria specific to the driving simulation sub-study

Inclusion criteria
- BEAMS participants recruited South Australia or New South Wales (six participating sites); - Less than 30 minutes away from the driving assessment centre (by car); - Sufficiently fit to go to the driving-assessment centre three times in one week; - Willing to participate.
Exclusion criteria
- SLUMS score suggestive of dementia (≤20/30 for people who completed high school; (≤19/30 for people who did not complete high school); - Motor disability limiting the ability to operate the driving simulator; - History of unstable vertigo; - Evidence of acute confusional state.

BEAMS = Breathlessness, Exertion and Morphine Sulphate study; SLUMS = St Louis University Mental Status Examination

6.4.4 Randomisation

The block randomisation used in the BEAMS study ensured that, at each site, participants were evenly allocated to the three possible interventions (placebo, sustained-release morphine 8 mg, or 16mg). Although not all BEAMS participants at each site were included in this sub-study, block

randomisation also increased the chances of having a relatively even number of participants per arm in the driving simulation assessments. Research nurses identified and approached potential participants for this sub-study. All participants who were interested in getting further information about the study were referred to the researcher (DF) who provided a detailed explanation of the study procedures, clarified potential questions, and scheduled the driving-simulator assessments. All participants provided written informed consent before enrolling.

6.4.5 Study procedures

6.4.5.1 Participants' pre-assessment instructions

Participants were instructed to take the study medication (i.e., placebo, or regular sustained-release oral morphine 8 mg, or 16mg) as instructed by the study nurses, and continue taking their other long-term medications. Participants could maintain their usual intake of coffee but were asked to refrain from consuming any alcohol or recreational drugs on the days they were scheduled to drive on the simulator. Driving assessments could be conducted at any time between 9:00 am and 4:00 pm. Having flexible driving-assessment times contributed to coordinating the driving simulation assessments with the main study procedures, so that participants were only required to visit the hospital or be visited once per day. As this sub-study was aiming to explore changes from baseline in people's driving-related skills (rather than differences between groups), such inter-individual flexibility did not compromise the validity of the study. However, each participant's driving tests were conducted at approximately the same time to reduce intra-individual variability (Banks et al., 2005).

6.4.5.2 Demographic and driving history

All participants provided demographic information as part of the BEAMS Study, which was also used for this sub-study. Before the first driving assessment, participants were asked to complete a short questionnaire enquiring about their current driving habits and their driving history

(Appendix 14). This questionnaire, which had been previously developed by the Adelaide Institute for Sleep Health (Repatriation General Hospital, Adelaide, South Australia), was adapted by the researcher to make it suitable for this population with severe chronic breathlessness. This questionnaire aimed to provide some context to each driver's experience on the road, which could influence their driving-simulator performance (Campos et al., 2017; Lindstrom-Forneri et al., 2010).

6.4.5.3 Assessment of driving related skills

Driving-related skills were assessed using the AusEd driving simulator, an Australian-designed, office-based simulator controlled by a steering wheel, accelerator and brake pedals (Banks et al., 2005; Desai et al., 2007; Vakulin et al., 2014). A computer screen displays the forward view from the driver's seat and a 0 to 120 Km/hour speedometer. The AusEd simulates a monotonous night-time drive on an Australian rural road. There are no other cars or traffic signs, with the exception of white dividing line markers and evenly spaced reflective markers on both sides of the road. A permanent engine-noise can be heard in the background. Occasionally, slow-moving trucks appear ahead of the driver, who is required to use the brake pedal and come to a complete stop. Once the driver brakes, trucks disappear, and the driving task can be resumed. The AusEd driving simulator was designed to evaluate fatigue and sleepiness, by recreating an environment that may predispose to or aggravate these symptoms (Desai et al., 2007). Additionally, the driving-simulation task is conducted in a dark room in order to simulate a monotonous night-time scenario, which is more likely to reduce alertness. The AusEd simulator is not validated for performance on the road. However, previous studies have shown that results achieved with the AusEd are reproducible (Desai et al., 2007), and the simulator is sensitive to performance impairments due to alcohol (Banks et al., 2004; Banks et al., 2005), sleep deprivation (Desai et al., 2006), sleep disorders (Cross et al., 2017; Desai et al., 2007; Vakulin et al., 2009) and benzodiazepines (Sarris et al., 2012). Somnolence and fatigue are also some

of the most common side effects reported by people who take regular, low-dose, sustained-release morphine for chronic breathlessness (Bausewein et al., 2010; Currow et al., 2020). Thus, the AusED simulator is particularly suited to explore the impact of regular, low-dose, sustained-release oral morphine in people with chronic breathlessness who are still seeking to drive.

6.4.5.4 Driving Assessment time-points

Driving-simulation assessments were conducted at:

- **Baseline**: before initiating the study medication (i.e., sustained-release morphine 8 mg *or* sustained-release morphine 16 mg *or* placebo). The baseline assessment provided reliable baseline data to which to compare subsequent assessments.

- **Day 3**: 48 hours after initiating the study medication. Low-dose, sustained-release oral morphine reaches steady-state plasma concentrations approximately 33-36 hours, if taken regularly as prescribed (Gourlay et al., 1997). Around this period, side effects such as sedation are expected to be worse. Any changes in participants' ability to operate the driving simulator would be expected to reach their peak around the time of this assessment.

- **Day 7**: seven days after initiating the study medication. With time, some of the acute side effects experienced with regular, low-dose, sustained-release oral morphine may subside as a result of neuroadaptation (Vella-Brincat & Macleod, 2007; Weaver & Bédard, 2012). This assessment aimed to explore whether potential changes in driving-simulation ability persist over time.

6.4.5.5 Driving-simulator task

Before each baseline assessment, participants had a 5-minute practice drive in order to become familiar with the driving simulator. This period of "acclimatisation" is recommended by the AusEd

manufacturers in order to reduce the learning effects from the simulator (Desai et al., 2007; Shechtman et al., 2007). Practice drives were not conducted before the second and third assessments. Each driving test consisted of a 30-minute driving task. Participants were instructed to drive in the centre of the left-hand lane, keep a 60 to 80 km/hour speed, and brake fully to come to a stop as soon as a truck appeared on the screen. They were also instructed to resume driving once a truck disappeared from the screen. Participants were alone in the room where the assessment was conducted for the full duration of the driving test. This procedure was implemented to ensure the researcher would not interfere, in any way, with the driving task. A camera attached to the computer screen recorded each participant during each driving assessment, while live-streaming the video to a second computer operated by the researcher. This allowed the researcher to oversee the participant during the entire length of the driving task without being physically present in their room. Additionally, the computer screen used by the researcher displayed both the participant and his computer screen display, so that participants' reactions could be matched with events occurring in the simulated driving. For example, this feature would allow observing whether a participant was dozing just before a crash. Hand-held transceivers were used to enable communication between the participant and the researcher just before and just after each driving assessments, and to communicate any problems experienced during the test.

6.4.5.6 Outcome measures

The *primary outcome* proposed for this prospective, observational sub-study were differences, by dose level (placebo, placebo, sustained-release morphine 8 mg, and 16 mg) in driving-simulation performance between baseline and Day 3. Differences between baseline and Day 3 were selected to understand whether low-dose, sustained-release oral morphine impacts driving-related skills, before neuroadaptation develops. Given that a single simulator output measure is insufficient to assess driving-related skills (Michaels et al., 2017), each driving-simulator performance was

assessed using four AusEd output measures used in previous studies evaluating drowsiness, fatigue, and the effect of other psychoactive medications (Desai et al., 2007; Vakulin et al., 2009; Vakulin et al., 2014). These included:

- Mean steering deviation from the median lane position during the drive (STDVM);
- Mean velocity deviation from 60-80 km/h (SPDEV);
- Mean reaction time (RTMN); and
- Number and type of crashes, including:
    - *Off-road events:* when the driver gets completely out of the road;
    - *Stand-still events*: when the driver stops driving for a period of 10 seconds or more; and
    - *Truck collisions*: when a truck is displayed on screen and the participant does not break quickly enough to avoid hitting the truck.

Secondary outcomes were differences in driving-simulation performance between Baseline and Day 7, and Day 3 and Day 7. Results from the driving simulator assessment were examined against other measures that could influence performance on the driving simulator, including:

- breathlessness scores: NRS scores for *worst*, *average*, and *distress* caused by breathlessness in the previous 24 hours (Gift & Narsavage, 1998; Wilcock et al., 1999);
- subjective sleep assessments: answers to the question “How did you sleep last night?” using a 4-point Likert scale, and scores in the Karolinska Sleepiness Scale just before each assessment (Åkerstedt & Gillberg, 1990; Reyner & Horne, 1998);
- presence of other symptoms (i.e., pain, drowsiness, tiredness, anxiety) measured with the revised version of the Edmonton Symptom Assessment Scale (ESAS-r) (Bruera et al., 1991).

6.4.5.7 Sample size

Considering that this was an exploratory prospective observational sub-study, no formal sample size calculation was undertaken. Given that sedation and fatigue are relatively common side effects reported in studies evaluating low-dose, sustained-release oral morphine for chronic breathlessness, it was estimated that a small sample size of 10 participants per arm (30 participants in total) would be sufficient to provide an indication about the direction and magnitude of the effect expected with regular, low-dose, sustained-release oral morphine.

6.4.5.8 Statistical analysis

Due to challenges in recruitment, it was impossible to achieve the expected sample size, and the small number of participants recruited was insufficient to conduct a formal statistical analysis. Instead, Excel was used to organise baseline data and driving-simulator outcomes for each participant. This step was important to facilitate comparing and contrasting driving-related outcomes across different time-points, and examining data against other outcome measures (i.e., intensity of breathlessness and other symptoms, and subjective sleep assessments). Additionally, visual representations of data displaying participants' driving outcomes were also created to facilitate comparisons between participants taking placebo, and those taking regular, low-dose, sustained-release oral morphine.

6.4.5.9 Ethical issues

Since this study was concerned with driving-related skills, potential participants who were still driving could have had concerns about underperforming on the simulator and potentially losing their driver's licence. Importantly, this sub-study was designed to detect changes from baseline in driving-simulator skills. The AusEd driving simulator recreates extremely monotonous road conditions, in order to facilitate detection of potential changes in alertness (Desai et al., 2007). However, it does not recreate real-world driving, as most people with chronic breathlessness living

in an urban setting are unlikely to experience the AusEd driving conditions regularly in real life. Thus, all participants were explained that decrements in driving-simulator performance would not result in losing their driver's licences. However, participants were also informed that any major changes in their ability to operate the simulator would be discussed and reported back to their general practitioners after obtaining their consent.

6.5 Results

6.5.1 Recruitment and retention

From the 176 participants recruited to the BEAMS study from August 2016 until November 2019, only 108 were included in this sub-study. Of those, 47 were located more than 30 minutes away from driving-assessment centres. Of the remaining 61 BEAMS participants, 32 were too frail and 23 declined to participate. Six BEAMS participants provided written informed consent to participate in the driving simulation sub-study, but one person withdrew consent shortly after, citing anxiety associated with the study procedures. Only 5 participants were included, of whom three were on placebo and two were on regular, sustained-release oral morphine 16 mg (Figure 6.1).

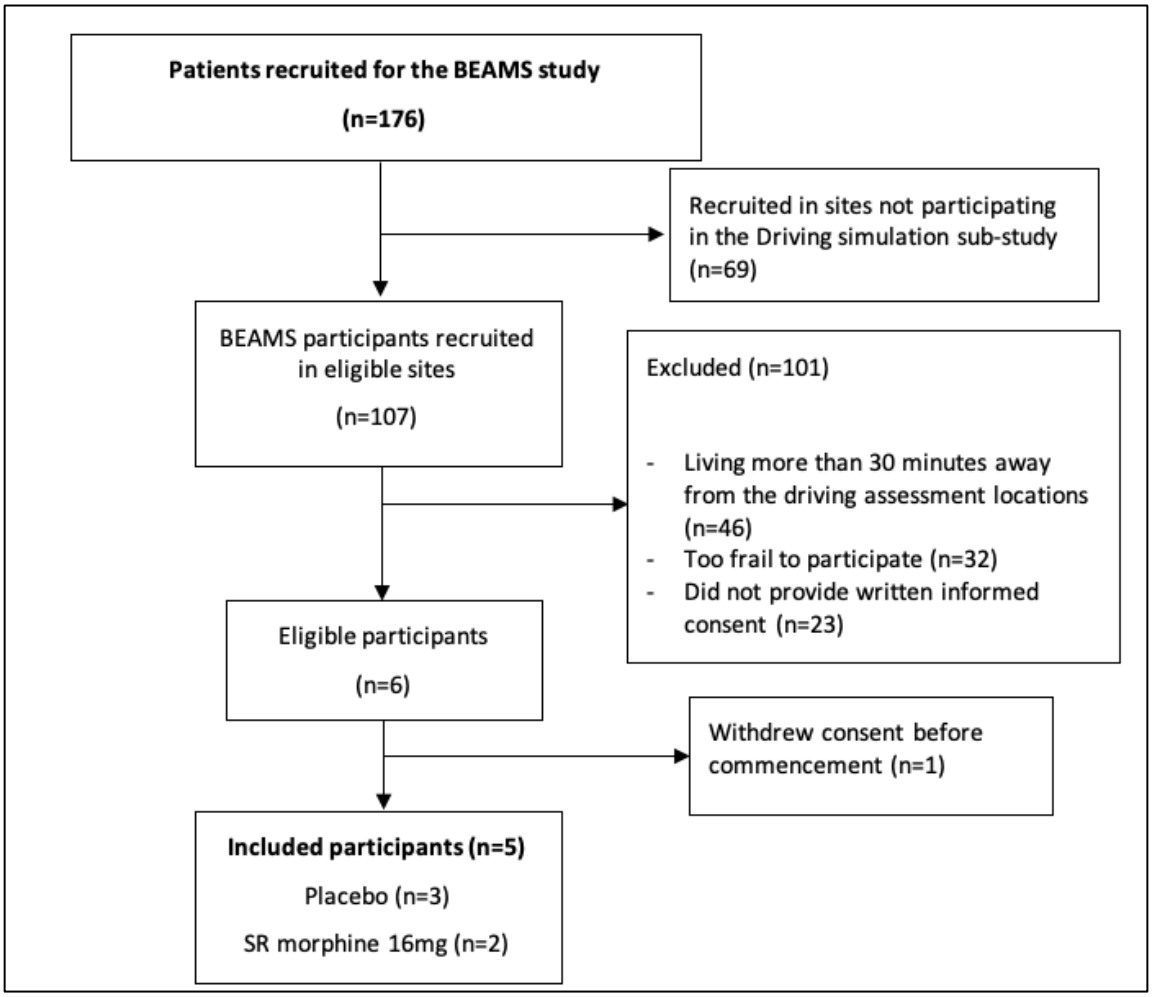

Figure 6.1 - Diagram of participants included in the driving simulation sub-study

6.5.2 Study participants

Participants (n=5) were mostly obese (BMI ≥ 30 kg/m^2) elderly men with multiple comorbidities, who were able to care for themselves, but unable to carry on normal activity or do active work (Australian Karnofsky Performance Status ≤ 70). One participant was on continuous supplemental oxygen therapy, and none of the participants presented with hypoxemia or hypercapnia at rest. Three participants were taking long-term medications that could potentially cause sedation, but doses had been optimised and stabilised over a period of several weeks, and there were no changes in therapy for the duration of the driving simulation sub-study. All participants showed

normal cognitive function for their level of instruction, as assessed by the SLUMS (Tariq et al., 2006) (Table 6.2).

Table 6.2 - Baseline characteristics of participants included in the driving simulation sub-study

Participants' Characteristics	Participant 1	Participant 2	Participant 3	Participant 4	Participant 5
Age (years)	76	65	72	79	87
Sex	Male	Male	Female	Male	Male
BMI (kg/m^2)	33.1	32.9	37.7	37.7	20.2
Charlson Comorbidity Index (age adjusted)	7	3	4	10	7
AKPS	70	80	70	50	70
mMRC	3	3	3	3	3
Supplemental oxygen	-	-	-	2L/minute (24h/day)	-
Respiratory rate (breaths / minute)	14	-	22	23	24
Estimated arterial blood oxygen saturation via pulse oximetry (%)	93	90	95	97	95
End tidal CO_2 (mm Hg)*	30	37	26	23	23
Medication (potentially sedative)	Nitrazepam 2.5 mg (before bed)	-	-	Citalopram 20 mg (morning)	Sertraline 25 mg (morning)
SLUMS	30	30	29	29	26

BMI = Body Mass Index; AKPS = Australian Karnofsky Performance Status; mMRC = modified Medical Research Council scale for breathlessness; SLUMS= Saint Louis University Mental Status Examination
*measured with a portable capnography device during quiet breathing

6.5.3 Driving experience and habits

All participants had driven for at least 45 years and were currently driving. Median hours driven in a week were 11, IQR [7 - 15.5]. No participants reported having had motor vehicle accidents in the previous three years. One participant (Participant 5) reported having had some near-miss accidents, due to "other drivers cutting in". All participants reported they never, or very rarely, felt sleepy whilst driving. All denied ever feeling unable to concentrate or nod off at the wheel whilst driving. Three participants reported stopping for breaks or naps frequently, when they felt tired.

6.5.4 Subjective assessments

6.5.4.1 Breathlessness

All participants reported an mMRC of 3 at Baseline and Day 7, corresponding to "stops for breath after walking about 100 metres or stops after a few minutes walking on the level" (Bestall et al., 1999; Stenton, 2008). All participants taking placebo (Participants 1, 2 and 4) showed improvement in at least one NRS measure of breathlessness. Participants 2 and 4 showed a progressive improvement in all breathlessness scores (i.e., *worst*, *average* and *unpleasantness of breathlessness*), from baseline to Day 7 (progressive reductions of up to 3 points in the NRS). Breathlessness scores for Participant 1 remained consistent across all time-points, except for *unpleasantness of breathlessness*, which showed a progressive 3-point reduction from baseline to day 7. Participants taking sustained-release oral morphine 16 mg showed improvement in almost all breathlessness scores from Baseline to Day 7. Participant 3 showed the greatest and most immediate reduction in *worst* and *average breathlessness* (i.e., 4-point reduction in the NRS), which persisted until Day 7. Participant 5 showed a 1-point reduction in worst and average breathlessness from baseline to Day 7, and a small increase in *unpleasantness of breathlessness* from Baseline to Day 3, which returned to original values on Day 7. Overall, reductions in *worst breathlessness* (the NRS measure that is more responsive to change) (Johnson et al., 2016) tended to be larger for people taking sustained-release morphine 16mg compared with placebo (Figure 6.2).

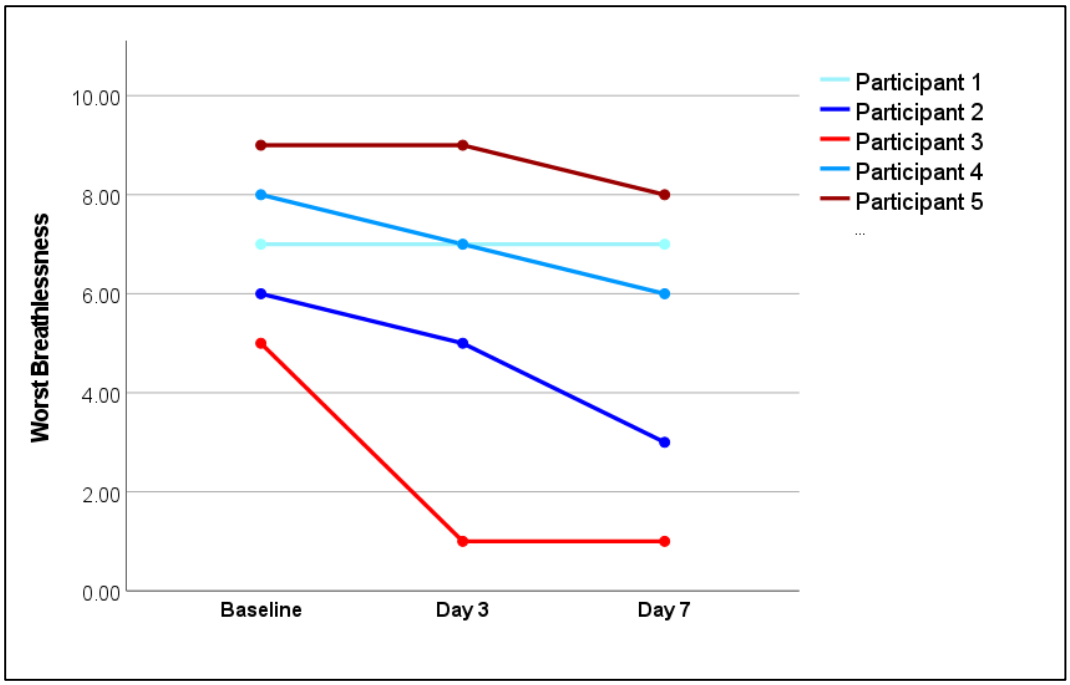

Figure 6.2 - Baseline to Day 7 variations in *worst breathlessness* scores.

6.5.4.2 Pain, drowsiness, tiredness, and anxiety

Four participants reported improvement in pain scores from Baseline to Day 7. Participant 3 (sustained-release morphine 16 mg) had the most accentuated reduction in pain scores (5 points in the 0-10 ESAS-r scale). Participant 5, who was also taking regular, sustained-release oral morphine, did not report pain at any point. Most participants reported low level drowsiness scores both at Baseline and Day 7 (ESAS-r ≤ 3). Participant 1 (placebo) and 5 (sustained-release morphine 16 mg) reported higher drowsiness scores, which remained stable across the week (ESAS-r = 4 and 8, respectively). Two participants taking placebo (1 and 2) showed a 2-point increment in tiredness scores from Baseline to Day 7 (4 to 6, and 3 to 5, respectively). The third participant taking placebo reported very low tiredness scores at Baseline (ESAS-r =2), which reduced further to Day 7 (ESAS-r =1). Participants taking sustained-release oral morphine 16 mg showed a 2-point reduction in tiredness scores from Baseline to Day 7 (Participant 3 = 2 to 0; Participant 5 = 10 to 8). Participants

reported low anxiety scores at Baseline and Day 7 (ESAS-r ≤ 3), with the exception of Participant 4, who reported moderate anxiety at Day 7 (ESAS-r = 4).

6.5.4.3 Perceived quality of sleep and subjective sleepiness

Most participants reported having slept "moderately well" or "very well" in the nights before driving-simulation tests, and these assessments were consistent across all time-points. Only Participant 1 (placebo) reported inconsistent sleep quality across different time-points ("poorly" before the baseline assessment, and "moderately well" before the remaining assessments).

Participants 1 and 2 (placebo) reported feeling "sleepy, with no effort to keep awake" (Participant 1) and "some signs of sleepiness" (Participant 2) in the Karolinska Sleepiness Scale, just before the Baseline driving-simulation. These scores improved on Days 3 and 7 to "alert" and/or "fairly alert"). Participant 4, also taking placebo, reported feeling "extremely alert" in the first assessment and "very alert" in the following ones. Participant 4 (sustained-release oral morphine 16 mg) felt "fairly alert" before the baseline assessment, "sleepy, but no effort to keep awake" in Day 3 assessment, and "neither alert nor sleepy" in Day 7 assessment. Participant 5, also taking sustained-release oral morphine 16mg, was feeling "alert" in the first two assessments, and "extremely alert" in the last assessment. Mean scores in the Karolinska Sleepiness Scale of sustained-release morphine 16mg compared with placebo are displayed in Figure 6.3.

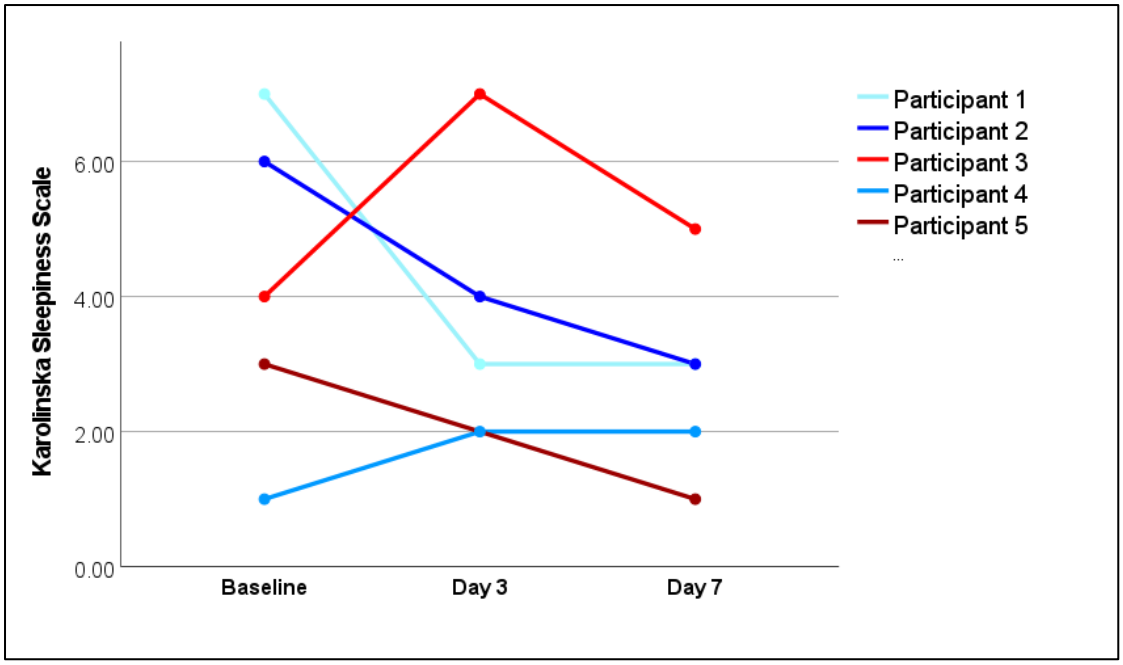

Figure 6.3 - Baseline to Day 7 variations in Karolinska Sleepiness Scale scores.

6.5.5 Driving-simulator assessments

All driving-simulator assessments were conducted during the week between 9:30 am and 3:30 pm. Intra-individual variations between assessments did not exceed one hour. Three participants were assessed in driving-simulator centres (Participants 1, 2 and 5), and two were assessed at home (Participants 3 and 4). Results for each participant are displayed in Tables 6.4 to 6.8 and Figure 6.4.

6.5.5.1 Steering Deviation

For the three participants taking placebo, mean steering deviation remained relatively stable from Baseline to Day 3 (Day 3 - Baseline absolute differences in means ± SD: Participant 1 = 2.4 ± 3.4 cm; Participant 2 = -1.2 ± 4.3 cm; Participant 4 = 1.5 ± 14.5 cm). For the two participants taking regular, sustained-release oral morphine 16 mg, there were marked increases in mean steering deviation from Baseline to Day 3 (Participant 3 = 25.4 ± 18.1 cm; Participant 5 = 67.7 ± 81.3 cm). For Participants 1 and 2 (placebo), mean steering deviation did not change considerably from Days 3 to 7 (Day 7 – Day 3 absolute differences in means ± SD: Participant 1 = 0.1 ± 1.3 cm; Participant 2

= -3.0 ± 3.1 cm). Participant 4 (placebo) showed a larger reduction in steering deviation from Days 3 to 7 (-18.9 ± 8.9 cm). Conversely, in people taking sustained-release oral morphine 16 mg, there were marked reductions in mean steering deviation from Days 3 to 7, to values below the baseline level (Participant 3 = -35 ± 8.0 cm; Participant 5 = -71.1 ± 74.8 cm).

6.5.5.2 Velocity Deviation

For the three participants taking placebo, mean velocity deviation from 60-80 Km/h remained relatively stable between Baseline and Day 3 (Participant 1 = -0.8 ± 2.3 Km/h; Participant 2 = -0.9 ± 0.4 Km/h; Participant 4 = 1.2 ± 0.7 Km/h). Participants taking sustained-release oral morphine 16 mg, showed a very slight (Participant 3 = 0.5 ± 2.2 Km/h) and a marked increase (Participant 5 = 14.5 ± 10.5 Km/h) in mean velocity deviation from Baseline to Day 3. For participants 1 and 2 (placebo), mean velocity deviation also did not change considerably from Days 3 to 7 (Participant 1 = 0.4 ± 1.0 Km/h; Participant 2 = -0.6 ± 0.4 Km/h). Participant 4 (placebo) showed a greater reduction in mean velocity deviation from Days 3 to 7 (-3.5 ± 1.8 cm). Participants taking sustained-release oral morphine 16 mg showed a more accentuated decrease from Day 3 to 7 (Participant 3 = -4.2 ± 2.5 Km/h; Participant 5 = -14.3 ± 6.5 Km/h) to values at, or below the baseline level.

6.5.5.3 Reaction Time

For the three participants taking placebo, mean reaction time decreased from Baseline to Day 3 (Participant 1 = -0.08 ± 0.12 seconds; Participant 2 = -0.17 ± 0.04 seconds; Participant 4 = -0.36 ± 0.16 seconds). Participants taking sustained-release oral morphine 16 mg showed an increase in mean reaction time from Baseline to Day 3 (Participant 3 = 0.18 ± 0.10 seconds; Participant 5 = 0.17 ± 0.08 seconds). For participants 1 and 2 (placebo), mean reaction time did not change considerably from Days 3 to 7 (Participant 1 = 0.01 ± 0.12 seconds; Participant 2 = -0.01 ± 0.04 seconds). Participant 4 (placebo) showed a very slight increase in mean reaction time from Days 3

to 7 (0.06 ± 0.17 seconds). Participant 3 (sustained-release oral morphine 16 mg) showed a more accentuated decrease from Day 3 to 7 (-0.24 ± 0.12 seconds). Participant 5 (sustained-release oral morphine 16 mg) exhibited an accentuated increase in mean reaction time from Day 3 to 7 (0.17 ± 0.27 seconds).

6.5.5.4 Crashes

Participants taking placebo did not experience crashes, in any of the driving assessments. Participant 3 (sustained-release morphine 16 mg) had one crash (stand-still event) in the Baseline driving assessment and one crash in Day 3 driving assessment (off-road event). The stand-still event experienced by Participant 3 at Baseline was caused by an attempt to correct the position of the brake pedal, which had moved during the drive. Participant 5 (sustained-release morphine 16 mg) had two crashes in the baseline driving assessment (stand-still events) and six crashes in Day 3 driving assessment (3 off-road, 3 stand-still events). There were no crashes in Day 7 driving assessment for any participant.

6.5.5.5 Video-recordings from driving-simulation sessions

All five participants remained alert during the driving-simulation assessments and engaged with the driving task. With the exception of Participant 3, who tried to adjust the position of the brake pedal during the Baseline driving-simulator assessment, there were no major unexpected events during simulation sessions.

Table 6.3 - Participant 1: driving-simulator and subjective assessments at each time-point (Baseline, Day 3 and Day 7), and mean differences between time-points.

		Participant 1 - Placebo					
		Baseline	Day 3	Day 7	Difference Day 3 – Baseline	Difference Day 7 – Day 3	Difference Day 7 – Baseline
Driving assessments	Time of the driving assessment	03:00 pm	03:30 pm	02:30 pm	-	-	-
	Steering deviation from the median lane position during the drive (cm)	48.2 (1.2)	50.6 (2.4)	50.7 (3.6)	2.4 (3.4)	0.1 (1.3)	2.5 (4.6)
	Velocity deviation from 60-80 km/h (km/h)	4.4 (2.4)	3.6 (1.3)	4 (0.9)	-0.8 (2.3)	0.4 (1.0)	-0.4 (2.0)
	Mean reaction time (sec)	1.03 (0.28)	0.95 (0.22)	0.96 (0.24)	-0.08 (0.12)	0.01 (0.12)	-0.07 (0.13)
	Total number of crashes	0	0	0	0	0	0
	- Off-road events	-	-	-	-	-	-
	- Stand-still events	-	-	-	-	-	-
	- Truck collisions	-	-	-	-	-	-
Subjective assessments	mMRC	3	-	3	-	-	0
	NRS breathlessness scores						
	- Worst	7	7	7	0	0	0
	- Average	3	3	3	0	0	0
	- Unpleasantness	4	2	1	-2	-1	-3
	How did you sleep last night?	Poorly	Moderately well	Moderately well	-	-	-
	Karolinska Sleepiness Scale	7	3	3	-4	0	-4
	Edmonton Symptom Assessment Scale - revised (ESAS-r)						
	- Pain	7	-	6	-	-	-1
	- Drowsiness	4	-	4	-	-	0
	- Tiredness	4	-	6	-	-	+2
	- Anxiety	1	-	3	-	-	+2

Table 6.4 - Participant 2: driving-simulator and subjective assessments at each time-point (Baseline, Day 3 and Day 7), and mean differences between time-points.

		Participant 2 - Placebo					
		Baseline	Day 3	Day 7	Difference Day 3 – Baseline	Difference Day 7 – Day 3	Difference Day 7 – Baseline
Driving assessments	Time of the driving assessment	10:20 am	10:00 am	10:00 am	-	-	-
	Steering deviation from the median lane position during the drive (cm)	37.2 (2.6)	36 (2.2)	33 (3.2)	-1.2 (4.3)	-3.0 (3.1)	-4.2 (3.4)
	Velocity deviation from 60-80 km/h (km/h)	1.9 (0.3)	1.0 (0.6)	0.4 (0.2)	-0.9 (0.4)	-0.6 (0.4)	-1.5 (0.3)
	Mean reaction time (sec)	0.90 (0.10)	0.73 (0.08)	0.72 (0.07)	-0.17 (0.04)	-0.01 (0.04)	-0.18 (0.04)
	No. Crashes	0	0	0	0	0	0
	- Off-road events	-	-	-	-	-	-
	- Stand-still events	-	-	-	-	-	-
	- Truck collisions	-	-	-	-	-	-
Subjective assessments	mMRC	3	-	3	-	-	0
	NRS breathlessness scores						
	- Worst	6	5	3	-1	-2	-3
	- Average	4	4	2	0	-2	-2
	- Unpleasantness	4	4	2	0	-2	-2
	How did you sleep last night?	Moderately well	Moderately well	Moderately well	-	-	-
	Karolinska Sleepiness Scale	6	4	3	-2	-1	-3
	Edmonton Symptom Assessment Scale - revised(ESAS-r)						
	- Pain	5	-	3	-	-	-2
	- Drowsiness	2	-	3	-	-	+1
	- Tiredness	3	-	5	-	-	+2
	- Anxiety	0	-	0	-	-	0

Table 6.5 - Participant 3: driving-simulator and subjective assessments at each time-point (Baseline, Day 3 and Day 7), and mean differences between time-points.

		Participant 3 – Morphine 16 mg					
		Baseline	Day 3	Day 7	Difference Day 3 – Baseline	Difference Day 7 – Day 3	Difference Day 7 – Baseline
Driving assessments	Time of the driving assessment	01:30 pm	01:30 pm	02:00 pm	-	-	-
	Steering deviation from the median lane position during the drive (cm)	63.2 (17.2)	88.6 (6.5)	53.5 (7.0)	25.4 (18.1)	-35 (8.0)	-9.7 (20.1)
	Velocity deviation from 60-80 km/h (km/h)	6.6 (1.8)	7.1 (3.2)	2.9 (0.7)	0.5 (2.2)	-4.2 (2.5)	-3.6 (1.3)
	Mean reaction time (sec)	1.34 (0.14)	1.52 (0.26)	1.28 (0.23)	0.18 (0.10)	-0.24 (0.12)	-0.06 (0.09)
	No. Crashes	1	1	0	0	-1	-1
	- Off-road events	0	1	0	+1	-1	0
	- Stand-still events	1	0	0	-1	0	-1
	- Truck collisions	0	0	0	0	0	0
Subjective assessments	mMRC	3	-	3	-	-	0
	NRS breathlessness scores						
	- Worst	5	1	1	-4	0	-4
	- Average	5	1	1	-4	0	-4
	- Unpleasantness	0	0	0	0	0	0
	How did you sleep last night?	Moderately well	Moderately well	Moderately well	-	-	-
	Karolinska Sleepiness Scale	4	7	5	+3	-2	+1
	Edmonton Symptom Assessment Scale – revised (ESAS-r)						
	- Pain	5	-	0	-	-	-5
	- Drowsiness	1	-	0	-	-	-1
	- Tiredness	2	-	0	-	-	-2
	- Anxiety	0	-	0	-	-	0

Table 6.6 - Participant 4: driving-simulator and subjective assessments at each time-point (Baseline, Day 3 and Day 7), and mean differences between time-points.

		Participant 4 - Placebo					
		Baseline	Day 3	Day 7	Difference Day 3 – Baseline	Difference Day 7 – Day 3	Difference Day 7 – Baseline
Driving assessments	Time of the driving assessment	12:00 pm	12:00 pm	12:00 pm	-	-	-
	Steering deviation from the median lane position during the drive (cm)	61.6 (8.3)	63.1 (8.1)	44.2 (2.9)	1.5 (14.5)	-18.9 (8.9)	-14.4 (10.0)
	Velocity deviation from 60-80 km/h (km/h)	3.7 (1.0)	4.9 (1.3)	1.4 (0.6)	1.2 (0.7)	-3.5 (1.8)	-2.3 (1.5)
	Mean reaction time (sec)	1.40 (0.45)	1.04 (0.19)	1.10 (0.47)	-0.36 (0.16)	0.06 (0.17)	-0.30 (0.22)
	No. Crashes	0	0	0	0	0	0
	- Off-road events	-	-	-	-	-	-
	- Stand-still events	-	-	-	-	-	-
	- Truck collisions	-	-	-	-	-	-
Subjective assessments	mMRC	3	-	3	-	-	0
	NRS breathlessness scores						
	- Worst	8	7	6	-1	-1	-2
	- Average	5	3	2	-2	-1	-3
	- Unpleasantness	4	2	2	-2	0	-2
	How did you sleep last night?	Moderately well	Moderately well	Moderately well	-	-	-
	Karolinska Sleepiness Scale	1	2	2	+1	0	+1
	Edmonton Symptom Assessment Scale – revised (ESAS-r)						
	- Pain	1	-	0	-	-	-1
	- Drowsiness	2	-	0	-	-	-2
	- Tiredness	2	-	1	-	-	-1
	- Anxiety	1	-	0	-	-	-1

Table 6.7 - Participant 5: driving-simulator and subjective assessments at each time-point (Baseline, Day 3 and Day 7), and mean differences between time-points.

		Participant 5 – Morphine 16mg					
		Baseline	Day 3	Day 7	Difference Day 3 – Baseline	Difference Day 7 – Day 3	Difference Day 7 – Baseline
Driving assessments	Time of the driving assessment	09:35 am	09:30 am	09:30 am	-	-	-
	Steering deviation from the median lane position during the drive (cm)	59.6 (5.0)	127.3 (79.2)	56.2 (6.9)	67.7 (81.3)	-71.1 (74.8)	-3.4 (8.1)
	Velocity deviation from 60-80 km/h (km/h)	8.6 (1.3)	23.1 (9.4)	8.8 (4.0)	14.5 (10.5)	-14.3 (6.5)	0.2 (5.0)
	Mean reaction time (sec)	0.61 (0.12)	0.71 (0.14)	0.88 (0.52)	0.17 (0.08)	0.17 (0.27)	0.274 (0.26)
	No. Crashes	2	6	0	+4	-6	-2
	- Off-road events	0	3	0	+3	-3	0
	- Stand-still events	2	3	0	+1	-3	-2
	- Truck collisions	0	0	0	0	0	0
Subjective assessments	mMRC	3	-	3	-	-	0
	NRS breathlessness scores						
	- Worst	9	9	8	0	-1	-1
	- Average	8	8	7	0	-1	-1
	- Unpleasantness	7	8	7	+1	-1	0
	How did you sleep last night?	Very well	Very well	Very well	-	-	-
	Karolinska Sleepiness Scale	3	-	1	0	-2	-2
	Edmonton Symptom Assessment Scale - revised (ESAS-r)						
	- Pain	0	-	0	-	-	0
	- Drowsiness	8	-	8	-	-	0
	- Tiredness	10	-	8	-	-	-2
	- Anxiety	3	-	4	-	-	+1

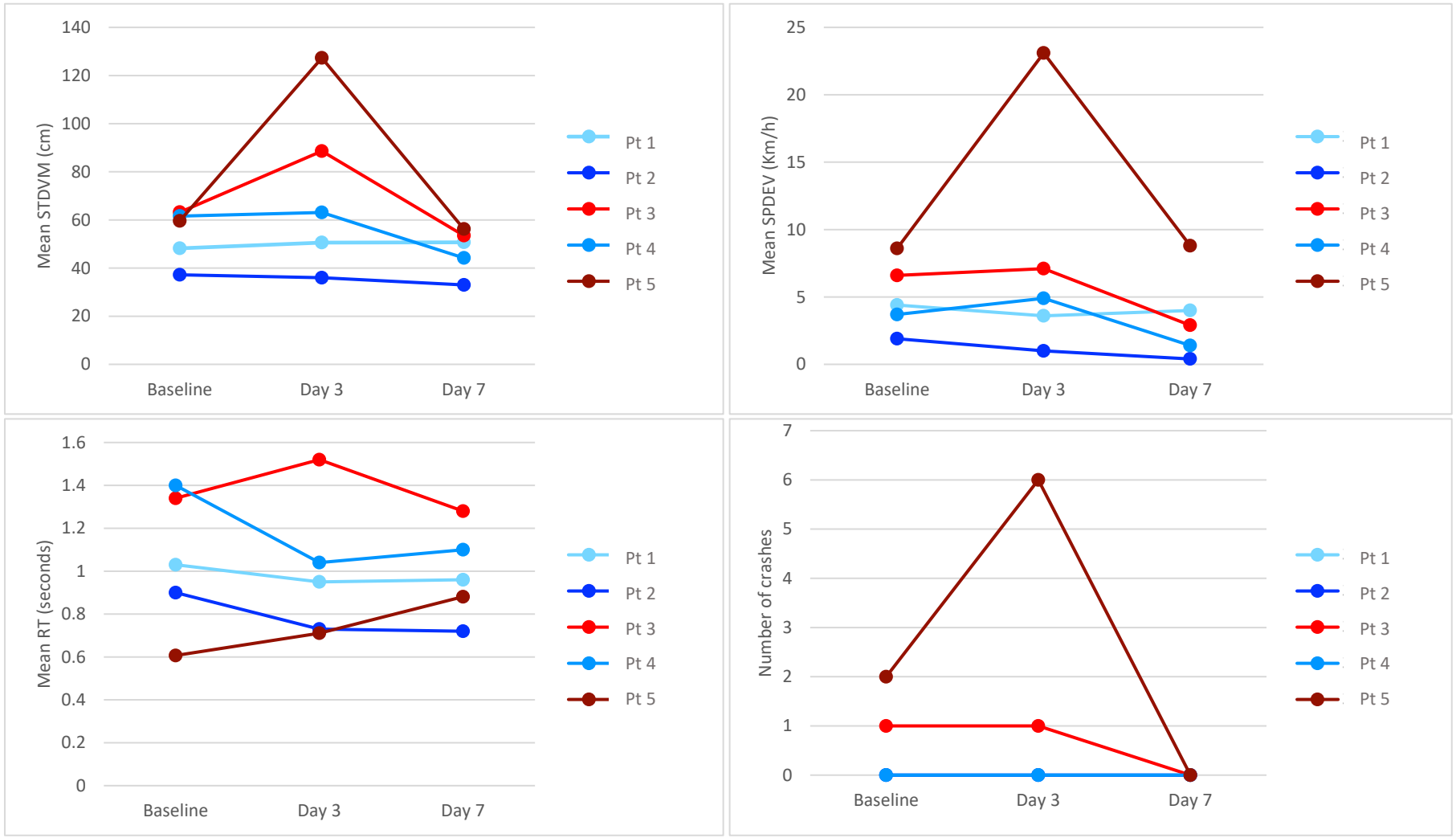

Figure 6.4 – Baseline to Day 7 variations in mean steering deviation from the median lane position during the drive (STDVM), mean velocity deviation from 60-80 km/h (SPDEV), mean breaking reaction time (RT), and number of crashes.
Blue lines = participants taking placebo; red lines = participants taking regular, sustained-release oral morphine 16 mg. Pt = Participant.

6.6 Discussion

This is the first prospective study exploring the impact of regular, low-dose, sustained-release oral morphine on people living with chronic breathlessness driving-related skills. The study design, population, intervention and driving-related outcomes were grounded on the best clinical and pharmacological evidence to generate results that were applicable to people living with chronic breathlessness who are taking this medication. Despite the challenges of recruiting to this study, results suggest that people taking regular, low-dose, sustained-release oral morphine and people taking placebo displayed different temporal patterns in some of the driving outcomes, across the three assessment days (i.e., Baseline, Day 3, Day 7). Specifically, regular, low-dose, sustained-release oral morphine seems to worsen performance on the driving-simulator in the first 48 hours of therapy, but this effect tends to subside after one week on stable medication.

6.6.1 Recruitment and retention

This sub-study had a high retention rate (Walters et al., 2017). Most people excluded were located more than 30 minutes away from driving-assessment locations, which would have required long commuting times (1-1.30 hours) for each driving assessment. Thus, each driving assessment would have required significant time and effort from these participants, *in addition* to the time required to complete the BEAMS study procedures. Lengthy travelling times and lack of consideration for one's physical limitations have been reported as important sources of perceived burden in RCTs, which needed to be taken into account (Mills et al., 2006; Naidoo et al., 2020). Additionally, the BEAMS study was an effectiveness study aiming to inform registration of regular, low-dose, sustained-release oral morphine for chronic breathlessness with international regulatory bodies, which entailed a regular collection of multiple outcome measures, requiring intense participant engagement (Currow et al., 2017). Thus, any included sub-studies had to consider the level of engagement required by the main trial, in a population that was severely limited by

breathlessness. As a result, while longer commuting times would have been possible in the context of a stand-alone driving-simulation study, they were particularly challenging in the context of the BEAMS study.

Of note, this sub-study implemented home-based driving-simulator assessments in an attempt to boost recruitment, by reducing the time and effort required from participants at each assessment time-point. However, home-based driving-simulator assessments required extra time to set-up the equipment at participants' homes and ensure there were no external factors compromising the integrity of the study (i.e., pets, phones ringing, other noises). This was often tiresome and time-consuming for participants, and challenging for the researcher, who was required to recreate, as closely as possible, the conditions offered in driving assessment centres. Thus, home assessments were not particularly helpful compared with laboratory-based assessments given that some settings were totally unsuitable.

In addition to these challenges, some people were deemed too frail to participate in this sub-study, and others chose not to provide written informed consent. Two factors may have contributed for these exclusions. Firstly, people who were experiencing severe limitations due to breathlessness may have chosen to restrict their participation to the main trial, and to other (less demanding) sub-studies. Secondly, some people who might have been willing to participate in this sub-study may have been deemed "too frail to participate" by study staff at each site. In addition to commuting times, the driving simulation sub-study required at least one hour of participants' time, at each assessment time-point (i.e., Baseline, Day 3, Day 7). It is likely that research staff were over-conservative as they selected participants to whom to present the driving simulation sub-study, in order to ensure they were not overburdening them with study assessments, and that they were still able to complete the BEAMS study.

Challenges in recruitment are unlikely to reflect loss of interest or incapacity to drive, as many of the people included in the BEAMS study were still driving, in line with previous research in the palliative care setting (Widman & Bergström, 2014). For example, from the 13 participants included in sub-study 1 (people's experiences), nine were still driving and reported driving was an important daily activity (Ferreira et al., 2020). However, only two of those participants also participated in this sub-study (i.e., driving-simulator assessments). Thus, it is likely that lack of participation is related to the factors detailed previously. Of the six participants deemed eligible for this sub-study, five completed all sub-study assessments and the only participant who withdrew did so before completing any driving-simulator assessment. These findings suggest that this sub-study was well tolerated by consenting participants, who were all able to complete it without jeopardising their ability to complete the BEAMS study assessments. As all participants were active drivers, these results may also indicate that participants who were included in this sub-study were more invested in contributing to a research project related to driving (McCann et al., 2010).

6.6.2 Trajectories of driving-simulator performance across timepoints

The AusEd is a relatively new driving simulator, which has been used to evaluate the impact of different medications on driving-related skills. However, none of these medications were therapeutic opioids, and results obtained in this sub-study are difficult to interpret in the context of the existing literature. Nevertheless, this driving simulation sub-study showed important differences between those taking regular, low-dose, sustained-release oral morphine 16 mg, and those taking placebo. Differences between the two groups were most obvious for STDVM, which is a particularly sensitive measure of driving impairment (Michaels et al., 2017; Ramaekers, 2003). People taking placebo exhibited relatively small variations in STDVM across the study timepoints, which were comparable to results from a previous study examining test results reproducibility in

the AusEd driving simulator (mean difference 1.9 ± 10.3 cm) (Desai et al., 2007). Conversely, people taking regular, low-dose, sustained-release morphine 16 mg had larger increments in mean STDVM 48 hours after initiating this medication, which returned to baseline-like values after one week of regular therapy. The sharp increase in mean STDVM seen in the first 48 hours falls outside the magnitude of normal intra-individual differences reported by Desai et al. (2007) in healthy people. Normal intra-individual differences may be different for people with chronic breathlessness, but it is possible that regular, low-dose, sustained-release oral morphine has a transient impact on cognitive and psychomotor skills in the first few days of therapy, which tends to subside completely after one week of regular therapy. These results are in line with previous research work reporting impaired cognitive and psychomotor performance in the first three days after initiating or up-titrating immediate-release oral morphine (Bruera et al., 1989; Kamboj et al., 2005). Moreover, these results mirror the findings from a previous German prospective study suggesting that there were no differences in driving-related psychomotor performance comparing Baseline and Day 7 after initiating treatment with regular therapeutic opioids for chronic non-cancer pain (Gaertner et al., 2008). This is important because, in some circumstances, people are still advised to refrain from driving for weeks after initiating or up-titrating therapeutic opioid doses (Austroads, 2017; Hegmann et al., 2014; Weir et al., 2017). This study raises the hypothesis that people taking regular, low-dose, sustained-release oral morphine up to 16 mg may be safe to drive one week after initiating therapy and up titrating their dose (Gaertner et al., 2008).

For mean SPDEV, results across different timepoints exhibit a similar pattern to STDVM although differences between groups were less clear. As a group, participants taking placebo showed less variation in mean SPDEV between assessments than people taking regular, low-dose, sustained-release oral morphine 16 mg. Similar to STDVM, participants taking regular, low-dose, sustained-release morphine 16 mg performed worse 48 hours after initiating the medication compared to

Baseline. However, these differences were small for Participant 3 (sustained-release morphine 16 mg) and of the same order of magnitude compared to one of the participants taking placebo (Participant 4). Importantly, by Day 7, both participants taking regular, low-dose, sustained-release oral morphine 16 mg had returned to (Participant 5) or improved (Participant 3) *beyond* their Baseline performance. In the AusEd, SPDEV is a measure of divided attention, because the speedometer is positioned outside the participants' road view, requiring them to divert their attention to gauge their simulated speed (Desai et al., 2007). A previous study has shown that PRN immediate-release oral morphine reduces performance on the Train Making Test (complex tracking task), a psychomotor test measuring visual attention and task switching (Kamboj et al., 2005), which supports results from this sub-study. By inducing sedation, regular, low-dose, sustained-release oral morphine may potentially affect alertness, attention and concentration during the first few days of therapy (Currow et al., 2020; Ferreira et al., 2016). Indeed, one participant taking sustained-release morphine 16 mg (Participant 3) reported more subjective sleepiness 48 hours after initiating the study medication compared with other timepoints. However, Participant 5, who registered the highest increase in mean SPDEV did not complete the Karolinska Sleepiness Scale on Day 3, making it difficult to understand if changes in alertness would have played a role in worsening SPDEV. Of note, reduction in breathlessness scores, from Baseline to Day 3 did not seem to contribute to maintaining or improving driving simulator performance. As driving is a sedentary activity, it may not trigger breathlessness in this population. As a result, reductions in breathlessness scores may not necessarily translate into improved attention and performance on the driving simulator.

For mean reaction time, there is no clear difference between people taking regular, low-dose, sustained-release oral morphine and participants taking placebo. The pattern observed in this sub-study is consistent with the STDVM and SPDEV results, highlighting that regular, low-dose,

sustained-release oral morphine may impact participants' reaction time in the first days of therapy. Similar results were reported by previous studies using different morphine doses and formulations (Kamboj et al., 2005; Strand et al., 2017). Importantly, for Participant 3 (sustained-release morphine 16 mg), reaction time decreased after one week of therapy to values below the Baseline assessment, but it increased further for Participant 5 (sustained-release morphine 16 mg). Factors contributing to these results are not clear. Importantly, there is considerably inter-individual variability in response and adaptation to therapeutic opioids (Dumas & Pollack, 2008). For example, while sedation frequently subsides a few days after therapy initiation, some people report persistent sedation with low-doses of regular, sustained-release morphine (Ferreira et al., 2016). Although Participant 5 felt more alert and reported less tiredness by Day 7 compared with Baseline, it is possible that psychomotor slowing may have persisted. Importantly, the level of psychomotor slowing exhibited by Participant 5 at Day 7 was not sufficient to cause any truck collisions. Thus, it is possible that the level of impairment experienced by Participant 5 is not sufficient to cause accidents on the road. This needs to be investigated in future studies.

Participants taking placebo did not experience any crash event in any of the driving-simulator assessments (i.e., Baseline, Day 3, Day 7). One participant taking regular, low-dose sustained-release oral morphine 16 mg experienced one crash in the Baseline assessment (stand-still event), one crash on Day 3 (off-road event), and no crashes in the final assessment. Importantly the mechanisms involved in both types of crashes experienced are different. The stand-still event at Baseline resulted from the participant's attempt to adjust the position of the brake pedal in the middle of the drive, but the participant was alert and fully engaged in the simulation task. However, the off-road event on Day 3 resulted from an inability to keep the vehicle within the left lane limits. No crashes were reported by Day 7, which may indicate that changes experienced by Day 3 may have progressively improved until Day 7. Interestingly, the second participant taking

regular, low-dose, sustained-release oral morphine 16 mg experienced two crashes in the Baseline assessment (both stand-still events), six crashes in Day 3 assessment (3 stand-still, 3 off-road events), and no crashes in the last assessment. This participant had a temporal progression pattern similar to Participant 3, with a seemingly worse driving-simulation performance on Day 3, which seemed to have improved by Day 7 (despite worsening reaction time). Similar to Participant 3, crashes experienced at Baseline and Day 3 were different in nature, with a substantial increase in off-road events by Day 3. Increase in off-road events from Baseline to Day 3, with return to Baseline values on Day 7 concur with results for STDVM, which is also a measure of road position that may reflect, above all, challenges in perceptual motor integration with regular, low-dose, sustained-release oral morphine in the first few days of therapy (Groeger, 2000; Prior et al., 2015).

These results do not necessarily translate into an increase in crash rate. This is because driving performance is a complex construct, resulting from non-linear interactions of people and their environment, and for which sensory, perceptual, cognitive, and psychomotor skills contribute only partially (Anstey et al., 2005; Fuller, 2005; Lindstrom-Forneri et al., 2010). In a real-world driving context, people's individual beliefs about driving, awareness of their own abilities, and strategies of self-regulation also play a role in determining outcomes on the road (Lindstrom-Forneri et al., 2010). For example, although older drivers are more likely to experience sensorial, perceptual, cognitive and psychomotor compromises, they are more likely to self-regulate by avoiding perceived risks (e.g., driving at night), in order to compensate for their limitations (Rudman et al., 2006). In this sub-study, all participants were experienced drivers, and none had had road accidents in the previous three years. However, most participants reported stopping frequently for naps or breaks as a self-regulation strategy. It is likely that people with chronic breathlessness are aware of their own limitations and implement adaptations to cope with their limitations (Rudman et al., 2006). Results from sub-study 1 (Chapter 4) support this assumption and highlight that

people's beliefs about regular, low-dose, sustained-release oral morphine may lead them to implement strategies to ensure they were not a hazard on the road (e.g., having a friend giving them feedback about their driving) (Ferreira et al., 2020). It is therefore possible that these people are not at risk of worse driving outcomes.

6.6.3 Strengths and limitations

This was an optional exploratory sub-study embedded in a multi-site RCT. Embedding this sub-study in a RCT allowed to explore prospectively, for the first time, the effects of initiating regular, low-dose, sustained-release oral morphine on driving-related skills of people with chronic breathlessness. Data collected as part of the main trial was used in the context of the sub-study, and results from the sub-study add to the outcomes of the main trial. However, the AusEd driving simulator has not been validated for outcomes on the road. Additionally, the sub-study included a very small number of participants, which limits the generalisability of the findings. Participants included were either taking placebo or regular, sustained-release oral morphine 16 mg. In Australia, it is currently recommended initiating therapy with a lower dose (10 mg), which is effective in most people who respond to morphine for breathlessness (Currow et al., 2011; Therapeutic Goods Administration, 2019). It is possible that using lower doses would have led to smaller differences in driving-simulator performance between Baseline and Day 3. While some people were assessed in driving-assessment centres, others were assessed in their homes, which may have contributed to inter-individual variability in outcome measures. However, each participant was always assessed in the same location, reducing intra-individual variability. These results do not translate to real-world driving performance, as the AusEd is not validated for outcomes on the road and people may have felt safer to make mistakes on the simulator, than what they would in a real-world driving context (Wynne et al., 2019). This sub-study did not include people with very recent respiratory or cardiac events, evidence of respiratory depression,

documented hypoventilation syndrome or alcohol abuse, which were part of the exclusion criteria for the BEAMS study. It also excluded people with cognitive impairment, motor disability and confusional states, which were exclusion criteria for this sub-study. As a result, there is a high chance of having selected a population less frail than the overall population with severe chronic breathlessness requiring therapy with regular, low-dose, sustained-release oral morphine (i.e., selection bias). Additionally, people may have adapted to the driving simulator over time (e.g., learning effect), which may explain some of the improvements in driving-simulation measures on the third driving assessment.

6.6.4 Implications for future research

Given the small number of people recruited and the exploratory/hypothesis-generating nature of this sub-study, the issue of driving for people with chronic breathlessness who are prescribed regular, low-dose, sustained-release oral morphine still needs to be investigated in a prospective study. Considering that this population is frail and that a driving-related study requires considerable time from participants, it is recommendable to plan for stand-alone studies in the future. In this context, it would be interesting to include at least one more driving-related assessment between Day 3 and Day 7 of therapy. If performance on the simulator is back to baseline values after seven days of regular, low-dose, sustained-release oral morphine as seen in this study, the point in which the inflection takes place needs to be determined. Future research also needs to focus on exploring driving as a complex task in people with chronic breathlessness taking regular, low-dose, sustained-release oral morphine. This includes:

- investigating the proportion of people with chronic breathlessness who are still driving despite severe limitations due to breathlessness;

- exploring the motivations, beliefs about driving and self-regulation strategies of people with chronic breathlessness, including those prescribed regular, low-dose, sustained-release oral morphine;
- conducting driving studies in the real-world setting, or with driving simulators that are validated for outcomes on the road in order to better inform policy related with driving whilst being treated with regular, low-dose, sustained-release oral morphine for chronic breathlessness;testing different doses of regular, low-dose, sustained-release oral morphine used in the context of chronic breathlessness (Currow et al., 2011; Therapeutic Goods Administration, 2019);
- identifying people who experience breathlessness while driving and comparing their driving-related outcomes with people who do not;
- linking driving-related outcomes with objective measures of physiological parameters and electroencephalography, in order to understand specific perceptual, cognitive and motor deficits potentially caused by regular, low-dose, sustained-release oral morphine.

6.6.5 Implications for clinical practice

Despite the small sample size and the preliminary nature of the findings, this sub-study generated a concerning signal for people taking regular, low-dose, sustained-release oral morphine. Although these findings cannot be used to guide clinical practice, it is important that clinicians are aware that there is a chance that regular, low-dose, sustained-release oral morphine leads to drowsiness in the first few days of therapy, even in small doses.

6.7 Conclusions

This was the first prospective sub-study exploring the impact of introducing regular, low-dose, sustained-release oral morphine in people with chronic breathlessness driving-related skills. The small number of people recruited, with only two participants taking regular, low-dose, sustained-release oral morphine 16 mg prevented drawing any conclusions. However, this study may inform the design of future studies in this field. Future prospective studies need to be designed as stand-alone studies, considering the limitations experienced by this population. It is also necessary to explore other aspects contributing for driving performance in people with chronic breathlessness taking regular, low-dose, sustained-release oral morphine, including their motivations for driving and self-regulation strategies, which can contribute to outcomes on the road. In clinical practice, it is important to be aware of the potential risks of driving while taking regular, low-dose, sustained-release oral morphine for chronic breathlessness, which may be limited to the first few days of therapy.

6.8 References

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CHAPTER 7 – GENETICS OF RESPONSE TO REGULAR, LOW-DOSE, SUSTAINED-RELEASE MORPHINE FOR CHRONIC BREATHLESSNESS - AN EXPLORATORY STUDY

7.1 Chapter preface

An overview of the existing evidence in Chapter 2 suggested that there is considerable interindividual variation in response to regular, low-dose, sustained-release oral morphine for chronic breathlessness. While younger age and higher baseline breathlessness have been shown to predict response to regular, low-dose, sustained-release oral morphine in the setting of chronic breathlessness (Johnson et al., 2013b), it is likely but unclear whether genetic factors may also influence response. This Chapter sets the context for and reports on a prospective study exploring the association between four genetic variations involved in opioid pathways, breathlessness, and response to regular, low-dose, sustained-release oral morphine. This is the first time these associations have been explored.

7.2 Introduction

7.2.1 Pharmacogenetics – definition and clinical relevance

Pharmacogenetics is a relatively recent field of knowledge defined as the study of variability in response to medications based on inherited genetic characteristics (Pirmohamed, 2001). In recent years, interest in pharmacogenetics has been growing, particularly due to the understanding that there is extreme heterogeneity in response to pharmacological interventions, which cannot be explained easily by environmental factors. For example, the ten most profitable drugs sold in the United States fail to produce benefit in at least three out of four patients (Schork, 2015). These interindividual variations in response to treatment were shown to result, at least in part, from genetic differences between individuals. It is now known that studying genetic variations for determining drug response is important in identifying people who may respond to a given treatment and those who are expected to have no benefit or even experience harms (Scott, 2011).

This understanding is important to personalise or tailor treatments according to each person's needs and likely response (Kalow, 2006). Pharmacogenetic studies may help to identify genetic factors predisposing to certain diseases, and also to specific syndromes (Nissenbaum et al., 2010; Winkelmann et al., 2000). In people with chronic breathlessness, pharmacogenetic studies can potentially identify people who are genetically predisposed to experience more intense breathlessness and who may benefit more from earlier interventions to reduce breathlessness. In addition, pharmacogenetic studies can help to identify people who are more likely to benefit from regular, low-dose, sustained-release oral morphine for symptomatic chronic breathlessness, and those who are unlikely to respond or more predictably experience harms.

7.2.2 Genotype and phenotype

G*enotype* is defined as "…the coding sequence of DNA base pairs for a particular gene…" whereas *phenotype* is defined as "…a trait resulting from the protein product encoded by the gene" (Kitzmiller et al., 2011, p.244). Together with environmental factors, the genotype contributes to inform the phenotype which reflects the clinical expression of a particular DNA sequence. Because humans are diploid organisms, their somatic cells express two copies of each gene, which are denominated *alleles*. Although the rough structure of each gene is constant within the population, there can be important variations in the DNA base pairs forming each allele. The most frequent form of each allele is denominated *wildtype* while the less frequent forms are denominated *variants*. Allele variation may lead to different clinical presentations of the same symptom or disease, influence pathways for medication metabolism as well as influence different responses to similar treatments (Giacomini et al., 2007).

7.2.3 Single nucleotide polymorphisms (SNPs)

Allele variants can emerge from a range of different DNA mutations, where the most common type are *single nucleotide polymorphisms* (SNPs) (Karki et al., 2015). SNPs are characterised by

addition, deletion or substitution of a single nucleotide in a specific allele, which can be found in at least 1% of the population (Brookes, 1999). Over recent years, research has been focusing on identifying SNPs and understanding their impact on the phenotypic characteristics (Collins et al., 1998). While most variants are neutral (i.e., they do not cause phenotypic changes), a small percentage occurs in coding genes resulting in observable clinical differences, including changes in disease susceptibility and altered response to specific therapies (Wang et al., 2013). In absolute terms, it is estimated that between 55,000 and 250,000 SNPs result in phenotypic alterations. Additionally, it is possible that some combinations of "neutral" SNPs are also able to produce functional changes (Chanock, 2001). By focusing on a particular symptom, disease or mechanism of action, it is possible to narrow down the number of SNPs potentially implicated in a given condition or symptom. However, given the multiplicity of mechanisms involved in the genesis of chronic breathlessness (i.e., different pathophysiologic processes specific to the underlying disease(s), involvement of multiple neural pathways), it is likely that multiple SNPs and combinations of SNPs contribute to interindividual variations in the symptom experience, as well as in response to treatments. Importantly, SNPs distribution in the overall population evolves very slowly, influenced primarily by the gradual forces of natural selective pressure (Shastry, 2007). Thus, findings from today will most likely inform the clinical approach to chronic breathlessness for multiple future generations.

7.2.4 SNPs, haplotype and epigenetics

SNPs are the consequence of unique, single point mutations that were passed to subsequent generations. As a result, each SNP is usually inherited together with a set of surrounding alleles that together constitute the *haplotype*. The combination of two haplotypes (in diploid organisms) forms the *diplotype.* Thus, a specific phenotypic presentation may be the result of not only a particular SNP, but also the allelic variants in its vicinity (Reich et al., 2001). Consequently, each

SNP and its surrounding alleles are in *linkage disequilibrium*, that is, their group frequency in the population is higher than one would expect if they were grouped together by chance (Reich et al., 2001; Salisbury et al., 2003). This information is important because the implications of a SNP for the phenotype expression may reflect the contribution of other genetic variations associated with that SNP, and more complex than one would expect based on the impact of a single base-pair substitution. Thus, like any other field, the haplotype needs to be taken into consideration when studying SNPs that can potentially influence the phenotypic expression of chronic breathlessness and its response to treatment.

In addition to variations in SNPs and haplotype, epigenetic changes may explain phenotypic differences between individuals. Broadly, epigenetics is defined as variations in genetic expression that are not caused by modifications in the DNA sequence (Peschansky & Wahlestedt, 2014). Specifically, epigenetics involves the participation of regulatory molecules that bind to specific DNA sequences and regulate their expression (Simmons, 2008). Based on this understanding, epigenetics was also described as "a bridge between genotype and phenotype" (Goldberg et al., 2007, p.635), that can be inherited or acquired through environmental influences (Simmons, 2008). Although this field of science is still relatively new, epigenetic changes have been increasingly implied in the expression of diseases and chronic symptoms (Descalzi et al., 2015; Feinberg et al., 2006). Thus, it is likely that epigenetic variations also contribute to the phenotypic expression of chronic breathlessness. Although potentially relevant for chronic breathlessness, epigenetic changes are outside the scope of this work and will need to be investigated in future work.

7.2.5 Genetics of chronic breathlessness and response to opioids

There is a scarcity of studies exploring the genetic factors influencing the experience of breathlessness acutely or chronically (Currow et al., 2015). However, randomised controlled trials

conducted in the setting of chronic breathlessness indicate there is high interindividual variability in both baseline breathlessness scores, breathlessness in objectively measured pathophysiology and in response to opioid therapy. A previous phase II, dose-increment study demonstrated that only two thirds of the people treated with 10 to 30 mg of once-daily, regular, sustained-release oral morphine experienced a clinically meaningful reduction in chronic breathlessness (Currow et al., 2011). Additionally, there was only a weak association between the morphine dose taken and the magnitude of breathlessness reduction (Currow et al., 2011). Although environmental factors may contribute to variations in the experience of breathlessness, it is likely that genetic differences in breathlessness pathways may account for some of the variability observed in these studies. Up to this point, factors such as sex, age, education, smoking habits, BMI and lung function were shown to be weak predictors of breathlessness, explaining only 13% of the variability observed (Gronseth et al., 2014). Younger age and higher baseline breathlessness are the only predictors of breathlessness reduction with opioid therapy identified so far, but they are also insufficient to explain the wide interindividual variability observed (Johnson et al., 2013b). A recent exploratory study also suggests that higher negative affect may be a predictor of breathlessness reduction with opioid therapy (Abdallah et al., 2019). Importantly, since genetic factors influence the phenotypic expression of multiple diseases (Altshuler et al., 2008) and symptoms (Cardno et al., 2002; Kendler et al., 2008), it is also likely they may help to explain the variability observed in people symptomatic with chronic breathlessness.

The only study investigating the influence of genetic factors on opioid response in chronic breathlessness was a large cross-sectional study investigating 112 candidate SNPs from 25 genes that have been implicated in opioid pathways - *OPRM1*, *OPRD1* and *OPRK1* (opioid receptors), *ARRB2*, *GNAZ* and *HINT1* (opioid signalling), *Stat6* (opioid receptor expression), *ABCB1* (transporter), *COMT*, *HRH1*, *ADRA2A*, *MC1R*, *TACR1*, *GCH1*, *DRD2*, *DRD3*, *HTR3A*, *HTR3B*, *HTR2A*,

HTR3C, *HTR3D*, *HTR3E*, *HTR1*, and *CNR1* (modulation) (Currow et al., 2015). This study included more than 2000 participants taking strong opioids for moderate to severe cancer pain. For people taking morphine, one SNP in the *HTR3B* gene (rs7103572) was shown to be associated with a three-times increased likelihood of experiencing more intense breathlessness despite taking the opioid, and no SNPs were shown to be associated with variations in the morphine dose taken. No significant associations were reported for other opioids including fentanyl and oxycodone. Importantly, the cross-sectional design of this study carries limitations. One is that breathlessness scores *prior* to morphine initiation were not available. Thus, it is unclear if there is an association between different SNPs and change in the *intensity of baseline breathlessness.* Additionally, *reduction of breathlessness after initiating morphine* (i.e., response) was also impossible to evaluate. As a result, it is unclear whether the observed differences in breathlessness scores between different *HTR3B* (rs7103572) genotypes resulted from different predispositions to experience chronic breathlessness, different responses to therapeutic opioids or both. Considering that endogenous opioids are heavily involved in generating the sensation of breathlessness in people with chronic breathlessness (Gifford et al., 2011; Mahler et al., 2009), it is likely that SNPs affecting the opioid pathways affect both the susceptibility to breathlessness and the response to therapeutic opioids in this group of patients.

Investigating the relationship between different SNPs and breathlessness is important to help identify people who are more likely to experience more intense breathlessness and who may require increased vigilance and more aggressive symptom management. Additionally, identifying pharmacogenetic differences in response to regular, low-dose, sustained-release oral morphine in a prospective study can facilitate the timely introduction of this medication in people who are more likely to respond, and avoid unnecessary burden for people who are more likely to be non-responders.

7.2.6 Potential parallels with the clinical setting of chronic pain

One major advantage of studying genetic factors influencing the experience of opioids for chronic breathlessness is the chance of drawing on the lessons learnt from the genetics of chronic pain. Given that breathlessness and pain share similar mechanisms and pathways, it may be possible to use lessons, in part, from pain to guide genetic studies in breathlessness (von Leupoldt et al., 2009). Most genetic studies conducted in the setting of pain focused on investigating the phenotypic consequences of individual SNPs or haplotypes (Obeng et al., 2017; Tammimaki & Mannisto, 2012). Hundreds of SNPs, combinations of SNPs and haplotypes were implied in the phenotypic expression of pain, some with obvious functional consequences (Kaye et al., 2019). From a practical point of view, investigating this wide range of SNPs in the context of breathlessness is possible but costly in terms of time and resources. Instead, this doctoral project focused on a relatively small number of SNPs, combination of SNPs and haplotypes that were selected based on the criteria proposed by Belfer et al. (2004) for prioritising the study of candidate genes in pain. These criteria include (Belfer et al., 2004):

i) Strength of evidence supporting its involvement in pain (breathlessness) pathways;

ii) Frequency of the allelic variant in the population; and

iii) Likelihood of functional impact.

Based on such criteria, the following SNPs, combinations of SNPs and haplotypes were included in this sub-study:

SNPs

- *OPRM1* rs1799971 (A118G) [chromosome 6];
- *COMT* rs4680 (Val158Met) [chromosome 22];
- *COMT* rs4818 [chromosome 22]; and
- *HTR3B* rs7103572 [chromosome 11].

Combination of SNPs

- *OPRM1* rs1799971 (A118G) *and COMT* rs4680 (Val158Met)

Haplotypes

- *COMT* rs4680 (Val158Met) *and COMT* rs4818

Each one of the studied SNPs, combination of SNPs and haplotypes are introduced below (Table 7.1).

Table 7.1 - Single nucleotide polymorphisms (SNPs) investigated in this sub-study and their characteristics

SNP	OPRM1 A118G (rs1799971)	COMT Val158Met (rs4680)	COMT Leu136Leu (rs4818)	HTR3B (rs7103572)
Chromosome	6	22	22	11
Molecular changes	Amino acid change from asparagine to aspartate	Amino acid change from valine to methionine	No changes in the amino acid sequence	No changes in the amino acid sequence
Wildtype allele	A	G	G	C
Variant allele	G	A	C	T
Genotype frequencies (European/Australian population)	AA: 70.2% AG: 27.2% GG: 2.6%	GG: 26.4% GA: 47.1% AA: 26.4%	GG: 16.9% GC: 46.7% CC: 36.4%	CC: 54.7% CT: 37.2% TT: 8.2%
Phenotype	Changes in μ-opioid receptor expression, ligand binding and signalling	Reduced COMT enzymatic activity and dopamine metabolism	Largely unknown	Largely unknown

7.2.6.1 OPRM1 rs1799971 (A118G)

The OPRM1 gene encodes the μ-opioid receptor, the primary action site for both endogenous and exogenous opioids. μ-opioid receptors are widely distributed in the brain, and they are particularly prevalent in the thalamus and areas of the limbic system such as the amygdala and the anterior cingulate cortex (Zubieta et al., 2003). Interestingly, these are also brain regions implied in the processing of unpleasant sensations such as pain and breathlessness, and one of the likely mechanisms of action by which morphine reduces both symptoms. As a result, SNPs in the OPRM1

gene may potentially influence both susceptibility to breathlessness and response to opioid therapy. The *OPRM1* gene may harbor more than two dozen of functional SNPs (Lötsch & Geisslinger, 2005; Somogyi et al., 2007). The most frequent and widely studied SNP of the *OPRM1* gene is the substitution of adenine to guanine at position 118 (A118G) of exon 1, on chromosome 6, resulting in an amino-acid exchange of asparagine by aspartic acid at position 40 of the μ-opioid receptor (Bond et al., 1998). At a functional level, this substitution eliminates a putative N-glycosylation site in the extra-cellular region of the receptor, disturbing the binding process between opioid and μ-opioid receptor (Bond et al., 1998). Interestingly, one of the first experimental studies exploring the functional consequences of *OPRM1 A118G* suggested that the G allele (variant) conditioned increased affinity of the endogenous opioid beta-endorphin for the μ-opioid receptor, which was also associated with increased potency (Bond et al., 1998). However, these functional differences were not observed for other endogenous or exogenous opioids, including morphine, fentanyl and methadone (Bond et al., 1998). Additionally, a meta-analysis of six experimentally induced pain studies (1753 participants) showed no significant differences in pain perception between G-allele carriers and homozygous wildtype (A/A) (Walter et al., 2013). Thus, there is currently no robust evidence suggesting that *OPRM1 A118G* confers protection against pain. In fact, studies evaluating the consequences of *OPRM1 A118G* on the efficacy and dose requirement of opioids for pain suggest opioids are less effective in G-allele carriers. A large meta-analysis of 5902 patients with acute post-operative pain revealed that people carrying at least one G allele (A/G, G/G) had higher post-operative pain scores and required higher doses of opioids at 24 hours after surgery than A/A (Lu, 2015). Similarly, a meta-analysis of 2118 people with cancer pain demonstrated that G-allele carriers required higher doses of opioids to achieve pain control than A/A homozygotes (Yu et al., 2019). It is now known that reduced opioid efficacy associated with the G allele results from both a reduction in opioid-receptor signalling and the expression of a smaller number of opioid receptors throughout the brain (Oertel & Lotsch, 2008;

Zhang et al., 2005). Importantly, the reduction in opioid-receptor signalling seems to be brain-structure specific. In this context, a *post mortem* study has suggested that a reduction in μ-opioid receptor signalling affects the secondary somatosensory cortex but not the ventral thalamus (Oertel & Lotsch, 2008). The relevance of these findings is that both structures are involved in pain (and breathlessness) processing. Therefore, changes in μ-opioid receptor signalling encoded by the G allele may result in highly variable (and unpredictable) changes in other structures involved in pain and breathlessness pathways. For example, it is still not known how the G allele affects μ-opioid receptors in the limbic system, including the amygdala, hippocampus, cingulate and pre-frontal cortexes, structures that are heavily involved in pain and breathlessness emotional networks. These questions will have to be elucidated in future studies examining the gene-dependent signalling of opioid receptors in different brain areas. Nevertheless, these findings highlight the relevance of investigating the role of *OPRM1 A118G* in the context of chronic breathlessness and its response to regular, low-dose, sustained-release oral morphine.

7.2.6.2 Catechol-O-methyltransferase (COMT)

The catechol-O-methyltransferase (*COMT*) enzyme is found both in the central nervous system and in the periphery, where it is responsible for metabolising catecholamines such as dopamine, adrenaline and noradrenaline (Andersen & Skorpen, 2009). It acts by adding a methyl group to these neurotransmitters converting them into inactive substances, regulating their extracellular concentration and facilitating their elimination (Zubieta et al., 2003). Within the central nervous system, *COMT* is particularly abundant in the pre-frontal cortex, where it is the main pathway responsible for terminating dopaminergic signal (Yavich et al., 2007). However, *COMT* is also present in other brain regions such as the striatum, amygdala and thalamus (Hong et al. 1998, Matsumoto et al. 2003). Catecholamines, particularly dopamine, have a central role in pain processing and modulation (Martikainen et al., 2018). Dopamine is able to produce analgesia mainly by activating inhibitory receptors (D2 receptors) in supra-spinal regions of the central

nervous system (Wood, 2008). Additionally, dopamine is a precursor of noradrenaline and adrenaline, which may produce both nociceptive and anti-nociceptive effects depending on the type of receptor activated (Wood, 2008). Breathlessness processing involves activation of brain regions that are similar to pain, including structures with high dopaminergic activity, such as the pre-frontal cortex and amygdala (von Leupoldt et al., 2009). Thus, it is likely that functional SNPs affecting the dopaminergic pathways produce both changes in chronic pain and chronic breathlessness processing.

Multiple SNPs in the *COMT* gene have been investigated in the context of pain (Tammimaki & Mannisto, 2012), but only one has been shown to directly affect the amino-acid chain of the *COMT* protein. The *COMT* rs4680 (Val158Met) is characterised by substitution of one valine by methionine, leading to decreased *COMT* activity and reduced inactivation of catecholamines. Additionally, there is evidence to suggest there is some interaction between the dopaminergic system and the opioid system within the brain. For example, people with the *COMT rs4680* variant also have reduced activation and increased density of μ-opioid receptors in the brain (Zubieta et al., 2003). Changes in the opioid system may be one of the mechanisms explaining variations in pain processing and response to opioids in people with *COMT* SNPs.

Interestingly, the isolated role of *COMT* rs4680 in pain processing is not completely clear. While there is evidence to suggest that the variant allele (A) increases sensitivity to pain (Hagen et al., 2006a; Zubieta et al., 2003) there are also studies showing no significant differences between genotypes (Armero et al., 2005; Hagen et al., 2006c). These contradictory findings suggest that other factors may dominate the process of pain perception. Importantly, the *COMT* gene can have other SNPs that can potentially affect protein expression and activity. Based on this, one study analysed the concomitant expression of four different *COMT* SNPs (*rs6269*, *rs4633*, *rs4818*, *rs4680*), showing that different haplotypes were associated with differences in pain sensitivity

(Diatchenko et al., 2005). These haplotype-dependent variations in pain sensitivity were categorised into three groups: *high*, *average* and *low* pain sensitivity (Diatchenko et al., 2005). These findings were later confirmed by other studies in people with post-operative pain and fibromyalgia (George et al., 2008; Vargas-Alarcón et al., 2007). Thus, it seems that interactions between SNPs may be crucial to determine sensitivity to pain.

The COMT rs4680 SNP was also explored in the context of response to opioid therapy in people with chronic pain. The available evidence is somewhat conflicting, which may be related to the multiplicity of study designs and phenotypes explored (Tammimaki & Mannisto, 2012). One study of morphine for cancer pain (207 participants) revealed that people who were homozygotes for the wild-type allele required on average 50% more morphine a day than people who were homozygotes for the variant allele (Rakvag et al., 2005). The mechanism implicated in this enhanced response is likely to be the increased number of μ-opioid binding sites encoded by the variant allele (Berthele et al., 2005; Zubieta et al., 2003). Furthermore, the fact that homozygous wildtype patients had higher circulating levels of both morphine and its metabolites compared with heterozygous and homozygous variant patients supports this hypothesis (Rakvag et al., 2005). However, the largest cross-sectional study of people with cancer and pain (2294 participants) conducted so far showed no association between *COMT rs4680* genotypes and opioid dose taken (Klepstad et al., 2011). Similar results were achieved by another cross-sectional study of 352 participants taking opioids for chronic pain of differing aetiologies (Lotsch et al., 2009). Importantly, it is interesting to note that these studies include different populations and a variety of opioids. In particular, Klepstad *et al.* and Lötsch *et al.* included a large percentage of people taking morphine, fentanyl and oxycodone, while Rakvåg *et al.* focused on people taking morphine only. It is possible, but not tested, that *COMT rs468*0 induces modifications in μ-opioid receptors that are specific to different opioids. For the purposes of studying *COMT rs4680* genotypes

associated with chronic breathlessness, it may be useful to explore the effects of different opioids separately.

7.2.6.3 5-Hydroxytryptamine type 3B (HTR3B) gene

Studies in animal models suggest that serotonin plays a role in pain modulation (Kayser et al., 2007). Importantly, there are multiple serotonin receptors involved in this process, which can stimulate or inhibit pain pathways depending on the qualities of the nociceptive stimuli (Millan, 2002). For example, while serotonin type 1 receptors (5-HT_1) are thought to have an anti-nociceptive role, serotonin type 2 and 3 receptors (5-HT_2, 5-HT_3) are thought to be pro-nociceptive (Patel & Dickenson, 2018; Zeitz et al., 2002). Furthermore, the 5-HT_3 receptor has been associated with pain catastrophising, which influences the emotional processing of pain (Horjales-Araujo et al., 2013). Multiple SNPs in genes coding for serotonin receptors were examined to understand their role in opioid response variability. The largest opioid pharmacogenetic study conducted so far included, amongst others, 36 SNPs in eight genes coding for serotonin receptors (Klepstad et al., 2011). There were no associations between different genotypes and opioid dose (Klepstad et al., 2011). Importantly, another analysis of the same cross-sectional data examined the relationship between the intensity of breathlessness, opioid dose and the same SNPs (Currow et al., 2015). In people taking morphine, the *rs7103572* SNP in the *HTR3B* gene was associated with a 3-time higher likelihood of having more intense breathlessness (Currow et al., 2015). Importantly, as mentioned before, this was a cross-sectional study focused on people with chronic pain. It did not evaluate response to morphine, that is, the degree of improvement after the introduction of morphine or other opioids. Thus, it is important to conduct prospective studies in people with chronic breathlessness in order to further investigate this SNP.

7.2.6.4 SNPs combinations

Genotype combinations of *OPRM1 rs1799971* and *COMT rs4680* have been explored before in the context of pain, but results are conflicting (Khalil et al., 2017). One cross-sectional study of 207 participants with cancer pain treated with stable doses of morphine revealed that OPRM1 homozygous wildtype and COMT rs4680 Met/Met required the lowest doses of morphine, which was approximately 60% of the dose required by those who were neither OPRM1 homozygous wildtype nor COMT rs4680 Met/Met (Reyes-Gibby et al., 2007). This difference persisted even after adjusting for potential confounders such as age, sex, performance status, time since cancer diagnosis and time using morphine (Reyes-Gibby et al., 2007). Similarly, a second cross-sectional study of 109 people treated with morphine for post-operative pain suggested that the combination of OPRM1 homozygous wildtype and COMT rs4680 Met/Met genotypes required less morphine than other participants, but the difference was not statistically significant (De Gregori et al., 2013). However, one study of 106 women receiving analgesia for labour with IV fentanyl revealed that women who were OPRM1 homozygous wildtype and COMT rs4680 Met/Met had the lowest rate of response to IV fentanyl compared with other genotypes (Landau, 2008). Moreover, the magnitude of reduction in pain scores assessed with a NRS for pain was also lower for this group (Landau et al., 2013). These findings are supported by a recent cross-sectional study of 153 patients with post-operative pain, in which participants who had COMT rs4680 Met/Met *and* OPRM1 AA or AG required higher doses of opioids to achieve pain control than the remaining combinations of these two genotypes (Khalil et al., 2017). There are obvious differences between these studies, including their sample size, population and type of pain investigated. Interestingly, similar to other studies of COMT SNPs, results seem to differ between studies using morphine and other types of opioids. This reaffirms the relevance of studying different types of opioids in the context of chronic breathlessness.

7.3 Aim

To prospectively explore the association between four frequent SNPs, breathlessness scores and response to therapy with regular, once-daily, low-dose, oral sustained-release morphine in people with chronic breathlessness.

7.4 Objectives

To investigate the relationship between intensity and unpleasantness of breathlessness at baseline, *and* response to regular, low-dose, sustained-release oral morphine with:

- four individual SNPs (*OPRM1* rs1799971, *COMT* rs4680, *COMT* rs4818, *HTR3B* rs7103572);
- COMT diplotypes [*COMT* rs4680 (Val158Met) *and COMT* rs4818]; and
- Combination of two SNPs (*OPRM1* rs1799971 and *COMT* rs4680)

7.5 Methods

7.5.1 Study design

An exploratory, prospective sub-study exploring the association of four SNPs (individually and in association) with breathlessness scores and response to regular, once-daily, low-dose, oral sustained-release morphine in people with chronic breathlessness. This sub-study was embedded in two separate Australian, phase III, double-blind, parallel-arm, placebo-controlled, randomised controlled studies evaluating the effectiveness of regular, once-daily, low-dose, oral sustained-release morphine for the symptomatic reduction of chronic breathlessness – the Morphine-Placebo study and the BEAMS study (Currow et al., 2018; Currow et al., 2017). From the 18 Australian health-care centres participating in the Morphine-Placebo and the BEAMS studies, all were invited to participate in this sub-study. Specific differences between the Morphine-Placebo and the BEAMS study are presented in Table 7.2.

Table 7.2 - Comparison between the two RCTs that recruited participants for this genetic analysis

Study	Morphine – Placebo study	BEAMS study
Design	Phase III, double-blind, parallel-arm, placebo-controlled, randomised controlled study	Phase III, double-blind, parallel-arm, placebo-controlled, randomised controlled study
Population	Adults with chronic breathlessness (any aetiology)	Adults with chronic breathlessness and COPD
mMRC eligibility	2 – 4	3 – 4
7-day Intervention	1:1 randomisation to: - Placebo; - Sustained-release morphine 20 mg.	1:1:1 randomisation to: - Placebo; - Sustained-release morphine 8 mg; - Sustained-release morphine 16 mg.
Primary outcome measure **(measured at the end of the 7-day period)**	Breathlessness *right now* measured with the 0 – 100 mm VAS for breathlessness	*Worst breathlessness* in the previous 24 hours measured with the 0 – 10 NRS for breathlessness
Outcomes of interest for the genetic analysis	*Worst*, *average* (previous 24 hours) and *unpleasantness* (right now) of breathlessness measured with the 0 – 100 mm VAS for breathlessness	*Worst*, *average* and *unpleasantness* of breathlessness in the previous 24 hours, measured with the 0 – 10 NRS for breathlessness
Setting	Outpatients of 14 palliative care and respiratory services across Australia	Outpatients of 18 palliative care and respiratory services across Australia

COPD = Chronic Obstructive Pulmonary Disease; mMRC = 0-4 modified Medical Research Council scale (higher scores correspond to lower levels of exertion achieved before being limited by breathlessness); VAS = 0 to 100mm visual analogue scale for breathlessness (0mm = "none"; 100mm = "worst possible" [intensity] or "the most unpleasantness I ever felt" [unpleasantness]); NRS = 0 to 10 numerical rating scale (0 = "no breathlessness"; 10 = "worst possible breathlessness").

7.5.2 Participants and setting

All participants enrolled in the Morphine-Placebo and BEAMS studies were eligible to participate in this sub-study. Participants included in the Morphine-Placebo differed from those included in the BEAMS study because they had different aetiologies of chronic breathlessness and an mMRC breathlessness score of 2 or higher corresponding to "walks slower than people of the same age on the level because of breathlessness *or* has to stop for breath when walking at own pace on the level" (Bestall et al., 1999). Other selection criteria were similar between these two studies (Currow et al., 2018; Currow et al., 2017).

Research nurses at each site identified and approached potential participants for this sub-study. All participants who were interested in getting further information were provided a detailed

explanation of the purpose and procedures related with the sub-study, followed by an opportunity to discuss the study in detail and clarify potential questions and concerns. All participants provided written informed consent before enrolling.

7.5.3 Sub-study procedures

7.5.3.1 General sub-study procedures

At each site, all consenting participants were asked to provide one single blood sample for pharmacogenetic analysis, in addition to the baseline blood samples collected as part of the Morphine-Placebo and the BEAMS studies. All outcome measures used in this sub-study were collected as part of the main studies procedures.

7.5.3.2 Sample collection and storage

Each sample of 2-9 mL was collected in an ethylenediaminetetraacetic acid (EDTA) tube and stored frozen at (at least) -20ºC, within the pathology department facilities at each participating site. At the end of the sub-study, all samples were then shipped frozen to the Department of Pharmacology in the University of Adelaide, South Australia, where they were analysed.

7.5.3.3 Sample analysis

Participants' blood samples were used to determine their genotypes with respect to the four SNPs included in this study (*OPRM1* rs1799971, *COMT* rs4680, *COMT* rs4818, *HTR3B* rs7103572). Chemicals, equipment and software used for genotyping are included in Table 7.3.

Table 7.3 - Chemicals, equipment and software used for genotyping

Chemicals
- 2X iTaq Universal Probes Supermix: Bio - Rad (Gladesville, New South Wales, Australia) - Nuclease-free water: Ambion R (USA) - Maxwell® 16 Blood DNA Purification Kit: Promega™ (Madison, Wisconsin, USA) - TaqMan® rs4680 genotyping assay C__25746809_50: Thermo Fisher Scientific (Scoresby, Victoria, Australia) - TaqMan® rs4818 genotyping assay C___2538750_10: Thermo Fisher Scientific (Scoresby, Victoria, Australia) - TaqMan® rs7103572 genotyping assay C__31034992_10: Thermo Fisher Scientific (Scoresby, Victoria, Australia) - Custom primers and probes (Sigma-Aldrich) - Agarose 1 (AMRESCO, Solon Ohio, USA) distributed by Astral Scientific (Gymea, New South Wales, Australia) - Omnigel-Sieve agarose (Edwards Instrument Co., Narellan) distributed by Adelab Scientific (Thebarton, South Australia, Australia) - Ethidium Bromide; Sigma-Aldrich - pUC19/Hpall DNA marker (Geneworks)
Equipment
- BioTek Microplate Reader: Millennium Science Pty Ltd (Mulgrave, Victoria, Australia) - Maxwell® 16 Magnetic Particle Processor: Promega™ (Madison, Wisconsin, USA) - QIAGEN QIAgility Robot: QIAGEN (Chadstone Centre, Victoria, Australia) - Hard - Shell® 96 - well PCR Plates: Bio - Rad (Gladesville, New South Wales, Australia) - CFX96 Real - Time System Bio - Rad (Gladesville, New South Wales, Australia) - Laboratory Centrifuge 4K15: SIGMA (Osterode, Germany) - Eppendorf Centrifuge 5418: Southern Cross Science (Edwardstown, South Australia, Australia)
Software
- DNA Quantification by Take3 Plate: Gen5 Software: Millennium Science Pty Ltd (Mulgrave, Victoria, Australia) - PCR: CFX Manager 3.0, Bio - Rad (Gladesville, New South Wales, Australia) - RStudio version 3.3.2 (Northern Ave, Boston, USA) - GraphPad Prism Software version 7.0 (La Jolla, California, USA)

7.5.3.3.1 DNA extraction and quantification

DNA was extracted from blood samples using Maxwell® 16 Blood DNA Purification Kits on a Maxwell® 16 Magnetic Particle Processor (Promega Corporation, Sydney, NSW, Australia), following the manufacturer's instructions. The obtained eluates were transferred to 1.5mL autoclaved Eppendorf tubes for storage and subsequent quantification.

In addition, DNA was also extracted from saliva samples of healthy volunteers (Barratt et al., 2014), so that they could be used as controls in the genotyping procedures. Saliva DNA extraction

was conducted using the Oragene PrepIT-L2P DNA Isolation Kit according to the manufacturer's recommended procedures (DNA Genotek Inc). Additionally, saliva DNA samples were purified using a chloroform clean-up which included:

- adding 1/20 volume of chloroform to the DNA solution in nuclease-free water [Thermo Fisher Scientific Inc (Thermo Fisher, USA)];
- vortexing for one minute; and
- centrifuging at 16,000 x g for fifteen minutes.

The aqueous layer containing DNA was then collected and DNA precipitated with 100% ethanol (volume 2:1) and sodium acetate 3M (volume 1/10:1). Samples were then centrifuged at 15,000 x g for 5 minutes and supernatant aspirated, before another wash with 70% ethanol. The saliva DNA samples were subsequently dried and resuspended in 50 uL nuclease-free water.

DNA was quantified using BioTek Microplate Reader and Take3 plate. All DNA quantification procedures were preceded by a quadruplicate blank read to determine background absorbance and check system precision. Spectrophotometric absorbance was utilised to identify and quantify DNA in the samples. DNA primarily absorbs radiation with an approximate wavelength of 260 nm which differs from proteins and other contaminants (e.g., residual reagents associated with the extraction protocol; typically absorbance 280 nm). Thus, the 260/280 ratio is useful to assess the degree of purity of a given DNA sample. Samples with 260/280 ratios ≥ 1.7 were considered adequate while samples with 260/280 ratios < 1.7 raised suspicions of contamination and were re-purified using chloroform and ethanol/sodium acetate (as above) or re-isolated.

The Take3 plate procedure also provided information about the DNA concentration in each sample. Concentrations ≥ 20 ng/µL were considered sufficient to proceed to genotyping while concentrations < 20 ng/uL were deemed insufficient for genotyping and the samples were either

re-isolated or concentrated using ethanol and sodium acetate solution as above. This step assured the quality of each DNA sample before advancing any further in the analysis.

7.5.3.3.2 Preparation for genotyping

Samples were normalized to a volume of 50µL each and a concentration of 20 ng/µL using QIAGEN QIAgility Robot, in preparation for RT-PCR. Reaction plates with the DNA samples were created using a master mix (specific for each SNP) plus the original DNA samples in a proportion of 19:1 (19µL MM + 1µL DNA sample). Master mix compositions for *OPRM1* rs1799971, *COMT* rs4680/rs4818 and *HTR3B* rs7103572 are presented in Tables 7.4 to 7.6.

Table 7.4 - Master mix composition for the *OPRM1* rs1799971 assay

Master mix products (*OPRM1* assay)	**Volume / DNA sample**
6 uM custom forward primer (CGGTTCCTGGGTCAACTTGT)	0.5 uL (150 nM)
6 uM custom reverse primer (GTGATGGCCGTGATCATGGA)	0.5 uL (150 nM)
Custom wild-type (A) probe: [6FAM]CACTTAGATGG[+C][+A]ACCTGTCCGACC[BHQ1]	0.5 uL (150 nM)
Custom variant (G) probe: [HEX]CACTTAGATGG[+C][+G]ACCTGTCCGACC[BHQ1]	0.5 uL (150 nM)
2X iTaq Universal Probes Supermix	10 uL
Nuclease-free water	7 uL
Total	19 uL

Table 7.5 - Master mix composition for the COMT rs4680 and rs4818 assays

Master mix products (*COMT* assays)	**Volume / DNA sample**
TaqMan primer/probe mix (C_59013445_10)	0.75 µL
2X iTaq Universal Probes Supermix	10 µL
Nuclease-free water	8.25 µL
Total	19 µL

Table 7.6 - Master mix composition for the HTR3B rs7103572 assay

Master mix products (*HTR3B* assay)	**Volume / DNA sample**
TaqMan primer/probe mix (C_31034992_10)	0.4 µL
2X iTaq Universal Probes Supermix	10 µL
Nuclease-free water	8.6 µL
Total	19 µL

This sub-study used polymerase chain reaction (PCR) to amplify the genome regions of interest before they could be analysed. The process of DNA amplification is conducted in a thermal cycler and requires the following products:

- the original DNA chain where the target genetic sequence is located;
- a forward and a reverse primer, one for each DNA strand (defined as sequences of nucleotides marking the target DNA for amplification);
- a thermostable DNA polymerase enzyme (to promote the binding of new nucleotides to an individual DNA strand leading to a newly formed double-strand DNA); and
- deoxynucleotide triphosphates (dNTPs; provide individual nucleosides which will be used as building blocks to form new DNA strands from primers).

The PCR process takes place in two phases:

1. Denaturation: The double-stranded DNA is separated into two single strands through a heating process (~95ºC);
2. Annealing (or hybridization) and elongation: Lower temperatures (typically ~50-72ºC) cause the binding of primers to the target DNA marking the target region for amplification; the forward primer will bind to one of the DNA strands and the reverse primer will bind to the complementary DNA strand. Then, the DNA polymerase facilitates the binding of free nucleotides forming a complementary DNA strand from each primary strand; two double strands are therefore formed from a single one.

The two phases of the PCR process are repeated for every new double strand formed creating millions of copies of the original target sequence, in an exponential fashion. The PCR assay needs to be optimised for every genetic sequence amplified, which involves careful assessment of primers, reagent concentrations and annealing temperatures. This optimisation ensures that

primers are specific to the target sequence (i.e., they do not bind to other DNA sequences) and that the amplification is as efficient as possible.

Real-time PCR (RT-PCR) is a relatively new laboratory technique that allows "real-time" monitoring of the DNA amplification process instead of obtaining a single result at the end. RT-PCR was used to conduct DNA amplification in this sub-study.

In addition to sequence amplification, new RT-PCR devices can discriminate between allelic variants while the PCR process is running. This new laboratorial technique known as *dual labelled probe allelic discrimination* requires two fluorescent oligonucleotide probes:

- Probe 1 – Specific for the first allele sequence (wild-type allele); and
- Probe 2 – Specific for the second allele sequence (variant allele).

Each probe integrates a fluorescent molecule in its 5' end named the *reporter* and a second molecule attached to the 3' end of each probe named the *quencher*. When the quencher and the reporter are together in the same probe, the reporter fluorescence is inhibited by a process defined as fluorescence resonance energy transfer. During the PCR elongation phase, the DNA polymerase cleaves the probe releasing and separating the reporter from the quencher which generates the fluorescent signal for that specific allele (i.e., wild-type or variant). In RT-PCR, the fluorescence of a given DNA product is measured for each cycle while the exponential amplification of the sequence of interest is occurring. Specific fluorescence will then increase throughout the process generating a plot matching the corresponding genotype (homozygous wildtype, homozygous variant, or heterozygous).

For this study, RT-PCR and dual labelled probe allelic discrimination were conducted separately for the four pre-selected SNPs: *OPRM1* (rs1799971), *COMT* (rs4680, rs4818) and *HTR3B* (rs7103572). A CFX96 real-time PCR system (BioRad) was used for these procedures. Thermocycling conditions

were 95°C for three minutes followed by cycles of 95°C for five seconds (denaturation) and an assay-specific optimised annealing temperature for 30 seconds (Table 7.7). Each cycle was followed by fluorescence recording, with allelic discrimination after 50 cycles.

Table 7.7 – Annealing temperatures used in each assay

Assay	Annealing temperature after optimisation and validation
OPRM1 rs1799971	71°C
COMT rs4680	67°C
COMT rs4818	68°C
HTR3B rs7103572	64ºC

7.5.3.3.3 Assay development, optimisation and validation

Annealing temperature optimisation was performed simultaneously with identification of putative genotyping controls using healthy control saliva DNA. After preparation for genotyping, healthy control saliva DNA samples were subject to RT-PCR and dual labelled probe allelic discrimination using the BioRad. Annealing temperatures between 60ºC and 72ºC were tested to identify the optimal annealing temperature for each SNP assay. The optimal annealing temperature for each SNP was defined as the temperature that provided the highest fluorescence with the least non-specific DNA amplification.

Putative control samples of each genotype identified during this process were then confirmed by Sanger sequencing. Sequencing primers for each assay were designed according to the following criteria: product size range of 150-300 base pairs (bp), primer GC content 40-60%, primer size between 18-22 base pairs, primer annealing temperature between 55-62°C, maximum of two GCs at the end of the primer, and maximum of 3 nucleotide repeats. Sequencing primer sequences for each assay were: *OPRM1* rs1799971 (primers in Table 4), *COMT* rs4680 (forward: TACTGTGGCTACTCAGCTGTGC, reverse: GTGAACGTGGTGTGAACACC) and rs4818 (forward:

GATCGTGGACGCCGTGATTC, reverse: CAGTGAACGTGGTGTGAACAC), *HTR3B* rs7103572 (forward: TTACCTGCTCCCGCCTCTTT, reverse: CGCCCTGCCTAAACCTTGTA).

Amplicons (DNA sequences which are the product of amplification) for sequencing were generated with primers using the following conditions:

- 1× iTaq Universal Probes Supermix;
- 150 nM each primer (forward and reverse); and
- 20 ng of DNA (20 µl reaction volume).

Reactions were subject to 95°C for three minutes followed by then 30 cycles of 95°C for five seconds and the assay-specific optimised annealing temperature for 30 seconds. PCR products were confirmed by 4% agarose gel electrophoresis with UV visualisation before submitting PCR products along with forward and reverse primers to the Australian Genome Research Facility for bi-directional Sanger (BigDye Terminator) sequencing. Study samples were then genotyped, with each assay run including two no-template controls (nuclease-free water) and positive controls of each genotype confirmed by Sanger sequencing.

7.5.4 Outcomes

The primary outcome for this sub-study were differences in self-rated intensity of *worst breathlessness* in the previous 24 hours, by individual genotype, combination of genotypes, haplotype and dose level (placebo, sustained-release morphine 8 mg, and 16 mg, 20 mg), on days 5 to 7.

Secondary outcomes included differences, by individual genotype, combination of genotypes, haplotype and dose level (placebo, sustained-release morphine 8 mg, and 16 mg, 20 mg) in self-rated average breathlessness in the previous 24 hours and *breathlessness right now*.

Self-rated breathlessness scores were collected using the VAS for breathlessness in the Morphine-Placebo study and the NRS for breathlessness in the BEAMS study. In order to aggregate results from both studies, NRS scores collected as part of BEAMS were converted into 0 to 100 VAS scores. This approach was used because previous patient-reported data has shown that NRS and VAS scores follow similar distributions (Johnson et al., 2013b; Powers & Bennett, 1999). In both Morphine-Placebo and BEAMS, *worst* and *average breathlessness* in the previous 24 hours were collected in the evening, at baseline and on days 5 to 7. Similarly, *unpleasantness of breathlessness* was collected in both trials, but they reported to different timeframes: *unpleasantness of breathlessness* right now (Morphine-Placebo study) and *unpleasantness of breathlessness* in the previous 24 hours (BEAMS study). Since there is a high positive correlation between scores of *breathlessness right now* and *breathlessness in the previous 24 hours*, *unpleasantness* scores from both studies were combined (Wade et al., 2017). Importantly, intensity of *breathlessness right now*, which was the primary outcome in the Morphine-Placebo study, has been shown to vary widely depending on circumstantial aspects (Johnson et al., 2016). As a result, this measure may be difficult to interpret and was not collected as part of the BEAMS study or this sub-study.

7.5.5 Sample size

This was an exploratory sub-study embedded in two randomised controlled trials. For this reason, no formal sample size calculation was undertaken. Procedures were relatively simple and some of the targeted SNPs were relatively infrequent in the general population. As a result, this sub-study aimed to recruit as many participants as possible, in order to facilitate comparison between different genotypes and different regular, low-dose, sustained-release oral morphine doses.

7.5.6 Statistical analysis

All participants who had scored *worst*, *average* or *unpleasantness of breathlessness* at least once were included in the analysis. Descriptive statistics were used to summarise the sample characteristics. For every measure of breathlessness, baseline differences between doses (i.e., placebo, sustained-release morphine 8mg, 16mg and 20mg) and SNPs genotypes (i.e., homozygous wildtype, heterozygous, homozygous variant) were explored using one-way ANOVA. For every measure of breathlessness, breathlessness differences between baseline and the mean of days 5 to 7 were explored, regardless of dose and genotype, using paired samples T-tests. One-way ANOVA was used to compare mean differences in breathlessness scores between baseline and the mean of days 5 to 7, irrespective of genotype. One-way ANOVA was also used to compare mean differences in breathlessness scores between baseline and the mean of days 5 to 7, irrespective of dose. Two-way ANOVA was used to investigate dose-by-genotype interactions. An ANCOVA model was used to investigate dose-by-genotype interactions having baseline breathlessness (i.e., *worst*, *average* or *unpleasantness*) as a covariate. Other covariates with the potential to influence response to regular, low-dose, sustained-release oral morphine (i.e., age) were not included in the ANCOVA model. Considering the small number of participants with certain genotypes, the ANCOVA model would be unreliable to predict the influence of multiple factors.

7.5.7 Ethical issues

This sub-study was designed to be minimally invasive for participants. As a result, when possible, blood samples required for pharmacogenetic analysis were collected as part of other collection procedures (i.e., blood collection for the main study or for routine clinical assessment). All outcome measures were collected as part of the Morphine-Placebo and the BEAMS study and required no additional time or effort from participants.

7.6 Results

7.6.1 Recruitment and retention

From the 287 participants recruited to the Morphine-Placebo study between February 2010 and July 2015, 216 did not provide a blood sample for this sub-study. Of those, 103 did not require blood collection as part of the main trial and samples for genetic analysis were also not collected; 100 participants were not invited to provide a blood sample for genetic analysis (recruited in sites without the capacity to collect and/or store the samples); four participants had difficult peripheral venous access and study nurses were unable to collect blood; two participants did not provide written informed consent for the pharmacogenetics study; and six participants did not collect blood samples for genetic analysis for unknown reasons. Seventy-one Morphine-Placebo study participants provided a sample for genetic analysis. Of those, three withdrew from the study before completing any baseline measure and seven were excluded because they did not complete any baseline measures of *worst*, *average* or *unpleasantness of breathlessness*. A total of 61 participants were included in the final analysis.

From the 165 participants recruited to the BEAMS study between August 2016 and June 2019, 58 did not provide a sample for genetic analysis. Of those, 24 participants did not collect a blood sample due to a change in study personnel, who had to become familiar with the study procedures; 20 did not provide written informed consent; and 14 samples were not sent to the University of Adelaide in time to be analysed, but they will be included in a future peer-reviewed publication. One-hundred and seven BEAMS participants provided a sample for analysis. Of those, 11 did not complete any baseline measures and were excluded from the analysis; one participant's sample was lost. Ninety-five BEAMS participants were included in the final analysis. A total of 156 participants coming from both the Morphine-Placebo and the BEAMS study were included in the genetic analysis (Figure 7.1).

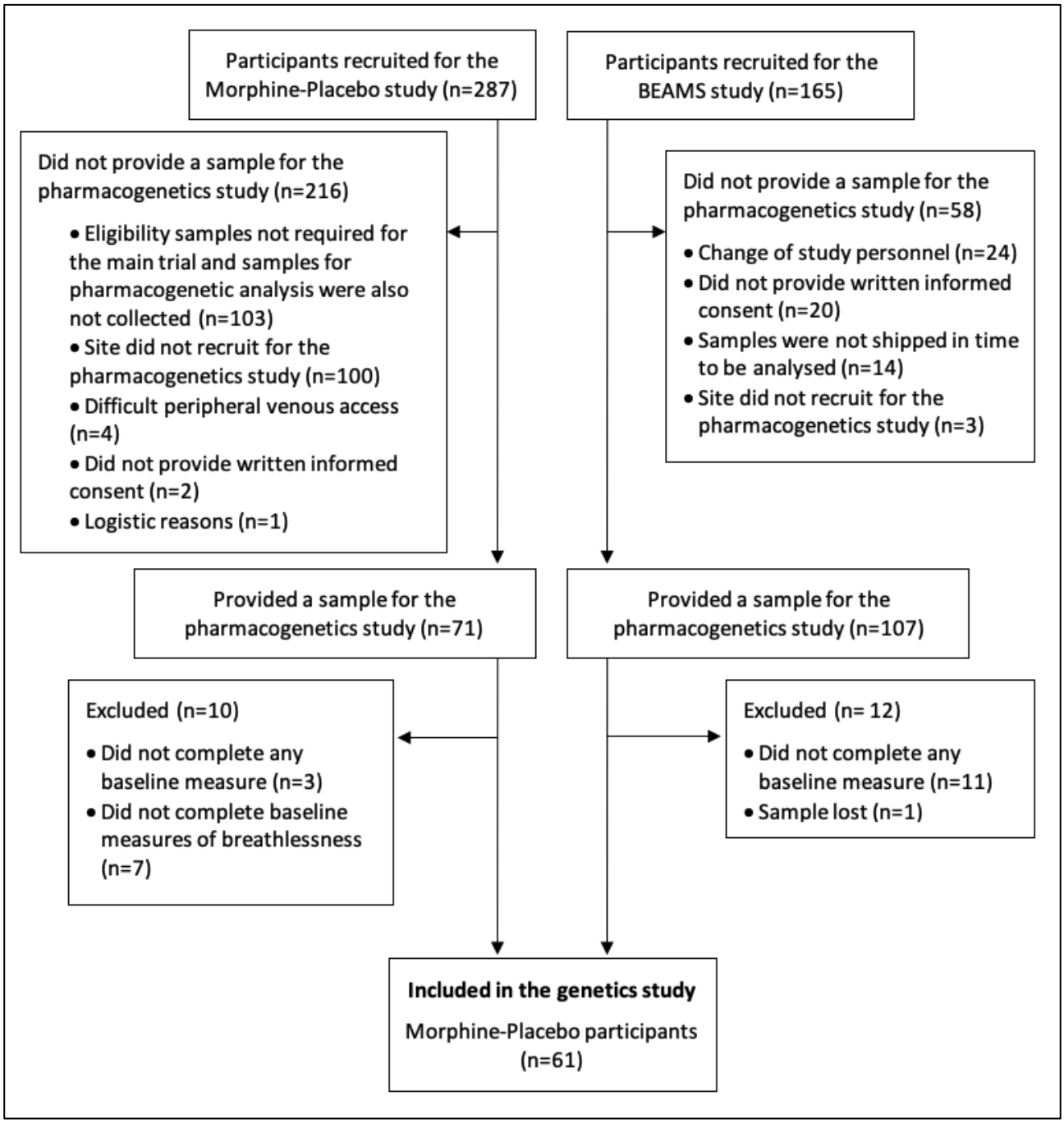


Figure 7.1 - Diagram of participants included in the genetics sub-study

Participants had a median age of 74 years (interquartile range [IQR] 68 – 79 years), 90 (57.7%) were male and 145 (92.9%) had COPD as the principal cause of breathlessness. Most had an mMRC 3 or 4 tolerating only low or very low levels of exertion before being limited by breathlessness (149 [94.8%]) and required occasional assistance on a daily basis (median AKPS 60

[IQR 60 – 70]). Almost half of the participants required regular or continuous use of supplemental oxygen (Table 7.8).

Table 7.8 - Participants' characteristics

		Morphine-Placebo (n=61)	BEAMS (n=95)	Total (n=156)
Age (years)	Median [IQR]	74.9 [68 – 80]	73.0 [67 – 78]	74 [68 – 79]
	Min, Max	44, 92	49, 93	44, 93
Gender, n (%)	Female	24 (39.3%)	42 (44.2%)	66 (42.3%)
BMI (kg/m^2)	Median [IQR]	24.7 [21 – 27]	26.8 [22 – 32]	25.5 [22 – 30]
	Min, Max	14, 43	11, 53	11, 53
Charlson Co-morbidity Index (adjusted to age)	Median [IQR]	5.0 [4 – 6]	5.0 [4 – 6]	5.0 [4 – 6]
	Min, Max	1, 11	2, 10	1, 11
Performance status (AKPS)	Median [IQR]	60.0 [60 – 70]	60.0 [60 – 70]	60.0 [60 – 70]
	Min, Max	50, 80	50, 80	50, 80
Smoking status, n (%)	Smoker	8 (13.1%)	19 (20.0%)	27 (17.3%)
	Ex-smoker	50 (82.0%)	74 (77.9%)	124 (79.5%)
	Never smoked	3 (4.9%)	2 (2.1%)	5 (3.2%)
mMRC breathlessness score at baseline, n (%)	2	7 (11.5%)	-	7 (4.5%)
	3	39 (63.9%)	79 (83.2%)	118 (75.6%)
	4	14 (23.0%)	16 (16.8%)	30 (19.2%)
Primary cause for breathlessness, n (%)	COPD	50 (82.0%)	95 (100%)	145 (92.9%)
	ILD	4 (6.5%)	-	4 (2.6%)
	Lung Cancer	2 (3.3%)	-	2 (1.3%)
	Mixed	3 (4.9%)	-	3 (1.9%)
	Other	2 (3.3%)	-	2 (1.3%)
Oxygen use	Yes n (%)	30 (49.2%)	40 (42.1%)	70 (45.8%)
Baseline median [IQR] breathlessness scores (converted 0-100 VAS)	"Worst"	67.0 [46 – 76]	65.0 [50 – 75]	65.0 [50 – 75]
	"Average"	45.0 [33 – 55]	50.0 [40 – 60]	50.0 [35 – 58]
	"Unpleasantness"	36.0 [16 – 52]	50.0 [20 – 60]	45.0 [20 – 60]

mMRC = 0-4 modified Medical Research Council scale (higher scores correspond to lower levels of exertion achieved before being limited by breathlessness); VAS = 0 to 100mm visual analogue scale for breathlessness (0mm = none; 100mm = "worst possible" [intensity] or "the most unpleasantness I ever felt" [unpleasantness]); AKPS = Australia-modified Karnofsky Performance Status (higher scores correspond to better performance status).

7.6.2 Hardy-Weinberg Equilibrium

Allele frequencies for *COMT* rs4818 and *HTR3B* rs7103572 deviated for the Hardy–Weinberg equilibrium, both with excess heterozygotes (p=0.03 and p=0.02, respectively). No genotyping errors were detected. There were no deviations from the Hardy–Weinberg equilibrium for *COMT* rs4680 and *OPRM1* rs1799971 and genotype frequencies.

7.6.3 Baseline breathlessness differences between genotypes

For *COMT* rs4680, there were no significant baseline differences in *worst* or *unpleasantness of breathlessness* between genotypes (p>0.8). There were small variations in *average breathlessness* between *COMT* rs4680 genotypes that did not reach statistical significance (G/G = 52.7±19.1mm [n=26], G/A = 47.1±14.9mm [n=88], A/A = 42.8±15.8mm [n=36]; p=0.06). There were no statistically significant differences in any measure of baseline breathlessness for *COMT* rs4818 genotypes (p>0.2). For *HTRB3* rs7103572, no significant differences were found between genotypes for *worst* and *unpleasantness of breathlessness* (p>0.2). There were significant differences between *HTRB3* rs7103572 genotypes for baseline *average breathlessness* (p=0.03) (C/C = 44.1±17.0mm [n=63], C/T = 50.4±15.3mm [n=77], T/T = 40.4±11.5mm [n=9]; Tukey *post hoc* test p=0.06 C/C vs C/T). No statistically significant differences were found in any measure of baseline breathlessness for *OPRM1* rs1799971 genotypes (p>0.4).

7.6.4 Breathlessness differences between baseline and days 5 to 7 for individual SNPs

All measures of breathlessness were reduced from baseline to days 5-7 (mean±SD reduction = 9.3±20.1mm [*worst*], 5.1±18.2mm [*average*], 7.7±21.1mm [*unpleasantness*]; p≤0.001), but with no significant treatment effect (p>0.1). Reduction in *average breathlessness* differed significantly between *COMT* rs4680 genotypes (p=0.03) (G/G = 11.2±22.3mm [n=24], G/A = 5.9±17.2mm [n=80], A/A = -1.4±15.7mm [i.e. increase] [n=32], Tukey *post hoc* test p=0.027 G/G vs A/A), and *HTR3B* rs7103572 genotypes (p=0.02) (C/C = 0.5±16.6mm [n=59], C/T = 7.3±18.5mm [n=68], T/T = 17.1±21.3mm [n=8], Tukey *post hoc* test p=0.04 for C/C vs T/T, independent of treatment (Figure 7.2). There were no statistically significant differences for other SNPs or other measures of breathlessness. However, the proportion of participants experiencing clinically meaningful improvements in *worst* and *average* breathlessness from baseline to days 5-7 was higher for the

people who had at least one variant allele (*worst* breathlessness: A/A = 41.5%; A/G = 71.4; G/G = 100%; *average* breathlessness: A/A = 35.4%; A/G = 47.6; G/G = 100%).

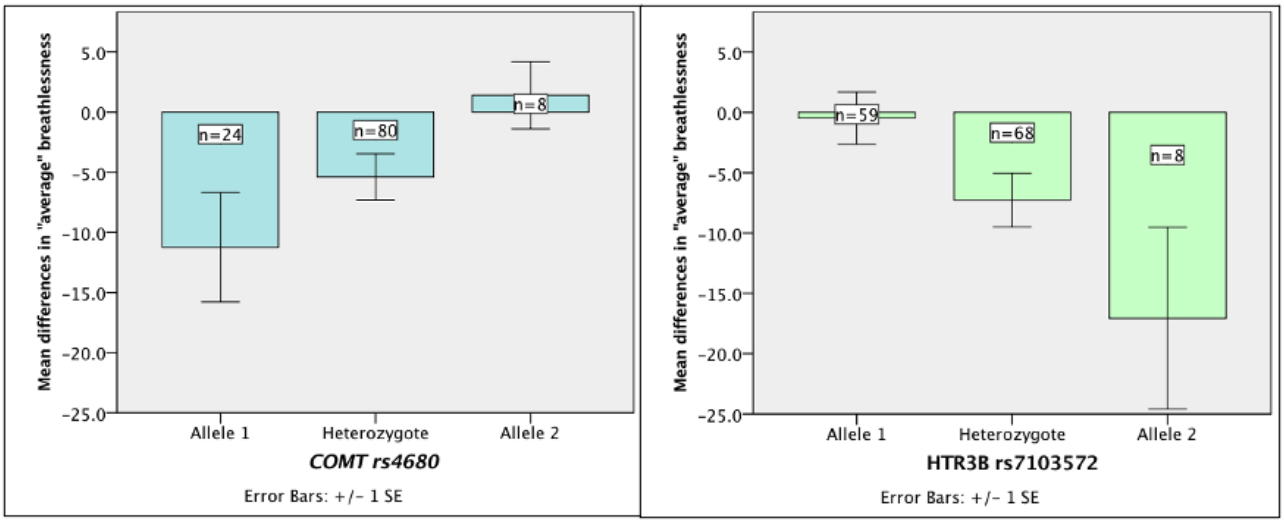
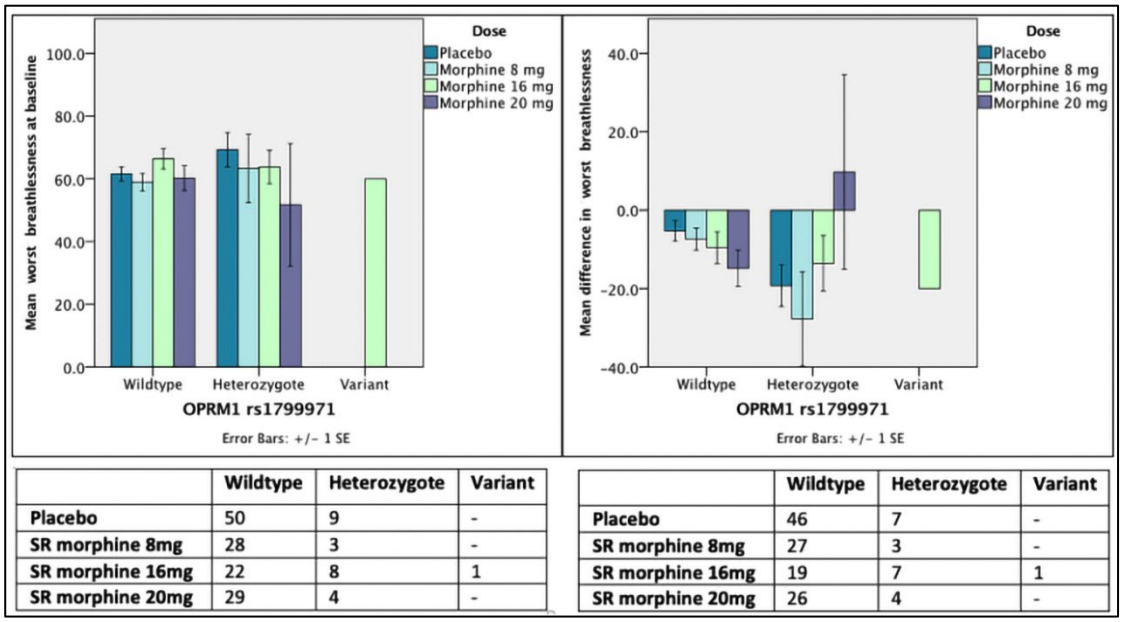


Figure 7.2 - Mean differences in *average breathlessness* scores (from baseline – days 5-7) for *COMT* rs4680 and *HTR3B* rs7103572 genotypes (error bars represent ± 1 standard error [SE])

Mean breathlessness scores at baseline and mean reductions in breathlessness scores from baseline to days 5 to 7, according to genotype and arm are displayed in Figures 7.3 to 7.10. In the two-way ANOVA using dose and genotype as independent variables, only differences in *average breathlessness* for *HTR3B* rs7103572 genotypes remained significant (p=0.03), independent of treatment (genotype-treatment interaction p=0.7). For *worst breathlessness*, there was a significant interaction between genotype and dose for *OPRM1* rs1799971 (p=0.02). However, two-way ANOVA Dunnet *post hoc* test (for each dose versus placebo within each genotype) did not show any statistically significant differences (p>0.7). Of note, the groups of *OPRM1* rs1799971 homozygotes wildtype, *COMT* rs4818 and *HTR3B* rs710357 homozygotes variant showed a pattern of greater reductions in *worst breathlessness* with increasing doses of regular, low-dose, sustained-release oral morphine, which was not seen for other genotypes.

In the ANCOVA models using dose and genotype as independent variables and baseline breathlessness as a covariate, higher baseline breathlessness was associated with larger

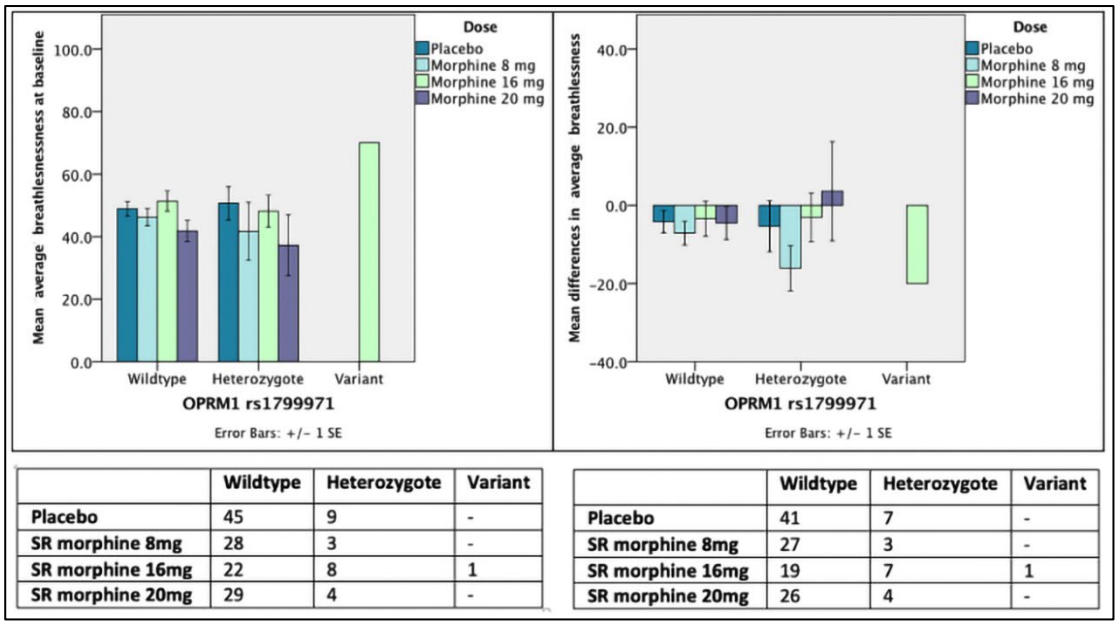
reductions in *worst*, *average* and *unpleasantness* scores from baseline to days 5 to 7, for all SNPs (p<0.002). Additionally, differences in *average breathlessness* remained significant for *HTR3B* rs7103572 genotypes (p=0.045), independent of treatment (genotype-treatment interaction p=0.2). Interaction between genotype and dose for *OPRM1* rs1799971 also remained significant (p=0.036).



	Wildtype	Heterozygote	Variant
Placebo	50	9	-
SR morphine 8mg	28	3	-
SR morphine 16mg	22	8	1
SR morphine 20mg	29	4	-

	Wildtype	Heterozygote	Variant
Placebo	46	7	-
SR morphine 8mg	27	3	-
SR morphine 16mg	19	7	1
SR morphine 20mg	26	4	-

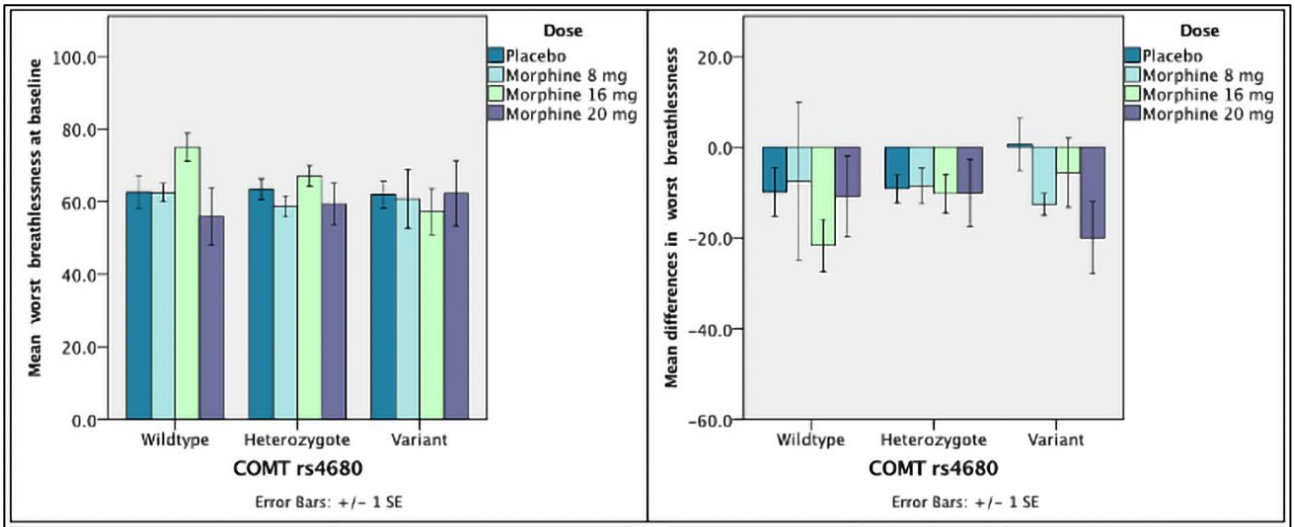
Figure 7.3 - Mean *worst breathlessness* at baseline (first graph) and mean reduction in *worst breathlessness* from baseline to days 5 to 7 (second graph), according to *OPRM1* rs1799971 genotype (error bars represent ± 1 standard error [SE])



	Wildtype	Heterozygote	Variant
Placebo	45	9	-
SR morphine 8mg	28	3	-
SR morphine 16mg	22	8	1
SR morphine 20mg	29	4	-

	Wildtype	Heterozygote	Variant
Placebo	41	7	-
SR morphine 8mg	27	3	-
SR morphine 16mg	19	7	1
SR morphine 20mg	26	4	-

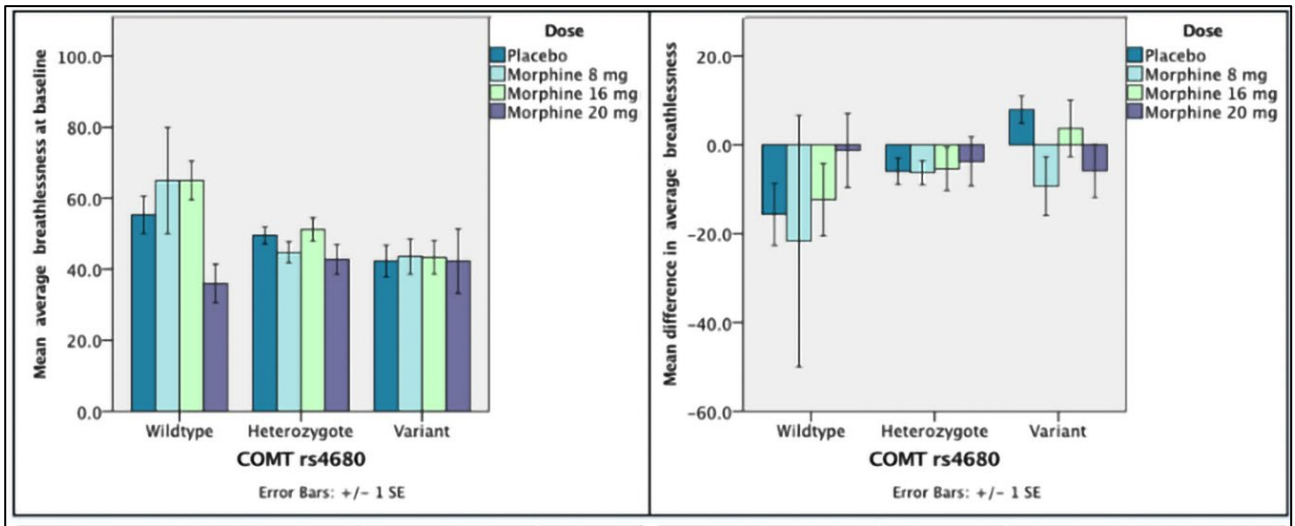
Figure 7.4 - Mean *average breathlessness* at baseline (first graph) and mean reduction in *average breathlessness* from baseline to days 5 to 7 (second graph), according to *OPRM1* rs1799971 genotype (error bars represent ± 1 standard error [SE])



	Wildtype	Heterozygote	Variant
Placebo	15	31	14
Morphine 8mg	2	22	7
Morphine 16mg	5	17	9
Morphine 20mg	7	20	6

	Wildtype	Heterozygote	Variant
Placebo	13	28	12
Morphine 8mg	2	21	7
Morphine 16mg	5	14	8
Morphine 20mg	7	19	4

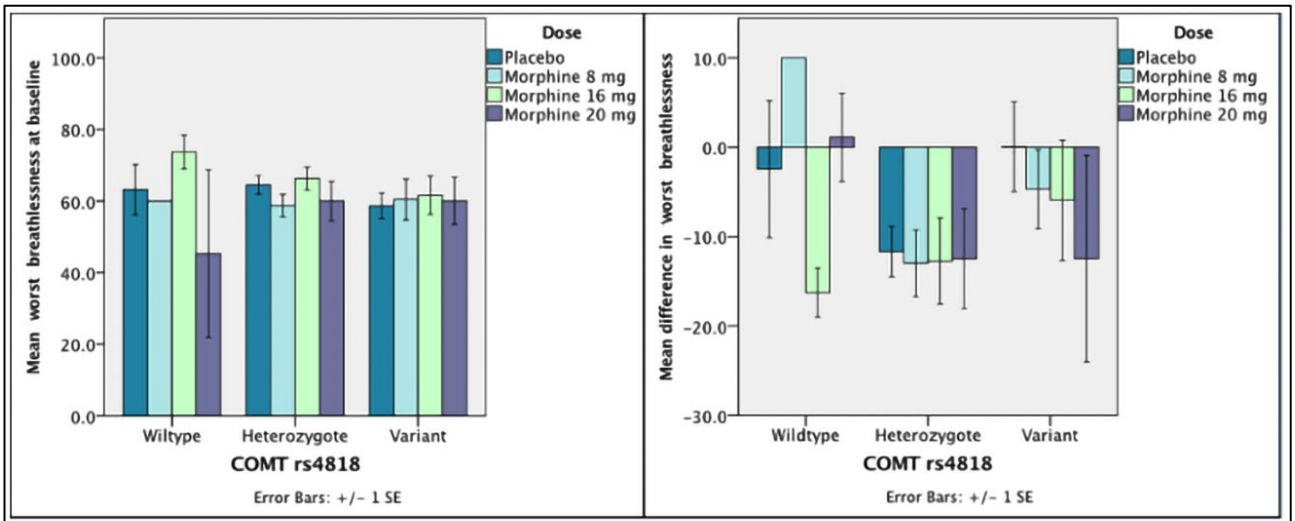
Figure 7.5 - Mean *worst breathlessness* at baseline (first graph) and mean reduction in *worst breathlessness* from baseline to days 5 to 7 (second graph), according to *COMT* rs4680 genotype (error bars represent ± 1 standard error [SE])



	Wildtype	Heterozygote	Variant
Placebo	12	29	14
Morphine 8mg	2	22	7
Morphine 16mg	5	17	9
Morphine 20mg	7	20	6

	Wildtype	Heterozygote	Variant
Placebo	10	26	13
Morphine 8mg	2	21	7
Morphine 16mg	5	14	8
Morphine 20mg	7	19	4

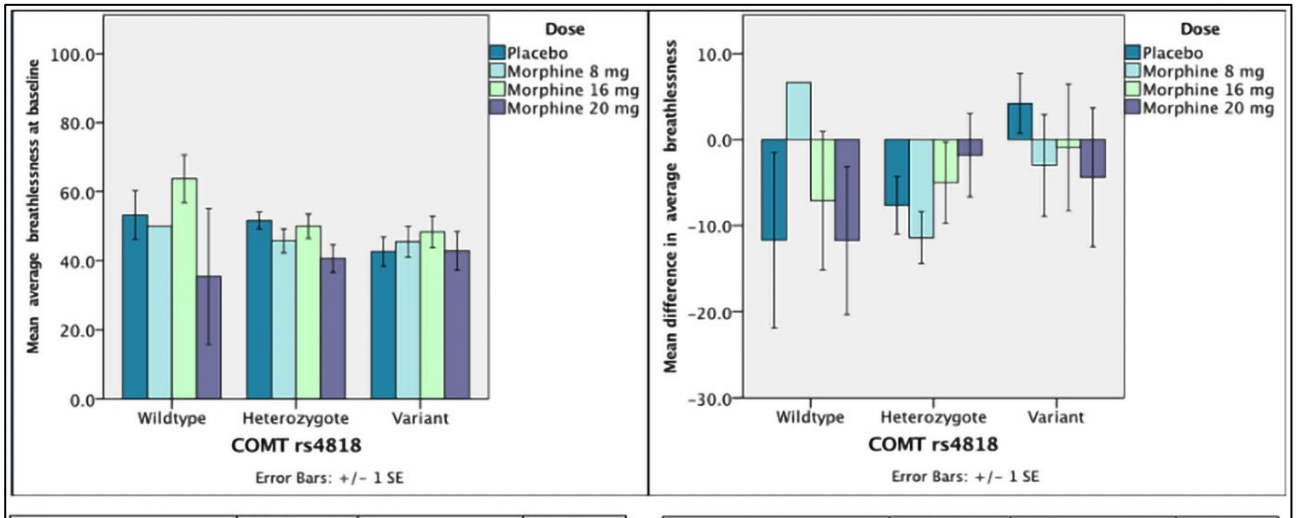
Figure 7.6 - Mean *average breathlessness* at baseline (first graph) and mean reduction in *average breathlessness* from baseline to days 5 to 7 (second graph), according to *COMT* rs4680 genotype (error bars represent ± 1 standard error [SE])



	Wildtype	Heterozygote	Variant
Placebo	9	34	16
SR morphine 8mg	1	20	10
SR morphine 16mg	4	15	12
SR morphine 20mg	2	18	13

	Wildtype	Heterozygote	Variant
Placebo	7	31	15
SR morphine 8mg	1	19	10
SR morphine 16mg	4	14	9
SR morphine 20mg	2	17	11

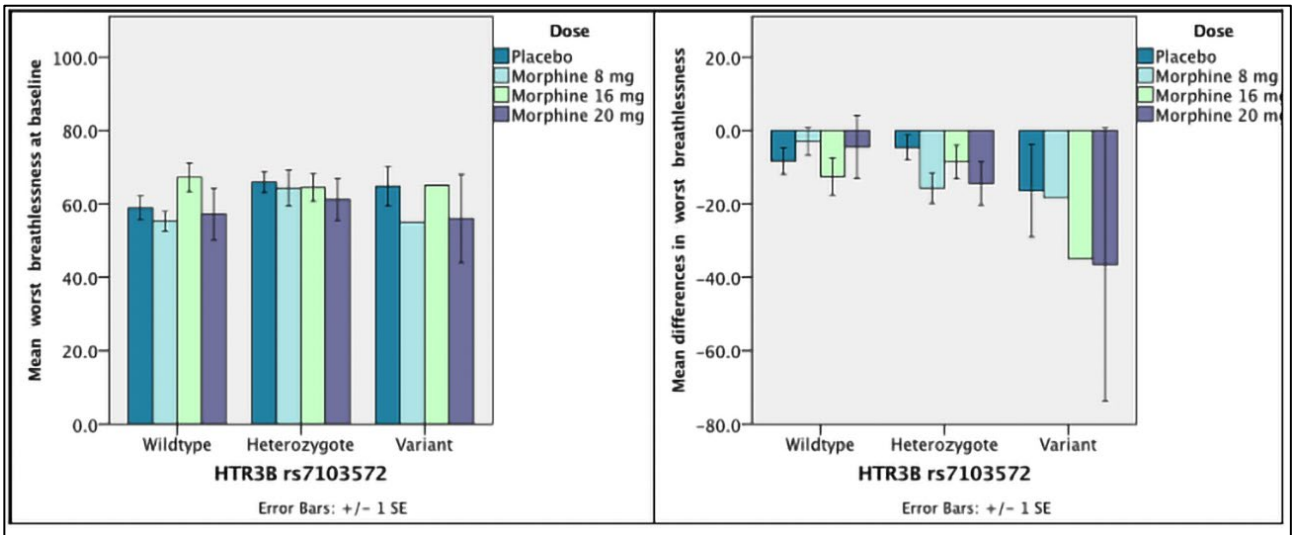
Figure 7.7 - Mean *worst breathlessness* at baseline (first graph) and mean reduction in *worst breathlessness* from baseline to days 5 to 7 (second graph), according to *COMT* rs4818 genotype (error bars represent ± 1 standard error [SE])



	Wildtype	Heterozygote	Variant
Placebo	7	31	16
SR morphine 8mg	1	20	10
SR morphine 16mg	4	15	12
SR morphine 20mg	2	18	13

	Wildtype	Heterozygote	Variant
Placebo	5	28	15
SR morphine 8mg	1	19	10
SR morphine 16mg	4	14	9
SR morphine 20mg	2	17	11

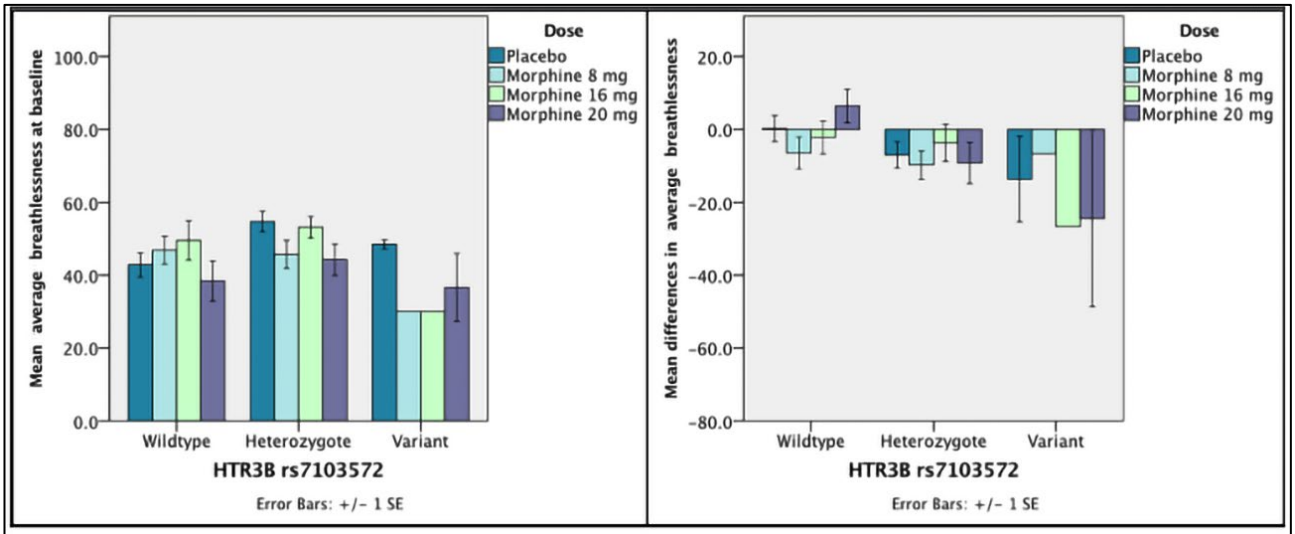
Figure 7.8 - Mean *average breathlessness* at baseline (first graph) and mean reduction in *average breathlessness* from baseline to days 5 to 7 (second graph), according to *COMT* rs4818 genotype (error bars represent ± 1 standard error [SE])



	Wildtype	Heterozygote	Variant
Placebo	26	29	4
SR morphine 8mg	16	14	1
SR morphine 16mg	11	19	1
SR morphine 20mg	13	17	3

	Wildtype	Heterozygote	Variant
Placebo	24	25	4
SR morphine 8mg	15	14	1
SR morphine 16mg	10	16	1
SR morphine 20mg	13	15	2

Figure 7.9 - Mean *worst breathlessness* at baseline (first graph) and mean reduction in *worst breathlessness* from baseline to days 5 to 7 (second graph), according to *HTR3B* rs3107532 genotype (error bars represent ± 1 standard error [SE])



	Wildtype	Heterozygote	Variant
Placebo	23	27	4
SR morphine 8mg	16	14	1
SR morphine 16mg	11	19	1
SR morphine 20mg	13	17	3

	Wildtype	Heterozygote	Variant
Placebo	21	23	4
SR morphine 8mg	15	14	1
SR morphine 16mg	10	16	1
SR morphine 20mg	13	15	2

Figure 7.10 - Mean *average breathlessness* at baseline (first graph) and mean reduction in *average breathlessness* from baseline to days 5 to 7 (second graph), according to *HTR3B* rs3107532 genotype (error bars represent ± 1 standard error [SE])

7.6.5 Breathlessness differences for COMT haplotype combinations (diplotype)

There were no statistically significant differences in mean baseline breathlessness scores between different COMT diplotypes (p>0.2), regardless of treatment. As an overall trend, there were greater reductions in breathlessness scores from baseline to days 5 to 7 for HPS/LPS diplotype and smaller reductions for APS/APS and APS/HPS, independent of dose (Figures 7.11 to 7.13). However, such differences were not statistically significant (p>0.3).

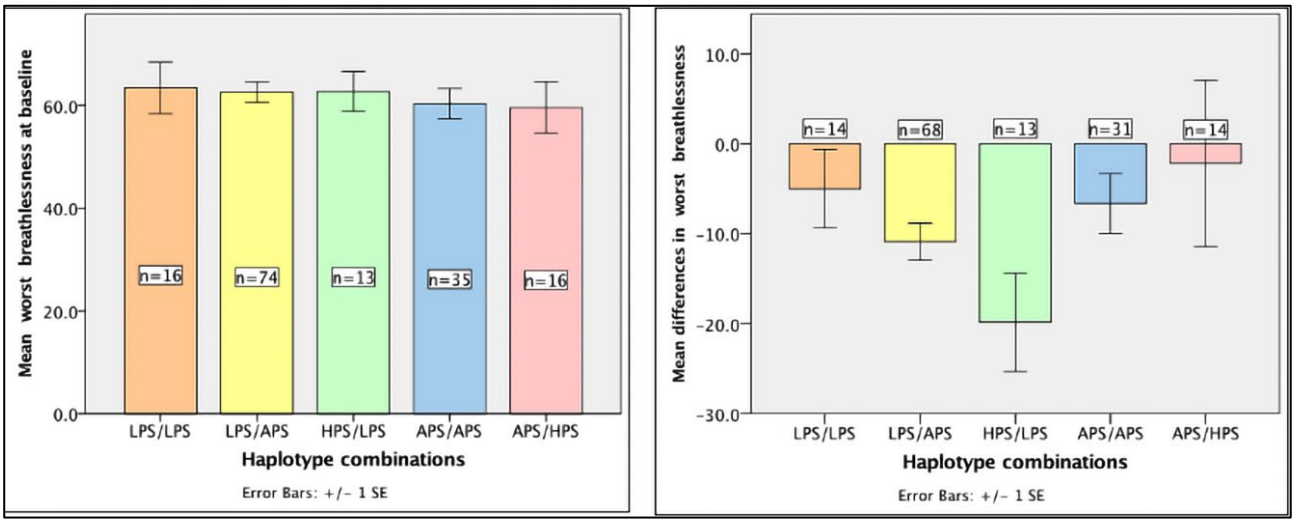


Figure 7.5 - Mean *worst breathlessness* at baseline (first graph) and mean reduction in *worst breathlessness* from days 5 to 7 (second graph), according to *COMT* diplotype (error bars represent ± 1 standard error [SE])

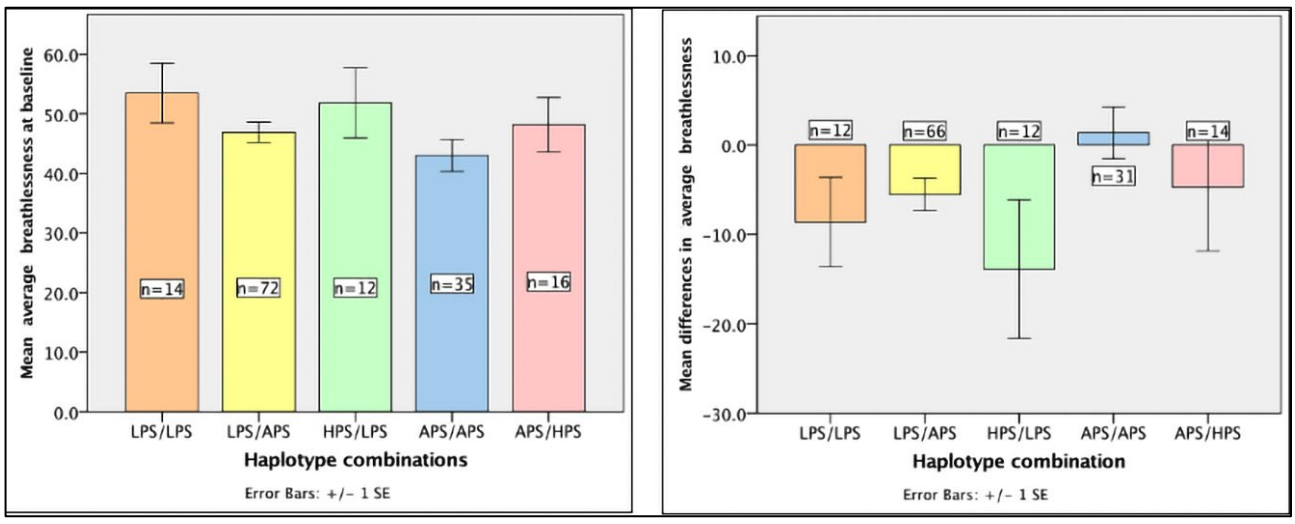


Figure 7.6 - Mean *average breathlessness* at baseline (first graph) and mean reduction in *average breathlessness* from days 5 to 7 (second graph), according to *COMT* diplotype (error bars represent ± 1 standard error [SE])

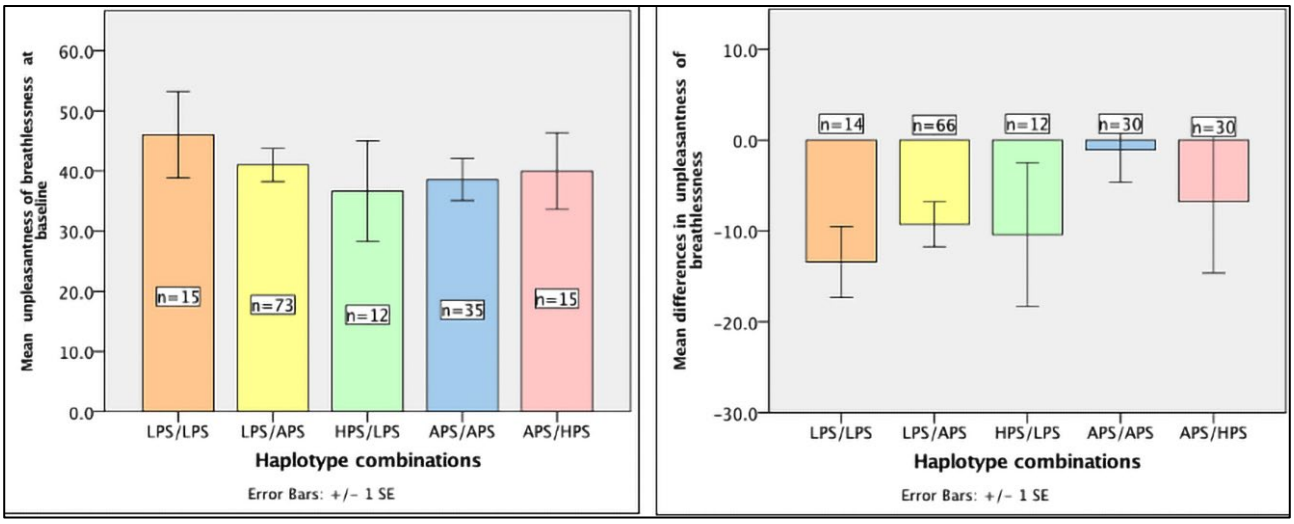
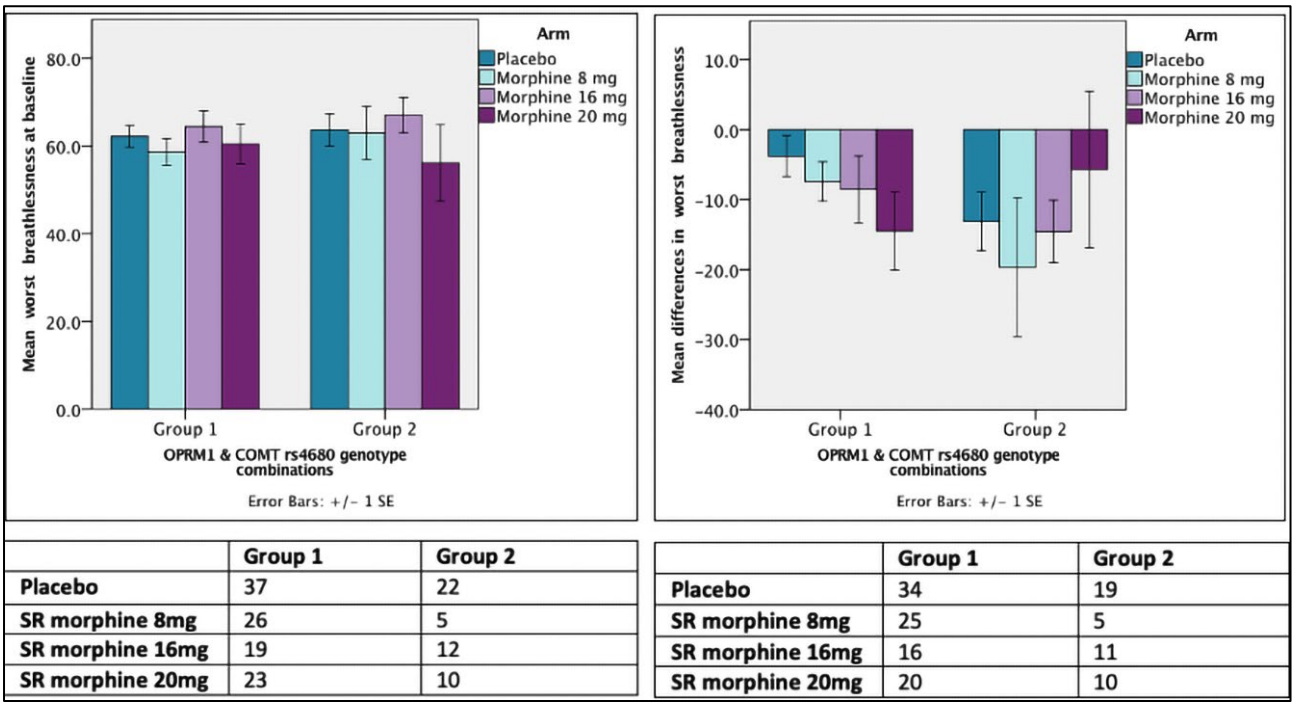


Figure 7.7 - Mean *unpleasantness of breathlessness* at baseline (first graph) and mean reduction in *unpleasantness of breathlessness* from days 5 to 7 (second graph), according to *COMT* diplotype (error bars represent ± 1 standard error [SE])

7.6.6 Breathlessness differences for associations of OPRM1 and COMT genotypes

There were no statistically significant differences in baseline breathlessness scores between Group 1 (OPRM1 rs1799971 wildtype and COMT rs4680 heterozygous or homozygous variant) and Group 2 (all other genotype combinations). There were also no significant group differences in reduction in *worst*, *average* and *unpleasantness of breathlessness* from baseline to days 5 to 7 ($p>0.2$), independent of treatment ($p\geq0.3$). However, there was a trend towards larger breathlessness reductions from baseline to days 5 to 7 in Group 2 compared with Group 1, for every measure of breathlessness (mean reductions in *worst breathlessness* Group 1 = 7.8±19mm [n=95], Group 2 = 12.5±22mm [n=45], p=0.2; mean reductions in *average breathlessness* Group 1 = 3.7±17mm [n=93], Group 2 = 7.4±21mm [n=42], p=0.3; mean reductions in *unpleasantness of breathlessness* Group 1 = 6.1±20mm [n=91], Group 2 = 11.1±22mm [n=44], p=0.2). Although not statistically significant, Group 1 exhibited increasing reductions in *worst breathlessness* with increasing doses of regular, low-dose, sustained-release oral morphine, which was not seen in Group 2 (Figure 7.14).



	Group 1	Group 2
Placebo	37	22
SR morphine 8mg	26	5
SR morphine 16mg	19	12
SR morphine 20mg	23	10

	Group 1	Group 2
Placebo	34	19
SR morphine 8mg	25	5
SR morphine 16mg	16	11
SR morphine 20mg	20	10

Figure 7.8 - Mean *worst breathlessness* at baseline (first graph) and mean reduction in *worst breathlessness* from days 5 to 7 (second graph), according to *OPRM1* rs1799971 and *COMT* rs4680 combinations (Group 1: *OPRM1* rs1799971 wildtype & *COMT* rs4680 heterozygotes / homozygotes variant; Group 2: all other combinations); error bars represent ± 1 standard error (SE)

7.7 Discussion

This was the first hypothesis-generating, prospective study exploring genetic factors that could potentially influence the intensity and unpleasantness of breathlessness in people with chronic breathlessness, before and after initiating regular, low-dose, sustained-release oral morphine. Findings suggest that different *COMT* rs4680 and *HTRB3* rs7103572 genotypes may result in different intensity of *average breathlessness* at baseline, and that the *HTRB3* rs7103572 genotype may also influence different magnitude of reduction in *average breathlessness* once the study medication is introduced. Such differences were not shown to be dependent on the treatment administered (i.e., placebo or regular sustained-release oral morphine in doses between 8 and 20 mg daily). For *OPRM1* rs1799971, the magnitude of reduction in *worst breathlessness* may also depend on the treatment and genotype although specific dose-by-treatment interactions need to be explored further. Importantly, this exploratory sub-study was not sufficiently powered to

determine between-genotype and between-arm differences. The fact that some statistically significant differences were identified indicates that these SNPs may have a critical role in chronic breathlessness and response to regular, low-dose, sustained-release oral morphine. Given this was an exploratory sub-study, examining the magnitude of breathlessness reduction in each group and apparent differences between groups, even when not statistically significant, may support pursuing new lines of research related to the genetics and pharmacogenetics of chronic breathlessness.

7.7.1 Deviations of the Hardy-Weinberg Equilibrium

COMT rs4818 and *HTR3B* rs7103572 allele and genotype frequencies in this sample deviated from what would be expected in the general population of origin (assuming that allele and genotype frequencies remain constant from generation to generation, in the absence of evolutionary factors) (Andrews, 2010). Deviations from the Hardy–Weinberg equilibrium with excess heterozygosity are frequently caused by genotyping errors (Chen et al., 2017), which were excluded in the current study by re-checking genotyping results (including for the possibility of cross-contamination), and data for possible mistakes in the results translation and data transfer. Given that no mistakes were identified during these procedures, other factors may have influenced the deviations observed. Small sample sizes can lead to a deviation from the Hardy–Weinberg equilibrium with higher heterozygous frequencies (Waples, 2015). Given that some genotypes included a small number of participants, it is likely that this factor may have played a role. Natural selection may also have influenced the genotype frequencies observed for *COMT* rs4818 and *HTR3B* rs7103572 (Waples, 2015). While participants included in this study needed to be experiencing a moderate-to-severe degree of functional impairment due to chronic breathlessness, they also needed to be sufficiently fit to be able to complete the study procedures (Currow et al., 2017). Considering that breathlessness is an independent predictor of mortality

(Nishimura et al., 2002), it is possible that heterozygosity produces a survival (and functional) advantage in people with chronic breathlessness, which would have influenced the genotype frequencies observed in this study (Waples, 2015). Genetic studies with larger sample sizes may help to shed some light on possible deviations from the Hardy–Weinberg equilibrium.

7.7.2 Differences in breathlessness according to genotype and treatment

Results from this sub-study suggest that *HTRB3* rs7103572 heterozygotes (C/T) may be predisposed to experience higher intensity of *average breathlessness* at baseline compared with wildtype homozygotes (C/C). Although not statistically significant, a similar pattern was detected for baseline *worst breathlessness*. These results would suggest that the variant allele contributes to the likelihood of more intense breathlessness, which is in line with previous findings from a sub-population taking morphine for cancer pain (Currow et al., 2015). Thus, it would be expected that the group of homozygotes for the variant allele (T/T) experienced the highest intensity of *average* and *worst breathlessness* at baseline, which is not the case in this sub-study. It is possible that T/T are in fact less susceptible to breathlessness compared with the other two genotypes, particularly before initiating regular, low-dose, sustained-release oral morphine. This hypothesis is supported by smaller standard deviations of the mean in this group compared with C/C and C/T, suggesting higher homogeneity in breathlessness scores. More likely, the small number of participants with the T/T genotype indicates that these results may not be representative of the overall population of homozygotes variant. Importantly, results from this sub-study also suggest that the variant allele may be associated with significantly larger reductions in *average breathlessness* after initiating treatment (T/T > C/T > C/C), independent of baseline breathlessness or the treatment administered. Between-genotype differences were also clinically meaningful (Johnson et al., 2013a). The pattern of response observed for *average* and *worst breathlessness* after seven days of regular, low-dose, sustained-release oral morphine also suggests there may be a dose-response

relationship in the group of homozygotes variant, which is not seen with other genotypes. Taking into account the small numbers of participants per genotype and arm, it is possible that between-arm differences were not detected due to lack of power. Additionally, the magnitude of response in the placebo arm may have contributed to the absence of between-arm differences, which will be discussed in detail in section 1.7.6. From a physiological point of view, activation of 5-HT_{3b} receptors is thought to increase nociception and may also contribute to more intense breathlessness by activating similar neuronal pathways (Patel & Dickenson, 2018; Zeitz et al., 2002). Morphine is an antagonist of 5-HT_3 receptors, which may contribute to the reduction of the sensation of breathlessness (Baptista-Hon et al., 2012). Thus, genetic variations in the *HTR3B* gene may potentially influence the extent of breathlessness reduction (or lack of it) produced with regular, low-dose, sustained-release oral morphine. Importantly, results from this genetic sub-study seem to contradict findings from Currow et al. (2015) cross-sectional study, who established an association between the T/T genotype had a 3-fold higher chance of experiencing more intense breathlessness in people taking morphine for cancer pain. However, the latter did not examine response (i.e., change in breathlessness scores after the introduction of morphine), and people were already taking morphine when the intensity of breathlessness was reported. Thus, results from these studies may in fact complement each other by generating the following hypothesis:

i) T-allele carriers may be predisposed to more intense baseline breathlessness than homozygotes wildtype (a pattern that may have been partially obscured in this sub-study due to reduced T/T genotype frequency);

ii) T-allele carriers may be predisposed to greater reductions in breathlessness with regular, low-dose, sustained-release oral morphine, independently of the intensity of baseline breathlessness. This pattern may have been masked by large responses in the placebo arm for T/T homozygotes;

iii) the magnitude of reduction in breathlessness experienced by T-allele carriers may not be sufficient to translate into lower breathlessness scores compared with other genotypes after initiating regular, low-dose, sustained-release oral morphine (i.e., if the T-allele group has higher breathlessness scores at baseline, they require large magnitudes of reduction in breathlessness intensity to level up with other genotypes).

These hypotheses need to be investigated in future, adequately powered prospective studies.

For COMT rs4680, differences in baseline "average" breathlessness scores between different genotypes (homozygous wildtype [G/G] > heterozygotes [G/A] > homozygous variant [A/A]) did not reach statistical significance, possibly due to lack of statistical power. Interestingly, this pattern contrasts with previous findings from the first experimental study examining the effects of COMT Val158Met for the perception of sustained muscular pain, which suggested that Met158 carriers were predisposed to experience more intense pain (Zubieta et al., 2003). A similar pattern of pain susceptibility was detected in a population-based study evaluating the association between different COMT rs4680 genotypes and non-migraine headache (Hagen et al., 2006b). However, there was a lack of association between COMT genotypes and susceptibility to chronic musculoskeletal pain in the same population (Hagen et al., 2006c). Similarly, there was no association between different COMT rs4680 genotypes and susceptibility to neuropathic pain (Armero et al., 2005). Interestingly, the last two studies do not report on medication taken by participants to improve their symptoms. It is therefore unclear whether these participants were taking any medication for chronic pain (including opioids) and whether there were differences in doses taken. This is important because different types and doses of analgesics may explain the absence of differences in pain intensity between genotypes. It is also interesting to note that the last two studies included participants with chronic pain rather than acute pain. It is possible that genotype differences manifest differently in chronic and acute pain (Brown et al., 2015; Jones et

al., 1994). In fact, there is increasing evidence suggesting that chronic pain is associated with reduced opioid receptor availability in the brain; however, it is unclear whether this results from an increased production of endogenous opioids, a reduction in opioid receptor expression, or a reduction in the number of neurons expressing opioid receptors (Thompson et al., 2018). Brain remodelling, with reductions in grey matter are seen in both chronic pain and chronic breathlessness, which may result from epigenetic changes affecting the expression of selective genes (Esser et al., 2016). In other conditions, different genotypes have been shown to have different susceptibility to epigenetic changes (e.g., DNA methylation), which can potentially produce unexpected phenotypical presentations (Bell et al., 2015; Kindt et al., 2018). Thus, variable epigenetic changes in COMT rs4680 genotypes induced by chronic breathlessness could explain the unexpected susceptibility to breathlessness found in this sub-study.

The pattern of response observed in this sub-study seems to suggest that the COMT rs4680 wildtype allele is associated with significantly larger reductions in *average breathlessness* (G/G > G/A > A/A), independent of baseline breathlessness or the medication taken. This is most likely not the case. Higher baseline breathlessness predisposes to larger reductions in breathlessness scores, which seems to be the case in this sub-study (i.e., after adjusting for baseline *average breathlessness*, between-genotype differences in response were non-significant) (Johnson et al., 2013b). Although response patterns to different doses of regular, low-dose, sustained-release oral morphine are dissimilar between different *COMT* rs4680 genotypes, no clear patterns could be discerned. Similar to *HTRB3* rs7103572, it is possible that a small sample size and large responses in the placebo arm contribute to the lack of differences between arms, within genotypes. Results from previous studies in the chronic pain setting are inconsistent, with at least one study suggesting an association between the presence of the G allele and larger morphine requirements for cancer pain (Rakvag et al., 2005), and others reporting no significant between-genotype

differences in opioid requirements (Klepstad et al., 2011; Lotsch et al., 2009). Differences between studies may be due to the use of different opioids agonists, which bind to different opioid receptors. Additionally, none of these studies examined response. From a physiological perspective, the variant allele could increase opioid-receptor expression which would potentiate response to opioids, including regular, low-dose, sustained-release oral morphine (Zubieta et al., 2003). However, chronic pain, and potentially chronic breathlessness, are associated with dysregulation of the dopaminergic and opioid systems which can affect *COMT* rs4680 genotypes differently (Wawrzczak-Bargiela et al., 2020). Thus, the role of *COMT* rs4680 in chronic breathlessness and potential response to regular, low-dose, sustained-release oral morphine needs to be investigated prospectively in future studies.

For *OPRM1* rs1799971 and *COMT* rs4818, no significant between-genotype or between-arm differences were detected at any timepoint. Of note, the group of homozygotes for the *COMT* rs4818 variant allele and the group of homozygotes for the OPRM1 wildtype allele showed a dose-response relationship pattern for *worst breathlessness*, suggesting these genotypes may be more responsive to regular, low-dose, sustained-release oral morphine. These results are aligned with previous cross-sectional studies reporting that the group of homozygotes for the *OPRM1* rs1799971 wildtype allele and the group of homozygotes for the *COMT* rs4818 variant allele required lower doses of opioids to achieve cancer pain analgesia (Campa et al., 2008; Hajj et al., 2017; Rakvag et al., 2008; Yu et al., 2019). However, this response pattern needs to be investigated in future, adequately powered prospective studies.

It is unclear why the strongest signals detected in this study were for *average breathlessness,* instead of *worst breathlessness* which may be more responsive to change (Lovell et al., 2019). Commonly, research participants are given the opportunity to rest before completing any study assessments (Wade et al., 2017). Because *average breathlessness* scores tend to be influenced by

the intensity of breathlessness experienced at the time of the assessment, between-genotype differences are likely to partially reflect differences in breathlessness at rest (Wade et al., 2017). Additionally, more fluctuations in breathlessness intensity throughout the day, may led to perceptions of higher "average" breathlessness (Stone et al., 2005; Wade et al., 2017). These results suggest that *HTRB3* rs7103572 and *COMT* rs4680 genotypes may modulate breathlessness by stabilising fluctuations in the intensity of breathlessness throughout the day, including at rest. However, occasional peaks in intensity of breathlessness (i.e., *worst breathlessness*) may be less affected.

7.7.3 Differences in response according to COMT diplotype

This sub-study found no baseline differences in breathlessness associated with COMT diplotype. However, different diplotypes have been shown to be associated with different sensitivity to chronic and acute pain (Diatchenko et al., 2005; George et al., 2008; Vargas-Alarcón et al., 2007). It is unclear whether these findings result from a true difference between diplotypes at baseline or of a small sample size in each group. However, no obvious signal for differences was observed (i.e., baseline breathlessness scores were very similar for different diplotypes), which raises the hypothesis that COMT diplotypes may not influence susceptibility to chronic breathlessness in the same way that they influence susceptibility to chronic pain. Importantly, while response to the study intervention was not statistically significant, the magnitude of *worst* and *average breathlessness* reduction tended to be larger for the low-pain sensitivity/high-pain sensitivity diplotype and smaller for the average-pain sensitivity/average-pain sensitivity diplotype, independent of treatment. These results are supported by a recent experimental RCT with healthy volunteers, reporting that the average-pain sensitivity haplotype was associated with a lower ischemic pain threshold after the administration of morphine, suggesting that morphine is less effective for ischemic pain in this group (Ho et al., 2020). Interestingly, the average-pain sensitivity

haplotype contains the variant alleles of both *COMT* rs4680 and rs4818, which have been shown to be associated with lower morphine requirements to achieve cancer pain control (Lloyd et al., 2017; Rakvag et al., 2008) and showed a more predictable pattern of response to regular, low-dose, sustained-release oral morphine (i.e., dose-response relationship) in this sub-study. However, similar to individual *COMT* genotypes, response in the placebo arm was of lower magnitude for the average-pain sensitivity/average-pain sensitivity diplotype containing the variant forms of the *COMT* rs4680 and rs4818 alleles and of higher magnitude for the low-pain sensitivity/high-pain sensitivity diplotype. Thus, it is possible that response in the placebo arm contributes to larger reductions in breathlessness for the low-pain sensitivity/high-pain sensitivity diplotype in the context of clinical trials, but not in the real world setting.

7.7.4 Differences in response depending on the genotype combination

In this sub-study, response to regular, low-dose, sustained-release oral morphine was not significantly different between genotype combinations. However, the patterns of response offer important insights. For example, the magnitude of breathlessness reduction from baseline to days 5-7 was larger for all measures of breathlessness in the group with at least one *OPRM1* rs1799971 variant allele and two *COMT* rs4680 wildtype alleles (Group 2), but these results seemed unrelated with treatment. Conversely, the group with two *OPRM1* rs1799971 wildtype alleles and at least one COMT rs4680 variant allele (Group 1), showed a smaller magnitude of response to the study medication (i.e., morphine or placebo), but with a dose-response relationship pattern for *worst breathlessness*, which is the measure of breathlessness that is usually more sensitive to change (Johnson et al., 2016). Importantly, Group 2 had a larger magnitude of response in the placebo arm compared with Group 1, which indicates that Group 2 may be more susceptible to the placebo effect and achieve better results as a whole in the context of clinical trial. The smaller magnitude of response observed in the placebo arm of Group 1 and the dose-response

relationship pattern may suggest this group is less susceptible to the placebo effect, but possibly more responsive to regular, low-dose, sustained-release oral morphine in the real world setting. This hypothesis is supported by results from previous observational studies in the acute and chronic pain settings reporting that the group carrying *OPRM1* rs1799971 wildtype allele and the *COMT* rs4680 variant allele (equivalent to Group 1 in this sub-study) required lower doses of opioids to achieve analgesia (De Gregori et al., 2013; Khalil et al., 2017; Reyes-Gibby et al., 2007). However, these findings need to be confirmed in future large-scale, prospective studies.

7.7.5 Differences in breathlessness according to treatment

All study arms showed significant reductions in breathlessness scores (*worst*, *average*, *unpleasantness*) from baseline to days 5-7, but there were no statistically nor clinically significant differences between them. Importantly, participants were recruited from two separate trials, conducted at different points in time, under different conditions. Doses used in each trial were also different (only the placebo arm was common to both trials). These factors may have contributed to conceal differences between treatments (Alemayehu, 2011). However, it is also important to note that the absence of between-arm differences was mainly caused by statistically significant responses in the placebo arm, rather than reduced active-treatment efficacy. Additionally, reductions in *worst breathlessness* in the placebo arm were also clinically significant, corresponding to smaller perceived changes in breathlessness (Johnson et al., 2013a). Large responses in the placebo arm are increasingly mentioned in the literature as an important phenomenon in clinical trials, which are discussed in more detail below.

7.7.6 Lack of between-arm differences and response in the placebo arm

This study was characterised by statistically significant reductions in breathlessness scores (*worst*, *average* and *unpleasantness*) in the placebo arm, independent of genotype, some of which were also clinically significant (Johnson et al., 2013a). Significant responses with placebo treatments

have been reported in the literature and identified as a challenge for the interpretation of results in clinical trials (Hunsley & Westmacott, 2007). Mean effect sizes of placebo interventions in double-blind RCTs are usually small but statistically significant, particularly when considering subjective symptoms such as pain or breathlessness (Hunsley & Westmacott, 2007). However, it is unclear if these responses reflect a true placebo effect (i.e., a true psycho-biological response) or if they result from other factors, including normal fluctuations in symptom intensity (characterising both chronic pain and chronic breathlessness) or a simple statistical phenomenon of regression to the mean (i.e., the closer a symptom score is to an extreme, the greater likelihood of being less extreme in the following measurement) (Price et al., 2008; Whitney & Von Korff, 1992). Additionally, even true psycho-biological responses to placebo are influenced by other external factors such as the relationship with the health-care provider, and the treatment environment (Bingel et al., 2011). These factors interact with individual patient characteristics (e.g., psychosocial context, beliefs, past experiences, expectations) to produce the placebo effect (Finniss et al., 2010).

Importantly, different genotypes were exposed to similar external conditions in this sub-study. As a result, differences in response to placebo across genotypes are likely directly influenced by the genotype itself, more than by environmental factors. Comparing responses in the placebo arm across genotypes can identify SNPs contributing to response in the placebo arm in people with chronic breathlessness. For example, in this sub-study, the presence of *COMT* rs4680 and rs4818 wildtype alleles seem to be associated with larger reductions in all measures of breathlessness in the placebo arm. Conversely, the presence of *OPRM1* rs1799971 and *HTRB3* rs7103572 wildtype alleles seem to be associated with smaller reductions in breathlessness in the placebo arm. These findings are interesting because these SNPs interfere with both the endogenous opioid and dopaminergic signals, which have been shown to be key components of placebo analgesia

(Zubieta & Stohler, 2009). Moreover, the magnitude of placebo-induced analgesia was shown to vary between different *OPRM1* rs1799971 and *COMT* genotypes (Hall et al., 2015; Peciña et al., 2015). However, between-genotype variations found in the literature seem to diverge from the findings of this study. For example, experimental studies with healthy volunteers suggest that G-allele carriers for OPRM1 rs1799971 (heterozygotes or homozygotes variant) have significantly reduced levels of μ-opioid system activation in the anterior insula, limbic system, thalamus and brainstem compared with homozygotes wildtype. For the same participants, decreased μ-opioid system activation was correlated with higher pain scores (sensory and affective domains) (Peciña et al., 2015). For *COMT* rs4680, healthy Met/Met carriers (homozygotes variant) were shown to experience higher magnitude of response to placebo analgesia after being subjected to experimentally induced pain (Yu et al., 2014). Additionally, genetic studies examining both SNPs concomitantly have shown that people who are *OPRM1* rs1799971 wildtype *and COMT* rs4680 Met carriers exhibit greater placebo responses than other genotype combinations (Aslaksen et al., 2018). Thus, results from this genetic sub-study are unexpected. However, it is important to note that most genetic studies exploring responses with placebo were conducted with healthy volunteers and pain was induced experimentally. It is unclear if results would be similar in people with chronic conditions such as chronic pain or chronic breathlessness.

7.7.7 Genetic, epigenetic and environmental influences

This discussion highlights two key points. Firstly, some of the observed between-genotype differences in breathlessness or breathlessness reduction with regular, low-dose, sustained-release oral morphine (e.g., OPRM1 rs1799971; *COMT* rs4680) are unexpected or inconsistent with the literature. Secondly, the magnitude of response in the placebo arm appears to be different between genotypes, and in some cases, also inconsistent with previous studies. These inconsistencies in response observed for different genotypes and genotype combinations require

further elucidation. However, the large majority of studies examining response to opioids according to genotype included healthy volunteers or people experiencing acute pain. This is a fundamentally different population from the populations experiencing chronic pain or chronic breathlessness. For example, chronic breathlessness is associated with systemic conditions (e.g., COPD, congestive heart failure, cancer) leading to a range of cardiovascular, metabolic, immune and behavioural changes (Chung & Adcock, 2008; Grivennikov et al., 2010; Yndestad et al., 2006). It is likely that these changes in the internal environment contribute to regulate epigenetic and genetic expression (Felger & Miller, 2012). Moreover, these changes also likely to interfere with the effect of endogenous and exogenous opioids (Rogers, 2020; Szabo et al., 2002; Zhang et al., 2004). For example, inflammatory molecules such as cytokines can desensitise opioid receptors which may become less responsive to their natural ligands. It is possible that the crosstalk between inflammation and the endogenous opioid system produces different effects according to different genotypes (Wawrzczak-Bargiela et al., 2020). The links between genetic, epigenetic and environmental influences need to be investigated in future studies evaluating response to regular, low-dose, sustained-release morphine for chronic breathlessness.

7.7.8 Limitations

This sub-study recruited from two separate RCTs, that included different populations of chronic breathlessness and used different doses of regular, low-dose, sustained-release oral morphine. Importantly, most people included in the Morphine-Placebo study had COPD as the primary cause of chronic breathlessness, which was the only primary cause of chronic breathlessness included in the BEAMS study. From the 14 centres participating in the Morphine-Placebo study, only eight collected samples for pharmacogenetic analysis. Reasons for not collecting samples for pharmacogenetic analysis are likely associated with local limitations in human and technical resources. A large proportion of participants who did not require blood sample collection as part

of the main study (i.e., had recent blood test results available), was also not included in this sub-study. It is possible that some participants may have chosen not to provide written informed consent for an additional invasive procedure. More likely, study staff may have chosen to prioritise the main trial (and less invasive sub-studies) in these situations, in order not to over-burden participants. This is a hypothesis-generating sub-study, whose findings are not generalisable for all people who live with chronic breathlessness associated with COPD. However, results raise some new hypothesis and point to new future research directions that are discussed below.

7.7.9 Implication for future research

Patterns of chronic breathlessness according to genotype need to be investigated in large-scale studies. More importantly, the patterns of chronic breathlessness reduction observed in this sub-study, need to be confirmed in larger, adequately powered prospective studies. Additionally, it is important to investigate how pathological changes associated with chronic breathlessness and its underlying causes may produce epigenetic changes and alter genetic expression of different genotypes.

7.7.10 Implications for clinical practice

Prescribing regular, low-dose, sustained-release oral morphine for chronic breathlessness in the clinical setting is still challenging due to large intra-individual variation in response (Johnson et al., 2012). Up to this point only two predictors of response to morphine had been proposed: higher intensity of baseline breathlessness and younger age (Johnson et al., 2012). This hypothesis-generating sub-study suggests that response to medication may also differ according to different genotypes, which needs to be investigated in larger prospective studies. Identifying specific genotypes or combinations of genotypes conditioning larger reductions in breathlessness and fewer harms with regular, low-dose, sustained-release oral morphine may open the door for personalised medicine in the field of chronic breathlessness.

7.8 Conclusion

This was the first prospective study exploring the influence of genetic factors in the intensity and unpleasantness of breathlessness of a population with chronic breathlessness, before and after initiating regular, low-dose, sustained-release oral morphine. Findings indicate that different *COMT* rs4680 and *HTRB3* rs7103572 genotypes may result in different intensity of *average breathlessness* at baseline, and that the *HTRB3* rs7103572 genotype may also influence different magnitude of reduction in *average breathlessness* once the study medication is introduced. Although no other statistically significant differences were identified, the patterns of response observed for all genotypes included in this sub-study suggest there is interest in exploring the same between-genotype differences in future adequately powered prospective studies. The role of pathological changes associated with chronic breathlessness needs to be further elucidated as it may influence epigenetic changes and modify genetic expression.

7.9 References

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CHAPTER 8 – THE IMPACT OF REGULAR, LOW-DOSE, SUSTAINED-RELEASE ORAL MORPHINE ON THE DIURNAL CORTISOL PROFILE OF PEOPLE WITH COPD AND SEVERE CHRONIC BREATHLESSNESS – AN EXPLORATORY, PROSPECTIVE SUB- STUDY

8.1 Chapter preface

Chapter 7 focused on the genetic factors associated with different responses to regular, low-dose, sustained-release oral morphine for the symptomatic reduction of severe chronic breathlessness associated with COPD. This chapter will examine response to regular, low-dose, sustained-release oral morphine beyond genetics by exploring the effect of this medication on the diurnal cortisol profile of participants, and its association with chronic breathlessness. Cortisol, commonly known as the 'stress hormone', is one of the final products of the hypothalamic-pituitary-adrenal axis, which is responsible for physiologic responses to threats and maintaining homeostasis. The diurnal pattern of cortisol production is frequently disrupted in chronic conditions, including chronic breathlessness, which has been shown to be associated with worse health outcomes, including mortality. By improving the sensation of breathlessness, it is theoretically possible that regular, low-dose, sustained-release oral morphine may decrease physiological stress and change the pattern of diurnal cortisol production over time, with the potential to improve health-related outcomes for people with chronic breathlessness associated with COPD.

8.2 Introduction

8.2.1 Stress: an overview

8.2.1.1 Stress and the stress response

Stress is defined as "a state of real or perceived threat to homeostasis that may challenge an organism's well-being" (Smith & Vale, 2006). All stimuli and events leading to stress are defined as *stressors* (Carrasco & Van de Kar, 2003; Chrousos & Gold, 1992; Ulrich-Lai & Herman, 2009). Thus, a wide range of physical, psychological and environmental stimuli may constitute potential

stressors (Murison, 2016; Selye, 1936). In this context, the sensations of acute or chronic breathlessness are likely to be closely linked with stress, because they are both products of potentially life-threatening sensations, and sources of fear and anxiety. Importantly, like breathlessness, stress has a subjective component, resulting from the interaction between the nature and intensity of potential stressors, and the person who experiences them (McEwen, 2007).

The brain is heavily involved in the perceptions and responses to stress. Cortical and sub-cortical structures are responsible for receiving and processing different afferent signals, identifying potential stressors, and triggering the *stress response*, which is characterised by a complex chain of physiologic and behavioural changes aiming to support the return to, or maintain homeostasis (Chrousos & Gold, 1992; De Kloet et al., 2005; Ulrich-Lai & Herman, 2009). Two key pathways are essential to generate, sustain and regulate the physiological response to stress: the autonomic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis.

Once a stimulus is interpreted as threatening, there is an immediate activation of the sympathetic division of the autonomic nervous system, which triggers rapid physiologic changes characterised as the *fight-or-flight response* (Cannon, 1915). Two sympathetic pathways are involved in generating the fight-or-flight response. The first one involves stimulation of pre-ganglionic neurons in the brainstem and spinal cord, which synapse with post-ganglionic neurons in the *paravertebral sympathetic chain*. When activated, post-ganglionic neurons release noradrenaline inducing a sympathetic response in peripheral organs (Charmandari et al., 2005). The second pathway involves stimulation of the *sympathetic adreno-medullar system*, in which pre-ganglionic neurons directly stimulate chromaffin cells in the adrenal medulla, releasing adrenaline and noradrenaline in the blood stream (McCorry, 2007). Overall, sympathetic activation results in a rapid, multi-organ response that increases cardiac output, accelerates the respiratory rate,

promotes catabolism and redirects blood flow to key organs such as the brain, heart and muscles (Chrousos & Gold, 1992). Importantly, while the sympathetic response is essential to react quickly to potential danger, it cannot be sustained for long periods. The hypothalamic-pituitary-adrenal (HPA) axis, consisting of the hypothalamus, pituitary and adrenal glands, is key to sustain, modulate and terminate the stress response (Smith & Vale, 2006).

Compared with the autonomic nervous system, the HPA axis is slower to respond to stressors but the response can be sustained for much longer periods (Ulrich-Lai & Herman, 2009). The HPA axis response to stress is initiated in the paraventricular nuclei of the hypothalamus. Activation of the paraventricular nuclei stimulates the secretion of corticotrophin releasing hormone (CRH) and arginine-vasopressin (AVP) in the hypophyseal portal system, which will quickly reach the anterior pituitary gland and stimulate the secretion of adrenocorticotropic hormone (ACTH) into the systemic circulation (Tsigos & Chrousos, 2002). Circulating ACTH binds to specific receptors in the adrenal cortex, stimulating the synthesis and secretion of glucocorticoids, predominantly cortisol in humans. Cortisol is then released in the bloodstream and distributed to all organs, promoting a range of metabolic, cardiovascular, behavioural and immune adaptive responses (Charmandari et al., 2005; Sapolsky et al., 2000). Physiological changes induced by cortisol aim to promote coping with stress, recovering from the stress episodes, and establishing effective physiologic adaptation (De Kloet et al., 2005). Regulation of HPA axis activity occurs by a mechanism of negative feedback. Circulating cortisol and ACTH have inhibitory effects on the hypothalamus and pituitary, contributing to stabilising and eventually terminating the stress response (Tsigos & Chrousos, 2002) (Figure 8.1).

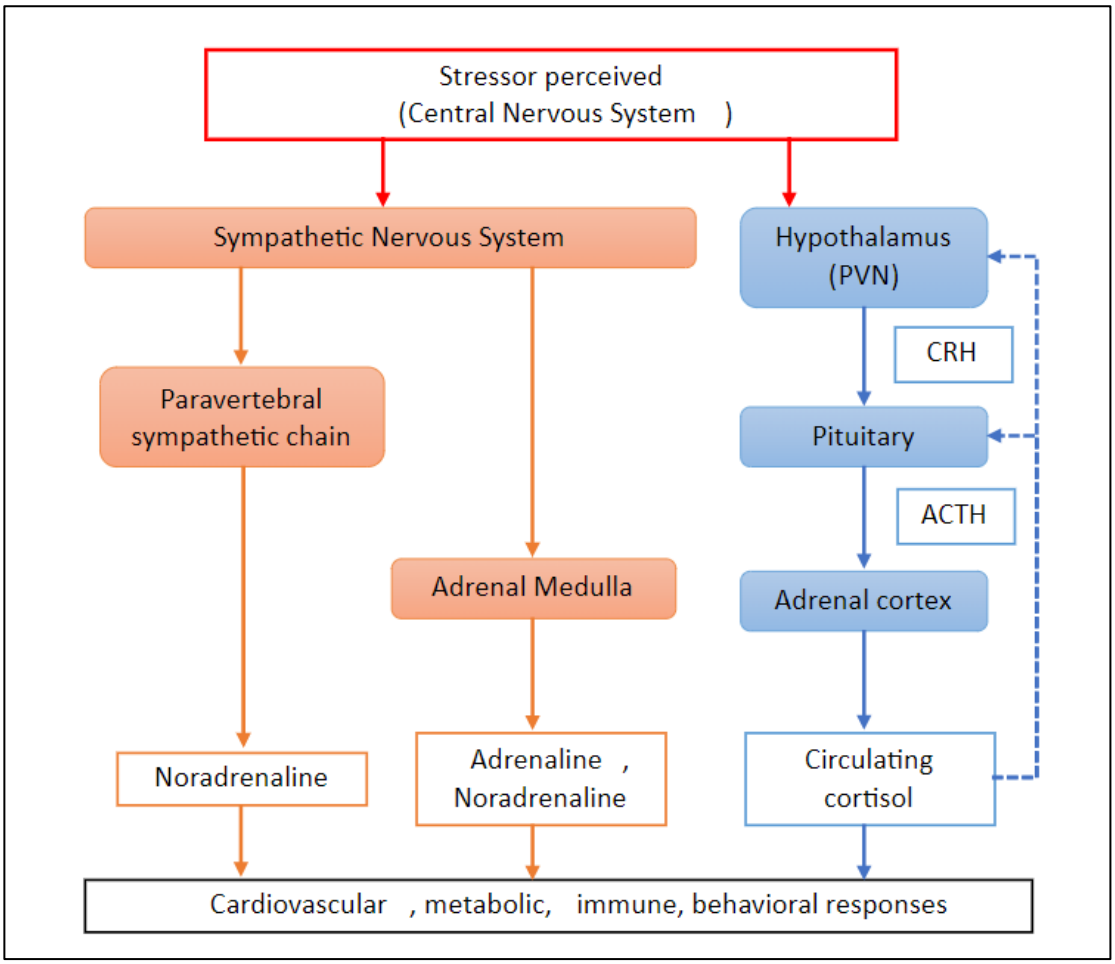

Figure 8.1 - Schematic illustration of the two major stress response pathways
Dash lines represent inhibitory pathways. PVN, paraventricular nucleus; CRH, corticotrophin releasing hormone; ACTH, adrenocorticotropic hormone

8.2.1.2 Types of stress response: reactive and anticipatory

Physiological and psychological stimuli are processed differently in the brain, with some important overlaps (Godoy et al., 2018). Based on such differences, two types of central stress response have been described – reactive and anticipatory (Herman et al., 2003). *Reactive stress responses* are typically responses to physiological stimuli, such as inflammation or chemoreceptor stimulation, which are mainly processed at the sub-cortical level, and are therefore reflexive and immediate (Dayas et al., 2001; Joëls & Baram, 2009; Ulrich-Lai & Herman, 2009). Physiological stressors are detected initially by the medulla, which triggers immediate sympathetic activation, while recruiting other sub-cortical structures responsible for regulating the sympathetic response (e.g., *nucleus tractus solitarius, locus coeruleus*) (Geerling et al., 2010). Concurrently, a signal is sent to

the paraventricular nucleus in the hypothalamus, which will activate the HPA axis and sustain the stress response. The limbic system, including the amygdala, hippocampus and pre-frontal cortex participate in the stress response to physiological stimuli, by processing information arising from sub-cortical centres and regulating the stress response from the top down (Ulrich-Lai & Herman, 2009). Of note, brainstem structures involved in the stress response to physiological stressors, such as *nucleus tractus solitarius*, are also strategic locations for receiving sensory information related to breathing (Zoccal et al., 2014). Thus, there may be an overlap between the central processing of discriminatory aspects of breathlessness, and the generation of reactive stress responses (Banzett et al., 2008; Lansing et al., 2009). From a functional point of view, this overlap would be valuable to effectively oversee one of the crucial aspects of a well-functioning body – breathing.

Different from reactive stress responses, *anticipatory stress responses* are typically triggered by psychological stimuli that conflict with innate or memory programs (Skoluda et al., 2015). Innate programs are common to all humans and ensure species survival (e.g., fear of unfamiliar situations or environments prompting increased alertness and defensiveness), while memory programs are acquired through exposure and experience, in a process of negative reinforcement. Anticipatory stress responses primarily activate the limbic system, including structures such as the amygdala, hippocampus, and pre-frontal-cortex (Godoy et al., 2018). These structures have direct projections to the paraventricular nuclei in the hypothalamus and an overall inhibitory effect in the HPA axis, under basal conditions (Godoy et al., 2018; Myers et al., 2012). Once a psychological stressor is detected, the amygdala triggers the sympathetic nervous system and the HPA axis, initiating the stress response (Myers et al., 2012). If the perceived intensity of the psychological stimuli is kept below a certain threshold, the pre-frontal cortex regulates the entire process, enhancing planning and adaptive behaviour changes. However, if the psychological stimulus becomes too intense, the

pre-frontal cortex is temporarily inactivated, and the stress response is mostly controlled by the amygdala and the hippocampus. Inactivation of the pre-frontal cortex inhibits the capacity to plan and make the necessary behavioural adjustments to stressful situations, while promoting the formation of fragmented memories (Arnsten et al., 2012; Diamond et al., 2007). These mechanisms underlying anticipatory responses are important for people with acute, chronic and acute-on-chronic breathlessness who may experience anxiety associated with breathlessness or breathlessness anticipation (Barnett, 2005; Esser et al., 2017; Hayen et al., 2017). Given the brain structures involved in anticipatory responses to stressors, it is likely that this type of response is closely linked with the affective pathways of breathlessness (Banzett et al., 2008; Lansing et al., 2009).

8.2.1.3 Phases of the stress response

Temporally, three phases characterise the stress response (Oitzl et al., 2010). The *acute stress phase* is characterised by both the sympathetic response and HPA activation. While the sympathetic response is almost immediate, HPA activation reaches its peak only 15 to 30 minutes after the stressor is perceived (De Kloet et al., 2005). Thus, this early phase of the stress response is mainly mediated by the central and peripheral effects of catecholamines (i.e., noradrenaline, adrenaline) which enhance arousal, attention and excitability (Oitzl et al., 2010). Additionally, early effects of cortisol are mostly mediated by its action in the mineralocorticoid receptors, which, in comparison, have higher affinity for glucocorticoids than the glucocorticoid receptors (De Kloet et al., 2019). Early cortisol effects mediated by mineralocorticoid receptors enhance and prolong the effects of catecholamines, sustaining the initial stress response and facilitating coping with the stressor (Oitzl et al., 2010).

The *recovery phase* is mediated by the cortisol effects in both mineralocorticoid and glucocorticoid receptors (Oitzl et al., 2010). Increasing saturation of glucocorticoid receptors in brain regions

associated with stress pathways, including the hypothalamus and pituitary gland, controls the amplitude and duration of the stress reaction by a process of *negative feedback* aiming to prevent the occurrence of damaging effects to the organism (Smyth et al., 2013). Additionally, persistent activation of mineralocorticoid receptors across all stages of the stress response is important to maintain neuronal integrity, which is challenged by the stress response itself (Nair et al., 2004; Oitzl et al., 2010). The recovery phase also includes activation of central structures responsible for rationalising and contextualising the experience (Joëls, 2018), preparing the progression to the adaptation phase.

The *adaptation phase* is also mediated by both mineralocorticoid and glucocorticoid receptors as well as amines and neuropeptides (Oitzl et al., 2010). In the adaptation phase, actions mediated by glucocorticoid receptors, amines and neuropeptides enhance the formation of memories associated with the stress reaction, which will promote adaptive behaviours and aid in the preparation for similar stressful contexts in the future (De Kloet et al., 2019). Importantly, strong emotional memories associated with the stressor will also be stored for future reference (Oitzl et al., 2010). In the context of breathlessness, previous experiences with this symptom and any associated memories will likely contribute to modulate the way a person reacts to future experiences of breathlessness.

8.2.2 A close look at the HPA axis

8.2.2.1 Normal HPA-axis activity

In healthy people, the HPA axis displays highly dynamic activity patterns, with marked fluctuations across the day. Such fluctuations are adaptive, allowing the body to adequately prepare and respond to regular daily events, rather than maladaptive. This dynamic state of equilibrium, in which physiologic variations promote stability and adaptation to the immediate environment, reflects the concept of *allostasis* (McEwen, 2007; Sterling & Eyer, 1988). Importantly, the concept of allostasis is broad, involving not only the HPA axis, but also coordinated action of multiple body

systems, including the immune, neuroendocrine and autonomic nervous systems (McEwen, 2008; Sterling & Eyer, 1988). As a result, multiple mediators interact in a non-linear fashion, in order to regulate all basic physiologic functions, such as the sleep/wake cycle, food intake, body temperature and activity levels (Kalsbeek et al., 2006; Takahashi et al., 2008). Understanding the complexity involved in allostasis is crucial to recognise all mechanisms leading to states of dysfunction and how to potentially reverse them. Nonetheless, this work offers a closer look at the role of the HPA axis in maintaining allostasis which involves understanding how the system operates under healthy physiologic conditions.

Under normal circumstances, the HPA axis exhibits two distinct activity patterns: 1) basal activity, and 2) acute reactivity to stress (Herman et al., 2003). The first one corresponds to the HPA-axis daily activity pattern in the absence of any stress, whose main role is to facilitate physiologic and behavioural adaptation to the predictable day-night cycles (McEwen & Wingfield, 2003). The second pattern, previously introduced in section 8.2.1.1, responds to unpredictable changes in the environment, which require additional physiologic boosts in order to ensure adaptation (McEwen & Wingfield, 2003). The HPA-axis basal activity pattern is further sub-divided into two rhythmic components: the circadian and the ultradian rhythms (Spencer & Deak, 2017). The *circadian rhythm* is a 24-hour physiological and behavioural cycle that is synchronised with the earth rotation, promoting adaptation to different times of day (Zee et al., 2013). Conversely, the *ultradian rhythm* is of shorter duration, repeating multiple times within 24 hours (Veldhuis et al., 1989). The circadian rhythm is largely the dominant pattern, on which the ultradian rhythm is superimposed.

The HPA-axis *circadian rhythm* is mostly controlled by the suprachiasmatic nucleus in the hypothalamus, which functions as the body 'master clock' (Moore & Eichler, 1976; Moore et al., 1991). Fluctuations in ambient light are sensed by photosensitive cells in the retina, which send

afferent information to the suprachiasmatic nucleus. The suprachiasmatic nucleus then regulates HPA-axis activity production through afferent projections to the paraventricular nuclei of the hypothalamus. Under normal circumstances, the diurnal cortisol secretion pattern shows an early-morning peak, with a subsequent decline throughout the day; a nadir around midnight; a gradual rise in cortisol levels in the first half of the sleep period, followed by a steep increase in the second half until reaching a new early-morning peak on the following day (Copinschi et al., 2015). These daily fluctuations in cortisol secretion mediate cardiovascular, metabolic, immune, and sleep-wake adaptations, and also learning and memory processes (Oster et al., 2017).

Importantly, extra-pituitary mechanisms independent of the HPA axis are also involved in regulating the circadian rhythm of cortisol production. Besides regulating HPA-axis activity, the suprachiasmatic nucleus sends projections to the adrenal cortex through multi-synaptic pathways, which contribute to regulate the circadian production of cortisol by modulating adrenal sensitivity to ACTH (Buijs et al., 1999; Ishida et al., 2005; Ulrich-Lai et al., 2006). This mechanism seems to be particularly important to regulate the early-morning cortisol rise, which diverges from the remaining pattern of cortisol secretion throughout the day (Clow et al., 2010; Wilhelm et al., 2007). More recently, other central and peripheral tissues have been shown to have secondary biological clocks, which exhibit and regulate the circadian rhythm in their local environment (Nader et al., 2010). These tissues include components of the HPA axis (e.g., corticotrophs in the anterior pituitary and steroid-producing cells in the adrenal cortex) (Oster et al., 2006), but also multiple other tissues and organs, such as the heart, lungs, kidney, liver and intestines (Oster et al., 2017). Secondary clocks exhibit intrinsic, independent activity that, under basal conditions, are highly synchronised with master-clock activity (Oster et al., 2017; Tsang et al., 2014). However, specific stimuli may uncouple peripheral and master-clock activity. For example, peripheral clocks are highly sensitive to meal timing, which induce changes in their intrinsic activity, modifying the

diurnal cortisol secretion pattern (Bahijri et al., 2013; Bogdan et al., 2001). More importantly, the existence of secondary clocks with independent activity in the lungs, may contribute to explain rhythmic fluctuations in breathlessness severity experienced by people with chronic breathlessness (Gibbs et al., 2014).

The HPA-axis basal activity pattern also exhibits *ultradian rhythmicity* demonstrated by short pulses of cortisol secretion, usually every 80 to 110 minutes, which do not seem to involve the participation of supra-pituitary structures (Spiga et al., 2016; Waite et al., 2012). This pattern of cortisol secretion may result from a physiological delay in feed-forward mechanisms between the pituitary and the adrenal glands, followed by a rapid feedback mechanism in the opposite direction (Conway-Campbell et al., 2010; Walker et al., 2010). Although the physiological relevance of ultradian rhythmicity is not fully understood, recent evidence suggests it plays a role in modulating glucocorticoid-receptor expression throughout the day (Flynn et al., 2018). Additionally, ultradian secretion of cortisol seems to be an important contributor to generate an adequate response to stress and maintain normal cognitive and physiological functions (den Boon & Sarabdjitsingh, 2017; Kalafatakis et al., 2018).

8.2.2.2 Disrupted HPA-axis activity

The concept of 'allostatic load' describes a state in which allostatic systems are exposed to sufficiently high cumulative physiologic burden, becoming disrupted and damaging for the body (McEwen, 1998; Seeman et al., 2001). Cumulative physiologic burden results from daily life experiences, including both minor and major life challenges, but also from behavioural responses to perceived stress (e.g., lack of sleep, overeating), which may contribute to increase the pressure over allostatic systems (Guidi et al., 2021; McEwen, 1998). Importantly, the threshold for physiological burden associated with disruption varies greatly depending on someone's genetic background, as well as their previous developmental and individual experiences (McEwen &

Seeman, 1999). Thus, similar to chronic breathlessness, an allostatic load state results from the intricate interplay of personhood and physiology.

In the past, four types of allostatic load have been proposed (McEwen, 2007; McEwen & Seeman, 1999). These include 1) a state of repeated exposure to stressors over a long period of time; 2) lack of adaptation to repeated exposure to the same stressor; 3) failure to switch off the stress response; and 4) failure to kick-start an adequate stress response, forcing other mediators, such as inflammatory cytokines, to over-compensate the imbalance (Figure 8.2). Interestingly, given that allostasis depends on the non-linear relationship between multiple body systems, imbalances in any one of these systems may also produce an allostatic load (system imbalance) (McEwen, 2008; McEwen, 2019). For example, excess production of inflammatory cytokines may disrupt the HPA axis, cardiovascular, and central nervous systems, which are forced to compensate for the dysfunction (McEwen, 2019; Schulkin, 2004). Allostatic load is therefore a systemic condition, with widespread effects on the body.

In this context, a recent systematic review of 267 studies examined the clinical significance of an increased allostatic load (Guidi et al., 2021). Higher allostatic load, identified by at least three different biological markers, was shown to be associated with worse physical and mental health across different settings (Guidi et al., 2021; Seeman et al., 2001; Seeman et al., 1997). In particular, higher allostatic load was associated with older age, chronic conditions (such cardiovascular disease and cancer), pain, poor sleep, and mood and anxiety disorders (Guidi et al., 2021). These results are relevant for people with chronic breathlessness, who are typically older and have multiple symptoms and comorbid conditions, which may produce higher allostatic load (Milton et al., 2008; Naughton et al., 2006). Indeed, higher allostatic load may be one of the mechanisms by which breathlessness increases mortality (Nishimura et al., 2002; Ryan et al., 2017).

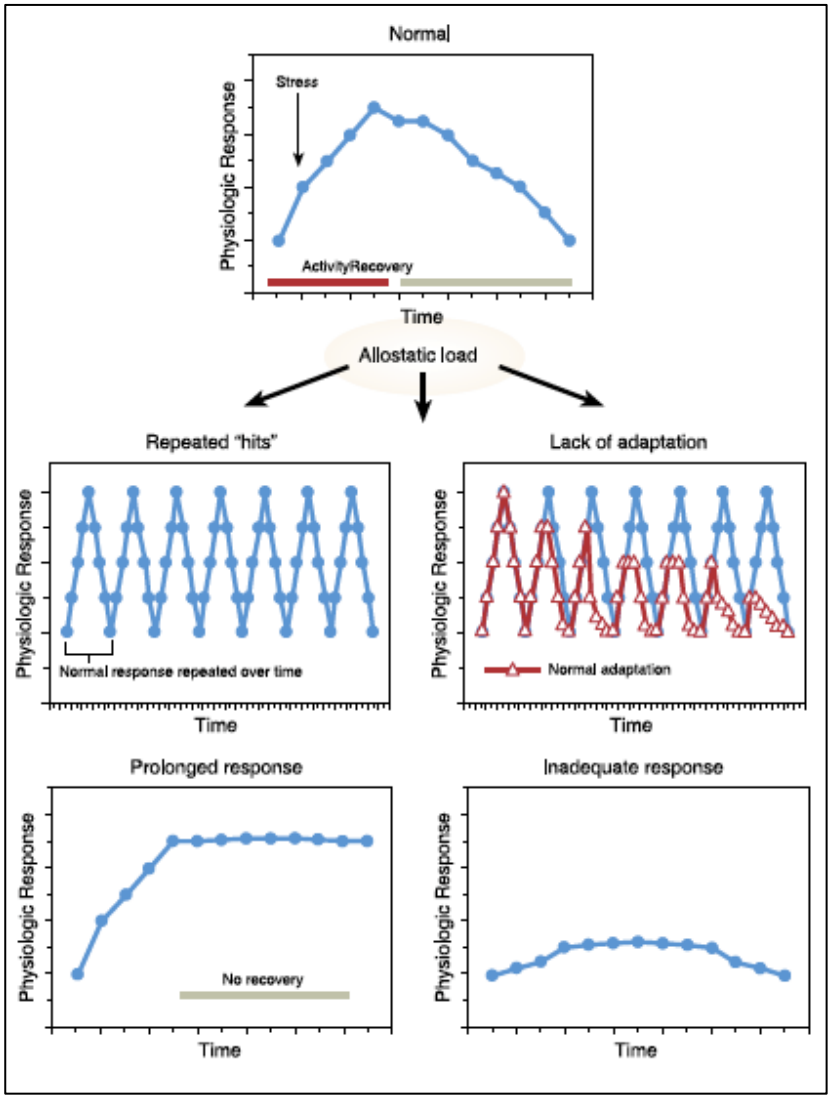

Figure 8.2 - Four different types of allostatic load
Top centre: normal allostatic response; *Top left*: repeated exposure to different stressors; *Top right*: lack of adaptation to the same stressor; *Bottom left:* failure to switch off the stress response; *Bottom right:* inadequate stress response, with compensation from other mediators (e.g., inflammatory cytokines). Copied from McEwen (2007) with permission from The American Physiological Society© (Appendix 15).

Allostatic load is best measured though clinical indicators and specific biomarkers (Seeman et al., 2004; Seeman et al., 2001). Specifically, allostatic load on the HPA axis is classically identified by disrupted patterns of cortisol secretion (Fries et al., 2005). However, such disruption patterns are not consistent across studies, suggesting a complex interaction between allostatic load and HPA-axis activity. In this context, results from a systematic review and metanalysis of 107 studies suggested that the pattern of cortisol disruption observed is highly dependent both on the stressor and on individual characteristics (Miller et al., 2007). Importantly, long-term exposure to

stress was associated with lower morning cortisol peak levels and higher afternoon cortisol levels, producing a flatter diurnal cortisol curve overall and higher total daily exposure to cortisol around the clock. Additionally, threats to physical integrity also produce flatter diurnal cortisol curves, with increased total daily exposure to cortisol. Moreover, uncontrollable stress follows a similar pattern, while stress perceived as controllable was associated with higher morning cortisol levels (Miller et al., 2007). These are important results in the context of chronic breathlessness. People with chronic breathlessness often experience breathlessness and disability for years (long-term exposure). They may also experience episodes of acute-on-chronic breathlessness that may be perceived as *unavoidable*, *uncontrollable*, or *physically threatening*. Thus, it is likely that chronic breathlessness in some people may produce allostatic overload and HPA axis disruption.

8.2.2.3 Measures of HPA-axis activity

Cortisol is one end-product of the HPA axis and a relatively stable molecule that is widely available in all body fluids (Spencer & Deak, 2017). Thus, cortisol is frequently used as a biomarker of the HPA axis activity (Adam & Kumari, 2009). Although classically measured in blood, cortisol can be accurately measured in saliva, with the advantages of being convenient and non-invasive (Kirschbaum & Hellhammer, 1994; Spencer & Deak, 2017). It is also important to note that cortisol is a liposoluble molecule. Only 5 to 10% of the circulating cortisol is in its free form, while the remaining 90-95% is linked to corticosteroid-binding globulin, albumin, and erythrocytes (Spencer & Deak, 2017). Thus, any conditions affecting erythrocytes or protein availability, will necessarily affect circulating cortisol levels. This is particularly important for people with chronic breathlessness, whose underlying condition(s) and comorbidities may predispose to a state of inflammation, with hypoproteinemia or anaemia of chronic disease.

In saliva, cortisol is present in its free form, and is therefore less prone to fluctuations. However, it is important to consider that people with chronic breathlessness, particularly those taking opioids,

may be prone to develop dry mouth as an anti-cholinergic effect (Moore & McQuay, 2005; Norden et al., 2015), which can hinder saliva sample collection. Importantly, new methods of saliva collection require very small samples, and salivary cortisol concentrations are not affected by the rate of salivary flow (Poll et al., 2007; Vining et al., 1983).

Because cortisol responds both to the circadian rhythm and to episodic stressors, it can be analysed from both perspectives (Smyth et al., 2013). However, analysing changes in the cortisol circadian rhythm may be particularly relevant in chronic conditions, which affect individuals on a permanent basis (Lupien et al., 2009). Importantly, the cortisol circadian rhythm seems to involve two different patterns, which seem to be regulated by different mechanisms (Smyth & Clow, 2020). In this context, peri-awakening studies have demonstrated a dissociation in the levels of ACTH and cortisol during the peri-awakening period, suggesting that the early-morning cortisol peak is under tighter control of extra-pituitary regulatory mechanisms compared with the basal diurnal cortisol secretion (Born et al., 1999; Wilhelm et al., 2007). Additionally, the sudden rise in cortisol levels after awakening seems to be a superimposed phenomenon on the normal diurnal cortisol curve, which is related to activation of distinct brain regions and associated with the awakening process (Clow et al., 2010; Wilhelm et al., 2007). One of these brain regions is the hippocampus, which classically is known for regulating memory and learning (Anand & Dhikav, 2012; Fries et al., 2009). More evidence supporting differentiation between the early-morning cortisol response and the basal diurnal cortisol curve comes from studies of monozygotic twins, which have demonstrated that the post-awakening rise in cortisol levels is highly dependent on genetic factors, while the basal diurnal cortisol curve is not (Kupper et al., 2005; Wust et al., 2000). For the reasons mentioned above, it is recommended to study these phenomena separately (Smyth & Clow, 2020).

8.2.2.3.1 The Cortisol Awakening Response (CAR)

The sharp rise in cortisol levels over the first 30 to 45 minutes after awakening is referred to as the cortisol awakening response (Clow et al., 2004; Pruessner et al., 1997). The *cortisol awakening response* (CAR) is believed to provide a physiologic 'boost', preparing the body for the somewhat dramatic transition from deep rest to an active state (Clow et al., 2010). The CAR is a consistent finding in multiple species, persisting even after repeated night-time awakenings (Dettenborn et al., 2007). Importantly, the CAR exhibits considerable inter- and intra-individual variability in healthy people. Most of this variability (up to 70%) is explained by day-to-day fluctuations and is seemingly adaptive, preparing the body to achieve optimal function on each day (Clow et al., 2010; Law et al., 2013; Ross et al., 2014). For example, anticipation of a challenging day ahead tends to enhance the CAR compared with anticipation of a resting day (Kunz-Ebrecht et al., 2004). Additionally, other factors such as the level of light exposure in the pre-awakening period, the time of awakening and smoking seem to be associated with the CAR amplitude (Adam et al., 2010; Adam et al., 2006; Kudielka & Kirschbaum, 2003). The CAR is also influenced by the level of physical and psychological health, which will be discussed in detail in section 8.2.3. Importantly, genetic factors seem to be key determinants of the CAR, explaining an important part of the variability observed in some studies (Kupper et al., 2005; Wust et al., 2000).

Measuring the CAR poses multiple challenges. Firstly, it requires collection of a minimum of three daily samples, one immediately after awakening, and the others at 30- and 45-minutes post-awakening, in order to effectively capture the peak cortisol concentrations (Clow et al., 2004; Stalder et al., 2016). Secondly, there is a narrow window to collect each sample, and failure to comply with the stipulated times will result in important variations (Stalder et al., 2016). In order to prevent measuring errors due to inadequate sampling, it is recommended that studies evaluating the CAR use both an objective measure of awakening time (e.g., actigraphy, polysomnography), *and* objective verification of sampling times, in addition to participants'

reporting (Lichstein et al., 2006; Stalder et al., 2016). Additionally, because the CAR is prone to important inter- and intra-individual variability, samples should be collected across a minimum of two consecutive days (Hellhammer et al., 2007). Thus, measuring the CAR is demanding for participants and researchers, and should not be attempted unless the above conditions are ensured (Smyth & Clow, 2020; Stalder et al., 2016).

8.2.2.3.2 Diurnal cortisol slope

The *diurnal cortisol slope* reflects the rate of cortisol decline from morning until evening (Adam & Gunnar, 2001; Adam & Kumari, 2009). In general, more accentuated declines are associated with better health physical and mental health outcomes (Adam et al., 2017). Although the diurnal cortisol slope shows less day-to-day fluctuations compared to the CAR, it is still subject to considerable variation depending on situational factors (Ross et al., 2014; Smyth et al., 1997). Collecting samples across a minimum of two days is an effective way to minimise the effect of such factors (Adam & Kumari, 2009; Kraemer et al., 2006; Ryan et al., 2016a). Additionally, sample collection needs to be synchronised with the time of awakening rather than with fixed timepoints, which has been shown to increase reliability of results (Adam & Kumari, 2009; Ryan et al., 2016a; Thorn et al., 2011). In the past, there was some debate regarding the timing of the first sample, for which multiple approaches have been used, including using the first awakening sample, the CAR-peak sample, or a mid-morning sample collected after the CAR period (Adam et al., 2017; Smyth et al., 2013). As the CAR and the basal diurnal cortisol curve seem to be different phenomena with no obvious correlation between them, it is currently recommended collecting the first sample after the CAR period, usually 3 hours after waking up (Edwards et al., 2001; Smyth & Clow, 2020). There is a lack of agreement regarding the optimal number of daily samples required to calculate the diurnal cortisol slope (Ryan et al., 2016a). More studies use a 4-sample protocol with collection at 3, 6-, 9-, and 12 hours after awakening, but there is some evidence to suggest that a 2-sample approach may provide similar results (Adam & Kumari, 2009; Smyth et al., 2013). Importantly,

most protocols collect the last sample closer to bedtime, usually 12 hours after waking up (Smyth et al., 2013).

Measuring the diurnal cortisol slope is less demanding for participants and researchers compared with measuring the CAR. This is because up to one-hour deviations from pre-determined collection times do not appear to impact on the slope substantially (Jacobs et al., 2005; Smyth & Clow, 2020). As a result, it is acceptable to rely on participants' self-reported awakening times, instead of using a combination of subjective and objective measures. However, it is important to highlight that one should not be used *as an alternative* to the other. Ideally, both patterns should be measured to provide an indication of the overall cortisol profile but, if that is not possible, researchers need to select the measure that best suits their research question, after taking into account the population, setting and resources with which they are working (Ryan et al., 2016a; Smyth & Clow, 2020). A schematic representation of the CAR and AUC is presented in Figure 8.3.

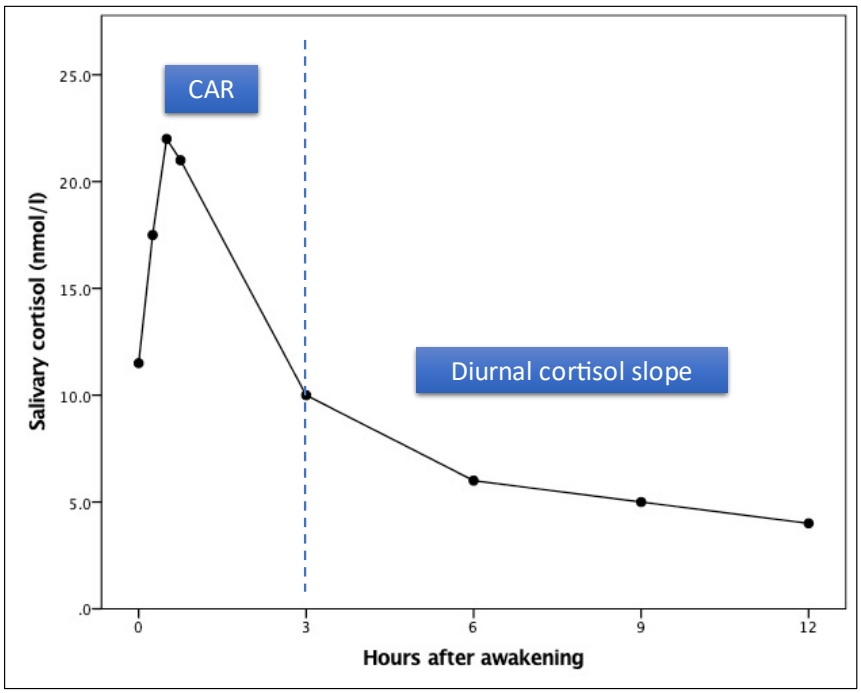

Figure 8.3 - Typical diurnal pattern of salivary cortisol in heathy people (values derived from the literature).
CAR, cortisol awakening response. Adapted from Smyth & Clow (2020) with permission from Springer© (Appendix 16).

8.2.2.3.3 Area under the curve

A third measure of interest is the area under the curve (AUC), which is a measure of the total cortisol output across the day (Steptoe & Serwinski, 2016). In the past, the AUC used to be measured using both CAR and diurnal cortisol slope datapoints. However, in light of the most recent evidence reporting the CAR and the diurnal cortisol slope as separate phenomena, it is advisable to measure their respective AUCs separately (Smyth et al., 2013). Importantly, the AUC complements other cortisol measures but provides little information when used in isolation. This is because chronic stress may be associated with both hypo- and hypercortisolism and it is the cortisol secretion pattern, more than the total cortisol output, that holds clinical significance (Adam & Kumari, 2009; Fries et al., 2005; Smyth et al., 2013). However, there is still interest in reporting the AUC as a secondary outcome measure to enhance interpretation of the CAR and the diurnal cortisol slope (Adam et al., 2016; Smyth et al., 2013).

8.2.3 HPA axis dysregulation in chronic disease

There is a robust body of evidence associating chronic stress with aberrant diurnal cortisol profiles. Specifically, chronic stress has been linked to changes in both the CAR (Steptoe & Serwinski, 2016) and diurnal cortisol slope (Adam et al., 2017). Importantly, chronic disease can be associated with different CAR abnormalities, which are frequently difficult to predict. For example, depression and anxiety have been reported to be associated with larger CARs in some studies, and lower CARs in others (Chida & Steptoe, 2009). However, there is evidence to suggest that higher CARs predict the risk of future mood disorders in people at risk (Vrshek-Schallhorn et al., 2013). In this context, an elevated CAR may reflect an attempt to adapt to a chronic stress state, which is followed by HPA-exhaustion (and smaller CARs) in more advanced disease. Conversely, post-traumatic stress disorder has been linked exclusively to smaller CARs, which may also reflect a state of constant exposure to high levels of stress with deficient HPA-axis adaptation (Wessa et al., 2006). Other conditions such as type 2 diabetes, metabolic syndrome, arterial hypertension, and

multiple sclerosis have been associated with abnormal CARs (Bengtsson et al., 2010; Hackett et al., 2014; Kern et al., 2013; Wirtz et al., 2007). Similar findings were reported for chronic symptoms such as fatigue, insomnia, and chronic pain (Steptoe & Serwinski, 2016). Importantly, possible associations between chronic breathlessness and CAR abnormalities have not been explored.

While chronic conditions are associated with different CAR findings, they seem to be consistently associated with flatter diurnal cortisol slopes, reflecting less variation in salivary cortisol concentrations across the day (Adam & Kumari, 2009). A recent systematic review and meta-analysis of 80 studies examined the evidence supporting the association between flatter diurnal cortisol slopes, and physical and mental health outcomes (Adam et al., 2017). Small but significant associations were found between flatter diurnal cortisol slopes and most of the outcomes analysed, including immune/inflammatory outcomes (r=0.288), cancer (r=0.231), fatigue (r=0.167), depression (r=0.106) and obesity/BMI/adiposity (r=0.093) (Adam et al., 2017). There was also a significant association between flatter diurnal cortisol slopes and higher mortality (average hazard ratio of 2.40 [CI 1.00 – 5.74], p=0.049) (Adam et al., 2017). Importantly, although the reported effect sizes are small, there is considerable variation in the design of the studies included, and in the methods and timepoints used for sample collection. These variations may have contributed to an under-estimation of true effect sizes (Adam et al., 2017). Importantly, flatter diurnal cortisol slopes are also seen in conditions typically associated with chronic breathlessness, such as COPD and lung cancer (Du et al., 2013; Du et al., 2014). However, there are very few studies exploring specific associations between chronic breathlessness and the diurnal cortisol slope.

8.2.4 Chronic breathlessness and HPA axis dysregulation

There is some initial evidence to suggest there is an association between chronic breathlessness and HPA dysregulation. Firstly, chronic breathlessness is a hallmark of many chronic and life-limiting illnesses that have been linked to HPA dysregulation (Abercrombie et al., 2004; Laghi et al., 2009).

Secondly, the mechanisms by which breathlessness influences mortality are still unknown (Barlera et al., 2013; Nishimura et al., 2002). It is possible that there is an intermediate link with HPA dysregulation, which has also shown to be a predictor of mortality (Hammer et al., 2016; Sephton et al., 2013). Thirdly, many central structures and pathways associated with the sensation of breathlessness are also involved in the stress response (Godoy et al., 2018; Pattinson & Johnson, 2014). In addition, chronic breathlessness is commonly associated with fatigue, anxiety, depression, and sleep disruption, which may all contribute to activating the chronic stress response (Borge et al., 2010; McNicholas et al., 2013; Yohannes et al., 2010). Thus, chronic breathlessness and chronic stress may co-exist for many people.

The link between chronic breathlessness and HPA dysregulation was suggested by one cross-sectional study of 110 participants, examining the salivary diurnal cortisol profile of people with chronic breathlessness and of healthy participants (Ryan et al., 2017). This study revealed that people with moderate-to-severe functional impairment due to breathlessness (mMRC 2 to 4) have dysregulation of their normal circadian rhythm of cortisol production, which translated into flatter diurnal cortisol slopes compared with people with mild/no functional impairment due to breathlessness (mMRC 0 or 1), and healthy controls ($p<0.001$ in the ANCOVA model for both comparisons). There was also a higher prevalence of flat and ascending daily cortisol slopes in people with moderate-to-severe functional impairment due to breathlessness (23.4%) compared to healthy controls (0%). Additionally, people with mild/no functional impairment due to breathlessness (mMRC 0 or 1) had flatter diurnal cortisol slopes compared with healthy controls ($p=0.024$). This analysis was adjusted for gender, age and socioeconomic status, which were different between groups (Ryan et al., 2017).

Importantly, this study also examined overall intensity of breathlessness over the previous 24 hours using the NRS, and the mastery domain of the Chronic Respiratory Questionnaire (CRQ). No

associations were found between these measures and the diurnal cortisol slope. Additionally, there were no significant relationships between changes in diurnal cortisol slope and other measures commonly associated with chronic breathlessness and/or stress (subjective sleep, perceived distress, anxiety, depression, mental wellbeing, comorbidities, or performance status). These results may suggest that the HPA axis dysregulation seen in people with chronic breathlessness is more likely to be associated with the functional impairment caused by breathlessness, rather than the symptom itself (Ryan et al., 2017). Importantly, the question associated with the NRS scale focused on *overall* breathlessness intensity over the previous 24 hours ("how much shortness of breath have you experienced over the past 24 hours?"). Using classic measures of *worst* and *average breathlessness* over the previous 24 hours may have led to different results (Lovell et al., 2019).

Given that Ryan et al. (2007) dichotomised mMRC into either *mild or no breathlessness* (mMRC 0-1) and *moderate-to-severe breathlessness* (mMRC 2-4), it is unclear if there are any differences in diurnal cortisol slope between mMRC 2, 3 and 4. These differences need to be explored in detail, as they may translate into different clinical outcomes.

8.2.5 Regular opioid therapy and dysregulation of the HPA axis

Central structures implicated in the stress response (e.g., hypothalamus, pituitary gland, and limbic system) are also densely populated by opioid receptors, suggesting these molecules may be heavily involved in stress modulation (Le Merrer et al., 2009). In addition, these same central structures and pathways seem to overlap, at least in part, with those associated with unpleasant sensations (e.g., pain and breathlessness), which frequently respond to opioid therapy (Pattinson & Johnson, 2014; von Leupoldt et al., 2009). Thus, there is interest in exploring the effects of opioids on the body response to stress.

Evidence from experimental studies suggests that endogenous opioids are primarily stress-response inhibitors, exerting their effects through the three main types of opioid receptors (i.e., μ, κ, and δ

opioid receptors) (Fountas et al., 2018). Such inhibition occurs by at least four different mechanisms. Firstly, opioid peptides reduce the sympathetic drive, by decreasing the central release of noradrenaline (Drolet et al., 2001; Valentino & Van Bockstaele, 2001). Secondly, they directly inhibit the synthesis and release of CRH from the hypothalamus, downregulating the synthesis and release of ACTH and cortisol (Drolet et al., 2001; Hellbach et al., 1998). Thirdly, they inhibit CRH indirectly, by inhibiting noradrenergic neurons that are responsible for the synthesis and release of CRH (Valentino & Van Bockstaele, 2001). Lastly, endogenous opioids are likely to have a direct inhibitory effect on the adrenal cortex, since the opioid receptor antagonist naloxone increases the concentration of circulating cortisol but not of ACTH (Coiro et al., 2011). Importantly, there are some differences in response mediated by different opioid receptors. While all opioid receptor types seem to have been implicated in inhibitory responses to stress, activation of κ-opioid receptors by dynorphin-like peptides may produce stress-like aversion (Land et al., 2009; McLaughlin et al., 2003), with an increase in cortisol levels in some people (Pfeiffer et al., 1986). Up to this point, mechanisms underlying inter-individual variation in opioid response are not fully elucidated.

Exogenous opioid agonists have shown to produce similar effects to endogenous opioid peptides. Compared with placebo, acute administration of intravenous morphine under basal (i.e., non-stressful) circumstances leads to a greater decrease in plasma concentrations of ACTH and cortisol over a period of three hours after injection (Zis et al., 1984). Similar effects were reported with a single administration of sustained-release morphine 30 mg (Allolio et al., 1987), and after acute administration of different formulations of other μ-opioid agonists (Bershad et al., 2015; Bershad et al., 2018; Watanabe et al., 2014). However, it is important to note that most studies fail to examine the short-term effects of therapeutic opioid-agonists in specific phases of the diurnal cortisol cycle (i.e., CAR and/or slope). Moreover, these studies are predominantly conducted with healthy volunteers, who may exhibit a relatively normal baseline diurnal cortisol curve. People with chronic

conditions are likely to have altered diurnal cortisol profile at baseline and may experience different effects with chronic opioid therapy. Thus, they need to be examined separately.

There is a wider body of work documenting the effects of chronic opioid therapy on the HPA axis (Fountas et al., 2020). Suppression of the HPA axis was observed in both people with chronic cancer and non-cancer pain taking long-term oral and transdermal opioids (Gibb et al., 2016; Lamprecht et al., 2018; Valverde-Filho et al., 2015). Many of these also exhibit blunted cortisol responses after synthetic ACTH administration, suggesting a mechanism of secondary adrenal insufficiency (Demarest et al., 2015; Gibb et al., 2016). Importantly, blunted cortisol responses were only observed in people taking higher doses of opioids (mean oral morphine-equivalent daily dose of ≥100 mg), and not in people taking a mean oral morphine equivalent daily dose <60 mg (Lamprecht et al., 2018). These results are relevant in the context of chronic breathlessness, suggesting that people taking regular, low-dose (≤30 mg /day), sustained-release oral morphine for the symptomatic reduction of chronic breathlessness may not develop dysregulation of the HPA axis. However, much of the evidence available comes from studies with a cross-sectional design, in which higher daily opioid doses may also reflect more severe symptoms, underlying disease, comorbidities, and polypharmacy, which may also contribute to, cause or aggravate HPA-axis dysfunction. Thus, the effect of regular, low-dose, sustained-release oral morphine on the HPA axis of people with chronic breathlessness is still largely unknown, and needs to be investigated prospectively.

8.3 Aim and Objectives

The aim of this study was to explore the effects of once-daily, regular, low-dose, sustained-release oral morphine on the diurnal salivary cortisol profile of people with severe chronic breathlessness associated with COPD.

Specific objectives of this hypothesis-generating study were to explore the:

- diurnal cortisol profile of people with severe chronic breathlessness associated with COPD, who were opioid naïve;
- shorter- and longer-term effects of once-daily, regular, low-dose, sustained-release oral morphine on the diurnal cortisol profile of people with severe chronic breathlessness associated with COPD;
- relationship between intensity of chronic breathlessness and diurnal salivary cortisol profile; and
- relationship between the diurnal cortisol profile and medication, performance status, sleep, anxiety, depression, well-being, and global impression of change with the study drug (i.e., morphine / placebo).

8.4 Methods

8.4.1 Study design and setting

This was an exploratory, prospective, repeated-measure sub-study embedded in the BEAMS trial, exploring the effects of regular, low-dose, sustained-release oral morphine on the diurnal cortisol profile of people with severe chronic breathlessness associated with COPD (Currow et al., 2017). From the 18 Australian health-care sites participating in BEAMS, all were invited to participate in this sub-study.

8.4.2 Study participants

Selection criteria for this sub-study were carefully chosen to maximise the number of participants on the study, while minimising major co-existing causes of HPA-axis disruption. People with severe chronic breathlessness associated with COPD are frequently affected by multiple comorbidities and are typically on several medications, which can interfere with the HPA axis and disrupt the diurnal cortisol secretion pattern. However, excluding people with common causes of cortisol profile disruption would result in very low recruitment and would not accurately represent this

population with chronic breathlessness. Instead, this sub-study focused on excluding only major causes of HPA axis disruption, which include conditions or medications with the ability to cause major fluctuations in the diurnal cortisol secretion pattern. Based on this, all participants recruited for the BEAMS trial were invited to participate in this sub-study, except if they were taking systemic corticosteroids (oral, intravenous) at any point, in the four weeks prior to baseline assessments, or taking subcutaneous insulin for diabetes. Systemic corticosteroids not only greatly disrupt the normal function of HPA axis, but they also exhibit cross-reactivity with salivary cortisol immunoassays, including the one used in this study (Granger et al., 2009). People with diabetes requiring therapy with insulin are more likely to have worse glycaemic profiles and high levels of insulin resistance, which were found to greatly disrupt the cortisol awakening response and the diurnal cortisol slope (Joseph & Golden, 2017; Joseph et al., 2015). Thus, they were also excluded from this sub-study.

Even though not all BEAMS participants at each site were included in this sub-study, the block randomisation used in the main trial increased the chances of having a similar proportion of participants per arm in the cortisol sub-study. Before sub-study commencement, the researcher (D.F.) organised individual training sessions with the study staff at each participating site, in which she explained reasons for conducting the sub-study and detailed sub-study procedures. Questions raised by the study staff were discussed and clarified. At the end of each session, a summary of all sub-study procedures and all sub-study documents were sent to the study staff by email. All participating sites were provided with the researcher's contact details for any additional issues requiring clarification.

Research nurses at each site identified and approached potential participants for this sub-study. All participants who were interested in getting further information were provided a detailed explanation of the sub-study procedures, followed by an opportunity to discuss the study in detail

and clarify potential questions and concerns. All participants provided written informed consent before enrolling.

8.4.3 General study procedures

At each site, all consenting participants took part in a one-on-one information session with the BEAMS study nurses before commencing the sub-study. These information sessions aimed to ensure that participants fully understood the sub-study procedures and got familiar with the study documents before proceeding with sample collection. In addition to the baseline measures collected as part of the BEAMS trial, participants were also specifically asked if they:

- were taking inhaled corticosteroids;
- had used systemic corticosteroids over the previous year;
- had a current or past history of psychiatric illness;
- had a diagnosis of diabetes not requiring insulin.

Different conditions and medications may interact with HPA-axis function either directly or indirectly. Inhaled corticosteroids have the potential to directly inhibit the cortisol production by a mechanism of negative feedback to the hypothalamus and pituitary. They may also leave some oral residue and change the saliva composition (Granger et al., 2009). Importantly, the only study exploring cortisol profiles in people with chronic breathlessness did not show any differences in the diurnal cortisol slope between people taking inhaled corticosteroids and those who were not (Ryan et al., 2017). Nevertheless, it is good practice to account for their potential influences. Similarly, chronic use of systemic corticosteroids may induce adrenal insufficiency, which may take up to one year to resolve (Younes & Younes, 2017). For this reason, the use of systemic corticosteroids over the past year was also noted. Psychiatric disorders such as anxiety, depression or post-traumatic stress disorder may disrupt the HPA axis function causing hypo- or hyper-cortisolaemic states (Adam et al., 2006; Adam et al., 2017; Wessa et al., 2006). Diabetes may

disrupt the CAR and the diurnal cortisol slope in proportion to the rise of HbA1c (Joseph & Golden, 2017; Joseph et al., 2015). Although people taking insulin are expected to have more severe disease and clear disruption of the HPA axis, those taking oral anti-diabetic agents are also likely to display aberrant diurnal cortisol profiles (Joseph & Golden, 2017; Joseph et al., 2015). As a result, these factors were accounted for in this sub-study.

Similar to previous work in this field, this sub-study focused on measuring the diurnal cortisol slope and the respective area under the curve (Ryan et al., 2017). As detailed before, measuring the CAR is demanding, requiring strict adherence to protocol collection times and the use of objective measures to verify participants' compliance. Additionally, non-compliance with strict collection times has been shown to be a significant problem in people with chronic breathlessness (Ryan et al., 2017). Considering the expected challenges in measuring the CAR in this frail population, this outcome measure was excluded from this sub-study protocol as recommended by current expert consensus guidelines (Stalder et al., 2016). Importantly, given the scarcity of studies investigating the diurnal cortisol slope and the AUC in the context of chronic breathlessness, the current sub-study was still appropriate and relevant.

8.4.4 Salivary diurnal cortisol samples collection

This sub-study involved saliva collection of multiple samples at up to four different times across the whole study (Baseline, Stage 1, Stage 3, and Stage 4). For each timepoint, participants were provided with a saliva self-collection pack, a diary for collection days, and a detailed instruction sheet specifying the sub-study procedures. Each saliva self-collection pack included six saliva-collection devices to collect saliva samples across two consecutive days (i.e., three samples per day). The sections below detail the timepoints and procedures related to the collection of saliva samples.

8.4.4.1 Collection time-points

Saliva samples were collected prospectively up to a maximum of four different timepoints, coinciding with specific timepoints of the BEAMS trial (Figure 8.4):

- **Baseline collection**: Baseline samples were collected on days -1 and 0, before initiating the study medication (i.e., fixed, regular, low-dose, sustained-release oral morphine or placebo); these samples provided stable baseline data on the salivary cortisol profiles of people with severe breathlessness associated with COPD, whose underlying disease was optimally treated and who were opioid naïve.
- **Stage 1 collection**: Stage 1 samples were collected on days 5 and 6 after initiating the study medication. By this stage, morphine would have reached plasma steady-state concentrations, providing stable data on the effects of regular, low-dose, sustained-release morphine (Gourlay et al., 1995). Additionally, most people who respond to regular, low-dose, sustained-release oral morphine, experience a reduction in breathlessness in the first 24 hours after successful titration of their therapy (Currow et al., 2013). Thus, there is interest in investigating if there are any immediate changes in the salivary diurnal cortisol profile associated with breathlessness reduction in the first few days of therapy. Additionally, by days 5 and 6, participants could be taking two different doses of sustained-release morphine (8mg or 16mg), allowing comparison between doses.
- **Stage 3 collection**: Stage 3 samples were collected on days 19 and 20 after initiating the study medication. By then, participants would have gone through two additional randomisations on days 7 and 14 (randomisations #2 and #3) and could have had their morphine doses increased. Dose increments beyond 16 mg of regular, low-dose, sustained-release oral morphine would increase the chance of responding for some participants who had not experienced a reduction in breathlessness with lower doses (Currow et al., 2011). Collection of saliva samples on days 19 and 20 was designed to compare shorter-term

changes in the diurnal cortisol profile between all five doses of study medication used in the BEAMS study (placebo, regular, low-dose sustained-release oral morphine 8 mg, 16 mg, 24 mg or 32 mg). Again, all participants would have reached new morphine steady-state concentrations, despite any dose increments on randomisations #2 and #3.

- **Stage 4 collection**: Stage 4 samples were collected after three months of taking a stable dose of the study medication (placebo, regular, low-dose sustained-release oral morphine 8 mg, 16 mg, 24 mg or 32 mg) in a blinded extension phase. This collection timepoint was included to explore the longer-term effects of different doses of regular, low-dose, sustained-release oral morphine on the diurnal cortisol profile and any associations with breathlessness reduction.

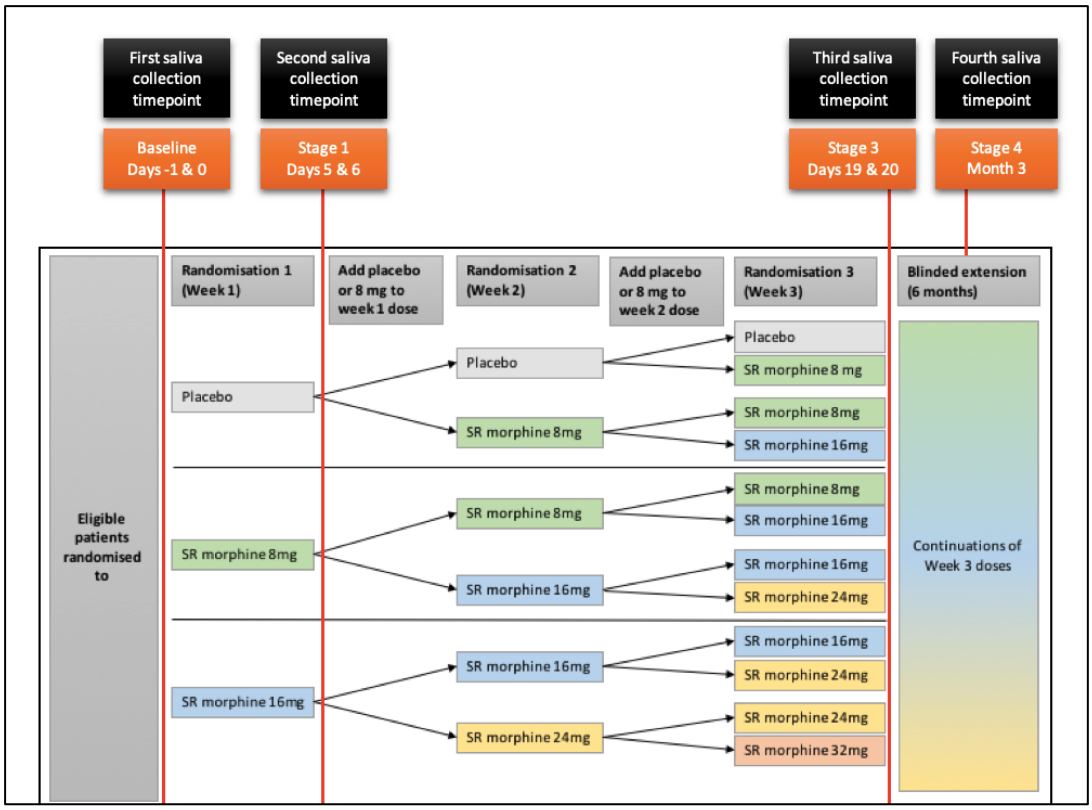

Figure 8.4 - Cortisol sub-study samples collection timepoints (Baseline, Stage 1, Stage 3, Stage 4)

8.4.4.2 Collection procedures

Samples were collected by participants at home. At each collection time-point, participants were required to collect six saliva samples across two consecutive days. The collection of three saliva samples per day provides sufficient data to calculate the diurnal cortisol slope and the AUC for each participant (Adam & Kumari, 2009; Kraemer et al., 2006). On each collection day, collection times were calculated based on the time of waking, according to current recommendations (Ryan et al., 2016a). Samples were collected at 3, 6 and 12 hours after waking up. Collection times were based on previous work in the field of chronic breathlessness and followed current recommendations for saliva cortisol measurements (Ryan et al., 2016a; Smyth et al., 2013). 'Waking time' was explained to participants as the time "when your eyes open and you are ready to get up" (Cohen et al., 2006).

Study staff were instructed not to perform any invasive procedures (e.g., venepuncture) on collection days, which could potentially activate the stress response and increase salivary cortisol levels (Kirschbaum & Hellhammer, 1989). In addition, participants were asked to restrain from eating, drinking, smoking, brushing their teeth or exercising 30 minutes before each collection, as these activities may either influence saliva composition and interfere with sample analysis, or induce transitory stress responses (Adam & Kumari, 2009; Kudielka et al., 2012). On each collection day, participants were asked to use a diary to register their waking time and calculate collection times for the day. After collection of each saliva sample, they were also asked to record any deviations from the proposed sampling times. Unexpected problems during sample collection (e.g., brushing teeth, eating, or smoking less than 30 min before collecting the sample) were also recorded, as well as whether the participant had been outdoors or had engaged in any form of exercise that day. Diaries were designed to facilitate participants' compliance and to identify deviations to the pre-defined sampling times and instructions.

Saliva samples were collected using the Salivette® Cortisol devices (SARSTEDT, Australia), each consisting of a synthetic swab stored in a plastic tube. At each collection, participants were instructed to chew on the swab for one minute before re-storing it in the plastic tube, according to the manufacturers' instructions. Salivary cortisol is relatively stable at room temperature and does not require immediate freezing (Nalla et al., 2015). As a result, participants were then asked to keep their samples in their fridge until collection by the study nurses 24 to 48 hours later. This procedure was adopted to avoid disturbing participants with additional study visits and facilitate compliance with both the parent BEAMS study and the sub-study. Each collection tube was pre-labelled with the participant's study identification number, collection timepoint, collection day, sample number and time after awakening (e.g., "Participant ID number / Baseline / Day 1 / Sample 1 / 3 hours"). For each collection day, each one of the three tubes displayed different labelling colours to facilitate identification of the correct tube to use (i.e., Sample 1 - red, Sample 2 - blue, Sample 3 - purple). Collection tubes were stored together in a zip-locked bag labelled with participant's study identification number, number of samples, and collection time-point (e.g., 'Participant ID number, 6 samples, Stage 3; Figure 8.5).

Figure 8.5 - Saliva collection tubes and packs.
Top left: Salivette® Cortisol devices (SARSTEDT, Australia) consisting of a plastic storage tube and a cotton swab; *Bottom left*: Example of the labelling system used in individual tubes; *Right*: Example of the cortisol pack provided to participants.

8.4.5 Sample storage

After each set of collection days (i.e., Baseline, Stage 1, Stage 3 or Stage 4), study staff collected samples and diaries from patients' homes and sent them to a central location for storage at the Flinders Medical Centre in South Australia. Express post was used to transport the samples to the central location. In days of extreme heat, the study staff at each participating site were asked to store the samples in their local fridge for up to four days before posting them. Cortisol is a relatively stable molecule at room temperature, but it can be degraded quickly when exposed to heat (Clements & Parker, 1998; Nalla et al., 2015). Thus, this measure was adopted to prevent sample deterioration. All samples were received at the central location and stored in a -30ºC freezer until the end of the study. The freezer temperature was constantly monitored and checked periodically. At the end of the study, samples were collected and transported in dry ice to the Stratech® facilities in New South Wales where they were analysed. Transport in dry ice aimed to avoid an additional freeze-thaw cycle, which may contribute to degrading cortisol (Garde & Hansen, 2005).

8.4.6 Measures to facilitate compliance

This study relied on study staff and participants to determine the appropriate collection days (based on the BEAMS trial schedule) and times (based on the participants' waking times). In order to prevent errors while making such determinations, specific strategies were put in place. As explained before, study staff had an initial training session to ensure they understood the collection timepoints and collection procedures. Written instructions were also provided to staff following the training session (Appendix 17). A checklist for staff was developed to assist them with determining whether a potential participant was eligible (Appendix 18). Additionally, a collection-day calculator was developed in Excel® to help calculate the collection days based on the baseline date.

Each participant had a training session with the study staff to ensure they were able to understand the study procedures, including the concept of "waking time" (Cohen et al., 2006) and how to calculate collection times. An instruction sheet detailing all study procedures was also provided to participants (Appendix 19). For each collection day, participants were asked to complete a diary where they recorded their time of waking, calculated the subsequent collection times and registered the actual time of each collection (Appendix 20). They were also asked to record any problems with sampling (e.g., eating or drinking less than 30 minutes before collection). The cortisol diary was designed to facilitate sample collection at the correct times and also to provide accurate information to be used in data analyses.

8.4.7 Sample Analysis

Samples were analysed by Stratech® in September 2019. All samples underwent one freeze-thaw cycle. On the day of the assay, all samples were thawed and analysed using an Enzyme Linked Immunosorbent Assay (ELISA) developed by Salimetrics LLC (USA), according to the manufacturers' instructions. Performance testing by Salimetrics indicates a high correlation between salivary cortisol and matched serum cortisol concentrations (r = 0.91). The lower limit of detection (assay sensitivity) is 0.08 nmol/L. Calculated intra- and inter-assay variability is 7.3% and 7.6%, respectively. Saliva cortisol results were provided to the researcher in an Excel^{R} spreadsheet, which also noted the macroscopic aspect of each sample and any problems noted during laboratory analyses (e.g., insufficient saliva to enable result).

8.4.8 Outcomes

The primary outcome proposed for this sub-study were differences, by dose level (placebo, sustained-release morphine 8 mg, and 16 mg) in the diurnal cortisol slope and respective AUC between Baseline and Stage 1. Differences between Baseline and Stage 1 were selected to explore

the steady-state, shorter-term effects of regular, low-dose, sustained-release oral morphine on participants' diurnal cortisol profile.

Secondary outcomes were differences in the diurnal cortisol slope and corresponding AUC between Baseline and Stages 3 and 4, and differences between Stages 1, 3 and 4. Changes in diurnal cortisol slope and AUC were examined while accounting for other variables which could potentially induce HPA changes, including:

- breathlessness scores: NRS scores for *worst*, *average*, and *unpleasantness* of breathlessness in the previous 24 hours (Gift & Narsavage, 1998; Wilcock et al., 1999);
- mMRC breathlessness grade (Bestall et al., 1999; Stenton, 2008);
- performance status assessed with the AKPS (Abernethy et al., 2005);
- quality of life measured using the EQ-5D-5L index (Herdman et al., 2011);
- subjective sleep quality measured with a 4-point Likert scale (Martins et al., 2016);
- anxiety and depression scores measured with the Hospital Anxiety and Depression Scale (HADS) (Hopwood et al., 1991; Zigmond & Snaith, 1983);
- global impression of change with the study medication (i.e., regular, low-dose, sustained-release oral morphine or placebo) measured with a 7-point Likert scale (Oxberry et al., 2012); and
- harms commonly associated with morphine (constipation, nausea, drowsiness) measured with 4-point Likert scales.

8.4.9 Ethical issues

This sub-study was designed to minimise the burden on a population who was already severely impacted by chronic breathlessness. As a result, study procedures were minimally invasive. The Salivette® Cortisol devices were chosen because they are easy to use and require a minimal amount of saliva compared with standard saliva collection methods. This collection method may also be

quicker and more comfortable for participants who may experience dry mouth (Moore & McQuay, 2005; Norden et al., 2015). Importantly, the Salivette® Cortisol devices were shown to be well tolerated by people with chronic breathlessness (Ryan et al., 2017). Additionally, collection of saliva samples and study measures were reduced to a minimum. The participants' diary was short and easy to complete, providing the minimum amount of information to assist participants with the study procedures and facilitate the study analysis. All other measures, including demographic information, measures of breathlessness, performance status, ESAS scores, quality of life and global impression of change were obtained from BEAMS study documents in order to prevent duplication of information and additional burden for participants.

8.4.10 Sample size

Given that this was a pragmatic, exploratory sub-study embedded in a randomised controlled trial, no formal sample size calculation was undertaken. A previous study reported that procedures used in this sub-study were acceptable for people with chronic breathlessness, and that compliance rates were similar to healthier populations (Ryan, 2015, p.131, 220). As a result, this sub-study aimed to recruit as many BEAMS participants as possible, in order to explore differences in effect sizes between placebo, 8 and 16 mg of regular, low-dose, sustained-release oral morphine, and to inform formal power calculations in subsequent studies.

8.4.11 Statistical Analysis

Normality tests (Shapiro-Wilk) were conducted for all numerical variables at each stage in order to determine the appropriate statistical test to use in the main analysis. Predictably, raw salivary cortisol concentrations were highly skewed in this sub-study. As a result, logarithmic transformation (Ln) was employed to normalise data distribution and facilitate inferential statistics (Sephton et al., 2000; Smyth et al., 1997). Raw cortisol values are presented for descriptive purposes only.

The diurnal cortisol slope was calculated for each participant, on each day, using the log-transformed cortisol values obtained from samples collected 3, 6 and 12 hours after waking. Compliance with sample collection times was verified by checking self-reported collection times recorded in participants' diaries. For each day, samples were deemed compliant if they had been collected within one hour either side of the pre-determined collection times (Jacobs et al., 2005; Smyth & Clow, 2020). Samples collected outside of this timeframe were deemed non-compliant. For participants with unrecorded collection times, compliance was assumed if the participant was compliant with other collection timepoints or if there was evidence of a declining diurnal cortisol slope. The impact of non-compliance in the diurnal cortisol slope and AUC was assessed by comparing means of compliant and non-compliant groups, at each sub-study stage, using unpaired t-tests (with participants with unrecorded collection times included in the non-compliant group).

For each participant, absolute differences between consecutive days' slopes were examined for consistency at each timepoint. If these absolute differences were greater than one standard deviation from the group mean day difference at each timepoint, slopes were considered "inconsistent" (Smyth et al., 1997). Slopes were also categorised as "inconsistent" when the slope direction differed between consecutive days' results. For people with consistent saliva cortisol daily slopes, these were aggregated by regressing log-transformed cortisol values for the two consecutive days (six samples) on sample collection time (Sephton et al., 2000). Consistent cortisol slopes were sub-categorised as "descending", "flat", or "ascending" if slopes were ≤ -0.05, between -0.05 and 0, or >0 (Smyth et al., 1997). Slope reliability across the two consecutive days was assessed separately for "consistent" and "inconsistent" categories using Pearson's correlation. This analysis aimed to confirm if the cut-offs used at each stage were adequate to distinguish between "consistent" and "inconsistent" diurnal cortisol profiles.

For the purpose of inferential statistics, consecutive collection days' samples were then aggregated for each participant, at each timepoint, irrespective of their categorisation. This procedure consisted in regressing all six cortisol values (from Days 1 and 2) against time.

The area under the curve of the diurnal cortisol decline was calculated with respect to ground (AUCg), using the same samples used for calculating the slope (3, 6 and 12 hours after awakening). The AUCg is a measure of total cortisol exposure from 3 to 12 hours, given by the formula (Pruessner et al., 2003):

$[(S1+S2)/2 \times T1)] + [(S2 +S3)/2 \times T2]$, in which

S1 = 3-hour cortisol value
S2 = 6-hour cortisol value
S3 = 12-hour cortisol value
T1 = 3 hours (time between the first and the second collection)
T2 = 6 hour (time between the second and the third collection).

Raw cortisol values were used to calculate AUCg, which was then log-transformed (Ln) in order to normalise the data for parametric inferential analysis. Data from consecutive collection log-transformed AUCg values were aggregated by calculating the average AUCg across the two days.

The pre-planned analysis for between-arm differences consisted of using repeated measures ANOVA to account for the effect of time on diurnal cortisol parameters measured in different stages. However, due to the low number of participants included in this sub-study, particularly in Stages 3 and 4, this analysis was simplified. For Baseline and Stage 1, between-arm comparisons were conducted using one-way ANOVA. Considering that ANOVA models were not statistically significant, no further analyses were conducted. For Stage 3 and 4, only descriptive statistics were used.

At each stage, relationships between diurnal cortisol profile (slope and AUCg) and breathlessness measures, other self-assessment measures and harms were explored using Pearson's or Spearman's correlation depending on the nature of the variable examined (i.e., numeric or ordinal) and its distribution (i.e., presence or absence of normal distribution). Potential influences of participants' baseline characteristics on the diurnal cortisol profile (slope and AUCg) was explored using Pearson's correlation for numerical variables, and unpaired t-tests for comparison of sub-groups defined by categorical variables.

8.5 Results

8.5.1 Recruitment, retention and compliance

From the 176 participants recruited for the BEAMS study, 105 were screened to this sub-study between August 2017 and August 2019. Of those, 82 were excluded because they were taking or had taken systemic steroids in the previous four weeks (n=27), were taking insulin for diabetes (n=2) or did not provide written informed consent to participate (n=53). Twenty-three participants were eligible and were included in the cortisol sub-study (Figure 8.6).

Of the 138 expected Baseline collections (23 participants x 6 samples), 83 (60.1%) samples were collected within one hour of the recommended collection times; four samples were collected within three hours of the recommended collection times (2.9%); and no collection time was recorded for 33 samples (23.9%). Three participants were excluded from the analysis. Reasons for exclusion were skipping the Baseline collection by mistake (6 samples; 4.3%); collecting invalid Baseline samples (6 samples; 4.3%); and lack of compliance/omission of multiple collection times with uncharacteristic data patterns (i.e., ascending cortisol slopes) (6 samples; 4.3%).

Of the 20 participants included in the baseline analysis, 17 provided valid saliva samples in subsequent collection timepoints (Stage 1: n=17; Stage 3: n=11; Stage 4 (Month 3): n=7). Of the 102 samples expected in Stage 1 (17 participants x 6 samples), 55 (53.9%) were collected within

one hour of the recommended collection times; three samples were collected within 3 hours of the recommended collection times (2.9%); no collection time was recorded for 39 samples (38.2%); and five samples were missing (4.9%). Of the 66 samples expected in Stage 3 (11 participants x 6 samples), 63 (95.5%) were collected within one hour of the recommended collection times and three samples were collected within 3 hours of the recommended collection times (4.5%). Of the 42 samples expected in Stage 4 (7 participants x 6 samples), 35 (83.3%) were collected within one hour of the recommended collection times; one sample was collected within 3 hours of the recommended collection times (2.4%); and no collection time was recorded for six samples (14.3%). Reasons for not progressing to subsequent stages are detailed in Figures 8.7 to 8.10.

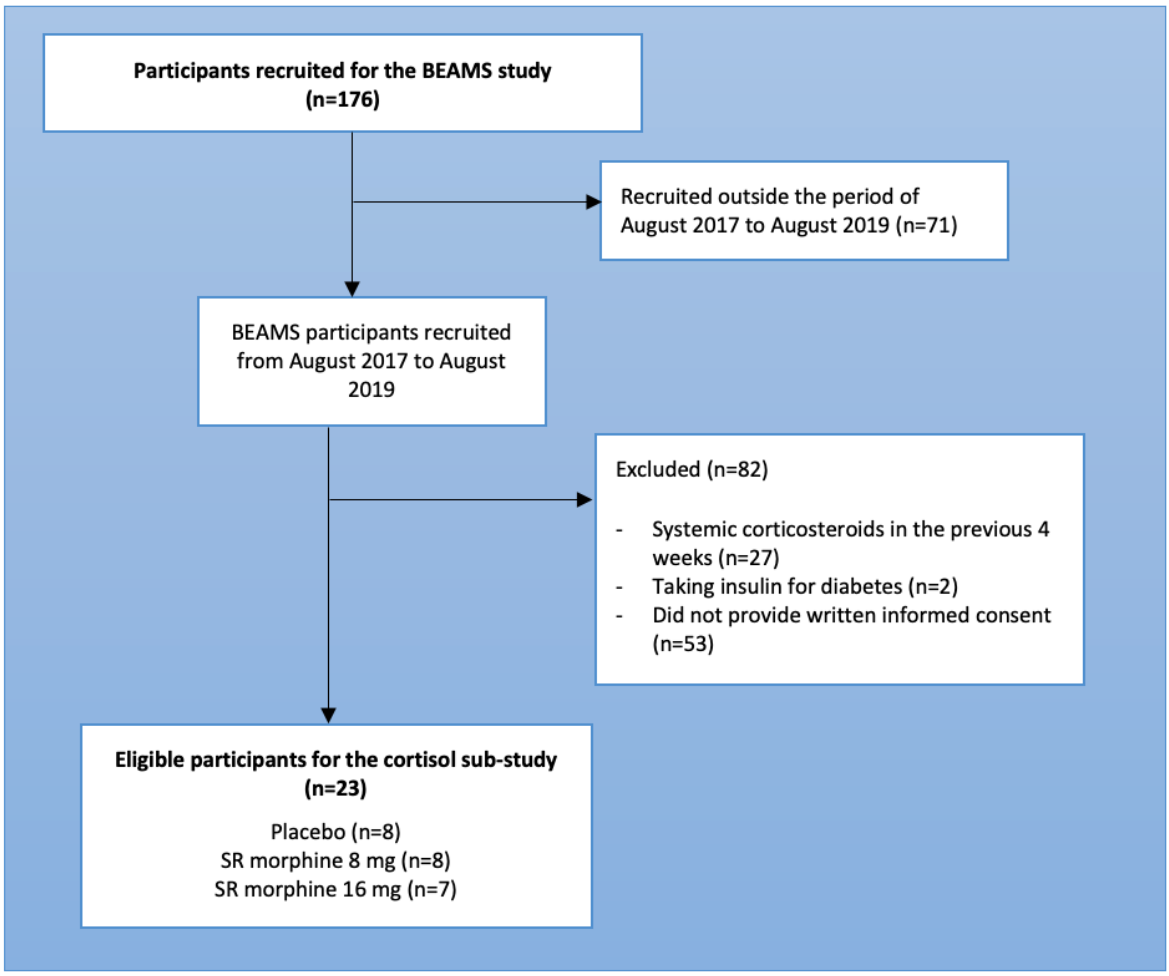

Figure 8.6 - Diagram of patients included in the sub-study

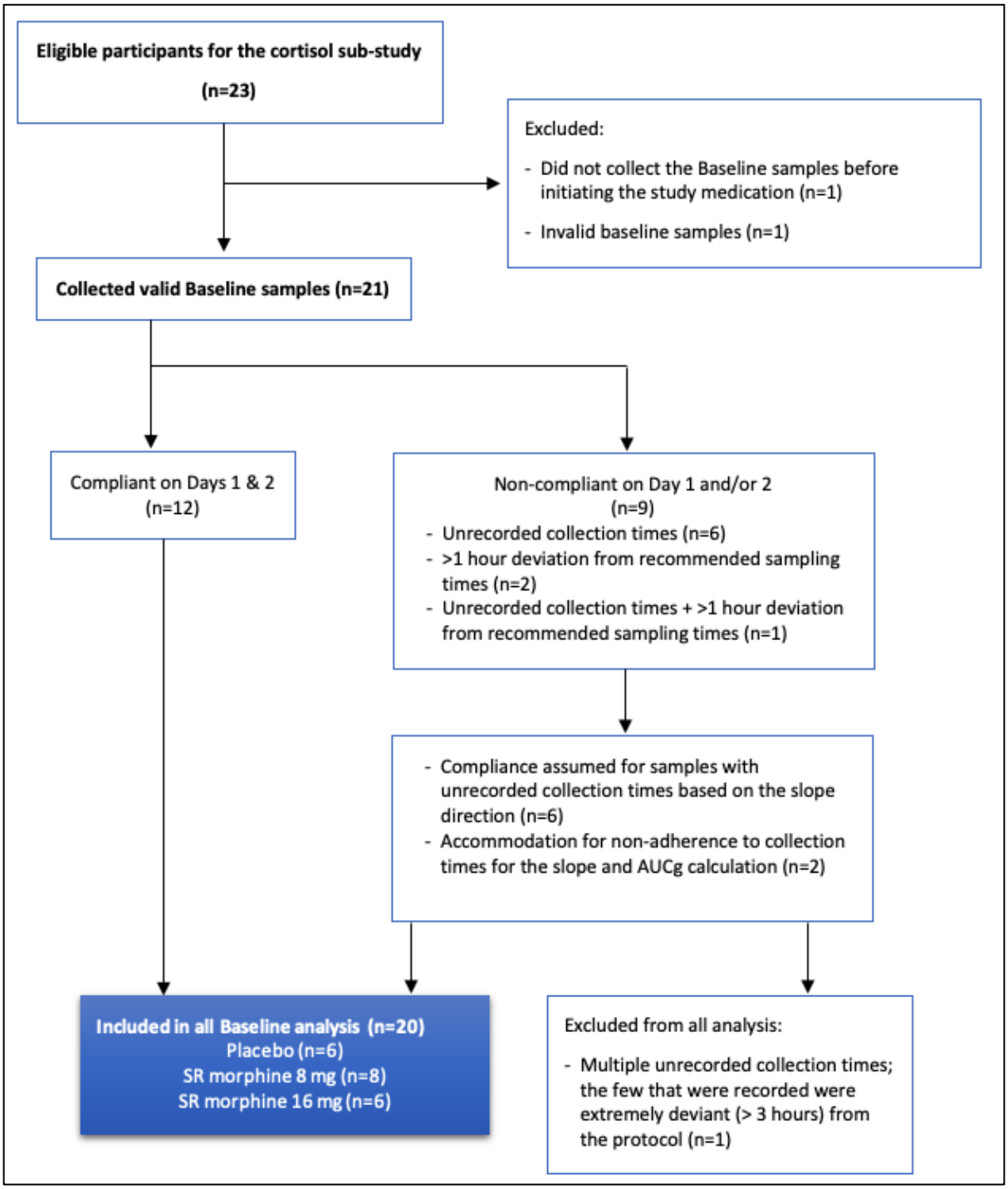

Figure 8.7 - Participants included in the Baseline analysis

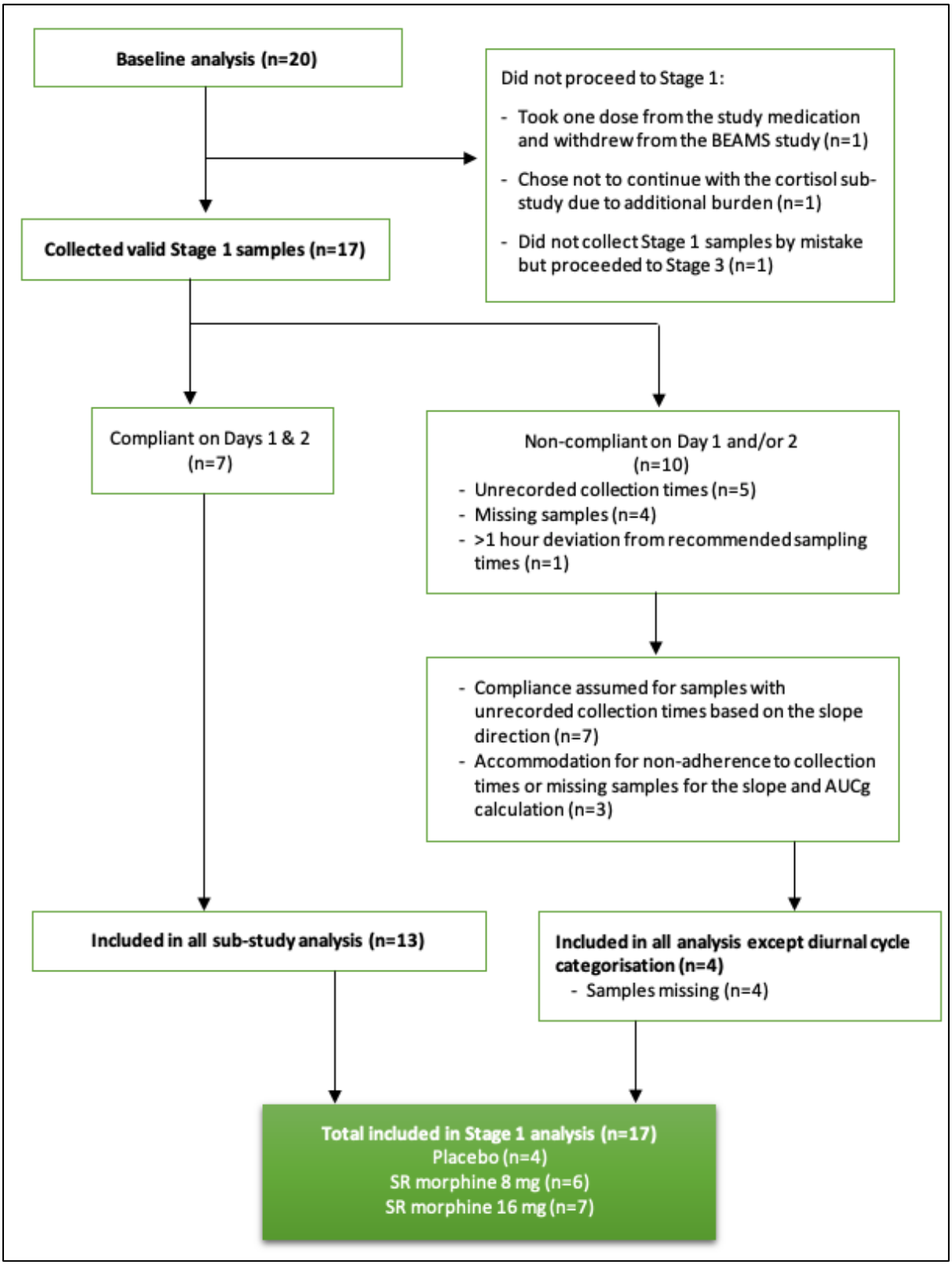

Figure 8.8 - Participants included in Stage 1 analysis

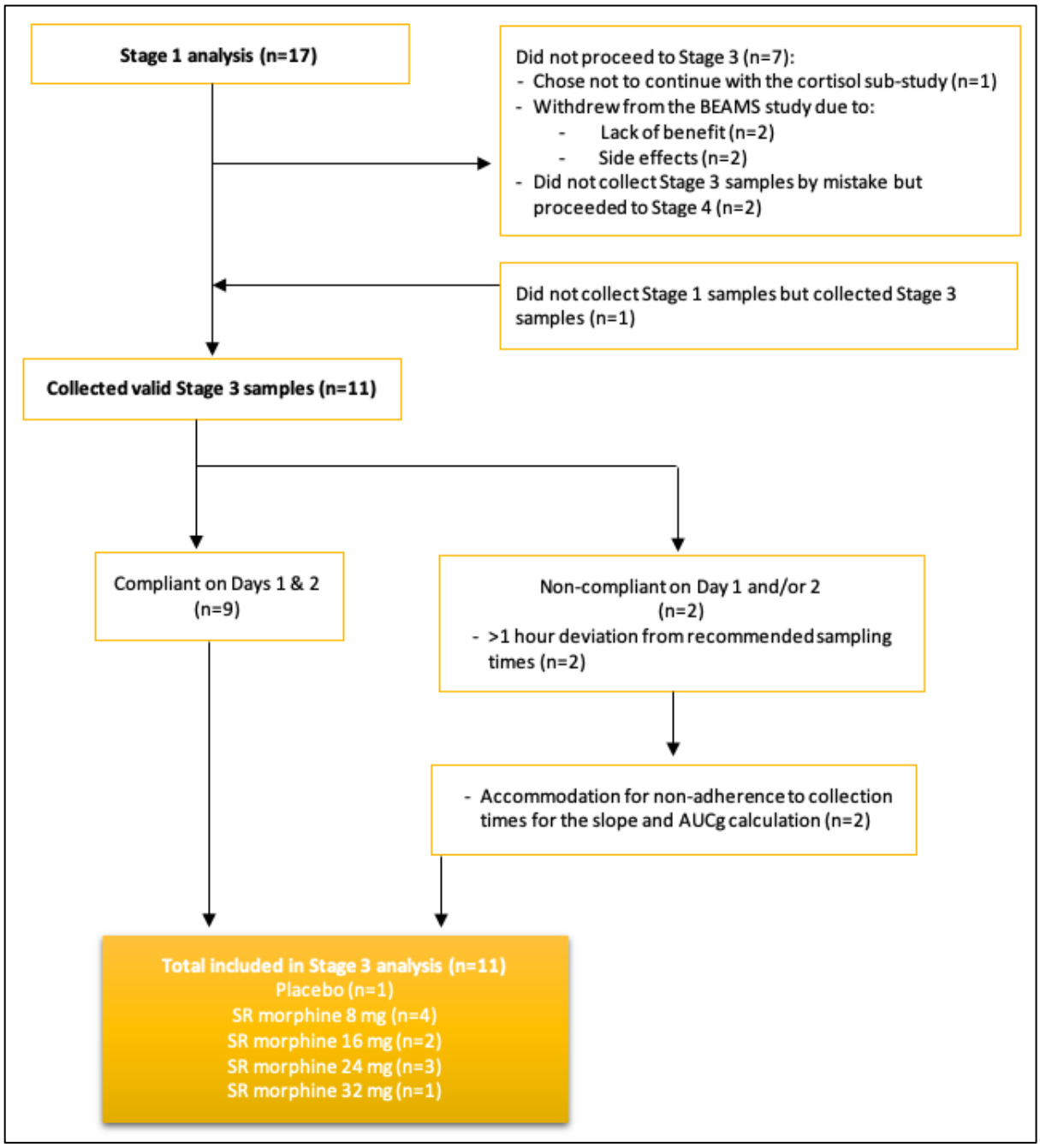

Figure 8.9 - Participants included in Stage 3 analysis

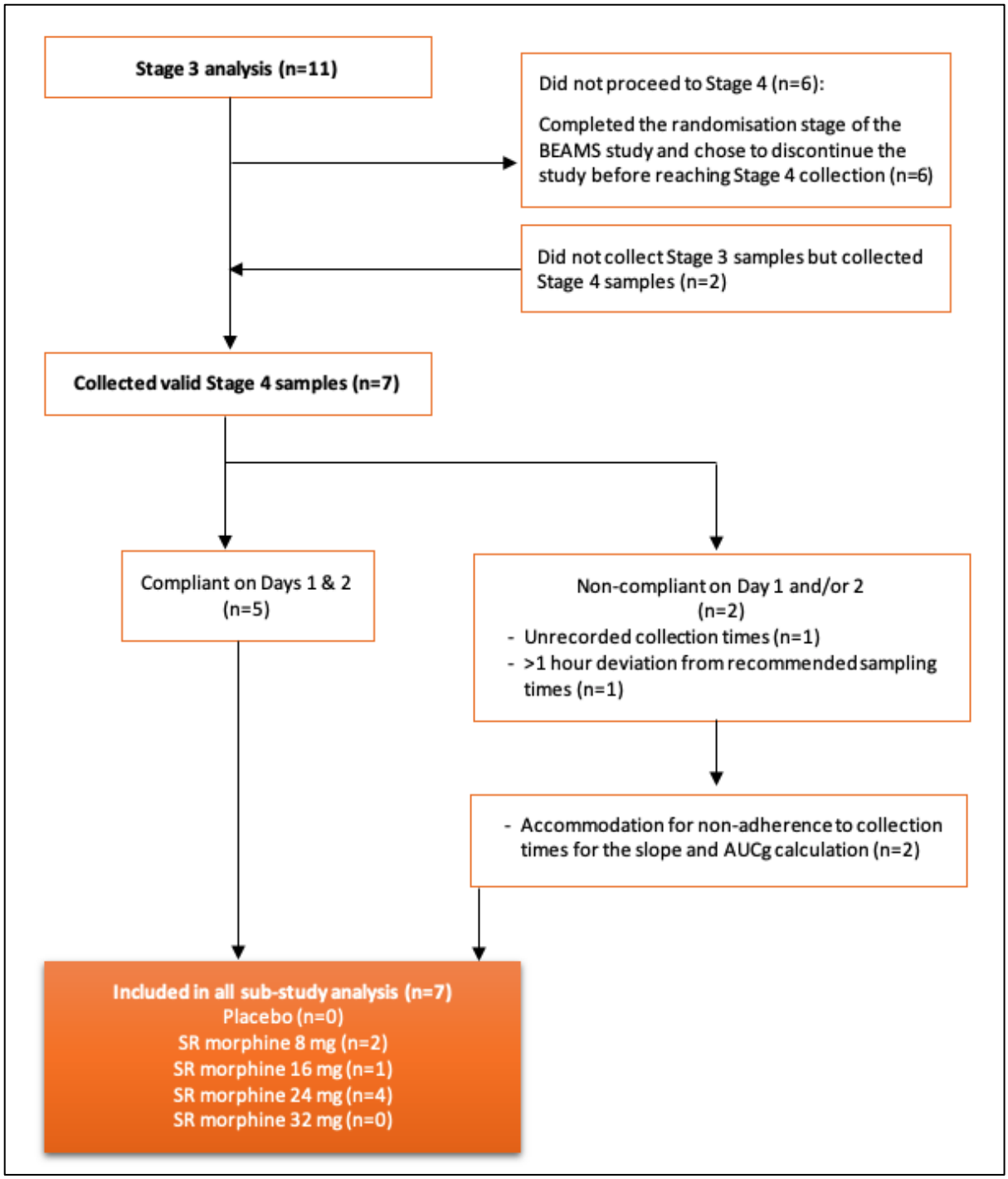

Figure 8.10 - Participants included in Stage 4 analysis

At each stage, the impact of non-compliance on diurnal cortisol slope and AUCg was assessed using unpaired t-tests to compare compliant and non-compliant sub-groups. No significant differences between compliant and non-compliant groups in any of the study stages (Baseline slope: t=0.92, p=0.37; Stage 1 slope: t=0.14, p=0.88; Stage 3 slope: t=-0.28, p=0.79; Stage 4: t=0.47, p=0.66; Baseline AUCg: t=0.94, p=0.37; Stage 1 AUCg: t=1.15, p=0.27; Stage 3 AUCg: t=-1.70, p=0.12; Stage 4 AUCg: t=-0.03, p=0.97).

8.5.2 Study Population

Participants (n=23) were mostly overweight elderly women, who were able to care for themselves but unable to carry on normal activity or do active work (Australia Karnofsky Performance Status ≤ 70). Most participants were former smokers and only two participants required long-term continuous supplemental oxygen. Approximately half of the participants had current histories of psychiatric illnesses (e.g., anxiety and/or depression), and more than half of those were taking long-term antidepressants. Doses of antidepressants had been optimised and stabilised over a period of weeks before study commencement. Most participants were medicated with a steroid inhaler, whose doses had been stable for at least one week prior to sub-study enrolment. Most participants had a carer defined as “the person who knew the participant best, provided the most help at home, and could help understand any changes experienced on trial” (Burns et al. 2011; Farquhar, 2016; Table 8.1). Baseline self-assessment summary measures are detailed in Table 8.2.

Table 8.1 - Baseline characteristics of participants included in the cortisol sub-study (clinician assessment measures), separated by study arm according to their allocation at baseline

Characteristics	Placebo (n=8) mean ± SD median (IQR)	SR morphine 8 mg (n=8) mean ± SD median (IQR)	SR morphine 16 mg (n=7) mean ± SD median (IQR)	Differences between arms*
Age (years)				
	72.8 ± 3.1 73.5 (71.0 – 74.8)	68.3 ± 8.3 69.0 (62.0 – 71.0)	72.1 ± 11.4 73.0 (71.0 – 79.0)	H(2)=3.75, p=0.15
Sex (male)				
	6 (75.0%)	3 (37.5%)	1 (14.5%)	χ^2=5.78, p=0.06
BMI (kg/m^2)				
	30.6 ± 6.0 30.9 (25.7 – 35.7)	31.9 ± 7.5 33.0 (29.0 – 35.4)	23.7 ± 7.9 23.5 (17.6 – 31.6)	F=1.49, p=0.25
Charlson Comorbidity Index - age adjusted				
	4.9 ± 1.1 4.5 (4.0 – 5.8)	4.8 ± 1.5 5.0 (4.0 – 6.0)	5.6 ± 1.1 6.0 (4.0 – 6.0)	H(2)=1.74, p=0.42
Australia-modified Karnofsky performance status (AKPS)				
80	1 (12.5%)	2 (25.0%)	3 (42.9%)	H(2)=1.51, p=0.47
70	5 (62.5%)	3 (37.5%)	3 (42.9%)	
60	2 (25.0%)	3 (37.5%)	1 (14.3%)	
Smoking status				
Current smoker	1 (12.5%)	2 (25.0%)	1 (14.3%)	χ^2=2.68, p=0.61
Former smoker	7 (87.5%)	5 (62.5%)	6 (85.7%)	
Never smoked		1 (12.5%)	-	
End tidal CO_2 (mmHg)[a]				
	30.8 ± 6.5 32.0 (24.6 – 35.3)	29.4 ± 4.6 28.5 (26.1 – 34.0)	25.5 ± 4.8 26.6 (23.0 – 29.0)	F=1.91, p=0.18
Oxyhaemoglobin saturation (%)				
	93.1 ± 2.4 93.0 (91.5 – 94.8)	91.9 ± 2.5 93.0 (89.0 – 94.0)	94.0 ± 1.4 94.0 (93.0 – 95.0)	F=1.72, p=0.21
Supplemental oxygen				
Yes	1 (12.5%)	1 (12.5%)	1 (14.3%)	χ^2=2.96, p=0.57
Relevant medical history				
Diabetes mellitus (type I or II)	0 (0.0%)	1 (12.5%)	1 (14.3%)	χ^2=1.18, p=0.55
Current history of psychiatric illness	4 (50%)	4 (50%)	3 (42.9%)	χ^2=0.10, p=0.95
Previous history of psychiatric illness	0 (0%)	1 (12.5%)	0 (0%)	χ^2=2.18, p=0.34
Relevant Medication				
Steroid inhaler	6 (75.0%)	7 (87.5%)	7 (100%)	χ^2=2.06, p=0.36
Anti-depressant	3 (37.5%)	2 (25.0%)	1 (14.3%)	χ^2=1.05, p=0.59
Hormone therapy	0 (0%)	1 (12.5%)	0 (0%)	χ^2=1.96, p=0.38
Immunosuppressant	0 (0%)	2 (25%)	1 (14.3%	χ^2=2.22, p=0.33
Chemo- or radiotherapy	0 (0%)	0 (0%)	0 (0%)	-
Carer availability				
Yes	5 (62.5%)	6 (75.0%)	5 (71.4%)	χ^2=0.53, p=0.77
No	2 (25.0%)	1 (12.5%)	2 (28.6%)	
No data	1 (12.5%)	1 (12.5%)	-	

BMI = body mass index; Symbols: *Statistical tests performed in order of reporting: Kruskal-Wallis test (non-normally distributed numerical variables), Chi-squared test (categorical variables), and one-way ANOVA (normally distributed numerical variables).
[a]*Measured with a portable capnography device during quiet breathing.*

Table 8.2 - Baseline characteristics of participants included in the cortisol sub-study (self-assessment measures) separated by study arm, according to their allocation at baseline

Characteristics	Placebo (n=8) mean ± SD median (IQR)	SR morphine 8 mg (n=8) mean ± SD median (IQR)	SR morphine 16 mg (n=7) mean ± SD median (IQR)	Total (n=23) mean ± SD median (IQR)
modified Medical Research Council (mMRC) breathlessness scale				
Grade 3	6 (75.0%)	8 (100%)	7 (100%)	χ^2=4.11, p=0.13
Grade 4	2 (25.0%)	-	-	
Breathlessness (0-10 numerical rating scale (NRS))				
Worst breathlessness	6.3 ± 1.9 6.0 (5.0 – 8.1)	4.5 ± 1.5 4.8 (3.0 – 5.9)	5.9 ± 1.4 6.0 (5.0 – 6.5)	F=2.49, p=0.11
Average breathlessness	5.1 ± 2.0 4.8 (3.5 – 6.9)	3.7 ± 1.1 3.8 (2.6 – 4.9)	4.6 ± 1.3 4.5 (3.5 – 5.0)	H(2)=2.51, p=0.28
Distress caused by breathlessness	4.4 ± 3.1 4.3 (1.6 – 6.9)	2.8 ± 2.4 2.3 (0.5 – 4.8)	4.1 ± 2.7 4.5 (1.5 – 5.5)	F=0.74, p=0.49
Quality of life (QoL) EuroQoL 5 domain 5 level measure (EQ-5D-5L)				
Mobility	2.0 ± 1.4 1.0 (1.0 – 3.8)	2.5 ± 1.1 3.0 (1.3 – 3.0)	2.0 ± 1.3 1.0 (1.0 – 3.0)	H(2)=0.89, p=0.64
Personal care	2.1 ± 1.4 1.5 (1.0 – 3.8)	1.6 ± 0.7 1.5 (1.0 – 2.0)	2.0 ± 1.2 2.0 (1.0 – 3.0)	H(2)=0.43, p=0.81
Activities	2.9 ± 1.5 3.0 (1.3 – 4.0)	2.8 ± 0.7 3.0 (2.0 – 3.0)	2.4 ± 1.0 2.0 (2.0 – 3.0)	H(2)=0.67, p=0.72
Pain and discomfort	1.9 ± 0.8 2.0 (1.0 – 2.8)	1.8 ± 0.7 2.0 (1.0 – 2.0)	1.7 ± 1.1 1.0 (1.0 – 2.0)	H(2)=0.48, p=0.79
Anxiety and depression	2.1 ± 1.4 1.5 (1.0 – 3.8)	2.1 ± 0.8 2.0 (1.3 – 3.0)	1.4 ± 0.8 1.0 – 2.0)	H(2)= 2.39, p=0.30
Perception of health (VAS)	64.0 ± 24.1 60.0 (41.3 – 84.5)	51.3 ± 18.9 52.5 (32.5 – 71.3)	64.3 ± 23.2 65.0 (40.0 – 90.0)	F=0.89; p=0.43
Hospital Anxiety and Depression scale (HADS)				
Anxiety sub-scale (0-21)	6.3 ± 4.9 6.0 (1.3 – 11.3)	7.3 ± 4.2 8.0 (4.0 – 11.0)	4.6 ± 3.5 3.0 (2.0 – 7.0)	F=0.73; p=0.49
Depression sub-scale (0-21)	6.6 ± 3.9 5.5 (4.3 – 10.3)	6.3 ± 3.9 5.0 (3.0 – 9.0)	4.1 ± 3.6 3.0 (2.0 – 7.0)	F=0.92; p=0.42
Perceived quality of sleep				
Very good	3 (37.5%)	1 (12.5%)	2 (28.6%)	χ^2=8.57, p=0.20
Good	4 (50.0%)	3 (37.5%)	1 (14.3%)	
Poor	-	4 (50%)	4 (57.1%)	
No sleep at all	1 (12.5%)	-	-	

VAS = Visual Analogue Scale. Symbols: *Statistical tests performed in order of reporting: Chi-squared test (categorical variables), one-way ANOVA (normally distributed numerical variables), and Kruskal-Wallis test (non-normally distributed numerical variables).

8.5.3 Individual diurnal cortisol slope categories

There were no significant differences between arms in the proportion of the four diurnal cortisol profile categories, in any of the study stages (Baseline: χ^2=2.86, p=0.83; Stage 1: χ^2=2.74, p=0.25; Stage 3: χ^2=2.06, p=0.72; Stage 4: χ^2=2.10, p=0.35).

At Baseline, the proportion of “descending” cortisol profiles was identical between arms and the most frequently observed (50.0%). “Inconsistent” profiles were also approximately

similar between arms (33.3-37.5%). A small proportion of flat diurnal cortisol profiles was observed in the placebo and the sustained-release oral morphine 16 mg arms (16.7%). A small proportion of ascending diurnal cortisol cycles was observed in the sustained-release oral morphine 8 mg arm (12.5%).

In stage 1, the proportion of descending diurnal cortisol cycles was higher for people taking regular, sustained-release oral morphine 8mg (80.0%), compared to people taking sustained-release oral morphine 16mg (50.0%). People in the placebo arm had the lowest proportion of descending diurnal cortisol cycles (25.0%). Conversely, people taking placebo had the highest proportion of inconsistent cycles (75.0%), followed by people taking sustained-release morphine 16mg (50%), and people taking sustained-release morphine 8mg (20%). No flat or ascending diurnal cortisol cycles were observed in any of the study arms.

In stage 3, the only participant taking placebo had a “descending” diurnal cortisol profile. There was a higher proportion of inconsistent diurnal cortisol profiles for people taking sustained-release morphine 8mg and 16 mg (50.0%). In the group taking sustained-release morphine 8mg, there was a similar proportion of people with descending and flat diurnal cortisol profiles (25.0%). In the group taking sustained-release morphine 16mg, there was a higher proportion of people with descending compared with flat diurnal cortisol cycles (33.3% versus 16.7%, respectively). There were no ascending diurnal cortisol profiles in any of the study arms.

In Stage 4, the only two participants taking sustained-release morphine 8mg had a descending cortisol profile. In the sustained-release morphine 16mg arm, an equivalent

proportion of people had “inconsistent” (40.0%) or “descending” diurnal cortisol profiles (40.0%). One participant had an ascending diurnal cortisol profile (20.0%).

Diurnal cortisol profile categorisation was determined based on cut-off values equivalent to one standard deviation from the group mean day difference at each timepoint (Baseline = 0.097; Stage 1 = 0.094; Stage 3 = 0.086; Stage 4 = 0.067). In order to assess whether this strategy was adequate to differentiate between “consistent” and “inconsistent” diurnal cortisol profiles, slope reliability across the two collection days was assessed separately for “consistent” and “inconsistent” groups at each timepoint. At all timepoints, the correlation (Pearson correlation coefficient) between Day 1 and Day 2 slopes was positive high or very high in those with a “consistent” profile (Baseline: r=0.86, p<0.001; Stage 1: r=0.83, p=0.02; Stage 3: r=0.75, p=0.09; Stage 4: r=0.96, p=0.01). For “inconsistent” profiles, correlations were negative and moderate at baseline (r=-0.69; p=0.09), positive and low in Stage 1 (r=0.005; p=0.99), negative and low in Stages 3 (r=-0.38; p=0.53) and negative and very high in Stage 4 (r=-1.0). No p-value is reported for the “inconsistent” group in Stage 4 that only included two participants) (Schober et al., 2018). High correlations for “consistent” profiles and low / negative correlations for “inconsistent” profiles support the use of the adopted cut-offs of one standard deviation from the group mean day difference at each timepoint.

8.5.4 Mean diurnal cortisol slope and mean cortisol AUCg across different stages

Baseline cortisol values ranged from 0.67 to 15.36 nmol/L in the placebo arm, 0.59 to 19.38 nmol/L in the sustained-release morphine 8mg arm, and 1.17 to 11.52 nmol/L in the sustained-release morphine 16mg arm. Ln-transformed mean diurnal cortisol slope was steeper for the arm taking sustained-release morphine 8mg (mean ± SD = -0.12 ± 0.09), followed by those taking sustained-release morphine 16mg (mean ± SD = -0.10 ± 0.07) and

by those taking placebo (mean ± SD = -0.09 ± 0.07). Ln-AUCg was higher for the arm taking sustained-release morphine 8mg (mean ± SD = 3.59 ± 0.40), followed by those taking sustained-release morphine 16mg (mean ± SD = 3.57 ± 0.32) and by those taking placebo (mean ± SD = 3.51 ± 0.62). The one-way ANOVA between-group analyses showed no significant differences between arms in the baseline Ln-transformed summary measures of diurnal cortisol slope [F (0.24), p=0.79] and AUCg [F (0.06), p=0.94; Table 8.3].

Table 8.3 - Baseline cortisol mean/median values in each arm

	Placebo mean ± SD median (IQR)* (n=6)	SR Morphine 8mg mean ± SD median (IQR)* (n=8)	SR Morphine 16mg mean ± SD median (IQR)* (n=6)	Between-arm differences†
3-hour cortisol (nmol/L)	4.99 ± 4.7 4.73 (2.7 – 7.4)	8.69 ± 5.6 7.93 (4.3 – 13.3)	6.10 ± 3.3 5.08 (3.4 – 9.5)	-
6-hour cortisol (nmol/L)	5.69 ± 4.5 4.23 (2.2 – 8.9)	4.01 ± 2.1 3.77 (2.3 – 5.7)	4.62 ± 1.8 4.13 (3.09 – 6.3)	-
12-hour cortisol (nmol/L)	2.28 ± 1.2 2.04 (1.1 – 3.5)	2.90 ± 2.1 2.04 (1.6 – 3.9)	2.53 ± 1.34 2.23 (1.9 – 2.4)	-
Ln diurnal slope† (Ln nmol/L/hr)	-0.09 ± 0.07	-0.12 ± 0.09	-0.10 ± 0.07	F=0.24, p=0.79
Cortisol AUCg (nmol.hr/L)	39.9 ± 23.7 29.9 (24.9 – 64.6)	39.8 ± 13.4 42.9 (28.8 – 49.3)	37.5 ± 12.6 31.5 (29.1 – 51.5)	-
Ln cortisol AUCg† (Ln nmol.hr/L)	3.51 ± 0.62	3.59 ± 0.40	3.57 ± 0.32	F=0.06, p=0.94

*Values are mean ± standard deviation (SD) and median (interquartile range), except for variables with normal distribution for which values are presented as mean ± SD only.
†Analysis conducted only in Ln-transformed cortisol measures with normal distribution (Levene's test p≥0.05).

Stage 1 cortisol values ranged from 1.58 to 22.91 nmol/L in the placebo arm, 1.22 to 15.87 nmol/L in the sustained-release morphine 8 mg arm, and 1.03 to 8.20 nmol/L in the sustained-release morphine 16mg arm. Contrary to baseline, Ln-transformed mean diurnal cortisol slope was steeper for the arm taking placebo (mean ± SD = -0.12 ± 0.10), followed by those taking sustained-release morphine 8mg (mean ± SD = -0.10 ± 0.05) and by those taking sustained-release morphine 16mg (mean ± SD = -0.08 ± 0.06). Ln-AUCg was higher for the arm taking placebo (mean ± SD = 3.85 ± 0.35), followed by those taking sustained-

release morphine 8mg (mean ± SD = 3.44 ± 0.45) and by those taking sustained-release morphine 16 mg (mean ± SD = 3.49 ± 0.28). The one-way, between-group ANOVA analyses showed no significant differences between arms in Stage 1 ln-transformed summary measures of diurnal cortisol slope [F (0.35), p=0.71] and AUCg [F (1.56), p=0.24; Table 8.4].

Table 8.4 - Stage 1 cortisol mean/median values in each arm

	Placebo mean ± SD median (IQR)	SR Morphine 8mg mean ± SD median (IQR)	SR Morphine 16mg mean ± SD median (IQR)	Between-arm differences†
3-hour cortisol (nmol/L)	10.35 ± 6.5 9.96 (5.2 – 13.8)	6.46 ± 4.2 4.87 (3.7 – 7.8)	5.52 ± 2.0 6.18 (3.0 – 7.1)	-
6-hour cortisol (nmol/L)	5.78 ± 4.1 4.18 (3.8 – 6.9)	3.40 ± 1.8 3.02 (1.9 – 4.5)	3.67 ± 1.5 3.44 (2.3 – 4.9)	-
12-hour cortisol (nmol/L)	3.26 ± 2.1 2.45 (1.9 – 4.7)	2.49 ± 1.5 2.01 (1.5 – 3.0)	2.90 ± 1.6 2.54 (1.5 – 4.3)	-
Diurnal slope (Ln nmol/L/hr)	-0.12 ± 0.10	-0.10 ± 0.05	-0.08 ± 0.06	F=0.35, p=0.71
Cortisol AUCg (nmol.hr/L)	51.3 ± 22.9 44.0 (34.5 – 75.3)	34.8 ± 16.4 28.5 (25.0 – 48.6)	34.4 ± 8.3 35.2 (26.1 – 41.6)	-
Ln cortisol AUCg (Ln nmol.hr/L)	3.85 ± 0.39	3.44 ± 0.45	3.49 ± 0.28	F=1.56, p=0.24

*Values are mean ± standard deviation (SD) and median (interquartile range), except for variables with normal distribution for which values are presented as mean ± SD only.
†Analysis conducted only in Ln-transformed cortisol measures with normal distribution (Levene's test p≥0.05).

In stages 3 and 4, there were small numbers of participants per arm. As a result, people taking sustained-release morphine doses of 16 mg or higher were collapsed into one single group for the purpose of descriptive statistics, and no formal comparative analysis was performed. Stage 3 cortisol values ranged from 2.01 to 7.35 nmol/L in the placebo arm, 0.62 to 8.65 nmol/L in the sustained-release morphine 8 mg arm, and 0.10 to 23.50 nmol/L in the sustained-release morphine ≥16 mg arms. Ln-transformed mean diurnal cortisol slope was steeper for the arms taking sustained-release morphine ≥16mg (mean ± SD = -0.12 ± 0.06, n=6), followed by those taking sustained-release morphine 8 mg (mean ± SD = -0.11 ± 0.09, n=4). The only participant taking placebo had a flatter mean-diurnal cortisol slope compared with the group means of those taking morphine (-0.10). Ln-AUCg was higher for the

participant taking placebo (3.50), compared with the mean ln-AUCg for the group taking sustained-release morphine 16mg (mean ± SD = 3.35 ± 0.92, n=6) and those taking sustained-release morphine 8mg (mean ± SD = 3.05 ± 0.21, n=4).

Stage 4 cortisol values ranged from 0.60 to 5.72 nmol/L in the sustained-release morphine 8mg arm, and 0.63 to 13.66 nmol/L in the sustained-release morphine ≥16mg group. There were no people taking placebo. Ln-transformed mean diurnal cortisol slope was steeper for the group taking sustained-release morphine ≥16mg (mean ± SD = -0.11 ± 0.07, n=5), compared with the arm taking sustained-release morphine 8mg (mean ± SD = -0.08 ± 0.02, n=2). Ln-transformed AUCg was higher for the group taking sustained-release morphine ≥16 mg (mean ± SD = 3.01 ± 0.60, n=5) compared with the arm taking sustained-release morphine 8mg (mean ± SD = 2.84 ± 0.64, n=2). Mean diurnal cortisol concentrations for different study stages are displayed in Figure 8.11.

Across different sub-study stages, the mean diurnal cortisol slope in the placebo arm tended to become steeper from Baseline to Stage 1 (mean ± SD = -0.09 ± 0.07 vs. -0.12 ± 0.10), and flatter from Stage 1 to Stage 3 (mean = -0.10). For the arm taking regular, low-dose, sustained-release oral morphine 8mg, the mean diurnal cortisol slope became progressively flatter from Baseline to Stage 4 (Baseline: mean ± SD = -0.12 ± 0.09; Stage: mean ± SD = -0.10 ± 0.05; Stage 3: mean ± SD = -0.11 ± 0.09; Stage 4: mean ± SD = -0.08 ± 0.02). For the arms taking regular, low-dose, sustained-release oral morphine ≥16mg, the mean diurnal cortisol slope became flatter from Baseline to Stage 1 (Baseline: mean ± SD = -0.10 ± 0.07; Stage 1: mean ± SD = -0.08 ± 0.06), but steeper than Baseline on Stages 3 (mean ± SD = -0.12 ± 0.06) and 4 (mean ± SD = -0.11 ± 0.07). For more advanced sub-study stages, those taking regular, low-dose, sustained-release oral morphine ≥16mg had steeper mean diurnal

cortisol slopes compared with other arms. Proportion of the four diurnal cortisol categories across sub-study stages and mean diurnal cortisol slope at each stage are presented in Figure 8.12.

Across different sub-study stages, the mean AUCg in the placebo arm tended to become higher from Baseline to Stage 1 (mean ± SD = 3.51 ± 0.62 vs. 3.85 ± 0.39), and lower from Stage 1 to Stage 3 (mean = 3.50). For the arm taking regular, low-dose, sustained-release oral morphine 8mg, the mean AUCg became progressively lower from Baseline to Stage 4 (Baseline: mean ± SD = 3.59 ± 0.40; Stage 1: mean ± SD = 3.44 ± 0.45; Stage 3: mean ± SD = 3.05 ± 0.21; Stage 4: mean ± SD = 2.84 ± 0.64). For the group taking regular, low-dose, sustained-release oral morphine ≥16mg, the mean AUCg became progressively lower from Baseline to Stage 4 (Baseline mean ± SD = 3.57 ± 0.32; Stage 1: mean ± SD = 3.49 ± 0.28; Stages mean ± SD = 3: 3.35 ± 0.92; Stage 4: mean ± SD = 3.01 ± 0.60). For more advanced sub-study stages, those taking regular, low-dose, sustained-release oral morphine ≥16mg had steeper mean AUCg compared with other arms.

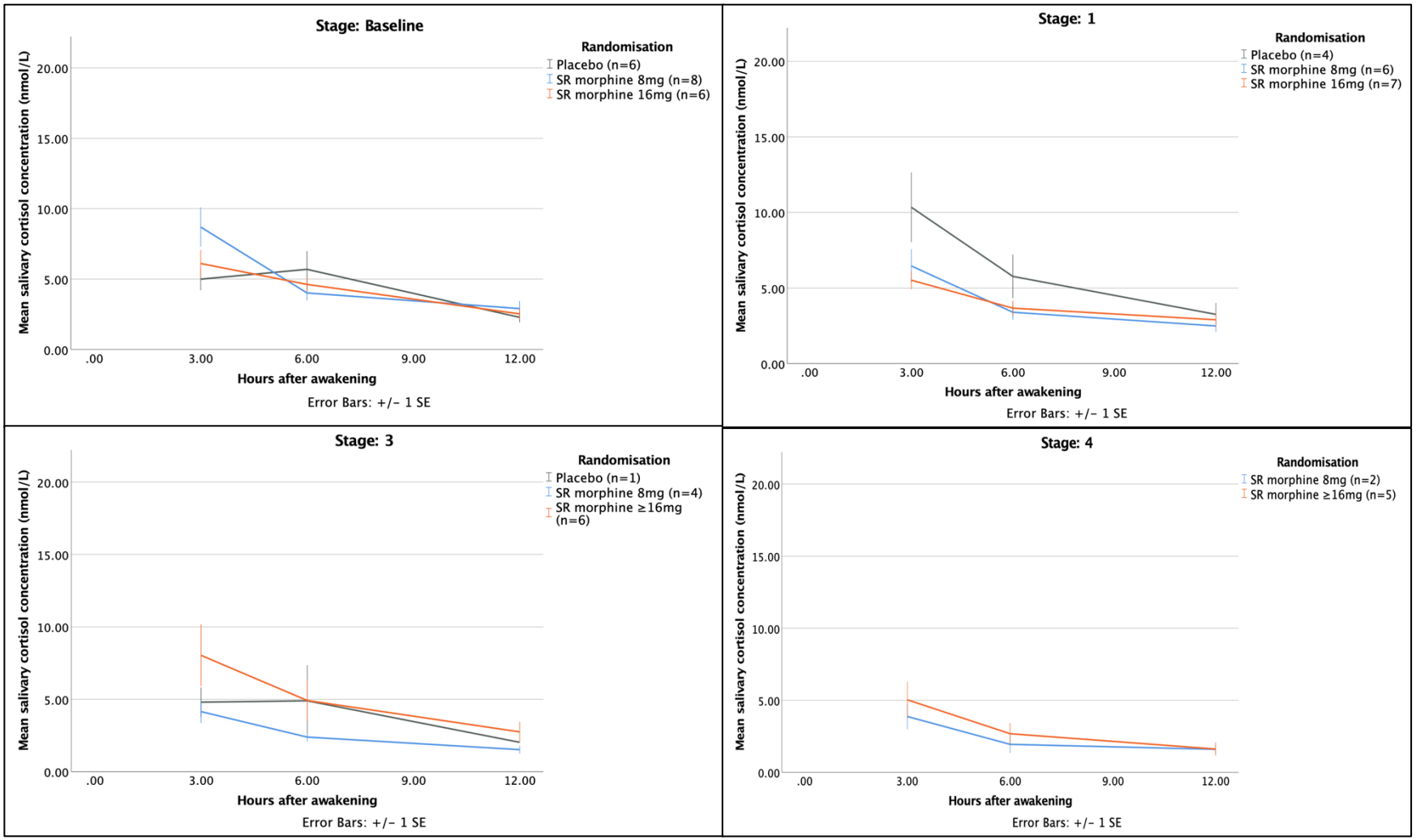

Figure 8.11 - Mean cortisol concentrations in each arm across different study stages.
Baseline (top left); Stage 1 (top right); Stage 3 (bottom left); Stage 4 (bottom right) (error bars represent standard error for each collection time).

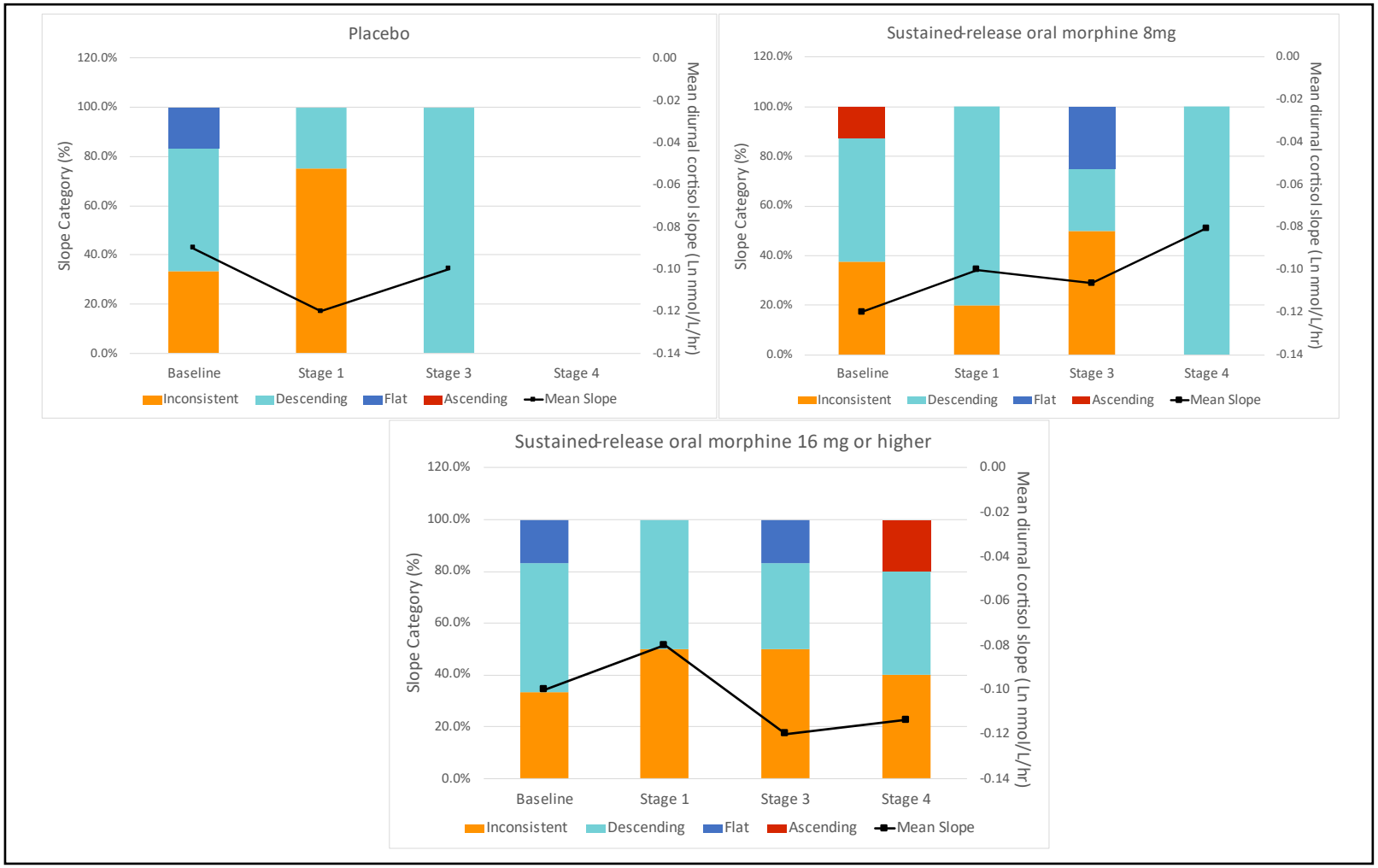

Figure 8.12 - Proportion of the four diurnal cortisol slope categories across sub-study stages and mean diurnal cortisol slope at each stage in the placebo (*top left*), sustained-release oral morphine 8mg (*top right*) and 16mg or higher arms (b*ottom*).

8.5.5 Relationship between breathlessness measures and diurnal cortisol profile measures

Given that there were no statistically significant differences in diurnal cortisol summary measures between arms in any of the study stages, results for each stage were collapsed into a single group for the analysis of breathlessness measures. There were no statistically significant correlations between summary cortisol measures (slope and AUCg) and any of the breathlessness measures, both at Baseline and Stage 1. However, in Stage 1, there were some moderate correlations between summary cortisol measures and measures of breathlessness that did not reach statistical significance. These included a correlation between ln-diurnal cortisol slope and mMRC (level of exertion at which breathlessness becomes limiting), with the slope becoming flatter as the mMRC decreased (*rs*=-0.45, p=0.07); and a correlation between ln-AUCg and *average breathlessness*, with ln-AUCg becoming lower for higher intensity of *average breathlessness* (rs=-0.45, p=0.07).

In stage 3, there was a moderate correlation between diurnal cortisol slope and mMRC grade, with the slope becoming flatter as the mMRC decreased, which was not statistically significant (*rs*=-0.56, p=0.08). There were no other noteworthy correlations between cortisol measures and breathlessness measures. In stage 4, there was a statistically significant correlation between diurnal cortisol slope and *average breathlessness*, with the slope becoming flatter for higher measures of *average breathlessness* (r=0.89, p=0.04; Appendix 21). There was also a strong correlation between diurnal cortisol slope and *worst breathlessness*, but this was not statistically significant (r=0.79, p=0.11). Some non-statistically significant correlations were detected between AUCg and breathlessness measures including *average* (r=-0.78, p=0.12), *worst* (r=-0.72, p=0.17), and *distress caused by breathlessness* (r=-0.46, p=0.44; Tables 8.5 and 8.6).

Table 8.5 - Correlations between breathlessness measures and diurnal cortisol slope

	Ln- Diurnal slope			
	Baseline (n=20)	Stage 1 (n=17)	Stage 3 (n=11)	Stage 4 (n=5)
Worst (NRS)	*r*=0.33 p=0.15	*r*=0.27 p=0.29	*r*=0.33 p=0.36	*r*=0.79 p=0.11
Average (NRS)	*rs*=0.30 p=0.21	*rs*=0.31 p=0.23	*r*=0.08 p=0.82	*r*=0.89 p=0.04
Distress (NRS)	*r*=-0.01 p=0.98	*r*=0.02 p=0.93	*r*=-0.37 p=0.29	*r*=0.10 p=0.87
mMRC	*rs*=-0.18 p=0.45	*rs*=-0.45 p=0.07	*rs*=-0.56 p=0.08	-

Table 8.6 - Correlations between breathlessness measures and AUCg

	Ln-AUCg			
	Baseline (n=20)	Stage 1 (n=17)	Stage 3 (n=11)	Stage 4 (n=5)
Worst (NRS)	*r*=0.04 p=0.88	*r*=-0.31 p=0.23	*r*=0.25 p=0.48	*r*=-0.72 p=0.17
Average (NRS)	*rs*=0.15 p=0.52	*rs*=-0.45 p=0.07	*rs*=0.08 p=0.82	*rs*=-0.78 p=0.12
Distress (NRS)	*r*=-0.01 p=0.98	*r*=-0.40 p=0.11	*r*=-0.12 p=0.75	*r*=-0.46 p=0.44
mMRC	*rs*=-0.26 p=0.27	*rs*=0.34 p=0.18	*rs*=-0.24 p=0.49	-

*NRS = Numerical rating scale for breathlessness

Of note, there were consistent positive correlations between different NRS breathlessness measures, across different stages. At baseline, there were strong and significant correlations between all NRS breathlessness measures (*worst* and *average*: *rs*=0.73, p<0.001; *worst* and *distress*: *r*=0.78, p<0.001; *average* and *distress*: *rs*=0.70, p<0.001). In stage 1, there was a strong correlation between *worst* and *average breathlessness* (*rs*=0.79, p<0.001), and *average* and *distress caused by breathlessness* (*rs*=0.82, p<0.001). *Worst breathlessness* was only moderately correlated with *distress caused by breathlessness* (*r*=0.53, p<0.002). In Stage 3, there were strong and significant correlations between *worst* and *average* (*r*=0.84, p<0.001), *worst* and *distress* (*r*=0.53, p=0.04), and *average* and *distress caused by*

breathlessness (*r*=0.75, p=0.001). In Stage 4, these correlations persisted (*worst* and *average*: *r*=1.00, p<0.001; *worst* and *distress*: *r*=1.00, p<0.001; *average* and *distress*: *r*=1.00, p<0.001).

8.5.6 Relationships between other self-assessment measures and diurnal cortisol profile measures

At baseline, there was a moderate and significant correlation between performance status (AKPS) and diurnal cortisol slope, with the slopes becoming flatter for lower performance status (*rs*=-0.66, p=0.001; Appendix 22). However, this same correlation was weak or negligible in stages 1 to 4. At baseline, there was also a moderate correlation between sleep quality and diurnal cortisol slope, with the slopes becoming flatter for worse subjective sleep quality in the night preceding saliva sample collection (*rs*=-0.61, p=0.005; Appendix 23). From baseline to stage 4, there was a progressive increase in the correlation coefficient (from negative to positive), indicating that by stage 4, cortisol slopes were flatter for people with better subjective sleep quality. Importantly, results from stage 1 to 4 were not statistically significant (stage 1: *rs*=-0.42, p=0.10; stage 3: *rs*=-0.29, p=0.43; stage 4: *rs*=0.58, p=0.31). Although not present at baseline, there was a moderate correlation between the diurnal cortisol slope and depression scores (HADS) in stage 1 (*r*=-0.50, p=0.04; Appendix 24), with the slope becoming flatter for higher depression scores. Additionally, the correlation coefficient for the relationship between diurnal cortisol slope and global impression of change increased from stage 1 to stage 4, holding statistical significance only in stage 4 (*rs*=0.98, p=0.01; Appendix 25), with slopes becoming flatter as the subjective sense of improvement decreased (Table 8.7). There were no significant correlations between results in any of the self-assessment measures and AUCg (Table 8.8).

Table 8.7 – Correlations between other self-assessment measures and diurnal slope

	Ln- Diurnal slope			
	Baseline (n=20)	Stage 1 (n=17)	Stage 3 (n=11)	Stage 4 (n=5)
AKPS	*rs*=-0.66 p=0.001	*rs*=-0.12 p=0.66	*rs*=-0.24 p=0.49	*rs*=0.00 p=1.00
QOL (EQ-5D-5L)	*r*=0.14 p=0.56	*r*=-0.14 p=0.59	-	*rs*=-0.62 p=0.27
Subjective sleep quality	*rs*=-0.61 p=0.005	*rs*=-0.42 p=0.10	*rs*=-0.29 p=0.43	*rs*=0.58 p=0.31
HADS – anxiety	*r*=-0.15 p=0.54	*r*=0.04 p=0.89	-	-
HADS – depression	*r*=0.09 p=0.73	*r*=-0.50 p=0.04	-	-
Global impression of change	-	*rs*=0.03 p=0.91	*rs*=0.10 p=0.78	*rs*=0.98 p=0.01

AKPS = Australian Karnofsky Performance Status; QOL (EQ-5D-5L) = Quality of life measured using the EQ-5D-5L questionnaire; HADS = Hospital Anxiety and Depression Scale. Subjective sleep quality measured with a 4-point Likert scale; Global impression of change measured with a 7-point Likert scale. Statistically significant correlations indicated in light grey.

Table 8.8 – Correlations between other self-assessment measures and AUCg

	Ln-AUCg			
	Baseline (n=20)	Stage 1 (n=17)	Stage 3 (n=17)	Stage 4 (n=17)
AKPS	*rs*=0.18 p=0.44	*rs*=0.09 p=0.24	*rs*=-0.14 p=0.68	*rs*=0.09 p=0.24
QOL (EQ-5D-5L)	*r*=0.03 p=0.91	*r*=0.32 p=0.21	-	*r*=0.32 p=0.21
Subjective sleep quality	*rs*=0.03 p=0.90	*rs*=0.24 p=0.35	*rs*=-0.28 p=0.43	*rs*=0.24 p=0.35
HADS – anxiety	*r*=0.29 p=0.23	*r*=-0.03 p=0.92	-	-
HADS – depression	*r*=-0.27 p=0.26	*r*=0.17 p=0.52	-	-
Global impression of change	-	*rs*=-0.19 p=0.47	*rs*=-0.14 p=0.68	*rs*=-0.46 p=0.43

AKPS = Australian Karnofsky Performance Status; QOL (EQ-5D-5L) = Quality of life measured using the EQ-5D-5L questionnaire; HADS = Hospital Anxiety and Depression Scale. Subjective sleep quality measured with a 4-point Likert scale; Global impression of change measured with a 7-point Likert scale.

8.5.7 Relationships between harms and diurnal cortisol profile measures

There were no noteworthy correlations between diurnal cortisol summary measures (slope and AUCg) and the presence of harms frequently associated with morphine (constipation, nausea, drowsiness), in any of the study stages.

8.5.8 Relationship between participants' baseline characteristics and diurnal cortisol profile measures

Baseline factors with the potential to influence HPA axis activity and cortisol levels were examined to explore their influence in this sub-study. At baseline, there was a strong correlation between the age-adjusted Charlson comorbidity index and the ln-AUCg, with the ln-transformed AUCg becoming lower for higher comorbidity indexes (r=-0.70, p<0.001; Appendix 26). There was also a moderate correlation between age and Ln-AUCg, with the ln-transformed AUCg becoming lower for more advanced age (r=-0.43). However, this result was not statistically significant (p=0.06; Table 8.9).

Table 8.9 - Correlations between summary ln-transformed diurnal cortisol measures and participant's baseline characteristics

	Age	BMI	CCI – age adjusted
Ln-Diurnal slope	*r*=-0.07 p=0.78 N=20	*r*=0.24 p=0.31 N=19	*r*=0.01 p=0.96 N=20
Ln-AUCg	*r*=-0.43 p=0.06 N=20	*r*=-0.11 p=0.66 N=19	*r*=-0.70 p<0.001 N=20

BMI = body mass index; CCI= Charlson comorbidity index

Sub-group analysis showed that the mean diurnal cortisol slope was significantly flatter for people with no history of psychiatric illness (-0.14 for the subgroup with a history of anxiety and/or depression versus -0.07 for the group with no history of anxiety and/or depression, t=2.46, p<0.02; Appendix 27). There were no statistically significant differences in mean

diurnal Ln-AUCg between these sub-groups. The mean ln-transformed AUCg was higher for the sub-group without a carer (3.49 in the sub-group with a carer versus 4.07 in the sub-group without a carer, t=-2.88, p=0.01; Appendix 28). There were no statistically significant differences in mean diurnal cortisol slopes between these sub-groups. Sub-group analysis for the use of systemic steroids over the previous year was not possible due to very low reporting numbers.

Analysis of other sub-groups did not show any statistically significant differences (Table 8.10).

Table 8.10 – Subgroup analysis for clinical factors potentially impacting the mean diurnal slope and mean diurnal AUCg at baseline

	Ln-Diurnal slope	Ln-AUCg
Sex	Male (n=9): -0.10 (±0.07) Female (n=11): -0.11 (±0.08) t=0.30, p=0.77	Male (n=9): 3.59 (±0.47) Female (n=11): 3.54 (±0.43) t=0.23, p=0.73
Smoking status	Former (n=16): -0.10 (±0.08) Others (n=4): -0.10 (±0.09) t=0.12, p=0.90	Former (n=16): 3.56 (±0.47) Others (n=4): 3.55 (±0.32) t=-0.05, p=0.96
Supplemental oxygen use	No (n=17): -0.11 (±0.08) Yes (n=2): -0.05 (±0.05) t=-1.07, p=0.30	No (n=17): 3.53 (±0.45) Yes (n=2): 3.75 (±0.48) t=-0.65, p=0.52
Diabetes mellitus (type I or II)	Yes (n=2): -0.09 (±0.02) No (n=18): -0.11 (±0.08) t=0.76, p=0.46*	Yes (n=2): 3.58 (±0.17) No (n=18): 3.56 (±0.46) t=0.07, p=0.95
Current or previous history of psychiatric illness	Yes (n=9): -0.14 (±0.06) No (n=11): -0.07 (±0.07) t=-2.46, p=0.02	Yes (n=9): 3.57 (±0.48) No (n=11): 3.55 (±0.42) t=0.07, p=0.94
Steroid inhaler use	Yes (n=17): -0.10 (±0.07) No (n=3): -0.11 (±0.11) t=0.06, p=0.96	Yes (n=17): 3.51 (±0.42) No (n=3): 3.84 (±0.49) t=-1.22, p=0.24
Antidepressant use	Yes (n=6): -0.15 (±0.06) No (n=14): -0.08 (±0.08) t=-1.75, p=0.10	Yes (n=6): 3.50 (±0.53) No (n=14): 3.58 (±0.41) t=-0.37, p=0.72
Immunosuppressants use	Yes (n=3): -0.13 (±0.07) No (n=17): -0.10 (±0.08) t=-0.54, p=0.60	Yes (n=3): 3.50 (±0.19) No (n=17): 3.57 (±0.47) t=-0.27, p=0.79
Carer availability	Yes (n=15): -0.11 (±0.08) No (n=3): -0.11 (±0.10) t=-0.09, p=0.93	Yes (n=15): 3.49 (±0.33) No (n=3): 4.07 (±0.25) t=-2.88, p=0.01

8.5.9 The impact of physical activity on the diurnal cortisol profile measures

In the 40 cortisol diaries returned, participants reported going outside in all collection days. In most cases (n=38) they had also engaged in some form of physical exercise. As a result, it was impossible to conduct a sub-group analysis to identify the influence of such factors on the diurnal cortisol profile (slope and AUCg).

8.6 Discussion

This sub-study followed on previous work from Ryan et al. (2017), who conducted the first and only study exploring the diurnal cortisol profile in people with chronic breathlessness. This sub-study differed from the work of Ryan et al. (2017) by focusing on people with severe chronic breathlessness (mMRC 3 or 4) who had COPD. More importantly, this was the first prospective sub-study aiming to examine changes in the diurnal cortisol profile of people with severe chronic breathlessness as regular, low-dose, sustained-release oral morphine was introduced and continued.

8.6.1 Proportions of the four diurnal cortisol slope categories

Proportions of the four diurnal cortisol slope categories at baseline (i.e., descending, flat, ascending, inconsistent) were very similar to what was previously reported in a population with chronic breathlessness (mMRC ≥ 2) of different aetiologies, but smaller than the proportion reported for healthy volunteers (Ryan et al., 2017). Given the likely association between chronic stress and chronic breathlessness, these results were expected. HPA axis dysregulation and flatter diurnal cortisol curves are seen in multiple conditions associated with chronic breathlessness, including COPD, and they are usually an indication of poor health (Abercrombie et al., 2004; Adam et al., 2017; Laghi et al., 2009). Importantly, the striking similarity between the proportions of diurnal cortisol slope categories in this sub-

study and those reported by Ryan et al. (2017), *despite differences in mMRC*, is interesting. Given that this sub-study only included people with severe functional impairment due to chronic breathlessness (i.e., mMRC 3 and 4) and that more breathlessness is usually associated with poorer health, it would be reasonable to expect a larger proportion of flatter diurnal cortisol slopes compared to the previous study. However, the relatively small sample sizes included in both studies and the small number of people with mMRC 2 in the first study, may have contributed for the absence of differences. Differences between mMRC grades need to be explored in future studies with larger sample sizes.

Differences in the proportions of the four diurnal cortisol slope categories between different study stages and doses were not identified, possibly due to the small number of participants in each arm, which decreased as the sub-study progressed. However, by Stage 4, only people taking regular, low-dose, sustained-release oral morphine were taking part in this sub-study and none had flat diurnal cortisol slopes. It is possible that those reaching stage 4 had more "net benefit" with the study medication, after weighing benefits and harms (Ferreira et al., 2016), which could be associated with steeper slopes (indicative of better health) (Adam et al., 2017). However, given the very small number of participants included in each stage, it is possible that these results were obtained by chance.

8.6.2 Arm differences in mean diurnal cortisol slope and mean cortisol AUCg across different stages

In Stage 1, differences between arms in mean diurnal cortisol slopes and AUCg were not statistically significant but showed an interesting pattern that was not present at Baseline (i.e., placebo > sustained-release morphine 8mg > sustained-release morphine 16mg). Moreover, the longitudinal pattern of response varied between arms, with those taking higher doses of sustained-release morphine (i.e., ≥16mg) displaying flatter cortisol slopes in

the shorter term (i.e., Stage 1) and steeper cortisol slopes in the longer term (i.e., Stages 3 and 4), which was not seen in other arms. These observations may suggest that regular, low-dose, sustained-release oral morphine ≥16mg may flatten the diurnal cortisol slope in the shorter term, while having the opposite effect in the long term (Steptoe & Serwinski, 2016). The shorter-term findings from this sub-study are in line with previous research showing that modified-release oral morphine 30 mg (12-hour formulation) reduces serum ACTH and cortisol levels up to three hours after acute administration (Allolio et al., 1987). However, the effects on diurnal cortisol slope and AUCg were never examined (Allolio et al., 1987). From a pharmacokinetic perspective, modified-release morphine induces higher maximum plasma concentrations compared with sustained-release oral morphine (24-hour formulation used in this study) (Gourlay et al., 1995), which could result in greater inhibition of the HPA axis. However, it is unclear if different pharmacokinetic characteristics translate to pharmacodynamic differences. Given the consistent reports of HPA axis suppression after opioid administration, it is possible that regular, low-dose, sustained-release oral morphine produces some inhibition of the HPA axis, with associated changes in the diurnal cortisol slope and AUCg (Lamprecht et al., 2018; Palm et al., 1997). However, it is important to define the magnitude of changes observed, their duration (i.e., shorter-term or longer-term) and their clinical significance, as they may differ from other morphine formulations and doses. More importantly, it is necessary to understand how regular, low-dose, sustained-release oral morphine affects the HPA axis *in the context of chronic breathlessness*, according to the "net benefit" (i.e., overall effect, weighing benefits and harms) achieved.

8.6.3 Stage differences in diurnal cortisol profile according to breathlessness severity

Another interesting finding from this sub-study is that, in Stages 1 and 3, there were moderate correlations between lower functional impairment due to breathlessness (i.e.,

lower mMRC) and flatter diurnal cortisol slopes. These results seem to conflict with the previous findings from Ryan et al. (2017), showing an association between *higher* functional impairment due to breathlessness (i.e., mMRC) and flatter diurnal cortisol slopes. Additionally, these results seem to diverge from the patterns observed for *worst* and *average* intensity of breathlessness in Stages 1 and 3 of this sub-study (i.e., flatter diurnal cortisol slopes for higher breathlessness scores). It is unclear what may have led to these results. Most likely, the lower number of participants in Stages 1 and 3 and the fact that mMRC was scored by clinicians may have contributed to the disparities observed (Ekström et al., 2019).

Ryan at al. (2017) had previously identified a signal for a possible correlation between breathlessness intensity and diurnal cortisol slope that did not reach statistical significance (i.e., cortisol slope becoming flatter for higher NRS breathlessness scores). This sub-study adds to these findings by suggesting a similar direction of signal for *worst* and *average* breathlessness. The lack of statistical significance for *worst* and *average* breathlessness in these studies may be related to the small sample sizes included. However, given the overlap between breathlessness and central stress pathways, it is likely that more intense breathlessness leads to greater HPA axis dysfunction (Godoy et al., 2018; Pattinson & Johnson, 2014).

Correlations between *worst* and *average* breathlessness and diurnal cortisol slope were stronger in Stage 4 compared with previous stages, with the diurnal cortisol slope becoming flatter for higher breathlessness scores. Correlations between *worst* and *average* breathlessness and AUCg were also stronger in Stage 4, with the AUCg becoming smaller for higher breathlessness scores. Reasons for these differences between stages are unclear. The

sample size included in Stage 4 was small and may have over-estimated the strength of these correlations. However, people choosing to progress to Stage 4 may have had greater sustained benefit with regular, low-dose, sustained-release oral morphine. It is possible that, within the group of responders (i.e., people deriving benefit from the intervention), diurnal cortisol slopes became steeper *with time* according to the degree of benefit. These findings are further supported by the Stage 4 significant correlation between global impression of change and diurnal cortisol slope, with slopes becoming steeper as the subjective sense of improvement increased. Although opioids have an overall inhibitory effect on the HPA axis, small doses of regular, sustained-release oral morphine in people with chronic breathlessness may actually have the opposite effect (Fountas et al., 2020; Gibb et al., 2016). Chronic breathlessness is likely a state of prolonged exposure to stress resulting in increased allostatic load and dysregulation of the HPA axis (Ryan et al., 2014). In turn, dysregulation of the HPA axis is likely to aggravate breathlessness by upregulating systemic inflammation, which contributes to skeletal muscle dysfunction and respiratory muscle fatigue (Braun et al., 2011). It is possible that regular, low-dose, sustained release oral morphine interrupts or slows down this worsening cycle in people who derive benefit, leading to an improvement in HPA axis function in the long-term. However, increasing doses beyond the level of benefit, may possibly lead to detrimental effects on the HPA axis without any additional benefit. The long-term effects of regular, low-doses sustained-release oral morphine on the HPA axis of people with chronic breathlessness need to be investigated in future larger prospective studies.

8.6.4 Stage differences in diurnal cortisol profile according to other measures

Results from previous cross-sectional studies in the cancer setting suggest that diurnal cortisol slopes tend to become flatter as performance status decreases (Kim et al., 2012;

Mormon et al., 2002; Weinrib et al., 2010). This sub-study suggests a similar pattern in a population with chronic breathlessness associated with COPD. The only previous study examining diurnal cortisol profile in a population with chronic breathlessness did not show a significant correlation between performance status and diurnal cortisol slope, but the sample size was small, which may have led to a type II error. However, the direction of this correlation ($r=-0.23$, $p=0.08$) was similar to what was found in this sub-study (Ryan et al., 2017). Of note, the population included in the first study was more heterogeneous, comprising people with different aetiologies and functional impairment due to chronic breathlessness (Ryan et al., 2017). It is likely that these differences within the population may have acted as confounders, contributing to underestimate the association between performance status and diurnal cortisol slope. Importantly, significant correlations between diurnal cortisol slope and performance status were only observed at baseline in this sub-study. This absence of differences in subsequent stages may result from the smaller sample sizes, with low variability in AKPS scores. However, participants were also offered different interventions from baseline onwards (i.e., placebo or different doses of regular, low-dose, sustained-release oral morphine) with the potential to affect both the diurnal cortisol slope and performance status. The small number of participants in each arm, did not allow investigation of possible contributions of regular, low-dose, sustained-release oral morphine dose for variations observed between stages. Conducting a larger prospective study to investigate relationship between performance status and diurnal cortisol slope before and after the introduction of regular, low-dose, sustained-release oral morphine is key, bearing in mind the prognostic value of performance status in populations with chronic breathlessness (Ban et al., 2016). In fact, decreased performance status and function may be one of the mechanisms by which breathlessness predicts mortality (Ryan et al., 2017).

Subjective sleep quality was also correlated with diurnal cortisol slope at baseline, with the slopes becoming flatter for worse subjective sleep quality in the night preceding saliva sample collection. These findings are aligned with results from cross-sectional studies suggesting that worse subjective sleep quality is associated with flatter cortisol slopes in people with cancer (Chang & Lin, 2017; Hoyt et al., 2016). From a physiological point of view, there is a reciprocal relationship between HPA axis function and sleep, which are key determinants of the circadian rhythm (Balbo et al., 2010; Buckley & Schatzberg, 2005; McEwen & Wingfield, 2003). While sleep has an inhibitory effect on the HPA axis, activation of the HPA axis has an inhibitory effect on sleep (Minkel et al., 2014; Weitzman et al., 1983). States of chronic stress tend to dysregulate circadian systems producing both sleep and HPA axis dysfunction, which are predictors of worse health (Buysse, 2014; Taylor et al., 2003). Thus, diurnal cortisol slope and subjective sleep quality may be phenotypical markers of chronic stress in populations with chronic breathlessness, that together, may help to characterise people's health status and perhaps mortality. Importantly, from Baseline to Stage 4, there was a progressive inversion of the correlation direction, with the slopes becoming flatter for better subjective sleep quality in Stage 4. Stage 1 to 4 correlations were not statistically significant, which may have resulted from the smaller sample sizes included. However, most participants were overweight or obese, which predisposes to obstructive sleep apnoea and worse sleep quality (Algul et al., 2009; Peppard et al., 2013; Peppard et al., 2000). While regular, low-dose, sustained-release oral morphine was shown to improve subjective sleep quality in people with chronic breathlessness, it is unclear if these changes have any association with BMI (Martins et al., 2016). In people who are overweight and suffer from obstructive sleep apnoea, regular, low-dose, sustained-release oral morphine may potentially aggravate the condition by causing somnolence and depressing the

chemoreceptor response to changes in arterial partial pressures of carbon dioxide, oxygen and variations in pH (Wang et al., 2013). Indeed, for these people, minor daily fluctuations in respiratory rate and $ETCO_2$ may reflect larger changes during sleep when the central drive is the rescue mechanism from periods of hypopnea/apnoea (Eckert et al., 2007). Thus, sleep disruption and sleep-disordered breathing may have been a confounder in this sub-study after the initiation of regular, low-dose, sustained-release oral morphine.

Previous studies have demonstrated that depression is associated with flatter diurnal cortisol slopes, including in people diagnosed with potential causes of chronic breathlessness (Adam et al., 2017; Du et al., 2013; Ho et al., 2013). This sub-study showed the opposite pattern, with the slopes becoming significantly steeper for higher depression scores in Stage 1. Moreover, sub-group analysis at baseline demonstrated significantly steeper diurnal cortisol slopes for people with current or previous history of psychiatric illness. Anxiety or coexistence of anxiety and depression may have contributed for the baseline findings. In a previous systematic review and meta-analysis, the presence of anxiety symptoms was not significantly associated with changes in the diurnal cortisol slope (Adam et al., 2017). However, the direction and magnitude of the correlation suggested that the slopes tend to become steeper in the presence of anxiety symptoms, which may be due to hyperarousal with elevated morning cortisol (Adam et al., 2017; Clark & Watson, 1991). In this sub-study, most participants with past or current history of psychiatric illness had anxiety or a combination of anxiety and depression, which may have contributed to steeper slopes in this sub-group. However, results achieved in Stage 1 are still unexpected and contrary to the previous study in the field of chronic breathlessness (Ryan et al., 2017). Such results may be due to the small sample size included in Stage 1 and potential effects caused

by the study medication. Future prospective studies need to investigate the potential effects of regular, low-dose, sustained-release oral morphine on the HPA axis of people with chronic breathlessness and depressive symptoms.

8.6.5 Participants' baseline characteristics and the diurnal cortisol profile

This sub-study showed a correlation between ln-transformed AUCg (i.e., measure of total diurnal cortisol exposure) and age-adjusted Charlson comorbidity index, with the AUCg becoming lower for higher age-adjusted morbidity scores. Age seems to play a role in the strength of this correlation, given that there was also a moderate (but non-significant) correlation between age and ln-AUCg, with ln-AUCg becoming lower for more advanced age. In elderly populations, increasing age was previously associated with hypercortisolism (Ice, 2005; Kudielka et al., 1999; Smyth & Clow, 2020). The only study of people with chronic breathlessness suggested that increasing age was associated with flatter slopes and higher ln-AUCg (Ryan, 2015, p. 151). Thus, results from this sub-study are unexpected and may be a consequence of the small sample size included. However, a recent study comparing people with COPD with different BODE grades (i.e., score obtained based on BMI, FEV1, mMRC grade, and exercise capacity measured in a 6-minute walk test) (Muza et al., 1990) reported that as the BODE grade increased (i.e., more severe disease), cortisol levels and adrenal gland size decreased (Wei et al., 2021). Moreover, as the BODE grade increased, levels of C-reactive protein also rose (Wei et al., 2021). As COPD progresses, there is an increase in systemic inflammation that is thought to be both a cause and a consequence of chronic breathlessness (Ryan et al., 2016b). Importantly, chronic inflammation has been previously associated with hypoactivity of the HPA axis (Chrousos, 1995, 2000). Considering that chronic breathlessness associated with COPD progresses slowly, it is likely that elderly people have more advanced disease, with higher degrees of inflammation and greater HPA

axis dysfunction, which would explain results from this sub-study. The link between inflammation and dysregulation of the HPA axis in people with chronic breathlessness needs to be explored in future studies.

In this sub-study, the mean ln-transformed AUCg was higher for the sub-group without a carer, with no significant differences in diurnal cortisol slopes. Importantly, only three participants reported not having a carer and results must be interpreted with caution. Loneliness and lack of social support have been previously associated with flatter diurnal cortisol curves both in healthy adults and people with chronic disease due to lower cortisol output across the day (i.e., lower AUCg), which contrasts with findings from this sub-study (Schutter et al., 2017). However, the absence of a carer does not necessarily translate into loneliness or the absence of a social support network. Thus, there is interest in investigating the association between social support and HPA axis function in people with chronic breathlessness in future studies.

One important finding from this study is the absence of any noteworthy correlations between harms commonly associated with morphine and changes in the diurnal cortisol profile. Nausea and drowsiness may be present in the first few days of morphine therapy but tend to subside rapidly after initiation of regular therapy. All cortisol samples were collected after at least five days of regular, low-dose, sustained-release oral morphine, when there were few reported cases of these harms, which may explain the absence of significant correlations. Although some participants reported constipation, it was usually mild or moderate and unlikely to contribute to substantial disruption of the HPA axis (Kiefte-de Jong et al., 2011).

8.6.6 Limitations

Embedding this exploratory sub-study in a multi-site RCT allowed prospectively exploring, for the first time, the effects of regular, low-dose, sustained-release oral morphine on the HPA axis of people with chronic breathlessness. Data collected as part of the BEAMS study was used in the context of this sub-study, and results from this sub-study can help to understand outcomes of the main trial. However, people with severe chronic breathlessness are often frail and study staff were particularly mindful not to overburden participants. Thus, it is likely that most participants not providing written informed consent were deemed too frail to comply with the sub-study requirements, *in addition* to the main trial. Compliance with the sub-study procedures was assessed by self-report, which may not be an accurate reflection of actual compliance. Collection days were pre-determined to align with outcomes for the main trial. Activity levels on these days were variable, which may have influenced the results. Given the small sample size included in this hypothesis-generating sub-study, results cannot be generalised.

8.6.7 Implications for future research

Future large-scale prospective studies need to focus on identifying the temporal relationship between the development of chronic breathlessness and changes in the HPA axis. This investigation is part of a strategy to understand the mechanisms of chronic breathlessness in order to develop therapies targeting these mechanisms. Moreover, this sub-study identified a potential link between performance status and subjective sleep quality in people with chronic breathlessness, and HPA axis dysfunction. Thus, these may be contributing factors for worse health outcomes in this population and should be explored as covariates in future studies. Additionally, given that chronic breathlessness is associated with HPA axis dysregulation, there is interest in evaluating the safety and effectiveness of

interventions targeting the HPA axis (e.g., melatonin). It is important to explore the effects of regular, low-dose, sustained-release oral morphine on the HPA axis, and their relationship with changes in intensity of breathlessness, functional impairment due to breathlessness and "net effect" weighing benefits and harms. This will clarify whether regular, low-dose, sustained-release oral morphine can induce long term changes in the HPA axis and whether reductions in breathlessness contribute to these changes.

8.6.8 Implications for clinical practice

This was a hypothesis-generating study, designed to point to future research directions and whose results are not generalisable. However, results suggest that different clinical and phenotypic markers (i.e., higher age, worse performance status, worse perceived sleep quality and higher intensity of breathlessness) may contribute to HPA axis dysfunction in people with chronic breathlessness. Given the association between HPA axis dysfunction and worse health outcomes, it is important that clinicians focus on evaluating and, if applicable, on optimising these markers. In people with chronic breathlessness and COPD taking regular, low-dose, sustained-release oral morphine, it is important to identify and treat obstructive sleep apnoea, which can potentially be aggravated by this medication and worsen people's perceived sleep quality.

8.7 Conclusions

This was the first study exploring the diurnal cortisol profile of a population with COPD and severe functional impairment due to chronic breathlessness. This was also the first prospective study exploring changes in the diurnal cortisol profile of people with COPD and severe chronic breathlessness as regular, low-dose, sustained-release oral morphine was introduced and continued. Based on the pattern, direction, and magnitude of results, it is

possible that higher age, worse performance status, worse perceived sleep quality and higher intensity of breathlessness may contribute to HPA dysfunction in people with chronic breathlessness. These variables need to be investigated in future, adequately powered, prospective studies. Given the small number of participants included in each arm, future studies need to focus on understanding the effects of regular, low-dose, sustained-release oral morphine in people with COPD and chronic breathlessness. It is possible that people deriving more “net benefit” with regular, low-dose, sustained-release oral morphine, also may potentially improve their diurnal cortisol profile, likely leading to better health outcomes. Alternatively, improvements in HPA axis function may generate a sense of wellbeing that people attribute to morphine.

8.8 References

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CHAPTER 9 – REGULAR, ORAL, SUSTAINED-RELEASE ORAL MORPHINE FOR CHRONIC BREATHLESSNESS IN PULMONARY ARTERIAL HYPERTENSION: A RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED, CROSSOVER STUDY

9.1 Chapter preface

As highlighted in Chapter 2, there is evidence to suggest that regular, low-dose, sustained-release oral morphine is the best pharmacological treatment for chronic breathlessness, irrespective of the underlying cause (Johnson et al., 2013b). However, this evidence is based on studies in which COPD, congestive heart failure and cancer were largely over-represented compared with other aetiologies of breathlessness (Abernethy et al., 2003; Currow et al., 2011; Johnson et al., 2002; Oxberry et al., 2011). It is not clear whether people with different causes of chronic breathlessness derive the same benefit from taking this medication. To answer this question, the last sub-study of this doctoral program investigated the effects of regular, low-dose, sustained-release oral morphine for chronic breathlessness in a population with pulmonary arterial hypertension, a relatively rare cause of chronic breathlessness.

9.2 Publication Reference

The results of Sub-study 6 were published in 2018 in Journal of Pain and Symptom Management, an international peer reviewed journal targeting clinicians and other healthcare workers undertaking clinical work in palliative care and pain management. This chapter contains an edited version of the published manuscript (Appendix 29).

> Ferreira DH, Ekström M, Sajkov D, Vandersman Z, Eckert DJ, Currow DC. Extended-Release Morphine for Chronic Breathlessness in Pulmonary Arterial Hypertension—A Randomized, Double-Blind, Placebo-Controlled, Crossover Study. Journal Pain Symptom Management. 2018 Oct 1;56(4):483-92.

Number of citations: 11

Journal of Pain and Symptom Management: Impact factor: 3.249; Scimago Journal Ranking 2018: 9/122 (Anesthesiology and Pain Medicine), 53/363 (Neurology [Clinical]), 3/140 (Nursing [Miscellaneous]).

9.3 Introduction

Pulmonary hypertension is a chronic disease defined by an abnormally increased pulmonary artery pressure at rest (>20 mmHg) measured by right heart catheterization (Hoeper et al., 2013a). It can develop as a stand-alone disease or as a consequence of other conditions affecting the heart and lungs (Hatano et al., 1975). Regardless of the underlying cause, pulmonary hypertension has a poor prognosis if left untreated with an average survival time of 2.8 years (D'Alonzo et al., 1991). Despite the development of multiple therapeutic options for this condition over the past 20 years, pulmonary hypertension is still a chronic progressive disease leading to premature mortality, disability and economic burden to the health care system (Sikirica et al., 2014).

9.4 Pulmonary arterial hypertension (PAH) definition and classification

Pulmonary Arterial Hypertension (PAH) is one of five sub-groups of pulmonary hypertension, which is associated with specific histopathologic variations and aetiologies (Prior et al., 2016; Simonneau et al., 2013). Specifically, PAH is characterised by endothelial proliferation of the pulmonary arteries leading to progressive luminal obstruction, increased pulmonary vascular pressure and increased resistance to blood flow (Prior et al., 2016). As a consequence, there is also significant increase in the right heart afterload and development of right ventricular hypertrophy and congestive heart failure, which ultimately results in death (Strange et al., 2012). Several aetiologies of PAH have been identified and include PAH with no apparent cause (idiopathic); heritable PAH; PAH associated with drugs and toxins; PAH associated with multiple systemic

disorders (i.e., connective tissue disease, human immunodeficiency virus infection, portal hypertension, congenital heart disease and schistosomiasis); and persistent pulmonary hypertension of the newborn. More recently, it has been found that some people with PAH have long-term sustained vasodilation responses to calcium channel blockers. Although the mechanisms for these sustained responses are not fully understood, those who respond to this medication have significantly better prognosis, which justifies its inclusion as a separate PAH sub-group. Conversely, diagnosis of significant pulmonary venous/capillary involvement suggested by DLCO < 50% and severe hypoxemia is associated with poor prognosis and was also recently included as a separate sub-group of PAH (Table 9.1).

Table 9.1 - Updated classification of pulmonary hypertension

Group 1 – Pulmonary Arterial Hypertension (PAH)
1.1 Idiopathic PAH
1.2 Heritable PAH
1.3 Drug- and toxin- induced PAH (e.g., aminorex, fenfluramine, desfenfluramine, benfluorex, methamphetamines)
1.4 Associated with: 1.4.1 Connective tissue disease 1.4.2 HIV infection 1.4.3 Portal hypertension 1.4.4 Congenital heart disease 1.4.5 Schistosomiasis
1.5 Long term responders to calcium channel blockers
1.6 PAH with overt features of venous/capillaries (pulmonary veno-oclusive disease /pulmonary capillary haemangiomatosis) involvement
1.7 Persistent PH of the newborn syndrome

Copied from Simonneau et al. (2019) with permission from the ©ERS 2021 (Appendix 30).

9.4.1 PAH prevalence and clinical significance

The true prevalence of PAH in the general population is still unknown, possibly due to its overlap with other chronic conditions (Orem, 2017). Population-based studies report a prevalence of 15 to 60 cases per million people (Peacock et al., 2007) and an annual incidence of 2.4 to 15 cases per million people, per year (Galie et al., 2016; Peacock et al., 2007). Until recently, PAH was thought to be more prevalent in young adults, but it is now known that it affects all age groups, ethnicities and socio-economic backgrounds (Orem, 2017). Women are more susceptible than men, but men have worse prognosis (Escribano-Subias et al., 2012; Mair et al., 2014; Shapiro et al., 2012). It is

unclear whether such differences are caused by sex hormones, which seem to predispose to the development of PAH but constitute an advantage in terms of survival (Austin et al., 2013). Independent of these group differences, the annual incidence of PAH has been increasing, possibly because people live longer due to the development of new treatments (Wijeratne et al., 2018). As people live longer, there is an increasing need of effectively treating symptoms associated with PAH, which includes breathlessness that is highly frequent and debilitating in this population.

9.4.2 Chronic breathlessness associated with PAH

Similar to COPD, chronic breathlessness associated with PAH starts insidiously and gets progressively worse over time. In the early stages of the disease, people with PAH frequently present breathlessness on exertion even in the absence of important haemodynamic changes (Montani et al., 2013). The diagnosis of PAH occurs typically later in the course of the disease, when people are already experiencing severe functional limitations. Previous population-based studies have shown that there is a delay in the diagnosis of PAH of more than two years from the onset of symptoms (Badesch et al., 2010; Humbert et al., 2010; Montani et al., 2013). Delays in diagnosis also occur in other conditions associated with chronic breathlessness, because people progressively restructure their lives around breathlessness until the symptom becomes unmanageable (Houtchens et al., 2011). Importantly, given that PAH is a rare disease whose symptoms mimic other chronic and life-limiting illnesses, clinicians may take additional time to consider and establish its diagnosis (Blasi, 2012).

Over the course of PAH, 98% of the people will be affected by breathlessness which is both the earliest and the most prevalent symptom reported (Rich et al., 1987). Breathlessness associated with PAH is likely to become chronic as the disease progresses, often causing significant symptom burden and functional limitations (Guillevin et al., 2013). By the time of diagnosis, most people with PAH have chronic breathlessness of stage III or IV of the New York Heart Association (NYHA)

classification, corresponding to “marked limitation in activity due to symptoms, even during less-than-ordinary activity (e.g., walking short distances [20-100 metres]); comfortable only at rest” and “severe limitations; experiences symptoms even while at rest; mostly bed-bound patients” (New York Heart Association, 1994). Thus, chronic breathlessness needs to be promptly identified and treated in this population, in order to optimise their wellbeing and quality of life.

9.4.3 The impact of chronic breathlessness associated with PAH

Chronic breathlessness associated with PAH has a significant impact on patients’ and their carers’ well-being. A large-scale survey conducted in five European countries revealed that PAH is associated with breathlessness leading to severe functional limitations, impacting basic daily activities such as working, shopping and performing household chores (Guillevin et al., 2013). In the same study, participants reported feelings of frustration, anger, low self-esteem, and a sense of being worthless due to the limitations experienced (Guillevin et al., 2013). Additionally, in a cross-sectional survey conducted in the United States, people living with PAH were shown to have significantly impaired physical and mental health-related quality of life (Taichman et al., 2005). Close to 70% of these people were living with chronic breathlessness (Taichman et al., 2005). In addition, anxiety and depression are common in patients with PAH, particularly in advanced stages of disease, and associated with worse physical and mental quality of life (Halimi et al., 2018; Verma et al., 2016).

Carers also experience significant burden associated with PAH and its symptoms. Chronic breathlessness associated with PAH considerably impacts on carers’ lives, forcing them to reorganise their daily activities to respond to the patients’ needs (Zhai et al., 2017). For a proportion of carers, employment is affected, which results in important reductions in household income for many families (Ferrari et al., 2013; Guillevin et al., 2013). Additionally, carers often feel overwhelmed by the responsibility of having to provide continuous care to patients (Zhai et al.,

2017). Not surprisingly, relationships between patients and carers change in the course of the disease (Ferrari et al., 2013). For those who are partners, the quality of their sexual life decreases due to the symptomatic burden imposed by chronic breathlessness (Guillevin et al., 2013). As a result, the carer may feel more distant to the patient, causing additional distress to the family unit (Guillevin et al., 2013).

In summary, living with chronic breathlessness associated with PAH results in multiple losses for patients and their carers. As a result, treating chronic breathlessness associated with PAH is as important as treating chronic breathlessness associated with other, more frequent, conditions. Thus, there is a pressing need to develop therapies that specifically target the symptomatic reduction of chronic breathlessness in this population.

9.4.4 Pathogenesis and pathophysiology of chronic breathlessness associated with PAH

The mechanisms of chronic breathlessness associated with PAH are still relatively unknown (Dumitrescu et al., 2017). PAH is characterised by specific pathological changes in the *pulmonary arteries' endothelium*, which include plexiform lesions, endothelial proliferation, fibrosis and *in situ* thrombosis (Clarke, 2002; Pietra et al., 1989). These abnormalities contribute to progressive obstruction and increased resistance in the pulmonary vasculature, leading to a range of secondary pathophysiological changes.

9.4.5 Local changes in the pulmonary arteries' endothelium

The hallmark of PAH is a dysfunction of the pulmonary arteries endothelium (Rai et al., 2008). The endothelium plays a major role in maintaining normal vascular function (Galley & Webster, 2004), which includes control of vascular tone, platelet function, coagulation and fibrinolysis, leucocyte traffic to extravascular tissues and angiogenesis (Pearson, 2000). Thus, endothelial dysfunction associated with PAH leads to major changes in the structure and function of pulmonary arteries, with profound systemic implications. Specific endothelial changes present in PAH include an

increase production of vasoconstrictors (e.g., thromboxane, endothelin-1, serotonin) and a *reduction in vasodilators* (e.g., nitric oxide and prostacyclin), favouring cellular proliferation, vascular remodelling and *in situ* thrombosis (Farber & Loscalzo, 2004; Prins & Thenappan, 2016). These pathological changes contribute to the development of endothelial lesions affecting primarily small to medium-sized arterioles, which continue to develop to partially or completely obliterate the vascular lumen (Pietra, 1994; Tuder et al., 2007). Importantly, cellular proliferation and vascular remodelling associated with PAH evolves to affect all three layers of vessel walls (i.e., intima, media and adventitia) (Guignabert et al., 2013). In later stages of the disease, these lesions become infiltrated by fibroblasts, myofibroblasts and immune cells forming *plexiform lesions* (Sakao et al., 2009). As a result, the vascular bed becomes thicker and harder, which increases vascular resistance substantially (Guignabert et al., 2013).

Local inflammation is a central feature associated with PAH, which occurs early in the course of the disease, contributing to trigger vascular remodelling (Huertas et al., 2014). Lung tissue of patients with PAH shows severe infiltration by inflammatory cells such as macrophages, mastocytes, dendritic cells and B and T lymphocytes (Rabinovitch et al., 2014), which correlate with the severity of the disease (Stacher et al., 2012). Conversely, regulatory T cells, which are critical to maintain immune-system homeostasis, are decreased around affected arteries (Rabinovitch et al., 2014). Importantly, inflammation and immune phenomena are major stimulants of pulmonary C-fibers (Manning & Mahler, 2001; Nishino, 2011), and one possible mechanism of chronic breathlessness in this population.

9.4.6 Systemic changes associated with PAH

Overall, pathophysiologic changes associated with PAH lead to decreased cardiac output, impaired gas exchange, decreased tissue perfusion, systemic inflammation and deregulation of the immune response (Dumitrescu et al., 2017; Kherbeck et al., 2013). With time, increased resistance in the

pulmonary arteries exposes the right ventricle to increased afterload. Consequently, right ventricular hypertrophy develops, which increases the contractile capacity of the heart and maintains stroke volume and right ventricular output (Hsu et al., 2016). As PAH progresses, persistent exposure to increased arterial resistance may put too much pressure on the heart leading to dilated cardiomyopathy and congestive heart failure. At this point, right ventricular output may become insufficient to maintain adequate lung perfusion, and people start to progressively develop chronic breathlessness and symptoms such as fatigue, chest pain and dizziness (Tran et al., 2018).

The consequences of inadequate right ventricular output include a mismatch between pulmonary ventilation and perfusion (Liu et al., 2014). This mismatch is one of the mechanisms leading to persistent hyperventilation observed in people with PAH (Tran et al., 2018). Importantly, due to decreased lung perfusion, hyperventilation is partially inefficient, increasing the pulmonary dead space (i.e., the volume of ventilated air that is not involved in gas exchange) more than the actual alveolar ventilation (i.e., the volume of ventilated air that is involved in gas exchange) (Farina et al., 2018; Tran et al., 2018). However, excessive physiologic dead space is not the only mechanism involved in PAH-associated hyperventilation. People with PAH have increased central chemoreceptor sensitivity, with marked ventilatory responses to changes in CO_2 and O_2 during exercise (Farina et al., 2018; Vicenzi et al., 2016). The mechanisms behind this increased sensitivity are not known but it may be related to adjustment of the range of CO_2, O_2 and H^+ levels imposed by the increased physiologic dead space (Wensel et al., 2004). By increasing the uncoupling between ventilatory demand and actual ventilation, the ventilation-perfusion mismatch and the increased chemoreceptor response are thought to be some of the key mechanisms contributing to chronic breathlessness associated with PAH (Dumitrescu et al., 2017; Tran et al., 2018).

Similar to COPD, dynamic hyperinflation may also be an important contributor for chronic breathlessness associated with PAH (Richter et al., 2012). A recent study suggested that dynamic hyperinflation accounts for 50-60% of the changes in Borg rating scale for breathlessness reported by people with PAH during exercise (Laveneziana et al., 2015). One proposed mechanism for the dynamic hyperinflation observed in PAH is compression of bronchioles by surrounding small arteries undergoing inflammation and remodelling (Meyer et al., 2002). Independent of the underlying mechanisms, dynamic hyperinflation may alter the chest wall mechanics and stimulate pulmonary stretch receptors and mechanoreceptors, contributing to chronic breathlessness associated with PAH.

Similar to other chronic diseases, skeletal muscle dysfunction, increased catabolism and systemic inflammation are a likely important contributor to chronic breathlessness in PAH (Manders et al., 2015). As explained in Chapter 1, these changes were shown to lead to an over-activation of the sympathetic nervous system, which has been previously demonstrated in people with PAH (Naeije & van de Borne, 2009). Additionally, chronic breathlessness associated with PAH decreases people's functional capacity. As people feel more breathlessness, it is likely that they tend to avoid overexertion, which contributes to speed up deconditioning (Johnson & Clark, 2016).

Another possible mechanism of chronic breathlessness in PAH is the blunted increase in maximum systemic oxygen extraction capacity during exercise (Tolle et al., 2008). Theoretically, insufficient oxygen delivery to the periphery would increase maximum systemic oxygen extraction capacity in order to preserve aerobic metabolism (Tolle et al., 2008). The blunted response observed in people with PAH may be a reflexion of skeletal muscle dysfunction mentioned previously (Taivassalo et al., 2003). Although not demonstrated in PAH, impairment of muscle blood flow may be an additional mechanism contributing to decreasing oxygen delivery, promoting skeletal

muscle dysfunction and impairing the capacity to extract oxygen at peak exercise (Esposito et al., 2011; Sullivan et al., 1989).

In summary, there are multiple mechanisms contributing to chronic breathlessness associated with PAH, for which target therapies have been developed. The next section highlights current treatments of chronic breathlessness associated with PAH and the potential role of regular, low-dose, sustained-release oral morphine in this setting.

9.4.7 Treatment options for breathlessness associated with PAH

As explained in Chapter 2 of this thesis, current guidelines recommend a three-step approach to the treatment of chronic breathlessness, irrespective of the underlying cause (Marciniuk et al., 2011). The first step includes optimising treatment for the underlying disease and ensuring that reversible causes of breathlessness are addressed. The second and third steps include, respectively, the implementation of non-pharmacological and pharmacological measures for the symptomatic reduction of chronic breathlessness, which are independent of the disease causing chronic breathlessness and more oriented towards symptomatic improvement.

9.4.7.1 Optimising PAH-specific treatment

Optimising the treatment of PAH involves three different steps (Galie et al., 2016):

- *Step 1*: Referral to an expert centre, general measures and supportive therapy;
- *Step 2*: Pharmacological treatment directed to specific pathophysiologic mechanisms; and
- *Step 3*: Review of the treatment strategy with institution of a combination of drugs and/or proposal to lung transplantation.

9.4.7.1.1 Step 1: Referral to an expert centre, general measures, supportive therapy

Given that PAH is a relatively rare disease, referral to expert centres is recommended before initiating therapy (Galie et al., 2016; Klinger et al., 2019). More recently, early referral to palliative care has also been recommended due to the heavy symptom burden and possible distress

imposed by the disease (Klinger et al., 2019). Specifically, psychosocial support and advanced care planning are beneficial from early stages of the disease, in order to facilitate coping and decrease anxiety associated with a life-limiting illness (Galie et al., 2016). Supportive pharmacological treatments for PAH may be considered in selected patients. Oxygen therapy is recommended for people with hypoxaemia ($PaO_2 \leq 60$ mmHg or oxyhaemoglobin saturation ≤ 91%) (Galie et al., 2016). Diuretics are recommended for people with signs of right ventricular dysfunction, including peripheral oedema (Cohn, 2001). Digoxin is effective in improving cardiac output in people with right ventricular dysfunction, but the long-term effects on cardiac function are unknown; its use is reserved for selected patients who develop atrial tachyarrhythmias (Galie et al., 2016). Importantly, anaemia due to iron deficiency is common in people with PAH and associated with reduced exercise capacity and potentially more breathlessness (Rhodes et al., 2011; Ruiter et al., 2014). Although the mechanisms associated with iron deficiency in PAH are still being investigated, it appears that iron supplementation may increase exercise-capacity in these patients. Thus, iron status needs to be routinely assessed in this context (Galie et al., 2016).

9.4.7.1.2 Step 2: Pharmacological treatment directed to specific pathophysiologic mechanisms

Over the past 20 years, pathways involved in the pathophysiology of PAH have been partially elucidated, which prompted the development of new targeted medications, aiming to reverse vascular remodelling and preserve right ventricular function (Blasi, 2012). Current pharmacological agents target three specific pathways: prostacyclin, endothelin and nitric oxide (Galie et al., 2016; Humbert et al., 2004).

Prostacyclin analogues promote vasodilation and inhibits cellular proliferation (Humbert et al., 2004). The prostacyclin analogue *epoprostenol* is the most effective drug for the treatment of PAH, leading to significant improvement in the 6-minute walk test, quality of life and survival (Barst et al., 1996; Galie et al., 2016). Importantly, it also significantly reduces the symptomatic

burden of breathlessness, measured with the Dyspnoea-fatigue index (Feinstein et al., 1989). However, this medication requires continuous infusion through a tunnelled catheter, which in not convenient for patients. In alternative, inhaled *iloprost* is another prostacyclin analogue that was shown to reduce breathlessness measured with the Mahler Dyspnoea Index, improve NYHA functional class and increase the distance walked in the 6 minute-walk test (Olschewski et al., 2002). One disadvantage of this medication is that it requires six to nine administrations per day (Olschewski et al., 2002), which in not convenient for patients and might affect treatment compliance.

Endothelin receptor antagonists inhibit vasoconstriction and cellular proliferation (Humbert et al., 2004). The oral agents *ambrisentan*, *bosentan* and *macitentan* are part of this pharmacological class. *Bosentan* and *ambrisentan* have been shown to improve breathlessness measured with the Borg scale, improve function and improve the distance walked in the 6-minute walk test after 12 and 16 weeks of therapy respectively (Galie et al., 2008a; Rubin et al., 2002). For people with mildly symptomatic PAH, *bosentan* was associated with less worsening in function and better performance in the 6-minute walk test after six months of therapy, compared with placebo (Galie et al., 2008b). However, there were no differences in breathlessness scores measured with the Borg scale between the two arms (Galie et al., 2008b). In this case, the slower decline in functional capacity observed in the *bosentan* group may be a direct reflection of a slower worsening in breathlessness. In other words, people may have higher breathlessness thresholds in the *bosentan* group, which is not captured by the Borg scale score. *Macitentan* is a relatively new endothelin receptor antagonist that has also shown to increase functional capacity and reduce both morbidity and mortality in people with PAH (Pulido et al., 2013).

Phosphodiesterase type 5 inhibitors produce acute vasodilation and inhibit cellular proliferation (Humbert et al., 2004). The oral agents *sildenafil* and *tadalafil* are included in this group, which

have been shown to improve distance walked in the 6-minute walk test (Galie et al., 2009; Galie et al., 2005) and delay time to clinical deterioration compared with placebo (Galie et al., 2009).

The oral agents *riociguat* and *selexipag* are more recent pharmacological therapies available to treat PAH. *Riociguat* is a soluble guanylate cyclase stimulator, that is able to increase the production of cGMP independent of the nitric oxide levels (Ghofrani et al., 2013), promoting vasodilation and decreasing cellular proliferation. Compared with phosphodiesterase type 5 inhibitors, riociguat offers the advantage of increasing the production, rather than inhibiting the breakdown of cGMP. This is important because PAH is associated with a state of nitric oxide / cGMP deficiency and reducing the breakdown of reduced amounts of cGMP may not be the best approach (Prior et al., 2016). Riociguat has been demonstrated to be effective for people with symptomatic PAH, participants' levels of breathlessness measured with the Borg scale, activity levels and distance walked in the 6-minute walk test after 12 weeks (Ghofrani et al., 2013).

Selexipag is an alternative to prostacyclin analogues, whose use is limited by the practical issues raised before (Barst et al., 1996). Similar to prostacyclin analogues, selexipag is an agonist of prostacyclin receptors. However, this drug is pharmacologically more stable and can be taken orally twice a day. In a phase III trial, selexipag improved the results in the 6-minute walk test and the number of complications associated with PAH compared with placebo (Sitbon et al., 2015). However, there were no differences in functional status after 26 weeks of therapy (Sitbon et al., 2015).

In addition to the treatments mentioned before, for people who respond to a vasodilation challenge during right heart catheterisation, **calcium channel blockers** are recommended. However, the proportion of responders amongst people with PAH is low, particularly with long-term therapy (Sitbon et al., 2015). Calcium channel blockers improve hemodynamic parameters,

functional capacity and survival (Sitbon et al., 2015). However, this therapy needs to be carefully monitored due to the risk of systemic hypotension (Rose-Jones & McLaughlin, 2015).

9.4.7.1.3 Step 3: Review of the treatment strategy with institution of a combination of drugs and/or proposal to lung transplantation

Combination therapy, or the use of two or more classes of drugs at the same time, is increasingly recommended based on encouraging results from multiple trials (Galie et al., 2016). Combined treatments targeting different pathways are more likely to achieve greater symptomatic improvement (Galie et al., 2016). Interestingly, all the currently available drugs focus on increasing vasodilation and reducing cellular proliferation. Despite the increasing evidence suggesting that inflammation and immunity are key features of PAH, there are still no effective drugs targeting these mechanisms.

Atrial septostomy is a highly selective procedure reserved for people with end-stage PAH, who exhibit severe syncopal symptoms or are awaiting lung transplantation (Sandoval et al., 1998). Atrial septostomy improves clinical symptoms, including chronic breathlessness, and improves exercise endurance (Reichenberger et al., 2003; Sandoval et al., 1998).

Pulmonary transplantation is indicated for selected patients who fail to improve on standard medical treatment for PAH. However, low availability of organ donors and delays in referral limit the number of people who are able to receive a transplant (Galie et al., 2016).

9.4.7.2 Non-pharmacological treatments

As in other conditions causing chronic breathlessness, pulmonary rehabilitation and supervised exercise programs are beneficial for people with PAH, leading to important improvements in functional capacity and quality of life (Grünig et al., 2012; Koudstaal et al., 2018; Missana et al., 2020). Other non-pharmacological treatments for chronic breathlessness are detailed in Chapter 2. Of note, most non-pharmacological interventions recommended for chronic breathlessness

were tested in populations with more common causes of chronic breathlessness. It is not clear whether such treatments would achieve similar results in people with PAH. However, given some of the common mechanisms underlying chronic advanced disease (i.e., inflammation, skeletal muscle dysfunction, sympathetic activation), it is likely that some of the treatments would be effective in the PAH context.

9.4.7.3 Pharmacological treatment of chronic breathlessness associated with PAH – the role of regular, low-dose, sustained-release oral morphine

Despite the multiple therapeutic options available for PAH, 25% of the patients with PAH will not experience symptomatic improvement (Sajkov et al., 2010). For the 75% of people who do, PAH is likely to progress over time with development of increasing and persisting breathlessness, despite disease-specific treatments. For patients in NYHA III and IV, there is a point at which no other treatments are available to change the clinical course of their PAH. Therefore, other therapies, directed at improving the symptomatic burden of breathlessness need to be considered. Regular, low-dose, sustained-release oral morphine is recommended for chronic breathlessness that cannot be alleviated with the strategies mentioned above. However, such recommendations are based on clinical trials that included predominantly people with COPD and cancer (Johnson et al., 2013b). It is not clear if regular, low-dose, sustained-release oral morphine would be equally effective in people with chronic breathlessness associated with PAH. Theoretically, regular, low-dose, sustained-release oral morphine could be of benefit primarily by modulating the central perception of breathlessness (Sgherza et al., 2002). Importantly, considering the lack of palliative strategies for the reduction of chronic breathlessness in this population, the effectiveness of regular, low-dose, sustained release morphine ought to be investigated in this context.

9.5 Aim and objectives

The aim of this sub-study was to assess the effects of once-daily, regular, low-dose, sustained-release oral morphine for chronic breathlessness associated with PAH.

The objectives of this sub-study were to evaluate whether once-daily, regular, low-dose, sustained-release oral morphine:

- Reduced the intensity of breathlessness;
- Reduced functional impairment due to chronic breathlessness;
- Had an acceptable safety profile; and
- Improved perceived quality of sleep.

9.6 Methods

9.6.1 Study Design and Setting

This was a multi-site, randomised, placebo-controlled, double-blind, crossover study conducted between March 2009 and December 2016. Participants were recruited from both outpatients and inpatients units from two Australian health-care centres: Southern Adelaide Palliative Services in South Australia and Austin Health in Victoria.

9.6.2 Participants

Eligible participants (i) were aged 18 or older, (ii) had a diagnosis of PAH based on the World Health Organisation Classification (Simonneau et al., 2004); (iii) had breathlessness despite optimally treated PAH, as judged by the participant's respiratory physician; (iv) had secondary heart failure class III or IV based on the New York Heart Association function classification (New York Heart Association, 1979); (v) had a calculated creatinine clearance of more than 10 mls/min, calculated using the MDRD equation (Levey et al., 1999); (vi) had optimised haemoglobin levels (haemoglobin of at least 10 g/dL, or the treating clinician had reviewed the haemoglobin result and confirmed the participant was on maximal treatment); (vii) was on stable medication over the previous seven days, including oxygen supplementation; (viii) was able and willing to complete the study diary; and (ix) able and willing to provide informed consent. Optimal treatment was assessed on a case-by-case basis and included treatment with a dual endothelin antagonist and/or

a phosphodiesterase inhibitor at the time the patient was being assessed for participation on trial. Of note, the disease-specific treatment of PAH has evolved over the years in which the study was open for recruitment. All people were given the best treatment available at the time they were assessed to participate in the study.

Exclusion criteria were (i) on regular opioid medication; (ii) known hypersensitivity to morphine or any of the morphine sulphate capsules components; (iii) central hypoventilation syndrome that could potentially be aggravated by opioids; (iv) use of monoamine oxidase inhibitors in the previous two weeks, or proposed use during the study; (v) AKPS of less than 50 corresponding to requiring “considerable assistance and frequent medical care” (Abernethy et al., 2005) at the time the patient was being assessed for participation on trial; (vi) cognitive impairment, defined by a Mini-mental State Examination score of less than 24 out of 30 at baseline (Folstein et al., 1975); (vii) uncontrolled nausea or vomiting, or evidence of gastrointestinal obstruction; (viii) pregnancy or breastfeeding; and history of opioid misuse.

9.6.3 Interventions

Each participant was randomised to one week of once-daily, regular, low-dose, sustained-release oral morphine 20 mg or one week of placebo. This was followed by a washout period of one week. In the third week, participants received the treatment they had not taken initially (i.e., placebo or regular, low-dose, sustained-release oral morphine 20 mg). Blinded docusate and senna was offered as prophylaxis against constipation, which is a frequent side effect of opioids. Additional doses of open-label docusate and senna were made available for all participants to take as needed throughout the study.

9.6.4 Outcomes

This study was designed before the NRS was established as the preferred unidimensional measure of breathlessness in clinical trials and before *worst breathlessness in the previous 24 hours* was

defined as the NRS breathlessness measure that is more sensitive to change and more meaningful for participants (Johnson et al., 2016; Lovell et al., 2019). As a result, this primary outcome of this study was the difference in self-rated mean intensity of *breathlessness right now* on the last three days of each treatment. Intensity of breathlessness *right now* was collected using the VAS for breathlessness (Gift, 1989) and scores were collected separately for morning and evening to evaluate the possibility of end-of-dose failure (Hall & O'Lenic, 2012). This choice of primary outcome reflected the best knowledge in the field of chronic breathlessness at the time the study was designed.

Secondary outcomes included between-treatment differences in the following measures:

- *Average* and *worst* breathlessness in the previous 24 hours, rated using the VAS for breathlessness (measured in the evening only) (Gift, 1989);
- Level of exertion achieved before being limited by breathlessness, measured with the self-rated mMRC scale for breathlessness (Bestall et al., 1999; Stenton, 2008);
- Self-rated quality of sleep measured using a four-item Likert scale and breathlessness impact on sleep using a dichotomous (i.e., yes/no) rating (Martins et al., 2016);
- Safety measures including respiratory rate, oxyhaemoglobin saturation, and end-tidal carbon dioxide levels ($EtCO_2$); and
- Frequency and severity of harms using the five-point National Cancer Institute Common Terminology Criteria of Adverse Event reporting version 3.0 (Trotti et al., 2003).

9.6.5 Randomisation

A computer number generator was used to randomise the participants in blocks of four with an equal allocation ratio. The Southern Adelaide Health Service clinical trials pharmacist was responsible for the randomisation, which was double-blind, ensuring that both participants and health-care providers were unaware of the treatment being administered. There was no contact

between clinical-trials pharmacists and participants and the medication was dispensed in accordance with the randomisation schedule.

Medications were dispensed weekly in order to prevent mistakes (i.e., taking the active medication in the placebo week or the other way around). The medication was supplied in two separate bottles, one containing the study medication (i.e., morphine or placebo) and a second one containing the laxative or the placebo laxative.

9.6.6 Ethics approval

Ethics approval was obtained from the Flinders Clinical Research Ethics Committee (No. 253/08, date 25/02/2009) and the Austin Health Human Research Ethics Committee, and the trial was registered (ACTRN12609000209291) before recruitment commenced (Appendix 31).

9.6.7 Sample size considerations

The original sample size calculation for this study was estimated based on a previous crossover trial in which 38 participants with different aetiologies of breathlessness provided sufficient statistical power to detect a treatment effect of regular, low-dose, sustained-release oral morphine on the intensity of breathlessness (Abernethy et al., 2003). This study analysis has shown that the treatment sequence interaction was not significant (P = 0.27); thus, a linear mixed model was fitted with treatment (morphine vs. placebo), sequence (morphine-placebo vs. placebo-morphine), and time of day (AM vs. PM) as independent variables (Abernethy et al., 2003). The residual within-subject variance was 82.8, and the estimated treatment effect was 3.7 mm, with a 95% CI of 0.8 - 6.6 mm. To allow for sampling variability, the one-sided upper 95% confidence interval of the within-subject variance was calculated using the bootstrap (2000 replications) and it was found to be 112.0. This would provide a CI for the treatment effect having an approximate width of 7 mm. Assuming that variability of breathlessness scores was broadly similar in the present population, it was estimated that 50 participants would provide 80% power

to detect a 7 mm difference in the VAS with an alpha of 0.05, allowing for 20% dropout rate as a clinically detectable difference (Johnson et al., 2013a).

9.6.8 Statistical analysis

SPSS 23.0 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, version 23.0, Armonk, NY: IBM Corp.) was used to conduct descriptive statistics describing the flow of participants throughout the study, the baseline characteristics of the sample, and breathlessness scores. Because this study did not recruit to target, the analysis was modified to inform about progression to a phase III trial. As a result, this study was analysed as an early phase study, following the recommendations proposed by Cocks & Togerson (2013).

By the time this study was analysed, the minimally clinically important difference in the intensity of chronic breathlessness had been defined as an absolute difference of 9mm in the VAS (Johnson et al., 2013a). Given the difficulties with recruitment, the aim became to determine if regular, low-dose, sustained-release oral morphine 20mg was likely to achieve a reduction of 9mm in the VAS for *breathlessness right now* in both morning and evening, which is equivalent to an effect size of approximately 0.4 (Johnson et al., 2013a). For an effect size of 0.4, a sample size of 186 ($1-\beta=0.8$, $\alpha=0.05$) would be required in a fully powered parallel-arm trial, which corresponds to an approximately sample size of 18 in a parallel-arm pilot study (Cocks & Torgerson, 2013). Assuming that there is less variability in breathlessness scores in a crossover study, the sample included in the present study (19 participants) would be adequate.

Cohen's *d* effect sizes for the difference between the two treatments were calculated for the primary endpoint and additional breathlessness measures. The one-sided 80% CIs of the effect sizes were examined to determine whether they excluded an effect size of zero or less (i.e., favouring placebo), which would suggest that a fully powered trial would be unlikely to detect a

statistically or clinically significant difference (i.e., an advantage of 9 mm for the morphine treatment).

This study used a modified intention-to-treat analysis for crossover studies. In parallel-arm studies, intention-to-treat analyses ensure that all randomised participants are included in the statistical analysis according to the arm they were originally assigned (McCoy, 2017). In crossover studies, some participants withdraw before completing the second intervention period, preventing comparison between interventions (Mills et al., 2009). In this crossover study, only participants providing sufficient data for both intervention periods were included in this study analysis. This study is reported based on the CONSORT criteria (Moher et al., 2010).

9.7 Results

9.7.1 Recruitment and retention

Of 50 people assessed formally between March 2009 and December 2016, nine were already taking opioids, nine were unwilling to participate in this study and eight were not eligible for other reasons, such as advanced disease states or poor functional status. Twenty-three participants (46%) were eligible and randomised. Four participants withdrew, all while taking regular, low-dose, sustained-release oral morphine (Table 9.2). Of those, three participants stopped the study due to common harms attributable to morphine (nausea, vomiting, drowsiness) and one participant stopped the study due to lethargy. Nineteen participants completed both treatment periods and were included in the analysis (Figure 9.1).

Table 9.2 - Reasons for withdrawal of four participants from the study

Participant	Treatment on day of withdrawal	Reason for withdrawal	Attribution
1	Morphine	Dizziness and vomiting	Probable
2	Morphine	Nausea and vomiting	Probable
3	Morphine	Drowsiness and confusion	Probable
4	Morphine	Lethargy and accelerated worsening of performance	Possible

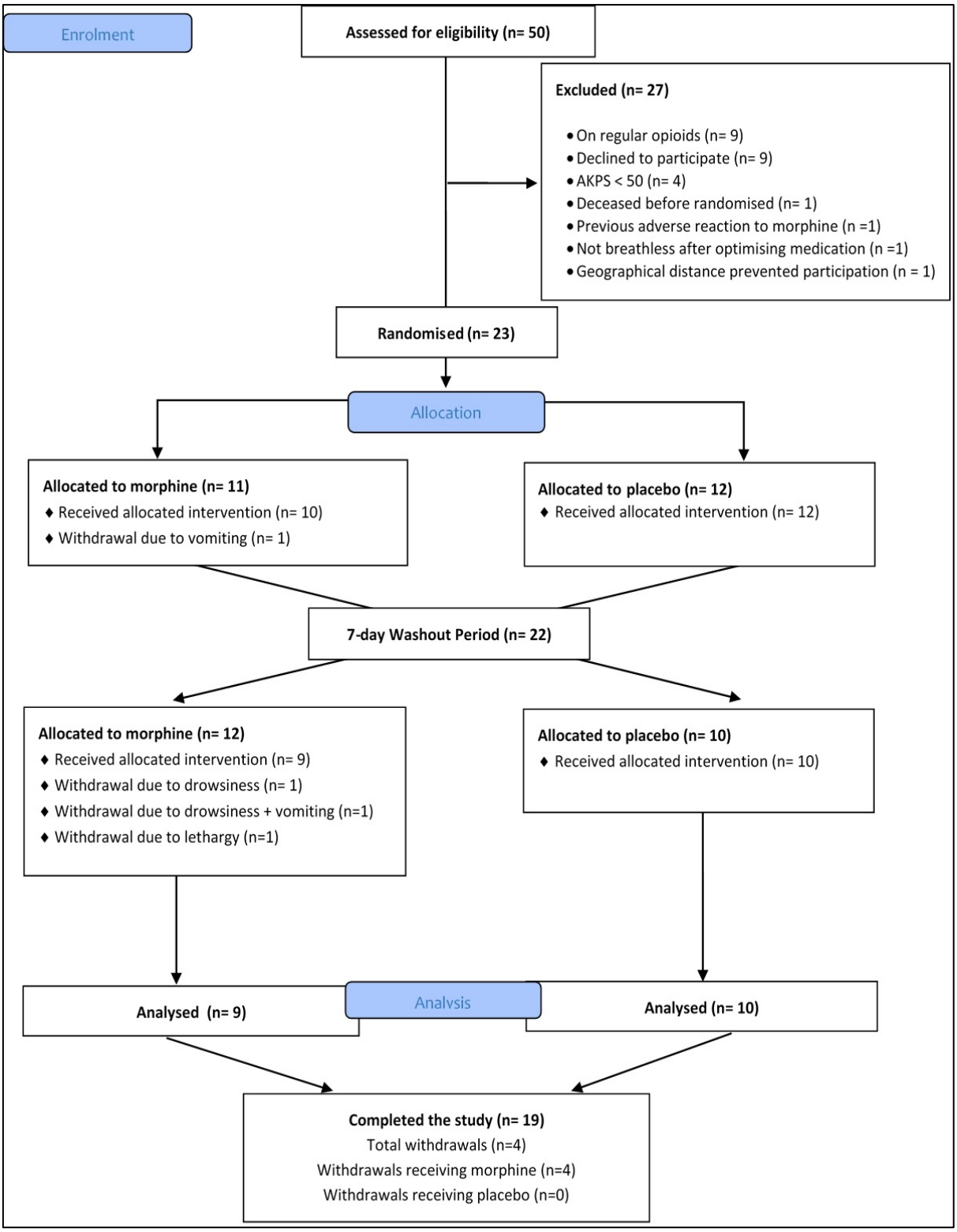

Figure 9.1 - Flow of participants in the crossover study

9.7.2 Study population

Participants (n=23) were mainly overweight or obese elderly women. Seven were on supplemental oxygen. Most participants (84%) had idiopathic PAH. More than half of the participants (65%) were unable to carry on normal activity or do active work (AKPS ≤ 70; Table 9.3).

Table 9.3 - Screening characteristics of participants (n=23). Values are mean ± standard deviation or median (IQR) unless stated otherwise; BMI (Body mass index)– Kilograms (Kg)/Square meter(m^2).

Characteristics	
Age (years)	64 ± 11
Male Gender	n=7 (30%)
BMI (Kg/m^2)	30 ± 6.0
Australia-modified Karnofsky Performance Status	70 (60 – 80)
90 – Able to carry on normal activity; minor signs or symptoms of disease	n=3 (13%)
80 – Normal activity with effort; some signs or symptoms of disease	n=5 (22%)
70 – Cares for self; unable to carry on normal activity or to do active work	n=9 (39%)
60 – Able to care for most needs; requires occasional assistance	n=4 (17%)
50 – Considerable assistance and frequent medical care required	n=2 (9%)
Diagnosis	
Idiopathic PAH	n=16 (84%)
PAH associated with connection tissue disease	n=3 (16%)
Proportion receiving supplemental oxygen	n=7 (30%)
Rate of oxygen delivery (l/min)	2.3 ± 0.95
Charlson Index - age adjusted	3.8 ± 1.7
Respiratory rate (breaths/min)	21 ± 5
Oxyhaemoglobin saturation (%)	95 (92-97)
End tidal CO_2 (mmHg)[a]	26 ± 7
Baseline breathlessness “right now” – morning (mm on VAS)	38 ± 23
Baseline breathlessness “right now” – evening (mm on VAS)	37 ± 22
Baseline average breathlessness previous 24 hours (mm on VAS)	44 ± 21
Baseline worst breathlessness previous 24 hours (mm on VAS)	61 ± 20

[a]*Measured with a portable capnography device during quiet breathing*

9.7.3 Breathlessness measures

Considering the last three days of each treatment, mean breathlessness scores for breathlessness *right now* were *higher* with regular, sustained-release oral morphine 20mg compared with placebo both for morning [mean (M) ± standard deviation (SD) 31.7 ± 25 mm vs. 26.9 ± 22 mm] and evening (M±SD 33.5 ± 28 mm vs. 25.6 ± 21 mm). Similarly, breathlessness scores were higher with regular, sustained-release oral morphine 20mg for *average breathlessness* in the previous 24 hours (M±SD 43.7 ± 26 mm vs. 38.7 ± 24 mm) and *worst breathlessness* in the previous 24 hours (M±SD 55.6 ± 27 mm vs. 51.2 ± 23 mm; Table 9.4). Figure 9.2 shows the mean breathlessness scores for the seven days on each treatment. Participants mMRC scores on the last day of each

treatment were not different between regular, sustained-release oral morphine 20mg [median (IQR) 2 (1 – 3)] and placebo [median (IQR) 2 (1 – 3)].

Table 9.4 - Sustained-release (SR) morphine 20mg compared with placebo scores on the intensity of breathlessness in the last 3 days of each treatment period.

	Breathlessness Intensity (VAS score in mm)[a]						
	SR Morphine 20mg (n=19)			Placebo (n=19)			Effect size of the group difference
	Mean	SD	95% CIs	Mean	SD	95% CIs	
Right Now - Morning	31.7	25	20.7 to 42.7	26.9	22	17.0 to 36.8	-0.22 (-0.6 to 0.2)
Right Now - Evening	33.5	28	20.5 to 46.5	25.6	21	16.2 to 35.0	-0.33 (-0.8 to 0.1)
Average - previous 24h	43.7	26	31.7 to 55.7	38.7	24	27.7 to 49.7	-0.20 (-0.7 to 0.2)
Worst - previous 24h	55.6	27	43.6 to 67.6	51.2	23	41.2 to 61.2	-0.29 (-0.7 to 0.1)

[a]Breathlessness is measured with the visual analogue scale (VAS) for breathlessness, with zero as "no breathlessness" and 100 as "worst possible breathlessness".

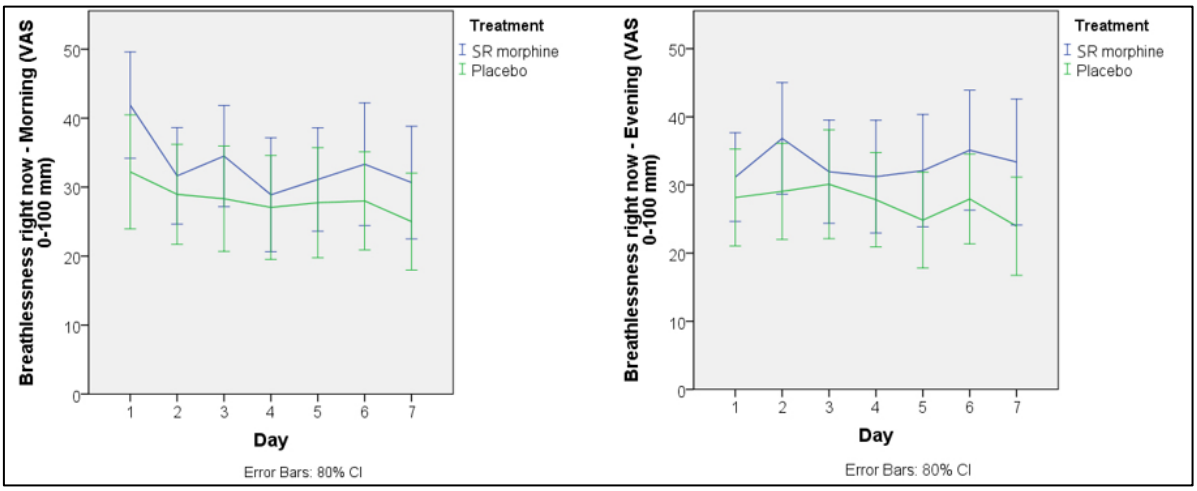

Figure 9.2 - Mean scores of breathlessness right now across the 7 days on each treatment, separated by morning and evening

9.7.4 Sleep

Most participants stated either *good* or *very good* quality of sleep whether they were on regular, sustained-release oral morphine 20mg or placebo. Six participants felt they had better sleep quality while on sustained-release oral morphine 20mg, three while on placebo and nine participants reported no difference between treatments. Only one participant in the morphine arm and two in the placebo arm stated that their sleep was disturbed by breathlessness.

9.7.5 Harms

Respiratory rate in breaths per minute (bpm) was lower with regular, low-dose, sustained-release oral morphine 20mg (M±SD 19.7 ± 5.3 bpm) compared with placebo (M±SD 21.4 ± 5.5 bpm), and $ETCO_2$ levels were higher with regular, sustained-release oral morphine 20mg (M±SD 30.8 ± 6.2 mmHg) compared with placebo (M±SD 28.5 ± 6.5 mmHg). Pulse oximetry was slightly lower with regular, sustained-release oral morphine (M±SD 92.6 ± 6.3% vs. 94.3 ± 2.9%; Table 9.5.

Table 9.5 - Comparison between respiratory rate, end-tidal carbon dioxide ($ETCO_2$) and pulse oximetry at the end of each treatment.

	Sustained-release morphine		Placebo		Effect size of the group difference (95% CI)
	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)	
Respiratory rate (bpm)[a]	19.6 ± 5.3	20 (15-24)	21.4 ± 5.5	22 (17-24)	**1.08 (0.4 to 1.8)**
$ETCO_2$ (mmHg)	30.8 ± 6.2	31 (27-33)	28.5 ± 6.6	28 (26-33)	**-0.83 (-1.5 to -0.2)**
Pulse oximetry (%)	92.6 ± 6.3	94 (90-96)	94.3 ± 2.9	95 (93-96)	**0.50 (-0.2 to 1.1)**

On the last day of each treatment, significantly more participants had nausea without alteration of the eating habits with regular, sustained-release oral morphine 20mg [(n=5 vs. n=1). Similarly, nine participants stated either occasional (n=6) or persistent (n=3) constipation with regular, sustained-release oral morphine 20mg, while no participant stated constipation with placebo (n=0; Figure 8.3).

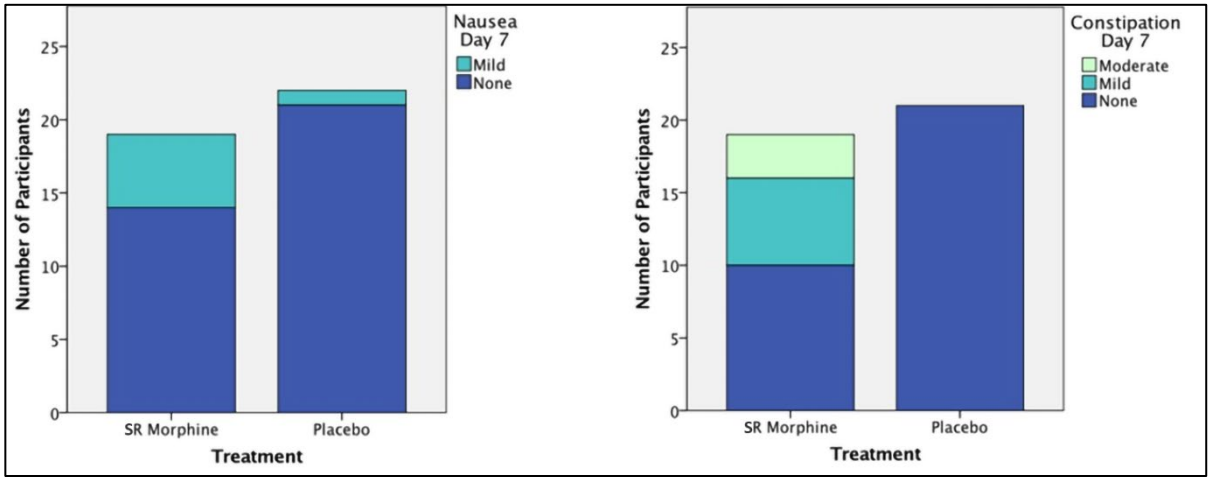

Figure 9.3 - Nausea and constipation after seven days with each treatment

Smaller differences were found for somnolence (regular, low-dose, sustained-release oral morphine n=11 vs. placebo n=9). Confusion was slightly higher with placebo (regular, low-dose, sustained-release oral morphine n=0 vs. placebo n=2). Vomiting was not reported with any of the treatments (Table 9.7).

Table 9.6 - Harms of morphine compared with placebo on Day 7. Values for sustained-release morphine and placebo are in absolute number of participants (percentages).

Harms (Day 7)	Sustained-release morphine (n=19)	Placebo (n=19)
Nausea	**5 (36%)**	**1 (5%)**
Vomiting	0 (0%)	0 (0%)
Constipation	**9 (47%)**	**0 (0%)**
Confusion	0 (0%)	2 (9%)
Somnolence	11 (58%)	**9 (41%)**

9.7.6 Clinical characteristics of people responding to regular, low-dose, sustained-release oral morphine

Of the 23 participants included in this study, 7 (30.4%) experienced a reduction in the primary outcome breathlessness *right now* (morning or evening) with regular, low-dose sustained-release oral morphine. Compared with those who did not respond, those who experienced a reduction in breathlessness were younger (mean age 57.9 years versus 66.6 years) and had more intense baseline breathlessness *right now* in the morning (mean breathlessness *right now* in the morning 48.1mm versus 34.0mm). There were no differences between groups in gender, AKPS, oxygen therapy, BMI, age-adjusted Charlson comorbidity index and other baseline VAS breathlessness scores.

9.8 Discussion

This was the first RCT evaluating regular, low-dose, sustained-release oral morphine for chronic breathlessness associated with PAH. Findings show that the direction and magnitude of effects favour placebo over regular, low-dose, sustained-release oral morphine in every important

outcome measure and that regular, low-dose, sustained-release oral morphine generated consistently more harms. In addition, recruitment was very challenging.

9.8.1 Recruitment and retention

Only 50 participants were formally assessed for this study during a period of more than seven years in two large university teaching hospitals. Of those, only 23 were eligible to participate, which highlights that successful recruitment occurred in less than 50% of cases. Significantly, the research team recruiting for this trial is one of the world-leading teams in chronic breathlessness clinical trials research and has repeatedly recruited successfully to similar populations in other conditions that cause chronic breathlessness. Thus, it is important to reflect on reasons why the recruitment was not successful. Firstly, PAH is a very rare disease (Wijeratne et al. 2018). Although both sites included in this trial are now categorised as PAH specialist centres with greater access to this population, current recommendations to refer all patients with PAH to such services only became available late in the recruitment period (Galie et al., 2016; Klinger et al., 2019). Secondly, despite the broad eligibility criteria, recruitment was limited by participants' performance status and previous exposure to opioids. Low performance status is an expected finding bearing in mind this population's age, disease severity and comorbidities. In addition, over the seven years the study was open for recruitment, robust evidence became available for the use of opioids in people with chronic breathlessness. Thus, it is unsurprising that some potential participants were already taking opioids before consideration for inclusion in the trial. However, inclusion of data coming from participants who were not opioid naïve or had very low performance status would skew the study analysis and, therefore, they were excluded.

9.8.2 Breathlessness

Although this study was unable to give a definitive answer on the efficacy of regular, low-dose, sustained-release oral morphine to reduce PAH-associated chronic breathlessness, there was no

favourable efficacy signal in the primary or secondary outcome measures. Importantly, all measures of breathlessness presented negative effect sizes demonstrating that placebo performed consistently better than regular, sustained-release oral morphine to reduce chronic breathlessness associated with PAH. In fact, considering one of the primary outcomes for this study - breathlessness *right now* in the morning – a sample size of 71,516 participants would be required in a large-scale trial to achieve a statistically and clinically significant difference between morphine and placebo in favour of morphine (Cocks & Torgerson, 2013). This contrasts with previously published studies of regular, low-dose, sustained-release oral morphine for chronic breathlessness in the setting of other aetiologies where modest sample sizes generated clinically and statistically significant differences (Abdallah et al., 2017; Abernethy et al., 2003; Ekstrom et al., 2015; Jennings et al., 2002). Such differences may be associated with different mechanisms of breathlessness underlying different diseases. Of note, the subgroup of people who responded to regular, low-dose, sustained-release oral morphine was younger and had higher baseline breathlessness compared with the subgroup of non-responders. Age and higher baseline breathlessness had been previously identified as predictors of response to opioid therapy for chronic breathlessness of other aetiologies (Johnson et al., 2013b). This study suggests that these factors may also influence response in the context of chronic breathlessness associated with PAH.

9.8.3 Potential pathophysiologic mechanisms

Regular, low-dose, sustained-release oral morphine seems to be particularly effective for chronic breathlessness associated with COPD (Abdallah et al., 2017; Abernethy et al., 2003; Ekstrom et al., 2015; Verberkt et al., 2020). It is possible that differences in the mechanisms of chronic breathlessness associated with COPD and PAH help to explain different responses to regular, low-dose, sustained-release oral morphine. Common mechanisms underlying PAH and COPD-associated breathlessness include dynamic hyperinflation with consequent changes in the lung/chest wall mechanics; increased physiologic dead space; inflammation; skeletal muscle

dysfunction and increased sympathetic drive (Dumitrescu et al., 2017; Farina et al., 2018; Vicenzi et al., 2016). Consequently, such mechanisms are unlikely to explain the differences in response to regular, low-dose, sustained-release oral morphine. However, there are recognisable differences between the two conditions. While PAH is characterised by increased chemoreceptor sensitivity and consequent hyperventilation (Farina et al., 2018), COPD is associated with low ventilatory responses to CO_2 (Scano et al., 1995; Van de Ven et al., 2001). Enhanced chemoreceptor sensitivity in PAH may trigger high afferent signalling to cortical and sub-cortical centres involved in chronic breathlessness perception, even with minor physiological stimuli (Farina et al., 2018). Thus, it is possible that people with PAH experience more frequent and/or more intense breathlessness than people with COPD. However, it is also important to note that people with COPD commonly present with lung hyperinflation, which may restrict their capacity to increase their ventilation in response to progressive increases in CO_2. Thus, it is still unclear whether people with COPD have blunted chemoreceptor activity or just a mechanic incapacity to increase ventilation despite chemoreceptor reactivity.

Inflammation is a hallmark of both PAH and COPD. Local inflammation in both PAH and COPD stimulates C-fibre receptors, which may cause breathlessness. Importantly, airway inflammation predominates in COPD while arterial inflammation dominates in PAH. While μ-opioid receptors predominate in the lung, k-opioid receptors are more abundant in the pulmonary arteries (Zhou et al., 2017). It is possible, although not tested, that different therapeutic opioids with higher affinity for k-opioid receptors (e.g., oxycodone) would have achieved larger breathlessness reductions. Of note, oxycodone was recently evaluated in a population with COPD as the predominant cause of chronic breathlessness, for whom it seems to be ineffective to reduce chronic breathlessness, causing more harms (Ferreira et al., 2020). These results may further contribute to the hypothesis that different local opioid receptors are involved in different conditions. However, the therapeutic

effect of oral opioids for chronic breathlessness seems to be largely due to their central, rather than peripheral action (Currow et al., 2019; Mahler et al., 2009). As a result, this study raises the hypothesis that the central mechanisms of chronic breathlessness may differ between COPD to PAH. These potentially different mechanisms need to be investigated in future studies.

Overall, PAH seems to share multiple mechanisms of chronic breathlessness with congestive heart failure (Dumitrescu et al., 2017), for which the effectiveness of regular, low-dose, sustained-release oral morphine has not yet been established. A recent phase III RCT comparing regular, sustained-release oral morphine 20mg with placebo for chronic breathlessness associated with congestive heart failure did not show significant differences in breathlessness scores after four weeks of therapy (Johnson et al., 2019). Although this study did not recruit to target, there were more harms in the morphine arm leading to more withdrawals (Johnson et al., 2019). These results may suggest that shared mechanisms between congestive heart failure and pulmonary arterial hypertension, may contribute to unresponsiveness to morphine and higher susceptibility to harms.

Based on the mechanisms described above, the question that arises here is whether the morphine doses offered by these trials are too low to produce a symptomatic benefit in people with PAH or chronic heart failure. However, many people experienced harms, which suggests that morphine is probably ineffective in these participants and that increasing the doses would only increase toxicity. Thus, different responses to regular, low-dose, sustained-release oral morphine seem to reflect that not all chronic breathlessness is the same, challenging findings from almost a decade ago and current assumptions in the chronic breathlessness field (Johnson et al., 2013b).

9.8.4 Toxicity and withdrawals

A key finding from this study was that harms such as nausea and constipation occurred more frequently with regular, low-dose, sustained-release oral morphine than placebo at the end of the

intervention period. Interestingly, while constipation is a common long-term effect of therapeutic opioids, nausea is usually reported only over the first few days of therapy and tends to disappear with therapy continuation. The fact that nausea remained present after seven days of regular, low-dose, sustained-release oral morphine contrasts with other studies published so far (Abernethy et al., 2003; Oxberry et al., 2013) and suggests a detrimental effect of regular, low-dose, sustained-release oral morphine in the population with PAH. Additionally, all study withdrawals occurred during the treatment period with regular, low-dose, sustained-release oral morphine and were likely related to this medication (Ferreira et al., 2016). Of note, there were no cases of major respiratory depression, which is in line with the results of previous studies showing no evidence of clinically significant respiratory depression in people with chronic breathlessness treated with regular, low-dose opioids (Currow et al., 2020; Johnson et al., 2020; Verberkt et al., 2020). This finding contributes to strengthen the idea that small doses of regular, sustained-release oral morphine do not pose a life-threatening risk for people with respiratory disease.

9.8.5 The role of obesity

The population included in this study were mainly elderly women who were overweight or obese. Although this is not necessarily the typical PAH population, PAH is increasingly diagnosed in elderly people and the prevalence is higher in females (Hoeper & Gibbs, 2014; Hoeper et al., 2013b). However, it is not clear whether this profile matches the clinical characteristics of people more affected by PAH-associated chronic breathlessness. Nevertheless, these findings should be interpreted according to the population considered.

Previous work has demonstrated that obesity is associated with more severe chronic breathlessness (Currow et al., 2017). Obesity is likely to contribute to chronic breathlessness by different mechanisms including decreased lung compliance, decreased lung volumes, reduced diffusion capacity, increased workload on intercostal muscles, and higher chances of sleep

disorder breathing (Costa et al., 2016; El-Gamal et al., 2005; Jensen et al., 2009). Thus, it is possible that any potential benefits produced by regular, low-dose, sustained-release oral morphine may have been tampered by the multiple detrimental effects induced by obesity on the respiratory system. The influence of obesity on response to regular, low-dose, sustained-release oral morphine for chronic breathlessness needs to be explored in future research.

9.8.6 Strengths and limitations

This was the first randomised, placebo-controlled study investigating the effectiveness of regular, low-dose, sustained-release oral morphine for chronic breathlessness associated with PAH. The study was rigorously conducted and used validated outcome measures. Given the magnitude and direction of signal favouring placebo in every measure of breathlessness, higher chance of harms in the morphine arm, and the calculated sample size required for an adequately powered study, this study clearly contra-indicates the progression to a phase III study. Recruitment for this study occurred over a period of seven years. Pharmacological treatments targeting the underlying mechanisms of PAH evolved considerably during this time period, and participants recruited in the later stages of this study were offered considerably more therapeutic options before enrolling. As a result, time may have been a significant factor influencing results. Despite not reaching target recruitment, it is unlikely that the results would have been different if the pre-planned sample size had been achieved. This study included mostly women, who were obese. It is unclear if results would have been different for a different population. Breathlessness measurement was not standardised for level of exertion, and it is unclear if daily activity levels increased with the administration of regular, low-dose, sustained-release oral morphine. However, contrary to other studies of regular, low-dose, sustained-release oral morphine, there was a consistent worsening in every measure of breathlessness after morphine and an increase in harms. Additionally, as detailed in Chapter 4, patients are likely to constantly exert to their limits to compensate for the limitations imposed by chronic breathlessness (both before and after the introduction of new

medications). Thus, it is unlikely that they would engage in activities inducing higher levels of breathlessness after the introduction of morphine.

9.8.7 Implications for future research

The major research direction from this study is to understand the pathways for the perception of breathlessness in people with PAH given the very different results to all other studies conducted until now. This also requires careful review of data from studies to date that include heterogeneous aetiologies of breathlessness. These should be re-analysed with and without people with PAH to understand the net effect when those with PAH are excluded.

9.8.8 Implications for clinical practice

Results from this sub-study have major clinical implications. Up until recently, evidence suggested that regular, low-dose, sustained-release oral morphine would be effective to reduce chronic breathlessness of multiple aetiologies. Based on findings from this study, regular, low-dose, sustained-release oral morphine may not offer benefit to people with PAH, particularly to obese elderly women. It is recommended that clinicians exercise caution in prescribing regular, low-dose, sustained-release oral morphine to this population. When it is effective, regular, low-dose, sustained-release oral morphine is likely to produce a clinical response in the first 24 to 48 hours after initiating therapy (Currow et al., 2013). Considering that this study is insufficient to prove lack of benefit, some people may benefit from a short trial of regular, low-dose, sustained-release oral morphine to examine if they derive benefit without significant harms. This is a reasonable option, given that this medication seems to be safe in people with respiratory disease, including PAH.

9.9 Conclusions

This first study of regular, low-dose, sustained-release morphine for PAH-associated chronic breathlessness does not support the progression for a large phase III randomised-controlled trial

given the rate of recruitment, lack of a signal for improvement with morphine and the quantified potential for harms. These findings also raise the hypothesis that PAH may be the first diagnostic group with a type of chronic breathlessness unresponsive to regular, low-dose, sustained-release oral morphine. Understanding the underlying mechanisms of PAH-associated chronic breathlessness and people's response to morphine therapy is key for future research.

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CHAPTER 10 - CONCLUDING DISCUSSION

10.1 Chapter preface

The aim of this programme of research was to explore aspects related to the safety and effectiveness of regular, low-dose, sustained-release oral morphine for chronic breathlessness. This chapter highlights and integrates the main findings from the six studies described in Chapters 4 to 9, highlighting original and significant contributions to current knowledge and discussing findings in the context of the broader literature. These main findings from the thesis are divided into the following areas:

1) The lived experience of severe chronic breathlessness associated with COPD;
2) The lived experience of initiating and continuing regular, low-dose, sustained-release oral morphine for the symptomatic reduction chronic breathlessness associated with COPD
3) Safety of regular, low-dose, sustained-release oral morphine for severe chronic breathlessness associated with COPD in everyday life;
4) Effectiveness of low-dose, sustained-release oral morphine for severe chronic breathlessness; and
5) Challenges in conducting research in populations with severe functional impairment due to chronic breathlessness.

This chapter concludes with suggestions for future research directions in the field of chronic breathlessness.

10.2 The lived experience of severe chronic breathlessness associated with COPD

Within this programme of research, Sub-study 1 (Domain 1 – experiences of chronic breathlessness) described the context in which regular, low-dose, sustained-release oral morphine was being introduced and continued. The aim was to understand what life was like for patient-

carer dyads before the introduction of regular, low-dose, sustained-release oral morphine for chronic breathlessness associated with COPD, so that changes experienced with the study medication would also be more readily recognised and understood.

While there were multiple studies exploring the experiences of chronic breathlessness of patients and carers individually (Gysels et al., 2007; Hutchinson et al., 2018), Sub-study 1 (Domain 1 – experiences of chronic breathlessness) adds to current knowledge by describing how patients and carers *coexist* and *respond* to the shared circumstances of severe chronic breathlessness associated with COPD. Consequently, this sub-study identified both individual and shared vulnerabilities, which may require individual and joint therapeutic interventions. For example, an important finding from this sub-study is that both patients and their carers experience the breathing, thinking and functioning cycles of chronic breathlessness, described by the breathing-thinking-functioning model of chronic breathlessness (Spathis et al., 2017). Dealing with daily fluctuations in breathlessness (*breathing*), experiencing anxiety associated with acute-on-chronic breathlessness (*thinking*) and the shrinking of their physical and relational world (*functioning*) describes the lived experience of both patients and, both separately and together, their carers. However, carers describe an *intense* and *continuous experience of fear and concern*, while patients described they had learnt to adapt to their condition and would only experience fear in situations of sudden and unpredictable breathlessness. From a practical point of view, these findings concur with previous research suggesting that intervention plans for chronic breathlessness should also encompass carers (Farquhar, 2017). Moreover, developing interventions that are specific for carers may reduce their anxiety relating to chronic breathlessness and their ability to cope with this syndrome (Farquhar, 2016; Farquhar et al., 2017).

Previous work had demonstrated that chronic breathlessness had an extensive impact on patients' and carers' daily lives, forcing them to re-structure their routines around chronic breathlessness

(Ek et al., 2011; Gabriel et al., 2014). This study adds to these findings by describing that patients and carers work as a team to optimise function for each person in the dyad, but also *for the dyad as a whole*. These goals are achieved by creating a new dynamic in which patients try to be as active as possible and carers reduce their levels of activity so the patient can keep up. As a result, targeting the dyad *as one entity* in the treatment of chronic breathlessness may be of benefit.

Findings from Sub-study 1 (Domain 3 – self-reported driving) highlight driving as one of the most important daily activities for some people with chronic breathlessness and their carers, because it promotes independence and facilitates mobility in people who are already severely restricted in their daily lives (Kochovska et al., 2020). Given the dynamic imposed by chronic breathlessness within the dyad, it is also likely that any independence achieved or maintained by patients benefits carers (Bergs, 2002; Ferreira et al., 2020b). Importantly, although both patients and carers reported that chronic breathlessness does not seem to affect patients' ability to drive, some patients reported that acute-on-chronic breathlessness does affect their concentration on the road. These findings are important because they highlight that, for some people with chronic breathlessness, driving can be one of the few activities they are able to maintain and the vehicle to facilitate their engagement with the world. Thus, in some cases, clinicians' goals should include optimising people's capacity to drive, which may involve treating breathlessness, while considering potential effects of interventions for the symptomatic reduction of chronic breathlessness on driving.

10.3 The lived experience of initiating and continuing regular, low-dose, sustained-release oral morphine for the symptomatic reduction of chronic breathlessness associated with COPD

Sub-study 1 (Domain 2 – perceptions of regular, low-dose, sustained-release morphine) explored patients' and carers' experiences with regular, low-dose, sustained-release oral morphine for the symptomatic reduction of chronic breathlessness associated with COPD. The study design allowed

participants to express freely enhancing, for the first time, a deeper understanding of the experience of taking this medication. It also allowed identifying barriers related to taking regular, low-dose, sustained-release oral morphine for chronic breathlessness that were relevant to patients and carers but unintentionally downplayed by clinicians and researchers.

One particularly important finding of Sub-study 1 (Domain 2 - perceptions of regular, low-dose, sustained-release morphine) is that breathlessness reduction is insufficient to influence people's choice of continuing regular, low-dose, sustained-release oral morphine for chronic breathlessness, particularly if any harms are experienced. In reality, the concept of "net effect" (i.e., perceived effect after weighing benefits and harms) is more likely to explain people's preferences for continuing regular, low-dose, sustained-release oral morphine long term. These findings are aligned with a previous pooled data analysis suggesting that participants' preference for regular, low-dose, sustained-release oral morphine over placebo is driven not only by the magnitude of breathlessness reduction but also by any harms experienced (Ferreira et al., 2016). However, this sub-study adds to previous research by identifying functional improvement, rather than intensity of breathlessness *per se*, as a major driver for wanting to take regular, low-dose, sustained-release oral morphine. These findings are consistent with findings from Domain 1 (experiences of chronic breathlessness) and previous qualitative work describing the importance of independence and function for people with chronic breathlessness associated with COPD (Ferreira et al., 2020b; Gysels et al., 2007; Gysels & Higginson, 2010). Additionally, these findings suggest that there is interest in using measures of function as the main outcomes in randomised controlled trials evaluating opioids for chronic breathlessness. In fact, it is interesting to note that most phase III studies using unidimensional measures of intensity of breathlessness as the primary outcome measures (e.g., NRS, VAS scores) failed to demonstrate that regular, low-dose, sustained-release oral morphine reduces chronic breathlessness (Currow et al., 2020; Johnson et al., 2019).

However, the only study using a multidimensional outcome measure (which included questions about function) as the primary outcome showed that regular, low-dose, sustained-release oral morphine was significantly superior to placebo (Verberkt et al., 2020). The best outcome measures for people with chronic breathlessness need to be further explored in future studies. Importantly, patients' functional improvement also seems to benefit carers.

In fact, it is possible that patients and carers have the perception of both *individual* and *collective benefit*, further increasing the likelihood of choosing to continue regular, low-dose, sustained-release oral morphine long term. The dyadic experience with this medication needs to be investigated in future qualitative studies.

Sub-study 1 (Domain 2 - perceptions of regular, low-dose, sustained-release morphine) also highlighted the existence of selected individuals who seem to experience larger reductions in symptomatic breathlessness with regular, low-dose, sustained-release oral morphine, translating into significant improvements in their mobility and independence. Importantly, previous RCTs have been shown what appears to be a more modest average signal for breathlessness reduction, suggesting that most people do not experience responses of this magnitude (Currow et al., 2020; Johnson et al., 2019; Verberkt et al., 2020). Factors contributing to this pattern of response with regular, low-doses sustained-release oral morphine in these participants are not clear. However, studying a larger group of people experiencing functional improvement with regular, low-dose, sustained-release oral morphine may shed some light on this issue.

Another key finding of Sub-study 1 (Domain 2 - perceptions of regular, low-dose, sustained-release morphine) is that participants with carers were more likely to be taking regular, low-dose, sustained-release oral morphine after terminating their participation in the main trial. In the context of COPD, carers have been shown to facilitate patients' adherence to medication (Bourbeau & Bartlett, 2008), which suggests they may not only be a care recipient but *also a*

potential co-worker with clinicians (Stajduhar et al., 2008). Findings from this sub-study concur with previous work and findings from Domain 1 (experiences of chronic breathlessness) by suggesting that carers are essential to manage chronic breathlessness and facilitate coping with harms induced by the medication (Ferreira et al., 2020b). Thus, it is likely that having a supportive carer contributes to having a better experience with regular, low-dose, sustained-release oral morphine, which warrants exploration in future studies.

Finally, in Sub-study 1 (Domain 3 – self-reported driving) the potential impact of regular, low-dose, sustained-release oral morphine on driving emerged as a major concern for some patients and carers, which highlights the importance of investigating whether these patients are able to drive safely.

10.4 Safety of regular, low-dose, sustained-release oral morphine for severe chronic breathlessness associated with COPD in everyday life

In Sub-study 1 (Domain 3 – self-reported driving), driving emerged as one of the most important daily activities for some people living with severe chronic breathlessness associated with COPD, which can potentially be affected both by chronic breathlessness and by therapy with regular, low-dose, sustained-release oral morphine. In this context, a previous systematic review had highlighted the heterogeneity of studies investigating the effects of therapeutic opioids on driving-related skills, and the importance of considering the person's context and the type and dose of opioid prescribed (Mailis-Gagnon et al., 2012). Based on these findings, Sub-study 2 (systematic review) adopted an original approach to this subject by carefully selecting the *type of studies* (reporting empirical data), *populations* (people with chronic pain or chronic breathlessness), *opioids* (therapeutic opioid agonists), and *outcomes* (driving-simulation, "real-world" driving, or driving outcomes) that would be relevant in the context of chronic breathlessness. Importantly, results from this systematic review flagged the complete absence of studies investigating the impact of regular therapeutic opioid agonists on driving-related skills of people with chronic

breathlessness. Moreover, only three studies were included in the final stage of this systematic review, all evaluating driving-simulation skills in people with chronic non-malignant pain (Galski et al., 2000; Menefee et al., 2004; Nilsen et al., 2011). Only one study was adequately powered to detect a difference in driving-simulation related outcomes and none was an RCT. As a result, another key finding of this systematic review was the scarcity of evidence for the impact of regular therapeutic opioid agonists (and certainly not regular *low dose* therapeutic opioids*)* on driving-related skills of people with chronic pain, a condition that exhibits some similarities with chronic breathlessness (i.e., affects similar populations and involves similar neural pathways) (Clark et al., 2014; von Leupoldt et al., 2009). These results are important indicating that there is a pressing need to conduct high quality prospective studies in this field, in order to better inform national and international guidelines, and support decision making in clinical practice.

Importantly, the limited number of studies of people with chronic non-malignant pain included in this systematic review suggested that stable doses of regular, therapeutic opioid agonists do not seem to cause any significant changes in driving-related psychomotor performance assessed by a driver simulator. These findings are aligned with previous studies suggesting that stable doses of opioids do not affect cognition or psychomotor performance in simple psychomotor tests (Bruera et al., 1989; Sjøgren et al., 2000). Studies included in the systematic review included a wide dose range, different short- and long-acting opioid formulations, and therapy had been stabilised for a period of weeks before enrolling. Based on these findings, it is possible that regular, low-dose, sustained-release oral morphine does not cause a substantial impact on the ability of people with chronic breathlessness to drive.

Another important finding of this systematic review was that more intense chronic pain may itself have a significant effect on driving skills. This is supported by previous evidence suggesting that there is a link between chronic pain and disruptions of attention and working memory (Dick &

Rashiq, 2007). However, all unpleasant sensations are likely to affect people's ability to concentrate to some degree. In this context, a previous cross-sectional study reported a close association between uncontrolled symptoms and perceived driving difficulties (Tuokko et al., 2007). Moreover, findings from Sub-study 1 (Domain 3 – self-reported driving) suggest that acute-on-chronic breathlessness affects people perceived ability to concentrate and drive safely (Ferreira et al., 2020a). Thus, it is important to ensure that people's symptoms are adequately monitored and controlled, given that they may have a greater impact on driving than stable doses of therapeutic opioid agonists.

Following this systematic review, Sub-study 3 (driving-simulation sub-study) was a hypothesis-generating study, exploring prospectively, for the first time, the impact of introducing regular, low-dose, sustained-release oral morphine in people with chronic breathlessness driving-related skills. Despite the very small number of participants included, there was a clear signal for worsening in driving-simulator outcomes 48 hours after initiating regular, low-dose, sustained-release oral morphine, which was not seen in the placebo arm. However, one week after initiating the study medication, driving outcomes were comparable to the baseline assessment, which suggests that while driving-related skills may potentially be affected by regular, low-dose, sustained-release oral morphine in the first few days of therapy, these effects subside quickly. There is a pressing need to investigate these findings in a future prospective study, given that people living with chronic breathlessness may be required to stop driving for long periods after initiating regular, low-dose, sustained-release oral morphine, which can negatively impact their health and wellbeing (Chihuri et al., 2016; Weir et al., 2017).

More importantly, there is interest in exploring driving as an everyday competence in people with chronic breathlessness (Lindstrom-Forneri et al., 2010). Driving competence (i.e., of what the driver is capable given the dynamic interaction between and within the individual and the

environment) results from multiple factors that include, but are not limited to, driving-related skills (Lindstrom-Forneri et al., 2010). As an example, people with chronic breathlessness may have difficulties concentrating on the road while experiencing acute-on-chronic breathlessness, but they may be safe to drive with their baseline level of breathlessness. Additionally, some people may struggle to drive in unfamiliar traffic routes, but they may be safe to drive in familiar ones. Moreover, people taking regular, low-dose, sustained-release oral morphine may be unsafe to drive if they experience sedation, but may be safer to drive if they experience large symptomatic reductions in breathlessness. In summary, contextual factors are important for driving performance, and they must be explored in people with chronic breathlessness to ensure that those who wish to drive are able to do so safely.

10.5 Effectiveness of low-dose, sustained-release oral morphine for severe chronic breathlessness

Besides investigating its safety, this doctoral programme also investigated factors associated with the effectiveness of regular, low-dose, sustained-release oral morphine for chronic breathlessness. These were divided into three categories:

i) Defining the sub-populations deriving more benefit;

ii) Possible mechanisms associated with breathlessness; and

iii) Possible linking mechanisms contributing to effectiveness.

The main findings for each category are described below.

10.5.1 Defining the sub-populations deriving benefit

Sub-studies 4 (genetic analysis) and 6 (crossover study of regular, low-dose, sustained-release oral morphine for chronic breathlessness associated with PAH) explored response to regular, low-dose, sustained-release oral morphine in different sub-groups of people with chronic breathlessness, to help define factors predicting larger reductions in symptomatic breathlessness.

Sub-study 4 was the first prospective study exploring the influence of specific genetic factors on response to regular, low-dose, sustained-release oral morphine, in people with chronic breathlessness associated with COPD. This sub-study adds to the literature by raising the hypothesis that different *HTRB3* rs7103572 genotypes may influence different magnitude of reduction in *average breathlessness* once regular, low-dose, sustained-release morphine is introduced. More importantly, the group of homozygotes for the variant allele, showed a dose-response relationship pattern once the study medication was introduced, which was not seen with other *HTRB3* rs7103572 genotypes. Although a previous population-based, cross-sectional study had identified that *HTRB3* rs7103572 genotypes predicted the likelihood of more intense breathlessness in people despite taking morphine for cancer pain, this is the first study suggesting *there may be an association with response* to regular, low-dose, sustained-release oral morphine (Currow et al., 2015). Additionally, results from this sub-study also suggest that, people with the variant allele may have higher chances of being super-responders (i.e., people with larger improvements in breathlessness defined as a ≥2-point reduction in the NRS for breathlessness) (Johnson et al., 2013a). These findings need to be explored in an adequately powered study, given that they could open the door to more personalised medicine in the field of chronic breathlessness.

Another key finding of this study was that different *HTRB3* rs7103572 and *COMT* rs4680 genotypes may influence differences in intensity of breathlessness, in people with severe chronic breathlessness associated with COPD, who are opioid naïve. However, between-genotype differences found in this sub-study seem to conflict with findings from previous studies in different settings (Currow et al., 2015; Hagen et al., 2006; Zubieta et al., 2003). The significance of these results needs to be investigated in future studies. However, it is possible that chronic breathlessness is associated with internal environmental changes leading to modifications in

epigenetic factors and genetic expression. Importantly, these environmental and epigenetic changes may affect each genotype differently, which may cause unusual patterns of susceptibility to chronic breathlessness. Epigenetic changes associated with chronic breathlessness are largely unknown and an important area of further exploration.

This sub-study also pointed to the potential influence of the *OPRM1* rs1799971 SNP in the reduction of breathlessness after initiating regular, low-dose, sustained-release oral morphine, but specific dose-by-treatment interactions could not be identified. Because there are very few people who are homozygotes for the variant allele in the general population, between-genotype differences must be explored in much larger prospective studies.

Overall, response in the placebo arm was considerably different between genotypes, requiring further exploration. In some cases, responses were clinically meaningful corresponding to large changes in breathlessness intensity (Johnson et al., 2013a). However, the pattern of response observed for each SNP or combination of SNPs, conflicted with previous findings in the pain setting. Importantly, opioid and dopaminergic pathways are both crucial for opioid response and placebo analgesia (Zubieta & Stohler, 2009). As mentioned before, potential epigenetic changes associated with chronic breathlessness may affect each genotype differently and modify not only patterns of susceptibility to chronic breathlessness but also the magnitude of response in the placebo arm. These findings highlight the importance of better understanding the mechanisms and central pathways modulating chronic breathlessness, and how they are influenced by different genotypes.

In addition to Sub-study 4 (genetics analysis), Sub-study 6 (crossover study of regular, low-dose, sustained-release oral morphine for chronic breathlessness associated with pulmonary arterial hypertension) also contributed to help define factors affecting response to regular, low-dose, sustained-release oral morphine for chronic breathlessness. Although this crossover study did not

recruit to target, there was a lack of any signal of improvement with regular, low-dose, sustained-release oral morphine in people with pulmonary arterial hypertension. Moreover, regular, low-dose, sustained-release oral morphine causes more harms. Power calculations based on these results suggest that a future study would require a sample size of more than 70.000 participants to achieve a statistically and clinically significant difference between arms, in favour of morphine (Cocks & Torgerson, 2013). Thus, this study adds to the literature by clearly demonstrating that progression to a large phase III randomised-controlled trial is not recommended. These results are of particular importance because they contrast with previously published studies of regular, low-dose, sustained-release oral morphine for chronic breathlessness of other aetiologies, where the direction and magnitude of signal consistently favoured morphine over placebo (Abdallah et al., 2017; Abernethy et al., 2003; Ekstrom et al., 2015; Jennings et al., 2002). Thus, Sub-study 6 is the first to define *disease* as an important factor influencing response to regular, low-dose, sustained-release oral morphine. Importantly, these results raise the hypothesis that there are different sub-types of chronic breathlessness, likely with different underlying mechanisms and requiring different interventions.

Findings from Sub-studies 4 (genetic analysis) and 6 (crossover study of regular, low-dose, sustained-release oral morphine for chronic breathlessness associated with pulmonary arterial hypertension) complement recent work defining the *type of opioid* as new factor influencing the effectiveness of regular, low-dose, sustained-release oral morphine for chronic breathlessness associated with COPD. A recent parallel-arm, randomised, placebo-controlled study of people with different aetiologies of chronic breathlessness, compared regular, low-dose, sustained-release oral morphine 20mg, with regular, low-dose, controlled-release oral oxycodone (5mg, eight hourly), and placebo (Currow et al., 2020; Ferreira et al., 2020c). While there was a signal for breathlessness reduction with regular, low-dose, sustained-release oral morphine compared with

placebo, there was no signal for breathlessness reduction with regular, low-dose, controlled-release oxycodone (5mg, eight hourly) (Ferreira et al., 2020c). It is unclear what may have led to these differences in response. However, while both morphine and oxycodone bind to μ-opioid receptors in the central nervous system, oxycodone has higher affinity to κ-opioid receptors, which are largely responsible for its antinociceptive effects (Kalso, 2007; Ross & Smith, 1997). The contribution of κ-opioid receptors for the genesis of chronic breathlessness is still unknown. However, these results also highlight the need of having a better understanding of the central mechanisms of chronic breathlessness, in order to develop effective treatments.

10.5.2 Possible mechanisms associated which breathlessness reduction

Sub-study 7 (salivary cortisol analysis) was the first prospective study exploring changes in the diurnal cortisol profile (diurnal cortisol slope and AUCg) of a population with COPD and severe chronic breathlessness as regular, low-dose, sustained-release oral morphine was introduced and continued. A previous cross-sectional study had suggested that people with chronic breathlessness had flatter cortisol slopes compared with healthy volunteers, and that slopes tended to become flatter for higher levels of functional impairment due to chronic breathlessness (Ryan et al., 2017). Sub-study 7 (salivary cortisol analysis) adds to these findings by identifying a similar proportion of people with chronic breathlessness with flatter cortisol slopes. Both of these studies support investigating the diurnal cortisol profile of people with chronic breathlessness in an adequately powered study, as this may potentially be useful to identify people who have increased risk of worse health outcomes in clinical practice (Adam et al., 2017).

The pattern, direction, and magnitude of signals identified in Sub-study 7 indicate that higher age, higher comorbidity scores, worse performance status, worse perceived sleep quality and higher intensity of breathlessness may potentially be associated with HPA axis dysfunction in people with chronic breathlessness. For performance status and intensity of breathlessness, the direction and

magnitude of signal from the only study of people with chronic breathlessness was similar to what was observed in this sub-study, suggesting these associations need to be investigated in adequately powered studies (Ryan et al., 2017). Importantly, these associations do not imply causality. Most likely, the underlying disease associated with chronic breathlessness contributes to a state of allostatic load with disfunction of the HPA axis and other body systems (Adam et al., 2017; Guidi et al., 2021). It is possible that these dysfunctions contribute to a constellation of symptoms and signs that include not only chronic breathlessness, but also increased comorbidities, functional limitations, and sleep disruption. In that sense, HPA axis dysfunction, chronic breathlessness, worse performance status, comorbid conditions and sleep disruption may be part of a constellation of findings reflecting higher allostatic load in people with chronic breathlessness (McEwen, 1998; Ryan et al., 2016). It is also possible that these conditions contribute to perpetuating and aggravating each other, further increasing the allostatic load, and that combined interventions targeting these systems may contribute to stabilising or partially reversing the state of allostatic load (McEwen, 1998; McEwen, 2007; McEwen & Seeman, 1999). These hypotheses need to be explored in future research work.

Another important hypothesis generated by this sub-study is that while high doses of opioids may contribute to HPA dysfunction, regular, low-dose, sustained-release oral morphine in the context of chronic breathlessness may potentially be beneficial. After one week of therapy with regular, low-dose, sustained-release oral morphine, the pattern of results indicates that diurnal cortisol slopes tended to be flatter for higher doses of morphine. However, longer-term data show that the mean slope tended to get steeper in the group taking regular, low-dose, sustained-release oral morphine ≥16 mg for later stages in the study. It is possible that people who provided longer-term data had *greater sustained* benefit with regular, low-dose, sustained-release oral morphine, which could potentially be translated into steeper slopes. Indeed, the high correlations between steeper

slopes, lower intensity of breathlessness and higher subjective sense of improvement after three months of therapy with regular, low-dose, sustained-release oral morphine suggest that this medication may potentially interrupt or slow down the worsening cycle of chronic breathlessness in people who derive benefit, leading to an improvement in HPA axis function in the long-term. However, increasing doses beyond the level of benefit, may possibly lead to detrimental effects on the HPA axis without any additional benefit. The magnitude, duration and clinical significance of shorter- and longer-term effects of regular, low-doses sustained-release oral morphine on the HPA axis of people with chronic breathlessness need to be investigated in future larger prospective studies.

10.5.3 Possible linking mechanisms contributing to effectiveness

This doctoral thesis explored the association between isolated factors (i.e., genetic factors, diurnal cortisol profile, aetiology of chronic breathlessness) with chronic breathlessness and response to regular, low-dose, sustained-release oral morphine for the reduction of symptomatic chronic breathlessness. However, these factors are likely to interact with each other, contributing to unique individual patterns of chronic breathlessness and of reduction in chronic breathlessness with regular, low-dose, sustained-release oral morphine. For example, some genetic polymorphisms, including *OPRM1* gene variations, are likely to influence the circadian rhythm of cortisol secretion and reactivity to stress (Arnett et al., 2016; Schwandt et al., 2011). Thus, it is also possible that the degree of HPA axis dysfunction associated with chronic breathlessness is partially determined by different genotypes. Moreover, different *COMT* rs4680 genotypes were also shown to lead to different HPA axis responses to naloxone, which underscores the intimate relationship between the HPA axis and the opioid system and raises the hypothesis that genetic factors may affect the way the HPA axis responds to regular, low-dose, sustained-release oral morphine and other opioids (Oswald et al., 2004). As detailed before, it is also possible that different genotypes have different susceptibilities to epigenetic changes (Bell et al., 2015; Kindt et al., 2018).

Epigenetic changes affecting genetic expression occur in response to changes in the internal and external environment and behaviour (Feil & Fraga, 2012). Most conditions associated with chronic breathlessness, and possibly chronic breathlessness itself, may lead to persistent inflammation (i.e., persistent changes in the internal environment) and multiple behavioural adaptations (e.g., avoiding daily activities triggering breathlessness) (Ryan et al., 2016). Consequently, inflammation may induce epigenetic changes, with consequent changes in genetic expression (Murata, 2018). Whether these epigenetic changes affect different genotypes differently is still a matter requiring investigation, particularly in the field of chronic breathlessness, for which the contribution of genetic and epigenetic influences is largely unknown.

It is also unknown how genetic and epigenetic characteristics relate to structural changes of breathlessness processing centres in people with COPD (Esser et al., 2016). It is possible that specific genetic variants predispose to susceptibility to these changes. Importantly, contrary to what was initially believed, the human brain is a dynamic system that is able to reorganise its structure, functions and connections in response to internal or external stimuli, a mechanism labelled *neuroplasticity* (Mateos-Aparicio & Rodriguez-Moreno, 2019). By studying brain structural changes associated with chronic breathlessness, it may be possible to identify and develop interventions that *promote* neuroplasticity and enhance people's more successful adaptation to chronic breathlessness.

10.6 Challenges in conducting research in populations with severe functional impairment due to chronic breathlessness

Conducting research in people with severe functional impairment due to chronic breathlessness requires specific considerations to ensure participants' wellbeing during the course of a research project and optimise adherence and completion. Most of the sub-studies included in this programme of research were embedded in a large RCT, which provided a unique opportunity to

explore research questions that were previously identified but left unexplored for years (Johnson et al., 2012). Hypothesis generated by these sub-studies can now be used to guide the design of future research projects, in the setting of chronic breathlessness, which will have better chances of achieving meaningful results. However, conducting an RCT with multiple sub-studies also contributed to limit the sample size included in each sub-study. People with severe chronic breathlessness are usually frail, and many suffer from multiple comorbidities that contribute to reducing their quality of life and limiting their ability to complete multiple study measures. Despite their physical limitations, most of the participants included in this research programme were also extremely committed to completing the study procedures, because they felt they were contributing to help other people with similar health challenges. As a result, most local research teams felt the need to select the sub-studies offered to participants according to their physical and psychological condition, in order to ensure they would reach the RCT primary endpoint without compromising their wellbeing.

Overall, sub-studies requiring blood or saliva sample collection were well tolerated by participants and could potentially be included in other RCTs and consecutive case series. However, genetic studies investigating specific SNPs need to account for the frequency of each genotype in the population of interest. For example, for the *HTRB3* rs7103572 SNP, the population frequency of homozygotes for the variant allele is very low (approximately 8%). Thus, large sample sizes are required to have a critical number of homozygotes for the variant allele and identify statistically significant differences between genotypes in an adequately powered study. From a practical point of view, conducting a large prospective study allows recruiting sufficient participants to detect a difference between genotypes, without the prohibitive costs and logistics of large RCTs.

Driving-simulation studies are time-consuming and demanding for participants. The time allocated for each driving-simulation session needs to account for travelling to and from driving-assessment

facilities, the length of practice sessions, and the study assessments themselves. Moreover, travelling to and from driving-assessment facilities needs to take into account participants' level of breathlessness. For example, it is necessary to ensure participants have available parking, very close to the assessment location, given that walking, even for short distances, may discourage participants from enrolling in these studies. Alternatively, providing paid transportation to and from driving-assessments locations may help to circumvent this issue. From a physical point of view, driving-simulation assessments may be challenging for participants with chronic breathlessness for different reasons. For example, some people may experience more intense breathlessness while driving. Others, who do not experience breathlessness while driving in a familiar context, may experience more performance anxiety and breathlessness when exposed to a new context (e.g., new driving route or simulator) or feel the pressure of wishing to perform well. Thus, researchers need to create a context in which participants feel as relaxed as possible to avoid aggravating people's breathlessness. Importantly, people with chronic breathlessness may also be reluctant to enrol in driving-assessment studies for fear of losing their drivers' licences, in case they perform poorly. Thus, potential participants need to be thoroughly informed about the possible consequences of their participation (i.e., that participation would never jeopardise their civil licence), whether they specifically enquire about it or not. Given the challenges associated with conducting driving assessments in this population, these should be designed as stand-alone studies.

Lastly, it is important to avoid studies with a crossover design in this population. Because crossover studies require participants to receive at least two different interventions separated by a washout period, they usually involve longer periods of participation. Considering that people with chronic breathlessness are particularly frail, they are more likely to withdraw after short periods of participation, which, in a crossover design, can jeopardise data analysis.

10.7 Future research directions

Future research directions for individual research questions explored in this doctoral thesis are detailed in the respective chapters. However, the combined findings of this research programme point to new avenues of research that need to be explored in future studies. These are described below.

10.7.1 Selecting the best outcome measures for people with chronic breathlessness

In future studies, it is important to identify the best outcome measures reflecting benefit for patients with chronic breathlessness. Findings from Sub-study 1 (Domain 2 – perceptions of regular, low-dose, sustained-release morphine) and Sub-study 5 (genetic analysis) seem to indicate that function is important for patients and a possible marker of allostatic load and mortality. There is also previous evidence from a randomised controlled trial suggesting that regular, low-dose, sustained-release oral morphine may improve health status in people with chronic breathlessness by improving health status, which includes activity levels (Verberkt et al., 2020). As a result, it is important to select outcome measures evaluating function in future studies of interventions for chronic breathlessness.

10.7.2 Predicting worse health outcomes and mortality associated with chronic breathlessness

Sub-study 5 (cortisol analysis) of this doctoral thesis raises the hypothesis that chronic breathlessness may be associated with a state of higher allostatic load, contributing to dysregulate multiple body systems and translating into a constellation of symptoms and signs. In its origin, it is likely that this state of allostatic load is caused by the condition leading to chronic breathlessness and not by chronic breathlessness itself. Indeed, most chronic conditions leading to chronic breathlessness may induce pathological changes that are likely to induce a state of allostatic load with increased pressure over multiple body systems (Guidi et al., 2021). As a result, it is possible that flatter cortisol slopes, higher comorbidity scores, worse perceived sleep, lower performance

status and higher intensity of breathlessness are all phenotypical markers of higher allostatic load in the context of chronic breathlessness. It is known that breathlessness is a predictor of mortality in people with multiple life-limiting conditions (Barlera et al., 2013; Nishimura et al., 2002; Pesola & Ahsan, 2014). However, together with breathlessness, other phenotypical markers may help to more accurately predict the people who are at a risk of having worse health outcomes, including mortality (Guidi et al., 2021). As a result, future research should focus on defining the role of these signs and symptoms as phenotypical markers predicting health outcomes in the population with chronic breathlessness.

10.7.3 Predicting safety and effectiveness of regular, low-dose, sustained-release morphine for chronic breathlessness

Another key aspect raised by Sub-studies 1 (Domain 2 – perceptions of regular, low-dose, sustained-release morphine), 4 (genetic analysis) and 6 (crossover study of regular, low-dose, sustained-release oral morphine for chronic breathlessness associated with pulmonary arterial hypertension) of this doctoral thesis is that there are substantial differences in people's experiences with regular, low-dose, sustained-release oral morphine for chronic breathlessness, and they response to it. While potential contributors for these variations were identified (e.g., genetic factors, underlying disease), they are unlikely to be sufficient to explain the interindividual variations observed in responses. One important consideration is that phenotypical factors associated with higher allostatic load may also predict response. This hypothesis is plausible in view of the fact that higher intensity of baseline breathlessness (possibly translating higher allostatic load) predicted response to regular, low-dose, therapeutic opioids for chronic breathlessness in one pooled data analysis (Johnson et al., 2013b). However, performance status was not a predictor of response in the same study (Johnson et al., 2013b). Considering that underlying disease may be a major driver of higher allostatic load, with increased pressure in multiple body systems, it would be interesting to examine potential predictors of response by

underlying disease and level of disease severity (Guidi et al., 2021). Moreover, it would also be interesting to examine if phenotypical markers of higher allostatic load correlated with the incidence of harms, including possible effects on people's ability to drive. In future studies, the role of obesity as a predictor of response to regular, low-dose, sustained-release oral morphine needs to be examined. Results from Sub-study 6 (crossover study of regular, low-dose, sustained-release oral morphine for chronic breathlessness associated with pulmonary arterial hypertension) indicate that morphine is likely to be ineffective in people with PAH, but the population included in this study was largely overweight or obese. Given that morphine is a lipophilic drug, and that obesity changes the percentage of body fat, endocrine signals and inflammatory status, it is possible that morphine requirements are different in obese patients (Lloret Linares et al., 2009). It is also possible that different genetic variants (including SNPs), contribute to different responses to morphine in obese patients (Lloret Linares et al., 2009).

Another key consideration is that epigenetic factors may interact with genetic factors, influencing structural brain changes and response to regular, low-dose, sustained-release oral morphine for the symptomatic reduction of chronic breathlessness. Epigenetics changes associated with chronic breathlessness are largely unexplored and an interesting field of future research. However, investigating links between allostatic load, epigenetic changes and genetic expression may be key to understand the mechanisms underlying chronic breathlessness and factors driving breathlessness reduction and harms experienced with regular, low-dose, sustained-release oral morphine.

10.7.4 Defining the neural pathways involved in chronic breathlessness reduction by regular, low-dose, sustained-release oral morphine

This doctoral work suggests that different genotypes (Sub-study 4 – genetic analysis) and underlying diseases (Sub-study 6 - crossover study of regular, low-dose, sustained-release oral

morphine for chronic breathlessness associated with pulmonary arterial hypertension) may influence differences in response to regular, low-dose, sustained-release oral morphine for chronic breathlessness. These findings point to the existence of *different types* of chronic breathlessness, whose neural mechanisms are yet to be identified as they are not necessarily related to laboratory models of acute breathlessness. A previous study has reported that magnetoencephalography is well tolerated by people with chronic breathlessness and could be used in future research (Johnson et al., 2015). However, participants would not be allowed to move to perform daily tasks potentially triggering more intense breathlessness. An alternative, the use of high-resolution electroencephalography, would allow participants to perform daily tasks while being monitored. These techniques would be useful to define different pathways of chronic breathlessness according to the underlying disease, and different pathways of response to regular, low-dose, sustained-release oral morphine and other interventions. There is also interest in correlating these findings with genetic, epigenetic, and clinical factors in order to more deeply understand the overall syndrome of chronic breathlessness and inform the development of interventions targeting its underlying mechanisms.

10.8 Conclusion

This programme of research was largely composed of hypothesis-generating studies exploring aspects related with the safety and efficacy of regular, low-dose, sustained-release oral morphine for the symptomatic reduction of chronic breathlessness. The main hypotheses generated will contribute to informing future research in this field. From a safety point of view, this work points to the relevance of driving in this population and the need to exercise caution when advising people with chronic breathlessness to drive or stop driving, particularly if initiating or titrating regular, low-dose, sustained-release oral morphine. This work also highlights that factors influencing effectiveness are likely to be multiple and complex. Thus, there is a need to

understand chronic breathlessness using multiple approaches including neuroimaging, genetic and epigenetic studies as well as clinical and biological markers.

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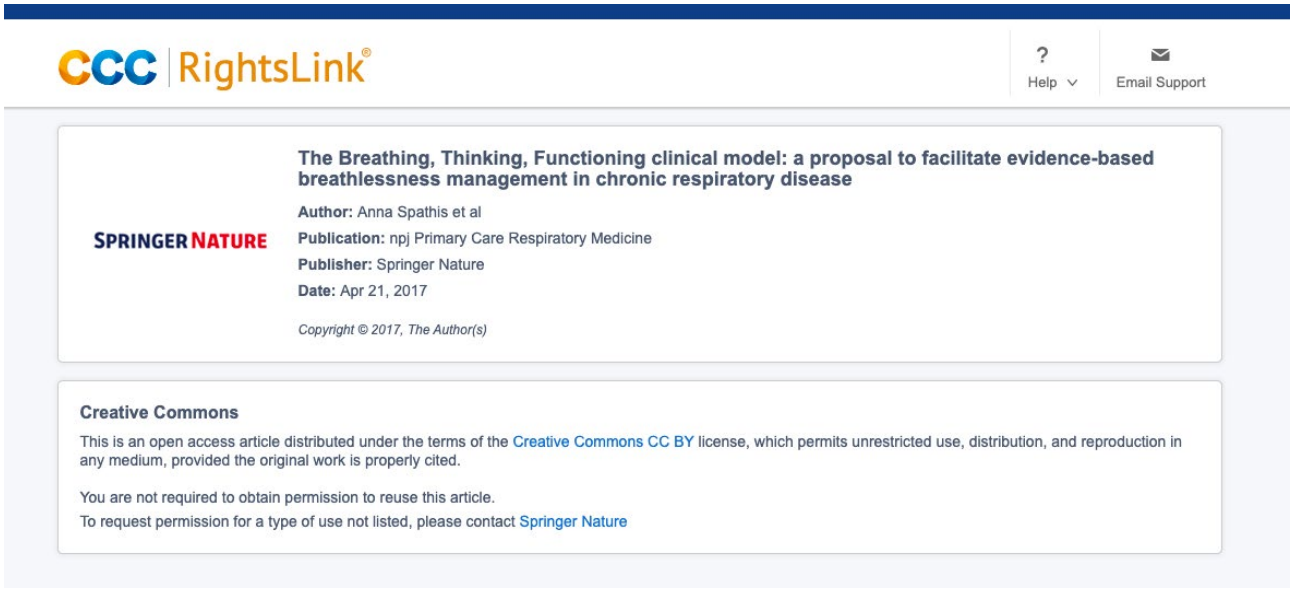
APPENDICES

Appendix 1 - Permission to use the figure depicting the Breathing-Thinking-Functioning Model of breathlessness. Depicted in this thesis as 'Figure 1.1', in Chapter 1.



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The Breathing, Thinking, Functioning clinical model: a proposal to facilitate evidence-based breathlessness management in chronic respiratory disease

Author: Anna Spathis et al

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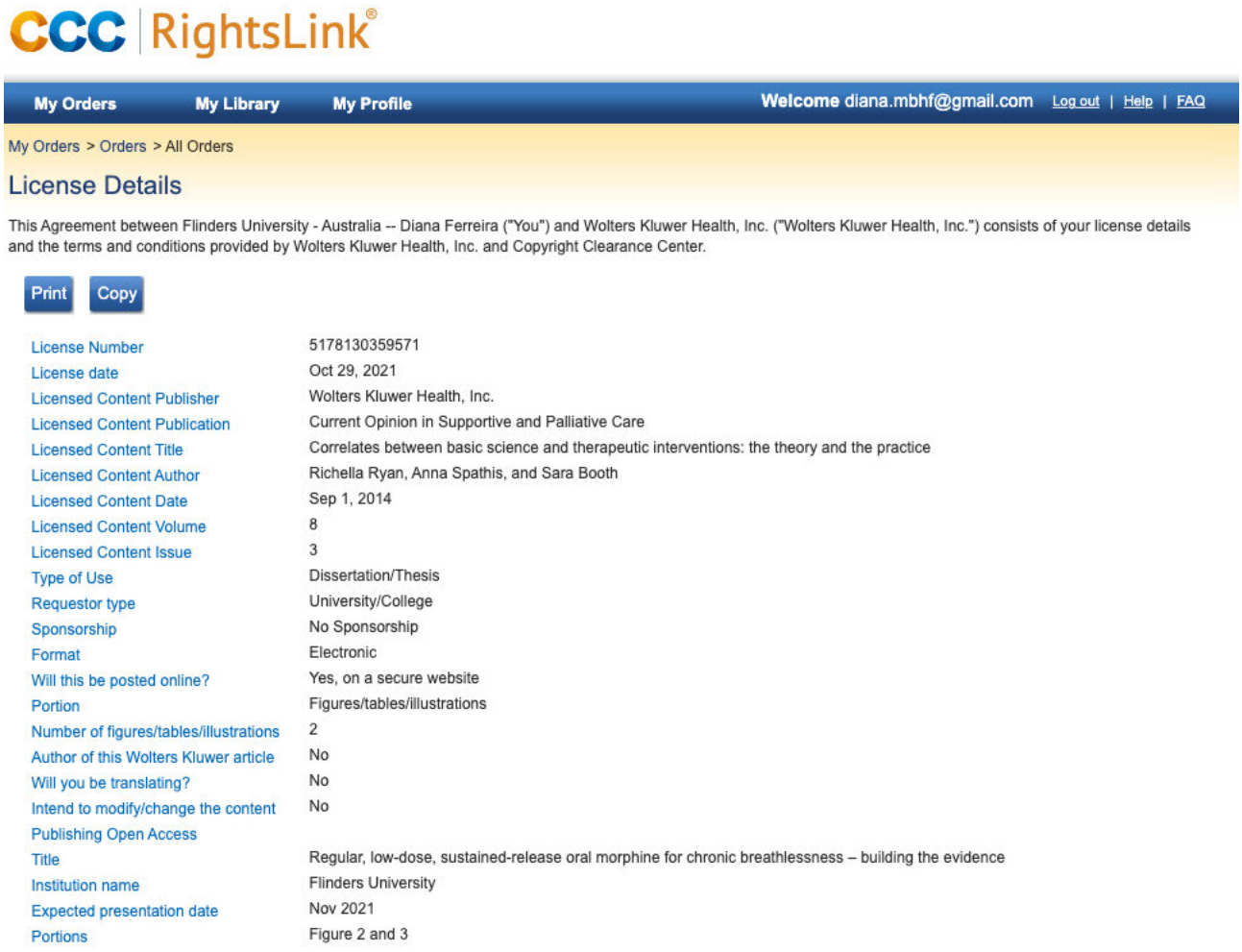

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Expected presentation date	Nov 2021
Portions	Figure 2 and 3

Appendix 3 – BEAMS study and Sub-study 4 (Genetics analysis) Participant Information and Consent Form.

Insert Header with institution's name or institution's letterhead

Executive Summary of the

Participant Information Statement for

Breathlessness, Exertion And Morphine Sulphate Study (BEAMS)

[Local Chief Investigator]

You are invited to participate in the above research study because of your diagnosis of Chronic Obstructive Pulmonary Disease (COPD, a term that arises from a range of conditions such as emphysema) and your doctor believes this could be a suitable treatment option for you. A detailed Information Statement about the study is attached and this is a summary of the essential information about the trial and where to find the relevant detailed information later in the Information Statement. You should read the Information Statement in full and discuss it with your family and medical practitioners before deciding to participate in this study. You may contact the study staff to discuss or ask questions about the study on [local phone number] or by email [local email address].

This study aims to compare the difference in benefits and side effects in people with breathlessness and Chronic Obstructive Pulmonary Disease taking once daily extended release morphing at up to four different dosing levels when compared to placebo. You may receive the study treatment or placebo. A placebo is a drug/infusion that looks like the study medication but has no active ingredients. For a full description of purpose and rationale for this research see pages 2 to 12.

Participation in this study is voluntary and refusal to participate or withdrawal from the study at a later stage will not affect the treatment you receive at *[department/hospital]*

If you decide to participate in this study you will need to attend the clinic for up to 5 visits over 4 weeks and for a further 6 months if you choose. The study visits will be approximately 1 hour and your travel and parking costs will be reimbursed. During these visits you will have a number of tests and assessments, such as a physical examination, blood tests and other medical assessments. The schedule for study visits and a full list of all tests and procedures is on page 3 - 6. After the study treatment has finished you will be telephoned once a week for 4 weeks.

The most common risks to participants from the study medication are: tiredness (sedation); nausea and vomiting; and constipation. A full list of the side-effects from the study drug and other risks associated with the study procedures see pages 9 – 10.

There is additional information about what information will be collected about you during the study on page 10, how that information will be used and your privacy protected on page 11 . Your rights as a participant, page 11 and additional regulatory information that we are obligated to provide on pages 11-13.

Please make sure you have completely understood what the study involves before you decide to participate.

Participant Information Sheet/Consent Form

Interventional Study - *Adult providing own consent*

[Insert site name]

Title	A pragmatic, phase III, multi-site, double-blind, placebo controlled, parallel arm, dose increment randomised trial of regular, low dose extended release morphine for chronic refractory breathlessness.
Short Title	Breathlessness, Exertion And Morphine Sulphate Study (BEAMS)
Protocol Number	030/15
Project Sponsor	Flinders University
Coordinating Principal Investigator/ Principal Investigator	Professor David Currow
Associate Investigator(s) *(if required by institution)*	*[Associate Investigator(s)]*
Location *(where CPI/PI will recruit)*	*[Location]*

1 Introduction

You are invited to take part in a research study into a new treatment for Chronic Obstructive Pulmonary Disease (a term that arises from a range of conditions such as emphysema). The objective is to investigate whether extended release morphine can improve the symptoms of breathlessness.

This Participant Information Sheet/Consent Form tells you about the research project. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully and ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your local doctor.

Participation in this research is voluntary. If you don't wish to take part, you don't have to. You will receive the best possible care whether or not you take part.

If you agree to participate in this study, you will be asked to sign the consent section. By signing it you are telling us that you:
- Understand what you have read
- Consent to take part in the research project
- Consent to have the tests and treatments that are described
- Consent to the use of your personal and health information as described.

You will be given a copy of this Participant Information Sheet/ Consent Form to keep.

2 What is the purpose of this research?

Chronic Obstructive Pulmonary Disease, sometimes called emphysema, is a major cause of suffering, reduced physical function, and increased mortality worldwide. Severe Chronic

Obstructive Pulmonary Disease affects about 235,000 people in Australia and is associated with a vicious cycle of breathlessness, reduced activity, and markedly reduced physical function.

Many doctors around the world use morphine (an opioid) to relieve the sensation of breathlessness. This study will measure the benefits that morphine may have in reducing the breathlessness you experience as part of your Chronic Obstructive Pulmonary Disease. When low doses of morphine are taken for the physical symptoms of breathlessness over a relatively short time period and under the guidance of an experienced doctor, as in this research project, they are not likely to cause addiction. Addiction requires drug seeking behaviour and is very different to the therapeutic use of morphine for breathlessness.

Morphine is approved in Australia to treat pain. However it is not approved to treat breathlessness from Chronic Obstructive Pulmonary Disease. Therefore, it is an experimental treatment it must be tested to see if it is an effective treatment.

This research project has been initiated by the study doctor, Professor David Currow and a large team of international experts in the field. Funding has been provided by the National Health and Medical Research Council with the study medications being supplied by Mayne Pharma Group Limited.

In some people's minds, the use of morphine is associated with advanced terminal care. This is not necessarily the case. Based on knowledge developed over the last 20 years, morphine and other opioids can offer significant benefits to a wide range of people to manage their breathlessness symptoms and help to keep them functioning as well as possible.

The aim of this research project is to compare the difference in benefits and side effects in people with breathlessness and Chronic Obstructive Pulmonary Disease taking once daily, extended release morphine at up to four different dosing levels when compared to placebo.

Several other important questions will also be answered:

1. Are different doses of morphine in people with breathlessness and Chronic Obstructive Pulmonary Disease safe.
2. If improvement in breathlessness occurs at low doses of morphine, do people obtain even more benefit if the dose of morphine is increased
3. To find out if benefit continues and for how long
4. To explore if the lowest dose (8mg) can last until the next dose
5. Explore if it is possible to predict who might get benefit or side effects
6. To measure if low dose morphine has any effect on general health status, quality of life, activity levels, anxiety or depression.
7. Understand the longer term benefits and harms
8. Evaluate if people have any preference to continue the study medications because of their perceived benefit?
9. Do people experience withdrawal symptoms when the study medication ceases?

3 What does participation in this research involve?

If you agree to participate in this research project, you will be asked to sign the Participant Consent Form. Once you have signed the Participant Consent Form you will then be asked to commence the research project.

In summary:

- You will undergo 2 days of initial assessment during which you will complete a diary and wear a wristband to measure your activity.
- After this you will be allocated to take morphine or placebo for one week.
- At the end of week one, provided you are happy to continue, you may then continue on study medication, at increasing doses for up to a total of 3 full weeks, with a visit at the end

of each week. Each week will require a visit to the study team for about an hour, and the completion of a 24 hour diary and a number of assessments and questionnaires.
- There will be a total of 5 visits over the total study period, provided you wish to continue to participate.
- At the end of 3 weeks of study medication you can then chose to continue on study medication for an additional 6 months, with assessments and visits regularly during that time.

In detail the research project involves the following:

Visit 1
Stage 0. Initial assessment
If you agree to participate and the study is suitable for you, you will be asked to complete 2 full days of a diary (in the morning and evening each day) in order to become accustomed to completing the diary regularly and to provide the research team with baseline information about your breathlessness, symptoms and physical function. The diary will take less than 5 minutes to complete each morning and each evening.

Your physical function or activity level will be further measured by a monitor called a FitBit® which the research nurse will ask you to strap to your non-dominant wrist and wear everywhere for 2 full days.

> *A FitBit is a device that monitors your activity throughout the day; it records steps and the amount of time spent sitting, lying down and sleeping. It is a small, lightweight device (think of plastic watch) and is worn on the wrist. It can be worn under your clothes and in the shower.*

Time period: The visit takes about 1 hour, and diary entries of about 5 minutes each morning and evening.

Visit 2
Stage 1 – Randomisation #1
At completion of the 2 days you will again meet with the research team. They will review the information from the 2 days and complete the remaining baseline assessments. These will include some questionnaires about your quality of life and sleep, measures about your physical function and information about any current symptoms and problems you may be experiencing.

A physical examination and a medical history will be performed to collect some general information regarding your health. Other general information, including your age and ethnicity, will be recorded.

At the completion of this you will be informed if the study is suitable for you to continue on the research project. If the study is suitable you will enter Stage 1 of the research.

In Stage 1 of the research, a member of the research team will measure your blood pressure, temperature, respiratory rate, and pulse. The amount of oxygen in your blood will be measured by a small device that slips on your finger (a pulse oximeter). A measurement of how much carbon dioxide you breathe out will be performed by using a special nasal tube, similar to the tubing for delivering oxygen, which collects the carbon dioxide and is recorded on a respiratory monitoring machine called a capnograph.

You will be asked questions about your ability to perform daily activities, your breathlessness, and any side effects you may be experiencing. You will be asked about any prescription medication, over-the-counter preparations, herbal and homeopathic remedies or supplements you are currently taking. You will also be asked to complete some questionnaires about your quality of life, questions about hospital or health services you have visited, and support that you are currently receiving.

You will then be randomised* to one of three different treatments:

- Placebo**(and a placebo tablet that appears identical to the medication to reduce any symptoms of constipation), or
- 8mg morphine (and medication to reduce any symptoms of constipation), or
- 16mg morphine (and medication to reduce any symptoms of constipation).

**Randomisation - Sometimes we do not know which treatment is best for treating a condition. To find out we need to compare different treatments. We put people into groups and give each group a different treatment. The results are compared to see if one is better. To try to make sure the groups are the same, each participant is put into a group by chance (random). This is a double-blind study. This means that neither you nor your study doctor will know which treatment you are receiving. However, in certain circumstances your study doctor can find out which treatment you are receiving.*

***Placebo – A placebo looks like the genuine medicine but contains no active ingredient. Only pharmacy staff will know what medication patients are given, as they will be responsible for dispensing the required tablets on the randomisation. The research staff, doctors and nurses will not know which medication is being given to you. You will continue to receive your usual medication and care even if you receive the placebo, you will not go without treatment. The reason for using placebo tablets is to make sure the researchers interpret the results in a fair and appropriate way and avoids study doctors or participants trying to guess which treatment they are taking.*

The study medications will be provided by the hospital and explained to you by the research team prior to you leaving. You will commence taking the study medications the next day in the morning and take the medication every morning for the next 7 days. You will be asked to continue to complete the diary every evening and every morning for the 7 days you are taking the study medications.

All participants will be also provided with information about how best to manage breathlessness, based on the current literature and expertise, and also a battery operated hand held fan. This will be provided no matter which treatment you receive.

This visit will take approximately 1 hour and 30 minutes.
Time period: 1 week

Visit 3
Stage 2 – Randomisation #2

If the benefits you experienced from Stage 1 outweigh the side effects you report then you will be asked to continue in the research and progress to Stage 2 for a further one week of treatment. If, however, you report more side effects than benefit, you will exit the study at this visit.

During this visit a member of the research team will perform the same tests and questionnaires as those during visit 2.

You will again be randomised* this time with the addition of a further one of two different treatments (the capsule will appear the same, but the pellets within the capsule will be changed):

- Placebo** (and a placebo tablet that appears identical to the medication to reduce any symptoms of constipation), or
- 8mg morphine (and medication to reduce any symptoms of constipation)

You will continue on the study medication at the new dose the next day in the morning, at this point you will be taking 2 capsules containing morphine (between 8mg and 24mg) or placebo. As before, you will be asked to complete the dairy every evening and every morning for the 7 days you are taking the study medications.

An appointment will be made with the research team for you to meet with them at the end of the 7 days.
Time period: 1 week

Visit 4
Stage 3 – Randomisation #3
If the benefits you experienced from Stage 2 outweigh the side effects then the study is suitable for you and you can progress to Stage 3.

On this visit a member of the research team will perform the same tests and questionnaires as those during visits 2 and 3. The FitBit will be provided a second time to wear for the following week.

You will again be randomised* this time with the further addition of either one of two different treatments (the capsule will appear the same, but the pellets within the capsule will be changed):

- Placebo** (and a placebo tablet that appears identical to the medication to reduce any symptoms of constipation), or
- 8mg morphine (and medication to reduce any symptoms of constipation)

You will continue on the study medication at the new dose the next day in the morning, at this point you will still be taking 2 capsules containing morphine (dosing between 8mg and 32mg) or placebo. As before, you will be asked to complete the dairy every evening and every morning for the 7 days you are taking the study medications.

An appointment will be made with the research team for you to meet with them at the end of the seven days.
Each of these weekly visits will take approximately 30 minutes.
Time period: 1 week

The entire period of the research project is determined by your response and side effects. If the research is suitable for you the time period can range from 1 week and 2 days, to 3 weeks and 2 days.

Visit 5
Stage 4 - continuation
If the benefits you experienced from Stage 3 outweigh the side effects then the study is suitable for you and you can progress to Stage 4 where you will continue on the Stage 3 study medications for a period up to six months.

The medications will remain blinded, however this stage will help the research team to establish if there are longer term benefits and/or side effects from the study medication.

Once again at the beginning of this stage a member of the research team will perform the same tests and questionnaires as those in previous weeks.

You will be asked to complete a twice daily diary once every 7 days while you remain on Stage 4. A member of the study team will arrange appointments with you every 2 weeks, and telephone every week in between visits to check how you are going. At each visit you will be assessed for side effects and changes in your condition and quality of life. Each visit will take about 20 minutes and each telephone call will take about 10 minutes.
Time period: Up to a maximum of 6 months

Follow-up contact (after you stop taking the study medication)
The research team will telephone you weekly for a period of up to four (4) weeks after you have completed the study medication regardless of which Stage you exit the study. The purpose of

this is to assess your activity levels, breathing, time in hospital and need for hospital admissions. Each of these telephone calls will take approximately 15 minutes.

After the research is completed, your symptoms and condition will be managed according to the usual practice of your treating doctor.

There are no additional costs associated with participating in this research project, nor will you be paid. All medication, tests and medical care required as part of the research project will be provided to you free of charge.

You may be reimbursed for any reasonable travel, parking, meals and other expenses associated with the research project visits.

If you decide to participate in this research project, the study doctor will inform your local doctor.

4 What do I have to do?

If you agree to participate in this research it is important that you follow all instructions and attend each appointment made for you. You must ensure that you take the study medications as instructed, and inform the research team if you experience any problems. If you miss a dose of the study medication on any day, do not take twice the dose the next day, but inform the study team that a specific dose has been missed.

You need to ensure that the diary in completed at the times specified, and that the FitBit® is kept in place for the specified times.

You can take all of you other current medications and continue all other treatments, there is no restriction on your activity or lifestyle. However, you need to contact the research team if any of your medications are changed or new ones are started. You must avoid any other medications that contain opioids or codeine. There are many medications that contain codeine that can be bought from a supermarket or pharmacy, these include: panadeine, panadeine forte, and other combinations of paracetamol or aspirin with codeine, and many cough medicines. You will be provided with a list of medications to avoid.

You must make sure the medications are kept in a safe place, and NOT taken by anyone else, be extra careful around children. If anyone else takes your study medication you must call emergency services for treatment of the other person, and the study investigator will need to be contacted to break the treatment code.

Morphine can make you drowsy, especially in the first few days. If you feel affected by the study medication, such as more drowsy, less alert, or less coordinated than usual, you should avoid driving or operating machinery.

5 Other relevant information about the research project

There will be a total of 171 people participating in this study, with [insert number for each site] expected to participate from this site. This research will be conducted in 18 hospitals across South Australia, Victoria, New South Wales and Queensland.

There are a number of sub-studies attached to this main study, and you may be asked if you are interested in learning more about these. If you are interested, each or any of these sub-studies will be explained to you in detail and you will be asked to sign a separate consent for them. You are under no obligation to participate in any sub-study. You can participate in the main study without participating in any sub-study. The sub-studies include:

1. A sub-study to learn more about people's genetic make-up that may determine different responses to opioids. You will be asked to consent to this study within this information sheet and consent form.

2. A sub-study to learn more about how the body uses and breaks down morphine.
3. A sub-study to learn more about the changes in sleep patterns and quality when people take the study medications.
4. A second sub-study to learn more about the changes in sleep patterns while staying overnight in a sleep unit.
5. A sub-study to learn more about the impact on driving

6 Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

If you do decide to take part, you will be given this Participant Information Sheet / Consent Form to sign and you will be given a copy to keep.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with *[Institution]*.

This section is also relevant to any sub-studies.

7 What are the alternatives to participation?

You do not have to take part in this research project to receive treatment at this hospital. Other options are available; including continuation of your standard treatment. Your study doctor will discuss these options with you before you decide whether or not to take part in this research project. You can also discuss the options with your local doctor.

This section is also relevant to any sub-studies.

8 What are the possible benefits of taking part?

While we intend that this research furthers medical knowledge and may improve symptoms of breathlessness for people with Chronic Obstructive Pulmonary Disease in the future, it may not be of direct benefit to you.

9 What are the possible risks and disadvantages of taking part?

Medical treatments often cause side effects. You may have none, some or all of the effects listed below, and they may be mild, moderate or severe. If you have any of these side effects, or are worried about them, talk with your study doctor. Your study doctor will also be looking out for side effects.

There may be side effects that the research team do not expect or do not know about and that may be serious. Tell your study doctor immediately about any new or unusual symptoms that you get.

Many side effects go away shortly after treatment ends. However, sometimes side effects can be serious, long lasting or permanent. If a severe side effect or reaction occurs, your study doctor may need to stop your treatment. Your study doctor will discuss the best way of managing any side effects with you.

The risks of participating in this research are:

Physical risk
You will be monitored regularly by qualified research staff to make sure your symptoms and any side effects are controlled. You will be carefully assessed for the likelihood of any of these

events occurring, and you will be closely monitored during the research project for any of these effects by the research team.

Having blood (or tissue sample) taken may cause some discomfort, bruising, minor infection or bleeding. If this happens, it can be easily treated.

Very common side effects which may affect more than one person in every 10:
Sedation. Most patients experience initial drowsiness. Drowsiness usually clears in three to five days.
Nausea and vomiting. Nausea and vomiting are an early unwanted effect of regular opioid therapy.
Constipation. As with all opioid analgesics, constipation is a common occurrence. Constipation will be treated in this study with the prescription of laxatives, people participating in the study will be encouraged to take these regularly.

Common side effects which may affect more than one person in every 100 (excluding the very common side effects above):
Heart conditions. Fast heart rate, low blood pressure, very slow heart rate, irregular heartbeats, faintness may develop.
Nervous system. Feelings of confusion, light headedness, weakness, insomnia, dizziness, headache, involuntary muscle contractions, muscle weakness, thought abnormalities, occasionally hallucinations and, uncommonly, agitation, malaise, mood changes, vision abnormalities, and seizure may occur.
Gastrointestinal. Dry mouth, loss of appetite, indigestion, abdominal pain, constipation, cramps, taste alterations, spasm in the bowel.
Genitourinary. Urinary retention or hesitance, spasm of the urinary tract, loss of menstrual cycle, reduced libido or potency.
Respiratory. Slower or shallow breathing, bronchospasm and reduced cough reflex.

Uncommon side effects which may affect more than one person in every 1000 (excluding the common and very common side effects above):
The major side effects associated with opioids are respiratory depression and, to a lesser degree, circulatory depression. Respiratory arrest, shock and cardiac arrest have occurred following oral or injectable use.

Changes to the way your liver works, fluid in the lungs or collecting in the lower legs and changes to the way your body regulates hormones which may result in excess fluid and salt build up.

General effects: Allergic reaction, anaphylactic reaction, skin rashes including contact dermatitis, facial flushing, pinpoint pupils, muscle weakness and oedema or swelling.

Docusate with senna laxatives (the laxative used in this study) may cause abdominal discomfort, such as colic or cramps. Prolonged use or overdose may lead to diarrhoea or dehydration (excessive loss of water).

The effects of extended release morphine on the unborn child and on the newborn baby are not known. Because of this, it is important that research project participants are not pregnant or breast-feeding and do not become pregnant during the course of the research project. You must not participate in the research if you are pregnant or trying to become pregnant, or breast-feeding. Both male and female participants must avoid pregnancy during the course of the research. You should discuss effective methods of avoiding pregnancy with your study doctor.

As extended release morphine is still being tested for its use in the management of breathlessness, there may be other side effects that are not known at this time despite its widespread use. The research team will be monitoring you closely and will make sure you are looked after appropriately. You will be provided with a list of side effects that you and your family or carers need to be aware of.

You will be informed of any significant new findings that may affect your decision to continue in this research.

10 What will happen to my test samples?

You will be asked to provide to provide a number of blood samples as part of this research. Three samples will be taken to check if it safe for you to participate in this research (your blood count and liver and kidney function). These samples are required in order for you to participate. If possible, results from recent blood tests will be used to avoid another blood test.

A further blood sample will be taken to measure the level of testosterone in your blood, this will also be repeated if you chose to continue for the 6 month extension phase. This is because morphine has been shown to change testosterone levels in some people and further knowledge about this effect in people with Chronic Obstructive Pulmonary Disease is being sought.

All blood samples will be taken by the pathology service and the results will be placed in your medical record. All samples will be destroyed in accordance with the usual practice of the pathology service.

You will be asked to provide additional consent at the end of this form for additional collection of your blood during the research project.

This additional blood collection will be for pharmacogenetic research. Genes, which we inherit from our parents, may control the way we react to or handle a medicine. Pharmacogenetics is the study of differences in how our bodies respond to or handle medicines. This pharmacogenetic research project is looking at genetic differences to better understand why some people have a better response than others when they get the same medicine. If it appears that there is a difference in the way people respond to or handle morphine, the study investigators may study these differences using your genes or genetic material taken from your blood sample.

If you choose to take part in this sub-study, you will be asked to provide a small sample of blood which will be collected at the same time that a routine blood test is obtained during the main study and again when you return for your week two visit. In the unlikely case that there is a problem processing your sample, then we may ask you to give a further sample.

The blood sample for this part of the research will be stored frozen in a secure freezer in the pathology department. Samples will be stored until there are a number for a few participants and then transferred to secure, centralised storage at Adelaide University at regular intervals. Your samples will be labelled with your Identification Number. No personal details will be included. The investigators may store your sample for up to 15 years after the last participant completes the main study or the investigators may destroy your sample at an earlier time.

11 What if new information arises during this research project?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your study doctor will tell you about it and discuss with you whether you want to continue in the research project. If you decide to withdraw, your study doctor will make arrangements for your regular health care to continue. If you decide to continue in the research project you will be asked to sign an updated Consent Form.

Also, on receiving new information, your study doctor might consider it to be in your best interests to withdraw you from the research project. If this happens, he/ she will explain the reasons and arrange for your regular health care to continue.

This section is also relevant to any sub-studies.

12 Can I have other treatments during this research project?

Whilst you are participating in this research project, you will not be able to take morphine or other opioid medications for your Chronic Obstructive Pulmonary Disease or for other reasons. It is important to tell your study doctor and the research team about any treatments or medications you may be taking, including over-the-counter medications, vitamins or herbal remedies, acupuncture or other alternative treatments. You should also tell your study doctor about any changes to these during your participation in the research project. Your study doctor should also explain to you which treatments or medications need to be stopped for the time you are involved in the research project.

13 What if I withdraw from this research project?

If you decide to withdraw from the project, please notify a member of the research team before you withdraw. This notice will allow that person or the research supervisor to discuss any health risks or special requirements linked to withdrawing. If you do chose to withdraw you will be asked to complete a short questionnaire each day for 3 days to ensure that you are not experiencing any morphine withdrawal symptoms that may need to be treated. You are asked to not stop the study medications without first discussing this with the study investigator.

If you do withdraw your consent during the research project, the study doctor and relevant research team will not collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law. You should be aware that data collected by the research team up to the time you withdraw will form part of the research project results. If you do not want them to do this, you must tell them before you join the research project.

14 Could this research project be stopped unexpectedly?

This research project may be stopped unexpectedly for a variety of reasons. These may include reasons such as:

- Unacceptable side effects
- The drug being shown not to be effective
- The drug being shown to work and not need further testing

15 What happens when the research project ends?

At completion of your participation in the research, ongoing treatment will be discussed between you and your treating doctor. The study medication will only be available to you during the 5 phases of the research project.

When the research is completed (in about 3 years), the results will be widely distributed. A summary of the results will be provided to all the participating hospitals.

This section is also relevant to any sub-studies.

16 What will happen to information about me?

All information collected from you for this research will be stored using an Identification Number, only the study team will have access to the code that links your ID number with you.

By signing the Consent Form you consent to the study doctor and the research team collecting and using personal information about you for the research project. Any information obtained in connection with this research project that can identify you will remain confidential. You will be allocated an Identification Number, and only this number will be used when the study data is examined and presented in an aggregated manner, no individuals will be identified. Your

information will only be used for the purpose of this research project and it will only be disclosed with your permission, except as required by law.

Information about you may be obtained from your health records held at this and other health services for the purpose of this research. By signing the consent form you agree to the study team accessing health records if they are relevant to your participation in this research project.

Your health records and any information obtained during the research project are subject to inspection (for the purpose of verifying the procedures and the data) by the relevant authorities and authorised representatives of the Sponsor, Flinders University, the institution relevant to this Participant Information Sheet, *[Name of institution]*, or as required by law. By signing the Consent Form, you authorise release of, or access to, this confidential information to the relevant study personnel and regulatory authorities as noted above.

It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that you cannot be identified, except with your permission.

Information about your participation in this research project may be recorded in your health records.

In accordance with relevant Australian *and/or [Name of state/territory]* privacy and other relevant laws, you have the right to request access to your information collected and stored by the research team. You also have the right to request that any information with which you disagree be corrected. Please contact the research team member named at the end of this document if you would like to access your information. The research data will be securely stored for 15 years after the research is completed and will be destroyed at this time.

Any information obtained for the purpose of this research project that can identify you will be treated as confidential and securely stored. It will be disclosed only with your permission, or as required by law.

This section is also relevant to any sub-studies.

17 Complaints

If you suffer any injuries or complications as a result of this research, you should contact the study doctor as soon as possible, who will assist you in arranging appropriate medical treatment. If you are eligible for Medicare, you can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

If you become upset or distressed as a result of your participation in the research, the study doctor will be able to arrange for counselling or other appropriate support. Any counselling or support will be provided by qualified staff who are not members of the research project team. This counselling will be provided free of charge.

Participation in this study does not impact on your basic legal right to seek compensation; however, if you do suffer harm, you may receive compensation without litigation. In addition, you may have a right to take legal action to obtain compensation for any injuries or complications resulting from the research. You do not give up any legal rights to compensation by participating in this research project.

This section is also relevant to any sub-studies.

18 Who is organising and funding the research?

This research project is being conducted by Professor David Currow and the Palliative Care Clinical Studies Collaborative.

If knowledge acquired through this research leads to discoveries that are of commercial value to Mayne Pharma Group Limited, the study doctors or their institutions, there will be no financial benefit to you or your family from these discoveries.

Flinders University will receive a payment from National Health and Medical Research Council for undertaking this research project.

No member of the research team will receive a personal financial benefit from your involvement in this research project (other than their ordinary wages).

This section is also relevant to any sub-studies.

19 Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the HREC of Hunter New England (15/12/16/3.06).

The conduct of this research project at the [name of site] has been authorised by the [name of organisation]. [insert SSA reference number]

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

20 Further information and who to contact

The person you may need to contact will depend on the nature of your query.

If you want any further information concerning this project or if you have any medical problems which may be related to your involvement in the project (for example, any side effects), you can contact any of the following people:

Clinical contact person

Name	*[Name]*
Position	*[Position]*
Telephone	*[Phone number]*
Email	*[Email address]*

For matters relating to research at the site at which you are participating, the details of the local site complaints person are:

Complaints contact person

Name	
Position	*[Research Governance Officer or other officer*
Telephone	*[telephone number]*
Email	*[Email address]*

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Reviewing HREC approving this research and HREC Executive Officer details

Reviewing HREC name	Hunter New England Human Research Ethics Committee

HREC Executive Officer	Dr Nicole Gerrand
Address	Manager, Research Ethics and Governance Unit, Hunter New England Human Research Ethics Committee, Hunter New England Local Health District, Locked Bag 1, New Lambton NSW 2305
Telephone	(02) 49214950
Email	Hnehrec@hnehealth.nsw.gov.au

A3

Consent Form

Interventional Study - *Adult providing own consent*

Title	A pragmatic, phase III, multi-site, double-blind, placebo controlled, parallel arm, dose increment randomised trial of regular, low dose extended release morphine for chronic refractory breathlessness.
Short Title	Breathlessness, Exertion And Morphine Sulphate Study (BEAMS)
Protocol Number	030/15
Project Sponsor	Flinders University
Coordinating Principal Investigator/ Principal Investigator	Professor David Currow
Associate Investigator(s)	*[Associate Investigator(s)]*
Location	*[Location]*

Declaration by Participant

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I give permission for my doctors, other health professionals, hospitals or laboratories outside this hospital to release information to Flinders University concerning my disease and treatment for the purposes of this project. I understand that such information will remain confidential.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the study without affecting my future health care.

I understand that I will be given a signed copy of this document to keep.

Name of Participant (please print) _____

Signature _____ Date _____

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, the research project.

Note: All parties signing the consent section must date their own signature.

I understand that, if I decide to discontinue the study treatment, I may be asked to attend follow-up visits to allow collection of information regarding my health status and safety. Alternatively, a member of the research team may request my permission to obtain access to my medical records for collection of follow-up information for the purposes of research and analysis.

I consent to the storage and use of blood samples taken from me for use, as described in section 10 of the Participant Information Sheet, for:

- This specific research project
- Other research that is closely related to this research project
- Any future research.

By signing this consent section, I agree to the use of my blood samples for pharmacogenetic testing, as outlined in Section 10 of the Participant Information Sheet. This is an optional part of the study, and I can still participate in the main study even if I do not agree to provide blood samples for this part of the research.

Name of Participant (please print) _____

Signature _____ Date _____

Name of Witness* to Participant's Signature (please print) _____

Signature _____ Date _____

* Witness is not to be the investigator, a member of the study team or their delegate. In the event that an interpreter is used, the interpreter may not act as a witness to the consent process. Witness must be 18 years or older.

Name of Study Doctor/ Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of and information concerning the research project.

Note: All parties signing the consent section must date their own signature.

Appendix 4 – Sub-study 1 (semi-structured interviews) Participant Information and Consent Forms (patient and carer).

Insert Header with institution's name or institution's letterhead

Participant Information Sheet/Consent Form

Participants' and Caregivers' Sub-study - *Adult participant providing own consent*

[Insert site name]

Title	A pragmatic, phase III, multi-site, double-blind, placebo controlled, parallel arm, dose increment randomised trial of regular, low dose extended release morphine for chronic refractory breathlessness.
Short Title	Breathlessness, Exertion And Morphine Sulphate Study (BEAMS) – Participants' and Caregivers' Sub-study
Protocol Number	030/15
Project Sponsor	Flinders University
Coordinating Principal Investigator/ Principal Investigator	Diana Ferreira (PhD Candidate) / Professor David Currow
Associate Investigator(s) *(if required by institution)*	Dr Peter Allcroft
Location *(where CPI/PI will recruit)*	Southern Adelaide Palliative Services

Part 1 What does my participation involve?

1 Introduction

You are invited to participate in a research project. We are inviting you to participate because you provide care for somebody experiencing severe breathlessness as a symptom associated with their disease. The study aim is to help us find better ways of managing this symptom. **The purpose of this form is to explain the study and why we are asking patients to be involved.**

This Participant Information Sheet/Consent Form tells you about the research project. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully and ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your local doctor.

Participation in this research is voluntary. If you don't wish to take part, you don't have to. You will receive the best possible care whether or not you take part.

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:
- Understand what you have read
- Consent to take part in the research project
- Consent to have the tests and treatments that are described
- Consent to the use of your personal and health information as described.

You will be given a copy of this Participant Information Sheet/ Consent Form to keep.

2 What is the purpose of this research?

Chronic Obstructive Pulmonary Disease, sometimes called emphysema, is a major cause of suffering, reduced physical function, and increased mortality worldwide. Severe Chronic Obstructive Pulmonary Disease affects about 235,000 people in Australia and is associated with a vicious cycle of breathlessness, reduced activity, and markedly reduced physical function.

This sub-study aims to understand what is like for you living with chronic breathlessness and your perception and views on the use of morphine for this symptom. If you or your caregiver have no experience with this medicine you are still invited to participate in this sub-study. Talking to you about breathlessness is important to understand the full extent to which this symptom affects your life. Your views about morphine for breathlessness are important to understand why people may accept or not this medicine as a treatment.

3 What does participation in this research involve?

You are asked to consider this sub-study at the time of considering your own participation in the BEAMS study. You may wish to participate only in the BEAMS study, in this sub-study or both:

1. If you choose to participate in the BEAMS study, general information will be collected about you as part of the main study, and you will be asked to give an interview to the sub-study investigator at the end of your participation in the main study.

2. If you choose to participate on this sub-study but not on the BEAMS study you will be asked to be interviewed.

3. If your caregiver does not wish to participate in an interview along with you, your interview can still take place.

If you are participating in the BEAMS study and you choose to consent to this sub-study, you will be required to provide some general information about yourself as part of the main study. Information collected as part of the main study will be used in this sub-study.

If you are not participating in the BEAMS study and agree to participate in this sub-study, you will be asked some general questions about yourself which should take approximately 5 minutes. This is to complete the information we will collect with the interviews.

For all participants, interviews will be conducted separately with you and your caregiver individually at a time and place of your convenience. Each interview will take approximately 30-45 minutes to complete. If you, at any stage, do not wish to proceed with this study, you are entitled to refuse further participation. Your medical care will not be compromised because of that.

4 What do I have to do?

If you agree to participate in this research it is important that you follow all instructions and provide some general information about yourself. The study nurse will help you through this process if necessary. You will also be asked for a contact (phone or email). This is for the researcher to contact you and schedule the best time and location to conduct the interview.

5 Other relevant information about the research project

This research will be conducted in South Australia.

6 Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

If you do decide to take part, you will be given this Participant Information Sheet / Consent Form to sign and you will be given a copy to keep.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your treatment or your participation in the main study.

7 What are the possible benefits of taking part?

While we intend that this research furthers medical knowledge and may improve symptoms of breathlessness for people with Chronic Obstructive Pulmonary Disease in the future, it will not be of direct benefit to you.

8 What are the possible risks and disadvantages of taking part?

We will ask you to answer to some questions about living with chronic breathlessness. There is a small risk that answering these questions may cause you to reflect on your life and situation and cause you to be distressed. The study nurses will talk to you about these feelings and will stop the questionnaire if you feel unable or too upset to continue.
If you feel too tired or too breathlessness during the interview, you may complete the interview during the following days. Also, if some new concerns about your disease arise during the interviews, the research team will discuss them with you and answer your questions.

9 What happens when the research project ends?

When the research is completed (in about 3 years), the results will be widely distributed. A summary of the results will be provided to all the participating hospitals.

Part 2 How is the research project being conducted?

10 What will happen to information about me?

You should be aware that the results of this study may be processed by computer, but no names or identifying information will be used in the data entered on the computer. All records containing personal information will remain confidential and no information which could lead to identification of any individual will be released.

Your identity will not be disclosed in the event of any publication arising from this study. It is possible that the participants' health records and information may be disclosed to other agencies such as the sponsor, regulatory bodies (including the Therapeutic Goods Administration) and Ethics Committees. This will only occur when necessary and the provisions of Australian privacy law will be complied with.

In accordance with relevant Australian *and/or [Name of state/territory]* privacy and other relevant laws, you have the right to request access to your information collected and stored by the research team. You also have the right to request that any information with which you disagree be corrected. Please contact the research team member named at the end of this document if you would like to access your information. The research data will be securely stored for 15 years after the research is completed and will be destroyed at this time.

Any information obtained for the purpose of this research project that can identify you will be treated as confidential and securely stored. It will be disclosed only with your permission, or as required by law.

11 Who is organising and funding the research?

This research project is being conducted by Professor David Currow, Ms Diana Ferreira and the Palliative Care Clinical Studies Collaborative.

If knowledge acquired through this research leads to discoveries that are of commercial value to Mayne Pharmaceuticals, the study doctors or their institutions, there will be no financial benefit to you or your family from these discoveries.

Flinders University will receive a payment from National Health and Medical Research Council for undertaking this research project.

No member of the research team will receive a personal financial benefit from your involvement in this research project (other than their ordinary wages).

12 Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the HREC of Hunter New England 15/12/16/3.06.

The conduct of this research project at the [name of site] has been authorised by the [name of organisation]. [insert SSA reference number]

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

13 Further information and who to contact

The person you may need to contact will depend on the nature of your query.

If you want any further information concerning this project or if you have any medical problems which may be related to your involvement in the project (for example, any side effects), you can contact any of the following people:

Clinical contact person

Name	*[Name]*
Position	*[Position]*
Telephone	*[Phone number]*
Email	*[Email address]*

For matters relating to research at the site at which you are participating, the details of the local site complaints person are:

Complaints contact person

Name	
Position	*[Research Governance Officer or other officer*
Telephone	*[telephone number]*
Email	*[Email address]*

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Reviewing HREC approving this research and HREC Executive Officer details

Reviewing HREC name	Hunter New England Human Research Ethics Committee
HREC Executive Officer	Dr Nicole Gerrand
Address	Manager, Research Ethics and Governance Unit, Hunter New England Human Research Ethics Committee, Hunter New England Local Health District, Locked Bag 1, New Lambton NSW 2305
Telephone	(02) 49214950
Email	Hnehrec@hnehealth.nsw.gov.au

A4

Consent Form – Participants' and Caregivers' sub-study

Adult participant providing own consent

Title	A pragmatic, phase III, multi-site, double-blind, placebo controlled, parallel arm, dose increment randomised trial of regular, low dose extended release morphine for chronic refractory breathlessness.
Short Title	Breathlessness, Exertion And Morphine Sulphate Study (BEAMS) Participants' and Caregivers' Sub-Study
Protocol Number	030/15
Project Sponsor	Flinders University
Coordinating Principal Investigator/ Principal Investigator	Diana Ferreira (PhD Candidate) / Professor David Currow
Associate Investigator(s)	Dr Peter Allcroft
Location	Southern Adelaide Palliative Care Services

Declaration by Participant

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the study without affecting my future health care.

I understand that I will be given a signed copy of this document to keep.

Name of Participant (please print) _____

Signature _____ Date _____

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, the research project.

Note: All parties signing the consent section must date their own signature.

Participant Information Sheet/Consent Form

Participants' and **Caregivers'** Sub-study - *Adult caregiver providing own consent*

[Insert site name]

Title	A pragmatic, phase III, multi-site, double-blind, placebo controlled, parallel arm, dose increment randomised trial of regular, low dose extended release morphine for chronic refractory breathlessness.
Short Title	Breathlessness, Exertion And Morphine Sulphate Study (BEAMS) – Participants' and Caregivers' Sub-study
Protocol Number	030/15
Project Sponsor	Flinders University
Coordinating Principal Investigator/ Principal Investigator	Diana Ferreira (PhD Candidate) / Professor David Currow
Associate Investigator(s) *(if required by institution)*	Dr Peter Allcroft
Location *(where CPI/PI will recruit)*	Southern Adelaide Palliative Services

Part 1 What does my participation involve?

1 Introduction

You are invited to participate in a research project. We are inviting you to participate because you provide care for somebody experiencing severe breathlessness as a symptom associated with their disease. The study aim is to help us find better ways of managing this symptom. **The purpose of this form is to explain the study and why we are asking caregivers to be involved.**

This Participant Information Sheet/Consent Form tells you about the research project. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully and ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your local doctor.

Participation in this research is voluntary. If you don't wish to take part, you don't have to. You will receive the best possible care whether or not you take part.

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:

- Understand what you have read
- Consent to take part in the research project
- Consent to have the tests and treatments that are described
- Consent to the use of your personal and health information as described.

You will be given a copy of this Participant Information Sheet/ Consent Form to keep.

2 What is the purpose of this research?

Chronic Obstructive Pulmonary Disease, sometimes called emphysema, is a major cause of suffering, reduced physical function, and increased mortality worldwide. Severe Chronic Obstructive Pulmonary Disease affects about 235,000 people in Australia and is associated with a vicious cycle of breathlessness, reduced activity, and markedly reduced physical function.

This sub-study aims to understand what is like for you caring for someone with chronic breathlessness and your perception and views on the use of morphine for this symptom. If you or the person you provide care for have no experience with this medicine you are still invited to participate in this sub-study. Talking to you about breathlessness is important to understand the full extent to which the symptom of the person for whom you provide care affects your life. Your views about morphine for breathlessness are important to understand why people may accept or not this medicine as a treatment.

3 What does participation in this research involve?

You are asked to consider this sub-study at the time of considering your own participation in the BEAMS study. You may wish to participate only in the BEAMS study, in this sub-study or both:

1. If you choose to participate in the BEAMS study, general information will be collected about you as part of the main study, and you will be asked to give an interview to the sub-study investigator at the end of your participation in the main study.

2. If you choose to participate on this sub-study but not on the BEAMS study you will be asked to be interviewed.

3. If the person for whom you provide care does not wish to participate in an interview, your interview can still take place.

If you are participating in the BEAMS study and you choose to consent to this sub-study, you will be required to provide some general information about yourself as part of the main study. Information collected as part of the main study will be used in this sub-study.

If you are not participating in the BEAMS study and agree to participate in this sub-study, you will be asked some general questions about yourself which should take approximately 5 minutes. This is to complete the information we will collect with the interviews.

For all participants, interviews will be conducted separately with you and the participant individually at a time and place of your convenience. Each interview will take approximately 30-45 minutes to complete. If you, at any stage, do not wish to proceed with this study, you are entitled to refuse further participation. Your relative's medical care will not be compromised because of that.

4 What do I have to do?

If you agree to participate in this research it is important that you follow all instructions and complete the form with some general information about yourself. The study nurse will help you through this process if necessary. You will also be asked for a contact (phone or email). This is for the researcher to contact you and schedule the best time and location to conduct the interview.

5 Other relevant information about the research project

This research will be conducted in South Australia.

6 Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

If you do decide to take part, you will be given this Participant Information Sheet / Consent Form to sign and you will be given a copy to keep.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect the treatment offered to the person for whom you provide care, and it will not affect their participation in the main study.

7 What are the possible benefits of taking part?

While we intend that this research furthers medical knowledge and may improve symptoms of breathlessness for people with Chronic Obstructive Pulmonary Disease in the future, it will not be of direct benefit to your relative.

8 What are the possible risks and disadvantages of taking part?

We will ask you to answer some questions about your life caring for someone else. There is a small risk that answering these questions may cause you to reflect on your life and situation and cause you to be distressed. The study nurses will talk to you about these feelings and will stop the questionnaire if you feel unable or too upset to continue. Also, if some new concerns about your relative's disease arise during the interviews, the research team will discuss them with you and answer your questions.

9 What happens when the research project ends?

When the research is completed (in about 3 years), the results will be widely distributed. A summary of the results will be provided to all the participating hospitals.

Part 2 How is the research project being conducted?

10 What will happen to information about me?

You should be aware that the results of this study may be processed by computer, but no names or identifying information will be used in the data entered on the computer. All records containing personal information will remain confidential and no information which could lead to identification of any individual will be released.

Your identity will not be disclosed in the event of any publication arising from this study. It is possible that the participants' health records and information may be disclosed to other agencies such as the sponsor, regulatory bodies (including the Therapeutic Goods Administration) and Ethics Committees. This will only occur when necessary and the provisions of Australian privacy law will be complied with.

In accordance with relevant Australian *and/or [Name of state/territory]* privacy and other relevant laws, you have the right to request access to your information collected and stored by the research team. You also have the right to request that any information with which you disagree be corrected. Please contact the research team member named at the end of this document if you would like to access your information. The research data will be securely stored for 15 years after the research is completed and will be destroyed at this time.

Any information obtained for the purpose of this research project that can identify you will be treated as confidential and securely stored. It will be disclosed only with your permission, or as required by law.

11 Who is organising and funding the research?

This research project is being conducted by Professor David Currow, Ms Diana Ferreira and the Palliative Care Clinical Studies Collaborative.

If knowledge acquired through this research leads to discoveries that are of commercial value to Mayne Pharmaceuticals, the study doctors or their institutions, there will be no financial benefit to you or your family from these discoveries.

Flinders University will receive a payment from National Health and Medical Research Council for undertaking this research project.

No member of the research team will receive a personal financial benefit from your involvement in this research project (other than their ordinary wages).

12 Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the HREC of Hunter New England 15/12/16/3.06.

The conduct of this research project at the [name of site] has been authorised by the [name of organisation]. [insert SSA reference number]

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

13 Further information and who to contact

The person you may need to contact will depend on the nature of your query.

If you want any further information concerning this project or if you have any medical problems which may be related to your involvement in the project (for example, any side effects), you can contact any of the following people:

Clinical contact person

Name	*[Name]*
Position	*[Position]*
Telephone	*[Phone number]*
Email	*[Email address]*

For matters relating to research at the site at which you are participating, the details of the local site complaints person are:

Complaints contact person

Name	
Position	*[Research Governance Officer or other officer*
Telephone	*[telephone number]*
Email	*[Email address]*

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Reviewing HREC approving this research and HREC Executive Officer details

Reviewing HREC name	Hunter New England Human Research Ethics Committee
HREC Executive Officer	Dr Nicole Gerrand
Address	Manager, Research Ethics and Governance Unit, Hunter New England Human Research Ethics Committee, Hunter New England Local Health District, Locked Bag 1, New Lambton NSW 2305
Telephone	(02) 49214950
Email	Hnehrec@hnehealth.nsw.gov.au

Consent Form – Participants' and Caregivers' sub-study

Adult caregiver providing own consent

Title	A pragmatic, phase III, multi-site, double-blind, placebo controlled, parallel arm, dose increment randomised trial of regular, low dose extended release morphine for chronic refractory breathlessness.
Short Title	Breathlessness, Exertion And Morphine Sulphate Study (BEAMS) Participants' and Caregivers' Sub-Study
Protocol Number	030/15
Project Sponsor	Flinders University
Coordinating Principal Investigator/ Principal Investigator	Diana Ferreira (PhD Candidate) / Professor David Currow
Associate Investigator(s)	Dr Peter Allcroft
Location	Southern Adelaide Palliative Care Services

Declaration by Participant

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the study without affecting my future health care.

I understand that I will be given a signed copy of this document to keep.

Name of Participant (please print) _____

Signature _____ Date _____

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, the research project.

Note: All parties signing the consent section must date their own signature.

A4

Appendix 5 – Sub-study 3 (driving simulation) Participant Information and Consent Form.

Insert Header with institution's name or institution's letterhead

Participant Information Sheet/Consent Form

Driving Sub-study - *Adult providing own consent*

[Insert site name]

Title	A pragmatic, phase III, multi-site, double-blind, placebo controlled, parallel arm, dose increment randomised trial of regular, low dose extended release morphine for chronic refractory breathlessness.
Short Title	Breathlessness, Exertion And Morphine Sulphate Study (BEAMS) - Driving Sub-Study
Protocol Number	030/15
Project Sponsor	Flinders University
Coordinating Principal Investigator/ Principal Investigator	Professor David Currow
Associate Investigator(s) *(if required by institution)*	*[Associate Investigator(s)]*
Location *(where CPI/PI will recruit)*	*[Location]*

1 Introduction

You are invited to take part in this sub-study. This is because you have Chronic Obstructive Pulmonary Disease (emphysema), and you have kindly agreed to participate in the main study.

This Participant Information Sheet/Consent Form tells you about the sub-study. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully and ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your local doctor.

Participation in this sub-study is voluntary. If you don't wish to take part, you don't have to. If you don't wish to take part in the sub-study, you can still take part in the main study. You will receive the best possible care whether or not you take part.

If you decide you want to take part in this sub-study, you will be asked to sign the consent section. By signing it you are telling us that you:

- Understand what you have read
- Consent to take part in the research project
- Consent to have the tests and treatments that are described
- Consent to the use of your personal and health information as described.

You will be given a copy of this Participant Information Sheet/ Consent Form to keep.

2 What is the purpose of this research?

A sub-study is where specific additional information is collected while a person, such as yourself has already agreed to participate in a larger study. You can participate in the larger main study and NOT participate in a sub-study, but you are NOT able to participate in a sub-study without the main study.

This sub-study has been initiated by the study doctor, Professor David Currow and a large team of international experts in the field. No funding has been provided for this sub-study.

The aim of this sub-study is to explore the impact on driving in people with Chronic Obstructive Pulmonary Disease (emphysema) with the addition of small doses of morphine.

3 What does participation in this research involve?

If you agree to participate in this sub-study, you will be asked to sign the Participant Consent Form. Once you have signed the Participant Consent Form you will then be asked to commence this sub-study.

If you are from Adelaide, you will be asked to remain for longer following the baseline assessment for the main study for an additional 30 minutes.

If you are from Sydney, you will need to perform the study at the Neuroscience Research Australia, an institute located in Randwick.

You will be asked to complete a small questionnaire to understand your driving habits. A driving simulation task will then be performed. The AusEd driving simulator is designed to assess any changes in alertness or concentration in a clinical laboratory. The AusEd driving simulator consists of a computer display of a road and requires you to use a steering wheel and foot pedals to simulate driving a car. You will be instructed to brake in response to other vehicles and keep a speed within 60-80 km/h on the speedometer. You will have a number of small sticky probes attached to your head (similar to the sticky pads used to measure your heart rate) to monitor and measure subtle changes in your alertness and concentration
You will be asked to complete the same assessment for another 30 minutes on day 2 of the first week and again on day 7. This will mean 2 additional visits to the office.

Time period: Thirty minutes at baseline, day 2 and day 7 on the first week only.

There are no additional costs associated with participating in this sub-study, nor will you be paid. All medication, tests and medical care required as part of the sub-study will be provided to you free of charge.

You may be reimbursed for any reasonable travel, parking, meals and other expenses associated with the research project visits.

4 What do I have to do?

If you agree to participate in this sub-study it is important that you follow all instructions and attend each appointment made for you. You must ensure that you take the study medications as instructed, and inform the research team if you experience any problems.

You can take all of you other current medications and continue all other treatments, there is no restriction on your activity or lifestyle.

5 Other relevant information about the research project

There will be a total of 20 people participating in this sub-study, with equal numbers from each state. This research will be conducted in South Australia and New South Wales.

6 What are the possible benefits of taking part?

While we intend that this research furthers medical knowledge and may improve symptoms of breathlessness for people with Chronic Obstructive Pulmonary Disease (emphysema) in the future, it may not be of direct benefit to you.

7 What are the possible risks and disadvantages of taking part?

Although this simulates driving, some people may feel unwell as they start to use the driving simulator. These effects are not usually serious and last only a short time. If you feel unwell, the study will be stopped immediately.

The results of the driving simulation data will not be examined until the end of the study. Your individual results will not be shared with state driving regulators, nor will the results impact on your driving licence or conditions of driving.

If your diving skills get worse during the study, we will strongly recommend you to address this issue with your General Practitioner (GP). **The study staff will not inform your GP unless you give permission to do so.**

8 Can I have other treatments during this research project?

There will be no changes made to any of your other treatments, and your participation in the main study will not be affected during this sub-study.

9 What if I withdraw from this research project?

If you decide to withdraw from the sub-study, please notify a member of the research team before you withdraw. This notice will allow that person or the research supervisor to discuss any health risks or special requirements linked to withdrawing.

If you do withdraw your consent for this sub-study, it will not have any impact on your participation in the main study.

If you withdraw from the main study, you would also be withdrawn from this sub-study.

10 Could this research project be stopped unexpectedly?

This sub-study may be stopped unexpectedly for a variety of reasons. These may include reasons such as:

- Unexpected closure of the main study
- The equipment being inoperative or otherwise unable to process the data collected

11 Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the HREC of Hunter New England (15/12/16/3.06).

The conduct of this research project at the [name of site] has been authorised by the [name of organisation]. [insert SSA reference number]

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

12 Further information and who to contact

The person you may need to contact will depend on the nature of your query.

If you want any further information concerning this sub-study or if you have any medical problems which may be related to your involvement in the project (for example, any side effects), you can contact any of the following people:

Clinical contact person

Name	*[Name]*
Position	*[Position]*
Telephone	*[Phone number]*
Email	*[Email address]*

For matters relating to sub-study at the site at which you are participating, the details of the local site complaints person are:

Complaints contact person

Name	
Position	*[Research Governance Officer or other officer*
Telephone	*[telephone number]*
Email	*[Email address]*

If you have any complaints about any aspect of the sub-study, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Reviewing HREC approving this research and HREC Executive Officer details

Reviewing HREC name	Hunter New England Human Research Ethics Committee
HREC Executive Officer	Dr Nicole Gerrand
Address	Manager, Research Ethics and Governance Unit, Hunter New England Human Research Ethics Committee, Hunter New England Local Health District, Locked Bag 1, New Lambton NSW 2305
Telephone	(02) 49214950
Email	Hnehrec@hnehealth.nsw.gov.au

Driving Sub-study

Consent Form - *Adult providing own consent*

Title	A pragmatic, phase III, multi-site, double-blind, placebo controlled, parallel arm, dose increment randomised trial of regular, low dose extended release morphine for chronic refractory breathlessness
Short Title	Breathlessness, Exertion And Morphine Sulphate Study (BEAMS) - Driving Sub-Study
Protocol Number	030/15
Project Sponsor	Flinders University
Coordinating Principal Investigator/ Principal Investigator	Professor David Currow
Associate Investigator(s)	*[Associate Investigator(s)]*
Location	*[Location]*

Declaration by Participant

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the sub-study.

I give permission for my doctors, other health professionals, hospitals or laboratories outside this hospital to release information to Flinders University concerning my disease and treatment for the purposes of this sub-study. I understand that such information will remain confidential.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this sub-study as described and understand that I am free to withdraw at any time during the study without affecting my future health care.

I understand that I will be given a signed copy of this document to keep.

Name of Participant (please print) _____

Signature _____ Date _____

Name of Witness* to Participant's Signature (please print) _____

Signature _____ Date _____

* Witness is not to be the investigator, a member of the study team or their delegate. In the event that an interpreter is used, the interpreter may not act as a witness to the consent process. Witness must be 18 years or older.

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the sub-study, its procedures and risks and I believe that the participant has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, the research project.

Note: All parties signing the consent section must date their own signature.

I understand that, if I decide to discontinue the study treatment, I may be asked to attend follow-up visits to allow collection of information regarding my health status and safety. Alternatively, a member of the research team may request my permission to obtain access to my medical records for collection of follow-up information for the purposes of research and analysis.

Appendix 6 – Sub-study 5 (salivary cortisol analysis) Participant Information and Consent Form.

Insert Header with institution's name or institution's letterhead

Participant Information Sheet/Consent Form

Cortisol Sub-study - *Adult providing own consent*

[Insert site name]

Title	A pragmatic, phase III, multi-site, double-blind, placebo controlled, parallel arm, dose increment randomised trial of regular, low dose extended release morphine for chronic refractory breathlessness
Short Title	Breathlessness, Exertion And Morphine Sulphate Study (BEAMS) – Cortisol Sub-Study
Protocol Number	030/15
Project Sponsor	Flinders University
Coordinating Principal Investigator/ Principal Investigator	Professor David Currow / Diana Ferreira (PhD candidate – Flinders University)
Associate Investigator(s) *(if required by institution)*	*[Associate Investigator(s)]*
Location *(where CPI/PI will recruit)*	*[Location]*

1 Introduction

You are invited to take part in this sub-study. This is because you have Chronic Obstructive Pulmonary Disease, and you have kindly agreed to participate in the main study.

This Participant Information Sheet/Consent Form tells you about the cortisol sub-study. It explains the tests involved. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully and ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your local doctor.

Participation in this research is voluntary. If you don't wish to take part, you don't have to. You will receive the best possible care whether or not you take part.

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:
- Understand what you have read
- Consent to take part in the research project
- Consent to have the tests that are described
- Consent to the use of your personal and health information as described.

You will be given a copy of this Participant Information Sheet/ Consent Form to keep.

2 What is the purpose of this research?

A sub-study is where specific additional information is collected while you have already agreed to participate in a larger study. You can participate in the larger main study and NOT participate in a sub-study, but you are NOT able to participate in a sub-study without the main study.

This sub-study has been initiated by the study doctor, Professor David Currow and a large team of international experts in the field. No funding has been provided for this sub-study.

The aim of this sub-study is to explore how morphine affects the cortisol levels in people with Chronic Obstructive Pulmonary Disease. Cortisol is a hormone produced by the body in response to stress. In healthy people, cortisol levels vary across the day. For instance, when people get up in the morning, they require more energy to start the day so cortisol levels increase to help the body start functioning. In the evening energy requirements are lower and people are usually more relaxed so cortisol levels tend to be low. In people with breathlessness like you, cortisol levels tend to be constant across the day, meaning that they tend not to decrease substantially from morning to evening. This sub-study intends to see if morphine changes the typical cortisol profile in people with breathlessness.

3 What does participation in this research involve?

If you agree to participate in this sub-study, you will be asked to sign the Participant Consent Form. Once you have signed the Participant Consent Form you will then be asked to commence this sub-study.

This study will not require additional visits.

We will ask you to collect 3 saliva samples per day for 2 days. This will happen four times during the study, once at baseline, once at the end of week 1, once the end of week 3 and once at the end of 3 months in the extension period. A total of 24 saliva samples will be required during the sub-study. If you do not proceed to later stages of the BEAMS study, you will not be required to collect these samples. For each collection period you will take home 6 plastic tubes, each one with a small cylindrical swab. Each tube will be labelled with the day and expected time of collection. In each collection time, we ask you to chew on the swab for 1 minute and return it back to the respective plastic container. You can then store it in your own freezer until you see the study nurses again, the nurses will then take the samples with them. Keeping the samples cold and not frozen when you attend visits is acceptable. We will also ask you to fill a small questionnaire about the times in which you collected the samples which will take you less than 5 minutes per day.

Time period: 7 minutes per day (8 days).

There are no additional costs associated with participating in this sub-study, nor will you be paid. All tests required as part of the sub-study will be provided to you free of charge.

4 What do I have to do?

If you agree to participate in this sub-study it is important that you follow all instructions and attend each appointment made for you. You must ensure that you take the study medications as instructed, and inform the research team if you experience any problems.

You can take all of you other current medications and continue all other treatments, there is no restriction on your activity or lifestyle.

5 Other relevant information about the research project

All BEAMS study participants will be asked to participant in this sub-study. We expect a total of 75 people participating in this sub-study, with equal numbers expected in each state. This

research will be conducted in 18 hospitals across South Australia, New South Wales, Victoria and Queensland.

6 What are the possible benefits of taking part?

While we intend that this research furthers medical knowledge and may improve symptoms of breathlessness for people with Chronic Obstructive Pulmonary Disease in the future, it may not be of direct benefit to you.

7 What are the possible risks and disadvantages of taking part?

The risks of participating in this sub-study are:

Collecting saliva samples with an oral swab may cause local discomfort, particularly if you have dry mouth. If this happens, please discuss this situation to the research team.

8 What will happen to my saliva samples?

The saliva samples taken as part of this sub-study will be stored frozen in a secure freezer in the pathology department. Samples will be stored until there are a number for a few participants and then transferred to secure, centralised storage at Flinders University at regular intervals. Your samples will be labelled with your Identification Number. No personal details will be included. The investigators may store your sample for up to 15 years after the last participant completes the main study or the investigators may destroy your sample at an earlier time.

9 Can I have other treatments during this research project?

There will be no changes made to any of your other treatments, and your participation in the main study will not be affected by your participating in the sub-study.

10 What if I withdraw from this research project?

If you decide to withdraw from the sub-study, please notify a member of the research team before you withdraw. This notice will allow that person or the research supervisor to discuss any health risks or special requirements linked to withdrawing.

If you do withdraw your consent for this sub-study, it will not have any impact on your participation in the main study.

11 Could this research project be stopped unexpectedly?

This research project may be stopped unexpectedly for a variety of reasons. These may include reasons such as:

- Unacceptable side effects
- The saliva testing equipment being inoperative or otherwise unable to process the saliva samples.

12 Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the HREC of Hunter New England (15/12/16/3.06).

The conduct of this research project at the [name of site] has been authorised by the [name of organisation]. [insert SSA reference number]

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

13 Further information and who to contact

The person you may need to contact will depend on the nature of your query.

If you want any further information concerning this research project or if you have any medical problems which may be related to your involvement in the project (for example, any side effects), you can contact any of the following people:

Clinical contact person

Name	*[Name]*
Position	*[Position]*
Telephone	*[Phone number]*
Email	*[Email address]*

For matters relating to research at the site at which you are participating, the details of the local site complaints person are:

Complaints contact person

Name	
Position	*[Research Governance Officer or other officer*
Telephone	*[telephone number]*
Email	*[Email address]*

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Reviewing HREC approving this research and HREC Executive Officer details

Reviewing HREC name	Hunter New England Human Research Ethics Committee
HREC Executive Officer	Dr Nicole Gerrand
Address	Manager, Research Ethics and Governance Unit, Hunter New England Human Research Ethics Committee, Hunter New England Local Health District, Locked Bag 1, New Lambton NSW 2305
Telephone	(02) 49214950
Email	Hnehrec@hnehealth.nsw.gov.au

Cortisol Sub-study

Consent Form - *Adult providing own consent*

Title	A pragmatic, phase III, multi-site, double-blind, placebo controlled, parallel arm, dose increment randomised trial of regular, low dose extended release morphine for chronic refractory breathlessness
Short Title	Breathlessness, Exertion And Morphine Sulphate Study (BEAMS) – Cortisol Sub-Study
Protocol Number	030/15
Project Sponsor	Flinders University
Coordinating Principal Investigator/ Principal Investigator	Professor David Currow / Diana Ferreira (PhD Candidate – Flinders University)
Associate Investigator(s)	*[Associate Investigator(s)]*
Location	*[Location]*

Declaration by Participant

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the sub-study.

I give permission for my doctors, other health professionals, hospitals or laboratories outside this hospital to release information to Flinders University concerning my disease and treatment for the purposes of this sub-study. I understand that such information will remain confidential.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this sub-study as described and understand that I am free to withdraw at any time during the study without affecting my future health care.

I understand that I will be given a signed copy of this document to keep.

Name of Participant (please print) _____

Signature _____ Date _____

Name of Witness* to Participant's Signature (please print) _____

Signature _____ Date _____

* Witness is not to be the investigator, a member of the study team or their delegate. In the event that an interpreter is used, the interpreter may not act as a witness to the consent process. Witness must be 18 years or older.

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the sub-study, its procedures and risks and I believe that the participant has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, the research project.

Note: All parties signing the consent section must date their own signature.

I understand that, if I decide to discontinue the study treatment, I may be asked to attend follow-up visits to allow collection of information regarding my health status and safety. Alternatively, a member of the research team may request my permission to obtain access to my medical records for collection of follow-up information for the purposes of research and analysis.

Appendix 7 – List of ethical approvals obtained for this project (BEAMS sub-studies).

NSW GOVERNMENT Health
Hunter New England
Local Health District

2 February 2016

Professor David Currow
Palliative & Supportive Services
Flinders University
700 Goodwood Road
Daw Park SA 5041

Dear Professor Currow,

Re: BEAMS: A pragmatic, phase III, multisite, double-blind, placebo controlled, parallel arm, dose increment randomised trial of regular, low dose extended release morphine for chronic refractory breathlessness (15/12/16/3.06)

HNEHREC Reference No: 15/12/16/3.06
NSW HREC Reference No: HREC/15/HNE/502

Thank you for submitting the above protocol for single ethical review for a multi-centre study. This project was first considered by the Hunter New England Human Research Ethics Committee at its meeting held on **16 December 2015**. This Human Research Ethics Committee is constituted and operates in accordance with the National Health and Medical Research Council's *National Statement on Ethical Conduct in Human Research (2007)* (National Statement) and the *CPMP/ICH Note for Guidance on Good Clinical Practice*. Further, this Committee has been accredited by the NSW Department of Health as a lead HREC under the model for single ethical and scientific review. The Committee's Terms of Reference are available from the Hunter New England Local Health District website.

As part of the procedure for ethical approval of research involving humans in Hunter New England Health the above protocol has reviewed by the Clinical Trials Subcommittee, an advisory group of the Hunter New England Human Research Ethics Committee.

I am pleased to advise, the Hunter New England Human Research Ethics Committee has determined that the above protocol meets the requirements of the *National Statement on Ethical Conduct in Human Research* and following acceptance of the requested clarifications and revised recruitment documentation by Dr Nicole Gerrand Manager, Research Support & Development under delegated authority from the Committee, grants ethical approval of the above project.

The following documentation has been reviewed and approved by the Hunter New England Human Research Ethics Committee:

Document	Version	Date
NEAF	Submission Code: AU/1/3AC223	
Victorian Specific Module		22 December 2015
BEAMs Protocol 030/15	Version 1.0	17 November 2015

Hunter New England Research Support & Development Office
Locked Bag No 1
New Lambton NSW 2305
Telephone: (02) 49214950 Facsimile: (02) 49214818
Email: HNELHD-HREC@hnehealth.nsw.gov.au
http://www.hnehealth.nsw.gov.au/ethics/Pages/Research-Ethics-and-Governance-Unit.aspx

KADIAN® Morphine Sulfate Extended-Release Capsules		
KAPANOL CAPSULES Product Information		
Participant Information Statement and Consent Form	Master Version 1.2	1 February 2016
Caregiver Participant Information Statement and Consent Form	Master Version 1.1	22 December 2015
Home Sleep Sub-study Information Statement and Consent Form	Master Version 1.1	22 December 2015
Driving Sub-study Information Statement and Consent Form	Master Version 1.1	22 December 2015
PK/PD Sub-study Information Statement and Consent Form	Master Version 1.1	22 December 2015
Patient Study Card	Master Version 1.0	December 2015
Advertising Poster Patient Waiting areas PaCCSC	Master Version V1.0	December 2015
Participant Management Information Instructions	Version 1.0	December 2015
Participant Safety Poster	Master Version 1	December 2015
ResMed ApneaLink™ Plus PORTABLE MONITORING DEVICE Fact Sheet		
Visit schedule	Master Version 1.0	December 2015
Participant Diary	Master Version V1.0	December 2015
Modified Borg Dyspnoea Scale	Master Version 1.0	December 2015
Chronic Respiratory Questionnaire Self-Administered Standardized Format (CRQ-SAS) 2 TO 3 DAY RECALL First Administration	Master Version 1.0	December 2015
Chronic Respiratory Questionnaire Self-Administered Standardized Format (CRQ-SAS) 2 TO 3 DAY RECALL Follow-up Administration	Master Version 1.0	December 2015
EQ-5D-5L Health Questionnaire English version for Australia	Master Version 1.0	December 2015
Epworth Sleepiness Scale	Master Version 1.0	December 2015
Karolinska Sleepiness Scale		
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Edmonton Symptom Assessment System: (revised version) (ESAS-R)	Master Version 1.0	November 2015
COPD Assessment Test™ (CAT)	Master Version 1.0	November 2015
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ZARIT Caregiver Burden Interview	Master Version 1.0	December 2015
030 LungNet Advertising Article BEAMS	Version 1.1	December 2015

030 Advertising Article BEAMS	Version 1.1	December 2015
Advertising Poster Staff	Master Version 1.0	December 2015
030 Clinic Recruitment Card (Front and Reverse)	Version 1.1	December 2015
GP Letter	Master Version 1.0	December 2015

For the protocol: **BEAMS: A pragmatic, phase III, multisite, double-blind, placebo controlled, parallel arm, dose increment randomised trial of regular, low dose extended release morphine for chronic refractory breathlessness [Protocol 030/15 Version 1.0 dated 17 November 2015]**

Approval has been granted for this study to take place at the following sites:

- **Braeside Hospital, NSW**
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- **St Vincent's Hospital Melbourne, VIC**

Approval from the Hunter New England Human Research Ethics Committee for the above protocol is given for a maximum of **3** years from the date of this letter, after which a renewal application will be required if the protocol has not been completed.

The *National Statement on Ethical Conduct in Human Research (2007)*, which the Committee is obliged to adhere to, include the requirement that the committee monitors the research protocols it has approved. In order for the Committee to fulfil this function, it requires:

- A report of the progress of the above protocol be submitted at 12 monthly intervals. Your review date is **February 2017**. A proforma for the annual report will be sent two weeks prior to the due date.

- A final report must be submitted at the completion of the above protocol, that is, after data analysis has been completed and a final report compiled. A proforma for the final report will be sent two weeks prior to the due date.

- All variations or amendments to this protocol, including amendments to the Information Sheet and Consent Form, must be forwarded to and approved by the Hunter New England Human Research Ethics Committee prior to their implementation.

- The Principal Investigator will immediately report anything which might warrant review of ethical approval of the project in the specified format, including:

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http://www.hnehealth.nsw.gov.au/ethics/Pages/Research-Ethics-and-Governance-Unit.aspx

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- Serious adverse events that occur during the study or within six months of completion of the trial at your site should be reported to the Manager, Research Support & Development Office, of the Hunter New England Human Research Ethics Committee as soon as possible and at the latest within 72 hours.

- All other safety reporting should be in accordance with the NHMRC's Safety Monitoring Position Statement – May 2009 available at http://www.nhmrc.gov.au/health_ethics/hrecs/reference/_files/090609_nhmrc_position_statement.pdf

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- Unforeseen events that might affect continued ethical acceptability of the project.

- If for some reason the above protocol does not commence (for example it does not receive funding); is suspended or discontinued, please inform Dr Nicole Gerrand as soon as possible.

You are reminded that this letter constitutes ethical approval only. You must not commence this research project at a site until separate authorisation from the Chief Executive or delegate of your site has been obtained.

A copy of this letter must be forwarded to all site investigators for submission to the relevant Research Governance Officer.

Please quote **15/12/16/3.06** in all correspondence.

Should you have any concerns or questions about your research, please contact Dr Gerrand as per the details at the bottom of the page. The Hunter New England Human Research Ethics Committee wishes you every success in your research.

Yours faithfully

Content removed for privacy reasons

For: Ms M Hunter
Acting Chair
Hunter New England Human Research Ethics Committee

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Health
Hunter New England
Local Health District

2 February 2016

Professor David Currow
Palliative & Supportive Services
Flinders University
700 Goodwood Road
Daw Park SA 5041

Dear Professor Currow,

Re: BEAMS: A pragmatic, phase III, multisite, double-blind, placebo controlled, parallel arm, dose increment randomised trial of regular, low dose extended release morphine for chronic refractory breathlessness (15/12/16/3.06)

HNEHREC Reference No: 15/12/16/3.06
NSW HREC Reference No: HREC/15/HNE/502

Thank you for submitting the above protocol for single ethical review for a multi-centre study. This project was first considered by the Hunter New England Human Research Ethics Committee at its meeting held on **16 December 2015.** This Human Research Ethics Committee is constituted and operates in accordance with the National Health and Medical Research Council's *National Statement on Ethical Conduct in Human Research (2007)* (National Statement) and the *CPMP/ICH Note for Guidance on Good Clinical Practice*. Further, this Committee has been accredited by the NSW Department of Health as a lead HREC under the model for single ethical and scientific review. The Committee's Terms of Reference are available from the Hunter New England Local Health District website.

As part of the procedure for ethical approval of research involving humans in Hunter New England Health the above protocol has reviewed by the Clinical Trials Subcommittee, an advisory group of the Hunter New England Human Research Ethics Committee.

I am pleased to advise, the Hunter New England Human Research Ethics Committee has determined that the above protocol meets the requirements of the *National Statement on Ethical Conduct in Human Research* and following acceptance of the requested clarifications and revised recruitment documentation by Dr Nicole Gerrand Manager, Research Support & Development under delegated authority from the Committee, grants ethical approval of the above project.

The following documentation has been reviewed and approved by the Hunter New England Human Research Ethics Committee:

Document	Version	Date
NEAF	Submission Code: AU/1/3AC223	
Victorian Specific Module		22 December 2015
BEAMs Protocol 030/15	Version 1.0	17 November 2015

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KADIAN® Morphine Sulfate Extended-Release Capsules		
KAPANOL CAPSULES Product Information		
Participant Information Statement and Consent Form	Master Version 1.2	1 February 2016
Caregiver Participant Information Statement and Consent Form	Master Version 1.1	22 December 2015
Home Sleep Sub-study Information Statement and Consent Form	Master Version 1.1	22 December 2015
Driving Sub-study Information Statement and Consent Form	Master Version 1.1	22 December 2015
PK/PD Sub-study Information Statement and Consent Form	Master Version 1.1	22 December 2015
Patient Study Card	Master Version 1.0	December 2015
Advertising Poster Patient Waiting areas PaCCSC	Master Version V1.0	December 2015
Participant Management Information Instructions	Version 1.0	December 2015
Participant Safety Poster	Master Version 1	December 2015
ResMed ApneaLink™ Plus PORTABLE MONITORING DEVICE Fact Sheet		
Visit schedule	Master Version 1.0	December 2015
Participant Diary	Master Version V1.0	December 2015
Modified Borg Dyspnoea Scale	Master Version 1.0	December 2015
Chronic Respiratory Questionnaire Self-Administered Standardized Format (CRQ-SAS) 2 TO 3 DAY RECALL First Administration	Master Version 1.0	December 2015
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Approval has been granted for this study to take place at the following sites:

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Please quote **15/12/16/3.06** in all correspondence.

Should you have any concerns or questions about your research, please contact Dr Gerrand as per the details at the bottom of the page. The Hunter New England Human Research Ethics Committee wishes you every success in your research.

Yours faithfully

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For: Ms M Hunter
Acting Chair
Hunter New England Human Research Ethics Committee

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24 March 2016

Professor David Currow
Palliative & Supportive Services
Flinders University
700 Goodwood Road
Daw Park SA 5041

Dear Professor Currow

Re: BEAMS: A pragmatic, phase III, multisite, double-blind, placebo controlled, parallel arm, dose increment randomised trial of regular, low dose extended release morphine for chronic refractory breathlessness (15/12/16/3.06)

HNEHREC Reference No: 15/12/16/3.06
NSW HREC Reference No: HREC/15/HNE/502

Thank you for submitting a request for an amendment to the above project. This amendment was reviewed by the Hunter New England Human Research Ethics Committee. This Human Research Ethics Committee is constituted and operates in accordance with the National Health and Medical Research Council's *National Statement on Ethical Conduct in Human Research (2007)* (National Statement) and the *CPMP/ICH Note for Guidance on Good Clinical Practice*. Further, this Committee has been accredited by the NSW Department of Health as a lead HREC under the model for single ethical and scientific review.

I am pleased to advise that the Hunter New England Human Research Ethics Committee has determine the variation meets the requirements of the *National Statement on Ethical Conduct in Human Research* and has granted ethical approval for the following amendment requests:

- For the addition of John Hunter Hospital as study site;
- For the additional role for Professor Katherine Clark as principal investigator at John Hunter Hospital;
- For the addition of Noarlunga Health Services as study site;
- For the additional role for Dr Peter Allcroft as principal investigator at Noarlunga Health Services;
- For the Protocol (Version 1.1 dated 8 March 2016);
- For the Participant Information Statement/Consent Form (Master Version 1.3 dated 15 March 2016);
- For the Participant Information Sheet/Consent Form – Pharmacokinetic/pharmacodynamic Sub-study (PK/PD) (Master Version 1.2 dated 9 March 2016);
- For the Participant Information Sheet/Consent Form – Driving Sub-study (Master Version 1.2 dated 9 March 2016);
- For the Participant Information Sheet/Consent Form – Home Sleep Sub-study (Master Version 1.2 dated 9 March 2016);
- For the Home Sleep Sub-study Instructions for Patients (Version 1 dated March 2016);
- For the Participant Diary – Baseline (Version 2.0 dated March 2016);
- For the Participant Diary – Stage 1 (Version 2.0 dated March 2016);
- For the Participant Diary – Stage 2 (Version 2.0 dated March 2016);

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- For the Participant Diary – Stage 3 (Version 2.0 dated March 2016);
- For the Participant Diary – Stage 4 (Version 2.0 dated March 2016);
- For the Participant Diary – Exit Day (Version 1.0 dated March 2016); and
- For the Zarit Burden Interview ZBI-12 – Australia/English – Version of 24 December 2008 (Master Version 2.0 dated March 2016)

For the protocol: **BEAMS: A pragmatic, phase III, multisite, double-blind, placebo controlled, parallel arm, dose increment randomised trial of regular, low dose extended release morphine for chronic refractory breathlessness [Protocol 030/15 Version 1.0 dated 17 November 2015; Version 1.1 dated 8 March 2016]**

Approval from the Hunter New England Human Research Ethics Committee for the above protocol is given for a maximum of 3 years from the date of the approval letter of your initial application, after which a renewal application will be required if the protocol has not been completed. The above protocol is approved until **February 2019.**

Approval has been granted for this study to take place at the following sites:

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- If for some reason the above protocol does not commence (for example it does not receive funding); is suspended or discontinued, please inform Dr Nicole Gerrand, the Manager, Research Support & Development Office as soon as possible.

The Hunter New England Human Research Ethics Committee also has delegated authority to approve the commencement of this research on behalf of the Hunter New England Local Health District. This research may therefore commence.

Should you have any queries about your project please contact Dr Nicole Gerrand as per the contact details at the bottom of the page. The Hunter New England Human Research Ethics Committee Terms of Reference, Standard Operating Procedures, membership and standard forms are available from the Hunter New England Local Health District website.

Please quote **15/12/16/3.06** in all correspondence.

The Hunter New England Human Research Ethics Committee wishes you every success in your research.

Yours faithfully

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For: Professor M Parsons
Chair
Hunter New England Human Research Ethics Committee

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Health
Hunter New England
Local Health District

27 June 2016

Professor David Currow
Palliative & Supportive Services
Flinders University
700 Goodwood Road
Daw Park SA 5041

Dear Professor Currow

Re: BEAMS: A pragmatic, phase III, multisite, double-blind, placebo controlled, parallel arm, dose increment randomised trial of regular, low dose extended release morphine for chronic refractory breathlessness (15/12/16/3.06)

HNEHREC Reference No: 15/12/16/3.06
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I am pleased to advise that the Hunter New England Human Research Ethics Committee has determine the variation meets the requirements of the *National Statement on Ethical Conduct in Human Research* and has granted ethical approval for the following amendment requests:

Document	Version	Date
Protocol	Version 1.2	June 2016
Caregiver Participant Information Sheet/Consent Form	Master Version 1.2	19 June 2016
Driving Sub-study Participant Information Sheet/Consent Form	Master Version 1.3	2 June 2016
Patients' and Caregivers' Sub-study Caregiver Status and Demographics Form	Version 1	May 2016
Driving Sub-study Questionnaire	Version 1	June 2016
SLUMS Examination	Version 1	June 2016

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- **Royal North Shore Hospital - St Leonards, NSW**
- **Royal Melbourne Hospital – Parkville, VIC**
- **Fairfield Hospital - Prairiewood, NSW**
- **Bankstown Hospital – Bankstown, NSW**

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Health
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Daw Park SA 5041

Dear Professor Currow

Re: BEAMS: A pragmatic, phase III, multisite, double-blind, placebo controlled, parallel arm, dose increment randomised trial of regular, low dose extended release morphine for chronic refractory breathlessness (15/12/16/3.06)

HNEHREC Reference No: 15/12/16/3.06
NSW HREC Reference No: HREC/15/HNE/502

Thank you for submitting a request for an amendment to the above project. This amendment was reviewed by the Hunter New England Human Research Ethics Committee. This Human Research Ethics Committee is constituted and operates in accordance with the National Health and Medical Research Council's *National Statement on Ethical Conduct in Human Research (2007)* (National Statement) and the *CPMP/ICH Note for Guidance on Good Clinical Practice*. Further, this Committee has been accredited by the NSW Department of Health as a lead HREC under the model for single ethical and scientific review.

I am pleased to advise that the Hunter New England Human Research Ethics Committee has determine the variation meets the requirements of the *National Statement on Ethical Conduct in Human Research* and has granted ethical approval for the following amendment requests:

Document	Version	Date
Protocol	Version 1.2	June 2016
Caregiver Participant Information Sheet/Consent Form	Master Version 1.2	19 June 2016
Driving Sub-study Participant Information Sheet/Consent Form	Master Version 1.3	2 June 2016
Patients' and Caregivers' Sub-study Caregiver Status and Demographics Form	Version 1	May 2016
Driving Sub-study Questionnaire	Version 1	June 2016
SLUMS Examination	Version undated	

Hunter New England Research Support & Development Office
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http://www.hnehealth.nsw.gov.au/ethics/Pages/Research-Ethics-and-Governance-Unit.aspx

For the protocol: **BEAMS: A pragmatic, phase III, multisite, double-blind, placebo controlled, parallel arm, dose increment randomised trial of regular, low dose extended release morphine for chronic refractory breathlessness [Protocol 030/15 Version 1.0 dated 17 November 2015; Version 1.1 dated 8 March 2016; Version 1.2 dated June 2016]**

Approval from the Hunter New England Human Research Ethics Committee for the above protocol is given for a maximum of 3 years from the date of the approval letter of your initial application, after which a renewal application will be required if the protocol has not been completed. The above protocol is approved until **February 2019.**

Approval has been granted for this study to take place at the following sites:

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- All variations or amendments to this protocol, including amendments to the Information Sheet and Consent Form, must be forwarded to and approved by the Hunter New England Human Research Ethics Committee prior to their implementation.

- The Principal Investigator will immediately report anything which might warrant review of ethical approval of the project in the specified format, including:

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- Unforeseen events that might affect continued ethical acceptability of the project.

- If for some reason the above protocol does not commence (for example it does not receive funding); is suspended or discontinued, please inform Dr Nicole Gerrand, the Manager, Research Support & Development Office as soon as possible.

The Hunter New England Human Research Ethics Committee also has delegated authority to approve the commencement of this research on behalf of the Hunter New England Local Health District. This research may therefore commence.

Should you have any queries about your project please contact Dr Nicole Gerrand as per the contact details at the bottom of the page. The Hunter New England Human Research Ethics Committee Terms of Reference, Standard Operating Procedures, membership and standard forms are available from the Hunter New England Local Health District website.

Please quote **15/12/16/3.06** in all correspondence.

The Hunter New England Human Research Ethics Committee wishes you every success in your research.

Yours faithfully

Content removed for privacy reasons

For: Ms Mandy Hunter
Chair
Hunter New England Human Research Ethics Committee

Hunter New England Research Support & Development Office
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NSW GOVERNMENT Health
Hunter New England
Local Health District

4 July 2016

Professor David Currow
Palliative & Supportive Services
Flinders University
700 Goodwood Road
Daw Park SA 5041

Dear Professor Currow

Re: BEAMS: A pragmatic, phase III, multisite, double-blind, placebo controlled, parallel arm, dose increment randomised trial of regular, low dose extended release morphine for chronic refractory breathlessness (15/12/16/3.06)

HNEHREC Reference No: 15/12/16/3.06
NSW HREC Reference No: HREC/15/HNE/502

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I am pleased to advise that the Hunter New England Human Research Ethics Committee has determine the variation meets the requirements of the *National Statement on Ethical Conduct in Human Research* and has granted ethical approval for the following amendment requests:

Document	Version	Date
Patients' and Caregivers' Sub-study Caregiver Status and Demographics Form	Version 1.1	June 2016

For the protocol: **BEAMS: A pragmatic, phase III, multisite, double-blind, placebo controlled, parallel arm, dose increment randomised trial of regular, low dose extended release morphine for chronic refractory breathlessness [Protocol 030/15 Version 1.0 dated 17 November 2015; Version 1.1 dated 8 March 2016; Version 1.2 dated June 2016]**

Approval from the Hunter New England Human Research Ethics Committee for the above protocol is given for a maximum of 3 years from the date of the approval letter of your initial application.

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after which a renewal application will be required if the protocol has not been completed. The above protocol is approved until **February 2019.**

Approval has been granted for this study to take place at the following sites:

- **Braeside Hospital, NSW**
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- The Principal Investigator will immediately report anything which might warrant review of ethical approval of the project in the specified format, including:

    - any serious or unexpected adverse events

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The Hunter New England Human Research Ethics Committee wishes you every success in your research.

Yours faithfully

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For: Ms Mandy Hunter
Chair
Hunter New England Human Research Ethics Committee

Hunter New England Research Support & Development Office
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BEAMS Patients' and Caregivers' Sub-study Patients Participating Interview	Version 1	June 2016
BEAMS Patients' and Caregivers' Sub-study Patients Not Participating Interview	Version 1	June 2016

For the protocol: **BEAMS: A pragmatic, phase III, multisite, double-blind, placebo controlled, parallel arm, dose increment randomised trial of regular, low dose extended release morphine for chronic refractory breathlessness [Protocol 030/15 Version 1.0 dated 17 November 2015; Version 1.1 dated 8 March 2016; Version 1.2 dated June 2016]**

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The Hunter New England Human Research Ethics Committee wishes you every success in your research.

Yours faithfully

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For: Ms Mandy Hunter
Chair
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Health
Hunter New England
Local Health District

22 July 2016

Professor David Currow
Palliative & Supportive Services
Flinders University
700 Goodwood Road
Daw Park SA 5041

Dear Professor Currow

Re: BEAMS: A pragmatic, phase III, multisite, double-blind, placebo controlled, parallel arm, dose increment randomised trial of regular, low dose extended release morphine for chronic refractory breathlessness (15/12/16/3.06)

HNEHREC Reference No: 15/12/16/3.06
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Document	Version	Date
Patients' and Caregivers' Sub-study Caregiver – Adult participant providing own consent Participant Information Sheet/Consent Form	Master Version 1.1	July 2016
Patients' and Caregivers' Sub-study – Adult caregiver providing own consent Participating Information Sheet/Consent Form	Master Version 1.1	July 2016

For the protocol: **BEAMS: A pragmatic, phase III, multisite, double-blind, placebo controlled, parallel arm, dose increment randomised trial of regular, low dose extended release**

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morphine for chronic refractory breathlessness [Protocol 030/15 Version 1.0 dated 17 November 2015; Version 1.1 dated 8 March 2016; Version 1.2 dated June 2016]

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Health
Hunter New England
Local Health District

19 December 2016

Professor David Currow
Palliative & Supportive Services
Flinders University
700 Goodwood Road
Daw Park SA 5041

Dear Professor Currow

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HNEHREC Reference No: 15/12/16/3.06
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Document	Version	Date
Protocol	1.3	4 November 2016
Master Participant Information Sheet/Consent Form	1.4	30 November 2016
Driving Sub-study Master Participant Information/Consent Form	1.4	30 November 2016
Caregiver's Status and Demographics Form	1.2	August 2016
Greenwich Media Release	2	November 2016

For the protocol: **BEAMS: A pragmatic, phase III, multisite, double-blind, placebo controlled, parallel arm, dose increment randomised trial of regular, low dose extended release morphine for chronic refractory breathlessness [Protocol 030/15 Version 1.0 dated 17 November 2015; Version 1.1 dated 8 March 2016; Version 1.2 dated June 2016; Version 1.3 dated 4 November 2016]**

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The *National Statement on Ethical Conduct in Human Research (2007)*, which the Committee is obliged to adhere to, include the requirement that the committee monitors the research protocols it has approved. Ethics Approval will be ongoing subject to the following conditions:

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Yours faithfully

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Chair
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Health
Hunter New England
Local Health District

30 May 2017

Professor David Currow
Palliative & Supportive Services
Flinders University
700 Goodwood Road
Daw Park SA 5041

Dear Professor Currow

Re: BEAMS: A pragmatic, phase III, multisite, double-blind, placebo controlled, parallel arm, dose increment randomised trial of regular, low dose extended release morphine for chronic refractory breathlessness (15/12/16/3.06)

HNEHREC Reference No: 15/12/16/3.06
NSW HREC Reference No: HREC/15/HNE/502

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Document	Version	Date
Protocol Addendum – Patient and Caregiver Sub-study	1.1	9 May 2016
Master Morphine Information Sheet PaCCSC	1.0	March 2017
Master Patients' and Caregivers' Sub-study – Adult participant providing own consent – Participant Information Sheet/Consent Form	1.2	May 2017
Master Patients' and Caregivers' Sub-study – Adult caregiver providing own consent – Participant Information Sheet/Consent Form	1.2	May 2017

- For the addition Dr Peter Eastman as acting principal investigator at Barwon Health, McKellar Centre and Barwon Health, University Hospital Geelong, while Professor Peter Martin is on extended leave

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Health
Hunter New England
Local Health District

4 July 2017

Professor David Currow
Palliative & Supportive Services
Flinders University
700 Goodwood Road
Daw Park SA 5041

Dear Professor Currow

Re: BEAMS: A pragmatic, phase III, multisite, double-blind, placebo controlled, parallel arm, dose increment randomised trial of regular, low dose extended release morphine for chronic refractory breathlessness (15/12/16/3.06)

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Document	Version	Date
Protocol	1.4	11 April 2017
Cortisol Sub-Study Master Information Sheet and Consent Form	1.1	June 2017
030 BEAMS Cortisol Sub-study Instructions for Patients	1	April 2017
030 BEAMS Cortisol Sub-study Patients Diary	1	April 2017

For the protocol: **BEAMS: A pragmatic, phase III, multisite, double-blind, placebo controlled, parallel arm, dose increment randomised trial of regular, low dose extended release morphine for chronic refractory breathlessness [Protocol 030/15 Version 1.0 dated 17 November 2015; Version 1.1 dated 8 March 2016; Version 1.2 dated June 2016; Version 1.3 dated 4 November 2016; Addendum 1.0 Patients' and Caregivers' Sub-study Version 1.0 dated 16 June 2016; Addendum 1.1 Patients' and Caregivers' Sub-study dated 9 May 2017; Protocol 1.4 dated 11 April 2017]**

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Health
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6 July 2017

Professor David Currow
Palliative & Supportive Services
Flinders University
700 Goodwood Road
Daw Park SA 5041

Dear Professor Currow

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Document	Version	Date
030/15Caregiver Master Participant Information and Consent Form	1.3	March 2017
Greenwich Hospital addressing Breathlessness	-	undated

- For the addition of Dr Yet Hong Khor as co-investigator at Austin Health

For the protocol: **BEAMS: A pragmatic, phase III, multisite, double-blind, placebo controlled, parallel arm, dose increment randomised trial of regular, low dose extended release morphine for chronic refractory breathlessness [Protocol 030/15 Version 1.0 dated 17 November 2015; Version 1.1 dated 8 March 2016; Version 1.2 dated June 2016; Version 1.3 dated 4 November 2016; Addendum 1.0 Patients' and Caregivers' Sub-study Version 1.0 dated 16 June 2016; Addendum 1.1 Patients' and Caregivers' Sub-study dated 9 May 2017; Protocol 1.4 dated 11 April 2017]**

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Appendix 8 – Publication: Two faces of the same coin: a qualitative study of patients' and carers' coexistence with chronic breathlessness associated with chronic obstructive pulmonary disease (COPD) (included in Chapter 4).

Permission to use the manuscript in this thesis included

Ferreira et al. BMC Palliative Care (2020) 19:64
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BMC Palliative Care

RESEARCH ARTICLE Open Access

Two faces of the same coin: a qualitative study of patients' and carers' coexistence with chronic breathlessness associated with chronic obstructive pulmonary disease (COPD)

Diana H. Ferreira[1*], Slavica Kochovska[2], Aaron Honson[1], Jane L. Phillips[2] and David C. Currow[1,2]

Abstract

Background: Chronic breathlessness is a recognized clinical syndrome that severely impacts patients and carers, who become increasingly restricted in their daily activities. Often, patients become reliant on their carers, who are required to provide constant support. Although individual experiences of breathlessness have been previously investigated, there are few studies exploring contemporaneous experiences of breathlessness of the patient and their carer. This study aimed to understand the experience of severe chronic breathlessness in people with chronic obstructive pulmonary disease (COPD) from the perspective of the patient and carer unit.

Methods: A qualitative study embedded in a randomised, placebo-controlled effectiveness study (RCT) of regular, low-dose (≤32 mg/day), sustained-release morphine for chronic breathlessness associated with COPD. Recruitment occurred between July 2017 and November 2018 in one respiratory and palliative care services, in South Australia. Participants were community-dwelling patients with COPD and severe breathlessness (modified Medical Research Council scale 3 or 4) and their carers. Separate semi-structured interviews were conducted with patients and carers, recorded and transcribed verbatim. Analysis was informed by grounded theory using a constant comparative approach.

Results: From the 26 patients with a carer recruited for the RCT in South Australia, nine were interviewed in their homes. Six patients were men, median age 77 years. Carers were mostly women, who were their wives ($n = 6$), median age 70. Five themes emerged from the data: (1) shrinking world; (2) mutual adaptation; (3) co-management; (4) emotional coping; and (5) meaning in the face of death.

(Continued on next page)

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[1]Discipline, Palliative and Supportive Services, Flinders University, GPO Box 2100, Adelaide, SA 5001, Australia
Full list of author information is available at the end of the article

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(Continued from previous page)
Conclusion: Chronic breathlessness is a systemic condition that permeates all aspects of the patient's and carer's lives. Working as a team, patients and carers manage chronic breathlessness to achieve maximal function and well-being. Patients and carers share many aspects of the experience of breathlessness, but the carer seems particularly susceptible to emotional distress. Future chronic breathlessness interventions should target the patient and the carer, both together and separately to address their common and individual needs.

Trial registration: The main trial is registered (registration no. NCT02720822; posted March 28, 2016).

Keywords: Chronic breathlessness, Chronic obstructive pulmonary disease, Qualitative research, Patients, Carers

Background

Chronic breathlessness is defined as persisting breathlessness despite optimal treatment of the underlying causes(s), resulting in disability [1]. Chronic obstructive pulmonary disease (COPD) is the leading cause of chronic breathlessness worldwide and its incidence is increasing [2]. Chronic breathlessness in COPD is a predictor of mortality [3, 4] and is associated with severe disability [5].

Qualitative studies are critical in understanding the perspectives of people living with chronic conditions and/or advanced symptoms, and their carers. Up to this point, the experience of chronic breathlessness in COPD has been explored separately for patients and carers [6]. It is now recognised that patients' experiences of chronic breathlessness are complex and influenced by a range of physical, psychological, social and existential factors, [7, 8] creating challenges for its diagnosis and management. Previous research has shown that carers are also severely affected by chronic breathlessness with rates of depression and anxiety equal to that of patients [9, 10]. As breathlessness increases, more carer support is required, making this a potentially lonely and stressful role [11].

Importantly, there are many aspects of patients' and carers' lived experience of chronic breathlessness associated with COPD that need to be better understood. While individual experiences have been extensively explored, there are fewer studies exploring how each member of a patient-carer unit experiences the same symptom.

Understanding patients' and their carers' individual experiences and responses to the *same circumstances* of breathlessness and *how they coexist* could enable identification of factors that contribute to successful coping and adaptation to the symptom for both parties involved. These insights are important for informing new models of care that better meet the needs of this largely invisible palliative population.

Methods

Study aim

To understand the experience of living with, and responding to, severe chronic breathlessness in people with COPD from the perspective of the patient and their carer.

Design

This qualitative study was embedded in a phase III, effectiveness, randomised, placebo-controlled trial (RCT) evaluating sustained-release morphine for people with severe chronic breathlessness and COPD (BEAMS trial) [12]. This qualitative was undertaken to understand the patients' and their carers' experiences of breathlessness before commencing on the trial medication.

Setting and participants

Effectiveness studies ensure that the samples selected mimic as closely as possible the population of interest [13]. Therefore, the patients who had completed the BEAMS trial [12] in metropolitan South Australia were eligible to participate if they had a carer; COPD and chronic breathlessness; a modified Medical Research Council (mMRC) breathlessness score of 3 or 4 corresponding to "stops for breath after walking about 100 metres or stops after a few minutes walking on the level" and "too breathlessness to leave the house or breathlessness when dressing or undressing", respectively [14, 15]; were in a sufficient state of health to be interviewed; and willing and able to provide informed consent. Participating patients identified the existence of a primary carer, defined as "the person who knew the participant best, provided the most help at home, and could help understand any changes experienced on trial" [16]. All carers of participating patients were eligible to participate, unless they were unavailable or unwilling to do so.

Research team

The interviews were conducted by a medical practitioner, who was a full-time doctoral student (D.F.) and had formal training in qualitative research methodologies. A.H. is a university researcher with background in data collection and people-centered research designs. S.K. is a university researcher with a linguistics background and experience in communication in clinical and research settings. J.P. is an experienced qualitative researcher with a nursing and palliative care background. D.C. is an experienced palliative care clinical academic whose research focuses on chronic breathlessness.

Recruitment

Using convenience sampling, potential participants were identified and approached by telephone, by the BEAMS trial study nurses. If interested, they were then contacted by the interviewer (D.F.) for the first time. Participants chose the interview location that was more convenient to them, which could be either at home or at the hospital.

Data collection

Data collection occurred from July 2017 to November 2018. All verbally consenting participants were visited at home by a single researcher (D.F.), who conducted the interviews. In the beginning of the session, the researcher introduced herself, explained her background and research interests, stated her personal goals for the research project and explained the study in detail to both patient and carer, concurrently. Participants were encouraged to ask questions and discuss concerns about the study before providing written informed consent.

Demographic information was obtained for all participants. Single, face-to-face, semi-structured interviews were conducted separately with patients and their carers. Carers were specifically asked to leave the room where the interview with the patient was taking place. Carers where then interviewed in a separate room, while patients waited in the room they were initially interviewed in. Individual interviews provide a safe and private space for each individual, which facilitates the expression of concerns and emotions [17, 18]. All interviews used topic guides following Rocker et al. [19], adapted to reflect the framework of "total breathlessness" [8] (Additional file 1 and Additional file 2). Topic areas included daily activities, feelings, relationships, concerns, and hope. The patients included in this study were very frail and the research team was particularly mindful about minimising their participation burden, without compromising the methodological quality of the study. While patients and carers were not involved in the study design or recruitment, research nurses with extensive experience recruiting people with chronic breathlessness contributed to the design of the interview guides to ensure they were appropriate, applicable and relevant for the population targeted. A constant comparative approach was used to help identify new concepts emerging from the data that could be explored in subsequent interviews [20].

Interviews were recorded and transcribed verbatim (D.F.). Interview transcripts were not returned to participants in order to minimise burden for this very frail population [21]. Review of interview transcripts is a common technique employed to verify accuracy and correct potential errors but there is evidence to suggest they add little value and have the potential to create complications in the analysis [21]. In this qualitative study, potential misinterpretations were minimized by having a second researcher (A.H.) listen to each interview recording and check the transcription's accuracy. Participants were only contacted a second time if researchers who oversaw the transcription had any doubts about what participants had said. The researcher conducting the interviews collected field notes during each interview and also kept a reflexive journal with impressions about each participant-researcher interaction. The reflexive journal was compared with data emerging from the interviews, which was compared with data and used strategically to facilitate the interpretation of the findings. Data were collected until reaching a point of saturation (i.e. no new concepts were emerging from the data), as agreed by researchers (D.F., J.P., D.C.).

Data analysis

Data analysis was conducted in NVivo (V 11.4.0 for Mac) using a constant comparative approach guided by grounded theory principles [20, 22]. Open coding of the interview transcripts was conducted by two researchers (D.F., A.H.). Codes were then grouped into themes (D.F.); each theme was illustrated with several quotes to confirm coding validity (D.F., J.P.). Concepts emerging from the patients' and carers' data were further examined for any major differences between the two viewpoints (D.F., J.P., D.C.). A matrix summarised the findings of patients and their carers.

Ethical considerations

Ethics approval for the main trial and this qualitative study were obtained (Hunter New England Human Research Ethics Committee (HREC) Reference No. 15/12/16/3.06) and the BEAMS trial registered (registration No. NCT02720822, posted March 28, 2016; URL https://clinicaltrials.gov/ct2/show/NCT02720822). Written informed consent was obtained from all participants.

This study is reported following the COREQ framework [23].

Findings

From the 50 patients recruited to the RCT during the study period, only 26 had a carer and were eligible to participate. Of those 26 patients, the carer of five patients could not be interviewed because they were working long hours and a suitable interview time could not be arranged. Of the 21 patients with an available carer, 10 were not included because they were residing more than 70 km away from the city, requiring lengthily travelling for the researchers ($n = 5$); were experiencing rapid functional deterioration and were too frail to be interviewed ($n = 4$); were unable to be contacted ($n = 1$). Of the 11 patients with carers who were approached to participate, two declined participation citing fatigue (Fig. 1).

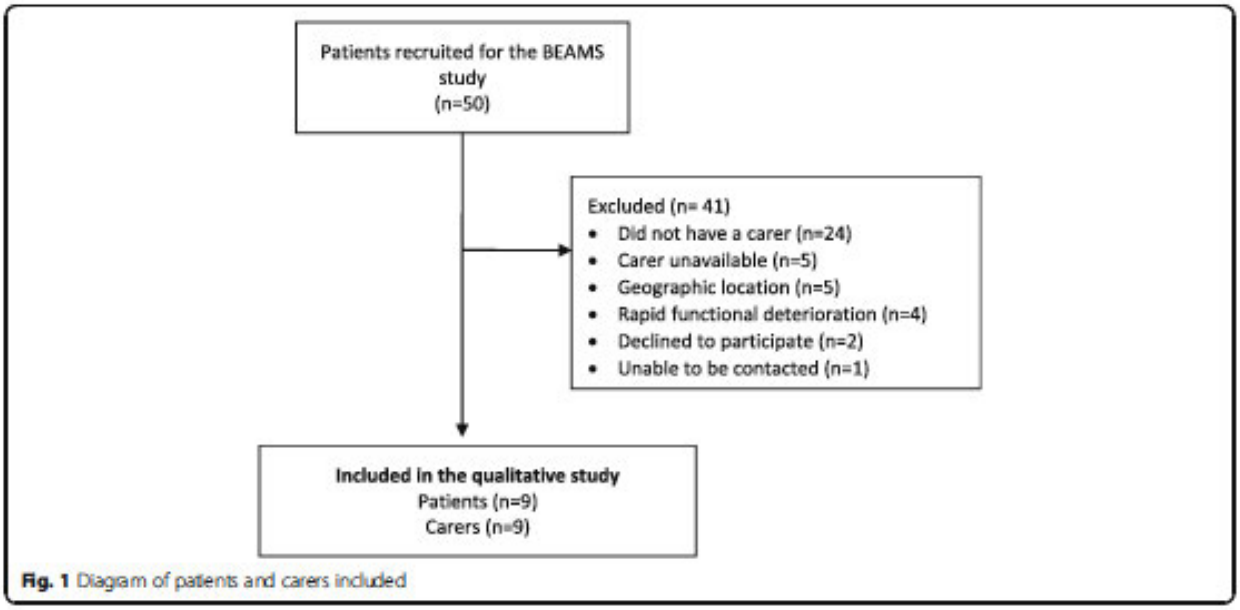

Fig. 1 Diagram of patients and carers included

Nine patients and their carers were separately interviewed in their homes (21–55 min each). Two out of three patients were men and the same proportion of carers were women (and spouses; Table 1). Patients (median age 77 years; interquartile range [IQR] 72–79) were from English-speaking backgrounds and lived in private residences. More than 50% of patients had completed high school. Most patients required occasional or considerable assistance (Table 2).

Carers (median age 70 years; IQR 69–79) had been living with the patients for many years and were solely providing patients' care. Seven carers provided hands-on care (median 4 years [IQR 3–5]; Table 3).

The following five themes described the participants' experience of breathlessness: (1) shrinking world; (2) mutual adaptation; (3) co-management; (4) emotional coping; and (5) meaning in the face of death (Table 4).

Shrinking world

Most patients described that breathlessness significantly impacted their activities of daily living and social lives. Within each patient-carer unit, the level of limitation experienced by carers was highly dependent on the severity of breathlessness experienced by the patients. Carers felt responsible for patients' wellbeing and spent most of their time with them. Occasionally, carers were forced to leave patients by themselves but they were constantly concerned and found it hard to disconnect from the carer's role.

"Well it takes me a long time to get from here to the bed and back. By the time I get there, I got to get on the nebulizer you know? I can get dressed by myself but I have a girl coming to shower me." [Patient 1]

"I have to go shopping and I bought myself a little emergency mobile phone which I haven't told

Table 1 Patients ($n = 9$) and their carers ($n = 9$)

Patient & carer ID number	Patient	Carer	Relationship with the patient
1	Female	Male	Husband
2	Male	Female	Wife
3	Female	Male	Son
4	Male	Female	Wife
5	Male	Female	Wife
6	Male	Female	Wife
7	Male	Female	Wife
8	Female	Male	Husband
9	Male	Female	Wife

Table 2 Patients characteristics ($n = 9$)

Median age (IQR)	77 (72–79)
Gender	
Female	3
Ethnicity	
Oceanian (Australia or New Zealand)	8
North-West European	1
Usual language spoken at home	
English	9
Residence	
Living in a private residence	9
Marital status	
Married or de facto	8
Widowed	1
Highest level of education	
Did not complete high school	4
Completed high school	1
Completed a trade certificate	2
University Degree	2
mMRC score at baseline	
3	9
NRS Worst breathlessness (24 h)	
4	1
6	2
7	3
8	2
9	1
AKPS	
50	3
60	3
70	3

mMRC 0–4 modified Medical Research Council scale (higher scores correspond to lower levels of exertion achieved before being limited by breathlessness), *NRS* 0 to 10 numerical rating scale (0 = no breathlessness, *10* worst possible breathlessness); *AKPS* Australia-modified Karnofsky Performance Status (higher scores correspond to better performance status)

Table 3 Carer's characteristics ($n = 9$)

Median age (IQR)	70 (69–79)
Gender	
Female	6
Ethnicity	
Oceanian (Australia or New Zealand)	6
North-West European	3
Highest level of education	
Did not complete high school	4
Completed high school	3
University degree	2
Marital status	
Married or de facto	9
Living with the patient	
Yes	8
No	1
Median time living with the patient (years) (IQR)	45 (21–56)
Hands on care	
Yes	7
No	2
For how long has the carer been providing hands-on-care? (median time in years) (IQR)	4 (3–5)
Time spent together weekly	
> 40 h	7
20–40 h	1
10–20 h	1
Other people involved in providing care	
No	9
Changes to employment status due to patient's condition	
No	9

anybody anything about it. It's just simply so I can ring home to check on her ... And I bought a walker for her hoping that she would use the walker." [Carer 1]

As the patient experiences more limitations associated with breathlessness, patient and carer reduce the time they spend apart. In such cases, the carer's life becomes almost as restricted as the patient. At the same time, there is an attempt to find strategies that enhance patient's function, allowing the patient-carer unit to perform at a higher level.

"We went to town about a month ago, we used to do quite a bit of that, become a tourist in your own town, sort of thing. We went there and I walked maybe 50 meters in North Terrace [a street]. I could not go any further. I just could not walk any further. So, that [mobility scooter] will fix our problem. I can even walk to the shops with J. [wife]." [Patient 9]

"I would like to go and do things with him, like go to the zoo, the art gallery, places like that but that is out of the question because I couldn't get the car close enough for him to even get in the place. To be able to walk to get in places. We can't get around. I don't go to everything that I would normally go to." [Carer 9]

Table 4 Results of the matrix used for analysis

Patients & Carers	Patient	Carer
1. **Shrinking world** Breathlessness shrinks the physical and relational world available to patients and carers and increases the time they spend together	• Restriction of daily activities • Restriction of independence • Good days and bad days	• Restriction of their own daily activities • Describe patients have good days and bad days • Hard to disconnect from the carer's role
2. **Mutual adaptation** Patient and carers work individually and together to create optimal functioning for both	• Keep as active as possible • Try to avoid over-exertion • Some push to the limit	• Take over some tasks • Slow down • Step in to prevent perceived over-exertion
3. **Co-management** Patient and carers have active and complementary roles in managing breathlessness	• Have an active role in managing breathlessness • Work with the carer to overcome breathlessness	• Have an active role in managing breathlessness • Degree of participation depends on patients' limitations • Step in situations of acute breathlessness
4. **Emotional coping** Emotional coping with breathlessness is difficult for patients, but harder for carers	• Annoyance • Frustration	• Frustration • Resentment • Feeling trapped • Giving up part of their identity
5. **Meaning in the face of death** Sense of meaning created by the relationship between patients and carers	• See death as natural (no fear) • Find meaning in their relationship with the carer	• Fear patients' death and their future • Try to bring joy and happiness to the patient

Independently of overall breathlessness severity, both patients and their carers described great daily variability in breathlessness intensity, using terms like "good days" and "bad days" to describe fluctuations and their impact on daily life. Occasionally, they would identify triggers (e.g. temperature, humidity) for such fluctuations, but mostly, they were unpredictable.

> *"I have good days and bad days. Some days, I can't get out of bed basically and other days is fine. (...) It is unexpected and you just take it day by day."* [Patient 8]

> *"There are good days and bad days. There are days in which she can't do much and she just sits down or lays on the bed and does not do much. And other days she has got a lot of energy and does a lot of other stuff. There are quite a few ups and downs. (...) In the end you just go with the flow, treat it from day to day, whatever comes up. Yeah."* [Carer 8]

Mutual adaptation

Within each patient-carer unit, attempts to reconcile the level of function of the patient with that of the carer were ongoing. While patients tried to be as functional as possible, carers learned how take over certain tasks so as not to allow the patient to over-exert. Both elements worked to keep each patient-carer unit as functional as possible under difficult circumstances.

> *"Occasionally, I try to do a bit of cooking. But I can't always do it. I can't do any cooking really when I am using this [points at the oxygen tube] because of the fire risk."* [Patient 6]

> *"He can't do anything which is very annoying - not to me, but to him - because he quite often says ... A couple of weeks ago he said "I'll cook you dinner". He was going to make a curry. He got up there and I have to switch his oxygen off - because of the gas, you see ... Two minutes later he said "I am sorry, I can't ... " and I said "It's ok you just sit down and relax and I'll do it".* [Carer 6]

In some circumstances, carers learned how to slow down to meet the patient level of function. This strategy seemed to allowed patients to keep as much autonomy as possible.

> *"We have a system. T. [son] takes me shopping and I can take a trolley in. And I can do my own shopping like that."* [Patient 3]

> *"Just be patient and let them take their time. When we go to the shops, I don't rush mum and we just go slow. Be patient."* [Carer 3]

Within each patient-carer unit, patients and carer had learned to adapt to breathlessness. In most cases, patients had developed an accurate sense of their exertional capacity, learning to push themselves to be as active as possible, while managing their breathlessness, including avoiding situations that created intense or unmanageable breathlessness. In these cases, carers trust the patient capacity to manage the degree of exertion they are able to tolerate.

> *"And I think you adapt to the problem. You know you have a problem so you adapt to it. So you create*

a situation where you don't get that short of breath, you know? Because you don't do things." [Patient 5]

"(...) he sits a lot and plays games on the computer and all that, so he knows when he can't do things. So yeah, that doesn't concern me." [Carer 5]

In other cases, the carer played an essential role in preventing what was perceived as overexertion causing excess breathlessness.

"I just don't want it to beat me. I know my limits and I will push myself to the limits." [Patient 7]

"The last couple of times we used the caravan, it was in the beginning of last year actually. It's an old caravan so it takes a lot of putting the annex part of it because it doesn't have a pull-out roof on it and it takes quite a while to put it up, but I have to say "Stop and sit down!" and he says "No, I want to get this done!" and I say "Well, you need to have a rest" so I say "I'll make you a coffee". So then he stops. Or we'll go and have lunch and come back and finish it, you know?" [Carer 7]

Co-management

In all patient-carer units, both members had active roles in managing breathlessness. However, carer participation in breathlessness management was largely dependent on the degree of limitations experienced by the patient. In cases where the patient was still reasonably independent, the carer was mainly responsible for more physically-demanding tasks such as shopping or cleaning. In such cases, there was still a clear separation of roles:

"My wife knows I have a problem and we just get on with it. I do most of the cooking and she does most of the cleaning." [Patient 7]

"I do a few jobs around the house but I don't have to do anything for him, really. He can dress himself and all things like that. I used to have to cut his toe nails ... But now, because we have a care plan, we go to the podiatrist." [Carer 7]

In cases where the patient required considerable assistance, carers had a particularly active role. Both patients and carers had developed strategies which allowed them to work as cohesive team to overcome the limitations imposed by breathlessness.

"Getting dressed is ... hands above the head is a problem. But the rest of it is fine, it is just slow. So J. [wife] comes in and helps me and we get through it together." [Patient 9]

"Like we had our granddaughter 21st birthday in the city and it took an hour and a half for him to get dressed. He would do one little thing and then he would get out of breath. And then I would go away and try to put something on myself and come back and do some small thing." [Carer 9]

Carers were particularly important in situations of acute, uncontrolled breathlessness, that could be sudden and unpredictable. In some cases, the patient is able to reach for carer's help but is unable to take further action.

"When that flu hit me, I couldn't breathe at all. It was so bad all of a sudden. M. [wife] had to call the ambulance." [Patient 4]

"When he had that flu, I called the ambulance and they came pronto. I know what to do in those cases because I've done it before, but it's a bit scary." [Carer 4]

Emotional coping

While most patients expressed annoyance at being unable to function fully independently, the sensation of daily breathlessness with which they had lived for so long, did not generate distress because they were familiar with the symptom and how to handle it. Conversely, daily breathlessness was an emotional challenge for carers who not only experienced a constant state of worry, but also felt the need to appear calm to patients.

"No, not scared [by daily breathlessness]. I tend to be a phlegmatic sort of guy; I have low anxiety levels. And I am used to it." [Patient 2]

"Just watching him trying to get his breath ... That is horrible to watch. And there is nothing you can do to help. Just keep him comfortable and be there, whatever he needs ... I try not to worry too much; I try to keep calm because I don't want him to get worse." [Carer 2]

Conversely, both patients and carers felt emotionally challenged by episodes of acute breathlessness (e.g. COPD exacerbations), which were described as "a worry", "scary" and "awful".

"But a couple of times, a couple of months ago, I had a real breathlessness attack and I could not

breathe. It that was quite scary but I managed it ok, I sort of did what I had to and I was ok." [Patient 8]

"It scares me [when she gets more intense breathlessness]. Very much! Especially when she has an infection or something a bit more serious, that is really scary." [Carer 8]

While some patients expressed being annoyed with their condition, their carers experienced more intense feelings, such as frustration and resentment, by being forced to step up to the carer's role. For some, being a carer made them give up a part of their identity, which created a sensation of being trapped in the carer's role.

"I get up in the morning, have breakfast, shower. I don't shower every day because I get so breathless showering. But when I do shower, then M. [wife] helps me sometimes. And then I sit down and I have my Ipad, I look at all the papers from all over the world and I just keep my brain working thinking about things but physically, I don't do anything at all. (...) sometimes I get bored. Bored you know? I think "what should I do next?"". [Patient 6]

"My life is boring! [laughs] I am a very outgoing person, I like the outdoors, and on a day like today you think "oh, let's get in the car and go!" But I have to think of him first because he can't walk from here to there before he gets breathlessness so I think "well ... just scrap it", and do nothing you know? So it makes it hard on me because I want to do things but I can't you know?" [Carer 6]

Meaning in the face of death

The relationship between patient and carer brought a sense of meaning to both parties and helped to withstand the limitations imposed by chronic breathlessness. For patients, their perspectives on life and death changed with the experience of chronic breathlessness. Many were aware of the severity of their condition but were not afraid to die. Unlike patients, their carers felt more concerned about the future and did not bring up the topic of death easily.

"No, not anymore [I don't worry about the future]. I look at it this way, if something is going to happen, it is going to happen. There is nothing you can do about it." [Patient 4]

"I wonder just how bad he's going to get ... What is going to be like further down the track." [Carer 4]

Within a patient-carer unit, both patient and carer were essential to ensure the patient kept living a meaningful life. For patients, an essential part of living a good life was being close to their carers. Carers were not only involved in dealing with the physical burdens of breathlessness but they also felt responsible for bringing meaning and joy to patient's lives.

"Life is pretty good, yeah. B. [husband] does everything and we are together all the time. He is a good doctor! A very good doctor [laughing]." [Patient 1]

"I buy her some flowers every fortnight and I put them in there so she can sit at the table and look at them. Just to introduce a bit of color and a variety into the family. I am trying to make it fairly compatible being at home (and I think for the last year she has been home now) I think she said she was happy I think, yeah." [Carer 1]

Discussion

This is one of the first studies exploring patients and carers co-existence with chronic breathlessness due to COPD. It highlights important issues for patients and carers individually, but also for the patient and carer as a unit. These findings suggest that patients and carers share the experience of chronic breathlessness, working as a team to overcome the restrictions imposed by this syndrome. Importantly, these findings also suggest that *both the patient and the carer* are active participants in the breathing-thinking-functioning cycles of chronic breathlessness [24].

Breathing

Both patients and carers reported that COPD associated breathlessness took over their lives. While patients experienced breathlessness on a daily basis and had learnt how to accept and adapt to the symptom, carers were frequently distressed by watching patients trying to catch their breath. Previous evidence suggests that carers of people with COPD feel they lack understanding about the experience of breathlessness and its causes [25]. More importantly, they are seldom involved in therapies aiming to optimise lung function and exercise tolerance [25]. Thus, frequent distress with daily breathlessness may be a consequence of lack of education for carers in this area.

Interestingly, the terms "good / bad days" are used by both patients and carers to describe daily fluctuations in breathlessness, in which a "good day" corresponds to being as functional as possible and a "bad day" to severely restricted daily activities. Fluctuations in breathlessness were previously described in a large prospective study examining breathlessness intensity in people with severe COPD, over a 6-month period, in which breathlessness

was measured monthly [26]. The current study suggests that fluctuations in breathlessness are frequent, with substantial daily variations. The concept of "good" and "bad" days has been described before in other qualitative work [5]. However, there is no understanding of the predictors of such fluctuations and the mechanisms behind them. These findings highlight the natural history of chronic breathlessness, and the need to develop specific interventions that can target daily fluctuations in breathlessness. Moreover, the descriptions of "good" and "bad" days are consistent between patients and carers, which indicates they share a common experience. Thus, specific interventions targeting "good" and "bad" days should target both the patient *and* the carer *together*.

Thinking

Within each patient-carer unit, both patients and carers reported distress due to breathlessness, with important differences between both. While patients' distress is focused on episodes of acute breathlessness which are sudden and unpredictable, carers live in a constant state of worry, which is further exacerbated with sudden episodes of unpredictable breathlessness. Although patients feel regularly annoyed for not being able to fully function, the daily experience of breathlessness does not seem to cause anxiety because it is predictable and manageable. However, unexpected surges of intense breathlessness (e.g. exacerbations of COPD) cause fear and anxiety because they are surprising and difficult to manage. In such situations, fear may itself contribute in aggravating breathlessness [27]. In general, the experience of breathlessness seems to be particularly distressing for carers, who are unable to disconnect from the carer's role, live in a permanent state of hypervigilance and force themselves to keep calm in order not to disturb patients. On top of that, carers are required to step up in situations of acute unpredictable breathlessness, whether they feel prepared for it or not. While breathlessness-induced emotional burden has been previously described for patients and carers [28, 29], this study adds to the literature by demonstrating that within the same patient-carer unit, similar experiences of breathlessness trigger different emotional responses in patients and carers. More importantly, situations that are not distressing for patients, may be severely distressing for carers. Such findings are important not only because they highlight carers' psychological vulnerability, but also because there is a significant association between the psychological well-being of patients and their carers [30]. Thus, it is important to implement psychological interventions that target both the patient *and* the carer. Importantly, patients and carers have specific emotional vulnerabilities that may require specific, *individual* approaches.

It is also important to note that patients' speech is underpinned by a sense of acceptance and adaptation to their condition. Patients acknowledge they may deteriorate and talk easily about dying. This acceptance may be related with the progressive nature of COPD providing time to process and adapt to new challenges, and the perception of having a self-inflicted disease (i.e. believing they are just living with the consequence of their actions) [31, 32]. On the contrary carers find it difficult to accept their role. They feel forced to give part of their identity, trapped in the carers role and have difficulties discussing death-related themes [11]. Thus, coping to the long-term consequences of breathlessness is also more challenging for carers, which may require specific interventions for carers.

Functioning

In this study, patients and carers reported that they saw their worlds shrink physically and socially due to chronic breathlessness. This limitation of each person's "living space" [5] has a profound impact on patients' and carers' wellbeing. Patient and carer become confined to activities at home and increasingly isolated [33]. This study highlights the concept of "mutual adaptation" in which there is an attempt to reconciliate the patient and the carer level of function so they can function *together*. As breathlessness progresses, patients become more accepting of their limitations [34], but they constantly strive to be as functionally independent as possible. For people with advanced diseases, not being a burden to their families [35] is often more important than having their symptoms under control. This helps to explain why patients are constantly working to their physical (and psychological) limits. Conversely, carers learn to either take over certain tasks or slow down to adapt to the patients' rhythm. Although a change in life rhythm has been previously reported in patients with COPD and their partners, that consisted mostly on carer's compromise to adapt to the patient's limitations [36]. This study suggests both carer and patient play an active role in this process.

Another important finding is that carers may be key intervenients to prevent over-exertion. It has been described that patients adapt to breathlessness by avoiding situations that may trigger unmanageable breathlessness and by careful planning each daily activity to minimize the consequences of breathlessness [31]. This study supports these findings by showing that patients push to their perceived limit while avoiding a degree of exertion that would trigger uncontrollable breathlessness. However, in some circumstances, there is a mismatch between patients and carers perceptions on what constitutes the "limit". One hypothesis is that the carer's perception of breathlessness is inaccurate, which is supported by previous research showing only fair patient-carer agreement in breathlessness ratings [37]. Alternatively, the carer may indeed play

a crucial role in preventing over-exertion. The presence of a carer may also contribute to increase patient's confidence to push themselves because there is help available if breathlessness becomes uncontrollable. These hypotheses need to be investigated in future work. Nevertheless, given that breathlessness is managed by patient and carer *together*, it is important to conciliate patient's and carer's views on what constitutes over-exertion.

This study also shows that patient and carer are both actively involved in managing breathlessness. Initially, breathlessness is managed by sharing tasks. At this point there is still a clear definition between the patient and the carer roles. This study shows that as breathlessness progresses, patient and carer transition to managing breathlessness as a cohesive team, which requires flexibility and constant adaptation by both parties. This is in line with previous work describing the lack of definition and unpredictability associated with the carer role in severe COPD [38].

Overall, both patient and carer work (individually and together) to withstand the limitations imposed by breathlessness. Carers, and particularly family carers, are a source of physical and emotional support for patients with advanced COPD [39]. Close relationships are essential in creating meaning in people's lives, contributing to their psycho-social well-being and, ultimately, their quality of life [40]. Because breathlessness leads to social isolation, the carer is frequently the only person providing a sense of connectedness with another person [41]. Thus, the carer is not only the person providing care but also the person providing meaning, and as such is essential in enhancing optimal co-existing with breathlessness. Given that breathlessness impacts on both patients and carers, and both elements play a role in breathlessness management, it was suggested that the patient-carer unit should be targeted as the unit of care [42]. This work supports this idea. However, it also highlights that patients and carers have specific needs, which need to be addressed separately.

Limitations

Although patients and carers were interviewed separately, they were aware of each other's presence in the house, which may have inhibited the expression of concerns. All interviews were conducted by the same interviewer (D.F.) for whom English is not a first language. Potential misinterpretations, however, were minimised by having a second researcher (A.H.), whose first language is English, check all interview transcriptions for accuracy. This is a qualitative study so its findings cannot be generalised. However, data checking and analyses were conducted by different researchers to minimise risk of bias. Furthermore, this study was embedded in a RCT and patients were asked to recall their experiences of breathlessness before the intervention was administered. The possibility of recall bias needs to be considered. Importantly, the main trial was an effectiveness study as opposed to an efficacy study. Effectiveness studies in this setting have demonstrated to have high external validity for the population of interest [13, 43]. This study included a high proportion of patients who had completed secondary education, which may not reflect the totality of the population seen in clinical practice. Patients who were living more than 1 hour away from the city centre were excluded due to lengthy travelling times, which may have excluded the perspectives of people who living in more remote areas. This study does not inform us about people with severe COPD who do not (and potentially could not) identify a carer.

Implications for future research

Chronic breathlessness was described as the product of breathing, thinking and functioning vicious cycles that generate and aggravate the syndrome [24]. This study identified that both patient and caregiver are active participants in those cycles. Framing patients' and carers' interventions in accordance with the breathing-thinking-functioning model of breathlessness facilitates the identification of factors that contribute to aggravate and ameliorate each cycle [24]. The complete identification of such factors may ultimately aid to develop an intervention programme that is appropriate for patient, carer and the patient-carer unit as a whole.

This study also underlines the importance of conducting future dyadic studies in the setting of chronic breathlessness, which not only examine the separate perspectives of patients and carer but also *how their relationship facilitates coping with breathlessness* and *what type of support they require*.

Implications for clinical practice

This study identifies crucial aspects of the patients' and their carers' experience with severe chronic breathlessness associated with COPD. Recommendations for clinical practice include:

- Functional losses due to breathlessness are devastating for patients and carers and should be proactively investigated in all stages of COPD.
- Understanding the natural history of COPD and its impact on daily fluctuations in chronic breathlessness may assist in tailoring future interventions for chronic breathlessness, especially self-management strategies involving patient and carer.
- Carers are severely affected by the experience of chronic breathlessness and their specific needs need to be assessed in clinical practice. From a service

point of view, the carer is both a care recipient and a co-worker with health professionals [44].
- Both patient and carer are essential in the effective management of chronic breathlessness. Both need to be targeted (together and separately) to optimise clinical outcomes in breathlessness associated with COPD.

Conclusions

Patients with COPD associated breathlessness and their carers report that breathlessness permeates all aspects of life. Patient and carer see their world shrink and cooperate to create optimal function for the patient-carer unit. A new dynamic is created with patients trying to be as active as possible, and carers trying to be less active so their partners can keep up. Involving both the patient and their carer is essential to create optimal management of chronic breathlessness. Chronic breathlessness is particularly heavy on carers, who feel constantly anxious and have difficulties adapting to their role. Interventions targeting the patient-carer unit but also the carer individually are suggested.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s12904-020-00572-7.

Additional file 1.
Additional file 2.

Abbreviations

COREQ: Consolidated criteria for reporting qualitative research; COPD: Chronic Obstructive Pulmonary Disease; RCT: Randomised controlled trial; mMRC: modified Medical Research Council scale; HREC: Human Research Ethics Committee; IQR: Interquartile range; NRS: Numerical Rating Scale; AKPS: Australia-modified Karnofsky Performance Status.

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Authors' contributions

DF, SK, AH, JLP and DCC were involved in conceiving and designing the study. Data collection was carried out by DF. DF, AH, JLP, DCC were responsible for data analysis and interpretation. DF wrote the first draft of the manuscript. DF, SK, AH, JLP and DCC contributed to subsequent drafts and were involved in the critical revision of the article for important intellectual content. All authors approved the final version of the article to be published.

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Availability of data and materials

The data of this study are available from the corresponding authors on reasonable request.

Ethics approval and consent to participate

The study was approved by the England Human Research Ethics Committee (Reference No. 15/12/16/3.06). All participants provided written informed consent to participate in this study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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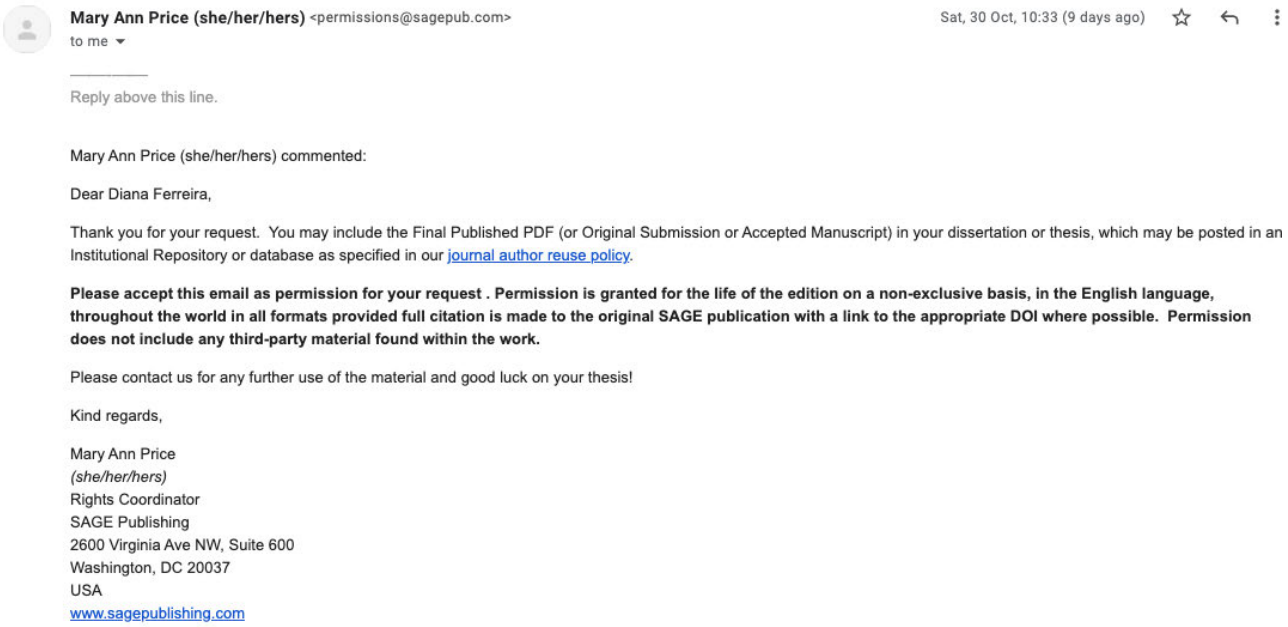
Appendix 9 – Publication: Patients' and caregivers' experiences of driving with chronic breathlessness before and after regular low-dose sustained-release morphine: A qualitative study (included in Chapter 4)

Permission to use the manuscript in this thesis included (obtained by email).



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Patients' and caregivers' experiences of driving with chronic breathlessness before and after regular low-dose sustained-release morphine: A qualitative study

Diana H Ferreira[1], Jason W Boland[2], Slavica Kochovska[3], Aaron Honson[1], Jane L Phillips[3] and David C Currow[1,2,3]

Abstract

Background: Chronic breathlessness is a disabling syndrome that profoundly impacts patients' and caregivers' lives. Driving is important for most people, including those with advanced disease. Regular, low-dose, sustained-release morphine safely reduces breathlessness, but little is known about its impact on driving.

Aim: To understand patients' and caregivers' (1) perspectives and experiences of driving with chronic breathlessness; and (2) perceived impact of regular, low-dose, sustained-release morphine on driving.

Design: A qualitative study embedded in a pragmatic, phase III, randomised, placebo-controlled trial of low-dose, sustained-release morphine (≈32 mg/24 h) for chronic breathlessness. Semi-structured interviews were conducted immediately after participants withdrew or completed the randomised, placebo-controlled trial. Informed by grounded theory, a constant comparative approach to analysis was adopted.

Setting/participants: Participants were recruited from an outpatients palliative care service in Adelaide, Australia. Participants included patients ($n = 13$) with severe breathlessness associated with chronic obstructive pulmonary disease and their caregivers ($n = 9$).

Results: Participants were interviewed at home. Eleven received morphine 8–32 mg. Three themes emerged: (1) independence; (2) breathlessness' impact on driving; and (3) driving while taking regular, low-dose, sustained-release morphine.

Conclusion: Driving contributed to a sense of identity and independence. Being able to drive increased the physical and social space available to patients and caregivers, their social engagement and well-being. Patients reported breathlessness at rest may impair driving skills, while the introduction of sustained-release morphine seemed to have no self-reported impact on driving. Investigating this last perception objectively, especially in terms of safety, is the subject of ongoing work.

Keywords

Driving, opioids, morphine, breathlessness, dyspnoea, caregivers, patients

What is already known about the topic?

- Chronic breathlessness is a debilitating syndrome, which can be ameliorated by small doses of regular, low-dose, sustained-release morphine in some people.
- Driving is important for most adults, including the ones with life-limiting illnesses associated with chronic breathlessness.
- Despite growing concerns about the impact of opioids on driving ability, there are no studies investigating people's experiences of driving with chronic breathlessness before or after initiating treatment with regular, low-dose, sustained-release morphine.

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What this paper adds?

- Being able to drive is important for people with chronic breathlessness and their caregivers because it provides them with a continuing sense of self-worth, independence, pleasure and widening life space.
- Episodes of intense breathlessness can impact on patients' perceived ability to drive, which is not easily perceived by caregivers.
- Although people have fears surrounding driving while taking morphine, regular, low-dose sustained-release morphine does not seem to impact on patients' self-perceived driving ability.

Implications for practice, theory and policy

- In clinical practice, it is important to enquire about peoples' perceived ability to drive with chronic breathlessness and the medications that they are prescribed.
- Clinical research should focus on investigating whether oral, low-dose sustained-release morphine impacts on patients' driving ability, particularly during initiating therapy and any subsequent dose increases.
- Understanding the impact of low-dose, sustained-release morphine on people's driving ability is essential to inform guideline development about who is able to drive safely and who is not.

Introduction

Chronic breathlessness persists and is disabling despite optimal treatment of the underlying disease(s).[1] Chronic breathlessness affects almost 10% of adults and 17% of those ⩾65 years.[2] Patients with chronic obstructive pulmonary disease (COPD) are particularly affected, with >90% reporting breathlessness at some stage.[3] Chronic breathlessness is physically and psychologically debilitating,[4] leading to increasing dependence, social isolation, and worse health-related and mortality outcomes.[5,6] Loss of independence is also profoundly distressing for caregivers, who struggle seeing their loved ones' decline.[7,8]

Driving provides a sense of freedom, independence, identity and hope.[9] Not driving worsens social isolation and is associated with worse health-related outcomes.[10,11] One quarter of people with life-limiting illnesses continue driving.[12] Although there is ample evidence that chronic breathlessness severely restricts people's everyday lives, the effect of chronic breathlessness on people's driving ability has not been explored.

Regular, low-dose (≤30 mg/day),[13] sustained-release morphine safely reduces chronic breathlessness in people with COPD.[14,15] Recently, low-dose, sustained-release morphine has been approved by regulatory bodies in Australia for the treatment of chronic breathlessness.[16] This is the first world approval of any medication for the symptomatic reduction of chronic breathlessness, likely increasing prescriptions for this indication. Simultaneously, there are concerns about safe driving while taking psychoactive substances, including prescribed opioids.[17] While high dose opioids can impair driving, it is unknown whether regular, low-dose, sustained-release morphine impacts on patients' ability to drive, particularly when initiating therapy and up-titration.[18]

This aim of this qualitative study was to elicit patients' and caregivers' perceptions about driving with chronic breathlessness and to understand their perceptions about driving as regular, low-dose, sustained-release morphine was introduced.

Methods

Design

A qualitative study embedded in a pragmatic, phase III, randomised, placebo-controlled trial (RCT) evaluating the effectiveness of sustained-release morphine for people with chronic breathlessness and COPD (breathlessness, exertion and morphine sulfate (BEAMS) trial).[19] The RCT had a parallel-arm, dose increment design. Participants were randomised to placebo, 8 or 16 mg of once-daily sustained-release morphine for 1 week, with possible additional blinded up-titrations, of 8 or 16 mg in weeks 2 and 3. Maximum daily doses of morphine by the end of the randomisation period ranged from 0 mg (placebo) to 32 mg (0, 8, 16, 24 or 32 mg), with chances of being on placebo after randomisation being 1:12. The trial primary outcome measure was change in intensity of 'worst breathlessness' in the previous 24 h, measured with a 0–10 numerical rating scale after 1 week of therapy. The pragmatic design ensured that participants included in the RCT were a close reflection of the population of interest.[20,21]

Setting and participants

Participants were recruited from the metropolitan region serviced be the Southern Adelaide Palliative Services, Australia. Participants included patients who had ceased their participation in the BEAMS trial[19] either by completion or withdrawal; and 'the person closest to the patient' ('caregiver'), if present.[22] This sampling provided a broad range of perspectives. All patients had COPD and chronic

Box 1. Interview guide used for patients and caregivers.

Questions asked to patients
1. How important is driving to you?
2. Before the study, was your breathlessness impacting your ability to drive?
3. Were there any changes in your ability to drive after initiating the study medication?

Questions asked to caregivers
1. How important is it for you that [*patient*] is able to drive?
2. Before the study, was [*patient's*] breathlessness impacting on his/her ability to drive?
3. Were there any changes in [*patient's*] ability to drive after initiating the study medication?

breathlessness; a modified Medical Research Council (mMRC) breathlessness score of 3 or 4 corresponding to 'stops for breath after walking about 100 meters or stops after a few minutes walking on the level' and 'too breathlessness to leave the house or breathlessness when dressing or undressing', respectively.[23,24] Participants were active drivers or people who had recently stopped driving and were still able to recall their experience of driving with severe chronic breathlessness. The latter group's perceptions contributed to expand the understanding of the experience of driving with this disabling syndrome, but were not questioned about their experiences of driving after initiating sustained-release morphine.

Research team

The interviewer (D.F.) has a medical background and was a full-time doctoral student with training in qualitative research. J.B. is Senior Clinical Lecturer and Honorary Consultant in Palliative Medicine with a medical and research background. A.H. is a university researcher with background in data collection and people-centred research. S.K. is a university researcher with a linguistics background. J.P. is a senior researcher with a background in palliative care nursing and qualitative research. D.C. is a researcher with expertise in chronic breathlessness.

Recruitment

Using convenience sampling, the trial nurses approached potential participants by telephone. If interested, they were then phoned by the interviewer (D.F.), with whom they had no previous contact. The interviewer explained the study's objectives and scheduled a face-to-face meeting with potential participants to answer questions and obtain written consent.

Data collection

Face-to-face, semi-structured interviews were conducted separately with patients and their caregivers at a location of their choice (July 2017–November 2018), providing participants with safe and private settings to express freely any concerns or emotions.[25,26] Interviews evaluated the overall impact of chronic breathlessness in people's daily lives and perceived changes after initiating study drug.[19] Given the lack of evidence examining experiences of driving in people with chronic breathlessness, the interviews included three questions about driving, analysed in a separate sub-study (Box 1).

Participants' responses were recorded and transcribed verbatim (D.F.). Field notes were collected, and the researcher kept a reflexive journal with impressions about each participant–researcher interaction. Interview transcripts were not reviewed by participants to minimise burden on people already debilitated due to chronic breathlessness, given minimal advantages from doing this.[27] Potential misinterpretations were minimised by having a second researcher (A.H.) listen to interviews' recordings, checking transcriptions for accuracy. Participants were only contacted again if there were disagreements between these researchers. Data were collected until saturation (i.e. no new concepts were emerging), as agreed between all researchers.

Data analysis

NVivo (V 11.4.0 for Mac) was used. The analysis was driven by the principles of grounded theory, using a constant comparative approach.[28–30] Given the lack of qualitative studies exploring people's experiences of driving with chronic breathlessness, an inductive approach to analysis was adopted.[31] The constant comparative approach helped identify new concepts emerging from the data that could be explored in subsequent interviews.[30] Two researchers independently conducted open coding (D.F., A.H.) of all transcripts, which were grouped into themes (D.F.); each theme was illustrated with several quotes to confirm coding validity (D.F., J.B., S.K., J.P.). Patients' and caregivers' viewpoints were then compared and contrasted.

Ethical considerations

The BEAMS trial was approved by relevant Human Research Ethics Committees (15/12/16/3.06) and was registered (NCT02720822). All participants provided written informed consent. The COnsolidated criteria for REporting Qualitative research (COREQ) framework is used to report this study.[32]

Results

Fifteen patients and 11 matched caregivers were invited to this study: 2 patients declined (so their caregivers were excluded); 13 patients and 9 caregivers were interviewed. Interviews took 20–55 min. Patients had a median age of 76 years (interquartile range (IQR): 68–78), nine of whom were men, living with their partners. All were still mobile outside their homes, but were severely restricted in their daily activities due to breathlessness (Table 1).

Eight of 13 patients were regularly driving and one drove occasionally. Only two of nine men had stopped driving, while two of four women had stopped driving. The four participants who had stopped driving had all driven regularly until recently (Table 2). Eleven patients took sustained-release morphine during the study (Table 3): 8 mg ($n = 4$), 16 mg ($n = 3$), 24 mg ($n = 3$) and 32 mg ($n = 1$).

Three major themes described the experience of driving for patients with chronic breathlessness and their caregivers: (1) independence, (2) breathlessness' impact on driving, (3) driving while taking regular low-dose sustained-release morphine (Table 4).

Theme 1 – independence

Being able to drive helped patients keep their sense of self and feeling useful. This was more noticeable in patients experiencing severe functional limitations due to breathlessness:

> Well, I suppose it's something that I don't do every day (driving) and you know, and I am doing something! Maybe that's the reason why. . . Well I've always enjoyed driving actually but more so now, more so now, yeah. . . Probably because it's something different in my life now, you know? I can do something! Whereas usually, I am just sitting. (Patient 8)

Table 1. Patients characteristics ($n = 13$).

Median age (IQR)	76 (68–78)
Gender	
Female	4
Ethnicity	
Oceanian (Australia or New Zealand)	11
North-West European	2
Usual language spoken at home	
English	13
Residence	
Living in a private residence	13
Marital status	
Married or de facto	9
Separated or divorced	2
Widowed	2
Highest level of education	
Did not complete high school	4
Completed high school	4
Completed a trade certificate	3
University Degree	2
mMRC score at baseline	
3	13
NRS worst breathlessness (24 h)	
4	2
6	3
7	4
8	3
9	1
10	1
AKPS	
50	3
60	6
70	3
80	1

IQR: interquartile range; mMRC: modified Medical Research Council Scale; NRS: Numerical Rating Scale; AKPS: Australian Karnofsky Performance Status.

Table 2. Driving status for participants on trial ($n = 13$).

Patient	Gender	Caregiver	Driving status	Reasons to stop driving
1	Female	Husband	Not currently driving	Deemed unfit to drive
2	Male	Wife	Active driver	–
3	Male	–	Active driver	–
4	Female	Son	Not currently driving	Sold the car after husband died
5	Male	Wife	Not currently driving	Deemed unfit to drive
6	Male	Wife	Active driver	–
7	Female	–	Active driver	–
8	Male	Wife	Active driver	–
9	Male	–	Active driver	–
10	Male	–	Not currently driving	Sold the car due to financial issues
11	Male	Wife	Active driver	–
12	Female	Husband	Active driver	–
13	Male	Wife	Active driver (occasionally)	

Table 3. Maximum morphine doses patients took while on the BEAMS trial (n = 13).

Participant	Doses of morphine on trial					Cessation time-point
	Week 1	Week 2	Week 3		Extension	
1	Placebo	8 mg	16 mg	End of randomisation stage	16 mg	Completed the study
2	16 mg	16 mg	16 mg		16 mg	Completed the study
3	Placebo	Placebo	8 mg		8 mg	Completed the study
4	Placebo	Placebo	Placebo		–	Withdrew after week 3
5	16 mg	16 mg	24 mg		24 mg	Withdrew during extension
6	8 mg	16 mg	24 mg		24 mg	Completed the study
7	16 mg	24 mg	32 mg		–	Withdrew after week 3
8	8 mg	8 mg	8 mg		8 mg	Completed the study
9	Placebo	8 mg	8 mg		8 mg	Withdrew during extension
10	8 mg	8 mg	8 mg		8 mg	Completed the study
11	Placebo	Placebo	Placebo		Placebo	Withdrew during extension
12	8 mg	16 mg	24 mg		24 mg	Completed the study
13	Placebo	8 mg	16 mg		16 mg	Completed the study

BEAMS: breathlessness, exertion and morphine sulfate.

Table 4. Comparative analysis of findings from patients and caregivers.

Patients and caregivers	Patient	Caregiver
1. Independence Driving widens the 'living-space' for both patient and caregiver	• Doing something • Being useful • Enjoyment and pleasure • Fear of losing their ability to drive • The most important activity	• Happy to see patients enjoy themselves • More independence if the patient is able to drive • Fear that patients lose their ability to drive
2. Breathlessness impact on driving Breathlessness does not impact on perceived driving	• Overall, breathlessness does not impact on driving • Breathlessness at rest can affect concentration and the ability to drive	• Breathlessness does not affect the patients' ability to drive safely • More confident about patients' driving skills than the patients themselves
3. Driving while taking low-dose sustained-release morphine Sustained-release morphine does not impact on perceived driving	• Did not perceive any changes in driving ability with the study drug • Fears associated with low-dose morphine – putting others at risk	• Did not perceived any changes in patients' driving ability with the study drug • Fears associated with low-dose morphine – patients' decline

Most patients reported that driving was one of the few activities that brought them a sense of joy and pleasure. Even those patients not required to drive (i.e. because their caregiver drove), still felt the need to drive at times for pure enjoyment:

> We have got the van and I drive the van. I love getting out in the country and driving. (Patient 12)

For caregivers, seeing their partners enjoy themselves was particularly important. They acknowledged the role of driving in widening the physical space available to both the patients and themselves, a space that had been severely reduced by breathlessness in most cases:

> Well, driving is important. . . There are certain things. . . When we go on holiday because he is not bothered about walking out on the streets, you know? (. . .) But we went to Barossa Valley last week, and I don't know if you have been there, but we went to Mengler's Hill to the look out. He got up there, well we drove up there of course, we got out of the car and we walked down a little bit to the picnic area there and he stayed there while I walked around and looked at it because walking down and up and down. . . [meaning it was tiresome for him]. So things like that you know? (Caregiver 11)

For some patients, driving was their most important activity. One patient without a caregiver explained that driving was key to maintaining relationships and roles, while also providing a sense of purpose:

> I get my adult daughter every Saturday for a while, she is profoundly autistic, she just had her 26th birthday yesterday and it is very important to her. So I have got to drive to go get her, drive to bring her back. So it's a very important thing, making sure I can still drive. (. . .) And that's the main reason, apart from that, it is just to get to the shop and the doctor which are a kilometer away. That's the only big one. (Patient 3)

Another patient explained that driving was the only out-of-home activity he was still able to do independently and that losing it would be extremely disturbing:

> Well, I think the most important thing to be able to do at the moment is to be able to drive because physically there is nothing I can do, I can't do anything. (Patient 8)

Overall, people who were still driving expressed fear about not being able to drive in the future. Driving was seen as an important marker of independence, and there was fear over any loss and its consequences:

> I couldn't give up driving, I couldn't do that [disturbed facial expression]. I think it's your independence, you know? And once that is taken away you're reliant on somebody else. . . (Patient 9)

For the four patients who had stopped driving, only one (male) reported that driving was important to maintain his independence. The other three patients (one male, two females) reported driving was not overly important because their caregivers could drive when needed:

> It gives me a lot more freedom to have the car. I don't do things that I would normally do. . . If I had the car and I felt like KFC for lunch, I can go and get it (laughing). . . or if I wanted to go out for dinner with someone, I could just go and do it. Whereas now, for me to walk to the bus stop to get a bus somewhere, it's just too hard. . . (Patient 10)

> I don't miss driving. B. (husband) does everything. We are together all the time anyway. (Patient 1)

Breathlessness' impact on driving

In general, patients and caregivers considered that breathlessness did not reduce patients' driving skills because it did not require over-exertion:

> Normally, I am fine. I don't get tired driving. (Patient 7)

Some patients reported they had situations in which they felt breathlessness at rest. When present, they felt their driving ability was affected. Strategies to overcome this limitation included not driving at all or using oxygen while driving. Interestingly, the use of oxygen in the car raised some concerns about its safety and legality:

> There were a couple of times in which I have been buggered a bit. I haven't had the oxygen the night before, so I will put the oxygen on the car and I will have the oxygen running while I am driving. Whether that's legal or not I don't know. (Patient 11)

One patient experiencing breathlessness at rest explained that breathlessness impacted on his concentration and hence ability to drive. When he drove, he felt anxious and concerned about his and other people's safety:

> For me it is not so much driving, but the concentration level about what is going on around. Stuff I used to take for granted, so I automatically did it before. Now, I have to make sure I do it. And it depends on the concentration because if it is concentrating on something that could end in a disaster, is a bit different to concentrating on something that might just a non-event anyway. (Patient 13)

Overall, caregivers' views matched patients' views. Most caregivers confirmed that patients drove safely despite their breathlessness. For the only patient who stated that driving was stressful (previous quote, patient 13), the caregiver thought he could still drive safely:

> Yes, usually when we go stay with our son at Wallaroo, he drives there. So he can. And he is quite good, I think. I don't notice any diminishing of his driving skills. I feel quite relaxed when he is driving. (Caregiver 13)

Driving while taking regular, low-dose sustained-release morphine

Participants' views on driving were quite uniform, irrespectively of the drug (i.e. morphine or placebo) and dose. Most patients and caregivers perceived that the study drug did not have any perceived adverse impact on patients' ability to drive, irrespectively of the study drug/dose:

> No, no problems (to drive while taking the study drug). (Patient 7 – maximum morphine dose: 32 mg)

> No, no, not at all. I don't think driving was affected (by morphine). (Caregiver 2 – maximum morphine dose: 16 mg)

Despite not perceiving any impact on driving with the study drug, a small number of participants were still concerned about the potential effects of morphine on driving. Most believed that the trial dose (up to 32 mg sustained-release morphine a day) could impair driving. One caregiver did not want the patient to continue with morphine because she believed morphine could lead to driving cessation. One patient took action to minimise any negative impact of morphine on his driving skills:

> I was concerned about. . . If he does take it, I think he wouldn't be able to drive (. . .) and I don't really want him to

> go on that because he loves driving and I think if he took it, that would be the end. I want him to be around for a few more years yet. (Caregiver 8 – maximum morphine dose: 8 mg)

> I have a friend coming here and he will sit with me (while I drive) and tells me what is going on with the driving. (. . .) I know they say if I am taking a quite powerful opioid drug that driving while under the immediate influence is probably not that smart. I would not be inclined to do it unless it was an emergency. (Patient 3 – maximum morphine dose: 8 mg)

Discussion

Main findings

This is the first study reporting patients' and caregivers' perspectives and experiences of driving with chronic breathlessness. In addition, the study was set in a study to compare before-and-after taking regular, low-dose, oral sustained-release morphine. Findings suggest that driving is crucial in helping patients with chronic breathlessness keep a sense of identity, purpose, independence and connection to the outside world, while also being a source of joy and comfort for both patients and caregivers. According to patients, breathlessness at rest can reduce their driving skills but the study drug (i.e. morphine/placebo) had no perceived impact on their ability to drive.

Similar to healthy individuals, owning and driving a private vehicle is perceived as an amenity offering people freedom of movement.[33] However, participants' reflections highlight that the ability to drive is particularly important for people experiencing severe functional limitations in other aspects of life due to chronic breathlessness and their caregivers. For these patients, driving is associated with a sense of identity and feeling useful. Similar findings were reported by a previous qualitative study of three focus groups: (1) low disability/broad life space, (2) high disability/broad life space, (3) high or low disability/constricted life space. Although all groups considered driving an important activity, the third group was the most affected by driving cessation which was perceived by them as devastating.[34] Importantly, the present study also shows that driving widens both patients' and caregivers' life space (i.e. the physical space in which they move and socially interact).[35,36] Previous evidence suggests that as patients become more restricted by chronic breathlessness, caregivers tend to adjust by slowing their life rhythm, also becoming more restricted.[37] Thus, it is likely that any strategies supporting patients' function (such as driving) may also positively affect caregivers.[35] Functional decline is one of the major contributors to driving cessation in older age.[11] Older adults who stop driving have twice the risk of depressive symptoms compared to those who continue driving.[11] Importantly, there is a significant association between the well-being of these patients and their caregivers.[38] Thus, risks and benefits for patients and caregivers need to be weighed carefully before advising patients not to drive.

Most patients considered that their chronic breathlessness did not impact on their driving primarily because driving was sedentary and did not trigger breathlessness. Patients who had experienced or were experiencing breathlessness at rest explained that breathlessness affected their concentration when driving. Previous research has highlighted potential effects of uncontrolled symptoms on people's driving skills.[39] Worsening breathlessness scores are associated with worsening performance in neuropsychological assessments, but any relationship with driving performance is unknown.[40] Worsening breathlessness scores are associated with increased chances of experiencing breathlessness at rest.[23] Thus, it is possible that patients with worse breathlessness are particularly at risk of having some degree of psychomotor impairment that could affect driving. Interestingly, caregivers did not seem to notice any changes in patients' ability to drive. This may result from patients' adaptation to breathlessness, including development of driving strategies that are not evident to caregivers (e.g. increased attention, driving slightly slower). Reportedly, the use of oxygen while driving may be one of these strategies. Using oxygen while driving is legal in most countries, but patients need to ensure oxygen tanks are adequately secured and respect specific state/country requirements. Given that driving cessation is also emotionally challenging for caregivers, caregivers may overlook changes in patients' driving ability in order to keep them driving.[41]

All participants agreed that their study drug/dose did not affect their perceived driving skills. Previous research had suggested that regular therapeutic opioid-agonists are unlikely to affect driving-related skills.[18] This study raises the hypothesis that low doses of sustained-release morphine may have no impact on driving even during therapy initiation and careful upward titration. This is in line with previous studies showing that uncontrolled symptoms are more likely to have an impact on driving than therapeutic opioids.[39] Despite that, both patients and caregivers were still concerned about potential side effects of sustained-release morphine that could affect their driving. Concerns about opioids are common among patients, caregivers and clinicians.[42,43] Interestingly, while patients' concerns were focused on safety for themselves and others, caregivers' were more concerned with patients' deterioration if they were to stop driving. Chronic breathlessness affects both patients and caregivers, involving both in symptom management and again reinforcing the patient–caregiver unit as the unit of care.[44]

This study suggests that initiating morphine for chronic breathlessness may raise concerns about driving for patients and caregivers, and those concerns need to be proactively addressed with both. Frequently, clinicians advise patients not to drive immediately after

taking opioids.[45] There is a need for further research to understand if patients taking regular, low-dose, sustained-release morphine are able to drive safely given the different pharmacokinetic profile they have to immediate-release oral morphine solutions.[46] The relation between breathlessness and driving performance whist on opioids must also be explored as current legal morphine limits for driving (where imposed) are far higher than the doses used in this study.[13]

Strengths and limitations

This is the first qualitative study reporting on people's experiences of driving with chronic breathlessness and the perceived effects of regular, low-dose sustained-release morphine on driving ability. The inclusion of people taking different doses of morphine and placebo provided a range of different perspectives that could be compared and contrasted. The qualitative design limits generalisability, but findings point to important questions and future research directions, particularly in the context of growing concerns about drug-affected drivers. This study is limited by looking at self-reported effects on driving. People tend to overestimate their own driving performance.[47] Most studies conducted in this field asked participants to rate their driving ability compared with the 'average driver', rather than assessing aspects of their own driving.[48] The latter has been shown to more accurately reflect driving performance, and is closer to the approach used in this study.[48,49] Similarly, caregivers' perception is not an optimal reflection of patients' driving skills, but their assessment of specific driving aspects correlates with on-the-road performance.[50] Opioids may affect cognitive function, which may affect self-perception.[51] However, it is less likely that would be the case with small doses of morphine.[52]

A strength of this study is that participants were recruited from a phase III RCT that allowed COPD-status and morphine-dose transparency. While the participants may not be representative of the overall population with severe breathlessness associated with COPD, the RCT had a pragmatic design to ensure high external validity.[20,21] Due to the main trial dose increment design, people were more likely to be taking morphine than placebo after the randomisation period (11:12 chance). This reduced the number of perspectives from people taking placebo, but increased the number of people who could provide useful information about morphine.

What this study adds

This study highlights that driving is important for people living with chronic breathlessness and their caregivers. It also suggests that regular, low-dose, sustained-release morphine does not impact on patients' perceived ability to drive. Based on these findings, there is a need to objectively evaluate the impact of chronic breathlessness on patients' driving ability. Previous studies focused on objective measures of disease severity but not on the symptom itself.[53] It is also important to understand if people are safe to drive with low doses of sustained-release morphine, particularly during therapy initiation and upward titration. Equally, the impact of uncontrolled symptoms such as chronic breathlessness on driving performance needs to be researched. There is a common assumption in the clinical setting that people should refrain from driving in the first hours or days after initiating any opioid. There are no published RCTs to confirm this should be the case with low-dose sustained-release morphine. Due to lack of evidence to support decision-making, clinicians may advise people taking low-dose sustained-release morphine to stop driving, but be aware that this may have severe implications for people's well-being and social functioning.

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Author contributions

D.H.F., J.L.P. and D.C.C. contributed to the study design; D.H.F. contributed to the acquisition of data; D.H.F., J.W.B., A.H., J.L.P. and D.C.C. contributed to data analysis; D.H.F. drafted the article; all authors have critically revised the articles and have approved the manuscript version to be published.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship and/or publication of this article: D.C.C. is an unpaid advisory board member for Helsinn Pharmaceuticals. He is a paid consultant and receives payment for intellectual property with Mayne Pharma and is a consultant with Specialised Therapeutics Australia Pty. Ltd. D.H.F., J.W.B., A.H., S.K. and J.L.P. disclose no competing interests relevant for this work.

Ethical approval and informed consent

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Data sharing

The study databases are available from the corresponding author on reasonable request.

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Appendix 10 – Carers Status and Demographic Form developed for Sub-study 1 (patients and carers' interviews)

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030/15 BEAMS Study

Patients' and Caregivers' Sub-study

Caregiver's Status and Demographics Form

To be completed by the Caregiver

Participant's Screening Number _ _ / _ _ / _ _ _ **Date** _ _ / _ _ / _ _ _ _

Caregiver's Initials ___ ___ ___
Date of Birth: _ _ / _ _ / _ _ _ _
Gender (circle one): F or M

Highest level of education (please tick one)		
1	Did not complete high school	
2	Completed high school	
3	Completed a trade certificate	
4	University degree	
5	Post graduate degree	
6	Other (Specify)	

Ethnicity Status (please tick one)		
1	Oceanian (Australia or New Zealand)	
2	Aboriginal or Torres Strait Islander	
3	North-West European	
4	Southern and Eastern European	
5	North African and Middle Eastern	
6	South-East Asian	
7	North-East Asian	
8	Southern and Central Asian	
9	People of the Americas	
10	Sub-Saharan African	

Marital Status (please tick one)		
1	Married or de facto	
2	Widowed	
3	Never Married	
4	Divorced or Separated	
5	Other (specify)	

Relationship to the participant (please tick one)		
1	Husband/wife/partner	
2	Parent	
3	Parent-in-law	
4	Daughter / Son	
5	Sister / Brother	
6	Friend	
7	Paid carer	
8	Other	

Do you currently live with the participant? (please tick one)		
1	Yes (complete below)	
2	No	
If yes For how long have you lived with the participant?		
_____ months *or* _____ years		

Do you provide hands-on care to the participant? (please tick one)		
1	Yes (complete below)	
2	No	
If yes **For how long have you been providing hands-on care to the participant?**		
_____ months *or* _____ years		

In the past week, how many hours on **average** have you spent with the participant? (please tick one)	
0-10 hours	
10-20 hours	
20-40 ours	
>40 hours	

Are there any other people involved in caregiving for the participant? (please tick one)		
1	Yes	
2	No	
If yes Please specify how many and number of hours per week		
_____ family members _____ friends _____ neighbours _____ paid carer	_____ hours per week _____ hours per week _____ hours per week _____ hours per week	

Employment Status				Has your employment status changed as a result of your caregiving role? (please tick one)		
Current Employment Status				1	Yes (please complete below)	
				2	No	
				If yes: What was your previous employment status?		
1	Employed full time			1	Employed full time	
2	Employed part time			2	Employed part time	
3	On paid leave			3	On paid leave	
4	On unpaid leave			4	On unpaid leave	
5	Self-employed			5	Self-employed	
6	Retired			6	Retired	
7	Not employed			7	Not employed	
8	Other (specify)			8	Other (Specify)	

Appendix 11 – Interview guides developed for Sub-study 1 (patients and carers' interviews).

030/15 BEAMS Study

Participants' and Caregivers' Sub-study

Interview guide

(Patients participating in the main study)

Participant's Screening Number _ _ / _ _ / _ _ _ **Date** _ _ / _ _ / _ _ _ _

Drop Out □ **Study Stage** _____
Conclusion □

You have been asked to participate in this study because you have emphysema and feel shortness of breath…

Before taking the study medication…

1. **Did shortness of breath affect your life? In what way?**
   - Were there any activities you cannot do?
     (e.g.: Get up, get dress, have a shower, cook, clean the house, do the loan, go out and have a walk, drive, sleep)
   - From the things you were not able to do, which ones were the most important to you?
   - How did you generally feel when you have shortness of breath? (Well adapted, anxious, concerned…)
   - Did your relationships change because of your shortness of breath? (ie: Spouse, family members, friends) If so, in what way?
   - What was the worst thing about being shortness of breath?
   - What were your hopes for the future?
   - Did you have any fears or concerns about the future?
   - Overall, do you think your quality of life changed as a result of being shortness of breath?

2. **What did you know about morphine before participating in the BEAMS study?**
   - What is it used for?
   - Effects (positive and negative)

3. **What was your source of information about morphine?**
   - General Practitioner, other clinician, other health professionals, TV, radio, social media, family, friends…

4. **Had you heard about using morphine for shortness of breath?**
   - What are your thoughts on this?
   - If the person mentioned other settings (drug abuse, substitution therapy, pain, etc) → Do you believe there are differences between the morphine given in other settings (drug abuse, substitution therapy, pain…) and morphine given for shortness of breath (route, dose, formulations)?

5. **What results were you expecting?**
   - Breathlessness, Other symptoms
   - Emotional status
   - Function
   - Other

6. **Did you have any fears or concerns about this medication?**
   - Effect on sleep
   - Effect on concentration
   - Effects on driving
   - Addiction, tolerance, side-effects
   - Other

7. **Did you discuss this medication with anyone before?**
   - [Caregiver], General Practitioner, other health professionals, family, friends…

<u>Now that you have completed the study</u>:

8. **Have your views on this medication changed over the study? In what way?**
   - Overall effects, concerns, other (positives and negatives)…

- Describe by study stage in possible (differences between weeks 1, 2, 3, extension phase)

9. **How easy it is taking this medication?**

10. **Has this medication changed your daily life? In what way?**
    - Breathlessness, other symptoms
    - Emotional well-being
    - Function
    - Relationships
    - Feelings about the disease (concerns, hopes)
    - Overall quality of life

11. **Do you think this medication would benefit you enough to be on it long term?**
    - Why / Why not?

12. **Do you have any advice to other people with emphysema and breathlessness?**

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030/15 BEAMS Study

Participants' and Caregivers' Sub-study

Interview guide

(Caregivers participating in the main study)

Participant's Screening Number _ _ / _ _ / _ _ _ **Date** _ _ / _ _ / _ _ _ _

Drop Out ☐ **Study Stage** _____
Conclusion ☐

You have been asked to participate in this study because [participant] has emphysema and feels shortness of breath, and has identified you as the person that knows him/her best...

Before taking the study medication...

1. **Was your life affected by [patient's] shortness of breath? In what way?**
   - Were there things you could not do?
   - From the things you were not able to do, which ones were the most important to you?
   - How did you use to feel about [participant's] shortness of breath? (Well adapted, anxious, concerned...)
   - Did your relationships change because of [participant's] shortness of breath? (ie: Spouse, family members, friends) If so, in what way?
   - What was the worst thing about [participant's] shortness of breath?
   - What were your hopes for the future?
   - Did you have any fears or concerns about the future?
   - Overall, do you think your quality of life changed as a result of [participant's] shortness of breath?

2. **What did you know about morphine before participating in the BEAMS study?**
   - What is it used for?
   - Effects (positive and negative)

3. **What was your source of information about morphine?**
    - General Practitioner, other clinician, other health professionals, TV, radio, social media, family, friends…

4. **Had you heard about using morphine for shortness of breath?**
    - What are your thoughts on this?
    - If the person mentioned other settings (drug abuse, substitution therapy, pain, etc) → Do you believe there are differences between the morphine given in other settings (drug abuse, substitution therapy, pain…) and morphine prescribed by a doctor or nurse for pain or breathlessness (route, dose, formulations)?

5. **What results were you expecting?**
    - Breathlessness, Other symptoms
    - Emotional status
    - Function
    - Other

6. **Did you have any fears or concerns about this medication?**
    - Effect on sleep
    - Effect on concentration
    - Effects on driving
    - Addiction, tolerance, side-effects
    - Other

7. **Did you discuss this medication with anyone?**
    - [Participant], General Practitioner, other health professionals, family, friends…

<u>Now that [participant] has completed the study</u>:

8. **Did your views on this medication changed over the study? In what way?**
    - Overall effects, concerns, other (positives and negatives)…
    - Describe by study stage in possible (differences between weeks 1, 2, 3, extension phase)

9. **How easy it is taking this medication?**

10. **Has this medication changed your daily life?**
    - Things you could not do
    - Emotional well-being

- Relationships
- Feelings about the disease (concerns, hopes)
- Overall quality of life

11. **Do you think this medication would benefit [participant] enough to be on it long term?**
    Why / Why not?

12. **Do you have any advice for other people providing care or support for people with emphysema and shortness of breath?**

Appendix 12 – Publication: The impact of therapeutic opioid agonists on driving-related psychomotor skills assessed by a driving simulator or an on-road driving task: A systematic review (included in Chapter 5).

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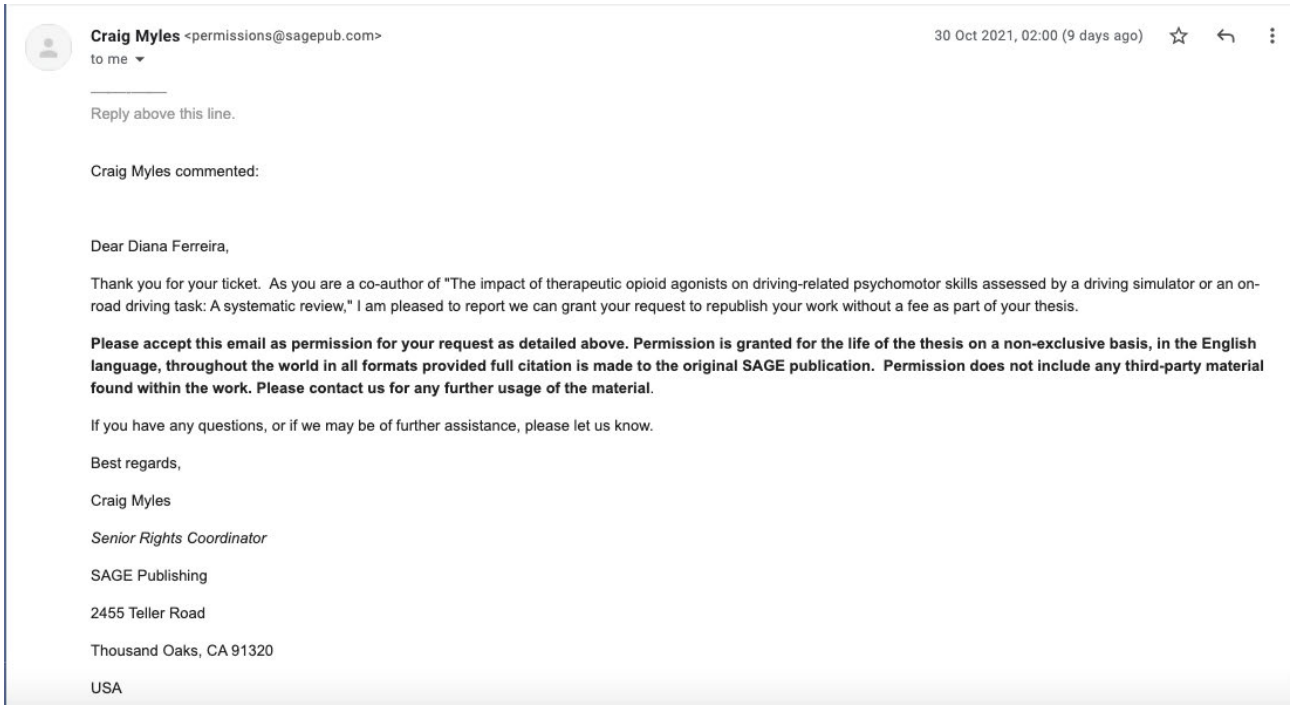

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The impact of therapeutic opioid agonists on driving-related psychomotor skills assessed by a driving simulator or an on-road driving task: A systematic review

Diana H Ferreira[1], Jason W Boland[2], Jane L Phillips[3], Lawrence Lam[3] and David C Currow[1,2,3,4]

Abstract

Background: Driving cessation is associated with poor health-related outcomes. People with chronic diseases are often prescribed long-term opioid agonists that have the potential to impair driving. Studies evaluating the impact of opioids on driving-related psychomotor skills report contradictory results likely due to heterogeneous designs, assessment tools and study populations. A better understanding of the effects of regular therapeutic opioid agonists on driving can help to inform the balance between individual's independence and community safety.

Aim: To identify the literature assessing the impact of regular therapeutic opioid agonists on driving-related psychomotor skills for people with chronic pain or chronic breathlessness.

Design: Systematic review reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis statement; PROSPERO Registration CRD42017055909.

Data sources: Six electronic databases and grey literature were systematically searched up to January, 2017. Inclusion criteria were as follows: (1) empirical studies reporting data on driving simulation, on-the-road driving tasks or driving outcomes; (2) people with chronic pain or chronic breathlessness; and (3) taking regular therapeutic opioid agonists. Critical appraisal used the National Institutes of Health's quality assessment tools.

Results: From 3809 records screened, three studies matched the inclusion criteria. All reported data on people with chronic non-malignant pain. No significant impact of regular therapeutic opioid agonists on people's driving-related psychomotor skills was reported. One study reported more intense pain significantly worsened driving performance.

Conclusion: This systematic review does not identify impaired simulated driving performance when people take regular therapeutic opioid agonists for symptom control, although more prospective studies are needed.

Keywords

Opioids, opioid agonists, chronic pain, chronic breathlessness, driving simulator, driving performance, driving outcomes

What is already known about the topic?

- Being able to drive is important for most adults.
- Not being able to drive is associated with worse health-related outcomes.
- Different studies, from different participant groups, using differing assessment tools, show conflicting results on the impact of opioids on driving-related psychomotor skills.

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What this paper adds?

- There is a paucity of studies evaluating the impact of opioid agonists on driving-related psychomotor skills in participants with chronic pain or chronic breathlessness.
- Stable doses of opioid agonists may pose no increased driving risk to people using them for long-term symptom control.
- Pain may have a negative impact on people's performance, itself more significant than regular therapeutic opioid agonists.

Implications for practice, theory or policy

- There is a need to further investigate what is the impact of therapeutic opioid agonists for long-term symptom control on people's driving skills.
- Prospectively collected data need to focus on specific populations, opioid formulations and driving outcomes as regular therapeutic opioid agonists are initiated, titrated and maintained.
- Defining which specific groups of patients may be able to drive or not drive safely will contribute to informed decision-making by clinicians faced with providing advice to patients and their families, with the potential to improve health-related outcomes.

Introduction

For many adults, driving is a key daily activity, strongly associated with personal freedom and independence.[1] Not being able to drive impacts on one's self-image, limits the ability to work, impairs independence for many basic activities and reduces overall quality of life.[1,2] Driving cessation is associated with social isolation[3] which has been associated with decrements in several health-related domains, higher risk of being admitted into long-term care facilities and higher mortality.[4–6] Being unable to drive is associated with doubling of depressive symptoms.[6–8]

For patients with chronic conditions requiring palliative care, being able to drive is still important. From a cohort of 173 people with life-limiting illnesses, 23% were current drivers and 16% still considered it an option.[9] Almost all patients mentioned that keeping their driving licences was important stating reasons such as identification, hope and emergencies.[9]

Concurrently, many people with chronic conditions live with a significant symptom burden requiring a range of management strategies including the use of regular therapeutic opioid agonists.[10,11] Regular therapeutic opioid agonists are currently recommended as the first-line treatment for moderate to severe cancer pain,[12] moderate to severe chronic non-malignant pain when other medications fail to provide relief[13] and for reducing chronic breathlessness when symptom relief is unattainable with optimal treatment of underlying causes.[14,15] When initiated, titrated and managed using the best available evidence, regular therapeutic opioid agonists have been shown to be safe, have minimal potential for addiction and improve quality of life.[15,16]

Despite their benefits, some studies evaluating the efficacy and safety of therapeutic opioids report high incidences of dizziness, sedation[17] and cognitive and psychomotor impairment,[18–20] while others report no significant problems.[21–23] A systematic review on this topic identified that most studies are heterogeneous and fail to report confounders, limiting the generalisability of results.[24]

To address this gap, this systematic review is based on the best available evidence in relevant populations, covering pure opioid agonists. Outcomes were selected to minimise heterogeneity of study design or populations where possible. This study therefore investigates the effect of regular therapeutic opioid agonists for chronic pain or chronic breathlessness on driving safety.

Opioids

Type of opioids

Opioids have heterogeneous pharmacokinetic and pharmacodynamic profiles which influence clinical responses.[25,26] For example, opioids bind with different affinities to the opioid receptors.[27] Full agonists have high affinity to opioid receptors, producing maximum clinical effect. These opioids do not have a ceiling effect for analgesia, and the dose selected is the one that produces maximum clinical effect with manageable adverse events.[27] Other classes of opioids (e.g. partial agonists, mixed agonists–antagonists) have a sub-optimal action on the opioid receptors. These classes have a celling effect which limits the dose escalation.[27]

Even within opioid agonists, there are substantial differences. For example, methadone is an opioid agonist that also has action as an antagonist of N-methyl-D aspartate (NMDA) receptors.[28] NMDA receptors play an important role in memory dysfunction and cognition,[29] meaning any

effect observed on driving performance may be caused by this mechanism of action rather than its effect on opioid receptors. As such, within opioid class, differences must be considered when evaluating driving performance.

Routes of administration and formulations

Oral opioids are available in two formulation types: immediate release and extended release.[30] Long-acting opioid formulations are now recommended as first-line options for prolonged therapy.[31,32] Their pharmacokinetic profiles show less fluctuations in plasma concentration, higher minimum plasma concentration (C_{min}) and longer time with maximum concentrations (T_{max}).[33] This is important because a lower C_{max} can potentially be associated with fewer adverse events[34] including sedation, cognitive impairment and psychomotor performance. Transdermal (TD) formulations are similar to oral extended-release formulations because they allow a slow diffusion of the drug to the bloodstream which also enables steady plasma concentrations over a prolonged period.[35] Other formulations (e.g. intravenous, intranasal, buccal, sublingual, rectal) exhibit variable pharmacokinetic characteristics[36] and are not recommended as first-line, regular therapy.

Opioid agonist dose

Sedation is a common side effect of opioids that may impact on cognition, psychomotor performance and driving ability. Some longitudinal studies have suggested that high doses of opioids may cause cognitive impairment, while low opioid doses may not.[37] There is a wide therapeutic window for opioids in healthy individuals[38] due to genetic and acquired influences.[39] While pharmacokinetic characteristics contribute to inter-individual differences in opioid response, pharmacodynamic adaptations play a crucial role in changes in opioid response longitudinally.[39] For example, the μ-opioid receptor, the most important mediator for analgesia and sedation[27] has a highly dynamic pattern of expression. This receptor is over-expressed in peripheral inflammatory states[40] frequently associated with pain and breathlessness but under-expressed in other situations like chronic opioid exposure.[41]

As such, some specific situations, rather than the opioid dose per se, need to be considered in the clinical setting:

1. *Dose initiation*. Single-dose studies show that side effects of opioids are accentuated when therapy is initiated.[42,43] Most people rapidly develop tolerance to opioid-induced sedation,[44] allowing safe driving.[45]
2. *Upwards dose titration*. Patients taking therapeutic doses of opioids may experience increased sedation and cognitive and psychomotor impairment following an increase in their regular opioid dose.[18]
3. *High steady state*. Opioid agonists bind to the opioid receptors in a log-linear fashion.[25] As opioid agonist doses increase, symptom relief improves or side effects emerge.[25] After this point, sedation, cognitive and psychomotor impairment may persist even with stable doses.

Patients taking opioids for chronic breathlessness constitute a particular case because the doses required to relieve this symptom are particularly low (up to 30 mg/day oral morphine equivalent dose).[46] As such and for the purpose of this work, this cut-off was used to differentiate high dose and low dose. This is important because it is currently not fully understood the effects of such small doses in patients-related psychomotor skills, particularly in steady state.

Population who stop driving

Among the elderly population, the most common reason to stop driving is impairment as a result of medical problems.[47] This population has a higher incidence of chronic conditions[48] that reduce mobility and require treatment with multiple medications.[49] Additionally, chronic pain or chronic breathlessness are often present and require symptomatic treatment and palliative approaches.[50–52] For the purpose of this work, chronic pain is defined as 'ongoing or recurrent pain, lasting beyond the usual course of acute illness or injury or more than 3–6 months, and which adversely affects the individual's well-being'.[53] Chronic breathlessness is defined as 'breathlessness that persists despite optimal treatment of the underlying pathophysiology and that results in disability'.[54] Understanding the real effects of long-term opioids in patients' driving-related skills is therefore challenging because many factors (e.g. age, chronic diseases, chronic symptoms and other medications) may interact to produce cognitive and psychomotor impairment.[55,56] These factors need to be taken into account when considering any driving outcomes in this population.

Measures of driving performance

The current best way to evaluate driving skills is an on-the-road driving test[57] which consists of a 100-km drive on a public highway, under regular traffic conditions. Because it is time-consuming, this test is difficult to apply in clinical or research settings. As such, researchers have been looking for alternative outcome measures that could accurately predict on-road outcome.[58] Driving is a task requiring numerous skills, including concentration over long periods of time, being able to receive multiple sensory stimuli, process them, make decisions and respond appropriately.[59] This requires preserved cognitive abilities like concentration, attention, perceptual skills, insight and

memory.[60] Based on this, batteries of cognitive and psychomotor tests are frequently used as quick and easy predictors of on-road driving performance.[61] However, research indicates these tests or combination of tests are poor predictors of driving performance.[58,62,63] In fact, a battery of five psychometric tests has been shown to have a total predictive value of only 33.4% to the on-the-road driving test.[58] A good alternative to these tests is driving in a simulator because they have higher external validity to detect drugs' (alcohol or illicit drugs) or sleep disorders' detrimental effects on driving.[64–67] There is increasing evidence driving simulators are able to predict driving outcomes on the road.[68,69]

Research questions

Given the methodological research issues when considering the use of regular therapeutic opioid agonists and driving, a broad research question was developed with progressively narrower sub-questions:

Research question

Does treatment with regular therapeutic opioid agonists for long-term symptom control (chronic pain, chronic breathlessness) impact on driving-related psychomotor skills as assessed by a driving simulator or an on-road driving task?

Sub-questions

1. Are people taking therapeutic regular opioid agonists for long-term symptom control (chronic pain, chronic breathlessness) able to drive safely?
2. Do any data specifically relate to either:
   (a) Prescribed extended-release or TD formulations?
   (b) Prescribed low doses (≤30 mg/day oral morphine equivalent dose) or is there a dose–response relationship?
   (c) Both (a) and (b)?

Methods

This systematic review is reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement.[70]

Design

Systematic review

Protocol and registration

This systematic review protocol was registered in PROSPERO – international prospective register of systematic reviews (Registration Number CRD42017055909; available in https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017055909).

Eligibility criteria

English language, peer-reviewed studies were included if they reported empirical data on driving simulation, 'real-world' driving or driving outcomes in adults taking therapeutic opioid agonists for long-term symptom control. Studies using opioid agonists with a strong action on NMDA receptors (e.g. methadone) were excluded. By acting both on the opioid receptors and NMDA receptors, they have the potential to cause cognitive side effects by different mechanisms. As such, it would be difficult to generalise results to other opioid agonists. Anaesthesia and surgical settings were excluded because of single dose or short-term exposure, and the likelihood of exposure to other centrally acting medications, surgical interventions and invasive procedures that all could influence driving ability.[71] Studies conducted with populations with severe renal or hepatic impairment were also excluded because opioid agonists are, to different extents, metabolised/excreted by these organs.[72]

The participant/intervention/control/outcome/setting (PICOS) for this systematic review is in Table 1.

Information sources and search strategy

The following databases were systematically searched up until 15 January 2017: MEDLINE (Ovid, 1946–2016), PubMed (Non-MEDLINE subset only which includes citations not yet or never-to-be indexed for MEDLINE), Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effect), EMBASE (Ovid, 1974–2016), Scopus and the Cumulated Index to Nursing and Allied Health Literature: CINAHL (EBSCOhost).

The final search strategy included two sets of terms. Set 1 was designed to include all the literature relating to opioids, particularly the most common opioid agonists used in clinical practice. Set 2 was created to capture all terms related to driving-related psychomotor skills which included driving simulation, driving tasks and driving outcomes (e.g. accidents). Within each set, terms were combined using the Boolean Operator 'OR'. Both sets were then combined using the Boolean Operator 'AND' (Table 2). Pain and breathlessness were not included as a separate set of terms, but they were hand searched at a later stage from the list of retrieved articles.

Before running the final search strategy, a preliminary search of MEDLINE was conducted to identify suitable Medical Subject Headings (MeSH terms) and useful text words included in titles and abstracts. A detailed search

Table 1. PICOS.

P (Population)	Adults (≥18 years) requiring opioid agonists for pain or breathlessness control
I (Intervention)	Therapeutic regular opioid agonists for chronic pain or chronic breathlessness Sub-group examination of: 1. Extended-release or transdermal formulations 2. Low doses (≈≤30 mg/day oral morphine equivalent dose) or dose–response relationship 3. Both 1 and 2
C (Comparison)	Placebo/no intervention/control group
O (Outcome)	Impairment on driving-related psychomotor skills as assessed by: - Driving simulator - On-the road driving tasks - Driving outcomes (e.g. accidents)
S (Setting)	Hospital, community, ambulatory

Table 2. MEDLINE search strategy: conducted in December 2016.

#	Searches	
1	analgesics, opioid/ or codeine/ or fentanyl/ or hydromorphone/ or morphine/ or oxycodone/	Set 1
2	(opioid* or codeine or fentanyl or hydromorphone or morphine or oxycodone).tw.	
3	or/1–2	
4	automobile driving/ or driving under the influence/ or Accidents, Traffic/	Set 2
5	((abilit* or competen* or skill* or task* or simulation* or aptitude* or perform* or capacit* or capab* or function* or risk* or safe* or unsafe or impair* or danger* or influence or fit* or unfit or impact or advice or cessation or restrict*) adj4 driv*).tw.	
6	(automobile* or car or cars or road or traffic or accident* or crash*).tw.	
7	reaction time/	
8	(react* adj2 time*).tw.	
9	or/4–8	
10	3 and 9	
11	Animals/ not (Human/ and Animals/)	
12	(Letter or comment or editorial or news or case reports).pt.	
13	10 not (11 or 12)	
14	limit 13 to English language	

was then constructed in MEDLINE (Ovid; Table 2) and translated for each database of interest (Appendix 1). Consultation with a specialist research librarian was undertaken to ensure that the search strategy was appropriate.

Grey literature was searched using Google, Google Scholar, the Australian New Zealand Clinical Trials Registry (ANZCTR), the ClinicalTrials.gov database and the ProQuest Dissertations & Theses Database (PQDT). Additionally, the reference lists of relevant articles were hand searched.

Study selection

Relevant articles were managed using Endnote X7 (Thomson Reuters, Philadelphia, PA, USA). First, duplicates were removed. Subsequently, articles that did not match the eligibility criteria were excluded. Two authors (D.H.F., J.L.P.) independently reviewed all titles and abstracts in order to assess their relevance for inclusion. Full-text papers were retrieved for all those fulfilling the inclusion criteria or anywhere there was equivocation using title and abstract alone. Full texts of all remaining relevant studies were then assessed. Specific reasons were provided for any articles excluded at this stage. Disagreement at all stages was resolved by discussion or recourse to a third author (D.C.C.).

Data extraction process

Data from potentially relevant studies were extracted by two authors (D.H.F., J.W.B.). A Data Extraction Form was developed to collect information from potentially relevant studies. Fields included year of publication, journal, title, first author, country, settings, study design, time period, number of subjects, % men, mean age, diagnose, type of opioid agonist, dose, acute or chronic administration (≥7 days), route, formulation, type of test performed and outcomes. The data collection forms were complied with randomised controlled trials, observational studies, systematic reviews and meta-analyses.

Quality and risk of bias appraisal

Critical appraisal of the included studies was conducted using the quality assessment tools from the National Institutes of Health (NIH).[64] The NIH tools can accommodate a range of study designs. All included studies were independently rated by two researchers (D.H.F., J.W.B.) for quality and risk of bias. Incongruences in rating were discussed in order to achieve a consensus.

Synthesis of results

Given the variety of study designs, a narrative synthesis was conducted based on the methods described by Popay et al.[73]

Results

Study selection

The initial systematic search retrieved a total of 6553 articles: MEDLINE (n = 1179), PubMed (non-MEDLINE content only) (n = 221), Embase (n = 2197), CINAHL (n = 64), Cochrane Database of Systematic Reviews (n = 3), Cochrane Central Register of Controlled Trials (n = 234), Database of Abstracts of Reviews of Effect (n = 5) and Scopus (n = 2650). Three more articles were found by hand search. A total of 3809 articles remained after removal of duplicates. After screening title and abstract, 29 papers had full text assessed, 26 excluded, leaving three articles meeting inclusion criteria (Figure 1).

Study characteristics, quality and bias

Of the three included studies, one was a cross-sectional study,[74] one had a pre- and post-test design[75] and one was a case-control study[76] (Table 3). All were published between 2000 and 2011. Two studies were conducted in the United States[75,76] and one in Norway.[74] The quality of studies was 'good' or 'fair' according to the NIH quality assessment tools (Table 4). The heterogeneity in methodology and reporting made a meta-analysis impossible.

Population and setting

All studies included participants with chronic non-malignant pain followed in outpatient pain clinics. Mean age in the opioid group (N = 59) was 43–48 years old.[74–76] For two of the studies, diagnosis in the opioid group (N = 43) included musculoskeletal conditions (62.8%), neuropathic pain (32.6%), abdominal pain (2.3%) and chronic headache (2.3%). The third study[76] reported additional diagnoses of fibromyalgia and reflex sympathetic dystrophy, but distribution of participants in each diagnostic group was not reported. Mean pain intensity was reported in all studies using Numerical Rating or Visual Analogue Scales (NRS, VAS). Menefee et al.[75] reported a statistically and clinically significant reduction in mean pain scores between the baseline visit and the stabilisation visit (mean VAS score at baseline = 67; mean VAS score at the stabilisation visit = 53; p = 0.02). Nilsen et al.[74] reported no significant differences between the chronic pain group taking opioids (mean NRS score = 5.8) and the first control group of participants with chronic pain not taking opioids (mean NRS score = 5.5; p = NS) over the week prior to the assessment. Additionally, pain scores did not differ significantly between groups at the time of the first (NRS scores = 4.8 and 4.6, respectively; p = NS) and second driving assessments (NRS scores = 5.1 and 5.7, respectively; p = NS). However, a significant difference in the average pain score over the preceding week was reported between the chronic pain group and the second control group (healthy volunteers; NRS scores = 5.6 and 0.4, respectively; $p < 0.05$).[74] Galski et al.[76] reported no significant differences in pain scores between the active (mean NRS score = 3.48 ± 2.4) and the control group (mean NRS score = 3.66 ± 2.5) at the time of the driving assessments.

Type of opioids, dose, formulations and routes reported

All studies included only participants on regular therapeutic opioid agonists. One study included only short-acting opioids and two studies included only extended-release formulations as regular therapy.[76] Nilsen et al. included participants taking regular oral codeine. Menefee et al.[75] included participants taking TD fentanyl only with a maximum of three *pro re nata* (PRN) tablets of acetaminophen 325 mg/oxycodone 5 mg/day during the titration period (75). Galski et al.[76] included participants taking long-acting opioids which comprised controlled-release oral morphine and TD fentanyl. PRN opioids including hydromorphone and oxycodone were allowed. Doses utilised in this study were not reported. Fentanyl doses ranged from 25 to 75 µg/h in the Menefee et al.'s study[75] with a median dose of 50 ug/h (oral morphine daily equivalent doses: 60–180 mg, median 120 mg).[77] Codeine doses ranged from 120 to 270 mg/day in the study from Nilsen et al.[74] with a median dose of 180 mg (oral morphine daily equivalent doses: 12–27 mg, median 18 mg).[77]

Driving outcomes

Overall, studies found no significant changes in driving-related outcomes with opioid agonists (Table 5).

Nilsen et al.[74] tested the participants twice on the same day coinciding with peak and trough codeine blood concentrations, respectively. Reaction times, steering precision and missed signs were analysed in rural and urban driving settings. No significant differences were found between participants with chronic pain taking codeine (n = 20) and participants with chronic pain free of opioids

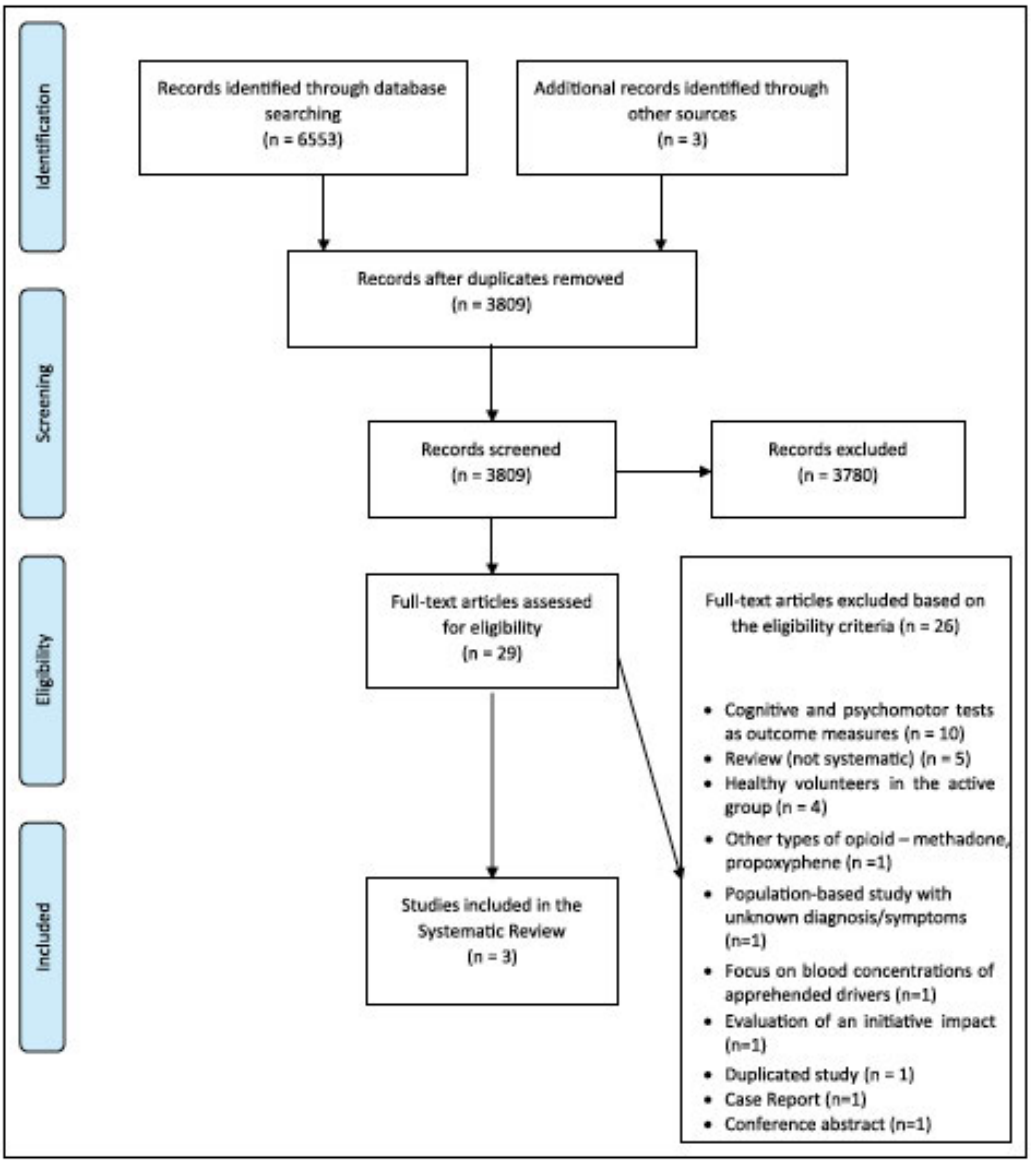

Figure 1. PRISMA diagram.

($n = 20$) in any of the study measures ($p > 0.5$; confidence interval (CI) 95%). However, the chronic pain group ($n = 40$) performed significantly worse compared with healthy controls in all study parameters ($p < 0.036$).

Menefee et al. subjected participants to four different driving tasks where simple braking reaction time, cue reaction time, destination driving and evasive action were evaluated. For the first three tasks, the average of errors in breaking, steering, speed and signalling were calculated to achieve a final score. Evasive action was measured using the average time spent to take appropriate action in three different driving situations. This study found no significant differences in driving simulator performance parameters before and after fentanyl therapy ($p \geq 0.2$).[75]

Galski et al.[76] found no significant differences in driving parameters (number of errors in braking, steering, accelerating, speed and signalling) between participants with chronic pain taking opioid agonists and cerebrally compromised participants accessed as fit to drive after an on-the-road driving test.

Discussion

Summary of evidence

This research highlights the paucity of studies evaluating the impact of regular opioid agonists in driving-related psychomotor skills of participants with chronic pain or

Table 3. Summary of studies characteristics.

Study	N subjects	N (% men)	Population	Mean age (years)	Design	Comparison	Time period	Formulation	Type of assessment	Outcome	Statistical power
Nilsen et al.[74]	60 (20 per group)	50%	Participants with chronic non-malignant pain	43.2 codeine group; no significant differences between groups	Cross-sectional	Oral codeine (12–27 mg OME/day, mean 18 mg OME/day) versus matching chronic pain participants not using codeine versus matching healthy volunteers	NA	Rapid release	Driving simulator	Primary outcome: reaction time (s) to traffic-sign symbols and missed reactions. Secondary outcome: steering precision (pixels).	A total of 20 subjects per group provide over 80% power for detecting a difference with $p < 0.05$
Menefee et al.[75]	23	26%	Participants with non-malignant pain	47	Pre- and post-test design	Fentanyl TD (60–180 mg OME/day, median 120 mg OME/day); participants tested before and after exposure	Before initiating drug versus after 1 month of stable dose	Extended-release	Driving simulator	Average of errors in the following tasks: simple braking reaction time, cue reaction time, destination Driving. Average of time spent to take appropriate action in 3 different driving scenarios (evasive action).	No reference
Galski et al.[76]	16 opioid group; 327 historical control group	NA	Participants with non-malignant pain	48.38	Case-control study	Opioid agonist in stable doses versus cerebral compromised participants previously cleared to drive	NA	Slow or extended-release	Driving simulator	Number of errors in braking, steering, accelerating, speed and signalling	No reference

OME: Oral morphine equivalent; NA: not applicable; TD: transdermal.

Table 4. NIH Quality Assessment Tools (Critical appraisal).

Questions	Study		
	Nilsen et al.[74]	Menefee et al.[75]	Galski et al.[76]
	NIH Quality Assessment Tool for observational cohort and cross-sectional studies	NIH Quality Assessment Tool for before–after (pre–post) studies with no control group	NIH Quality Assessment of case-control studies
1. Research question/objectives clearly stated	Yes	Yes	Yes
2. Study population clearly identified	Yes	Yes	Yes
3. Similarity between sample and population of interest	Yes	Yes	No
4. Application of the eligibility criteria	Yes	Yes	Yes
5. High% of eligible participants enrolled or randomly selection of eligible participants	No	Yes	Yes
5. Sample size calculation	Yes	No	No
6. Exposure preceded outcome	Yes	Yes	Yes
7. Definition and consistent measures of exposure	Yes	Yes	Yes
8. Definition and consistent measures of outcomes	Yes	Yes	Yes
9. For exposures that vary in amount or level, measurement of different levels of the exposure as related to the outcome (e.g. categories of exposure or exposure measured as continuous variable)	Yes	NA	NA
10. Blinding of outcome assessors	NR	NR	No
11. Loss to follow up ≤20% (included in the analysis)	Yes	Yes	NA
12. Time frame adequacy	Yes	NA	NA
13. Measurement of confounding variables	Yes	NA	No
14. Measurement of effects at a group level	NA	NA	NA
Classification (Good, Fair, Poor)	*Good*	*Good*	*Fair*

NIH: National Institutes of Health; NR: not reported; NA: not applicable.

breathlessness, the most common symptoms requiring the use of therapeutic opioids and other palliative interventions. All three studies included in this review report data on participants with chronic non-malignant pain demonstrates the lack of evidence available for participants with chronic cancer pain or chronic breathlessness. Additionally, only one study provided a power calculation.[74] Nevertheless, all three studies showed no negative impact on participants' driving-related skills when compared to control groups which suggests that participants with chronic non-malignant pain on stable doses of regular therapeutic opioid agonists can drive safely.

Are participants on therapeutic, regular opioid agonists for chronic pain or chronic breathlessness able to drive safely? All three studies filled the inclusion criteria for this question. All studies reported similar results: for participants with chronic non-malignant pain, *regular therapeutic* opioid agonists did not significantly impair driving-related psychomotor skills.[74–76] This is line with results from a previous review that examined the effects of opioids on opioid-dependent/tolerant participants' driving-related skills that found no association between opioids and changes in driving-related outcomes.[45] These results are also similar to those published in a previous observational work showing no effect of opioids on the driving ability of participants with chronic pain.[23] Byas-Smith et al. evaluated two groups of participants with chronic pain through a community-driving task and an obstacle course task. The first group was not taking opioids, and the second group was taking stable doses of opioids for chronic pain. No significant differences were found between groups in all

Table 5. Driving simulator performance: specific outcomes.

	Simulator Measures					
		CP taking codeine, Group 1 Mean (SD)	CP no opioids, Group 2 Mean (SD)	Healthy Volunteers, Group 3 Mean (SD)	p values (Group 1 versus 2; Groups 1 + 2 versus 3)	Statistical test
Nilsen et al.[74]	Reaction time rural test (choice reaction)[b]	0.96 (0.14)	0.93 (0.11)	0.84 (0.13)	$p = 0.53$; $p = 0.026$[c]	Multiple regression
	Reaction time urban test (simple reaction)[b]	0.87 (0.21)	0.88 (0.13)	0.76 (0.13)	$p = 0.98$; $p = 0.035$[c]	
	Missed reactions rural test	Because missed reactions in the rural condition were <1% only the results for the urban condition were reported				
	Missed reactions urban test[a,b]	10.20 (CI 95% (8.85–11.69))	10.85 (CI 95% (9.45–12.39))	6.10 (CI 95% (5.07–7.28))	$p = 0.19$; $p = 0.001$	
	Steering precision rural test	The steering precision results were equal				Poisson regression
	Steering precision urban test	The steering precision results were equal				
Menefee et al.[75]		Before fentanyl Mean (SD)		On fentanyl Mean (SD)	p value	Wilcoxon signed-rank test
	Simple breaking reaction time (s)	0.90 (0.17)		0.91 (0.18)	0.74	
	Cue recognition reaction time (s)	0.88 (0.17)		0.91 (0.23)	0.72	
	In-town driving, errors made	13.2 (4.4)		13.0 (3.6)	0.20	
	Highway destination driving, errors made	5.3 (2.4)		5.3 (2.8)	0.24	
	Evasive action reaction time (s)	0.90 (0.03)		0.76 (0.36)	0.29	
Galski et al.[76]		CP taking opioids		CCompromised Participants	p value	Analysis of variance (ANOVA); Tukey's honest significant differences (HSD) test: differences between CP taking opioids and CCompromised; participants who passed the behind-the-wheel driving test (post-hoc comparisons)
	Basic acceleration % errors	3.50 ± 6.26		7.15 ± 11.47	No significant difference	
	Basic signalling % errors	14.63 ± 15.01		23.30 ± 20.27	No significant difference	
	Basic breaking % errors	31.25 ± 26.22		37.66 ± 23.12	No significant difference	
	Basic steering distance	56.19 ± 24.74		70.74 ± 20.47	No significant difference	
	Evasive action braking distance	39.83 ± 19.33		48.95 ± 25.95	No significant difference	
	Evasive action braking % valid	73.44 ± 24.95		65.17 ± 31.55	No significant difference	
	Evasive action steering distance	75.79 ± 39.36		69.46 ± 37.44	No significant difference	
	Evasive action steering % valid	43.79 ± 32.09		40.86 ± 29.67	No significant difference	
	Threat recognition braking distance	113.74 ± 22.13		125.95 ± 34.22	No significant difference	
	Threat recognition braking % valid	82.50 ± 29.10		60.47 ± 33.63	$p < 0.05$	
	Threat recognition steering distance	102.88 ± 32.72		117.99 ± 25.10	No significant difference	
	Threat recognition steering % valid	75.00 ± 28.75		78.59 ± 27.51	No significant difference	

CP: chronic pain participants; CCompromised: cerebral compromised; SD: standard deviation; CI: confidence interval.
[a]Mean numbers of long reaction times (>3.95 s) for each subject (out of 104 possible reaction times for each subject).
[b]No significant differences were found between high (peak) and low (trough) blood concentration levels ($p > 0.05$).
[c]Age-adjusted p values and differences.

specific measures of driving ability, even though different types of opioids were included.[23] Importantly, no studies reporting data on participants with chronic cancer pain or chronic breathlessness filled the inclusion criteria for this review which highlights an important research gap.

Extended-release or TD formulations. The inclusion criteria for this question encompassed participants taking regular, extended-release oral or TD opioid agonists which are frequently prescribed for long-term therapy.[32] Two studies were included in this group: one using TD fentanyl[75] and other several types of strong opioid agonists in controlled-release formulations.[76] Controlled-release opioid agonists showed no significant impact on driving simulator performance even with the addition of occasional PRN opioids for incidental pain. Based on the current available evidence, it is difficult to know if the use of extended-release opioids agonists represents any advantage compared with immediate release preparations when considering participants driving performance. However, one study comparing the two types of formulations has found that participants reported statistically significant more tiredness after a titration period with the immediate release formulation[78] which could potentially cause a detrimental impact on participants' driving-related skills.[76] Studies comparing these two types of formulations should then be developed to bring light into this issue.

Low doses (dose–response relationship). Nilsen et al.[74] was the only study using low doses of opioids (median dose 18 mg oral morphine equivalent dose). This dose range is effective in reducing the sensation of breathlessness in most participants with chronic breathlessness,[15] and its importance should be highlighted. Importantly, these findings are similar to the ones from Menefee et al.[75] (median oral morphine equivalent dose 120 mg) and Galski et al.[76] (unknown doses). One theory is based on the fact that neuroadaptation quickly develops following exposure to an unchanged dose of an opioid agonist.[61] This corroborates findings from previous studies showing that stable doses of opioids fail to produce cognitive impairment, while therapy initiation and uptitration produce significant cognitive and psychomotor impairment.[18,61] However, epidemiological data suggest that very low doses of opioids (defined as doses <20 mg of oral morphine equivalent a day) may be safer than higher doses when it comes to performance on the road[79] even when controlling for potential confounders like age, hospitalisations, other medication use and number of emergency department visits in the previous year. Further research should also take this factor into consideration.

Prescribed extended-release, low-dose opioid agonists. No study was available evaluating the effects of therapeutic, regular, low-dose, extended-release opioids for pain or breathlessness on driving-related psychomotor performance. As such, the answer to this question remains unknown. Further research should focus on examining the effects of low-dose, extended-release opioid formulations in participants' driving ability.

Impact of pain and breathlessness. Pain and breathlessness are often reported by participants suffering from chronic diseases like cancer, degenerative joint disease and chronic cardiorespiratory diseases among others.[50,51] In fact, participants that are suffering from pain are more likely to report breathlessness, and participants with breathlessness have also a higher prevalence of pain.[80] Additionally, pain and breathlessness commonly emerge and subside together which highlights the association between the two symptoms.[80] One explanation is that both symptoms share common neural pathways especially in the limbic region.[81] Another important idea is that both pain and breathlessness may be a reflection of the same underlying disease process. Whatever the extent of influence of these factors, these symptoms commonly occur in similar populations which motivated its inclusion together in this review.

An interesting finding from the only a priori adequately powered study in this review[74] is that participants with chronic pain (taking and not taking opioids) performed significantly worse than healthy volunteers after adjusting for age, gender, education, driving experience, personality traits, emotional stability and extraversion. This corroborates previous findings suggesting that uncontrolled pain is a stronger influence on cognitive and psychomotor performance than prescribed opioids.[82,83] Importantly, the difference in mean pain scores reported between the chronic non-malignant pain group and the healthy volunteer group was not only statistically significant but also clinically significant (pain NRS mean score 5.6 and 0.4, respectively).[84] Although no studies were found for participants with breathlessness, there is evidence suggesting that an increase in the intensity of breathlessness correlates with worsening driving-related neuropsychological performance skills.[85] These studies highlight that symptom intensity may influence driving performance and should be taken into account as potential confounders when analysing the impact of opioids in populations with chronic pain or chronic breathlessness.

Strengths

This systematic review was conducted in line with the methodology proposed by the PRISMA Statement.[70] This is the first systematic review assessing opioids and driving-related psychomotor skills with a focus on population, intervention and outcomes. The selection criteria were carefully thought to include (1) a representative population of people with chronic conditions, (2) the most common types of prescribed opioids selected based on current pharmacologic knowledge, (3) the most robust outcome measures. It is also

important to highlight that the simulators used in the studies included in this systematic review have been previously validated for on-road driving.[68,69] This approach prevented the inclusion of a heterogeneous group of studies whose results would not be generalisable.

Limitations

Only three studies were included in this review as a result of the selection criteria applied. This is regarded by the authors as both a strength and a limitation. On the one hand, the population, opioids and outcomes selected are relatively homogeneous which would allow the generalisability of results to this group of participants. On the other hand, the scarcity of studies available means the conclusions cannot be definitive. This systematic review only included articles published in English which may have increased the risk of selection bias. Also, given the heterogeneity of study designs, a meta-analysis could not be performed.

Recommendations for future research

Currently there is a lack of studies assessing the impact of therapeutic opioid agonists in people's driving-related skills. All the studies included in this systematic review selected a population of participants with chronic non-malignant pain, and the results obtained may not be generalisable for participants with chronic malignant pain or chronic breathlessness. However, it is important to note that chronic pain is a common feature of non-malignant life-limiting diseases, and the results of this work are important for this population.[86] Nonetheless, future research should also focus on populations with chronic malignant pain and chronic breathlessness.

The impact of oral extended-release and TD formulations during the titration phase on cognitive and psychomotor skills is unknown, although studies in other populations suggest they may have fewer adverse events.[34,78] Another important issue to explore in future research is the true impact of different intensities of pain/breathlessness in driving outcomes as they might be important predictors of poorer driving performances.

Clinical implications

Although opioids are currently recommended as the first-line treatment for moderate to severe pain, many clinicians remain reluctant to use them.[87] Fear of side effects is one of the top concerns identified by clinicians.[87,88] One problem is that clinicians may withhold or withdraw opioid therapy from people who could potentially benefit from this therapy. Additionally, clinicians' beliefs and a poor clinician–patient relationship have been shown to decrease adherence to taking analgesics as prescribed.[89,90]

The studies included in this review suggest that participants with chronic non-malignant pain are able to drive safely while taking regular, stable doses of a therapeutic opioid agonist. One important factor to take into consideration is that uncontrolled symptoms like pain and breathlessness may contribute to worsen driving-related psychomotor skills and performance on the road, to a greater extent than opioids.[74,82]

Conclusion

This systematic review examined the literature about driving-related psychomotor performance of people with chronic pain or chronic breathlessness taking opioid agonists. Despite the evidence supporting the use of opioids for symptom reduction in these populations, their effects on driving need further exploration. From the limited available studies, for people with chronic non-malignant pain, stable doses of therapeutic opioid agonists do not seem to cause any significant changes in driving-related psychomotor performance. More intense chronic pain may have a significant effect on driving skills and should be carefully monitored and controlled. Clinicians are recommended to use their best clinical judgement to advise patients to drive or not to drive based not only on the regular therapeutic opioid agonist prescribed but also on their comorbidities, symptoms and pre-morbid driving abilities.

Declaration of conflicting interests

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Appendix 13 – Search strategies applied to different databases (Sub-study 2 – systematic review).

Appendix 1

Specific database searches

Database totals.

Name of database	Total citations retrieved by search strategy (n)
Ovid MEDLINE In-Process & Other Non-Indexed Citations and Ovid MEDLINE 1946 to Present	1179
PubMed (non-MEDLINE content only)	221
Ovid Embase (1974–2016 Dec 21)	2197
CINAHL (EBSCOhost)	64
Cochrane Database of Systematic Reviews, Issue 3 of 12, March 2016 (Cochrane Library, Wiley)	3
Cochrane Central Register of Controlled Trials, Issue 2 of 12, February 2016 (Cochrane Library, Wiley)	234
Database of Abstracts of Reviews of Effect, Issue 2 of 4, April 2015 (Cochrane Library, Wiley)	5
Scopus	2650
Total citations retrieved	**6553**
Total after duplicates removed	**3809**

Ovid MEDLINE (In-process and other non-indexed citations subset and 1946 to present subset)

Searched 22/12/16
Search Strategy:

#	Searches	Results
1	analgesics, opioid/ or codeine/ or fentanyl/ or hydromorphone/ or morphine/ or oxycodone/	77,492
2	(opioid* or codeine or fentanyl or hydromorphone or morphine or oxycodone).tw.	121,825
3	or/1–2	141,998
4	automobile driving/ or driving under the influence/ or Accidents, Traffic/	52,659
5	((abilit* or competen* or skill* or task* or simulation* or aptitude* or perform* or capacit* or capab* or function* or risk* or safe* or unsafe or impair* or danger* or influence or fit* or unfit or impact or advice or cessation or restrict*) adj4 driv*).tw.	25,331
6	(automobile* or car or cars or road or traffic or accident* or crash*).tw.	181,971
7	reaction time/	99,930
8	(react* adj2 time*).tw.	38,471
9	or/4–8	343,322
10	3 and 9	3682
11	Animals/ not (Human/ and Animals/)	4,782,881
12	(Letter or comment or editorial or news or case reports).pt.	3,613,936
13	10 not (11 or 12)	1300
14	limit 13 to English language	1179

PubMed (non-MEDLINE subset only)

Searched 22/12/16
$N = 221$
((opioid*[tiab] or codeine[tiab] or fentanyl[tiab] or hydromorphone[tiab] or morphine[tiab] or oxycodone[tiab]) AND (((abilit*[tiab] or competen*[tiab] or skill*[tiab] or task*[tiab] OR simulation*[tiab] OR aptitude*[tiab] or perform*[tiab] or capacit*[tiab] or capab*[tiab] or function*[tiab] or risk*[tiab] or safe*[tiab] or unsafe[tiab] or impair*[tiab] or danger*[tiab] or influence[tiab] or fit*[tiab] or unfit[tiab] or impact[tiab] or advice[tiab] or cessation[tiab] or restrict*[tiab]) AND driv*[tiab]) OR automobile*[tiab] or car[tiab] or cars[tiab] or road[tiab] or traffic[tiab] OR accident*[tiab] OR crash*[tiab] OR reaction time*[tiab] OR 'time to react' [tiab]) AND English[la]) NOT Medline[sb]

Cochrane library

Searched 22/12/16
Total $n = 242$

- Cochrane Database of Systematic Reviews: Issue 3 of 12, March 2016
  - $N = 3$
- Cochrane Central Register of Controlled Trials: Issue 2 of 12, February 2016
  - $N = 234$
- Database of Abstracts of Reviews of Effect: Issue 2 of 4, April 2015
  - $N = 5$

(opioid* or codeine or fentanyl or hydromorphone or morphine or oxycodone) AND (((abilit* or competen* or skill* or aptitude* or perform* or capacit* or capab* or function* or risk* or safe* or unsafe or impair* or danger* or influence or fit* or unfit or impact or advice or cessation or restrict*) NEAR/4 driv*) OR automobile* or car or cars or road or traffic OR accident* OR crash* OR (react* NEAR/2 time*))

Embase 1974 to 2016 December 21

Searched 22/12/16

#	Searches	Results
1	morphine/ or fentanyl/ or narcotic analgesic agent/ or oxycodone/	153,867
2	codeine/	19,122
3	hydromorphone/	7875
4	(opioid* or codeine or fentanyl or hydromorphone or morphine or oxycodone).tw.	147,571
5	or/1–4	224,692
6	driving ability/	6512
7	car driving/ or traffic accident/	61,867
8	car driver/ or driver/ or driver licence/	11,632
9	((abilit* or competen* or skill* or task* or simulation* or aptitude* or perform* or capacit* or capab* or function* or risk* or safe* or unsafe or impair* or danger* or influence or fit* or unfit or impact or advice or cessation or restrict*) adj4 driv*).tw.	27,496
10	(automobile* or car or cars or road or traffic or accident* or crash*).tw.	212,196
11	reaction time/	70,983
12	(react* adj2 time*).tw.	44,812
13	or/6–12	348,259
14	5 and 13	3335
15	exp animal/ not (exp animal/ and human/)	4,637,800
16	nonhuman/ not (nonhuman/ and human/)	3,722,654
17	15 or 16	5,960,445
18	(editorial or letter or note).pt. or (case report or case series or case stud*).ti.	2,449,948
19	14 not (17 or 18)	2513
20	limit 19 to english language	2197

Scopus

$N = 2650$
Searched 22/12/16
((TITLE-ABS-KEY ((opioid* OR codeine OR fentanyl OR hydromorphone OR morphine OR oxycodone)) AND SUBJAREA (mult OR medi OR nurs OR vete OR dent OR heal OR mult OR arts OR busi OR deci OR econ OR psyc OR soci)) AND (TITLE-ABS-KEY ((((abilit* OR competen* OR skill* OR task* OR simulation* OR aptitude* OR perform* OR capacit* OR capab* OR function* OR risk* OR safe* OR unsafe OR impair* OR danger* OR influence OR fit* OR unfit OR impact OR advice OR cessation OR restrict*) W/4 driv*) OR automobile* OR car OR cars OR road OR traffic OR accident* OR crash* OR (react* W/2 time*))))) AND NOT ((KEY (animal* AND NOT (animal* AND human*)) OR TITLE (rat OR rats OR murine OR mice))) AND (LIMIT-TO (DOCTYPE, "ar") OR LIMIT-TO (DOCTYPE, "re") OR LIMIT-TO (DOCTYPE, "cp") OR LIMIT-TO (DOCTYPE, "ip")) AND (LIMIT-TO (LANGUAGE, "English"))
Limited to:

- English language
- Document types article, review, conference paper, article in press.

Excluded:

- Articles with rat, rats, mice or murine in title or Animals in keywords without also Humans.

CINAHL

Saved under AVVCRG login
Searched 22/12/16
$N = 64$

#	Query	Limiters/Expanders
S1	(MH "Analgesics, Opioid") OR (MH "Codeine") OR (MH "Fentanyl") OR (MH "Alfentanil") OR (MH "Dihydromorphinone") OR (MH "Morphine") OR (MH "Oxycodone")	Search modes – Boolean/Phrase
S2	TI ((opioid* or codeine or fentanyl or hydromorphone or dihydromorphinone or morphine or oxycodone)) OR AB ((opioid* or codeine or fentanyl or hydromorphone or dihydromorphinone or morphine or oxycodone))	Search modes – Boolean/Phrase
S3	S1 AND S2	Search modes – Boolean/Phrase
S4	(MH "Automobile Driving+") OR (MH "Vehicle Operation")	Search modes – Boolean/Phrase
S5	TI (((abilit* or competen* or skill* or task* Or simulation* or aptitude* or perform* or capacit* or capab* or function* or risk* or safe* or unsafe or impair* or danger* or influence or fit* or unfit or impact or advice or cessation or restrict*) N4 driv*)) OR AB (((abilit* or competen* or skill* or task* or simulation* or aptitude* or perform* or capacit* or capab* or function* or risk* or safe* or unsafe or impair* or danger* or influence or fit* or unfit or impact or advice or cessation or restrict*) N4 driv*))	Search modes – Boolean/Phrase
S6	TI (automobile* or car or cars or road or traffic OR accident* OR crash*) OR AB (automobile* or car or cars or road or traffic OR accident* OR crash*)	Search modes – Boolean/Phrase
S7	(MH "Accidents, Traffic")	Search modes – Boolean/Phrase
S8	(MH "Reaction Time")	Search modes – Boolean/Phrase
S9	TI react* N2 time* OR AB react* N2 time*	Search modes – Boolean/Phrase
S10	S4 OR S5 OR S6 OR S7 OR S8 OR S9	Search modes – Boolean/Phrase
S11	S3 AND S10	Search modes – Boolean/Phrase
S12	PT Letter or editorial or commentary or case study	Search modes – Boolean/Phrase
S13	s11 NOT S12	Search modes – Boolean/Phrase

Appendix 14 – Driving questionnaire developed for Sub-study 3 (driving simulation).

PaCCSC

030/15 BEAMS Study

Driving Sub-Study Questionnaire

Patients' Screening Number _ _ / _ _ / _ _ _ **Site Number ____**

Date _ _ / _ _ / _ _ _ _ **Time __:__**

This questionnaire is part of the **driving sub-study** and it takes approximately **10 minutes to complete**. You are going to be asked a few questions about your driving history. Please respond as accurately as you can.

Most drivers have had an accident at some time. We would like to ask you about any accidents in the **last 3 years**. Include any accident where **someone was injured**, the **police were called** or a **vehicle was damaged and required repair**.

1. **Do you have a valid drivers' license?**
   - ☐ Yes
   - ☐ No

2. **Have you ever driven a motor vehicle?**
   - ☐ Yes
   - ☐ No *(your questionnaire is now complete)*

3. **Do you currently drive a motor vehicle?**
   - ☐ Yes
   - ☐ No

BEAMS Motor Vehicle Accident Questionnaire V1 June 2016

4. **How many <u>years</u> have you been driving for?** _____ years

5. **How many <u>hours a week</u> do you drive?** _____hours

6. **Have you had any <u>motor vehicle accidents</u> in the last 3 years?**
   - □ Yes
   - □ No *(Please skip to question 11)*

7. **Please list the number of <u>accidents</u> <u>involving another vehicle</u>:** _____ accidents

8. **Please list the number of <u>accidents</u> with <u>no other vehicle involved</u>:** _____accidents

9. **Were any of these <u>accidents</u> associated with <u>being sleepy</u>?**
   - □ Yes
   - □ No

10. **Were any of there <u>accidents</u> associated with being <u>unable to concentrate</u>?**
    - □ Yes
    - □ No

11. Over the last year, did you have any situations where you were about to crash, but an accident did not occur (near-miss accident)?

□ Yes

□ No (*please skip to question 16)*

12. Please list the number of near-miss accidents involving another vehicle:

_____ near-miss accidents

13. Please list the number of near-miss accidents with no other vehicle involved:

_____ near-miss accidents

14. Were any of these near-miss accidents associated with being sleepy?

□ Yes

□ No

15. Were any of these near-miss accidents associated with being unable to concentrate?

□ Yes

□ No

16. Please tell us how often the following events occur:

How often do you….	(Please tick) Every trip	Every 2-3 trips	Every 4-10 trips	Less than every 10 trips	Never
Feel so sleepy whilst driving on highways that you fear falling asleep					
Feel unable to concentrate on the road					
Nod off at the wheel whilst driving on highways					

17. Do you use any of the following <u>strategies to stay awake and alert</u> <u>while driving</u> and how often do you use each strategy?

	How often do you use this strategy? (please tick) Every trip	Every 2-3 trips	Every 4-10 trips	Less than every 10 trips	Never
Drink caffeine or other stimulating substances					
Listen to radio/music					
Adjust window or air conditioning					
Stop for a break or nap					

Appendix 15 – Permission to use the figure depicting the four different types of allostatic load. Depicted in this thesis as 'Figure 8.1', in Chapter 8.

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Author/Editor	AMERICAN PHYSIOLOGICAL SOCIETY (1887-)	**End Page**	904
		Issue	3
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87

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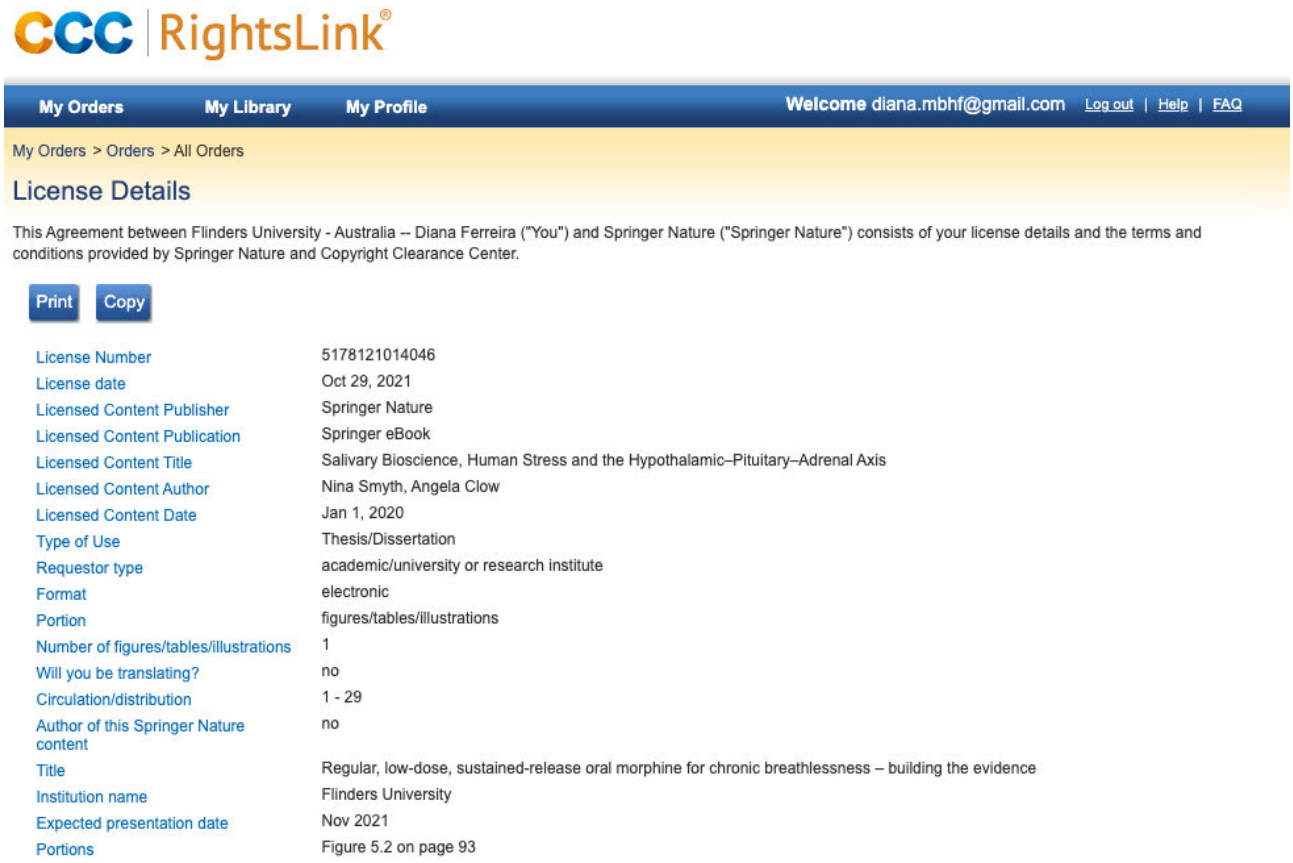
Title	Regular, low-dose, sustained-release oral morphine for chronic breathlessness – building the evidence	**Institution name**	Flinders University
		Expected presentation date	2021-11-05
Instructor name	Prof. David Currow		

Appendix 16 – Permission to use the figure depicting the typical diurnal pattern of salivary cortisol in heathy people. Depicted in this thesis as 'Figure 8.2', in Chapter 8.



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Author of this Springer Nature content	no
Title	Regular, low-dose, sustained-release oral morphine for chronic breathlessness – building the evidence
Institution name	Flinders University
Expected presentation date	Nov 2021
Portions	Figure 5.2 on page 93

Appendix 17 – Written instructions sent to study staff by email following training sessions for Sub-study 5 (salivary cortisol analysis).

Thank you for taking the time to discuss the cortisol sub-study.

Here is a summary of the info that might help:

Documents (attached):

- PICF cortisol sub-study
- Patient cortisol diary
- Staff Checklist
- Instructions for patients
- New study dates calculator

Exclusion criteria:

- Systemic steroids in the last 4 weeks (oral and IV)
- Patients taking insulin
- Avoid taking a blood sample on the collection days

Time points (Always 2 consecutive days):

- Baseline
- Week 1
- Week 3
- After 3 months in the extension phase

3 samples per day:

- **Register the time of awakening (as soon as the patient wakes up)**
- **1st collection:** 3 hours after waking up
- **2nd collection:** 6 hours after waking up
- **3rd collection:** 12 hours after waking up

Complete the diary with the sampling times. Keep the samples in the fridge/freezer before sending them.

Post the samples back to PaCCSC in the pre-paid envelopes we will send you.

Thank you and please let me know if you have any questions,
Have a great day,
Diana

Appendix 18 – Checklist developed to help determine eligibility for Sub-study 5 (salivary cortisol analysis).

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030/15 BEAMS Study

Cortisol Sub-study

Participant Details

Participant ID	__/__/____	
Information Session (date)		
Baseline collection days (dates)		
Stage 1 collection days (dates)		
Stage 3 collection days (dates)		
Extension (3 months) collection days (dates)		

Preparation for the research session

- Cortisol Sub-study Participant Information and Consent Form (PICF)
- 6 tubes + swabs for saliva collection
- Participant Diary
- Information sheet for participants

Screening and Eligibility

Has the patient taken any systemic steroids over the past 4 weeks?	Yes ☐	No* ☐
Does the participant suffer from insulin-dependent diabetes?	Yes ☐	No* ☐

**If you reply 'yes' to one of these questions, the participant is not eligible for this sub-study*

Baseline Information

Is the participant taking a steroid inhaler?	Yes ☐	No ☐
Did the patient take any systemic steroid (oral, IV) over the past year?		
Does the participant have any current or past history of psychiatric illness (e.g. anxiety, depression, etc)? Please indicate the condition.	Yes ☐	No ☐
	Past history ☐	Current history ☐
	Please indicate the Condition _____	
Does the participant suffer from non-insulin dependent diabetes?	Yes ☐	No ☐

Information to Study Nurses:

1. The research team is asked to review the cortisol sub-study with the participants.

2. This sub-study takes place at:

    - **Baseline (for consecutive 2 days)**
    - **End of week 1 (for 2 consecutive days)**
    - **End of week 3 (for 2 consecutive days)**
    - **Extension period - end of Month 3 (for 2 consecutive days)**

3. Participants are required to collect **3 saliva samples per day.**

4. Samples from **different days** will be located in **separate plastic bags.**

5. **The participant can get up at his/her usual time, so the sampling timings will depend on the time he/she wakes that day.**

6. Samples should be collected at **3**, **6** and **12 hours after awakening**. Please explain the concept of "awakening time" to the participant. ***The awakening time is as soon as the participant is aware of being awake for the day and will not go back to sleep.***

7. Please ensure the participant understood the collection times, ***particularly for the last sample*** (all samples are collected with a 3 hour interval with the exception of the last one that is collected 6 hours after the second sample).

8. The participant should be instructed to:
    - **Not to eat** or **drink, smoke, brush his/her teeth or exercise for *30 minutes before* collection of each sample.**
    - Document **unusual physical activity** (of any kind) in the diary.
    - Store the samples in the **fridge** or **freezer (if more than 7 days of storage)** until collection by the study nurse. **Do not leave the samples directly exposed to sunlight or extreme heat**.

9. Remind the participant to **complete the diary** every time he/she collects a sample.

10. Remind the participant to store the samples in the **fridge (or freezer if they are keeping the samples for more than 7 days)** until collection.

Special attention should be given to the following aspects:

- The participant ***should not be involved in blood collection*** **on the collection days for this sub-study.** That will influence the study results.
- Please collect **6 saliva samples** on each visit after collection.
- ***Please post the samples back to PaCCSC as soon as possible (if possible in the same day)***. If this is not possible please keep the samples in the **fridge** (or freezer if you are keeping them for more than 7 days) until postage.

Appendix 19 – Participant instruction sheet developed for Sub-study 5 (salivary cortisol analysis).

PaCCSC

Palliative Care Clinical Studies Collaborative

030/15 BEAMS Study

Cortisol Sub-study – Information Sheet

Your collection days will be:

Time-point	Study Days	Dates
Baseline	**Day 1**	
	Day 2	
Week 1	**Day 1**	
	Day 2	
Week 3	**Day 1**	
	Day 2	
Extension	**Day 1**	
	Day 2	

Instructions:

1. This sub-study takes place at:
   a. **Baseline** (for 2 consecutive days)
   b. **End of week 1** (for 2 consecutive days)
   c. **End of week 3** (for 2 consecutive days)
   d. **Extension period - end of Month 3** (for 2 consecutive days)

2. You are required to collect **3 saliva samples per day.**

3. Samples from **different days** will be located in **separate plastic bags.**

4. **You can get up at your usual time; the sampling timings will depend on the time you wake up.**

5. Samples should be collected at **3**, **6** and **12 hours** **after awakening**. *For instance if you wake up at 7 am, the 1st sample should be collected at 10 am, the 2nd at 1pm and the 3rd at 7 pm.* ***The awakening time is as soon as you are aware of being awake for the day and will not go back to sleep.***

6. Please do not **eat** or **drink**, **smoke**, **brush your teeth** or **exercise** for ***30 minutes before*** you collect each of the saliva samples.

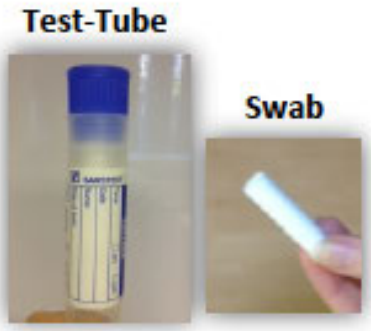
7. Sample collection:
   a. **Make sure you are using the correct tube**. Your diary and the label on the tube will tell you which one you should be using.

   b. Take off the cap from the **test-tube**. It is best to push it to the side and then pull.

   c. Remove the '**swab**' (small white roll of material-see diagram) from the tube.

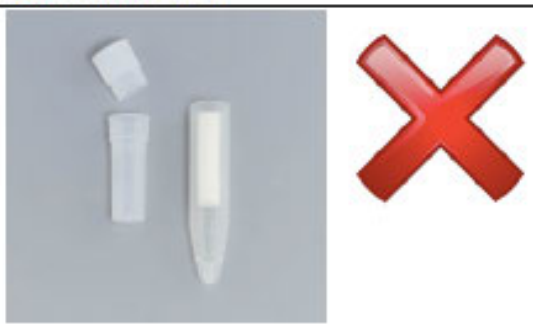
   d. Place the swab in your mouth and gently chew on it until it is soaked. This will usually take about **1-2 minutes**.

   e. Once the swab is soaked, place it back in the tube, **trying not to use your hands**.



DO: Place the swab in the smaller inner tube (located inside the larger tube).

Please DO NOT: remove the smaller, inner tube and place the swab in the larger inner tube



   f. **Put the cap on securely**, and place the tube in the **plastic bag** provided for that sampling day.

   g. **Write down the time** that you collected the saliva in your **diary**.

   h. **Store the samples** in the **fridge** until collection by the study nurse. If you are keeping the samples for **more than 7 days** please keep them in the **freezer** instead. **Do not expose the samples to direct sunlight or extreme heat.**

Appendix 20 – Cortisol diary for collection days developed for Sub-study 5 (salivary cortisol analysis).

PaCCSC
Palliative Care Clinical Studies Collaborative

030/15 BEAMS Study

Cortisol Sub-study – Participant Diary

Participant Screening Number __ / __ / ___

Baseline ☐ Week 1 ☐ Week 3 ☐ Extension – Month 3 ☐

This is your diary for the saliva samples. You will need to complete this diary 4 times during the study. Please note, your honesty is very important to us in analysing the data. Therefore, please state the *times in which you should collect the samples* for each sample, *even if it is different from the time you actually collected the samples*.

Day 1 __ / __ / __ **(date)**

1. **Please indicate what time you woke up? __ __ : __ __ (24 hour format)**
Please note: The awakening time is as soon as you are aware of being awake for the day and will not go back to sleep.

2. **Please write down your collection times based on your awakening time.**

Collection Day	Tube	Collection Time (post-awakening)	Time in which you should collect the samples (24h format)	Time you actually collected the samples (24h format)	Any problems with sampling? (i.e. brushed teeth, ate, smoked, etc)
1	1	3 hours	__ __: __ __	__ __: __ __	
1	2	6 hours	__ __: __ __	__ __: __ __	
1	3	12 hours	__ __: __ __	__ __: __ __	

3. **Did you go outdoors today? Yes ☐ / No ☐**

4. **Did you engage in any exercise (any form) today? Yes ☐ / No ☐**

Day 2 _ _/ _ _ / _ _ (date)

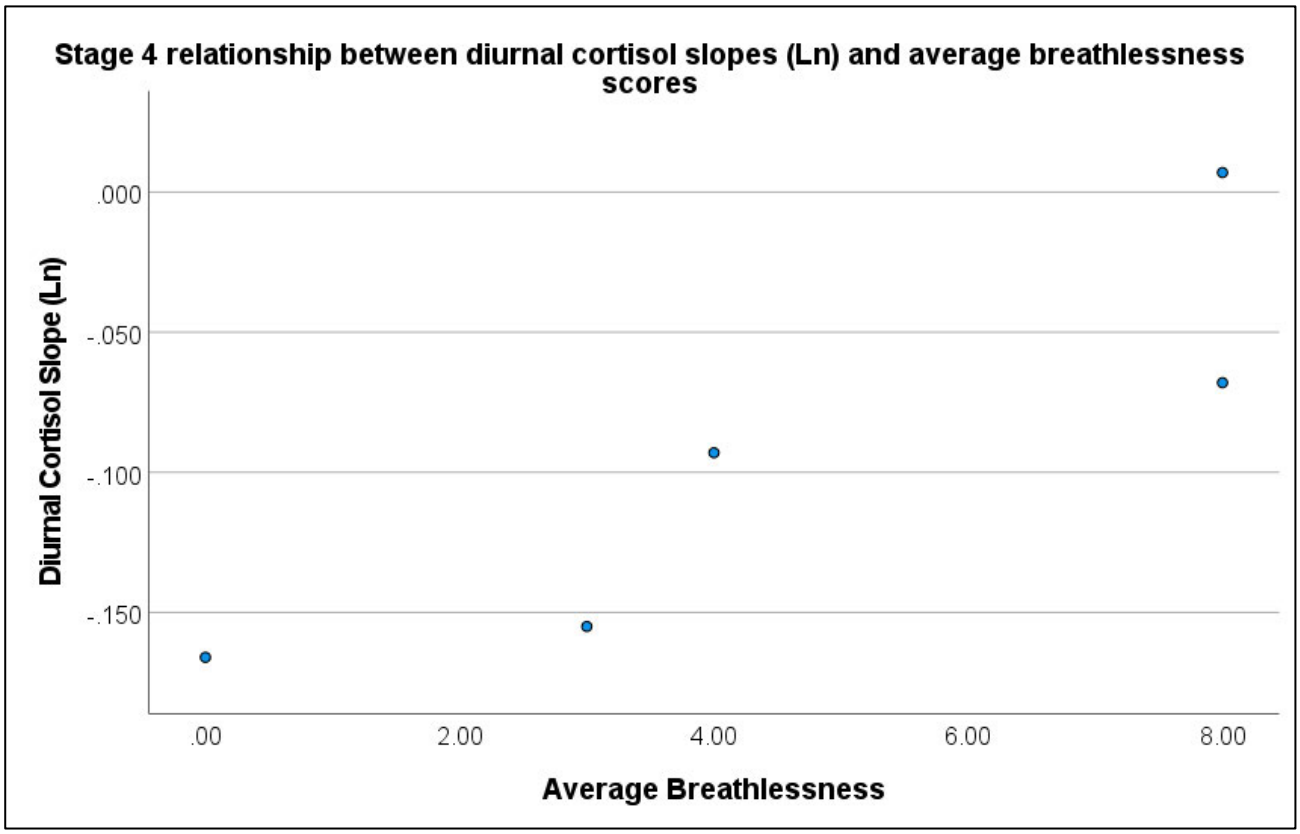
1. **Please indicate what time you woke up? __ __ : __ __ (24 hour format)**
   Please note: The awakening time is as soon as you are aware of being awake for the day and will not go back to sleep.

2. **Please calculate your collection times based on your awakening time.**

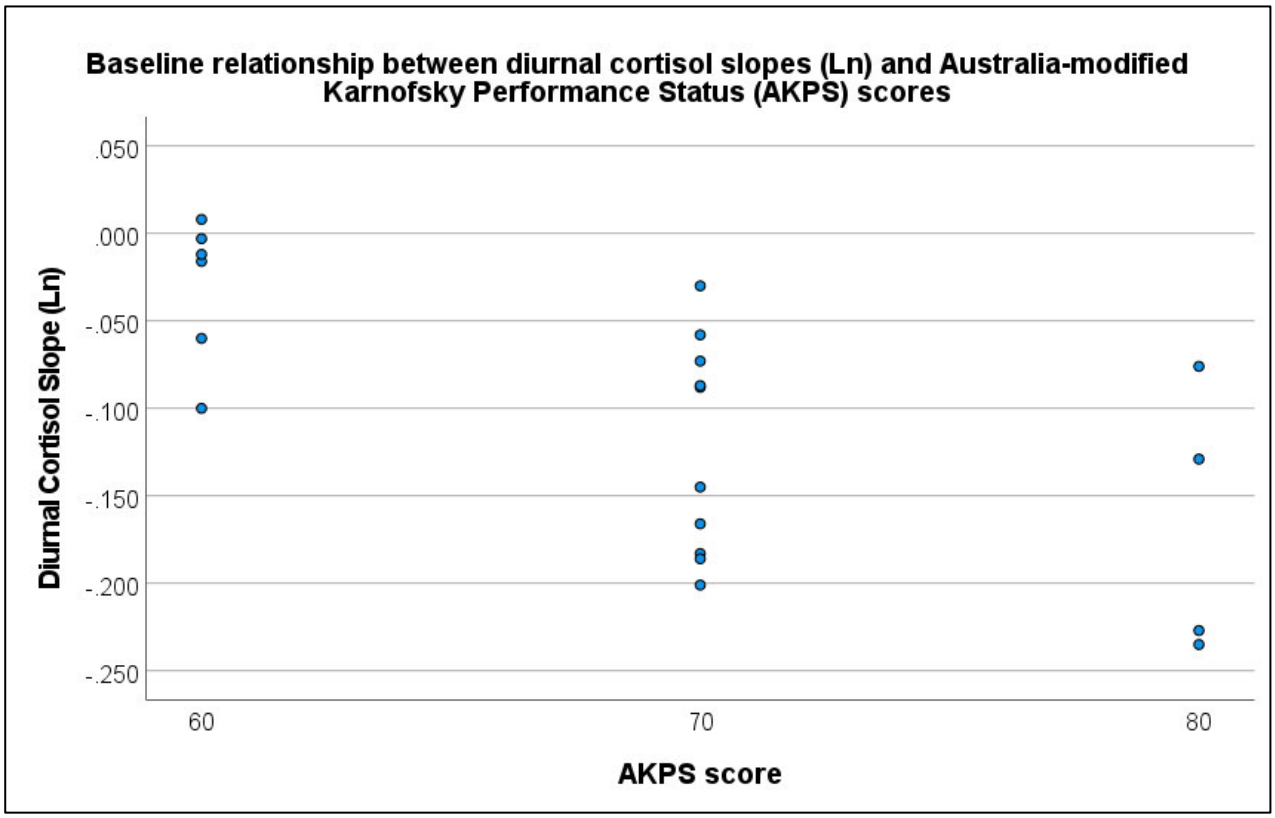
Collection Day	Tube	Collection Time (post-awakening)	Time in which you should collect the samples (24h format)	Time you actually collected the samples (24h format)	Any problems with sampling? (i.e. brushed teeth, ate, smoked, etc)
2	1	3 hours	__ __: __ __	__ __: __ __	
2	2	6 hours	__ __: __ __	__ __: __ __	
2	3	12 hours	__ __: __ __	__ __: __ __	

3. **Did you go outdoors today? Yes ☐ / No ☐**
4. **Did you engage in any exercise (any form) today? Yes ☐ / No ☐**

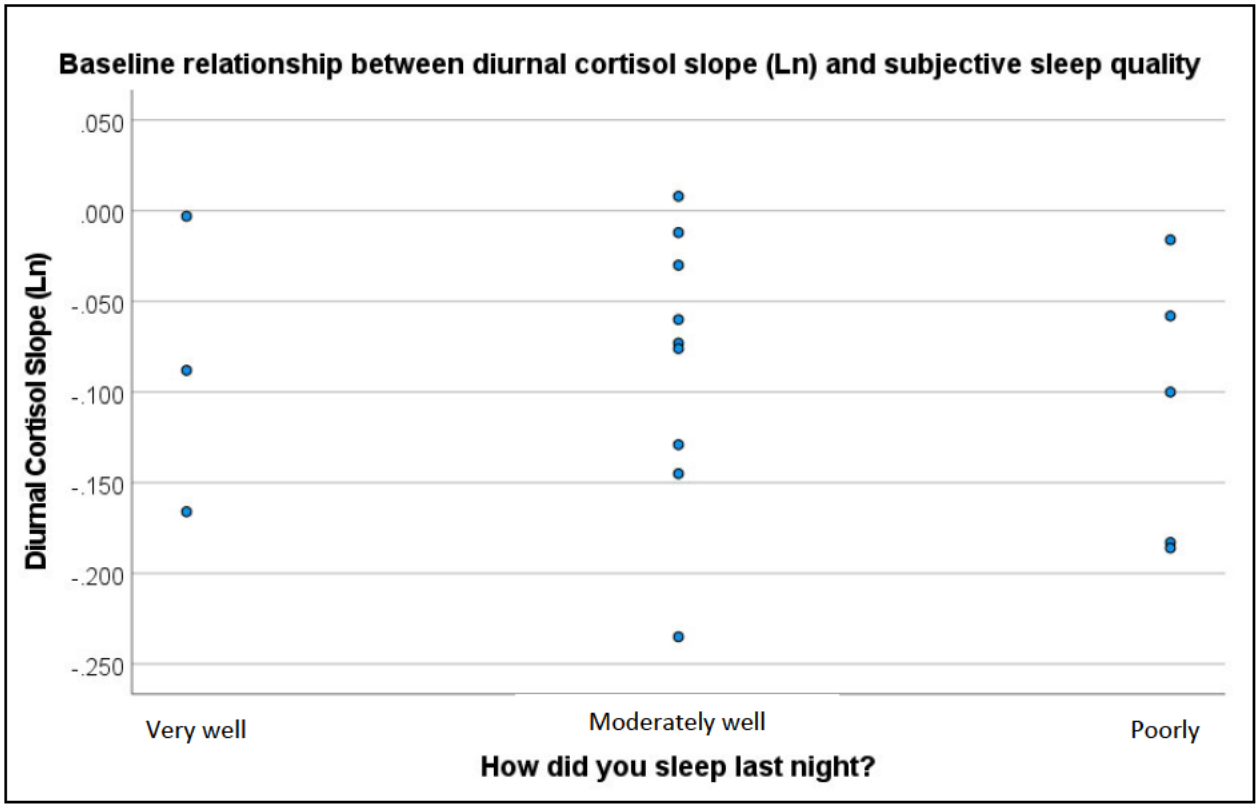
Appendix 21 – Stage 4 relationship between diurnal cortisol slopes (Ln) and average breathlessness scores



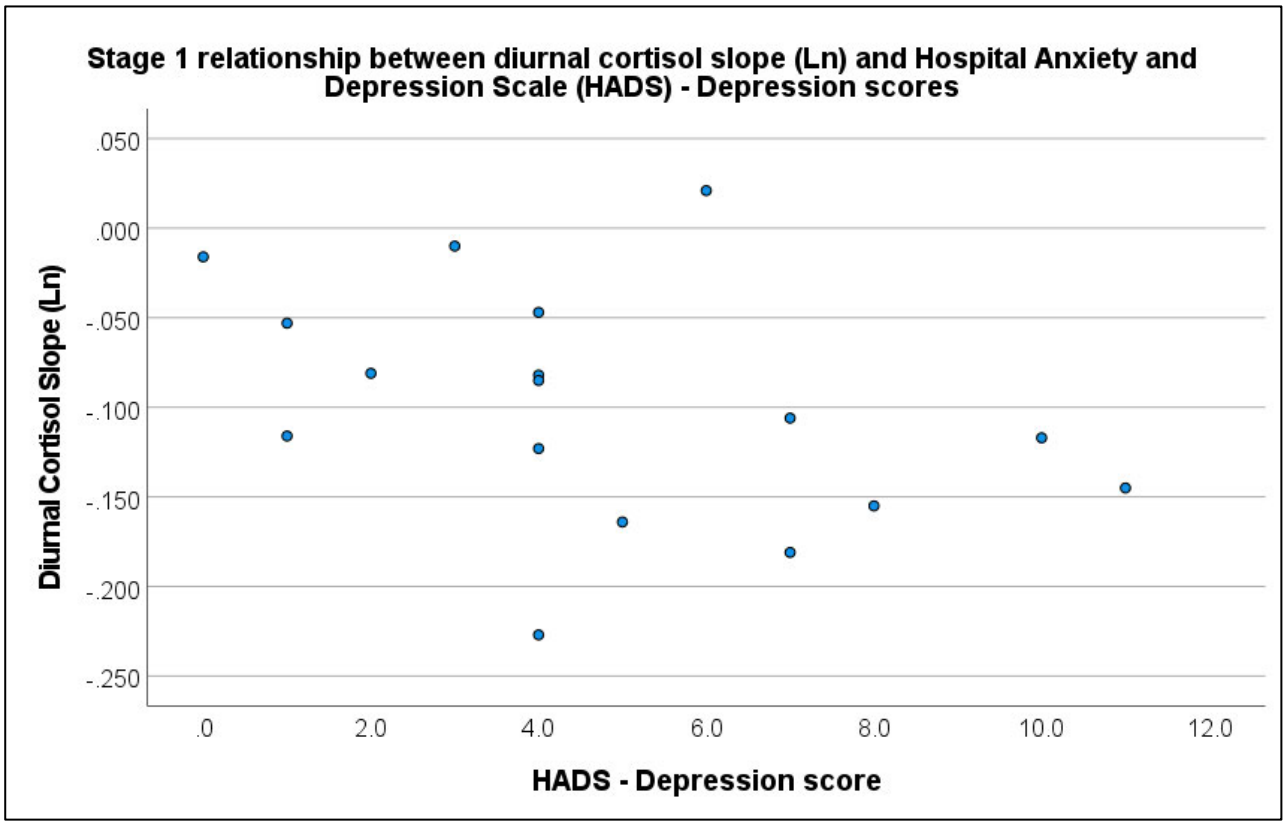
Appendix 22 – Baseline relationship between diurnal cortisol slope (Ln) and Australia-modified Karnofsky Performance Status (AKPS)



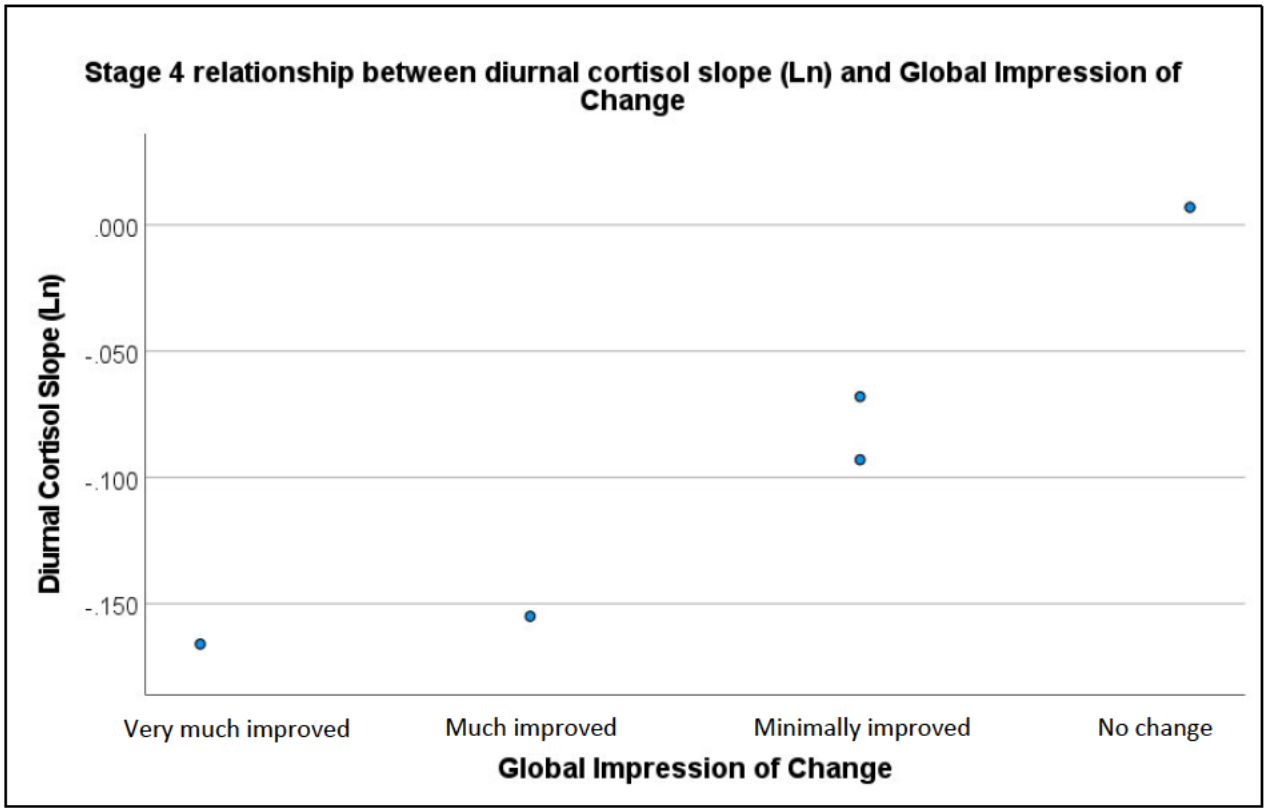
Appendix 23 – Baseline relationship between diurnal cortisol slope (Ln) and subjective sleep quality



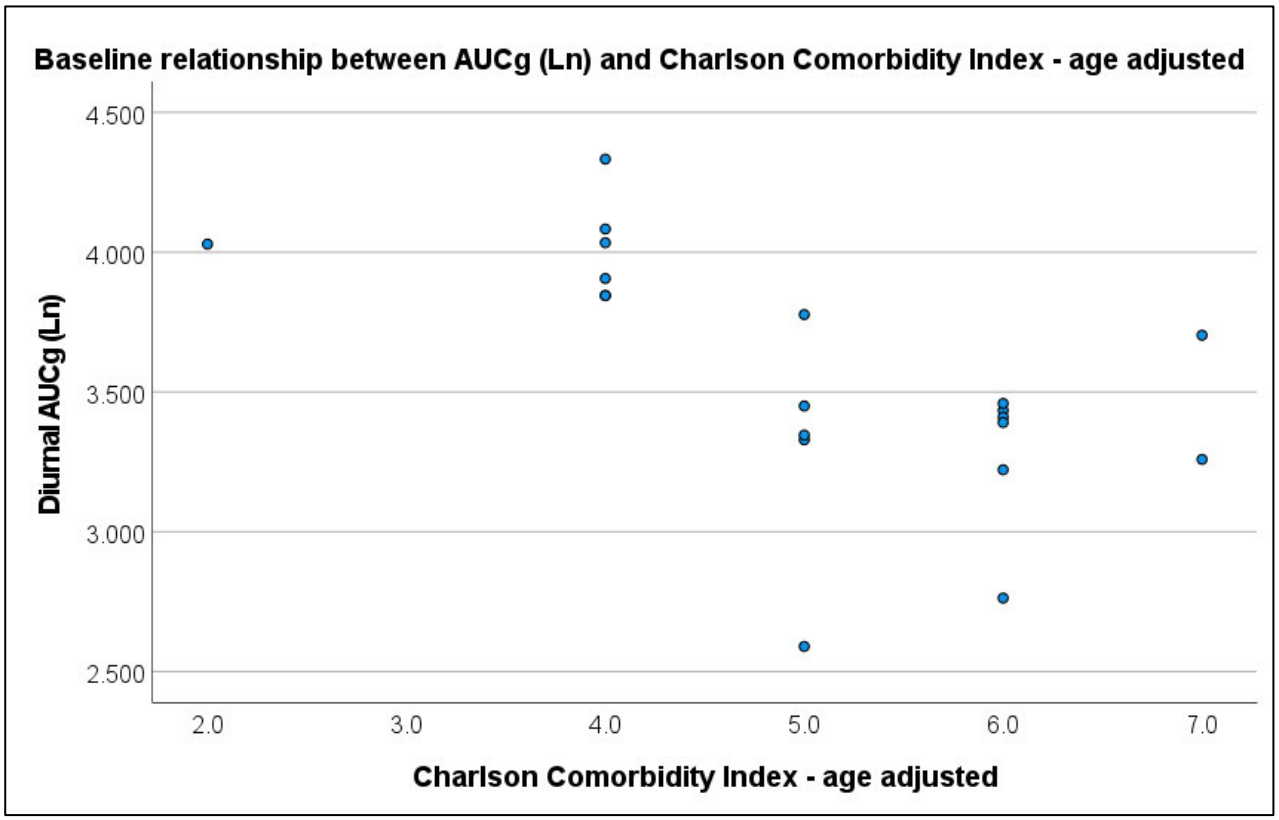
Appendix 24 – Stage 1 relationship between diurnal cortisol slope (Ln) and Hospital Anxiety and Depression Scale – Depression scores



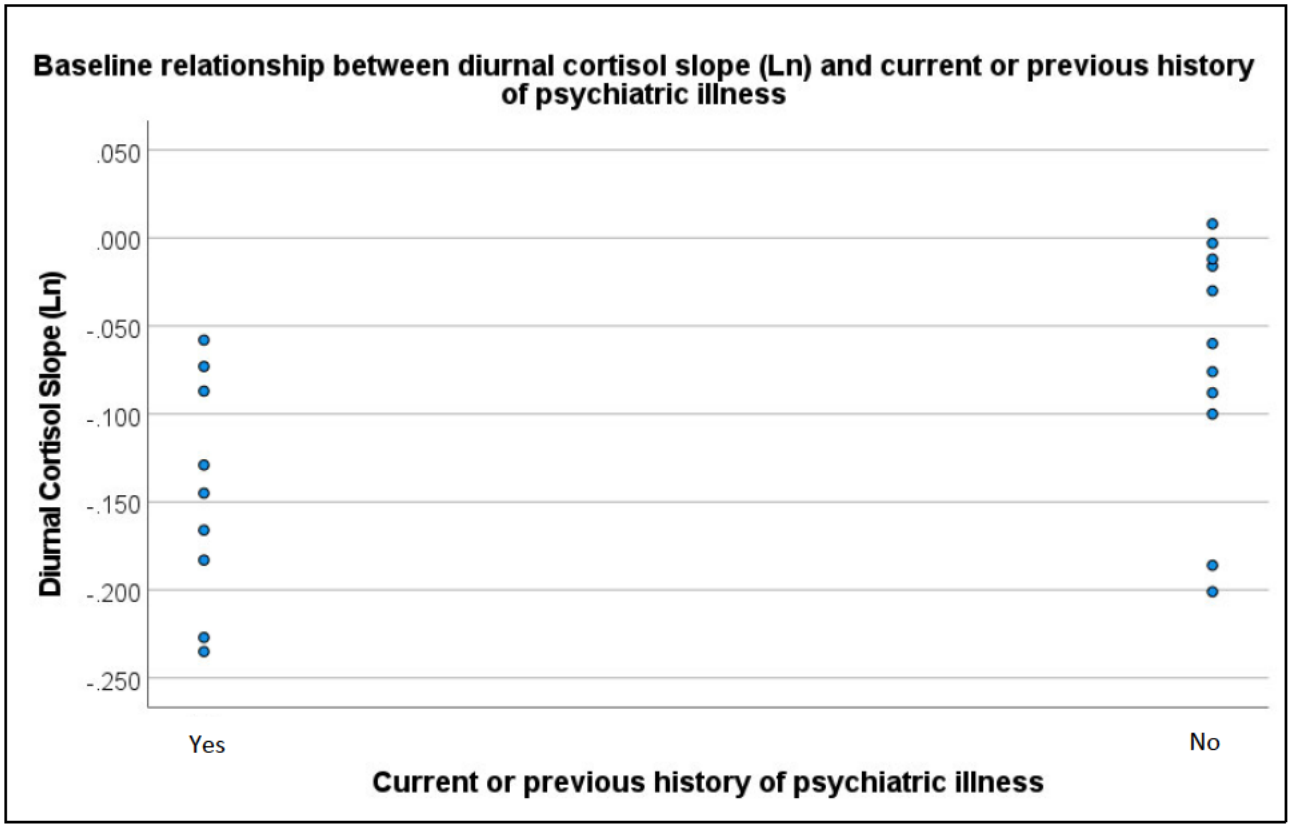
Appendix 25 – Stage 4 relationship between diurnal cortisol slope (Ln) and Global Impression of Change



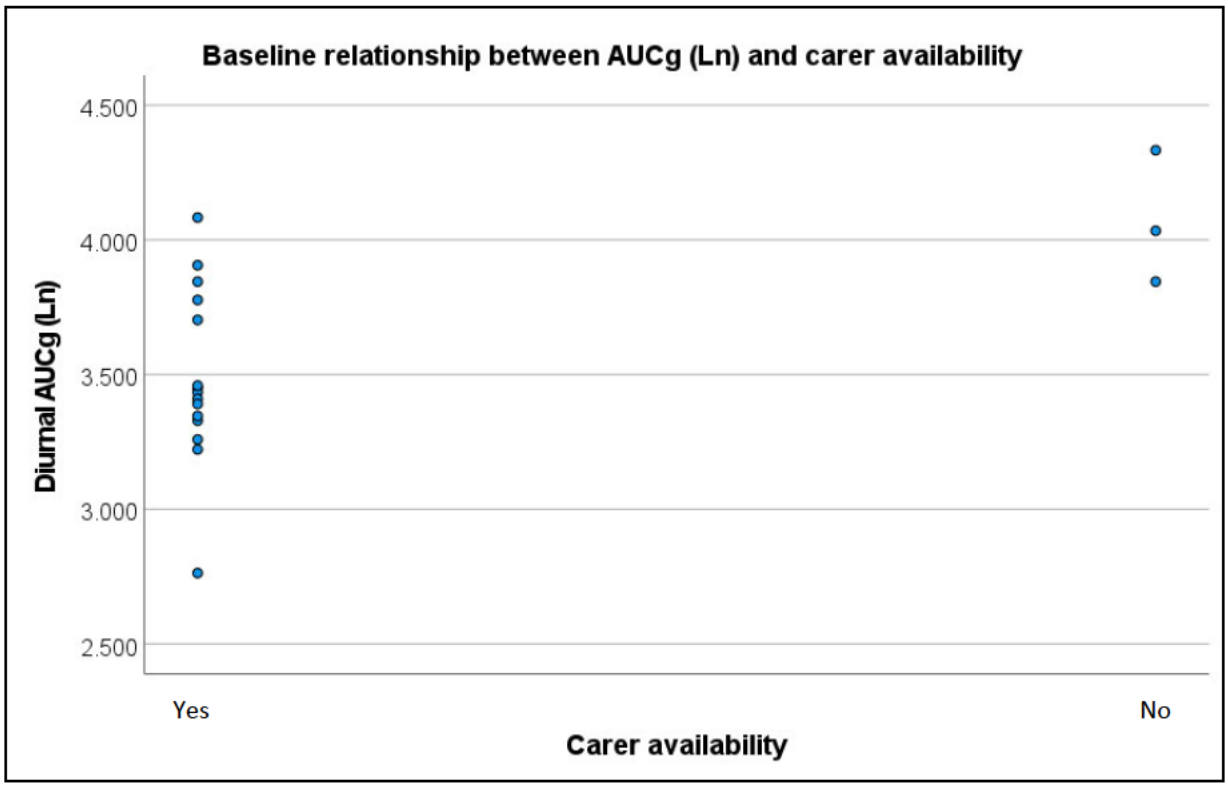
Appendix 26 – Baseline relationship between AUCg (Ln) and Charlson Comorbidity Index – age adjusted



Appendix 27 – Baseline relationship between diurnal cortisol slope (Ln) and the existence of current or previous history of psychiatric illness

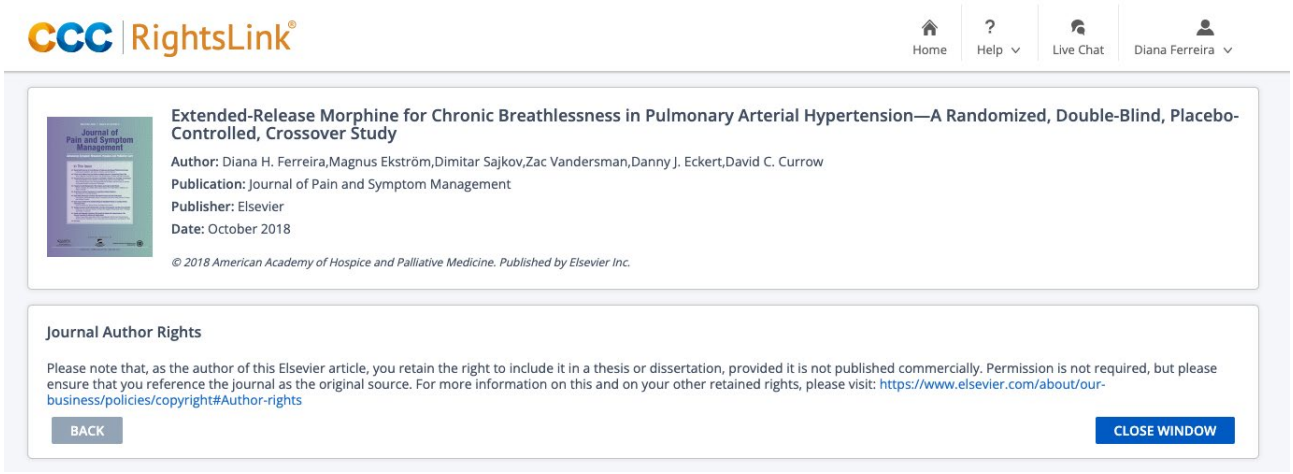


Appendix 28 – Baseline relationship between AUCg (Ln) and carer availability



Appendix 29 – Publication: Extended-Release Morphine for Chronic Breathlessness in Pulmonary Arterial Hypertension: A Randomized, Double-Blind, Placebo-Controlled, Crossover Study (included in Chapter 9)

Permission to use the manuscript in this thesis included



Original Article

Extended-Release Morphine for Chronic Breathlessness in Pulmonary Arterial Hypertension—A Randomized, Double-Blind, Placebo-Controlled, Crossover Study

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Abstract

Context. Pulmonary arterial hypertension (PAH) affects people of all ages and is associated with poor prognosis. Chronic breathlessness affects almost all people with PAH.

Objectives. This randomized, placebo-controlled, double-blind, crossover study aimed to evaluate the effects of regular, low-dose, extended-release (ER) morphine for PAH-associated chronic breathlessness.

Methods. Participants with PAH-associated chronic breathlessness were randomized to 1) seven days of ER morphine 20 mg, 2) seven-day washout, and 3) seven days of identically looking placebo, or vice versa. Primary end points were breathlessness "right now"—morning and evening—measured with a Visual Analogue Scale. Secondary end points included additional breathlessness measures, quality of life, function, harms, and blinded treatment preference (ACTRN12609000209291).

Results. Within a period of seven years, 50 patients were assessed in detail and 23 (46%) were randomized (despite broad eligibility criteria). Four participants withdrew while taking morphine. Nineteen participants completed the study. Breathlessness "right now" was higher on morphine compared with placebo both for morning [mean (M) ± SD 31.7 ± 25 mm vs. 26.9 ± 22 mm; effect size (80% CI) = −0.22 (−0.6 to 0.2)] and evening [(M ± SD 33.5 ± 28 mm vs. 25.6 ± 21 mm; effect size (80% CI) = −0.33 (−0.8 to 0.1)]. All secondary measures of breathlessness were higher with morphine as were nausea and constipation.

Conclusion. This study does not support a Phase III study of ER morphine for people with PAH-associated chronic breathlessness. Recruiting to the target sample size was difficult, the direction of effect in every measure of breathlessness favored placebo and morphine generated more harms. J Pain Symptom Manage 2018;56:483–492. © *2018 American Academy of Hospice and Palliative Medicine. Published by Elsevier Inc. All rights reserved.*

Key Words

Chronic breathlessness, pulmonary arterial hypertension, morphine, randomized controlled trial, effectiveness study

Introduction

Pulmonary arterial hypertension (PAH) is a "chronic disorder of the pulmonary vasculature"[1] characterized by increased pressure in the pulmonary artery (≥25 mm Hg at rest).[2] According to the World Health Organization (WHO) classification, PAH

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corresponds to the first diagnostic group of pulmonary hypertension, which includes idiopathic PAH, heritable PAH, and PAH secondary to drugs/toxins and systemic conditions.[1] Although rare, PAH can affect adults of all ages[3] and has a poor prognosis with a five-year survival rate of 57% after diagnosis.[4]

Breathlessness affects approximately 98% of people with PAH, and it is both the earliest and the most prevalent symptom.[5] For many patients with advanced disease, PAH-specific treatments fail to provide adequate symptom relief and breathlessness becomes chronic.[6] Chronic breathlessness is highly distressing[7] and demands a specific clinical approach that treats the symptom at the same time as underlying etiologies.

Regular, low-dose oral, extended-release (ER) morphine may relieve chronic breathlessness in people with advanced respiratory and cardiac diseases.[8–10] In a secondary analysis of clinical trials, improvement in breathlessness scores was independent of the underlying etiology,[11] suggesting that low-dose ER morphine may have a role in reducing PAH-associated breathlessness. However, only one participant with pulmonary hypertension as the primary cause of breathlessness was included in this analysis.[11]

To date, no study has been conducted to investigate pharmacological agents for the symptomatic reduction of chronic breathlessness in PAH. Understanding the net effect (benefits and harms) of ER morphine for PAH-associated chronic breathlessness is crucial to inform care for these patients. This randomized controlled trial (RCT) aimed to investigate the effects and safety of low-dose, ER morphine for chronic breathlessness associated with PAH. The null hypothesis was that there was no difference between placebo and ER morphine for the relief of chronic breathlessness in PAH.

Materials and Methods

Study Design and Setting

This prospective, randomized, placebo-controlled, double-blind, crossover study was conducted in two Australian health care centers: Southern Adelaide Palliative Services (South Australia) and Austin Health (Victoria).

Participants

Participants were recruited from respiratory outpatient clinics and inpatients units. Adult participants were included if they had optimally treated PAH as assessed by their treating respiratory physician. The diagnosis of PAH was based on the WHO classification[1]. Optimal treatment of PAH was assessed individually and included treatment with a dual endothelin antagonist and/or a phosphodiesterase inhibitor at the time the person was being assessed for participation in the trial. (Of note, the disease-modifying treatment of PAH has continued to evolve during the conduct of the study, and people who were treated were given state-of-the-art treatment before entering the study. Patients were stabilized on the treatment regimen for several months and were still breathless.

Other inclusion criteria for this study were 1) secondary heart failure Class III or IV of the New York Heart Association functional classification[12] corresponding to marked limitation of physical activity due to breathlessness or breathlessness at rest, 2) calculated creatinine clearance of >10 mmol/L, 3) optimized hemoglobin levels, and 4) on stable medications over the previous seven days. Exclusion criteria included 1) regular opioid medication, 2) known hypersensitivity to morphine, 3) central hypoventilation syndrome, 4) use of monoamine oxidase inhibitors in the previous four weeks or proposed use during the study, 5) Australian Karnofsky Modified Performance Status < 50,[13] 6) cognitive impairment (baseline Mini–Mental State Examination < 24),[14] 7) uncontrolled nausea or vomiting, 8) gastrointestinal obstruction, 9) pregnancy or breastfeeding, or 10) history of opioid misuse.

Interventions

Each participant was randomized to one week of Arm A or B, one-week washout, and one week of the treatment they did not receive initially. The active arm consisted of once-daily morning 20 mg Kapanol (ER morphine) capsule orally for seven consecutive days and two docusate with sennosides daily as prophylaxis against constipation. The control arm consisted of identical-looking placebo Kapanol and placebo docusate with sennosides. Participants were given additional open-label docusate with sennosides to take as needed throughout the three-week study.

Outcomes

The primary outcome was difference in mean breathlessness scores "right now" on the last three days of each treatment week collected in participant diaries using a 0–100 mm Visual Analogue Scale (VAS). The last three days were chosen because morphine blood concentrations would be in steady state with this ER formulation. Differences in scores were calculated separately for morning and evening.

Secondary outcomes were between-treatment differences in the following:

- Mean scores of self-rated "average" and "worst" breathlessness in the previous 24 hours for the last three days of each treatment arm using the VAS;
- Self-rated quality of life measured using the McMaster Chronic Respiratory Questionnaire—Dyspnoea subscale[15];
- Best self-rated modified Medical Research Council breathlessness score[16];
- Self-rated quality of sleep measured using a four-item Likert scale and breathlessness' influence on sleep using dichotomous rating (yes/no);
- Respiratory rate, pulse oximetry, and end-tidal carbon dioxide ($ETCO_2$);
- Frequency and severity of harms using the five-point National Cancer Institute Common Terminology Criteria of Adverse Event reporting version 3.0 (NCI Criteria)[17]; and
- Participants' blinded preference for one of the study arms.

Randomization

A computer number generator selected random permuted blocks of four with an equal allocation ratio. The Southern Adelaide Health Service clinical-trials pharmacist conducted the randomization in a double-blind fashion (to participants and care providers). Clinical-trials pharmacists at each site had no contact with potential participants and dispensed study medications according to the randomization schedule.

Medications for Days 1–7 and for Days 15–21 were provided separately. Two bottles were supplied to each participant at each stage: one containing the study drug (ER morphine or placebo) and a similar one containing the laxative (active drug or placebo).

Sample Size Considerations

The original sample size calculation was estimated based on a previous study with similar design, in which 38 participants with different breathlessness etiologies provided sufficient statistical power to detect a treatment effect of ER morphine on breathlessness.[18] This study analysis has shown the treatment-sequence interaction was nonsignificant ($P = 0.27$), thus a linear mixed model was fitted with treatment (morphine vs. placebo), sequence (morphine-placebo vs. placebo-morphine), and time of day (AM vs. PM) as independent variables. The residual within-subject variance was 82.8, and the estimated treatment effect was 3.7 mm, with a 95% CI of 0.8–6.6 mm. To allow for sampling variability, the one-sided upper 95% CI of the within-subject variance was calculated using the bootstrap (2000 replications) and it was found to be 112.0. This would provide a CI for the treatment effect having width approximately 7 mm. Assuming that variability of breathlessness scores was broadly similar in the present population, it was estimated that 50 participants would provide 80% power to detect a 7 mm difference in the VAS with an α of 0.05, allowing for 20% dropout rate as a clinically detectable difference.[19]

Although this study did not reach target recruitment, it could still inform if it was appropriate to progress to a large Phase III trial.[20] Importantly, a recent secondary analysis of three chronic breathlessness studies established the minimally clinically important difference as 9 mm in the VAS for chronic breathlessness.[19] Consequently, the minimally clinically important difference was used in this study analysis instead of the 7 mm difference achieved in the initial sample size calculation. Given the difficulties with recruitment, we aimed to determine if ER morphine is likely to achieve a reduction of 9 mm in the VAS for breathlessness "right now" in both morning and evening, which is equivalent to an effect size of approximately 0.4.[19] This would exclude an effect size of zero or less and inform if progression for a full-scale trial was adequate.[20] In a fully powered parallel-arm trial, a sample size of 186 ($1 - \beta = 0.8$, $\alpha = 0.05$) would be required, which corresponds to approximately a sample size of 18 in a parallel-arm pilot study.[20] Assuming that there is less variability in breathlessness scores in a crossover study, this present study sample (19 participants) would be adequate.

Statistical Methods

Because it was impossible to achieve the expected sample size, this study was analyzed as an early-phase study following the recommendations by Cocks and Torgerson.[20] SPSS 23.0 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, version 23.0, Armonk, NY: IBM Corp.) was used to conduct descriptive statistics that evaluated the flow of participants through the study, the sample's baseline characteristics, and breathlessness scores.

Given that this study was analyzed as an early-phase study, no formal statistical analysis was planned between groups. Descriptive statistics were used to report all outcome measures. Cohen's d effect sizes for the difference between the two treatments were calculated for the primary end point and additional breathlessness measures. The 80% CIs of the effect sizes were examined to determine whether they excluded an effect size of zero or less (i.e., favoring placebo), which would suggest that a fully powered trial would be unlikely to detect a statistically or clinically significant difference (i.e., an advantage of 9 mm for the morphine

treatment). This study is reported based on the CONSORT criteria.[21]

Results

Recruitment and Retention

Of 50 people assessed formally between March 2009 and December 2016, nine were already taking opioids, nine were unwilling to participate in this study, and eight were not eligible for other reasons, such as advanced disease states or poor functional status. Twenty-three participants (46%) were eligible and randomized. Nineteen participants completed both treatment periods and were included in the analysis (Fig. 1). Four participants withdrew, all while taking morphine (Table 1). Three participants stopped the study owing to common harms attributable to morphine (nausea, vomiting, drowsiness). One participant stopped the study owing to lethargy.

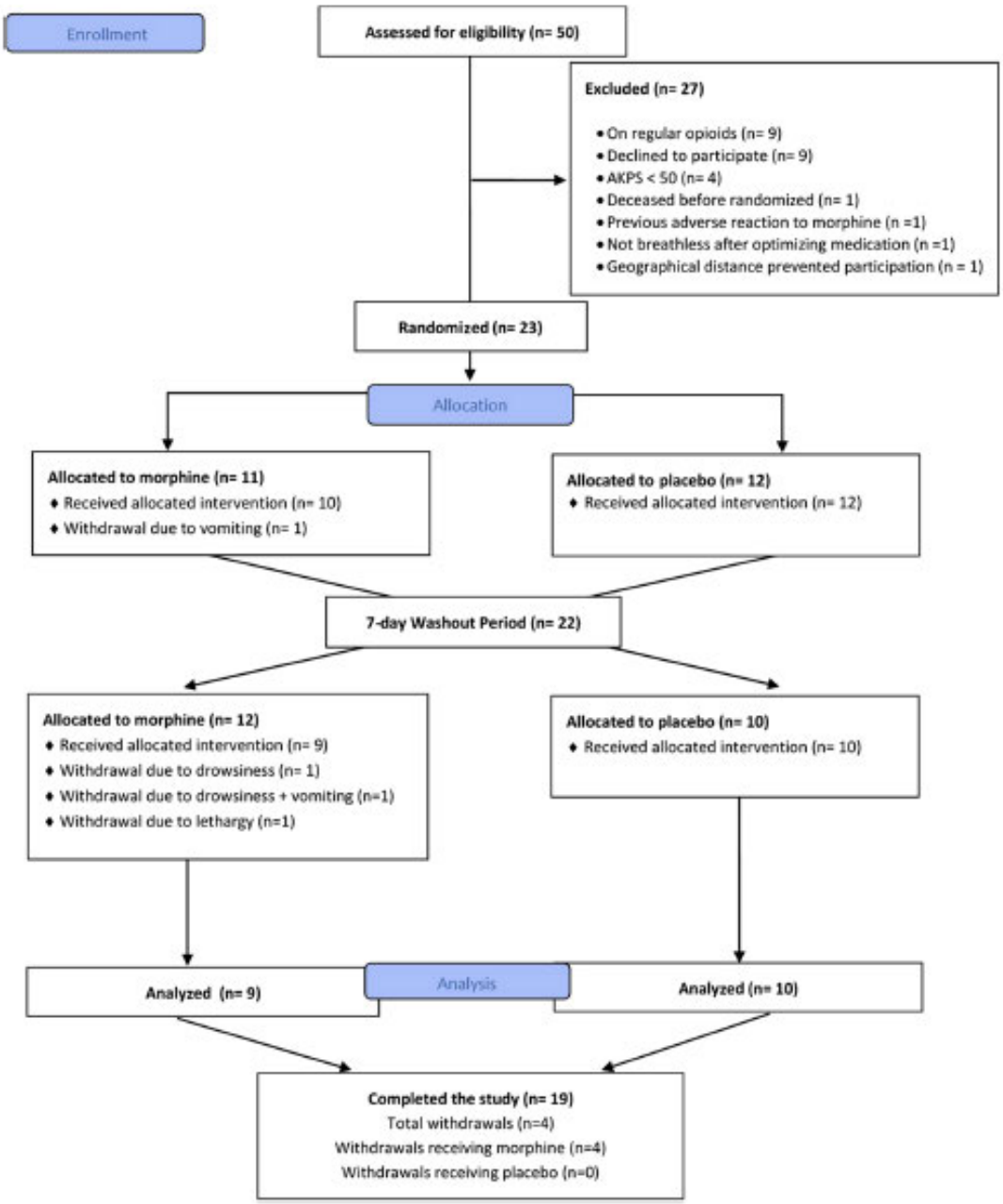

Fig. 1. Flow diagram of participants on study. AKPS = Australian Karnofsky Performance Status.

Table 1
Reasons for Withdrawal of Four Participants From the Study

Participant	Treatment on Day of Withdrawal	Reason for Withdrawal	Attribution
1	Morphine	Dizziness and vomiting	Probable
2	Morphine	Nausea and vomiting	Probable
3	Morphine	Drowsiness and confusion	Probable
4	Morphine	Lethargy and accelerated worsening of performance status	Possible

Study Population

Participants (n = 23) were mainly overweight or obese elderly women. Seven were on supplemental oxygen (Table 2). Most participants (84%) had idiopathic PAH. More than half of the participants (65%) were unable to carry on normal activity or do active work (Australian Karnofsky Modified Performance Status ≤ 70).

Breathlessness

Considering the last three days of each treatment, mean breathlessness scores for breathlessness "right now" were higher with morphine compared with placebo for both morning [mean (M) ± SD 31.7 ± 25 mm vs. 26.9 ± 22 mm] and evening (M ± SD 33.5 ± 28 mm vs. 25.6 ± 21 mm). Similarly, breathlessness scores were higher with morphine for average breathlessness in the previous 24 hours (M ± SD 43.7 ± 26 mm vs. 38.7 ± 24 mm) and worst breathlessness in the previous 24 hours (M ± SD 55.6 ± 27 mm vs. 51.2 ± 23 mm; Table 3). Figure 2 shows the mean breathlessness scores for the seven days on each treatment.

Sleep and Quality of Life

Most participants stated either good or very good quality of sleep whether they were on ER morphine or placebo. Six participants felt they had better sleep quality while on ER morphine, three while on placebo, and nine participants reported no difference between treatments. Only one participant in the morphine arm and two in the placebo arm stated that their sleep was disturbed by breathlessness.

Scores in the CRQ-SAS Dyspnoea Domain Score were similar between the two interventions (M ± SD morphine 4.3 ± 1.8 vs. placebo 4.0 ± 1.5). Similarly, participants' modified Medical Research Council score on the last day of each treatment was not different between morphine [median (interquartile range) 2 (1–3)] and placebo [median (interquartile range) 2 (1–3)].

Table 2
Screening Characteristics of Participants (N = 23)

Characteristics	
Age (yrs)	64 ± 11
Male gender	n = 7 (30%)
BMI (kg/m2)	30 ± 6.0
AKPS	70 (60–80)
90—Able to carry on normal activity; minor signs or symptoms of disease	n = 3 (13%)
80—Normal activity with effort; some signs or symptoms of disease	n = 5 (22%)
70—Cares for self; unable to carry on normal activity or to do active work	n = 9 (39%)
60—Able to care for most needs; requires occasional assistance	n = 4 (17%)
50—Considerable assistance and frequent medical care required	n = 2 (9%)
Diagnosis	
Idiopathic PAH	n = 16 (84%)
PAH associated with connection tissue disease	n = 3 (16%)
Proportion receiving supplemental oxygen	n = 7 (30%)
Rate of oxygen delivery (L/minute)	2.3 ± 0.95
Charlson Index—age adjusted	3.8 ± 1.7
Respiratory rate (breaths/minute)	21 ± 5
Estimated arterial blood oxygen saturation via pulse oximetry (%)	95 (92–97)
End tidal CO_2 (mm Hg)[a]	26 ± 7
Baseline breathlessness "right now"—morning (mm on VAS)	38 ± 23
Baseline breathlessness "right now"—evening (mm on VAS)	37 ± 22
Baseline average breathlessness previous 24 hours (mm on VAS)	44 ± 21
Baseline worst breathlessness previous 24 hours (mm on VAS)	61 ± 20
Baseline breathlessness score (CRQ-SAS Dyspnoea Domain Score)	3.6 ± 1.3

BMI = body mass index; AKPS = Australian Karnofsky Performance Status; PAH = pulmonary arterial hypertension; VAS = Visual Analogue Scale.
Values are mean ± SD or median (interquartile range) unless stated otherwise.
[a]Measured with a portable capnography device during quiet breathing.

Harms

Respiratory rate in breaths per minute (bpm) was lower with ER morphine (M ± SD, 19.7 ± 5.3 bpm) compared with placebo (M ± SD, 21.4 ± 5.5 bpm), and $ETCO_2$ levels were higher with ER morphine (M ± SD, 30.8 ± 6.2 mm Hg) compared with placebo (M ± SD, 28.5 ± 6.5 mmHg). Pulse oximetry was slightly lower with ER morphine (M ± SD, 92.6 ± 6.3% vs. 94.3 ± 2.9%; Table 4).

On the last day of each treatment, significantly more participants had nausea without alteration of the eating habits with morphine [(n = 5 vs. n = 1). Similarly, nine participants stated either occasional (n = 6) or persistent (n = 3) constipation with morphine while no participant stated constipation with placebo (n = 0; Fig. 3). Smaller differences were found for somnolence (ER morphine n = 11 vs. placebo n = 9). Confusion was slightly higher with placebo (ER morphine n = 0 vs. placebo n = 2). Vomiting was not reported with any of the treatments (Table 5).

Table 3
ER Morphine Compared With Placebo Scores on the Intensity of Breathlessness in the Last Three Days of Each Treatment Period

VAS Breathlessness Time Points	Breathlessness Intensity (VAS Score in mm)[a]						
	ER Morphine ($n = 19$)			Placebo ($n = 19$)			Effect Size of the Group Difference (80% CI)
	Mean	SD	95% CIs	Mean	SD	95% CIs	
Right now—morning	31.7	25	20.7 to 42.7	26.9	22	17.0 to 36.8	−0.22 (−0.6 to 0.2)
Right now—evening	33.5	28	20.5 to 46.5	25.6	21	16.2 to 35.0	−0.33 (−0.8 to 0.1)
Average—previous 24 hours	43.7	26	31.7 to 55.7	38.7	24	27.7 to 49.7	−0.20 (−0.7 to 0.2)
Worst—previous 24 hours	55.6	27	43.6 to 67.6	51.2	23	41.2 to 61.2	−0.29 (−0.7 to 0.1)

ER = extended-release.
[a]Breathlessness is measured with the Visual Analogue Scale (VAS) for breathlessness, with zero as "no breathlessness" and 100 as "worst possible breathlessness."

Blinded Participants' Preference

Only six participants stated dissatisfaction with the study drug, three at the end of each active arm. Most participants reported being either satisfied or very satisfied with the study medication, whether that was morphine or placebo ($n = 12$ vs. $n = 11$, respectively).

Discussion

This first trial evaluating ER morphine for chronic breathlessness associated with PAH has shown that the direction and magnitude of effect favor placebo over ER morphine in every important outcome measure and that ER morphine generated consistently more harms. In addition, recruitment was very challenging.

Only 50 participants were formally assessed for this study during a period of more than seven years. Of those, only 23 were eligible to participate, which highlights that successful recruitment occurred in less than 50% of cases. Significantly, the research team recruiting for trial is one the world-leading teams in chronic breathlessness clinical trials research and has repeatedly recruited successfully to similar populations in other conditions that cause chronic breathlessness. Thus, it is important to reflect on reasons why the recruitment was not successful. First, PAH is a very rare disease with a prevalence of 5–52 per million[22–24] and an estimated incidence of 1.1–2.4 cases per million per year.[25] Second, despite the broad eligibility criteria, recruitment was limited by participants' performance status and previous exposure to opioids. These are expected findings given this population's age and comorbidities. However, inclusion of these participants' data would disrupt the study analysis, and therefore, they were excluded.

Another key finding is that harms such as nausea and constipation occurred more frequently with ER morphine than placebo at the end of the seven-day period. Interestingly, while constipation is a common long-term effect of opioids, nausea usually affects patients only over the first few days and disappears with therapy continuation. The fact that nausea remains after seven days of ER morphine contrasts with other studies published so far[18,26] and suggests a detrimental effect of ER morphine in the population with PAH. In addition, all study withdrawals occurred during the ER morphine treatment period and were likely related to morphine.

Notably, there were no cases of major respiratory depression, which is in line with the results of a

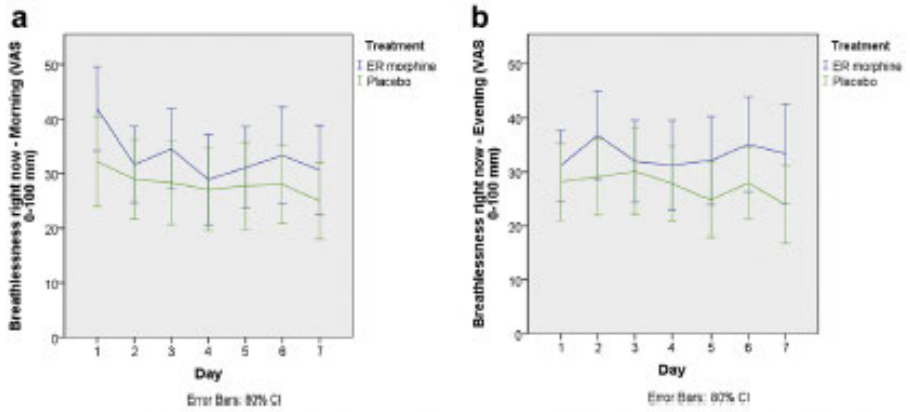

Fig. 2. Mean scores of breathlessness "right now." ER = extended-release; VAS = Visual Analogue Scale.

Table 4
Differences in Vital Signs at the End of Each Treatment

Vital Signs	ER Morphine		Placebo		Effect Size of the Group Difference (95% CI)
	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)	
Respiratory rate (bpm)[a]	19.6 ± 5.3	20 (15–24)	21.4 ± 5.5	22 (17–24)	1.08 (0.4 to 1.8)
$ETCO_2$ (mm Hg)	30.8 ± 6.2	31 (27–33)	28.5 ± 6.6	28 (26–33)	−0.83 (−1.5 to −0.2)
Pulse oximetry (%)	92.6 ± 6.3	94 (90–96)	94.3 ± 2.9	95 (93–96)	0.50 (−0.2 to 1.1)

ER = extended-release; IQR = interquartile range; $ETCO_2$ = end-tidal carbon dioxide.
[a]Breaths per minute.

previous meta-analysis showing no evidence of clinically significant respiratory depression in people with chronic breathlessness treated with regular, low-dose opioids.[27]

An interesting finding is that the people included in this study were mainly elderly women who were overweight or obese. Although this is not necessarily the typical PAH population, PAH is increasingly diagnosed in elderly people and the prevalence is higher in women.[3,28] In addition, it is not clear whether this profile matches the clinical characteristics of people more affected by PAH-associated breathlessness. Nevertheless, these findings should be interpreted according to the population considered.

This study population was largely overweight, some of whom may have had obstructive sleep apnea (OSA). OSA is frequently associated with PAH[29] and was not an exclusion criterion for this study. In people with OSA, morphine may potentially aggravate the condition by causing somnolence and depressing the chemoreceptor response to changes in arterial partial pressures of carbon dioxide, oxygen, and variations in pH.[30] Indeed, for these participants, minor daily fluctuations in respiratory rate and $ETCO_2$ may reflect larger changes during sleep when the central drive is the rescue mechanism from periods of hypopnea/apnea.[31] Thus, sleep disruption and sleep-disordered breathing may have been a confounder and limited the therapeutic efficacy of ER morphine on breathlessness despite high self-rated quality of sleep with ER morphine.

In addition, a recent physiology study in people with OSA showed that 40 mg of MS Contin did not reduce Borg-score ratings to single-breath inspiratory resistive loads compared to placebo.[32] While this experimental paradigm focused on the acute mechanical components of breathing discomfort, which may differ to the multidimensional clinical scenario of breathlessness, people with sleep-disordered breathing often have blunted respiratory sensation.[33,34] Thus, a lack of breathlessness improvement with morphine in people with sleep-disordered breathing may reflect a floor effect, but further investigation is needed.

Although this study was unable to give a definitive answer on the efficacy of ER morphine to reduce PAH-associated chronic breathlessness, there was no favorable efficacy signal in the primary or secondary outcome measures. Importantly, all measures of breathlessness present negative effect sizes demonstrating that placebo performed consistently better than ER morphine for breathlessness. In fact, considering one of the primary outcomes for this study —breathlessness "right now" in the morning—a sample size of 71,516 participants would be required in a large-scale trial to achieve a statistically and clinically significant difference between morphine and placebo in favor of morphine.[20] This contrasts with previously published studies of low-dose morphine for chronic

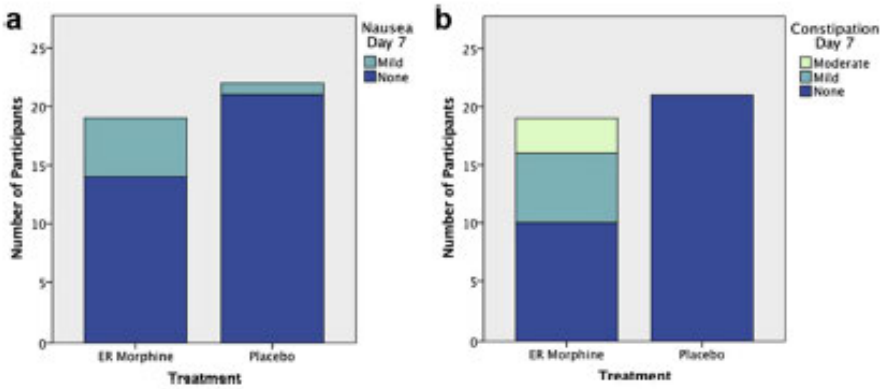

Fig. 3. Nausea (a) and constipation (b) after each treatment. ER = extended-release.

Table 5
Harms of Morphine Compared With Placebo on Day 7

Harms (Day 7)	ER Morphine ($n = 19$)	Placebo ($n = 19$)
Nausea	5 (36%)	1 (5%)
Vomiting	0 (0%)	0 (0%)
Constipation	9 (47%)	0 (0%)
Confusion	0 (0%)	2 (9%)
Somnolence	11 (58%)	9 (41%)

ER = extended-release.
Values for ER morphine and placebo represent absolute number of participants (percentages).

breathlessness in the setting of other etiologies where modest sample sizes generate clinically and statistically significant differences.[10,18,35,36] A recent meta-analysis revealed that opioids significantly improve the sensation of breathlessness in participants with severe chronic obstructive pulmonary disease.[10] Similar results were found in heart failure.[36,37] A previous crossover RCT encompassing participants with differing breathlessness etiologies showed that ER morphine was significantly more effective than placebo in safely reducing the intensity of breathlessness.[18] Interestingly, a post hoc pooled analysis of 213 people with chronic breathlessness has also shown that the underlying disease did not predict response to opioid therapy.[11] However, this analysis included a relatively low number of participants in each diagnostic group.

This study used ER morphine formulations because they are taken less often than immediate-release morphine formulations and therefore more convenient for patients. Morphine serum concentrations are more stable with ER formulations with lower maximum plasma concentrations (C_{max})[38,39] and higher trough concentrations, which may be associated with fewer adverse events and more sustained benefits.[40] In the setting of pain, ER formulations have been shown to be more effective than immediate-release formulations during initiation leading to more rapid analgesia with fewer harms.[41]

However, harms leading to withdrawal in only one arm and ER morphine's inability to improve any measure of breathlessness in this study suggest that ER morphine may have little or no benefit in people with PAH. This opioid-unresponsive chronic breathlessness may be due to different peripheral and central mechanisms of the disease and will require further research to be fully understood.

The major research direction from this study is to understand the pathways for the perception of breathlessness in this group of patients given the very different results to all other studies conducted until now. This also requires careful review of data from studies to date that include heterogeneous etiologies of breathlessness. These should be reanalyzed with and without people with PAH to understand the net effect when those with PAH are excluded.

Conclusions

This first study of low-dose ER morphine for PAH-associated chronic breathlessness does not support the progression for a large-phase III RCT given the rate of recruitment, lack of a signal for improvement with morphine, and the potential for harms quantified. These findings also raise the hypothesis that PAH may be the first diagnostic group with a type of chronic breathlessness unresponsive to morphine. Understanding the underlying mechanisms of PAH-associated chronic breathlessness and patients' response to morphine therapy is a key for future research.

Disclosures and Acknowledgments

Ethics approval was obtained from relevant Health Human Research Ethics Committees, and the trial was registered (ACTRN12609000209291) before recruitment commenced. All participants gave informed written consent.

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David C. Currow is an unpaid advisory board member for Helsinn Pharmaceuticals. He is a paid consultant and receives payment for intellectual property with Mayne Pharma and is a consultant with Specialised Therapeutics Australia Pty. Ltd. Danny J. Eckert serves as a consultant for Bayer outside the topic of the current article. Diana H. Ferreira, Magnus Ekström, Dimitar Sajkov, and Zac Vandersman disclose no competing interests relevant for this work.

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Appendix 30 - Permission to use the table with the updated classification of PAH. Depicted in this thesis as 'Table 9.1', in Chapter 9

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to me

Dear Diana,

Thank you for your enquiry.

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Haemodynamic definitions and updated clinical classification of pulmonary hypertension
Gérald Simonneau, David Montani, David S. Celermajer, Christopher P. Denton, Michael A. Gatzoulis, Michael Krowka, Paul G. Williams, Rogerio Souza
European Respiratory Journal 53 (1) 1801913; **DOI:** 10.1183/13993003.01913-2018 Published 24 January 2019
Material: Table 2
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Appendix 31 - Ethical approvals obtained for Sub-study 6 (Regular, low-dose, sustained-release oral morphine for chronic breathlessness associated with PAH).

Southern Adelaide Health Service / Flinders University
FLINDERS CLINICAL RESEARCH ETHICS COMMITTEE

Government of South Australia
SA Health

Annual Review/Progress/Final Report Form

Date: 9th November 2009

Project ID: 253/08

Title: A prospective, randomised, placebo-controlled, double-blind, cross-over study of the efficacy of sustained-release low dose morphine in the subjective sensation of dyspnoea due to maximally treated primary pulmonary hypertension in opioid naive participants.

Lead Investigator: Prof. David Currow

Site Investigator: Dr Dimitar Sajkov

Project status: In progress

Number of participants recruited: 9

Anticipated completion date: January 2012

Brief statement of results if complete or in progress: (attach & submit final report if available)

Recruitment for this study is currently only conducted through the Primary Pulmonary Hypertension (PPH) Clinic at the Flinders Medical Centre (FMC) and has been slower than anticipated, one reason being that our target population at this site is small and due to complex co morbidities and pain issues many potential participants are already being treated with opioids.

Also to be eligible to participate in the study participants must be maximally medically treated which includes an 8 week exercise/rehabilitation programme, so participants cannot be approached to enter study until this programme is completed. Other participants have been excluded as they live too far outside the greater metropolitan area.

Therefore to increase our ability to achieve the target number of 40 participants, a new site at the Austin Hospital in Melbourne has been approached and is currently seeking approval from their Ethics Committee.

Is recruitment complete: No

Has the project been conducted according to the protocol approved by FCREC? YES

Has the project been conducting according to the terms and conditions of approval, including the reporting of SAE's? YES - please note there have been no SAEs to date.

Have research data and records been appropriately maintained and kept secure? YES

1

Southern Adelaide Health Service / Flinders University
FLINDERS CLINICAL RESEARCH ETHICS COMMITTEE

Government of South Australia
SA Health

Date: 9th November 2009

Regarding: Project ID: 253/08

Title: A prospective, randomised, placebo-controlled, double-blind, cross-over study of the efficacy of sustained-release low dose morphine in the subjective sensation of dyspnoea due to maximally treated primary pulmonary hypertension in opioid naive participants.

Investigator: Prof. David Currow

Site Investigator: Dr Dimitar Sajkov

I have read and reviewed the safety document(s) listed below: (use the precise name/title/sequence or registry number noted on the document)

(a) **Annual Report**

The document(s) identify the following serious events:

Please note there have been no SAEs to date for this study so no Yearly Digest of SAEs has been included.

The implications of these events for the conduct of the trial/research are:
(Only 1 choice is acceptable)

1. **The trial will continue without alteration**

Name: **Dr Dimitar Sajkov**

Content removed for privacy reasons

Date: Note: This document may only be prepared by the principle investigator submitting the original protocol(s) to the Ethics Committee and while the investigator may attach the source document s/he must summarize the content issues in his/her own words.

Austin Health

Austin Hospital

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www.austin.org.au

Human Research Ethics Committee
Research Ethics Unit
Henry Buck Building
Austin Hospital

TO: **Prof Christine McDonald**
Respiratory and Sleep Medicine
Austin Campus

PROJECT: A prospective, randomised, placebo controlled, double blind, cross over study of the efficacy of sustained release low dose morphine in the subjective sensation of dyspnoea due to maximally treated primary pulmonary hypertension in opioid naive participants.

PROTOCOL NO:
PROJECT NO: H2010/04011

FROM: **Ms Jill Davis, Research Ethics Unit Manager**

DATE: 10 November 2010

RE: **Protocol Version 1.3 dated 26 June 2009**
MIMS Prescribing Information Kapanol and Oxycontin
Participant Information and Consent Form Version 4 dated 15 October 2010
Participant daily diary (instructions and single question)
Charlson Comorbidity Index
Dyspnoea Visual Analogue Scale (VAS)
Medical Research Council (MRC) Dyspnoea Scale
Dyspnoea Exertion Scale (DES)
Global Impression Scale
Chronic Respiratory Questionnaire Dyspnoea Subscale (QOL)
Australian Modified Karnovsky (AKPS)
Folstein Mini Mental Status Examination (MMSE)
EORTC 30 QOL
Caregiver QOL Index
Cancer (CQOLC)
Lifespace

Approval Period: **10 November 2010 – 10 November 2013**

Agenda Item: 5.4 (sep 2010)

Further to my letter dated 23 September 2010 concerning the above detailed project, I am writing to acknowledge that your response to the issues raised by the Human Research Ethics Committee at their meeting on 16 September 2010 is satisfactory.

This project now has full ethical approval for a period of three years from the date of this letter.

Before the study can commence you must ensure that you have:

- A signed Clinical Trial Agreement
- Signed indemnities
- A copy of the CTN acknowledgment from the TGA. Please note a copy of the acknowledgement is to be forwarded to the Research Ethics Unit.
- For trials involving radiation it is your responsibility to ensure the research is added to the Austin Health Management Licence issued by Department of Human Services – Radiation Safety Section prior to study commencement should it be required (check your Medical Physicist Report). The HREC must be notified when the research has been added to the licence.
- It is a requirement that a progress report is submitted to the Committee annually, or more frequently as directed. Please note a final report must be submitted for all studies. Should you plan for your study to go beyond the 3-year ethics approval, please request in writing an extension of ethics approval prior to its lapsing. If your study will not commence within 12 months, a request must be forwarded to the HREC justifying the delay beyond 12 months. Should such a request not be received, ethics approval will lapse and a resubmission to the HREC will then be necessary.
- After commencement of your study, should the trial be discontinued prematurely you must notify the HREC of this, citing the reason.
- Any changes to the original application will require a submission of a protocol amendment for consideration as this approval only relates to the original application as detailed above.
- Please notify the HREC of any changes to research personnel. All new investigators must be approved prior to performing any study related activities.
- It is now your responsibility to ensure that all people (i.e. all investigators, sponsor and other relevant departments in the hospital) associated with this particular study are made aware of what has been approved.

The Committee wishes to be informed as soon as practicable of any untoward effects experienced by any participant in the trial where those effects in degree or nature were not anticipated by the researchers. The HREC has adopted the NHMRC Australian Health Ethics Committee (AHEC) Position Statement 'Monitoring and reporting of safety for clinical trials involving therapeutic products' May 2009

Please ensure you frequently refer to the Research Ethics Unit website http://www.austin.org.au/Page.aspx?ID=415 for all up to date information about research and ethical requirements.

DETAILS OF ETHICS COMMITTEE:
It is the policy of the Committee not to release personal details of its members. However I can confirm that at the meeting at which the above project was considered, the Committee fulfilled the requirements of the National Health and

Medical Research Council in that it contained men and women encompassing different age groups and included people in the following categories:

Chairperson Ethicist Lawyer Lay Man Lay Woman Person fulfilling a Pastoral Care Role Person with Counselling Experience Person with Research Experience		**Additional members include:** • Chairs of all sub committees, or nominees • Other persons as considered appropriate for the type/s of research usually being considered

I confirm that the Principal Investigator or Co-Investigators were not involved in the approval of this project. I further confirm that all relevant documentation relating to this study is kept on the premises of Austin Health for more than three years.

The Committee is organised and operates according to the National Statement on Ethical Conduct in Human Research (NHMRC The National Statement) and the Note for Guidance on Good Clinical Research Practice (CPMP/ICH/135/95) annotated with TGA comments (July 2008) and the applicable laws and regulations; and the Health Privacy Principles in The Health Records Act 2001.

PLEASE NOTE: The Committee requests that the Research Ethics Unit ethics@austin.org.au) is informed of the actual starting date of the study as soon as the study commences. A written notice (e-mail, fax or letter) is considered the appropriate format for notification.

Southern Adelaide Clinical Human Research Ethics Committee

Government of South Australia
Southern Adelaide Health Service

28 January 2014

Dear Dr Sajkov

This is a formal correspondence from the Southern Adelaide Clinical Human Research Ethics Committee (SAC HREC). Whilst this official title of the committee has changed the committee is still properly constituted under AHEC requirements with the registration number EC00188. This committee operates in accordance with the "National Statement on Ethical Conduct in Human Research (2007)." This department only uses email correspondence for all documents unless prior arrangements have been made with the manager. No hard copy correspondence will be issued.

Application Number: 253.08

Title: A prospective, randomised, placebo-controlled, double-blind, cross-over study of the efficacy of sustained-release low dose morphine in the subjective sensation of dyspnoea due to maximally treated primary pulmonary hypertension in opioid naïve participants

Chief investigator: Dr Dimitar Sajkov

The Issue: The Southern Adelaide Clinical Human Research Ethics Committee (SACHREC) has issued a further approval for the above project under our expedited review program recognising that there have been neither amendments to the project nor any other changes that require fresh ethical scrutiny.

Note & File: Extension request dated 10 January 2014

Approval Period: 28 January 2014 to 27 January 2016

Please read the terms and conditions of ethical approval below, as researchers have a significant responsibility to comply with reporting requirements and the other stated conditions.

For example, the implications of not providing annual reports and requesting an extension for research prior to approval expiring could lead to the suspension of the research, and has further serious consequences.

Please retain a copy of this approval for your records.

Flinders Medical Centre

The Flats G5 – Rooms 3 and 4

Flinders Drive, Bedford Park

SA 5042

T: 08 8204 6453

F: 08 8204 4586

E:Research.ethics @health.sa.gov.au

TERMS AND CONDITIONS OF ETHICAL APPROVAL
Final ethical approval is granted subject to the researcher agreeing to meet the following terms and conditions.

As part of the Institution's responsibilities in monitoring research and complying with audit requirements, it is essential that researchers adhere to the conditions below.

Researchers have a significant responsibility to comply with the *National Statement 5.5.* in providing the SAC HREC with the required information and reporting as detailed below:

1. **Compliance** with the *National Statement on Ethical Conduct in Human Research* (2007) & the *Australian Code for the Responsible Conduct of Research* (2007).
2. To **immediately report to SAC HREC** anything that may change the ethical or scientific integrity of the project.
3. **It is the policy of the SAC HREC not to provide signed hardcopy or signed electronic approval letters**, as our office is moving to electronic documentation. The SAC HREC office provides an unsigned electronic PDF version of the study approval letter to the Chief Investigator/Study Manager via email. These email approvals are generated via the email address research.ethics@health.sa.gov.au which can be linked back to the SAC HREC.
4. **Report Significant Adverse events (SAE's)** as per SAE requirements available at our website.
5. **Submit an annual report on each anniversary of the date of final approval** and in the correct template from the SAC HREC website.
6. **Confidentiality** of research participants MUST be maintained at all times.
7. A copy of the **signed consent form** must be given to the participant unless the project is an audit.
8. Any **reports or publications derived from the research** should be submitted to the Committee at the completion of the project.
9. All requests for **access to medical records** at any SAHS site must be accompanied by this approval email.
10. To **regularly review the SAC HREC website** and comply with all submission requirements, as they change from time to time.
11. The researchers agree to use **electronic format** for all correspondence with this department.
12. Researchers are reminded that **all advertisements/flyers** need to be approved by the committee, and that no promotion of a study can commence until final ethics and executive approval has been obtained. In addition, all media contract should be coordinated through the FMC media unit.

Kind regards
Rhiannon Kitik
Administration Officer
SAC HREC