MANAGEMENT OF DELIRIUM AT THE END OF LIFE – DEVELOPING AN EVIDENCE BASE

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Glossary

α	Cronbach's alpha
κ	Cohen's kappa statistic
AA	Anticholinergic activity
ACB	Anticholinergic Burden Score
ACP	Aged care psychiatry
ACTRN	Australian and New Zealand Clinical Trials Registry number
AD	Alzheimer's disease
ADD	Assessment of Discomfort in Dementia protocol
ADL	Anticholinergic drug load Activities of daily living
AE	Adverse event
AIBL	Australian Imaging, Biomarkers and Lifestyle
AIN	Assistants in nursing
AKPS	Australia – modified Karnofsky Performance Status Scale
ARS	Anticholinergic Risk Scale
BD	Twice daily (*bis die*)
BOMC	Blessed Orientation Memory Concentration Cognitive Assessment
BUN	blood urea nitrogen
CAM	Confusion Assessment Method
CAM-ICU	Confusion Assessment Method – Intensive Care Unit
CCI	Charlson Comorbidity Index
CI	95% Confidence Interval
CIRS	Cumulative Illness Rating Scale
CNPI	Checklist of Nonverbal Pain Indicators

CNS	Central nervous system
CRAS	Clinician Rated Anticholinergic Scale (initial version)
CRAS-M	Clinician Rated Anticholinergic Scale – modified version
CSF	Cerebrospinal fluid
CT	Computerised Tomography
CTD	Cognitive Test for Delirium
DBI	Drug Burden Index
DEC	Delirium Etiology Checklist
DEQ	Delirium Experience Questionnaire
DI	Delirium Index
DMSS	Delirium Motor Subtype Scale
D-Pap	Delirium Palliative Prognostic Score
DRS	Delirium Rating Scale
DRS-R98	Delirium Rating Scale – Revised 98
DSI	Delirium Symptom Interview
DSM	Diagnostic and Statistical Manual
DSMB	Data Safety Monitoring Board
DSM III	Diagnostic and Statistical Manual of Mental Disorders, third edition
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders, third edition – revised
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, fourth edition
DSM-IV-R	Diagnostic and Statistical Manual of Mental Disorders, fourth edition – revised
ECOG	European Cooperative Oncology Group
EDA	European Delirium Association
EEG	Electroencephalogram

ELISA	Enzyme-Linked Immunosorbent Assay
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer- Quality of Life Questionnaire – core 30 questions
EPS	Extrapyramidal side effects
ESRS	Extrapyramidal Symptom Rating Scale
FACIT-Pal	Functional Assessment of Chronic Illness Therapy scale – Palliative care
FAM-CAM	Family Confusion Assessment Method
FSD	Full syndromal delirium
GABA	Gamma-aminobutyric acid
GCS	Glasgow Coma Scale
GEE	Generalised estimating equations
Gllamm	Generalised linear latent and mixed models
GP	General Practitioner
HC	Healthy controls
HELP	Hospital Elder Life Programme
HR	hazard ratio
HSCT	haematopoetic stem cell transplant
3H-QNB	tritiated quinuclidinyl benzilate
ICD	International Classification of Disease
ICD-10	International Classification of Disease version 10
ICU	Intensive care unit
ID	Identification number
IQCODE	Informant Questionnaire on Cognitive Decline in the elderly
ISRCTN	International standard randomised controlled trial number register
KPS	Karnofsky Performance Scale

LAR	Legally Authorised Representative
LHPA	Limbic-hypothalamic-pituitary-adrenal
MBP	Myelin Basic Protein
MCI	Mild Cognitive Impairment
MDAS	Memorial Delirium Assessment Scale
MMSE	Mini-Mental State Examination
MO	Medical oncology
MRC	Medical Research Council
MSAS	Memorial Symptom Assessment Scale
NICE	National Institute for Health and Clinical Excellence
nM	Nanomol
NOPPAIN	Non-Communicative Patients' Pain Assessment Instrument
NuDesc	Nursing Delirium Screening Scale
OR	Odds ratio
PACSLAC	Pain Assessment Checklist for Seniors with Limited Ability to Communicate
PADE	Pain Assessment for the Dementing Elderly scale
PAINAD	Pain Assessment in Advanced Dementia
PaP	Palliative Prognostic Score
PCT	Palliative Care Trial
PIM	Potentially Inappropriate Medications
prn	*Pro re nata*, as required or as needed
QT Interval	The relationship between two conduction points on an electrocardiograph (ECG)
QT_c	QT interval, corrected for heart rate
r	Spearman's rank correlation (rho)

RASS	Richmond Agitation Sedation Scale
RCT	Randomised controlled trial
ROC	Receiver operator curve
S100B	S100 calcium binding protein B
SAA	Serum anticholinergic activity
SAE	Serious adverse events
SAPS	Southern Adelaide Palliative Services
SC	Subcutaneous
SCARED	Stressful Caregiving Response to Experiences of Dying Questionnaire
SCID	Structured clinical interview for DSM-IV diagnoses
SD	Standard deviation
SE	Standard error
SPMSQ	Short Portable Mental Status Questionnaire
SSD	Subsyndromal delirium
START	Screening Tool to Alert doctors to Right Treatment
STOPP	Screening Tool of Older Persons' potentially inappropriate Prescriptions
UK	United Kingdom
US	United States
VTA	Ventral tegmental area

Abstract

Aim: Delirium in the palliative care population is a prevalent and distressing problem. To improve delirium recognition and management understanding of how clinical decisions are made for patients with a palliative diagnosis and delirium is crucial. Cholinergic mechanisms are considered important in the pathophysiology of delirium but has not been explored in the palliative population. This thesis aims to explore clinical decision-making in the management of delirium from medical and nursing perspectives, to understand the contribution of anticholinergic mechanisms in delirium pathophysiology and how these impact on outcomes, and to develop clinical trial designs which can assess net clinical benefit of delirium therapies in the palliative setting.

Methods: The thesis presents four distinct studies, and a clinical trial protocol with results to date. The first study utilises survey methodology to determine medical specialists' views on care location, investigations, and management of delirium in advanced cancer. In the second study, qualitative methods explored nurses' views on delirium symptoms, management choices, and their views on what caused distress for the person with delirium and their family. Anticholinergic medication use was mapped longitudinally to death, and associations with symptoms, quality of life, functional status and health-service utilisation were explored. The third study comprised serum anticholinergic activity on admission to an inpatient palliative care unit and its association with prevalent and incident delirium in palliative care patients with advanced cancer, after consideration of other demographic and aetiological factors. In the final study, a clinical trial compared the efficacy of risperidone, haloperidol and placebo in delirium in palliative care, discussing robust trial design to determine net clinical benefit of therapies for delirium.

Results: Significant variability in delirium care from both medical and nursing perspectives exists. Anticholinergic medication is predominantly symptom control medication associated with reduced function, dry mouth and difficulty concentrating, but not health-service utilisation nor survival. Delirium occurrence was not associated with anticholinergic medication or serum anticholinergic activity. Comorbid illness severity, benzodiazepine dose and presence of cerebral metastases on admission predicts delirium.

Implications: Some of the variability seen in clinical practice relates to an evidence practice gap with implications for translation of the delirium evidence base into practice; equally, there are some aspects of delirium care unique to the palliative population. Anticholinergic prescribing in palliative care has potential impacts on function, symptoms and quality of life; however, not on delirium occurrence. Vigilance is needed for the palliative patient with comorbid illness and cerebral metastases, as their chance of developing delirium is high. Well-designed and feasible randomised controlled trials can be conducted to evaluate delirium therapies, and this can also be achieved in the palliative population. Statistical methods need to adequately power the study, and account for delirium fluctuation and other factors influencing delirium outcomes. Standardised treatment algorithms and a contingency for participants whose symptoms escalate and safety or distress is an issue are important. Legislative frameworks can ensure balance of protection of those who lack decision-making capacity, with ethical proxy consent and advancement of the evidence base to improve delirium care.

Declaration

I certify this that this thesis does not incorporate without acknowledgement 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 in made in the text.

Meera Agar Date

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Chapter 1: Introduction

Delirium is common in people with life-limiting illnesses, and the prevalence increases before death. Delirium is associated with significant patient, caregiver and health professional distress. Delirium significantly interferes with cognition at a time when intact mentation is greatly valued. The morbidity and mortality associated with delirium is high, and uses significant healthcare and hence societal resources.

Despite having such a significant impact, and the high priority placed by people with life limiting illnesses on the avoidance of cognitive decline immediately prior to death, there is a paucity of evidence regarding delirium in the palliative setting. This includes understanding the population-specific factors involved in aetiology, pathophysiology, and prediction of risk in palliative settings. Equally, evaluations of interventions are needed. This includes interventions aimed at prevention or risk modification, and pharmacological and non-pharmacological management of delirium aimed at reducing incidence, severity and duration of delirium, and control of its symptoms. Strategies in the palliative setting need to allow a balance of inappropriately aggressive versus unduly fatalistic approaches to investigation of potentially reversible underlying causes and management. The literature reviewed in some topic areas has evidence from both palliative and non palliative populations, whereas as in others the discussion is exclusively derived from one population or the other. Where available the context will be set derived from what is known about delirium in general, followed by a discussion of the palliative care specific knowledge.

1.1 Definitions

Delirium is a complex syndrome with multifactorial aetiology, characterised by disturbance of cognition, arousal and attention.[1 2] The term ‘delirium’ is derived from the Latin word *delirare*, which literally means ‘go out (deviate) of the

furrow' (*lira*, Latin for furrow).[3] From *delirare* a now obsolete English verb *delire* was derived, which had the meaning 'to go wrong, to go astray, to rave, to wander in mind, to be delirious or mad'.[3] The word delirium was introduced into the medical literature in first century A.D., however, it had some ambiguity as it was used as a general term for insanity, and more specifically for a transient acute mental disorder associated with febrile illness.[3]

The current internationally agreed classifications of delirium are found in the *Diagnostic and Statistical Manual* (DSM), with the most current edition being edition IV revised (DSM-IV-R), and the *International Classification of Disease* (ICD), current version 10 (ICD-10).[4 5] The major components of the DSM-IV-R classification are disturbance of consciousness, a change in cognition, short and fluctuating chronology, and presence of an underlying medical condition.[4 5] The ICD-10 describes impairment of consciousness and attention, global disturbance of cognition, psychomotor disturbance, disturbance of sleep – wake cycle, and emotional disturbance.[5] There are some deficiencies in these classifications as they do not consider subsyndromal nor persistent delirium, inattention which has emerged as a crucial feature of delirium is not clearly identified as a core symptom, and guidance is needed for specific diagnostic criteria for delirium in the semiresponsive patient and the person with coexistent dementia.

Subsyndromal delirium (SSD) is a disorder with some features of delirium, but which does not meet the full diagnosis.[1 6-8] The concept of SSD is discussed in more detail in Section 1.5. SSD is not included in either DSM-IV-R or ICD-10 classifications.

1.2 Historical development of the classification systems of delirium

This section presents a review of the historical development of the clinical descriptions and classification of delirium, as well as the explanatory hypotheses that underpin them. An understanding of the historical perspective is important as it describes the challenges of nomenclature that hindered earlier research and provides a longitudinal perspective to interpret the literature.[3] The salient features of delirium meticulously identified by these historical medical writers has left us with a vivid clinical picture which closely resembles what we call delirium today,

albeit hindered by inconsistency in the terms used to label it.[3] The clinical descriptions of delirium have remained remarkably consistent since early descriptions in second century A.D.[3]

The clinical features and prognosis of delirium were recognised over 2,500 years ago.[3] Western medical writers from the time of Hippocrates provide descriptions of an acute mental disorder termed *phrenitis*, which was 'symptomatic to other disease', featuring cognitive and behavioural disturbance, restlessness and disordered sleep.[9 10] On the other hand, *lethargus* was described as the opposite of *phrenitis* with features of listlessness, inertia and memory loss, and had a poor prognosis.[11] *Lethargus* could convert into *phrenitis*, and vice versa, representing an understanding of a mixed subtype of delirium.

In the *Book of Epidemics*, Hippocrates (460–366 B.C.) describes key features of the delirium syndrome including association with physical (especially febrile) disease, unpredictable lucid intervals, diurnal course with nocturnal exacerbation, insomnia, visual hallucinations, shifting moods, restlessness and 'wandering of the wits'.[3(p6)] Prognosis was also mentioned, as illustrated by the following description: 'cases of silent delirium, when the patient turned very quiet and insensible, the prognosis was apt to be grave.'[3(p6)] Hippocrates illustrated the value of astute clinical observation, which, when lacking in clinicians today, still contributes to the under-detection of delirium.[3 12]

Greek and Roman writers (25 B.C.–200 A.D.) continued to use the terms *phrenitis* and *lethargus*, but also wrote about the management of delirium with physiological and psychological approaches including rest and sleep, cautious use of opium or henbane (plant of the family solanaceae with foliage containing scopolamine and other tropane alkaloids) to induce sleep for those with *phrenitis*, lighting of the room, and familiar people in attendance.[3]

The concept of a predelirious or prodromal phase *paraphrenitis* was identified in the 16th century, and could include symptoms such as insomnia, headache, and disturbing dreams.[3] There was also an increased understanding that delirium could occur in a wide range of systemic diseases and also in relation to surgery.[3] The patient's constitution, the nature of the cause (for which a thorough search was

necessary), and the treatment offered were thought to predict outcomes.[3] Authors also continued the focus on non-pharmacological approaches suggesting light diet, attendance by one's closest friend, the need to speak softly, and, if troubled by light, a darkened room.[3] These early writers contributed to the multidimensional model we currently utilise for the management of delirium and predictors of outcomes that still hold true today.

In the 17th century the concept of delirium evolved, with views that it was a symptom not a disease. This led to considerations of pathogenesis including relationship to the sleep – wake cycle, disordered secretions in the brain, and chemical theories of disease.[3 9]

In the late 18th century *phrenitis* and *lethargus* were unified in the English word delirium.[3] Prior to this the word delirium had a double meaning: as a general description for insanity, and to refer to an acute mental disorder associated typically with a febrile illness.[3] It was also hypothesised that delirium was dependent on 'inequality of the brain' and was related to 'diminution in the energy of the brain', an early reference to the relationship of delirium with a disordered cerebral metabolism.[3]

The 19th century recognised delirium as a transient cognitive and behavioural disorder, due to brain dysfunction from a wide range of organic causes, and it was considered a non-psychiatric disorder.[3] This era marked separation of psychiatry from medicine, with asylums used for those with chronic psychiatric illness. Thus most progress relating to delirium came from non-psychiatrists at this time.[3] The theory of 'clouding of consciousness' was added to the concept of delirium, along with negative (loss of function of higher centres) and positive (activity of other brain centres released from control) aspects of psychopathology.[3] Negative aspects included disordered orientation, memory, thinking, and altered consciousness, whereas positive aspects were misidentification of people and places, illusions, delusions, hallucinations, abnormal emotions and disturbed behaviour. This was also the time that the term 'confusion' came into use in the published literature, which involved inability to think, reduced perceptual discrimination and defective memory—continuing the inconsistency and multiplicity for both terminology and classification of delirium.[3] The effect on

capacity was described, with the person with delirium still having lucid moments and understanding what is being said in their presence, but at other times utterances and actions could occur without intent or free will.[3]

A century later, a sentinel work was the meticulous observations by Wolff and Curran, who in 1935 described the phenomenological features of 106 of their patients from three medical and psychiatric services in New York and London in great detail. The patients presented with severe behavioural disturbance, marked restlessness and vivid hallucinations necessitating psychiatric admission, with alcohol withdrawal a predominant aetiology.[3 13]

Another turning point occurred in 1959, when Engel and Romano highlighted the concept of a syndrome of cerebral insufficiency as a unifying hypothesis for delirium, derived from their findings of slowing of activity on an electroencephalogram (EEG) and the associated cognitive abnormalities.[12] They began the scientific enquiry into pathophysiological mechanisms of delirium, and attempted to correlate and develop a unified concept of clinical, psychological and electroencephalographic data on delirium.[12] Importantly, the first experimental studies of delirium induced by anticholinergic agents were conducted in the 1960s, leading to the acetylcholine hypothesis in delirium pathogenesis.[14] In these studies 74 psychotic patients were administered the anticholinergic agent Ditran intravenously, and it was found delirium was induced within five to 15 minutes in 28 cases, with symptoms of restlessness, perceptual disturbance, and fluctuation of consciousness.[14] The EEG in these patients showed dissolution of alpha activity and enhanced slow and fast frequency bands.[14] A second group (n = 14) had a different reaction, with withdrawal, incoherent speech, and reduced psychomotor activity.[14]

1.3 Nosology of delirium

The two main nosological systems are the DSM and the ICD.[1 15 16] The first DSM (DSM-I) was published in 1952. Prior to this up to four systems of nomenclature existed.[15] It was only from DSM-III (1980) that organic disorders were clearly conceptualised.[15] Equally in the prior ICD version (revision 9[17]), delirium was not specifically listed. In DSM-III (1980) and DSM-III-R (1987) delirium was included under the category of organic mental disorders/syndromes.[18 19]

Table 1 outlines the key differences and similarities between DSM-III (1980), DSM-III-R (1987), DSM-IV (1994), DSM-IV-R (1995) and ICD-10 (1993). The major difference between the essential features of delirium in DSM-III and III-R was that 'clouding of consciousness' was replaced with 'reduced ability to maintain and shift attention to external stimuli', and disorganised thinking (as manifested by rambling, irrelevant and incoherent speech) was included.[1 18-20] Studies that prospectively evaluated the use of DSM-III and III-R in the clinical setting were reviewed to inform changes for inclusion in DSM-IV (see Table 2).[21-24] This evaluation was a major point of difference in the development of DSM-IV compared to DSM-III and III-R, which were based on expert committee deliberation alone.

In DSM-IV delirium is subdivided into aetiological groups (general medical condition, substance induced, multiple aetiology and not otherwise specified), as it was found that the requirement in DSM-III and III-R for a single aetiological factor was not reflective of delirium in clinical practice.[1] Some of the criteria were found to be difficult to assess in the medically ill. Some examples where differential diagnoses were problematic include sleep disturbance due to multiple factors, decreased psychomotor activity due to being bedbound and speech abnormalities due to hearing loss.[21] In DSM-IV these features have been moved to associated features, which may be present but are not required for diagnosis.[25] This means DSM-IV has the benefit of simplified criteria.[25] The evolution of the classifications over time has meant the emphasis has shifted from extensive lists of symptomatology, to a focus on two essential pathophysiological concepts of disordered attention (arousal) and cognition.[26] Perceptual disturbance also has become more central, and with DSM-IV it is now possible to diagnose delirium with perceptual disturbance but without cognitive disturbance.[21] DSM-IV also distinguishes dementia alone, delirium alone or delirium superimposed on dementia; although delirium is not phenomenologically different in these two groups it was recognised that pre-existing cognitive impairment is a major risk factor for delirium development.[1 27] The National Institute for Health and Clinical Excellence (NICE) guidelines on delirium diagnosis, prevention, and management[28] also recommend the DSM-IV criteria, which is used as the

standard operational definition of delirium, with ICD-10 deemed as too restrictive due to stricter inclusion criteria and additional diagnostic requirements.

Table 1 Comparison of classifications of delirium[1 4 5 15 18 19 26]

Criteria	DSM-III (1980)	DSM-III-R (1987)	DSM-IV (1994) DSM-IV-R (1995)	ICD-10 (1993)
Conscious-ness[a]	Clouding of consciousness (reduced clarity of environment)	Reduced ability to maintain attention to external stimuli	Disturbance of consciousness (reduced clarity of awareness of environment)	Impaired consciousness or attention (on a continuum from clouding to coma)
Attention and awareness[a]	Reduced capacity to shift focus and maintain attention to environmental stimuli	Reduced ability to appropriately shift attention to new external stimuli	Reduced ability to focus, sustain or shift attention	Reduced ability to direct, focus, sustain or shift attention
Cognitive and perceptual disturbance	Disorientation and memory impairment *Perceptual disturbance is listed in associated symptoms*	Disorganised thinking (as indicated by rambling, irrelevant or incoherent speech) *Perceptual disturbance is listed in associated symptoms*	A change in cognition (such as memory deficit, disorientation or language disturbance) *or* development of perceptual disturbance (misperception, illusion or hallucination) *that is* not better accounted for by a pre-existing, established or evolving dementia.	Global disturbance of cognition: a) perceptual distortions b) illusions c) hallucinations (most often visual) d) impairment of abstract thinking and comprehension (with or without transient delusions) e) impairment of immediate recall, with relatively intact remote memory f) disorientation for time and place, and person in some cases
Chronology	Develops over a short period of time (hours/days) Tends to fluctuate over course of a day	Develops over a short period of time (hours/days) Tends to fluctuate over course of a day	Develops over a short period of time (hours/days) Fluctuates	Not commented on

Criteria	DSM-III (1980)	DSM-III-R (1987)	DSM-IV (1994) DSM-IV-R (1995)	ICD-10 (1993)
Associated symptoms	At least two of the following: a) perceptual disturbance (misinterpretations, illusions, or hallucinations) b) speech that is at times incoherent c) disturbance of sleep – wake cycle, with insomnia or daytime sleepiness d) increased or decreased psychomotor activity	At least two of the following: a) reduced level of consciousness b) perceptual disturbance (misinterpretations, illusions, or hallucinations) c) disturbance of sleep – wake cycle, with insomnia or daytime sleepiness d) increased or decreased psychomotor activity e) disorientation to time, place or person f) memory impairment (e.g. inability to learn new material or remember past events, such as history or current episode of illness)	Associated features are listed in the explanatory text but not in the diagnostic criteria in DSM-IV-R. The associated features are: a) disturbance of sleep – wake cycle b) disturbed psychomotor behaviour c) emotional disturbance, and rapid unpredictable shifts from one emotional state to another (fear, depression, irritability, anger, euphoria, lability or apathy) d) calling out or screaming may occur e) impaired judgment	a) Psychomotor disturbance: - hypo or hyperactivity - change in flow of speech - enhanced startle reaction b) Disturbance of sleep – wake cycle: - insomnia - total sleep loss - daytime drowsiness - disturbing dreams or nightmares c) Emotional disturbances: - depression - anxiety or fear - irritability - euphoria - apathy, wandering perplexity
Criteria for identifying organic factor	Evidence from history, physical examination or laboratory tests of a specific organic factor judged to be aetiologically related to the disturbance	Either: a) evidence from history, physical examination or laboratory tests of a specific organic factor judged to be aetiologically related to the disturbance, or b) in the absence of such evidence an organic factor can be presumed if cannot be accounted for by any non-organic mental disorder	Evidence from history, physical examination or laboratory findings that the disturbance is caused by the direct physiological consequence of a general medical condition.	The presence of underlying medical condition presumed

[a] Disorders of consciousness and attention are listed as one joint criteria in all the classifications but have been separated in this table for clarityDSM – Diagnostic and Statistical Manual; DSM-IV-R – Diagnostic and Statistical Manual of Mental Disorders, fourth edition – revised; ICD – International Classification of Disease

Table 2 DSM-IV-R criteria for delirium due to a general medical condition

CRITERIA	
A	Disturbance of consciousness (i.e. reduced clarity of awareness of the environment) with reduced ability to focus, sustain, or shift attention
B	A change in cognition (such as memory deficit, disorientation, language disturbance) or the development of a perceptual disturbance that is not better accounted for by a pre-existing, established or evolving dementia
C	The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day
D[a]	There is evidence from the history, physical examination, or laboratory findings that the disturbance is caused by the direct physiological consequences of a general medical condition[a]

[a] There is an allowance in DSM-IV-R to classify:
1) delirium due to multiple aetiologies where criteria D is, 'There is evidence from the history, physical examination, or laboratory findings that the delirium has more than one aetiology'
2) delirium due to substance withdrawal where criteria D is, 'There is evidence from the history, physical examination, or laboratory findings that the symptoms in criteria A and B developed during, or shortly after withdrawal syndrome'
3) delirium not otherwise specified—delirium is suspected to be due to a general medical condition or substance withdrawal; however, there is insufficient evidence to establish a specific aetiology.
DSM-IV-R – Diagnostic and Statistical Manual of Mental Disorders, fourth edition – revised

1.3.1 People without cancer

Two studies[25 29] in non-cancer populations compare the major nosological classifications for delirium, exploring comparative prevalence and prognosis by using the various classifications. One excluded patients with cancer, and the other did not describe the diagnoses in detail, so it is unclear how many patients with the diagnosis of advanced cancer were included. These studies are described in more detail below.

The first study tested DSM-IV criteria in a cross-sectional study of 477 patients of two populations (nursing home residents and acute geriatric inpatients) to compare prevalence rates in demented and non-demented subjects.[25 30] The patients were assessed by an extensive interview (by two experienced geriatricians blinded to each other's rating, with each determining if the patient met the diagnosis of delirium according to operationalised criteria of DSM-III, DSM-III-R, DSM-IV and/or ICD-10.[25] Of the four classification systems, DSM-IV criteria demonstrates higher sensitivity for delirium diagnosis, especially in the acutely ill subgroup without prior dementia, and this is attributed to the simplified criteria.[25 30] On multivariate analysis, significant contributors to delirium diagnosis using DSM-IV were new onset of perceptual disturbance, disturbance of consciousness, and disorganised thinking in patients with dementia; and perceptual disturbance, motor disturbance, and disorientation in those without dementia.[25] ICD-10 was found to be restrictive due to high number of specific requirements for diagnosis.[25]

The second study was a secondary analysis combining two data sets: a randomised controlled trial (RCT) of management of delirium and a consecutive prospective cohort of 322 elderly medical inpatients which also included non-delirious patients, comparing the sensitivity and specificity of delirium diagnosis by DSM-III, DSM-IV and ICD-10 criteria.[29] The inclusion criteria for both cohorts were age 65 years and older, and admission to medical service. Patients who did not speak English or French, and patients with cerebrovascular disease, cardiac disorder requiring cardiac monitoring or cancer were excluded. The total combined sample included 128 participants with delirium and dementia, 40 with delirium only, 94 with dementia only and 60 with neither disorders. Patients who

had symptoms of delirium documented in nursing notes and/or a score of 3 or more on the Short Portable Mental Status Questionnaire (SPMSQ)—a 10-item questionnaire that assesses orientation, memory and concentration—were assessed for delirium using the Confusion Assessment Method (CAM) administered by a research nurse within 48 hours of admission. Delirium symptoms were documented utilising the Delirium Index (DI) and the Informant Questionnaire on Cognitive Decline in the elderly (IQCODE) to determine the presence of dementia. The symptom presentation was used to classify the patients against DSM-III, DSM-IV and ICD-10 criteria, and comparisons were made using DSM-III-R as criterion standard.[29] DSM-IV criteria (100%) were more sensitive than DSM-III (96%) or ICD-10 (61%); however, DSM-IV had the lowest specificity (71%) compared to DSM-III (90%) and ICD-10 (91%). The lower specificity for DSM-IV was accounted for by its inclusion of patients who were not included when using DSM-III due to the lack of disorganised thinking (most of these patients had hypoactive delirium).[29] The low sensitivity of ICD-10 is due to its requirement for five criteria to be met for diagnosis, compared to three for DSM-IV and four for DSM-III.[29] This study also concludes that DSM-IV criteria are the most inclusive, in both patients with and without dementia. Some limitations are that the power for the secondary analysis was not described, as sample size was based on primary outcomes of the randomised trial of delirium management and delirium prognosis studies.[29] The implications are that DSM-IV is less likely to lead to false negatives (especially in those with hypoactive delirium), and could potentially lead to false positives (those with hypoactive symptomatology due to other differential diagnoses), so the net impact is not clear.

There is currently much discussion about the modifications required for DSM-V as it is developed, with its release scheduled for May 2013.[31] Suggested changes are based on recent evolution in the understanding of delirium phenomenology, and practical challenges faced by clinicians' operationalising the criteria when making a diagnosis of delirium. Challenges posed for DSM-V to address include defining differing courses of delirium temporal patterns (acute transient, recurring and persistent), SSD, and delirium in the context of dementia to provide more direct guidance to clinicians.[32] The current definitions are one or mutual

exclusion, with the dementia diagnostic criteria referring to ‘deficits not occurring exclusively in the course of delirium’ and similarly in delirium that cognitive change ‘is not better accounted for by a pre-existing, established or evolving dementia.[32]

There will also be revision in ICD classifications with the pending development of ICD-11 due to be released in 2015, again focused on refinement related to recent evidence, studies which have demonstrated the lower sensitivity of ICD-10, and practical guidance for clinicians.[33]

Suggestions cited in the literature for revised criteria in ICD-11 include[33,34,37,38]:

1. acknowledgment of the need to consider symptoms over a timeframe (not a single brief assessment) and the ability to have a contribution of third party information and collateral history) especially for symptoms which fluctuate

2. focusing on ‘attention’ as a core sign of delirium due to recent data supporting predominance of disordered attention with good correlation with other cognitive features[34]

3. separation of the definitions of clouding of consciousness and reduced attention, and clarification of the criteria regarding whether both are required or whether changes in attention are deemed as evidence for clouding of consciousness

4. reducing the focus on memory which is equally affected in dementia (and hence more difficult to determine changes from baseline), and orientation, which is also abnormal in dementia and prone to fluctuate so abnormalities may be missed at assessment

5. guidance for assessment when a patient is extremely drowsy; a common phenomenon in delirium that often makes assessing cognition impossible

6. reconsideration of the time frame for delirium fluctuation. Phenomenological studies have demonstrated variability in how symptoms fluctuate with the time course of fluctuation not necessarily within 24-hour time frame, especially in hypoactive delirium[35 36]

7. attribution of aetiology needs to consider multiple aetiologies being the norm[34 37 38] not the exception, and that in 10% of cases no clear aetiology can ever be determined

8. acknowledgment that delirium due to alcohol may also be multifactorial—consideration of whether classification separately overly simplifies delirium causation in this group

9. specific guidance on the diagnosis of delirium in the context of dementia

10. the duration and course of delirium needs to consider sustained (one to four-weeks' duration) and persistent delirium over one-month duration

11. consideration of the definitions of SSD, given the link to prognosis.[33]

The number of refinements to consider for both ICD-11 and DSM-V is a testament to the rapid evolution in work describing phenomenological profiles and delirium outcomes, and hence reflects progress in the field since 1995. Further research is needed to determine whether sleep – wake disturbance, thought processes and content abnormalities, and perceptual disturbance can add to the sensitivity of delirium diagnosis, with the key challenge being that these symptoms are unlikely to have a role as essential criteria as they are nonspecific and also not always present.[33] The DSM-V and ICD-11 may also provide an opportunity to better align the two systems.[33]

1.3.2 People with cancer

In the cancer patient population DSM-IV criteria have been used to prospectively study precipitating factors of delirium, and to determine psychometric properties of the Memorial Delirium Assessment Scale (MDAS).[38-40] There have not been studies to determine the psychometric properties of DSM-IV compared with earlier criterion in the cancer or palliative care population.

DSM-IV-R remains the current international gold standard for delirium definition despite its limitations and consideration of further refinements. The DSM-IV-R definition of delirium (Table 2) was used for all the studies in this thesis. Specific delirium assessment scales have been developed to operationalise these criteria for clinical use; these are discussed in Section 1.7.2.

1.4 Delirium phenomenology

Delirium classifications have focussed on determining the core features required to make a diagnosis. The features seen in clinical practice include a broader range of symptoms. The frequency and the specificity of these symptoms have been part of the debate in developing delirium definition, classification and measurement instruments. Current understanding is that delirium includes essential diagnostic symptoms (inattention, reduced level of arousal), core features which occur highly consistently (sleep – wake cycle disturbances, motor activity changes, disorganised thinking), as well as other features which are more variable (psychosis, affective symptoms).[41]

The frequency of the respective core and non-core symptoms are demonstrated in various studies, with the range across the studies as follows: core diagnostic symptoms of attentional deficits 97%–100%, and thought process abnormalities 54%–79%; other core symptoms of disorientation 76%–96%, memory deficits 88%–96%, sleep – wake disturbance 92%–97%, motoric alterations 24%–94%, language disturbance 57%–67%; and the non-core symptoms such as perceptual disturbance 50%–63%, delusions 21%–31% and affective changes 43%–86%.[34 41-46] These studies include populations with delirium referred to hospital liaison psychiatry (n=227)[42], general medical and surgical patients (n=58)[43], patients undergoing haematopoeitic stem cell transplant (n=90), elderly medical inpatients with delirium and dementia (n=128) compared to delirium alone (n=40)[45], and finally a study of elderly patients (n=168)[46]. There is heterogeneity in the populations studied, and the method symptoms were assessed (clinician assessment using DSM criteria, delirium scale). The studies did not exclude those with reduced level of arousal and Fann et al prorated the delirium scale score if the patients conscious level did not allow score completion.

1.4.1 Psychomotor subtypes of delirium

The classification of delirium into hypoactive (hypoalert), hyperactive (hyperalert) and mixed subtypes is widely accepted, and was recognised in early reports of delirium as described previously.[3 47] The differences seen in psychomotor aspects of delirium are particularly relevant in clinical practice where the patient with the hypoactive subtype appears lethargic and drowsy,

responds slowly to questions and does not initiate movement. This presentation often leads to misdiagnosis or under-diagnosis.[47] This compares to the hyperactive subtype, which is associated with restlessness, agitation and psychomotor overactivity.[47] These clinical manifestations pose different management issues, so this in itself is an important reason for differentiating the subtypes in this way.[48]

The construct validity of this subtype classification with both psychomotor and motoric symptoms was investigated in a prospective cohort of 183 geriatric medical and psychiatric inpatients with DSM-III defined delirium.[47] Two geriatricians and a geriatrician psychiatrist made the DSM-III delirium diagnosis.[47] The method of identification of delirium symptomatology was by a checklist of 19 symptoms covering different clinical dimensions (perception of self and environment, mental and motor functioning, psychopathology, neuro-vegetative symptoms) with a rating on a four-point scale (absent to severe) on interview or clinical examination within the previous 24 hours.[47] The psychometric properties of this checklist are not clearly described, and inter-rater reliability was not established. The aetiology of delirium was determined by medical record review.[47] Lack of systematic identification of aetiology is a weakness of this study, as other investigators propose that the phenomenological profile of delirium could be related to delirium aetiology.[49] Factor analysis identified two clusters of symptoms:

1. hyperactive (agitation, hyper-reactivity, aggressiveness, hallucinations, delusions)

2. hypoactive (decreased reactivity, motor and speech retardation, facial inexpressiveness).[47]

The authors did not present figures on how many participants would fall into the two clusters based on these symptoms groups. The analysis was reduced to 154 subjects from the initial cohort of 183 due to missing data; however, the reasons for this or the characteristics of this group were not described. More than 50% of the cohort was receiving psychoactive drugs, which may also impact on psychomotor behaviour.[47]

Similarly, other studies used cross-sectional cohorts, including two studies in cancer and advanced disease, and a single assessment for delirium symptoms, for example, the Delirium Rating Scale (DRS) or MDAS, also arrived at with two of three clusters using factor analysis. Typically, these clusters have one composite of cognitive symptoms and one or two neuro-behavioural groups.[39 44 50-54]

Each study used a different combination of cognitive, neuropsychiatric and behavioural symptoms to both define motoric subtype or to measure; hence the symptom structure of delirium in the earlier literature may not present the complete picture. The key difficulty is that no validated tool has been developed to delineate subtypes, so the methodology of studies continue to vary greatly.[55] Equally, DSM criteria do not include categories to define psychomotor subtypes, and its simplified criteria have no method for describing the phenomenology of delirium.[56 57] Methods that have been used often focus on psychomotor activity using either/or:

1. presence or absence of particular psychomotor behaviours
2. quantitative measurement of psychomotor activity (wrist worn actigraphs)
3. validated scales to rate agitated behaviours (not specific for delirium).[48 58-61]

These rely on adequate history of the behaviour in question, or presence of the behaviour at the time of assessment.[48] They also rely on similar features being included in the classification, and many studies have included items which are not strictly motor behaviour, such as altered verbal content, levels of arousal, aggression, disturbance of emotion, and abnormalities of perception and thinking.[56] The other method is to assess the level of alertness, which is independent of abnormal behaviours.[43]

A study in 100 palliative care inpatients in Ireland shows poor concordance (34%) between these different methods of subtyping.[60] This study compared the Lipowski description[62] of hypoactive and hyperactive features, Liptkin and Levkoff schema[63] using the Delirium Symptom Interview (DSI), O'Keefe and Lavan schema[61] using the Brief Psychiatric Rating scale and Cohen Mansfield Agitation Inventory to define subtypes, and the Delirium Rating Scale-Revised 98 (DRS-R98)[64] motor items.

Focusing on purely motoric features[65], and using independent quantitative methods such as electronic motion analysis (accelerometry) may assist in determining the true relationships between clinical subtypes, aetiologies and outcomes.[66-69] More recent studies have taken this approach. Detailed exploration of the implication of change of classification during admission or treatment and subtypes stability over time, and what happens after therapeutic intervention is also lacking, with only one recent study in palliative care populations.[57]

A new motor subtype scale, the Delirium Motor Subtype Scale (DMSS), has recently been validated.[65] It uses 11 motor items derived from the prior methods described above; however, it has better specificity for delirium and demonstrated correlation with electronic motion analysis.[67 69] Four items are hyperactive features and seven hypoactive, and are rated present or absent. Two symptoms must be present from either hyperactive or hypoactive to meet those subtype criteria, whereas those who meet both criteria are deemed 'mixed' and those meeting no criteria 'no subtype'. This scale distinguishes motor activity from affective lability and psychotic symptoms.

A recent study assessed 100 consecutive palliative care patients in Ireland who had delirium (DSM-IV criteria).[70] Patients were assessed twice weekly with the DRS-R98 and the DMSS. Almost two thirds met the criteria for the same subtype throughout the delirium episode, whilst 38% had a highly variable course. Six per cent had no subtype, 28% hypoactive, 18% mixed and 10% hypoactive subtype throughout. Those who remained a mixed subtype through episodes seemed to have more severe delirium features, as rated on DRS-R98.[71] These findings need to be replicated in settings other than palliative care. This study may have missed fluctuations in motor features that occurred more frequently as assessments were only twice weekly, or could have been supplemented with continuous actigraphy. This study also explored associations with delirium aetiology.[72] The Delirium Etiology Checklist (DEC) was completed by the treating palliative care physician. The DEC categorises potential causes of delirium into 12 categories: drug intoxication, drug withdrawal, metabolic/endocrine disturbance, traumatic brain injury, seizures, infection (intracranial), infection (systemic), neoplasm (intracranial), neoplasm (systemic), cerebrovascular, organ insufficiency, and

central nervous system (CNS) and other systemic illness. Each is rated on a five-point scale for degree of attribution to the delirium episode, ranging from ruled out/not present/not relevant (0) to definite cause (4). The most common aetiologies seen were drug intoxication, metabolic disturbance, systemic infection and neoplasm. Only two patients had a single etiology rated as a probable cause for their delirium, whereas 19 patients had two etiologies, 42 patients had three, 20 patients had four and 17 cases five or more (mean 3.4 ± 1.2). Generalised estimating equations (GEE) were used to model relationships over time for subtypes, with aetiology (on DEC), medication exposure, adjusted for dementia status, gender and age. GEE takes into account that observations within a participant and between repeated measures are dependent. Antipsychotic (chlorpromazine equivalents) and benzodiazepines (diazepam equivalents) were correlated with motor agitation measured on item 7 of DRS-R98. Opioids (morphine equivalents) and corticosteroids (prednisolone equivalents) were not associated with motor subtype category at any time-point. Patients with hypoactive subtype throughout were more likely to die within 30 days of study entry than those with other subtype courses ($p = 0.03$).

The more recent studies by Meagher et al highlight why multivariate analyses need to adjust for other variables that may affect phenomenology, such as delirium severity, illness severity, prior cognitive impairment and concurrent neuroleptic or sedative use to be able to interpret the associations. Several studies have been limited by aetiological classifications that do not account for the multifactorial delirium common in clinical practice, with up to six medical diagnoses being identified in some studies.[35] The role of comorbid illness in the clinical presentation, when it is not directly aetiologically implicated also needs to be delineated.[63]

1.4.1.1 What are the pathophysiological correlates and clinical outcomes associated with psychomotor subtype

There has been much research effort to determine if delineation of subtypes has implications for differential diagnoses (other than delirium), aetiology of delirium, treatment and prognosis.[41] [48] [57] Differential diagnoses for the hyperactive group are diagnoses of psychosis or anxiety, and hypoactive delirium can mimic depression or uncooperative behaviour.[48]

The clinical characteristics of delirium are unlikely to be solely due to an abnormality of a single neurotransmitter pathway, and hence it has been considered feasible that different abnormalities may alter the phenomenology seen in particular psychomotor subtypes.[48] Some supporting evidence for this hypothesis exists in several studies. For example, increased γ – aminobutyric acid (GABA) activity has been demonstrated in hepatic encephalopathy, and glutamate is depleted in experimental liver failure, both of which may relate to the high prevalence of hyperactive delirium in this condition.[48] Equally, there are some neurotransmitter abnormalities that may be crucial in delirium but may not alter or vary the phenomenology. For example acetylcholine deficiency[73] caused by anticholinergic medication is most typically associated with hyperactive subtype, but has been associated with hyperactive, hypoactive and mixed presentations.[14] Circadian pathways and pro-inflammatory cytokines also have been implicated. Melatonin metabolite urinary 6-sulphatoxymelatonin also has been correlated with motoric subtype with the highest levels in hypoactive subtypes, followed by mixed, and the lowest levels in hyperactive delirium.[74] An exploratory study of 28 elderly patients after hip fracture demonstrated interleukin-6 levels during delirium were associated with the hyperactive and mixed subtype.[75] Localised neuroanatomical lesions are also associated with particular presentations. For example, hyperactivity has been linked with middle temporal gyrus damage and fronto-striatal injury associated with hypoactive presentations.[41]

The outcomes for the different subtypes are also of interest. In relation to prognosis there has been significant variation in the associations seen. Some studies demonstrate better prognosis in hypoactive subtype[76], hyperactive subtype[61], and those without disturbed motor behaviour[77]; however, on balance the evidence seems to point to the hypoactive subtype having poorer outcomes.[55] Other studies demonstrate differences in morbidity. For example, hypoactive groups may have more complications such as pressure sores, and hospital-acquired infections, whereas falls were more common in hyperactive presentations.[73] The majority of delirium treatment studies have not been designed to determine the effectiveness of treatment for motoric subtype, and further study is needed for both pharmacological and non-pharmacological

interventions.[55] It is thought that the heterogeneity in how subtype was measured is a key contributor to the variations in outcome seen.

1.4.1.2 Studies of delirium subtypes in cancer and palliative care

There has been rapid growth in literature focusing on delirium subtype in palliative care. These studies have been predominantly in advanced cancer and haematological malignancies, with a consistent feature being the relative predominance of the hypoactive subtype.[39 44 78-81] A study in a specialist palliative care inpatient unit in Edinburgh, Scotland, demonstrated a delirium prevalence of 29% (29/100) in 100 consecutive admissions utilising the CAM[a] and MDAS and 25/29 (80%) were identified as hypoactive using the MDAS psychomotor activity item.[80] This unit takes referrals for people with advanced cancer and non-cancer life limiting illnesses from community specialist palliative care nurses, General Practitioners (GPs) and local acute care hospitals (including a major cancer centre) for symptom control, rehabilitation, respite and terminal care.[80] The cohort was representative of the unit as the only exclusion was people with a Glasgow Coma Scale (GCS) of 3 (deep coma) on admission.[80] The first cohort of 100 patients had advanced malignancy, bar one participant with advanced heart failure, mean age 68.7 years, European Cooperative Oncology Group (ECOG) performance status[b] was 4 in 12%, ECOG 3 in 49%, ECOG 2 in 33% and ECOG 1 in 6%. This same group then repeated a point prevalence study in eight specialist palliative care units in Scotland, including 109 patients over a 48-hour period of assessment, and in this cohort 32 patients had delirium (29.4%) with 25 (78%) hypoactive subtype.[80] The mean age of the participants in the eight units included in the second cohort was 69 (range 63.7–82.8) years, and performance status mean score 2.5 (1.6–3.4).[80]

A Canadian study in a specialist acute inpatient palliative care unit of a consecutive cohort of 104 patients with advanced cancer diagnosed delirium in 42% of patients (n = 44/104) on admission using DSM-IV criteria, and incident delirium in a further 27 of the remaining 60 patients (45% of patients were

[a] For full description of Confusion Assessment Method and Memorial Delirium Assessment Scale see Section 1.7.2

[b] European Cooperative Oncology Group score which assesses general wellbeing and activities of daily life, with scores from 0 to 5, with 0 denoting fully active and 5 death

without prevalent delirium on admission, or 26% of the whole cohort).[38 39] Forty-five participants had hypoactive delirium (43%).[39] Delirium was diagnosed using a semi-structured interview to operationalise DSM-IV-R criteria and then had a physician-rated MDAS.[38] This unit is within a tertiary level university-affiliated teaching hospital, which receives referrals from acute care hospitals, hospices and home.[38] Participants were excluded if they had severe language or communication difficulties (e.g. tracheostomy, expressive dysphasia) (n = 3), or significant psychiatric illness (n = 1) that would interfere with delirium assessment. The mean age of the participants was 61 years.[38]

A study in a Japanese palliative care unit, which predominantly provides end-of-life care, followed 237 consecutive admissions with advanced cancer in a two-year period utilising DSM-IV-R criteria to diagnose delirium. The MDAS and DRS were used to further characterise the delirium episode.[79] Hyperactive and hypoactive delirium were defined using item 9 of the MDAS, which specifies decreased or increased psychomotor activity.[79] During admission, 213 out of the 237 developed delirium (90%). Mean age of the participants was 65 years, and mean palliative performance score was 22 (20 being the level where the patient is bedbound on a scale from 0–100, 100 being normal).[79] Eighteen per cent had hyperactive delirium (n = 44). On univariate analysis drug induced delirium was associated with hyperactivity and dehydration with hypoactivity. Multivariate analyses were not performed.

Similarly a study in a Taiwanese palliative care unit followed 457 inpatients, using the Chinese version of the DRS and psychiatrist assessment to determine delirium.[82] Delirium prevalence was 46.9% (n = 107), with hypoactive subtype 68.2% (95% Confidence Interval (CI): 59.4%–77.0%).[82]

A study of 99 patients in a Washington Cancer Research Centre undertaking their first allogeneic or autologous haematopoietic stem cell transplant shows delirium occurred in 50% of patients (n = 45).[44] The participants were monitored at baseline (one week pre-transplantation), during conditioning therapy and daily for 30 days post-transplantation for delirium, utilising the DRS. A score over 12 for two out of three consecutive assessments was defined as delirium.[44] Out of the 66 participants who had delirium, 86% were hypoactive, 12% were mixed, and 3%

hyperactive. The authors did not specify whether they utilised the MDAS or DRS for determining psychomotor subtype.

The more recent studies of Leonard et al[71] and Meagher et al[70 72] have been described in detail in Section 1.4.1.

1.5 Subsyndromal and persistent delirium

1.5.1 Subsyndromal delirium

Lipowksi first described SSD in 1983.[62] SSD is defined by the presence of any core delirium symptoms without full diagnostic criteria *or* cut-off scores on delirium rating scales that are below the diagnostic threshold.[83] The concept is supported by evidence that an association exists between the presence of delirium symptoms and clinical outcomes across the spectrum of isolated symptoms to patients meeting the criteria for a diagnosis of delirium.[76 84 85] It can present prior to an emerging full syndromal delirium (FSD) episode, linger following an FSD episode—sometimes persisting—or alternatively, periods of SSD can intersperse with FSD during recovery. The opponents to the concept of a subsyndromal presentation cite that in the case of delirium which is poorly recognised, symptoms which seem only to meet the criteria for SSD may in fact be misdiagnosed, or the diagnosis could relate to the sensitivity of the measurement system used.[84] Differential diagnoses of subsyndromal presentations also need to be considered, and include executive function or depressive symptoms and, unless this is formally evaluated, alternative diagnoses of depression and frontal lobe impairments could be missed.[8]

A study to determine the prognostic significance of SSD researched a cohort of 164 elderly medical inpatients who did not meet DSM-III-R criteria for delirium during the first week of admission, but had two or three of four core symptoms of delirium (clouding of consciousness, inattention, disorientation, perceptual disturbance).[85] Prior cognitive impairment, comorbidities and illness severity were formally assessed with validated tools, and used to assess outcomes in a multivariate regression model.[85] The cohort was classified into three mutually exclusive groups:

1. prevalent SSD at admission
2. incident SSD (during one week after admission)
3. no SSD (prevalent or incident).[85]

This study demonstrated that prevalent SSD resulted in longer hospital stays, increased post-discharge mortality, more symptoms of delirium, and lower functional and cognitive level at 12 months follow-up, than patients with no SSD.[85] The findings for incident SSD showed similar trends but were not statistically significant.[85] The number of patients lost to follow-up was provided, but their demographic and clinical parameters were not presented.

A prospective consecutive cohort of 325 elderly medical inpatients (≥65 years) with DSM-III defined delirium, used the DSI daily to assess the presence or absence of symptoms.[6 7 27] Illness severity, likely aetiology of delirium and prior cognitive impairment were assessed by review of the medical record.[27] A partial syndrome was defined in patients who did not meet DSM-III criteria, but had one or more new symptoms of clouding of consciousness, disorientation or perceptual disturbance on initial evaluation or during admission.[27] Outcomes for the DSM-defined delirium group and partial syndrome were assessed with a multivariate model, using age, prior cognitive impairment, gender and illness severity; however, prior intent for analysis of the partial syndrome or power calculation for outcomes relating to this were not described.[27] Partial syndrome was related to persistent symptoms, longer hospital stay after adjustment for age, gender, cognitive impairment and illness severity, but mortality was not higher than those with no symptoms.[27] The limitations of this study were that the partial syndrome analysis was not a primary outcome, DSM-III criteria were used, and the partial syndrome described may have been diagnosed as delirium by DSM-IV criteria (due to DSM-IV being more the inclusive criteria), and patients lost to follow-up were not clearly described. The covariates used in the regression model were not vigorously assessed, and relied on medical record review. The relationship of partial syndrome on admission to incident delirium was not described.

Another prospective cohort of 124 hip-fracture patients with CAM-defined delirium, underwent assessment with the MDAS, and has been described in detail

when considering delirium subtypes.[76] This study also looked at patients who did not fulfil the CAM criteria for delirium, but had symptoms and demonstrated poor outcomes (death at six months, nursing home placement) and were similar to 'mild' delirium (as defined by MDAS score).[76] A possibility is the MDAS classifies patients with mild delirium, due to being based on the more sensitive DSM-IV criteria, while the CAM criteria use the less sensitive DSM-III criteria.

SSD has been explored specifically in palliative populations. In the cohort of 100 palliative care unit inpatients described above, Meagher et al also explored features of subsyndromal and persistent delirium.[83] Though the cohort all met DSM-IV-R criteria for delirium, severity scores on DRS-R98 of 8–15 are considered subsyndromal in severity, a score range present in 27 participants at baseline. There were 323 follow-up assessments over six weeks in this cohort, and during this time only 190 (58%) met FSD criteria on DRS-R98 because many then met SSD score ranges as delirium resolved. All symptoms were found to continue through an episode of delirium, and also occurred in SSD in lesser severity (both prior to FSD or while resolution was occurring) with minimal fluctuation. There was an increasing dominance of DRS-R98 cognitive symptoms over time, namely increasing disturbances in orientation, short- and long-term memory, motor agitation, delusions, disorganised thinking and attention.

1.5.2 Persistent delirium

If FSD persists for longer periods of time (studies often define this as 30 days or more) this is termed persistent delirium.[86] Persistent delirium also affects outcomes, with increased mortality and complications, and reduced functional recovery seen (after adjustment for age, comorbidity, dementia and baseline functional status).[87-89] A study of 412 post-acute care residents, who had had delirium in hospital, found one-third met criteria for delirium on CAM at six months.[88] The patients with persistent delirium were 2.9 times more likely to die during the one-year follow-up than those whose delirium resolved (CI 51.9–4.4), and this was the case for those with and without dementia. There has not been detailed exploration of persistent delirium in palliative care, however the study by Meagher et al[83] described above did describe that symptom profile did change in

more prolonged episodes, where inattention and disorganised thinking were the most prominent DRS-R98 features distinguishing persistent delirium.

1.6 Epidemiology of delirium in cancer populations

The incidence and prevalence of delirium is difficult to establish due to the difficulty in defining diagnostic criteria, varying methodology and fluctuating clinical course.[90] The risk of delirium varies depending on patient population and the context of care.[90] Retrospective chart studies are unreliable due to the frequency of missing documentation and use of nonspecific terminology in medical records, so only studies with prospective methodology are considered in this section.[91]

In the cancer setting, several variables are of interest; those patients who are receiving active anticancer treatment, and location of care (acute oncology or hospital settings, palliative care inpatient unit settings, and those being cared for in the community). The predisposing or risk factors that need to be assessed in these populations to assist interpreting and comparing incidence and prevalence figures also needs further definition, as extrapolation of the model from geriatric populations may not be valid.[92]

Most studies have explored incidence and prevalence figures for patients with advanced cancer admitted to palliative care units and hospices; these studies are outlined in Table 3.[81 82 93-100] A recent systematic review[101] summarised eight studies since 1980 (time-point chosen as this was when delirium was first listed in DSM-III) with prospective assessment of delirium in the palliative care inpatient setting. The majority (99%) of all participants (n = 1079) across the eight studies[38 81 82 94 98-100 102] had advanced cancer, with only 11 with immunodeficiency and one person with cardiac failure representing non-cancer diagnoses.[101] Sample size was predominantly determined by the number of admissions to the units within the given study period, with mean of 120 participants (range 41–228).[101] There were several variations in study methodologies, with some using a two-step sampling approach—a delirium screening instrument followed by definitive diagnosis; different time-points for delirium assessment, and different assessors (medical or nursing clinical staff

versus research staff).[101] The terminal stage was variably defined from last weeks to last six months of life, with only one study collecting data within the six hours prior to death. Prevalence of delirium on admission ranged from 13.3%–42.3%.[101] Five studies measured delirium incidence after admission, with rates reported ranging between 3%–45%. Some studies only reported a frequency for the whole admission as a total, with frequencies of 26%–62% reported. Two studies reported the prevalence of delirium in the weeks or hours before death reporting rates of 59%–88% (within the last six hours of life).[38 81 103] This systematic review found that studies which used DSM-IV criteria reported higher prevalence (42%–88%) than earlier DSM or ICD-10 criteria (13.3%–32.8%).[101]

The figures for patients potentially receiving anticancer treatment can be indirectly obtained from the study of Tuma et al, a cohort which included patients referred to a neurology service from oncology acute care.[104]

Summary data are available in the recent NICE guidelines on delirium diagnosis, prevention, and management[28] providing the epidemiology in other health settings by way of comparison. The rates in general and geriatric medicine were from 16 studies, with median prevalence of 21.4% (range 18–32.6), and incidence of 15.2% (range 12.5–17.9); medical intensive care units (ICUs) from seven studies, with median prevalence 36.6% and incidence of 15.2%; and orthopaedic acute hip fracture from three studies, with median prevalence 22% (range 16.5–29.7) and incidence of 30.3% (range 12.5–48.1).[28] The median total delirium percentage (range) for the same settings were 23.7% (15–42) in general and geriatric medicine, 70.9% (48–83.3) in medical intensive care, and orthopaedic acute hip fracture 14.7% (12.5–22).[28] Interestingly, the median total delirium percentage (range) in emergency departments is 9.8% (9.6–11.1) based on four studies.[28] In comparison, palliative care populations have at least equivalent, but in more advancing disease much higher, delirium rates.

Table 3 Prevalence and incidence of delirium in cancer patients

Study (n)	Population	Other variables measures	Initial screening	Diagnostic criteria used	Incident delirium	Prevalent delirium (on admission)	Quality considerations
Massie 1983[93] (n = 19)	Terminally ill cancer patients on oncology ward	Delirium aetiology	nil	DSM-III criteria	Not studied	85% (n = 11)	Small sample size Sample identified as 'terminal' clinician judgement that 'would not survive hospitalization' No standardised method of delineating prior cognitive impairment
Minagawa 1996[94] (n = 93)	Japanese terminally ill cancer patients admitted to palliative care unit	Karnofsky performance status Site of metastatic disease Psychiatric assessment	MMSE	DSM-III-R using structured clinical interview	Not studied	28% (n = 26)	Structured clinical interview to determine DSM-III psychiatric diagnoses, including delirium
Lawlor 2000[38] (n = 113)	Patients with advanced cancer in an acute palliative care unit Included previous dementia and terminal delirium	Precipitating factors for delirium	MMSE on admission and twice weekly Delirium observational checklist scale every 8-hour shift	DSM-IV MDAS	45% (n = 27/60 who were delirium free on admission)	42% (n = 44) Terminal delirium hours before death 88% (n = 46)	Detailed definition of precipitating factors Delirium measure only every 72 hours
Tuma 2000[104] (n = 140)	Adults with systemic cancer and delirium referred to neurology service for altered mental state Excluded terminal care, and primary brain tumours	Precipitating factors of delirium Prior dementia Age Brain metastases	MMSE	DSM-III-R	n = 48 34%	n = 92 66%	Heterogenous population of cancer patients with some receiving active anticancer treatment Only delirium referred to neurology service, so likely more severe or hyperactive subtype only Data for 40 patients retrospectively collected

Study (n)	Population	Other variables measures	Initial screening	Diagnostic criteria used	Incident delirium	Prevalent delirium (on admission)	Quality considerations
Caraceni 2000[97] (n = 393)	Advanced cancer not receiving chemotherapy referred to palliative care program Solid tumours only	Brain metastases Performance status Gender Prediction of survival Hospitalisation Steroid or progestational treatment Blood transfusion	nil	DSM-III-R CAM	Not studied	n = 109 27.7%	Heterogenous cohort as included in patient and community settings Delirium assessment at one time-point only
Gagnon 2000[96] (n = 89)	Adults with cancer admitted to hospice with life expectancy less than 2 months	Age Gender Primary cancer site Opioid doseDehydration	Confusion rating scale	DSM-III-R CAM	32.8% (21/71 free of delirium on admission)	13.3% (11/83 who could undertake full delirium assessment)	Daily screening for delirium Only patients who screened positive went on to further assessment CRS needs further validation
Sarhill 2001[99] (n = 50)	Consecutive admissions to acute palliative medicine unit	Age Gender Diagnosis Brain metastases	Bedside confusion scale	nil	Not assessed	32% (n = 13)	Bedside confusion scale has limited psychometric testing and is only a screening instrument for delirium
Durkin 2003[98] (n = 224)	AIDS or advanced cancer	Psychiatric diagnoses	nil	ICD-10 criteria	3% (5/181 free of delirium on admission)	19% (n = 43)	Assessment only on admission and twice weekly
Lam 2003[81] (n = 102)	Inpatients in palliative care	Performance status	MMSE – Cantonese version	DSM-IV MDAS	40.2% (n = 33)	58.8% (n = 30/51)	MMSE not specific to screen for delirium

Study (n)	Population	Other variables measures	Initial screening	Diagnostic criteria used	Incident delirium	Prevalent delirium (on admission)	Quality considerations
Spiller 2006[100] Study 1 (n = 110) Study 2 (n = 109)	Study 1 – prospective cohort hospice inpatients Study 2 – 8 palliative care units (2 within general hospitals) point prevalence	Age Gender Performance status Brain metastases Dementia Psychiatric disorder Opioid toxicity Dehydration	MMSE CAM	MDAS DSM-III-R	Study 1 – 7% (5/73) Study 2 – not assessed	Study 1 – 29% (n = 29) Study 2 – 29.4% (n = 32)	No reporting of training of clinician raters in study 1
Fang 2008[82] (n = 457)	Palliative care inpatients	Medications used for delirium treatment		Delirium Rating Scale – Chinese version Psychiatric interview	Not assessed	46.9% (n = 107)	Assessments weekly

CAM – Confusion Assessment Method; CRS – Confusion Rating Scale; DSM – Diagnostic and Statistical Manual; DSM-IV-R – Diagnostic and Statistical Manual of Mental Disorders, fourth edition – revised; ICD – International Classification of Disease; MDAS – Memorial Delirium Assessment Scale; MMSE – Mini-Mental State Examination

1.7 Clinical measurement of delirium

Challenges for measurement of delirium relate to its fluctuating clinical course, progressive change in diagnostic criteria over time, and achieving a balance between instruments that are rapid and easy to administer versus more sophisticated tools requiring trained users.[26] Accurate measurement of delirium has importance epidemiologically (prevalence and incidence, outcomes, and comparisons across populations), clinically (assessment, measuring severity and response to treatment), and for research (pathophysiological correlates and investigation of new treatments).[105]

The instruments can be grouped into those for detection and screening, diagnosis, and evaluating severity of delirium.[26] The existing instruments can be grouped into four categories:

1. measures of cognitive function
2. delirium diagnostic instruments (based on DSM or ICD criteria, and assess for presence of absence of delirium)
3. delirium specific numeric rating scales (likelihood of diagnosis or estimating severity)
4. physiological correlates of delirium.[26 106]

The criteria by which delirium instruments need to be appraised are:

1. nosological system informing its development
2. component(s) of the delirium syndrome each measures;
3. reliability and validity;
4. sensitivity and specificity (positive and negative predictive value);
5. ease of use (time, burden on patient, training required, use by nonclinicians); and
6. population of its intended use.[26 106-108]

A critical issue is that of inter-rater reliability.[109] The three main sources of variance are patient, observer and random error.[109] The sources of patient variance are disease factors (delirium fluctuates) and difficulty in defining components of delirium such as consciousness in a non-arbitrary way.[109] To avoid error due to fluctuation single point interviews may be beneficial, however this risks choice of time point where symptoms are minimal and a diagnosis is not made. More work is needed to determine how crucial is the demonstration of fluctuation as a key discriminator for delirium diagnosis, which would then favour multiple time-points of assessment.[109] A delirium scale must also reliably discriminate delirium from cognitive impairment from other causes (predominantly dementia), so validation cohorts with delirium alone are problematic.[109] The most widely used scales show reasonable psychometric properties, but there still has not been a consensus on the core features that must be measured.[109] Test – retest reliability is difficult to establish due to fluctuation being a key diagnostic criteria.

1.7.1 Clinical measures of cognitive function

Measures of cognitive function assess the cognitive impairment aspect of delirium only, the benefit being they are rapid and accurate, with the downside being they are not specific to delirium.[26 106] Equally, delirium includes many other features apart from cognitive impairment.[26 106] The tests involve the patient responding (verbally or in writing) to mathematical or verbal manipulation tasks, answering direct informational questions, and/or performing tests of psychomotor skill (drawing or copying).[26] Some instruments integrate tests of many of the major cognitive functions–for example Mini-Mental State Examination (MMSE)–whereas others only test psychomotor capability.[26] Many of the psychomotor tasks require intact vision and motor function, both of which may be impaired in delirium.[26] The majority of cognitive tests have been developed and validated for use in dementia, and few have been adequately validated in delirium.[26]

Only cognitive scales with domains relevant to cognitive disturbance seen in delirium, those developed on DSM-IV criteria or those prior to DSM-IV that have been used in a large proportion of studies on delirium have been included (Table 4). The cognitive domains relevant to delirium include attention, concentration, memory, orientation (especially time and day) and possibly also visuo-spatial

function. A tool that contained a highly detailed orientation task (focusing on time of day, date, month, hospital, ward and suburb), and an attentional task such as digit span and memory registration, plus a visuo-spatial task such as clock drawing, would cover these domains.

The predominant role of cognitive testing, based on use in the current literature, is to allow large-scale screening for delirium; however, even for this purpose patients with delirium and only Mild Cognitive Impairment (MCI) may be missed.[26] It has not been clearly documented how commonly delirium in the absence of measurable cognitive impairment occurs, but several authors comment that it is rare in clinical practice.[24] The prevalence of pre-existing cognitive change or other diagnoses causing cognitive impairment also varies depending on the patient population, for example being very prevalent in elderly patients due to multiple causes.[24] This may not be the case in other populations. For example, a study to diagnose delirium in preoperative liver transplantation patients using DSM-III criteria, found pathological MMSE scores (≤24) in 25%, versus 3.6% of non-delirious patients, and hence in this population gave the MMSE a sensitivity of 33.3% and specificity of 96.4%.[110] This has implications for research determining prevalence and incidence, as screening using cognitive testing is often used to recruit the cohort of patients with delirium, and hence mechanisms to decipher the cause of cognitive impairment need to be vigorous. It also could be argued that unless the sensitivity of the cognitive test chosen is high, it is inappropriate for use in screening.

A study to investigate the performance of the MMSE items for predicting delirium in patients with cancer or receiving palliative care studied two cohorts of 290 general medical inpatients (median age 80 years) and 217 cancer inpatients (median age 62 years).[111] These cohorts were derived from two other studies looking at clinical management of delirium and prediction of pain intensity. The MMSE was administered on the day after hospitalisation. Complete MMSE forms were available for 66% (n = 217), and 41 (12%) had one or more items missing (most commonly the final two items that involved writing), and 71 (22%) declined to answer, as they were exhausted or were unable to do so. Stepwise logistic regression was used to identify the items that best discriminated the

diagnosis of delirium, which was defined as a total MMSE score <24.[111] The findings were that a combination of year, date, backward spelling, and copy a design was able to predict the total score.[111] The ICD-10 criteria for delirium diagnosis was used, but not blinded for MMSE status. All patients (n = 127) with MMSE ≤24, and 18% (15/82) of those with MMSE >24, had a diagnosis of delirium by ICD-10 criteria.[111] The age and educational background of patients was not assessed, and inter-rater reliability of MMSE was not assessed.

If cognitive testing is used for diagnostic purposes this will give high sensitivity for delirium, but lower specificity and large numbers of false positives.[26] Cognitive tests usually generate quantifiable scores; however, the severity of cognitive impairment may not correlate with the severity of other features; and dissociated symptomatology has been described with different prominence of cognitive and behavioural components.[26 112-114]

The use of cognitive assessment to investigate cognitive failure in cancer and palliative care populations has been common, and has lead to difficulties in interpreting the early literature in this area.[106] A systematic review by Hjermstad et al identified 22 studies examining cognitive failure and delirium in palliative care.[106] The MMSE was the most frequently used assessment tool (13 studies), with a delirium assessment tool used concurrently in only six of these studies (MDAS in three, and CAM in three).[38-40 94 115-123] The validity and reliability of the MMSE has not been documented in the palliative care setting, and is insensitive to mild cognitive change.[106] The prevalence rates provided by these studies mostly do not relate the figures to the full range of causes of cognitive impairment, and due to difficulty in administering cognitive tools to this patient population, for example with 25% of patients in one study unable to complete the MMSE, may also be under-representative.[106 118]

The Cognitive Test for Delirium[124] has been used in recent studies of delirium in the palliative care setting[70-72 83] to assess five neuropsychological domains – orientation, attention, memory, comprehension and vigilance. It is particularly useful for patients who are unable to speak or write, emphasizing nonverbal (visual and auditory) modalities allowing a cognitive assessment which is specific

for deficits common in delirium to be detected. Interestingly spatial span forwards seems to be able to distinguish between patients with delirium and dementia.[125]

More recently a computerized test (Edinburgh Delirium Test Box) to determine attentional deficits has been developed.[126] This system tests eight novel tasks measuring sustained visual attention, and shows good or excellent accurary in discrimination between delirium and dementia (receiver operating characteriscs area under the curve 0.80-0.94) and delirium and normal cognition (receiver operating characteriscs area under the curve 0.89-0.99).[126] Patients with delirium had marked deficits in sustained visual attention, which were mild or absent in the patients with dementia or normal cognition.[126]

Table 4 Delirium measurement instruments – cognitive testing

Instrument	Description of instrument	Study	Population studied	Method of Delirium diagnosis	Study objectives	Reliability	Validity	Sensitivity and specificity	Ease of use	Strengths and weaknesses
Cognitive Test for Delirium	Designed specifically for delirious patients, especially those who cannot speak. It tests orientation, visual memory, an conceptual reasoning.	Hart 1996[124]	Medical intensive care (n=77)	DSM-IIIR by senior consultant liaison psychiatrist	To test internal consistency, alternate form reliability and ability to discriminate delirium from dementia and acute psychiatric illness	α = 0.87	No patients with delirium ,schizo phrenia or depression were misclassified, but some dementia patients were incorrectly identified in delirium group	Sensitivity 100% Specificity 95% Optimal cut off to discriminate delirium from other disorders score <19	Designed to be brief, focussed on cognitive function and easy to administer	Cannot distinguish delirium from severe dementia in all cases Easy to administer and can be completed in situations were MMSE is difficult to conduct (ICU)
MMSE [127]	11 questions that evaluate: a) orientation to time and space b) memory c) attention and calculation d) language and constructional ability Scores range from 0–30, with 3 cut-off scores: 21–24 – mild impairment,	Folstein 1975[127]	Normal elderly from community, compared with psychiatric inpatients (diagnoses of dementia, depression, and psychiatric diagnoses, with specific criteria)	No delirium in cohort	To determine validity and reliability of a simplified scored form of cognitive mental status examination	Internal consistency: good to excellent α = 0.54–0.96 [26] varied depending on community or inpatient populations, and level of education Test retest reliability: generally good (α = 0.80) low test retest reliability in delirium (0.56), attributed to fluctuation in	Construct validity: Good correlation with other cognitive tests (BOMC and Weschler adult intelligence test), but only moderate correlations with psychomotor tests which measure specific dimensions[26]	Sensitivity of detecting cognitive change ranges from 52–87%, Specificity ranges from 76–82% in elderly and hospital patients[106] False positive rate up to 39%, and false negative 5%[107] In delirious cancer population sensitivity was	Non-clinicians can administer[127 129] Requires verbal and writing skills	Strengths: Simple to administer Normative data good[26] Translated in several languages[108] Weaknesses: Scores vary depending on education level, and English speaking ability[107] Not for use as validation instrument in
		Folstein 1984[131]	One-day prevalence sample and 83 consecutive oncology admissions	MMSE	To determine prevalence and incidence of cognitive impairment in cancer inpatients					

Instrument	Description of instrument	Study	Population studied	Method of Delirium diagnosis	Study objectives	Reliability	Validity	Sensitivity and specificity	Ease of use	Strengths and weaknesses
	11–20 – moderate impairment, 0–10 – severe Adjustments for age and education exist[128]	Anthony 1982[129]	Hospital patients on general medical ward	Psychiatrist standard clinical diagnosis using DSM-III criteria for delirium or dementia	To determine sensitivity and specificity of MMSE in patients not requiring psychiatric intervention, and of varying educational status	symptomatology compared with 0.9 for dementia[129] Inter-rater reliability: no data	Comparison with DRS moderate (r = 0.43)[26]	96% and specificity was lower (38%)[53] Serial MMSE testing more sensitive to deterioration than improvement in cognition, a fall of 2 points on MMSE was associated with 93% sensitivity and 90% specificity of diagnosis of delirium in elderly inpatients[130] A rise of 3 points was associated with 77% sensitivity and 75% specificity of resolution of delirium in elderly inpatients[130]		development of delirium scales (though often has been used for this purpose)[106] False negatives may be higher in patients with subtle cognitive change (right hemispheric lesions, mild or SSD, advanced cancer)[26] Writing and figure drawing may be difficult for delirious patients[108]
		Grassi 2001[53]	105 cancer patients referred for neurological consultation	CAM MDAS MMSE	Validation of Italian version of MDAS and DRS					
		O'Keeffe 2005[130]	Prospective cohort of acute geriatric inpatients	CAM Day 1 and Day 6 MMSE by blinded investigators	To determine the responsiveness of serial MMSE for diagnosis and monitoring of delirium					
MSQ[132]	Ten questions Orientation Remote and short-term memory	Kahn 1960[132]	Geriatric patients	Nil Psychiatrist rating of 'chronic brain syndrome'	To develop brief, objective and quantitative measures of mental functioning related to cerebral impairment	Unknown[26]	MSQ seems to correlate with psychiatrist rating of severity, but no correlations presented	Initial study provided no cut-off scores[132] Using cut-off of three errors – sensitivity of 45% and specificity of	Easy and fast to administer[26] Only requires verbal responses	Strengths: Ease of administration Cognitive screening for moderate to severe dementia[134]

Instrument	Description of instrument	Study	Population studied	Method of Delirium diagnosis	Study objectives	Reliability	Validity	Sensitivity and specificity	Ease of use	Strengths and weaknesses
		Fillen-baum 1980[133]	Random sample of community residents (n = 116), as part of a validity study of questionnaire base mental health assessment	Psychogeriatrician assessment of organic brain syndrome, with no standardised tests	To compare two brief tests of organic brain impairment, the MSQ and short portable MSQ			98%[133]		Weaknesses: Limited areas of cognition tested, but in cognitive domains relevant to delirium[107] Sensitivity for mild delirium low[26 134] Complete psychometric information lacking[26] Normative data lacking[26]
SPMSQ[135] 10 Questions Orientation Memory Attention Calculation		Pfeiffer 1975[135]	Community sample of 995 elderly patients	Clinical diagnosis of organic brain syndrome	Standardisation and validation of SPMSQ	Test retest reliability: r = 0.80[135]	Correlation with MSQ 0.88-0.97, and Weschler adult intelligence scale (r = 0.66)[133] Not adequately validated as a rating of cognitive severity[26]	26–68% sensitivity, and 91–98% specificity, in a variety of community and hospital populations with varying prevalence of cognitive disorders[107]	Quick and simple to use[26] Requires verbal and mathemat-ical ability[107]	Strengths: Quick and simple to us Weaknesses: Low sensitivity[107] Limited areas of cognition tested, but in cognitive domains relevant to delirium[107] Not sensitive for mild cognitive impairment[26]
		Wolber 1984[136]	Geriatric inpatients consecutive prospective cohort	Clinical diagnosis of organic brain syndrome	To further delineate psychometric properties of SPMSQ					
		Kaufman 1979[137]	Prospective cohort of 59 neurology inpatients	Clinical diagnosis of delirium, with no criteria given	To evaluate the CCSE as a screening device and to ascertain its validity in neurology patients					

α = Cronbach's alpha which measures internal consistency, a statistic calculated from the pairwise correlations between items. Internal consistency ranges between zero and one.
r = correlation coefficient
BOMC – Blessed Orientation Memory Concentration Cognitive Assessment; CAM – Confusion Assessment Method; DRS – Delirium Rating Scale; MDAS – Memorial Delirium Assessment Scale; MMSE – Mini-Mental State Examination; MSQ – Mental status questionnaire; SPMSQ – Short Portable Mental Status Questionnaire; SSD – subsyndromal delirium

1.7.2 Clinical delirium diagnostic instruments

DSM criteria have been accepted as the gold standard to assess and define delirium, and as described previously, have evolved over time.[26] Delirium diagnostic instruments have attempted to operationalise the DSM criteria.[26] The simplest operationalisation is individual clinician subjective judgment and interpretation of the DSM criteria from the clinical presentation, but a systematic methodology has been needed for research purposes and has also been utilised in clinical practice.[26] These delirium diagnostic instruments and the studies assessing their psychometric properties are outlined in Table 5. Some challenges of these scales include the inclusion of items assessing memory which will also be impaired in dementia, perceptual disturbance assessment is heavily reliant on the patient articulating this experience, and DRS-R98 does not include an item assessing level of arousal which is a core feature of delirium.

Delirium numeric rating scales generate a quantitative rating based on behavioural symptoms and cognitive impairment.[26] This quantitative score has been variably considered as a severity rating or alternatively reflects the degree of confidence in the delirium diagnosis; with most of these tools mixing these two concepts in their development.[26] As severity instruments, the difficulty in interpreting these data is the absence of an established gold standard for rating delirium severity against which to validate these tools, as the DSM and ICD criteria do not include a severity rating.[26] The majority of these tools were developed prior to DSM-III-R criteria and aim to identify confusion rather than delirium, and have limited psychometric testing, with the exception of the DRS and the MDAS.[26] The psychometric properties of these two instruments are outlined in more detail below. The complete range of delirium numeric rating scales are outlined in Table 6.

1.7.2.1 Memorial Delirium Assessment Scale

The MDAS is a brief, valid and reliable tool for assessing delirium severity in advanced cancer patients, and is easy to use for repeated assessment.[39 40] The MDAS was developed to be consistent with DSM-IV criteria, and its psychometric properties are summarised in Table 6.[40] Using a cut-off score of 13 in the initial population (n = 30) including AIDS and cancer patients it shows a

sensitivity of 70.6% and a specificity of 93.7% for discriminating delirious from non-delirious patients; a cut-off of 10 produces a sensitivity of 82.35% and a specificity of 75%.[40] A further study tested the psychometric properties of MDAS in 104 palliative care inpatients and found a cut-off score of 7 gave sensitivity of 98% and specificity of 96% and cut-off over 9 gave sensitivity of 88% and specificity of 99%.[39] Another study in 296 cardiac surgery patients demonstrated a cut-off score of 10 was most consistent with ICD-10 or DSM-IV-R criteria for delirium with 96.7% sensitivity and 95.7% specificity.[138] Internal consistency using Cronbach alpha coefficient was 0.9.[40] Inter-rater reliability varies depending on scale item, with an intra-class correlation coefficient r = 1 for disorientation and impaired digit span, and lowest for reduced attention (r = 0.69).[39] Five out of 10 MDAS items have inter-rater correlation coefficients above 0.8, and eight are above 0.7.[40] MDAS showed high correlation with another well-established delirium measure–the DRS, r = 0.88, $p < 0.0001$).[139] A study in 122 hip-fracture patients compared MDAS against CAM defined delirium.[76] The best cutoff value for average MDAS was a score of 5, yielding a sensitivity of 87% and specificity of 86% for delirium ($p < 0.001$). The best cut-off value for a maximum MDAS score was 9, yielding a sensitivity of 88% and specificity of 91% for delirium ($p < 0.001$). Validated Italian and Japanese versions are available for use in non-English speaking background patients.[140] [141] It is a continuous severity measure, and hence can identify SSD, which also has been associated with poorer outcomes.[76]

1.7.2.2 Delirium Rating Scale and Delirium Rating Scale – Revised-98

The DRS was developed from DSM-III criteria. It is a 10-item scale, originally developed with intention for use by clinicians with psychiatric training. Each item has a score from zero to four points, giving a maximum score of 32 points and a total score of 12 or above consistent with diagnosis of delirium. Using a cut-off point of 10, sensitivity was 0.82 and specificity 0.94. In contrast using a cut-off point of 8, sensitivity was higher (0.9) but specificity lower (0.82). A study comparing the DRS and CAM in 94 elderly patients, using a cut-off point of 12 on the DRS, found a high level of agreement with CAM—Cohen's kappa statistic (κ) = 0.777).[142]

The DRS was revised to address its inability to distinguish hypoactive and hyperactive delirium, add a scoring item for disturbance of attention and to provide clarity for the 'clouding of consciousness' item.[64] The new scale is called the DRS-R98, and is a 16-clinician-rated-item scale, with three items for diagnosis and 13 items scoring severity. DRS-R98 can distinguish delirium from dementia, schizophrenia and depression. Optimal cut-off points are 15.25 (sensitivity 0.92 and specificity 0.86) or 17.75 (sensitivity 0.92 and specificity 0.95). DRS-R98 correlates with DRS (Pearson's r = 0.83). Inter-rater reliability is good (α = 0.87) and internal consistency. These psychometric properties have been confirmed in subsequent studies, including Dutch and Spanish versions.[143-146] Test – retest reliability has been recently established in two longitudinal cohorts assessed with DRS-R98: 1) palliative care inpatients who were assessed twice a week for delirium (n=100), and 2) cohort post hip fracture (n=192) assessed daily until the eleventh post operative day.[147]

Using multivariate modelling techniques which can be applied to delirium which has by definition fluctuation in illness severity and highly variable duration of each episodes, demonstrated the overall reliability coefficient ($R_{\Lambda)}$ values ranged from 0.92 to 0.99, and estimate reliability coefficient ($R_{T)}$ values (average estimate for a single administration based on the analysis of data from multiple time points) ranged from 0.75 and 0.84 for the two datasets.[147] This confirms the DRS-R98 performs well to assess delirium phenomenology longitudinally over time.[147]

Table 5 Delirium diagnostic instruments

Instrument	Description of instrument	Study	Population studied	Delirium diagnosis	Study objectives	Reliability	Validity	Sensitivity and specificity	Ease of use	Strengths and weaknesses
CAM[148]	9 operationalised criteria of DSM III, with an algorithm of 4 criteria rated subjectively to establish diagnosis, based on symptoms manifested in the interview only An Adapted CAM has been developed for DSM IV criteria[149]	Inouye 1990[148 150]	56 general medical inpatients and geriatric outpatients, with and without delirium	Psychiatrist DSM III-R assessment (blinded evaluation) MMSE	To develop and validate a standardised CAM that enables non-psychiatric clinicians to detect delirium quickly in high-risk settings	Inter-rater reliability: Excellent (κ=0.81-1.0)[148] Coefficient of agreement between trained non-physician rater and geriatrician 0.91[151] Test re-test reliability: not tested	Convergent validity: Good as compared with cut-off scores of MMSE (κ= 0.64) Global accessibility rating (κ= 0.82), and the digit span (κ= 0.59) CAM adapted for DSM IV inter-rater reliability high (κ= 0.89), and convergent validity MMSE (r=0.84) and DRS (r=0.78)[149]	94-100% sensitivity and 90-95% specificity[148 152-154] 91–94% positive predictive value, 90–100% negative predictive value[148 152-154] CAM compared to DSM IV criteria had sensitivity of 81%, and specificity 84%[155] Positive predictive value was 76%, and negative predictive value 87%[155] CAM adapted for DSM IV sensitivity 90%, specificity 100%, positive predictive accuracy 100%, negative predictive accuracy 97%[149] In palliative care settings	Ease of administration (5 minutes)[26] Can be administered by trained non-clinicians[26] Method of training not specified in literature[26]	Strengths: Excellent psychometric properties Weaknesses: No value for assessing severity[26] Developed from DSM III criteria, and needs testing against DSM IV, with one initial study showing good psychometric properties if adapted for DSM IV[149] Well-trained evaluators needed
		Monette 2001[151]	110 elderly patients ≥ 66 years	CAM by lay interviewer and geriatrician, in emergency department independently	To compare results of CAM by lay interviewer and geriatrician, used as screening in emergency department					
		Laurila 2002[155]	Prospective cohort of acute geriatric inpatients	DSM III DSM IIIR DSM IV ICD-10 (independently and blinded to CAM status)	To compare sensitivity of CAM against operationalised criteria of DSM III, DSM IIIR, DSM IV and ICD-10					
		Gonzalez 2004[149]	153 elderly medical inpatients	DSM IV MMSE DRS	To test psychometric properties of adaptation of CAM based on DSM IV criteria					

Instrument	Description of instrument	Study	Population studied	Delirium diagnosis	Study objectives	Reliability	Validity	Sensitivity and specificity	Ease of use	Strengths and weaknesses
		Ryan 2009[156]	Palliative care inpatients (n = 106)	DRS-R98 CTD MDAS DSM IV (blinded to CAM status)	To determine the sensitivity and specificity of CAM administered by non-specialist hospital doctors in the palliative inpatient setting			sensitivity 0.88 (0.62-0.98) and specificity 1.0 (0.8-1.0) with training		
CAM-ICU	Uses non-verbal tasks, yes/no answers and simple commands to rate features of CAM algorithm Less detailed assessment is required in some domains than CAM[157]	Ely 2001[158 159]	Medical ICU patients	DSM IV diagnosis by delirium expert (geriatric psychiatry specialist)	To develop and validate an instrument for use in the ICU to accurately diagnose delirium in the critically ill	Inter-rater reliability: high between anaesthetist and nurse assessors (κ=0.79-0.95)		95–100% sensitivity and 89–93% specificity compared to DSM IV critieria[158 159] Compared to CAM sensitivity was 735 and specificity 100%[157]	Easy to use in ICU situation	Strengths: Good psychometric properties Weaknesses: CAM is more sensitive and may detect mild delirium better than CAM ICU
		McNicoll 2005[157]	Medical ICU patients	CAM MMSE	To compare CAM and CAM-ICU for detecting delirium in alert nonintubated older ICU patients					
DSI	7 domains (present/ absent format) using DSM III criteria[26] Departs from DSM III criteria by having 3 key symptoms: disorientation, perceptual disturbance, and disturbance of consciousness	Albert 1992[23] Levkoff 1992 and Liptzin 1991[27 160]	Hospitalised elderly medical or surgical inpatients	Physician assessment of three key symptoms: disorientation, perceptual disturbance, and disturbance of consciousness. (blinded to DSI status)	To develop a structured interview with clear operational criteria that could be used to define cases of delirium	Inter-rater reliability: excellent (κ=0.9)[23] Internal consistency reliability: α= 0.80 to 0.45[23]	Agreement on the presence of at least one symptom, comparing with physician diagnoses was excellent (κ=0.93)[23]	Sensitivity 90%, specificity 80%, positive predictive value 0.87, negative predictive value 0.84[23]	Long (at least 15 minutes) and difficult to administer, even after rater training[26] Can be administered by lay interviewers[26]	Strengths: Normative data and validity excellent Weaknesses: Large quantity of data for analysis is cumbersome even for research purposes

α = Cronbach's alpha which measures internal consistency, a statistic calculated from the pairwise correlations between items. Internal consistency ranges between zero and one, r = correlation coefficient

κ = Cohen's kappa statistic, which measures inter-rate agreement and takes into account agreement occurring by chance alone, CAM – Confusion Assessment Method; CAM-ICU – Confusion Assessment Method – Intensive Care Unit; CRS – Confusion Rating Scale; CTD – Cognitive Test for Delirium; DRS – Delirium Rating Scale; DRS-R98 – Delirium Rating Scale-Revised 1998; DSI – Delirium Symptom Interview; ICU – intensive care unit; MDAS – Memorial Delirium Assessment Scale; MMSE – Mini-Mental State Examination; NuDesc - Nursing Delirium Screening Scale

Table 6 Delirium numeric rating scales

Instrument	Description of instrument	Study (s)	Population studied	Delirium diagnosis	Study objectives	Reliability	Validity	Sensitivity and specificity	Ease of use	Strengths and weaknesses
Confusion rating scale[161]	4 domains: disorientation, communication, behaviour and delusions/hallucinate-ions Total scores 0 to 8 Does not include clouding of consciousness included in DSM III diagnosis of delirium	Williams 1986[161]	169 patients admitted for hip-fracture surgery	No delirium diagnosis, compared with SPMSQ	To develop a tool for nurses to detect confusion	Not known	78% agreement with independent SPMSQ ratings Moderate correlation with SPMSQ scores as indicator of 'severity' (r=0.22–0.51)	Not known	Fast Needs trained raters who know the patients	Strengths: Screening tool Used by nurses on ward, as a guide of what to look for to assess mental status Weaknesses: Psychometric properties unknown[26] Not a rating of severity, and compared with SPMSQ which also does not indicate severity[26]
NEECHAM confusion scale[162]	9 scaled items, with 3 subscales of assessment. Scores range from 30 (normal) to 8 (extreme confusion). Cut offs: 0–19 (acute confusion), 20–24 (mild confusion); 25–26 (not confused but high risk); 27–30 (normal). Domains are 1) alertness/attentiveness 2) sensory motor behaviour 3) stability of vital functions (arterial pressure, oxygenation, continence)	Champagne 1987 and Neelon 1996[162-164]	Two samples of elderly hospitalised patients with acute medical illness (n = 168 and 258).	DSM III criteria by trained research nurse (not clear if blinded)	To assess psychometric properties of NEECHAM confusion scale	Internal consistency: Good (α=0.90) Test re-test reliability: High (α=0.91). Inter-rater reliability: High (r=0.91) for trained research nurses	Modest correlation with nurse ratings of severity of confusion (r=0.46) and self-report (r = 0.4).Good correlation with MMSE (r = 0.75).	Cut-off score of 25 or less had sensitivity of 95% and specificity of 78% of DSM III diagnoses of delirium	Intended for nurses to administer but long and requires measurement of physical parameters (e.g. oxygen saturations) [26]	Strengths: Repeatable at frequent intervals[26] Minimal response form patients required[26] Interesting in its use of physiological parameters, hypothesised as early indicators of confusion or risk, to allow early intervention Weaknesses: Inclusion of physiological parameters causes problem with face validity[26]

Instrument	Description of instrument	Study (s)	Population studied	Delirium diagnosis	Study objectives	Reliability	Validity	Sensitivity and specificity	Ease of use	Strengths and weaknesses
D-scale[165]	58 items, each scored on a 4-point scale Assesses cognition, affect and behaviour in medically ill bedridden patients	Lowy 1973[165]	65 medical inpatients	No patients had clinically diagnosed organic brain syndrome	To determine preliminary norms for a variety of cognitive function tests in general medical inpatients, suitable to use for assessment of organic brain syndrome	No data	Excellent correlation with MMSE (r =–0.83)	No data	Trained rater Long and difficult to administer[26] Only 46 out of 70 undergoing MMSE could complete D scale[26]. Has been used in one series of terminally ill cancer patients[166]	Strengths: In-depth detail for the domains Weaknesses: Long and difficult to administer Psychometric information unknown
Global accessibility rating[127 167]	Simple visual analogue scale, rating degree of consciousness (published originally with MMSE) Rater's judgement of inability to sustain attention	Anthony 1985[167]	Hospitalised medical patients	Psychiatrist clinical diagnosis Using DSM III	To evaluate the global accessibility rating for screening for delirium in general medical ward patients	Test retest reliability was tested on consecutive days (r = 0.79).	Coefficient of agreement to MMSE low (κ=0.39)	Cut-off score of 80% of scales length had 90% sensitivity and 95% specificity compared with psychiatrist diagnosis[26] False positive ratio 31% and false negative 1%[26]	Simplicity is attractive, but requires training for raters	Strengths: Simplicity Weaknesses: Psychometric properties unknown. Does not address hyperactive delirium where state of consciousness is hyperalert[26] Does not differentiate simple sedation from intensity of delirium[26]
DRS[168 169] and DRS-R-98[170]	DRS: 10-item numeric rating scale integrating DSM III criteria, scoring from 0 to 3, or 0 to 4) with domains temporal onset, perceptual disturbance, hallucinations, delusions, psychomotor behaviour, cognitive	Trzepacz 1988[168]	20 delirious patients referred to consult liaison psychiatry. Control groups: 18 schizo-phrenia and dementia patients; 9 medically ill referred for	DSM III criteria and DRS one occasion by psychiatrist responsible for their clinical care	To develop a criterion based symptom rating scale and to determine its preliminary validity	Inter-rater reliability between two psychiatrists excellent (0.97) Internal consistency not tested, so unclear if all ten items required Internal consistency of	Not tested in terms of severity As diagnostic instrument missing intems essential in DSM III diagnosis (inattention and disorganised thinking)[26]	Cut-off score of 10 has sensitivity of 94% and specificity of 82%[171] No overlap in distribution of scores between delirium group and controls is	Instructions for scoring not clear	Strengths: Potential to measure severity but needs further assessment[172] Weaknesses: Psychometric properties not fully defined

Instrument	Description of instrument	Study (s)	Population studied	Delirium diagnosis	Study objectives	Reliability	Validity	Sensitivity and specificity	Ease of use	Strengths and weaknesses
	status, physical disorder, sleep wake cycle, mood lability, variability of symptoms		psychiatric disorders other than cognitive impairment or psychosis			Italian version (α=0.7)[53]	Correlation with MMSE low (r = –0.43)	a validation of diagnostic specificity rather than severity[26]		
	DRS-R-98: Revision includes two sections: 3 diagnostic items, and a 13-item severity scale, to grade symptom intensity	Trzepacz 2001[170]	5 comparison groups (delirious, dementia, schizophrenic, depressed and other psychiatric diagnoses) from medical, surgical inpatients and nursing home patients[170]	DSM IV criteria by psychiatrist Blinded to DRS results[170]	To establish validity and reliability of DRS-R-98, which was aimed to overcome shortcomings of DRS[170]	Internal consistency: α=0.87 for total scale, and α=0.87 for severity scale[170] Inter-rater reliability: Intraclass correlation coefficient 0.98 for total scale, and 0.99 for severity scale[170]	DRS-R-98 correlated with DRS (r=0.83) Correlation with CTD r = 0.62)[170] Ratings post treatment when no longer DSM IV defined delirium DRS-R-98 severity scale improved (mean 21.5 $\pm$ 5.6 to 5.2 $\pm$ 3.5 ($p < 0.001$)[170]	Cut-off scores for DRS-R-98 total score of 15.25 and 17.25 resulted in same sensitivity (92%), but higher cut-off had higher specificity (95%)[170] The best cut-off for severity scale was 15.25 with 92% sensitivity and 93% specificity[170]	Rater judgement may still be required for scoring Clear text to assist rating is provided	Strengths: Psychometric properties clearly described Demonstrated scores ability to show response to treatment and delirium resolution Weaknesses: Rater judgement may still be required for scoring
DI[173]	Direct observation of 7 symptoms of delirium adapted from CAM (attention, disorganised thinking, level of consciousness, memory, perceptual disturbance, motor disturbance), designed to be used in conjunction with MMSE Each item is rated 0–3	McCusker 1998[173]	Prospective cohort of medical admission ≥ 65 years	CAM (blinded to DI result)	To assess psychometric properties of DI	Inter-rater reliability: 0.88 between psychiatrists and research assistants, and 0.78 between research assistants[173] Internal consistency: α=0.74	Correlation with DRS r=0.84[173] Correlation with MMSE depends on if delirium, dementia or both (r = –0.79, –0.79, and –0.83 respectively [174] Low to good levels of external		Takes 5 to 10 minutes to perform, and can be administered by nurses and research assistants	Strengths: CAM assessment blinded to DI result. Inter-rater reliability tested Formal assessment of prior cognitive impairment Weaknesses: test retest reliability not evaluated
		McCusker 2004[174]	Prospective cohort of medical admission ≥ 65 years, with delirium, dementia or both	CAM (blinded to DI result)	To assess reliability, validity and responsiveness of an instrument to measure delirium severity					

Instrument	Description of instrument	Study (s)	Population studied	Delirium diagnosis	Study objectives	Reliability	Validity	Sensitivity and specificity	Ease of use	Strengths and weaknesses
	(absent to severe)						responsive-ness[174] Internal responsive-ness at 8 weeks follow-up, effect sizes were –0.6 and –0.74 for delirious patients with or without dementia, and the standardised response mean for both groups was –0.64			
MDAS[40]	10-item, 4-point observer rated scale, integrating cognitive and behavioural symptomatology derived from DSM IIIR and IV criteria	Breitbart 1997[40]	2 studies 1) 33 AIDS patients referred to psychiatry service, 2) 51 hospitalised delirious patients with cancer or AIDS	DSM III and DSM IV proposed criteria for delirium, dementia and psychiatric disorders by psychiatrist independently	To assess reliability and validity of a new measure of delirium in cancer and AIDS patients	Inter-rater reliability: α=0.92 (range from 0.64–0.99 for individual items) Internal consistency: α=0.91	Positive correlation with clinician rated delirium severity (r = 0.89)[40 76] Correlation with DRS high (r = 0.88) and MMSE (r = 0.91)	Using cut off of 13 sensitivity 70.6%, and specificity of 93.7% to distinguish delirious versus non-delirious cancer patients 1997[40]	Designed for use by experienced mental health professionals with limited training Requires 10 minutes for completion In the setting of severe delirium, profound fatigue and dyspnoea prorating of scores may be necessary in approximately 20%[39] Initial study states MDAS permits repeated	Strengths: Items derived from newer DSM criteria Ability to prorate scores is useful in clinical scenario of advanced cancer[39] May be useful as a diagnostic and severity tool Weaknesses: Prorating items may be detrimental in research setting as may introduce error/bias[39] Initial study may have been more severe delirium due to
		Lawlor 2000[39]	104 consecutive admissions to acute palliative care unit	DSM IV defined delirium (not blinded to MDAS status)	To further delineate psychometric properties of MDAS in cancer population	High level of correlation within the 2 factors identified (cognitive and neuro-behavioural (α=0.78)	Moderate Correlation with MMSE (r = –0.55) (but MMSE not conducted at same time as MDAS)[39]	A cut-off of 7 had sensitivity of 98% and specificity of 96%		

Instrument	Description of instrument	Study (s)	Population studied	Delirium diagnosis	Study objectives	Reliability	Validity	Sensitivity and specificity	Ease of use	Strengths and weaknesses
						Correlations among the scale items ranged from moderate to low (r=0.68-0.02) Inter-rater reliability: Highest for disorientation and impaired digit span item (r = 1.0) and lowest for reduced attention (r = 0.69) Percentage agreement on psychomotor classification was high (93 .8%)			administration with 24 hours[40]	referral to psychiatry service as recruitment strategy[40] MDAS may miss mild delirium Factor structure may relate to patho-physiological model (attention/arousal versus positive phenomena of altered perception)[53]
		Grassi[53]	105 consecutive cancer patients referred for psychiatric or neurological consultation	CAM DRS MDAS Italian versions	To validate the Italian versions of DRS and MDAS	Inter-rater reliability: not tested Internal consistency: α=0.89[53] Item-total correlation for the ten items ranged from 0.43 (item 7) to 0.82 (item 1)	Correlation with DRS (r = 0.76) and MMSE (r = –0.88) 2-factor structure identified (attention/arousal and perception and positive/psychotic phenomena)	Cut-off of 13 had sensitivity of 68% and specificity of 94%, with positive and negative predictive value of 95% and 63% respectively		

Instrument	Description of instrument	Study (s)	Population studied	Delirium diagnosis	Study objectives	Reliability	Validity	Sensitivity and specificity	Ease of use	Strengths and weaknesses
NuDesc	5-item scale, which includes 4 items of CRS plus a fifth item rating psychomotor retardation all rated from 0–2, with maximum score 10.	Gaudreau 2005[78]	146 prospective consecutive cohort of internal medicine and haematology oncology inpatients	CAM (blinded) CRS MDAS DSM IV criteria by both research nurses and psychiatrists	To test the psychometric properties of a simple continuous delirium assessment instrument	Interrater reliability: For the CAM assessment used for comparison between research nurse psychiatrists κ = 0.89	Face validity rated by specialist palliative care clinicians with experience in delirium Correlated with MDAS (r = 0.67), and DSM IV (r= 0.71)	Sensitivity 85.7% and specificity 86.8% with cut-off >1	Designed for repeated measures at each nursing shift Does not require patient participation Adapted to monitor the fluctuating symptoms of delriium	Strengths: Brief measure that can be repeated at each nursing shift. Weaknesses: Interrater reliability not assessed for NuDesc
		Radtke 2008 [175]	Recover room patient (n=154)	DSM IV	To identify a valid and easy to use test for early screening of delirium in the recovery room: comparing Confusion Assessment Method, Delirium Detection Score, Nursing Delirium Screening Scale	Not applicable	Not applicable	Sensitivity and specificity were 0.43 and 0.98 for the CAM, 0.14 and 0.99 for the DDS, and 0.95 and 0.87 for the Nu-Desc, respectively.		NuDesc was the most sensitive test

Instrument	Description of instrument	Study (s)	Population studied	Delirium diagnosis	Study objectives	Reliability	Validity	Sensitivity and specificity	Ease of use	Strengths and weaknesses
		Luetz 2010 [176]	Intensive care (n=156)	DSM IV	To identify a valid and easy to use test for early screening of delirium in the ICU: comparing Confusion Assessment Method, Delirium Detection Score, Nursing Delirium Screening Scale	interrater reliability for the CAM-ICU (kappa = 0.89) and for DDS and Nu-DESC (kappa = 0.79, 0.68).	Not applicable	The specificity of the CAM-ICU was significantly higher than that of the Nu-Desc (96% vs. 81%, p < 0.01). DDS showed poor sensitivity (30%), whereas the specificity was significantly higher compared with the Nu-DESC (DDS, 91%; Nu-DESC, 81%, p <0 .05).		CAM-ICU was the most sensitive

α = Cronbach's alpha which measures internal consistency, a statistic calculated from the pairwise correlations between items. Internal consistency ranges between zero and one.
r = correlation coefficient
κ = Cohen's kappa statistic, which measures inter-rate agreement and takes into account agreement occurring by chance alone.
CAM – Confusion Assessment Method; CTD – Cognitive Test for Delirium; D-Scale - Delirium Scale; DRS – Delirium Rating Scale; DRS-R98 – Delirium Rating Scale – Revised 1998; DI – Delirium Index; MDAS – Memorial Delirium Assessment Scale; MMSE – Mini-Mental State Examination; NuDesc – Nursing Delirium Screening Scale; SPMSQ – Short Portable Mental Status Questionnaire

1.7.3 Pain assessment in the delirious patient

Another area of assessment is considering how to assess pain and other symptoms in the patient with delirium, posing significant challenges in clinical practice. Given the overlapping features seen in the person in pain with delirium assessment is particularly difficult, and there is a lack of specific pain assessment tools for use in delirium. The current tools for pain assessment in those with cognitive impairment have been developed for use in dementia or chronic cognitive impairment and rely on behavioural, verbal, facial and/or physiological domains, all of which may be abnormal in delirium.[177 178] Strategies suggested include using a pain assessment tool designed for use in cognitive impairment and a delirium assessment scale; however, as discussed below there is considerable overlap in items that can be abnormal due to both pain and delirium.[179] Consideration of clinical conditions that may be more likely to cause either delirium or pain may aid in determining the most likely cause of the behavioural, facial or physiological cues seen. For example, known painful metastatic site, new onset joint swelling or past history of unstable angina may be precipitants of pain; whereas in someone with a urinary tract infection or where a psychoactive medication has been recently started, delirium may be more likely.

In cognitively impaired long-term care residents (n = 124) six observational pain measures were investigated in relation to their ability to measure pain in known painful situations when the delirium-related items agitation, restlessness, increased mental confusion, fear and anxiety, calling out, changes in sleep, and incoherent language were eliminated.[177] The six measures were the Assessment of Discomfort in Dementia protocol (ADD); the Checklist of Nonverbal Pain Indicators (CNPI); the Non-Communicative Patients' Pain Assessment Instrument (NOPPAIN); the Pain Assessment for the Dementing Elderly scale (PADE); Pain Assessment in Advanced Dementia (PAINAD); and the Pain Assessment Checklist for Seniors with Limited Ability to Communicate (PACSLAC). The number of items that needed to be deleted varied between the scales: four out of five for ADD (80% of total items), one of six for CNPI (16%), one of eight for NOPPAIN (12%), 22 of 60 for PACSLAC (37%), four of 14 for PADE (28%), and three of 15 for PAINAD (40%).[177] The participants were video recorded for three pain

conditions—baseline, during influenza vaccination and during movement-exacerbated pain.[177] All the measures were able to differentiate between pain and baseline states, and when items that overlap with delirium were not included the measures' ability to identify pain persisted (apart from ADD).[177] The scales that have the least number of overlap (CNPI and NOPPAIN), based on current evidence, may be the better choice when assessing pain in the delirious patient.

1.8 Risk factors and precipitants

Utilising STROBE criteria, five low to moderate quality studies[180] (Table 7) evaluated risk factors in cancer and haematological malignancies in the inpatient setting.[181] Over a 10-week period 26 out of 145 patients developed CAM-defined delirium.[181] Factors significantly associated with delirium occurrence in multivariate analyses in these various studies are advanced age, cognitive impairment, low albumin level, high blood urea nitrogen (BUN), high alkaline phosphatase, bone metastases, and presence of haematological malignancy, liver metastases, prior episode of delirium, opioids, corticosteroids and benzodiazepines.[181] Gaudreau[182 183] and Fann[184] provide initial insights into the role of psychoactive medications and delirium in the setting of malignancy, and these data are associated with the highest increase in risk. The other risk factors show only weak to moderate associations. Sections 1.8.1 and 1.8.2 provide a more detailed overview of the literature on the contribution of psychoactive medication.

The limitations of the study by Ljubisavljevic et al include the skew of population with people who had haematological malignancies, and that 82% were receiving cytotoxic chemotherapy indicating a more acute oncology setting.[181] This study also had a very small number of delirium episodes ('events') and utilised a large number of variables in the multivariate analysis so may have been underpowered.[181] Its strengths include use of daily assessment with validated delirium assessment tools, prospective design and the risk factors were chosen for appropriateness in the clinical setting.[181] The discriminant coefficients the variables of interest were -0.57 for older age, 0.41 for haematological malignancy, 0.41 for CNS involvement and 0.57 for bone metastases suggesting low to moderate predictive value. Tuma et al[104] only had a cohort with delirium and hence was only able to demonstrate associations, rather than undertake analyses to

determine contribution of pre-existing factors to delirium occurrence. The study by Fann et al[184] is in a population also with haematological malignancy undergoing haematopoetic stem cell transplant (HSCT), so also not directly comparable to the palliative population. However, there are some methodological strengths which deserve consideration as they can inform future studies. Current and past pain scores were included in the modelling, as opioid dose may be reflective on past, not current, pain scores. The statistical model also could account for time carrying covariates. Interesting, opioid dose (independent of pain intensity) was a stronger predictor of delirium onset, whereas pain contributed to severity of symptoms. Opioids are included in the anticholinergic scale used, so lack of significance may be due to omission of the opioids from the total score. The authors discuss the clinical implications of a balance of adequate pain control and avoidance of overuse of opioids. The methodological strengths of the study by Gaudreau et al[182] included that the assessment of medication exposure was done by research nurses blinded to delirium status, and the model of using time dependent covariates with cumulative daily doses accounted for. The model was not able to determine to what extent the effect was due to drug combinations being received rather than the individual agents alone.

In summary, advanced age, cognitive impairment, low albumin level, high blood urea nitrogen (BUN), high alkaline phosphatase, bone metastases, and presence of haematological malignancy, liver metastases, prior episode of delirium, opioids, corticosteroids and benzodiazepines have been associated with increased risk of delirium in cancer patients with solid tumours and haematological malignancies. The studies however were of variable methodological quality, and there were not comparable variables explored between the studies to confirm these associations in more than one study cohort.

Table 7 Studies exploring risk factors for delirium in cancer and palliative populations

Study	Population	Delirium assessment and rate	Type of analysis	Variables explored	Results
Tuma 2000[104]	140 patients with non-CNS cancers and delirium	DSM-III-R defined delirium by neurologist assessment	Stepwise forward logistic regression	Chemotherapy Brain irradiation CNS metastases	Chemotherapy and brain irradiation associated with worsening mental status over time in univariate analyses In multivariate analyses were not associated with persistent delirium mortality
Ljubisavljevic 2003[185]	113 oncology inpatients over 145 admissions 57% with haematological malignancies and 82% were receiving cytotoxic chemotherapy	CAM daily followed by structured clinical interview for DSM-IV criteria if positive 26 patients developed delirium (18%) delirium risk assessment on admission	Multivariate, using discriminant factor analysis	Gender CNS tumour Bone metastases Prior confusional state Alcohol abuse Corticosteroid use Cytotoxic chemotherapy Dehydration Sensory impairment Abnormal liver function Abnormal calcium Diagnosis (haematological versus other malignancies)	On multivariate analysis factors associated with delirium development were advanced age, cognitive impairment, haematological malignancy, low albumin and bone metastases The effect of bone metastases seems to be independent of presence or not of hypercalcaemia
Gaudreau 2005[182]	261 cancer inpatients in acute care setting over 28 days	Nu-desc	Cox regression models with time-dependent covariates to determine association of psychoactive medication variables with risk of delirium	Age Gender Primary cancer site Presence of metastases (surrogate marker of illness severity) Delirium on prior admission Dementia Benzodiazepines (oral lorazepam equivalents)	Prior history of delirium, liver metastases, benzodiazepines, corticosteroids and opioids were significant predictors of delirium in multivariate analyses Adjusted (for history of prior delirium and liver metastases) hazard ratios were 2.04 for >cumulative daily dose of oral lorazepam equivalents 2mg (p = 0.04), 2.67 for >cumulative daily dose of oral dexamethasone equivalents 15mg (p = 0.02) and 2.35 for

Study	Population	Delirium assessment and rate	Type of analysis	Variables explored	Results
			Cut-offs for medication cumulative daily equivalents were obtained by looking at distribution of doses in study population and using lower quartile or tertile as cut-off This gave dichotomous cut-offs of oral lorazepam equivalents 2mg, oral dexamethasone equivalents 15mg and subcutaneous morphine equivalents of 90mg	Corticosteroids (oral dexamethasone equivalents) Opioids (subcutaneous morphine equivalents) Anticholinergic agents (present or absent from list of 23 medications)	>cumulative daily dose of subcutaneous morphine equivalents of 90mg (p = 0.03)
Gaudreau 2007[183]	114 oncology inpatients in acute care	Nu-desc	GEE ORs representing risk of delirium were computed for each day of follow-up	Age Gender Primary cancer site Presence of metastases (surrogate marker of illness severity) Delirium on prior admission Dementia Benzodiazepines (oral lorazepam equivalents) Corticosteroids (oral dexamethasone equivalents) Opioids (subcutaneous morphine equivalents)	Daily risk of delirium was higher on any day of follow-up in patients exposed to greater than 90mg or subcutaneous morphine equivalent, after adjusting for corticosteroid, benzodiazepine and antipsychotic exposure (OR 1.37, p = 0.0033)

Study	Population	Delirium assessment and rate	Type of analysis	Variables explored	Results
				Antipsychotics (Oral haloperidol equivalents) Uncontrolled pain	
Fann 2011[184]	90 patients undergoing Myeloablative haematopoietic stem cell transplant	Delirium rating scale daily 45 (50%) experienced delirium.	Multivariate analysis using cox proportional hazards regression Current and lagged pain scores were included to account for acute and delayed effects of pain, and correlation between lagged pain and opioid use	Pre-transplantation variables: age, gender, executive functioning (Trail making B test with higher scores meaning less impairment), disease stage, donor cell type, mean alkaline phosphatase (one week prior), BUN (one week prior), and physical function (medical outcomes study – 12-item short form with higher scores meaning better function) Post transplantation variables: current and past mean pain score (on 0 to 10 verbal rating scale), daily opioids as morphine intravenous equivalent, benzodiazepine (oral lorazepam equivalent), corticosteroid (prednisone oral equivalent), anticholinergic (anticholinergic drug scale [186] but excluded opioids, benzodiazepines or corticosteroids to avoid double counting), cyclosporine levels, peak alkaline phosphatase level in last 96 hours, peak BUN level in last 48 hours, acute graft versus host disease, allogeneic donor cell type, and infection within 7 days before delirium assessment	Pre-transplantation risk factors for onset and higher severity of delirium were higher mean alkaline phosphatase (HR 1.02, CI 1.01 – 1.04) and BUN levels (HR 1.28, CI 1.14-1.43) Higher doses of opioid medications were the only post-transplantation Risk factor for delirium onset (HR, 1.05; CI, 1.02 to 1.08) Poorer pre-transplantation executive functioning' and higher opioid doses, current and prior pain, and higher BUN levels were post-transplantation risk factors for greater delirium severity (all $p < 0.01$)

BUN – blood urea nitrogen; CAM – Confusion Assessment Method; CI – 95% Confidence Interval; CNS – central nervous system, DSM-III-R – Diagnostic and Statistical Manual III-revised; DSM-IV – Diagnostic and Statistical Manual of Mental Disorders, fourth edition; GEE – Generalised estimating equations; HR- Hazard Ratio, NuDesc – Nursing Delirium Screening Scale; OR – odds ratio

1.8.1 Psychoactive medications as a risk factor for delirium

Many medications have been implicated with the risk or development of delirium, and a recent systematic review explored the studies that have quantified the strengths of these associations.[187] Most of these studies have been conducted in populations other than cancer and palliative care, but given the frequency of use of these medications in palliative care, consideration of this literature is important. The recent systematic review explored all RCTs, prospective cohort studies, and case control studies that reported medications and delirium in hospital patients and long-term care residents.[187] This review did not include the studies in malignancy previously described (Table 7). Studies have explored associations with neuroleptics, opioids, benzodiazepines, H_1 and H_2 antagonists, dihydropyridines, antimuscarinics, tricyclic antidepressants, antiparkinsonian medication, digoxin, steroids, and nonsteroidal anti-inflammatory medication.[187] It is also important to realize that in some cases these medications have a role in treatment or reducing risk of delirium, for example benzodiazepines in the management of alcohol withdrawal delirium[188], and opioids for post operative pain can reduce delirium risk (see section 1.8.3). Opioids are considered in detail in Section 1.8.2, and anticholinergic medication in section 1.12. The following sections outline in more detail the findings in relation to neuroleptics, benzodiazepines and corticosteroids.

Four studies[189-192] explored the temporal association of antipsychotic administration and delirium occurrence. One was a good quality randomised control trial of haloperidol 1.5mg daily versus placebo started preoperatively and continued for three days postoperatively[191] in elderly hip-fracture patients (n = 430). It supported no association with haloperidol and increased risk of delirium (relative risk 0.9, CI 0.6–1.3), and supported a trend to reduction in delirium severity and duration with haloperidol used prophylactically in this setting.[187] A Schor et al conducted a cohort study following 325 medical patients over 65 years, longitudinally for delirium occurrence (meeting DSM-III diagnostic criteria). Stepwise logistic regression analyses demonstrated medications which increased delirium risk in this cohort were antipsychotics (odds ratio (OR) 4.48, CI 1.19–4.84), and opioids (OR 2.54, CI 1.24–5.18). Benzodiazepines (OR 0.43

(0.23–0.81), systemic corticosteroids (OR 0.51, 0.16–1.67) and anticholinergic medication (OR 0.76, 0.41–1.43) use were not associated with delirium in this cohort.[192] The anticholinergic medications considered in this study were from the following list, included as the number of standard doses per patient (standard doses used in brackets) diphenhydramine (25mg), promethazine (25mg), meclizine (12.5mg), hydroxyzine (25mg) propanthaline bromide (15mg), benztropine mesylate (1mg), atropine sulphate injection (0.4mg) and oxybutynin chloride (5mg).[192] Exposure to medication was divided into three time-points: time up to hospital admission, time from hospital admission to time patient met DSM-III criteria for delirium, and time from onset of delirium until discharge or death, with the first two time periods used to explore delirium risk factors.[192] Of this cohort, 59 participants had malignancy (18%), with 12% (n = 11) in the delirium group.[192]

Six studies[189 190 192-194] explored whether there is a temporal relationship between benzodiazepine prescription and delirium, but most were of low or moderate quality. A definitive association has not been demonstrated. Two studies[193 194] explored whether there was a dose response relationship, and two studies[192 194] explored short- versus long-acting benzodiazepines. In a prospective cohort study[194], with matched controls in a mixed surgical population (n = 91, 154 matched controls) medication exposure was recorded for the 24-hour period before delirium developed, and the same post-operative period for the 154 matched controls. There was a trend to an association with delirium for postoperative exposure to long-acting benzodiazepines (OR, 5.4; CI, 1.0 to 29.2) compared to short-acting agents (OR2.6; CI 1.1 to 6.5). High-dose exposure to benzodiazepines also had a trend toward slightly stronger association (OR, 3.3; CI, 1.0 to 11.0) than low-dose exposures (OR 2.6; CI 0.8 to 9.1). The wide CIs indicate uncertainty about the significance of these trends.

A recent systematic review of 27 studies that systematically measured anticholinergic activity (AA)—serum AA assay or clinician rated list of drugs with known anticholinergic effects—correlating it with standardised measures of cognitive performance (acute effects on cognition (delirium), MCI or dementia), demonstrated a negative impact on cognition.[195] The studies exploring

anticholinergic medication and serum AA, and associations with delirium are outlined in Section 1.13.1 and Section 1.13.2 respectively.

1.8.2 Opioids as a risk factor for delirium

Several moderate quality studies (Table 8) show increased delirium risk associated with opioid medications in a range of clinical settings, including medical and surgical patients, post HSCT and cancer.[183 184 187 196 197] However, several studies have not been able to demonstrate an association.[185 194 196 198-202] Meperidine (pethidine) seems to be the opioid most consistently associated with delirium, both by parenteral and epidural routes.[194 203]

These studies need to be interpreted with the following considerations of methodological quality:

- Several studies were inadequately powered for multivariate analyses to allow realistic adjustment for a large number of other delirium risk factors.
- Multivariate analysis across the studies adjusted for different covariates (some more comprehensively than others), making comparison between studies difficult. In the regression models the reference group used has been no opioids in some studies and a threshold of opioid dose in others.[182]
- Several did not do daily delirium assessments, and most used delirium screening instruments to capture delirium occurrence hence 'events' could have been missed.[187 197]
- The definition of exposure is also variable with some studies calculating a dose equivalent (e.g. oral morphine equivalents) for each patient, others defining exposure as number of 'standard' doses administered; and the studies vary in whether they have considered all opioids together or looked at each individual opioid separately.[182]
- In general the cancer and haematological malignancy populations have been younger.[182-184 196]
- There has been little consideration of what will be defined as the 'at risk period' and considering 'exposure duration' (dose and time) which also may have an impact.

Table 8 Summary of studies exploring association of opioids as a class or individual opioids with delirium

Study	Agent	Setting	Type of analysis	Results (OR, RR, HR) CI
Schor 1992[192]	All opioids	Mixed medical/surgical	multivariate	OR 2.5 (1.2–5.2)*
Marcantonio 1994[194]	All opioids	Mixed surgical	matched	OR 1.4 (0.5–4.3)
Pandharipande 2006[204]	Fentanyl	ICU	multivariate	OR 1.2 (1.0–1.5)
Pandharipande 2006[204]	Morphine	ICU	multivariate	OR 1.1 (0.9–1.2)
Marcantonio 1994[194]	Meperidine (pethidine)	Mixed surgical	matched	OR 2.7 (1.3–5.5)[a]
Morrison 2003[203]	Meperidine (pethidine)	Orthopaedic	multivariate	RR 2.4 (1.3–4.5)[a]
Marcantonio 1994[194]	morphine	Mixed surgical	matched	OR 1.2 (0.6–2.4)
Marcantonio 1994[194]	Fentanyl	Mixed surgical	matched	OR 1.5 (0.6–4.2)
Marcantonio 1994[194]	Oxycodone	Mixed surgical	matched	OR 0.7 (0.3–1.6)
Marcantonio 1994[194]	Codeine	Mixed surgical	matched	OR 1.1 (0.4–3.6)
Gaudreau 2005[182]	All opioids (relative to ≤ 90mg SC morphine)	Oncology	multivariate	HR 2.12 (1.09–4.13)[a]
Gaudreau 2007[183]	All opioids (relative to ≤ 90mg SC morphine)	Oncology	multivariate	OR 1.38 (1.03–1.85)[a]
Fann 2011[184]	All opioids (SC morphine equivalent)	Post HSCT	multivariate	HR 1.05 (1.02–1.08)[a]

[a] Statistically significant (bold text) CI – 95% Confidence Interval; ICU – intensive care unit; IV – intravenous; HR – hazard ratio; HSCT – haematopoetic stem cell transplant; OR – odds ratio; RR – relative risk; SC – subcutaneous; Table reproduced from Agar 2012 with permission[179]

1.8.3 Uncontrolled pain as a risk for delirium

Poorly treated pain increased delirium risk postoperatively.[192 203 205 206] A prospective study of hip-fracture patients (n = 541) without delirium demonstrated that in patients who were cognitively intact, severe pain was associated with a nine-fold risk (CI 2.4–12.3) of developing delirium.[203] Receiving no opioid analgesia or a very low dose of an opioid (less than 10mg parenteral morphine equivalents) increased the risk of developing delirium for both cognitively intact and cognitively impaired patients, with relative risk of 5.4 (CI 2.4–12.3).[203] Another cohort of elderly medical and surgical inpatients (n = 325) also showed that poorly controlled pain during admission was an independent risk factor for delirium after adjusting for age and gender (OR 1.89, CI 1.09–3.29).[44] A study of patients 65 years and older undergoing elective major non-cardiac surgery (n = 333) showed moderate (OR 2.5, 1.5–4.2) and severe (OR 2.2, 1.2–4) preoperative resting pain (measured by visual analogue scale), and increased pain from baseline on post-operative Day one (OR 1.1, CI 1.01–.2) was associated with delirium within the first three post-operative days.[206] A study of 362 patients older than 50 years undergoing major non-cardiac surgery showed higher pain scores at rest were associated with an increased risk of delirium during the first three post-operative days (adjusted risk ratio 1.20, p = 0.04) after controlling for known preoperative risk factors for delirium (age, alcohol abuse, cognitive function, physical function, serum chemistries, and type of surgery), whereas pain with movement and maximal pain were not associated with an increased risk of delirium.[205] In comparison, there have been no studies exploring uncontrolled pain in the palliative setting, and this is a line of inquiry for future work on delirium risk in palliative populations.

1.8.4 Interaction between pain and delirium pathophysiology

It is not known if the changes that occur in delirium lead to neuro-pathological changes in pain pathways.[179] There is some commonality in the proposed neurotransmitter pathways implicated in both delirium and pain, which supports the possibility of some interaction occurring. For example, abnormalities are seen in pathways that mediate circadian rhythm, with abnormalities seen in both pain and delirium.[207-210] This is supported by results of a prospective study exploring

the occurrence of delirium in cancer patients (n = 104) that found the distribution of breakthrough analgesia was significantly different in patients with and without delirium. Patients without delirium tended to use more breakthrough analgesia ($p < 0.001$) in the morning, whereas patients with delirium tended to use more breakthrough analgesia in the evening and at night ($p = 0.02$).[207]

1.9 Reversibility in cancer and palliative populations

An understanding of the reversibility of delirium in advanced cancer and palliative populations is important in informing the balance of benefit versus burden of investigation of underlying causes of delirium and subsequent management.[211-214] Prior to the two studies described below, there was less recognition of the potential for reversibility, with some clinicians assuming it was part of the natural history of deterioration.[215 216] It is difficult to make direct comparisons between the studies due to the variability in the way precipitating factors were measured and defined, but irreversibility has been associated with infection (in particular non-respiratory infection), larger number of aetiologies for the delirium episode, organ failure, prevalent delirium and more severe delirium (in particular with more severe attention and visuo-spatial deficits).[38 104 215] The rates of reversal vary from 27%–49%[38 215] in specialist palliative care units, but up to 67%[104] in those with advanced cancer admitted in acute cancer care centres.

The prospective cohort study of advanced cancer patients (n = 113) admitted to a Canadian specialist acute inpatient palliative care unit described earlier also explored reversibility.[38] This study defined delirium improvement as at least a 25% reduction in MDAS score in association with improvement or resolution of the precipitating factor.[38] Precipitating factors were identified by three criteria (modified from Francis 1990)[217]:

1. evidence of presence from specific clinical, laboratory, or radiological findings
2. temporal association with the course of delirium consistent with a potential precipitating role

3. changes in severity of delirium in association with similar changes in precipitating factors.[38]

Specific definitions were provided for precipitating factors including metabolic and haematological abnormalities, and dehydration.[38] The semi-structured interview to determine if the participant met the DSM-IV criteria of delirium and MDAS score was repeated every 72 hours until delirium reversal or death.[38] The precise definition used for those episodes classified as 'reversed' is unclear, whether it was according to DSM-IV criteria or MDAS cut-off score was unspecified, nor the timeframe over which the reversal was established (i.e. one assessment meeting criteria for reversal or more). Reversal of delirium occurred in 49% (n = 46 out of 94 episodes) of delirium episodes.[38 212 218] The reversibility was similar in the group with delirium on admission, and those with incident delirium.[38] However, for first episode of delirium, reversibility was 56%, compared with 26% for a repeated episode.[38] Terminal delirium was defined as DSM-IV criteria for delirium being met at least six hours before death, and occurred in 88% (n = 46) of the 52 deaths.[38] The mean (± standard deviation (SD)) number of precipitating factors was 3.1 (±1.2) for reversed and 3.1 (±1.4) non-reversed delirium.[38] In descriptive analyses factors associated with nonreversible episodes were hepatic impairment, refractory hypercalcaemia, hyponatraemia, renal insufficiency. In univariate analysis hepatic encephalopathy and metabolic factors were associated with irreversibility. In multivariate analyses the most frequent aetiological factor associated with reversibility was psychoactive medication (mainly opioids), whereas lung involvement by cancer and infection causing hypoxia, and non-respiratory infection were more often associated with irreversible delirium.[38] The dichotomy of delirium populations in advanced cancer was highlighted, with both reversible and irreversible delirium as part of the physiological process of dying being seen.[38]

A study in an inpatient palliative care unit in Ireland[215] screened patients using the CAM[148] who had a high likelihood of delirium, who then went on to have delirium confirmed by a research physician using DSM-IV-R criteria, and phenomenology captured using the DRS-R98) and Cognitive Test for Delirium (CTD).[170] This unit receives referral from the local acute hospital, GPs and

specialist palliative care community nurses. Aetiology of the delirium was assessed using the Delirium Etiology Checklist[219] for 121 participants with delirium, and the mean DRS-R98 score was 20 ± 6.1 (consistent with delirium of moderate severity).[215] Similar to other studies, the mean number of precipitants per patient was 3.5 ± 2.2, with systemic neoplasm, CNS neoplasm, systemic infection, metabolic or endocrine disturbance, and organ failure frequent causes.[215] The mean age of the participants was 70.2 ± 11.7 years, but details of performance status or primary life-limiting illness was not provided. In the group with irreversible delirium organ failure as an aetiology was significantly higher ($p = 0.02$), severity rating on DRS-R98 was greater, and also more aetiologies for the delirium present per patient (3.7 ± 1.3 for irreversible delirium vs 2.0 ± 1.0 for reversible) ($p < 0.001$).[215] Delirium reversal was defined as no longer meeting DSM-IV criteria for delirium prior to death, and 27% were in the reversible group ($n = 33$) versus 73% irreversible ($n = 88$). Reversible delirium was more likely to be incident delirium (61%) than prevalent (39%), whereas prevalent delirium was more common in irreversible delirium (64% prevalent vs only 36% of cases incident) ($p = 0.03$). Reversible and irreversible delirium groups did not differ in number of medications or prescribing frequency of psychoactive drugs (antipsychotics, antidepressants, opioids, benzodiazepines, psycho-stimulants or steroids). The predictors of irreversible delirium in stepwise binary logistic regression were the greater number of aetiologies identified ($p = 0.02$), greater impairment of attention identified on CTD ($p = 0.04$) and more severe disturbance of visuospatial function identified on DRS-R98 ($p = 0.04$).

The similarities are that both studies clearly demonstrate two populations, one with reversible delirium and one where delirium is a terminal irreversible event. The frequency of reversibility varies, but ranges from a third to half of cases in specialist palliative care unit settings. There are inconsistent results in relation to organ failure associated with irreversibility, and psychoactive medications being associated with reversibility; but this may be due to how the factors were defined. Equally, the same factor may be potentially reversible in one patient, but irreversible in another.

An older case series also assessed reversibility of delirium.[104] It consisted of 140 patients (100 patients identified prospectively, and 40 patients retrospectively from a comprehensive neurology database) with systemic cancer (excluding CNS tumours) in a large inpatient cancer centre in the United States (US), who were referred to the neurology service for impaired mental status, with delirium diagnosed using DSM-III-R criteria. In this cohort, 34% had prevalent delirium on admission and 66% had incident delirium. In this case series 67% had multiple causes for the delirium identified (median number of three per patient—utilising the method from Francis 1990[217]), and in 67% delirium improvement occurred, as determined by the assessing neurologist.[104] The presence of infection and elevated prothrombin time were independently associated variables for persistent delirium.[104] Detailed analysis of reversible factors and response to intervention was not performed in this study; however, the aetiological factors were categorised and ranked on temporal and clinical relation to delirium episode.[104] Although there are methodological limitations of utilising a retrospective cohort, and predictors were not studied in detail, this study also supports the hypothesis of the potential for reversibility in over half of patients with delirium in advanced cancer in the acute setting.

An earlier study identified cognitive failure (MMSE score ≤ 24) in 34% (16/47) of patients with advanced cancer on admission to an acute palliative care unit.[115 220] Cognitive improvement, as measured by improvement in MMSE scores, occurred in 33% (22/66) of patients.[115 220] However, this study only assessed MMSE scores three times per week and did not use diagnostic criteria for delirium. However, it does support the potential for reversibility in the palliative setting of cognitive impairment due to delirium.[115 220]

1.10 Current hypotheses of the pathophysiology of delirium

Specific neurotransmitter systems and neuronal pathways are implicated based on the symptom profiles seen and some limited imaging studies.[221 222] The evidence points to delirium being more specific than just ‘acute brain failure’ of higher multiple cortical functions, often accompanied by generalised slowing on an EEG. Another theory is that more ‘global cortical failure’ may occur in severe illness,

whereas in other clinical situations more 'limited failure' of specific neurotransmitter systems occurs.[223] One approach has been to determine putative brain regions from what is known in other neuropsychiatric disorders, for example delusions in schizophrenia seem to be related to abnormalities of dopamine in the mesolimbic system and abnormalities in temporo-limbic circuits.[221] Brain regions involved in personality, mood, affect, sleep – wake cycles, cognition, thinking and language include prefrontal cortex, temporo-limbic structures, antero-medial thalamus, hypothalamic suprachiasmatic nucleus, brain stem nuclei and tertiary association polymodal sensory cortex.[221] These areas can be affected directly or can dysfunction due to abnormalities in connecting structures projecting to them. When brain lesions or physiological dysfunction directly affect these regions it is proposed delirium may be particularly severe and prolonged.[221] When the aetiology of delirium is not impacting on these regions directly, it is thought that the overall neurochemical or metabolic effects indirectly affect these regions, which may be more 'vulnerable' pathways.[221]

Flacker and Lipsitz undertook a review of animal and human studies, which studied the neurobiology of delirium.[223] The proposed neurotransmitter pathways and the clinical conditions associated with these abnormalities are summarised in Figure 1.

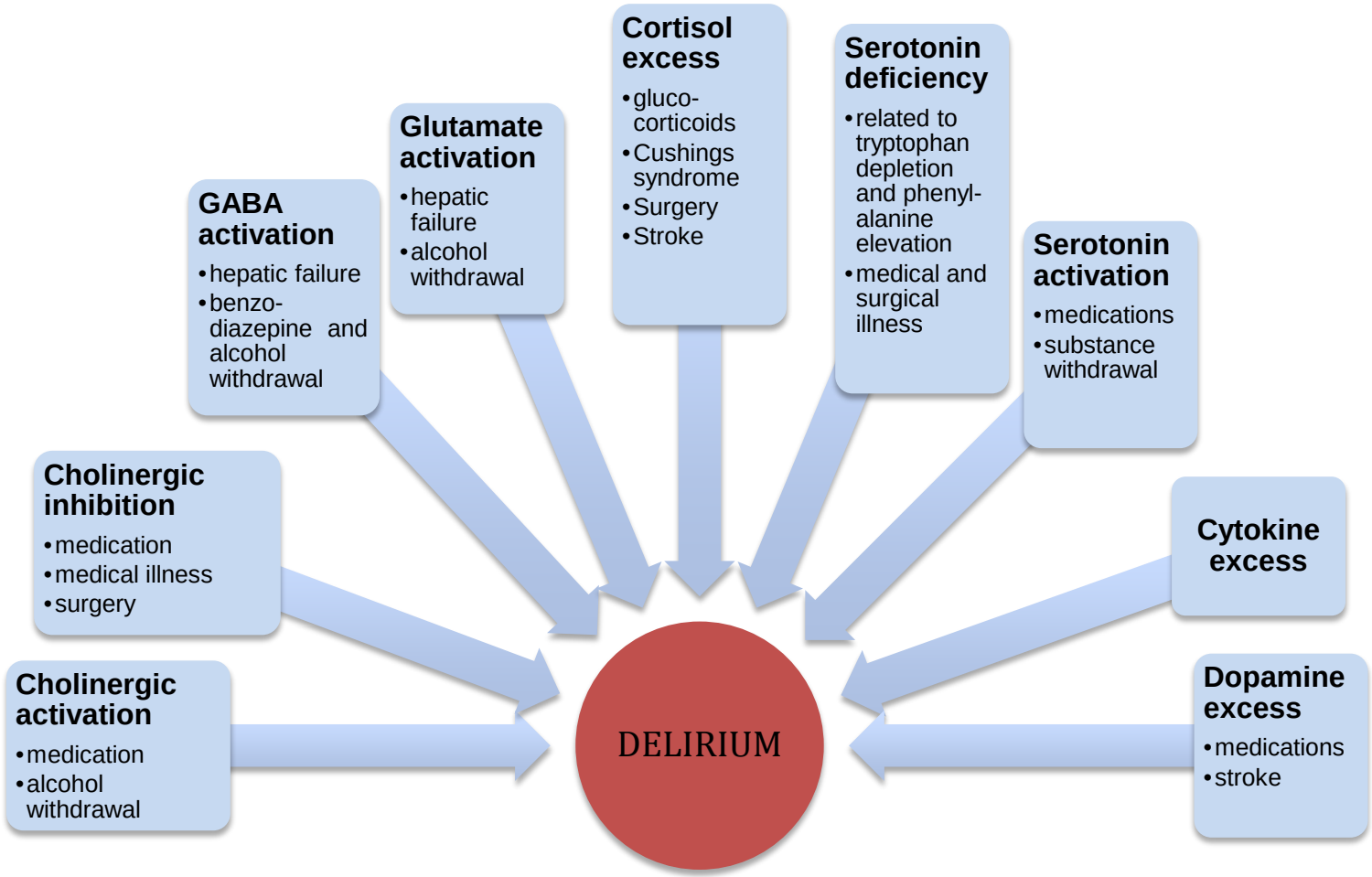


Figure 1 Proposed mechanism of delirium and clinical conditions that may mediate delirium through this neurotransmitter system (from Flacker and Lipsitz 1999)[223]

An evolving theory of causal pathways in delirium pathophysiology suggests mediating factors are divided into two categories: direct brain insults and aberrant stress responses.[224] Direct brain insults include those acute processes which compromise brain function by energy deprivation, metabolic abnormalities, trauma, haemorrhage, or direct neurotransmitter changes mediated by medication.[224] Examples of direct brain insults include hypoxia, hypotension, primary and secondary CNS tumours, and medications such as cholinergic antagonists, dopamine agonists and opioids.[224] In fact the medication triggers of delirium have been extremely informative in unpacking the potential neurotransmitter abnormalities that are involved in delirium.[224] A constellation of adaptive changes, termed 'sickness behaviour' occur in acute stress and non-CNS illness, which are initiated to conserve energy and minimise exposure to further infection or other stressors.[224] The constellation of symptoms seen include reduced attention, motivation, flattened affect, reduced activity, reduced appetite, and anhedonia.[224] Sickness behaviour is thought to be mediated by pro-inflammatory cytokines and prostaglandins.[224] In health these changes are adaptive; however, dysfunction of the stress response and heightened inflammatory responses occur in ageing and neuro-degeneration, conditions where equally abnormalities occur in cholinergic, dopaminergic and noradrenergic systems.[224]

It is proposed that the second major category of delirium pathophysiological mechanisms is due to overstimulation of stress responses or pathological reaction of target tissues to stressors.[224-226] These aberrant stress responses are mediated by humoral and neural signalling pathways, and interactions of these signals with the CNS or CNS pathology. The two types of aberrant stress responses proposed are exaggerated sickness behaviour and limbic-hypothalamic-pituitary-adrenal (LHPA) axis dysfunction.[224] In exaggerated sickness behaviour CNS production of cytokines and prostaglandins occurs, and systemic inflammatory signals can be conducted to the brain without compromise of the blood brain barrier (e.g. via vagus nerve, endothelial cells of brain vasculature, circumventricular organs and direct interaction with neurons).[224] The CNS response seems more severe if there is an existing inflammatory state in the brain, at sites of prior microglial activation (the brain's resident macrophages, which are activated in chronic neuro-

degeneration and primed to respond more vigorously to further stimulation).[224-226] Prior cholinergic deficiency in basal forebrain has also been shown to predispose to development of acute cognitive deficits upon subsequent inflammatory insult in rodent models.[227] Activation or dysfunction of LHPA axis can occur with a diverse range of stressors such as surgery, trauma, pain, medications (such as glucocorticoids) and systemic inflammation. It is also conceivable that the LHPA axis and CNS inflammation may interact to further exacerbate delirium.[224]

1.11 Cholinergic mechanisms in delirium

Cholinergic pathways are widespread in distribution in the CNS, travelling in discrete bundles in the white matter, with interneurons in the striatum, to reach all areas of the cortex. Important projections are to fronto-temporal cortex, cingulate gyrus, amygdala, hippocampus, limbic system and thalamus (especially antero-dorsal and medio-dorsal nuclei).[228] Important roles for acetylcholine and dopamine systems have been postulated in delirium pathophysiology. This involves cholinergic deficiency and dopamine excess, either absolute or relative to each other.[229] Acetylcholine plays a central role in consciousness and awareness, sleep, memory, motor activity, mood and attention (in particular via nicotinic and muscarinic receptors in the thalamus).[221 223] Acetylcholine also contributes to sensory gating of information, to allow selective attention and freedom from distraction.[228] The administration of anticholinergic substances to experimental animals and humans has resulted in characteristic manifestations of delirium. It is also proposed that age-related reduction in acetylcholine release and muscarinic function may be the mechanism by which older people have a higher risk of delirium.[223] Impaired acetylcholine synthesis may also play a role, for example hypoglycaemia has been shown to depress acetylcholine synthesis in the cortex and striatum.[223] The literature outlining associations with anticholinergic medication and serum anticholinergic activity (SAA), are outlined in section 1.12.

1.11.1 Concept of anticholinergic load

'Anticholinergic' burden that an individual is exposed to can be defined as the anticholinergic load generated by all of the medications (and their metabolites if relevant) with anticholinergic properties as well as endogenous anticholinergic substances (dynorphin A, Myelin Basic Protein (MBP), protamine), that some

evidence suggests are produced in acute illness.[230 231] There is evidence that many medications have anticholinergic properties, in addition to those traditionally labelled as anti-muscarinic medications, including commonly used medication such as warfarin, ranitidine, digoxin, codeine and diazepam.[232 233] Importantly, many of these medications are continued or commenced during the end-of-life care period. It is important to understand the cumulative anticholinergic load, and how this changes as a result of prescribing at the end of life is crucial, due the significant morbidity and even premature mortality potentially associated with this spectrum of unwanted effects. This will also assist clinicians by generating a more coherent framework in which to make decisions about discontinuation of medications no longer contributing a therapeutic benefit or substitution of medication with lower anticholinergic effects but the same or similar therapeutic benefit; and interpretation of the potential contribution of medications with anticholinergic action to the patient's symptoms.

1.11.2 Methods to calculate anticholinergic medication burden

Several methods of calculating anticholinergic drug burden are suggested in the literature, including Summers' initial classification in 1978, anticholinergic drug load (ADL), the Anticholinergic Burden Scale (ABS), and the Clinician Rated Anticholinergic Scale (CRAS).[234-238] The Drug Burden Index (DBI)[239] also considers sedative medication and anticholinergic medication, and hence does not exclusively measure anticholinergic medication.

The first to be described was the ADL, where Tune et al initially quantified the AA of the top 25 medications prescribed in the elderly, according to listings available in the 1980s.[240] Parent compounds were obtained directly from the pharmaceutical company involved in their production, and each drug was diluted to a standard concentration (10^{-8}M) and assessed using a competitive anticholinergic assay.[240] Anticholinergic levels were standardised using atropine as a reference.[240-243] Measured AA using this methodology was demonstrated for 13 drugs (cimetidine, codeine, digoxin, dipyramidole, frusemide, isosorbide dinitrate, nifedipine, theophylline, triamterene and hydrochlorothiazide combination, prednisolone, ranitidine and warfarin).[240] These early studies highlighted recognition that many other medications (as listed) that classically

were not considered anticholinergic may have anticholinergic properties that are clinically relevant. Since this time other medications have been released and further medications of interest classified according to anticholinergic potential, further expanding Tune's initial list.[244] Hence AA is available (ng/ml of atropine equivalents) for many common medications.[240-243] AA derived by this method needs to be interpreted with caution as the standard concentrations studied may not reflect biologically meaningful serum concentrations.[244] A summative measure to calculate an ADL by summing the AA for individual parent compounds can be calculated; however, it is unlikely to be a useful measure of clinical effects. These studies highlight recognition that many other medications that classically were not considered to have AA have anticholinergic properties that are clinically relevant.[244]

A similar study was performed by Chew et al in 2008.[245] Drug solutions were made from medication in tablet form utilising solvents based on solubility and stability profile of each medication (and lack of interaction in the assay) and added to 0.2 ml of drug-free serum.[245] Six clinically relevant drug concentrations were selected for each medication, spanning the range observed in older adults after multiple dose oral administration.[245] Average peak concentrations (C_{max}) of each medication was derived from published literature.[245] The AA was determined by the assay described above, with interpolation of the concentration—AA plots to determine AA at given $C_{max.}$[245] Thirty-nine of the medications tested in this way showed demonstrable AA, 22 in a dose-dependent manner and 17 only showing activity at highest doses.[245] Examples from this study include 50mg of nortriptyline would have an average steady state C_{max} of 59 ng/ml with estimated AA of 8.2 pmol/ml; 100mg of amitriptyline estimated AA of 52.8 pmol/ml; 10mg olanzapine estimated AA of 4.4 pmol/ml and 20 mg temazepam estimated AA of 0.6 pmol/ml.[245]

ADL may underestimate anticholinergic effect in the clinical situation, as potentially active metabolites or endogenous substances are not taken into account. Correlation between actual SAA measured from patient serum; and sum of listed individual AA derived *in vitro* from parent compounds (ADL) for the same patient's medication list has not been performed.

Summers developed a classification for estimating the risk of drug-induced delirium in 1978, and included 62 medications; however, these included other medications than purely those with known anticholinergic effects.[236]

Another method of calculating anticholinergic burden is the ABS.[238] The ABS is an additive score with each medication rated on a scale 0 (no anticholinergic effect) to 3 (high anticholinergic effect).[238] The details of how the medications have been classified have not been published, and it has only been utilised to explore patient outcomes in one study to my knowledge.[237]

The most comprehensive method currently available is the Clinician Rated Anticholinergic Scale – modified version (CRAS-M)[246] [247] which gives medication one of four ratings:

- Level 0 (no known anticholinergic properties)
- Level 1 (potentially anticholinergic as demonstrated by receptor binding studies)
- Level 2 (clinically significant anticholinergic effects are sometimes seen, usually at excessive doses)
- Level 3 (marked anticholinergic effects).

This allows calculation of a total anticholinergic score at each time-point for each participant.[246] [247] This classification was developed using reported anticholinergic effects in the literature, available laboratory data, and ratings of three independent geriatric psychiatrists; and was the approach utilised in this study to determine total anticholinergic score.[247]

The initial development of the CRAS (initial version) involved establishing a list of 340 medications reported to have anticholinergic effects and also those commonly used in geriatric populations; and includes those medications not traditionally deemed as anticholinergic.[248] These medications were then independently rated for anticholinergic effects by three geriatric psychiatrists, using scoring 0 for none, to 3 for high, based on knowledge and clinical experience.[248] The inter-rater reliability was assessed by evaluating concordance of mean and median values of the three clinician's ratings, and with Summers' drug risk numbers (if it was available) and laboratory data (if it was available).[248]

The CRAS-M was developed by re-evaluation of the CRAS (initial version) by three psychiatric pharmacists, and scores were modified only if compelling laboratory, receptor binding or clinically documented anticholinergic effects had been published.[249] The approaches to laboratory measurement of anticholinergic load are outlined in section 1.11.3.

The current limitations of any scoring system for ADL is weighting for dose (for example 25mg imipramine is scored the same as 150mg) or duration of exposure.[249] There also is no evidence to support the concept that drugs in each level of the classification are equally anticholinergic, or that the scores can be additive.[249] For example, a patient on three drugs with scores of 1 may not have the same anticholinergic effects as a person on one drug with a score of 3.[249] Other unaccounted factors are pharmacokinetic effects and active metabolites.[249] The relative central nervous system effect of an anticholinergic medication allocated a particular CRAS-M score may also vary, as well as the degree to which this leads to specific interactions with pathways implicated in delirium pathophysiology. The effect of medications with anticholinergic action may also vary in patients with different comorbidities, for example dementia. Serum anticholinergic level also reflects endogenous anticholinergic substances, which are not included in a score that is calculated from medications only.[249] Contributors to serum anticholinergic level are discussed in Section 1.11.3.

More recently two other scales have been developed (after completion of the studies contributing my doctoral thesis).

Rudolph et al developed the Anticholinergic Risk Scale (ARS).[250] ARS was developed by reviewing existing literature on anticholinergic effects, the National Institute of Mental Health Psychoactive Drug Screening Program and the Micromedex databases, to determine the anticholinergic effects of the 500 most prescribed drugs within one veteran healthcare system in the US. Similar to prior methods, ARS ranked medications on a scale of 0 to 3 according to the level of anticholinergic effects. Using the ARS, 249 patients aged 65 years and older attending geriatric or primary care ambulatory clinics were assessed to explore the association between the total anticholinergic burden of medications and the overall anticholinergic adverse effects as determined by a review of the medical

records. The mean ARS score ranged from 0.7 in the primary care clinic to 1.4 in the geriatric clinic. Higher ARS scores were associated with increased risk of both peripheral and central anticholinergic effects, with a relative risk ratio ranging from 1.3 to 1.9. ARS has been shown to be associated with a higher risk of anticholinergic adverse effects (determined by review of the veterans electronic medical record where a geriatric assessment is recorded including dry mouth and eyes, falls, dizziness, confusion and constipation) in 149 male veterans (adjusted (for age and number of medications) relative risk 1.3, CI 1.1–1.6). Though this scale does not differ from existing scales to measure anticholinergic load, the study has focussed on commonly used medications in one population and measured anticholinergic effects systematically.

Similarly, the Anticholinergic Cognitive Burden (ACB) scale[251] was developed utilising a Medline database from 1966 to 2007 to search for any study that measured the anticholinergic activities of a drug and evaluated the association with cognitive function (delirium, MCI, dementia or cognitive decline) in older adults. This list was presented to an expert interdisciplinary team that included geriatricians, geriatric pharmacists, geriatric psychiatrists, general physicians, geriatric nurses and aging-brain researchers. Subsequently, the team categorised the above medications into three classes of mild, moderate and severe cognitive anticholinergic negative effects (48 medications). The scoring system again was similar; medications with possible anticholinergic effects (as demonstrated by the SAA or the *in vitro* affinity to muscarinic receptors but with no clinically relevant negative cognitive effects) were given a score of 1. Drugs with established and clinically relevant cognitive anticholinergic effects were given a score of either 2 or 3, based on the drug blood-brain barrier permeability and its association with the development of delirium. All other drugs with no anticholinergic effects can be considered as having a score of zero.

1.11.3 Serum measures of anticholinergic activity

A serum anticholinergic radio-receptor assay has been developed to quantify SAA.[241 242] The underlying hypothesis was that SAA should be normally absent in humans, and any activity measured reflects effects of medication and other ingested exogenous substances.[252] More recently AA has been demonstrated in

elderly patients in acute illness independent of drug effects, which suggests that endogenous substances also contribute.[253,254] Implicated compounds include dynorphin A, MBP and cortisol.[244] Dynorphin A is an endogenous opioid (dynorphins are important in maintaining homeostasis through appetite control and circadian rhythms in particular in stressful situations). MBP is a protein believed to be important in CNS neuron myelination, and also MBP-related proteins are found in bone marrow and the immune system. The role of cortisol has been described in section 1.10. The advantage of SAA would be the ability to assess cumulative effects of multiple medications, as well as pharmacologically active metabolites.[242] It could allow for analysis of one simple continuous variable, rather than complex analysis of medication regimens.[244]

The technique involves adding patient's serum to membrane preparation from rat forebrain and striatum containing muscarinic antagonist, tritiated quinuclidinyl benzilate (3H-QNB) (radioactively labelled).[241] 3H-QNB bind specifically and avidly to muscarinic cholinergic receptors.[241] The incubation mixture consists of 200 μl of serum, 200μl of the rat brain preparation, 0.6 pmol of 3H-QNB (in 200μl), and volume made up to 2ml with phosphate buffer (50 nanomol (nM), pH 7.7).[241] Incubation is for 60 minutes at 22°C.[241] The assay is terminated by an isolation of ligand receptor complex by aspiration over glass fibre filters, and the receptor bound radioactivity is measured by liquid scintillation spectrometry.[241] Samples are compared with known concentrations of atropine (the internal standard), and the amount of QNB inhibition that would have been caused by known standard amount of atropine, with the displacement of 3H-QNB used to quantify SAA (atropine equivalents) in comparison to an atropine standard curve (the amounts of atropine used for standard curve were 0, 0.5, 1, 5, 10, 25, and 50nM). It does not measure protein bound drugs as serum proteins are not denatured and precipitated.[241]

Hence the potency of anticholinergic substances in a serum sample that bind to the muscarinic acetylcholine receptor present in the rat forebrain/striatum homogenate is determined by measuring its ability to inhibit the binding of 3H-QNB to the receptor. The ability of the anticholinergics to compete with 3H-QNB for binding sites is dependent on both the affinity of the anticholinergics for the

muscarinic receptors, the concentration of 3H-QNB, and the affinity of 3H-QNB for the receptors. The assay measures activity at all muscarinic receptor subtypes.[242]

1.12 Clinical studies of anticholinergic load

Four studies have objectively explored the relationship of anticholinergic medication burden and delirium, which did not consistently show an association with delirium occurrence or severity. There has been a larger number of studies exploring serum anticholinergic activity. A recent systematic review[255] of 27 studies which measured SAA correlated with standard measurements of cognitive function, demonstrated an association between AA of medications and either delirium, cognitive impairment or dementia, in all but two of the studies reviewed.[256 257] Of the 27 studies, 13 were cross-sectional, six case control and eight prospective or retrospective cohort studies.[255] Seventeen of the studies included in this review used the SAA, with the others using clinical knowledge in conjunction with medication lists with known anticholinergic effects. The delirium measures used in 70% of the studies were the CAM or CAM-Intensive Care Unit (CAM-ICU) or DSM-IV criteria, whereas the Saskatoon Delirium checklist, and DSI were used in the other 30% (both developed from DSM criteria).[255] These studies are discussed in detail in the following sections. No studies to my knowledge have explored anticholinergic load in cancer populations or palliative care.

1.12.1 Clinical studies of anticholinergic medication burden

Surprisingly few studies have explored the temporal relationship of prescription of anticholinergic medication and delirium. This section outlines studies that have quantified anticholinergic medications with one of the methods outlined in section 1.11.2.

A study of medical inpatients 65 years and older (n = 278) with diagnosed incident or prevalent delirium and a range of underlying illnesses showed an increase in delirium severity was significantly associated with anticholinergic medication exposure (CRAS-M) on the previous day, adjusting for dementia,

baseline delirium severity, length of follow-up, and number of medications rated as not having anticholinergic load that were taken.[247]

An age and gender matched case control study of 22 delirious stroke patients and 52 non-delirious patients (controls) were compared in regard to anticholinergic medications before the stroke and during hospitalisation. The list of medications with AA were derived from the Portugese government agency that regulates pharmaceutical products in Portugal. Medications were divided into neuroleptic and non-neuroleptic anticholinergics to avoid confounding effects of neuroleptics used to treat delirium. Medication use was quantified by the number of medications for each category. Delirium was assessed using the DSM-IV R criteria and the DRS. Anticholinergic medication during hospitalisation (OR 24.4, 95% CI 2.18–250), and those taken before stroke (OR 17.5, 95% CI 1–333.3) were independent predictors of delirium, after adjustment for age, gender, GCS score, presence of neglect). This study is limited by its small sample size, and inclusion of multiple variables in the model; it also quantified the absolute number of anticholinergic medications, but not the degree of anticholinergicity.

In a prospective cohort study (described previously in section 1.8.1)[194], with matched controls in a mixed surgical population (n = 91, 154 matched controls) medication exposure was recorded for the 24-hour period before delirium developed, and the same post-operative period for the 154 matched controls. Anticholinergics were recorded for 24 hours before delirium developed, and the same 24-hour postoperative period for controls. Anticholinergic medication was defined as administration of antihistamines, tricyclic antidepressants, antiemetics and certain neuroleptics (not specified in the paper).[194] Anticholinergics were only administered to 9% of the population, which limited statistical power; however, anticholinergics were not associated with delirium in this study (OR 1.5, 95% CI 0.6–3.4, p = 0.36).

A study of 147 participants aged 65 years and over with cognitive impairment, who screened negative to delirium on admission (using CAM) to general medical ward were followed for occurrence of incident delirium (also using CAM).[258] Anticholinergic medications were identified using the ACB list, and exposure was defined as any order for anticholinergic medications between time of admission

and the day before delirium (incident delirium group) or day before final delirium assessment (for those who did not develop delirium). Fifty-seven per cent of the cohort received at least one prescription for one 'possible' anticholinergic medication, and 28% received at least one order for a definite anticholinergic medication according to the ACB. After adjusting for baseline age, gender, cognition (on SPMSQ), CCI, the OR for developing delirium was 0.33 (CI 0.1–1.03) for those receiving possible anticholinergic medications, and 0.43 (0.11-1.63) for definite anticholinergic medications. This study did not account for the medication exposure as a time-dependent variable or the number of anticholinergic medications, and considered anticholinergic medication exposure as present or absent in the 'possible' or 'definite' categories of the ACB, whereas ACB can be used as an additive score. The ACB also does not provide the list of medications that were scored as no AA to ensure medications with AA were not inadvertently missed from the list.

1.12.2 Clinical studies of serum anticholinergic activity

There have been a number of studies in various clinical settings to determine whether serum AA can be a reliable predictor of delirium (Table 9) and/or cognitive impairment (Table 10). Several of these studies were performed prior to the availability of valid and reliable scales for delirium diagnosis, and used the MMSE.[242] The studies included in the systematic review of SAA and delirium are outlined in Table 9, with the addition of one study in surgical intensive patients [259] and two case reports.[260]

SAA has been significantly associated with presence and severity of delirium in post-cardiotomy, geriatric medical, post-electroconvulsive therapy and in intensive care settings.[242 261-264] There have been two negative studies, where no association has been seen in frail elderly[265], and intensive care patients.[256] Delirium resolution has also been associated with a fall in SAA when observed longitudinally, however this has only been explored in one study which only had a small number of participants whose delirium resolved (n=6).[242,266] Mean SAA reduced by half from 7.77 ± 2.37nM, to 3.92 ± 2.61NM when delirium had resolved.[266] Larger SAA decreases over time have been seen in patients with fever (n = 22), with reduction of SAA after resolution of fever in participants with

delirium and those who did not.[253] SAA during febrile illness was 3.35 ± 3.15 nM/ml and at 1 month follow-up 0.45 ± 0.65.[253]

In elderly medical patients, multivariate analysis demonstrated SAA was independently associated with delirium, using the variables impairment in activities of daily living (ADL), narcotic use, neuroleptic use, nursing home residence, prior cognitive impairment, admission diagnosis of infection and SAA.[189] A similar study in geriatric medical patients showed an association of high SAA with development of delirium following hospital admission.[264]

Changes in SAA have not always been related directly to discontinuation or reduction in anticholinergic medication, with delirium resolution associated with decrease in SAA, independent of anticholinergic medication changes.[244]

It has been presumed that SAA reflects central cholinergic activity but, this assumption does not have substantive, definitive evidence. Two small studies have explored the correlation of cerebrospinal fluid (CSF) to serum correlation of AA in young surgical patients pre-medicated with central anticholinergics (scopolamine or midazolam).[267] In the first study serum and CSF were taken from 36 elderly surgical patients undergoing surgery (excluding craniotomy, cardiovascular or thoracic surgery) who had no prior psychiatric or cognitive impairment history.[268] On the evening before surgery a mental status battery was administered (MMSE, Saskatoon delirium checklist score, a timed visual-motor performance test, Rey Auditory Verbal Learning test, and symbol digit modalities test score), and serum was collected.[268] The participants where then randomly allocated to receive intramuscular scopolamine (0.005mg/kg or 0.0025mg/kg if over 80 years) or a placebo.[268] The mental status battery was repeated 45 minutes to one hour after this premedication, and at induction of anaesthesia a second blood sample was taken, and 2ml of CSF in the nine participants who underwent spinal anaesthesia. Many patients had measurable SAA at pre-test with mean levels 9.1 ± 17.7 pmol/ml (atropine equivalents). The levels at induction of anaesthesia were significantly higher in those who had received scopolamine (n = 14, mean serum SAA 121.1, SD 85.5), compared to the placebo group (n = 16, mean SAA 11.7, SD 18.2) (p = 0.0001). In the nine participants with CSF specimen, five received scopolamine, with mean CSF SAA 74.2 (SD 44.8)

compared to placebo (n = 4) with mean CSF SAA 0 (SD 0) (p = 0.01), and the SAA correlated highly with CSF SAA (Spearman rank correlation coefficient = 0.69, p < 0.05). The groups were receiving a mean 2.2 other medications in 12 hours before surgery, with equivalent exposure to analgesics and hypnotics, and no recognised anticholinergics given within 24 hours before scopolamine/placebo administration. Two of the mental battery tests showed mild trends to worsening. There were differences in the Saskatoon delirium checklist score (mean score 33.3 (SD 4.1) in the scopolamine group, compared to 37 (SD 2.7) in the placebo group, after adjustment for pre-treatment score (analysis of covariance, F = 5.99, p = 0.02). In the Reys Auditory Verbal learning test the scopolamine group recalled fewer words over the five learning trials, although this was not statistically significant.

In the other study, blood and CSF were taken after routine premedication with oral midazolam 7.5mg and before spinal anaesthesia was administered from 15 patients admitted for urological surgery.[267] The mean serum SAA level (atropine equivalents) for all patients was 2.4 ± 1.7pmol/mol (range 0–5), while mean CSF SAA level was 5.9 ± 2.1 pmol/ml (range 2–12). The participant with CSF SAA of 12 had also been pre-treated with chlorazepate (a benzodiazepine derivative) 24 hours prior to surgery.[267] This study demonstrated CSF SAA levels were approximately 2.5 fold higher than blood levels.[267] The patients who had been taking anticholinergic medication for at least four weeks prior to surgery (classified according to Lu and Tune[269], and Tune and Egeli[270]) had slightly higher mean serum SAA 2.7 ± 1.7, and mean CSF SAA 6.4 ± 2.0, compared to patients who had not been taking any anticholinergics (mean SAA serum 1.1 ±1.0, and CSF 4.0 ± 1.7 respectively).[267] A significant correlation was seen between serum and CSF SAA (Pearson's r = 0.861, p < 0.001).[267]

Table 9 Studies of serum anticholinergic levels and delirium

Study	n	Population	Study design	Delirium diagnosis	Outcome measures	Findings	Comments
Tune 1981[261]	29	Post cardiac surgery	Elective cardiac surgery prospective cohort	Clinical diagnosis of delirium	Tachiscope to assess perceptive function MMSE SAA 24 hours after surgery, and then up to 3 times per week at same time as delirium assessment for 2 weeks	10/29 patients became delirious on clinical diagnosis 8/29 at 24 hours post-surgery 14/16 samples in clinical delirious participants had SAA >1.5pmol/ml compared to only 5/33 samples in non-delirious ($p < 0.001$) SAA of 1.5 pmol/mL atropine equivalents associated with increased risk of delirium ($p < 0.001$) Reduction in score on MMSE correlated with increase in SAA ($r = 0.83$, $p < 0.001$)	SAA was blinded to clinical state Delirium diagnosis was not standardised with use of a validated measure
Golinger 1987[263]	25	Surgical ICU	Cross-sectional study, with sample collected over 3-month period All patients present in the unit on the four measurements days—3 weeks apart over 3 months Excluded patients who had been previously interviewed, general anaesthesia during preceding 24 hours, no routine bloods, or not able to respond verbally	DSM-III criteria by researchers	DSM-III defined delirium SAA, and drug risk number according to Summers' classification used[236]	36 % (n = 9) had DSM-III defined delirium Mean $\pm$ SD levels (atropine equivalents) for delirious patients (4.67 ± 3.3 ng/ml) was significantly higher for delirious than non-delirious (0.81 ± 1.0 ng/ml) Mean drug risk number was higher for delirious group but not statistically significant	Used gold standard delirium criteria Statistical comparison used mean levels of SAA not predetermined cut-off score Included calculation of drug risk number No adjustment for other covariates such as age, anaesthetic used, surgical procedure, illness severity SAA not standardised to a specific time post operation DSM-III criteria, and single rater not blinded to SAA levels Prevalent delirium only not incident delirium Only patients with verbal ability included

Study	n	Population	Study design	Delirium diagnosis	Outcome measures	Findings	Comments
Miller 1988[271]	36	Elderly presurgical patients (59 years and older)	Randomised blinded study of placebo or 0.005mg/kg scopolamine (anticholinergic premedication)	Saskatoon delirium checklist, based on DSM-III criteria Were not expecting frank delirium to develop	MMSE Saskatoon delirium checklist Symbol digit modalities test Rey auditory verbal learning test	Low dose scopolamine results in low levels of serum AA (mean 9.1 ± 17.7 pmol/ml atropine equivalents), which was significantly different to controls. This caused measurable cognitive impairment in psychiatrically healthy older adults—scopolamine group recalled fewer words for fifth trial section of Rey Auditory Verbal learning test ($p < 0.01$)	Randomised double blind trial Used detailed mental status testing to detect mild changes Adjusted for pre-injection levels Excluded patients with prior cognitive change and on psychotropic medication
Tollefson 1991[243]	34	Nursing home residents	Randomised study of intervention to reduced calculated anticholinergic index[272] by at least 25% atropine equivalents from baseline SAA and psychometric testing on recruitment to study, and repeated at one month after intervention	Saskatoon delirium checklist Symptoms Signs, side-effect checklist	SAA and cognitive function in intervention and non-intervention groups Buschle selective reminding test MMSE Brief cognitive rating scale Weschler Memory Scale Letter cancellation test Psychogeriatric dependency rating scale Global deterioration scale	The pre-intervention calculated anticholinergic index (atropine equivalents mg/24 hours) was 4.3 ± 5.2, compared with post-intervention 1.3 ± 3.8, which was intended effect of intervention The pre-intervention SAA was 2.49 ± 3.9, compared with 1.89 ± 3.4 post-intervention (atropine equivalents) ($p < 0.0001$) The change in calculated anticholinergic index exceeded the difference in SAA in intervention group (no linear relationship shown) There was negative correlation with SDC ($p < 0.01$) and digits forward ($p = 0.03$) with 4-week SAA after intervention The nonintervention group showed no reduction of AA measured by SAA or calculated anticholinergic index	Blinded cognitive assessments to SAA Multiple measures of cognition used A single outcome measure in relation to cognition for which study was powered not described Population comorbidities not clearly defined

Study	n	Population	Study design	Delirium diagnosis	Outcome measures	Findings	Comments
Tune 1992[260]	2	2 case studies of homatropine ophthalmic solution	Case studies	DSM-III criteria for delirium	nil	N/A	Used gold standard delirium criteria Case studies
Tune 1993[259]	25	Surgical intensive care patients	Cross-sectional study DSM-III-R interview for delirium by psychiatrist Anticholinergic score determined by sum of atropine equivalents of parent solutions of medication taken in prior 24 hours to clinical assessment (10^{-8}mmol/l solutions) tested anticholinergic radioreceptor assay	DSM-III-R criteria by researchers (psychiatrists)	Delirium defined by DSM-III-R criteria	Prevalence of delirium was 36% (n = 9/25) Mean anticholinergic score was 7.09 $\pm$ 2.1 for delirium group compared with 5.00 $\pm$ 2.41 for nondelirious group (p = 0.045)	Used gold standard delirium criteria Use of AA of parent compounds has limitations as discussed
Mach 1995[266]	22	Elderly male hospitalised medical patients	Case control study with 11 male patients with delirium and 11 comparable male controls (aged $\geq$ 60 years). Premorbid dementia excluded SAA on recruitment in both groups, and at delirium resolution in delirium group. MMSE after delirium resolution	DSM-III-R operationalised criteria MMSE after delirium resolution	SAA	Mean SAA was higher in delirium (6.05 $\pm$ 2.97 nM atropine equivalents) than controls (3.38 $\pm$ 2.49nM) (p < 0.05) Mean baseline SAA (7.77 $\pm$ 2.37 nM) in delirium resolution (n=6) was higher than the SAA after delirium resolution (3.92 $\pm$ 2.61) (p < 0.05). Mean baseline SAA (7.77 $\pm$ 2.37 nM) in those whose symptoms persisted than in patients who had delirium resolution (3.99 $\pm$ 2.30) (p < 0.05). Mean SAA was significantly lower after delirium resolution (n=6), and not consistently related to change in anticholinergic medication reduction or cessation	Control group included. Used gold standard delirium criteria Second sample was not taken in non-delirious group to look at effect of acute illness without delirium) Only male patients and excluded dementia

Study	n	Population	Study design	Delirium diagnosis	Outcome measures	Findings	Comments
Flacker 1998[189]	67	Acutely ill older medical adults age ≥75 years	Consecutive cohort of general medical inpatients Covariates of cognitive impairment, comorbidity (CIRS), functional status (ADL), medication, electrolytes and white cell count. Anticholinergic medication classified as definite (list given), or possible (including those tested in radioreceptor assay) effects SAA was obtained on second day of admission	Diagnosis of delirium by CAM blinded to SAA DSI	SAA (stratified in quintiles) Quintile ranges were as follows: Quintile 1: 0–0.23 nM/200μL Quintile 2: 0.24-0.42 nM/200μL Quintile 3: 0.43–0.88 nM/200μL Quintile 4: 0.89–1.46 nM/200μL Quintile 5: 1.47–5.07 nM/200μL	Deliium occurred in 30% Mean SAA was 0.7 ± 0.8 nM/200μL in nondelirious group and 1.8 ± 1.6 nM/200μL in delirious group (p = 0.01) In multivariate regression analysis the SAA quintile was significantly associated with delirium, after adjusting for ADL impairment, admission diagnosis of infection, elevated white cell count (p = 0.006). Each increase in SAA quintile was associated with a 2.38 times increase in likelihood of delirium. Percentage of patients with delirium was 7.7% in quintile 1 and 61.5% quintile 5 The number of symptoms identified with DSI was greater with increasing quintile Anticholinergic (definite and possible) use was 93.6% in non-delirious and 80% in delirium group (not significant)	Delirium diagnosis was blinded to SAA results Covariates assessed with validated tools Anticholinergic medication classification clearly defined SAA analysed by quintile, rather than as continuous variable
Flacker and lipsitz 1999 [253]	22	Residents of long term care facility with acute febrile illness	Prospective cohort	DSI at 24 hours after fever, and at one month MMSE CAM	Cognitive Performance Scale CIRS SAA Number of medications	Delirium was present during febrile illness in 8/22 subjects (36%) SAA declined similarly in delirious and non-delirious subjects by 1 month follow-up (p < 0.001). SAA in delirious and non-delirious subjects were not statistically different. SAA during febrile illness was 0.67 ± 0.63 nM/200 μL and at 1 month follow-up 0.09 ± 0.13	Small sample size Small number of delirium episodes Only one interview during illness to detect delirium

Study	n	Population	Study design	Delirium diagnosis	Outcome measures	Findings	Comments
Mussi 1999[273]	61	Geriatric medical inpatients	Cross-sectional study	CAM	SAA Routine clinical and laboratory assessments	SAA in delirious patients was significantly higher (23.0 ± 15.5 ρmol/mL) than non-delirious (3.9 ± 8.4 ρmol/mL) ($p < 0.004$)	Only used screening instrument to define delirium (CAM)
Flacker and Wei 2001[231]	10	Elderly medical inpatients with no history of recent anticholinergic medication usage	Prospective cohort	CAM	SAA on second morning after admission	SAA was present in 8/10 patients Mean 0.69 (0.23–1.72) nmol/L per 200μL	Detailed definition of anticholinergic medication Small sample size
Plaschke 2007[256]	37	ICU patients	Prospective cohort study	CAM-ICU	SAA 48 hours after ICU admission Quantitative EEG	No differences in measured SAA were seen In patients with delirium (n = 17) there was a higher relative EEG theta power and reduced alpha power There was no correlation between SAA and EEG measurements	Only used screening instrument to define delirium (CAM-ICU)

Study	n	Population	Study design	Delirium diagnosis	Outcome measures	Findings	Comments
Thomas 2008[265]	61	Elderly over 80 years with acute medical illness	Cross-sectional study in a consecutive cohort	Expert consensus (geriatrician, neurologist, geriatric psychiatrist) DSM-IV criteria	On third day of admission within a 4-hour time frame SAA (one hour before EEG recording) Quantitative EEG CAM MMSE IQCODE Short portal mental status questionnaire DI DSM-IV-R criteria for dementia and delirium	31 participants had dementia without delirium, 15 had delirium in context of pre-existing dementia, and 15 were not cognitively impaired SAA was detectable in all but one patient, with mean 10.9 $\pm$ 7.1 pmol/ml EEG measures correlated with cognitive performance and delirium severity but not SAA levels	Comparison groups of dementia without delirium, cognitively unimpaired Cross-sectional measures Did not include participants with delirium and no prior cognitive impairment Total number of medications when are 'delirogenic' presented, without subset of anticholinergic medications

AA – anticholinergic activity; ADL – Activities of Daily Living, CAM – Confusion Assessment Method, CAM-ICU – Confusion Assessment Method-Intensive Care Unit; CIRS – Cumulative Illness Rating Scale; DI – Delirium Index; DSI – Delirium Symptom Interview; DSM-IV-R – Diagnostic and Statistical Manual of Mental Disorders, fourth edition; ECT – electroconvulsive therapy; EEG – electroencephalogram ICU – intensive care unit; IQCODE – Informant Questionnaire of Cognitive Decline in the Elderly; MMSE – Mini-Mental State Examination, nM – nanomol; SAA – Serum anticholinergic activity

Table 10 Studies of serum anticholinergic levels and anticholinergic use or cognitive change

Study	n	Population	Study design	Outcome measures	Findings	Comments
Tune 1980[241]	35	Psychiatric inpatients Schizophrenia and manic depression	Cross-sectional study Patients receiving anticholinergic (to prevent EPS) and neuroleptic medications prescribed by treating physician Single measure of SAA, and in 9 patients serial measures of SAA with increased anticholinergic medications Patients with delirium excluded	DMEPS	The single measurement of SAA was inversely associated with presence of acute EPS ($p < 0.001$) 20/32 patients had clinically detected extrapyramidal effects at SAA of 0.7 pmol per 0.2ml atropine equivalents In those with SAA <0.7 pmol/0.2ml EPS seen in 2/24 In the 9 patients where anticholinergic medications were increased reduction in DMEPS scores occurred and SAA increased	Only single measure of SAA after change in medication
Tune 1982[274]	24	Chronic schizophrenia	Stabilised schizophrenic patients on psychotropics Cross-sectional study	Free memory recall test Weschler Adult Intelligence Scale SAA	Inverse correlation between SAA and performance on memory task – recall scores ($r = 0.51$, $p < 0.01$)	SAA was blinded to clinical state Small sample, and one cross-sectional measure
Mondimore 1983[275]	20	Major depression (DSM-III defined) and post ECT	Cross-sectional study, with evaluations before, and 1 and 5 hours after ECT	MMSE score Confusional state post ECT defined as MMSE decline of 2 or more points	SAA of 15ng/ml atropine equivalents one hour after ECT was significantly associated with decline in MMSE ≥ 2, with 8/12 patients having MMSE decline with SAA of $\geq$ 15ng/ml, compared with 1/8 with levels lower ($p < 0.05$)	Pre and post evaluations performed. Determination of cut-off for SAA at 15ng/ml not described. No delirium assessment .Only one hour post ECT SAA presented in paper Not standardised for time from ECT or number of treatments No adjustment for other covariates such as age, medication usage, comorbidities, illness severity. Prospective follow-up only short duration

Study	n	Population	Study design	Outcome measures	Findings	Comments
Rovner 1988[276]	22	Nursing home residents with dementia	Cross-sectional study, with sample derived from 181 residents, and inclusion if consent from patient, family and physician	Cognitive impairment (MMSE) and self-care capacity (self-care subscale of psychogeriatric dependency rating scale) DSM-III-R by research assistant for chronic cognitive impairment	A wide range of SAA found (0.0–9.95 pmol/ml) Patients with levels of SAA above and below median (0.83 pmol/ml) for sample were compared, and those with levels above median had significantly higher self-care scores ($p < 0.025$), but no difference in MMSE scores Total number of drugs, number of anticholinergic drugs or drug doses did not predict AA	Method by which anticholinergic drugs were classified or effect of dosage not described. No adjustment for other covariates such as age, comorbidities, illness severity. DSM-III criteria, and single rater not blinded to SAA levels.
Theinhaus 1990[277]	28	Psychogeriatric patients admitted for psychotropic (neuroleptics or antidepressant) intitiation or dose adjustment n = 10 AD, and n = 18 no cognitive impairment	Prospective consecutive cohort of psychogeriatric patients admitted for psychotropic (neuroleptics or antidepressant) intitiation or dose adjustment SAA at recruitment and after 7 days of final dose adjustment (steady state achieved)	MMSE Digit retention span Self-rated memory scale All assessments blinded to SAA	Mean (±SD) SAA in nondemented group was 4.09 ± 4.83 μM and 3.50 ± 2.89 μM in AD group at baseline ($p < 0.01$) At steady state the mean (±SD) SAA in nondemented group was 6.66 ± 6.23 μM and 6.17 ± 4.47 μM in AD group at baseline ($p < 0.02$) Cognitive functioning was unchanged in non-demented group Selected measures of cognition showed significant further impairment in dementia group (measures of recognition ($p < 0.02$), forward digit span ($p < 0.01$), and recall ($p < 0.01$)	Measured SAA at steady state Blinded cognitive assessments to SAA Multiple measures of cognition used Control group may not be homogeneous Psychotropic titration was clinician decided, so not controlled study

Study	n	Population	Study design	Outcome measures	Findings	Comments
Nebes 1997[278]	36	Elderly patients with major depression	Cross-sectional study Recruited form geriatric inpatient unit and outpatient depression clinic DSM-IV diagnosis of major depression Hamilton rating scale for major depression Structured clinical assessment and SAA prior to commencement of antidepressant Population characteristics defined by dementia rating scale and Cumulative Illness Rating Scale-geriatric No delirium patients included	Verbal learning task of 15 unrelated words measuring immediate recall, learning curve, delayed recall, percent retention, delayed recognition	In 19 patients Mean SAA 0.28 $\pm$ 0.26 pmol/ml. 17 patient had no detectable SAA Comparison between depressed patient group, with no detectable SAA versus positive SAA, adjusting for age and HRS showed impaired recall ($p < 0.05$) and percent retention ($p < 0.05$) Cognitive impairment in depressed patients may be due to other causes apart from depression itself, and may assist in assessing cognitive toxicity with antidepressant therapy	Adjusted for age and differences in HRD scores Verbal learning task not an established measure
Tracy 1998[279]	22	Chronic schizophrenia on clozapine or risperidone	Two SAA were obtained 1 week apart in 22 patients with chronic schizophrenia (DSM-IV defined) taking stable dose of clozapine or risperidone for 30 days or over Aim was to determine anticholinergic burden from these medications, and the cognitive effects	Comparison of SAA and MMSE in clozapine and risperidone groups	Mean SAA at recruitment were significantly different ($p < 0.001$): Clozapine group: 4.35 $\pm$ 2.38 pmol/ml Risperidone group: 0.27 $\pm$ 0.28 pmol/ml This difference was maintained at 1 week No significant differences in MMSE between two groups, and did not correlate to SAA for whole sample or for the two groups Concluded the moderately high SAA associated with clozapine was not sufficient to cause cognitive impairment as measured by MMSE	Stable medication usage of one medication in each group Repeated SAA over time Only used global cognitive assessment with MMSE, which may not detect subtle changes

Study	n	Population	Study design	Outcome measures	Findings	Comments
Pollock 1998[280]	61	Elderly depressed patients (mean age 73.2 years)	RCT of paroxetine and nortriptyline to treat depression in elderly depressed	SAA at baseline and 1,4,6 weeks Plasma concentrations of paroxetine and nortriptyline	SAA for nortriptyline treated patients were significantly greater than paroxetine (p = 0.004) At 1 week the median change in SAA from baseline was 0.28 pmol (0. –2.28) atropine equivalents in nortriptyline group and 0 pmol for paroxetine Change in plasma levels of nortriptyline correlated with change in SAA (p = 0.01) At therapeutic plasma concentrations paroxetine has approx. 1/5 the antichol,inergic potential of nortriptyline	RCT Repeated measure of SAA. Correlated with plasma levels of medication
Carnahan 2002[249]	96	Elderly residents in rural long-term care facilities	Cross-sectional study	SAA CRAS-M	Mean SAA 0.91 ± 0.51 ρmol/0.2mL (range 0.09 ± 2.61) SAA was significantly correlated with CRAS (p-0.0087) but only 7.1% of variance explained	Compared a rating of medications list with SAA
Mulsant 2003[281]	201	Community based sample	Epidemiology study of prevalence of SAA in community based cohort	MMSE SAA No of anticholinergic medication	SAA was detectable in 180 (89.6%) mean 1.45 (range 0.05–5.70 ρmol/ml Logistic regression analysis indicated subjects with SAA above 90th percentile (≥2.80 ρmol/mL) were 13 times (OR 1.08-152.39) more likely than those with undetectable SAA to have MMSE score <24	Randomly selected sample Adjusted for age, gender, educational level, number of medications
Mulsant 2004[282]	86	Patients with DSM-IV defined dementia (AD, vascular or mixed)	Randomised double blind trial of olanzapine or risperidone over 6-week period Patients with delirium defined by CAM were excluded from study	Peripheral anticholinergic effects. Extra-pyramidal symptoms. Serum anticholinergic assay levels at baseline, Week 3 and 6 Antipsychotic drug levels	Olanzapine treated patients had significant increase in anticholinergic levels from baseline at Week 3, compared with no statistical difference in risperidone group The correlation between plasma antipsychotic concentration and AA was significantly greater in olanzapine treated group	Explored SAA in context of RCT treatment in dementia

Study	n	Population	Study design	Outcome measures	Findings	Comments
Chew 2005[283]	35	Patients admitted to geropsychiatric unit for treatment of behavioural disturbances in dementia	Baseline data from 35/50 participants in a clinical trial—continuation of pharmacotherapy for agitation in dementia, who had SAA measure available Current diagnosis of delirium excluded	SAA MMSE SIB	SAA was detectable in 16/26 (62%) of the 26 subjects who could complete the cognitive testing. Mean SAA was 1.06 (1.20) pmol/mL; (range: 0–3.70). Mean MMSE and SIB scores were 12.4 (8.5) and 76.3 (25.6), respectively Correlation between SAA and MMSE was significant (Spearman r = 0.398; n = 25; p = 0.049). SAA and SIB were also correlated, but not statistical significant (r = 0.405; n = 18; p = 0.095)	Small sample
Nebes 2005[284]	134	134 community dwelling elderly (aged 65–80) with no history of neurological or psychiatric disease, or narcotic use A neuropsychological battery was administered to exclude participants with incipient dementia		Number comparison test (psychomotor speed) Verbal N Back test (working memory) Serial pattern learning task Anticholinergic medication use SAA WMH on MRI F	Participants were divided into three SAA groups: undetectable SAA (n = 35); moderate SAA (0.25 to 3.9 pmol/mL) (n = 69); high SAA $\geq$ 4.0 pmol/mL) (n = 30) because of the highly skewed nature of the SAA distribution Relationship between WMH volume and performance on measures of speed of cognitive processing and implicit learning (the greater the volume of WMH, the poorer the performance) in the high SAA group but not in the two lower SAA groups	The original study was not designed to test a WMH and SAA interaction Arbitrary division of SAA into three groups Only adjusted for education as covariate
Brecht 2007[285]	Study 1 (n = 9) Study 2 (n = 7)	Study 1: 5 healthy volunteers and four patients post cardiac surgery Study 2: 7 healthy volunteers	Study 1 – serum taken 2 to 4 days post operatively or single sample in healthy volunteers with no medications for at least 3 days prior. Study 2 – serum taken after 150mg of oral amitriptyline. Study 1 serum taken from 0800 hours every 4 hours for 24 hour period. Study 2 serum was taken at baseline and 8 hours after amitriptyline	SAA	Study 1 – absolute SAA varied in a wide range from 1.2–14.5 atropine equivalents over 24 hours SAA levels were detected in healthy volunteers with individual variation. SAA in cardiac patients were lower Study 2 – mean SAA increased by 6.38 atropine equivalents at the peak amitriptyline concentration	Small number of subjects, predominantly healthy volunteers SAA post-surgery taken over 48 hours after surgical procedure when SAA changes may already be normalising

Study	n	Population	Study design	Outcome measures	Findings	Comments
Nebes 2007[286]	88	Community dwelling elderly (aged 65–80) with no history of neurological or psychiatric disease, or sedative hypnotic, antidepressant or antipsychotic use	Cross-sectional cohort	SAA motor performance (gait speed and simple manual response time)	SAA was relatively low in this group; however, an elevated SAA was associated with a significant slowing in both gait speed and simple response time	Cross-sectional

AA – anticholinergic activity; AD – Alzheimer's disease; CRAS-M – Clinician Rated Anticholinergic Scale-modified version; DMEPS – Di Mascio Extrapyramindal rating scale; ECT – electroconvulsive therapy; EPS – extrapyramidal side effects; MMSE – Mini-Mental State Examination, MRI-F Functional magnetic resonance imaging; nM – nanomol; RCT – randomised controlled trial; SAA – serum anticholinergic activity; SIB – Severe Impairment Battery; WMH – white matter hyperintenities

Table 11 Range of serum anticholinergic activity in different studies

Study	n	Population	Timing of serum anticholinergic activity specimen	Mean serum anticholinergic activity ± Standard Deviation
Delirium populations				
Tune 1981[261]	29	Post cardiac surgery	24 hours after surgery, and then three times per week in conjunction with delirium assessment	Mean not reported 7/8 who were delirious at 24 hours had SAA levels >1.5pmol/ml
Miller 1988[271]	36	Elderly pre-surgical patients (59 years and older) Randomised trial of pre-surgery intramuscular scopolamine/placebo	Evening before surgery (pretest) 45 minutes to one hour post injection	Pretest mean: mean 9.1 ±17.7 pmol/ml Postscopolamine group: 121.1 ± 85.5 pmol/ml Control group: 11.6 ± 18.2 pmol/ml
Golinger 1987[263]	25	Surgical ICU cross-sectional sample (presence or absence of delirium determined on that time-point)	Blood sample within 4 hours before mental status examination	Delirious patients: 4.67 ± 3.3 ng/ml non delirious: 0.81 ± 1.0 ng/ml
Tollefson 1991[243]	34	Nursing home residents randomly allocated into control group or intervention to reduce anticholinergic medication by at least 25% from baseline	At baseline, then 4 weeks after medication change to reduce anticholinergic load by 25%	Pre-intervention: Control: 3.58 ±3.8 ng/ml Intervention group: 2.49 ± 3.9 ng/mlPost intervention: Control: 3.23 ± 3.7 ng/ml Intervention group: 1.89 ± 3.4 ng/ml
Tune 1992[260]	2	2 case studies of use of homatropine ophthalmic solution	NA	N/A
Tune 1993[259]	25	Surgical intensive care patients	Cross-sectional – at recruitment	Did not measure SAA, but used parent compounds of medication patients were on to calculate anticholinergic score
Mach 1995[266]	22	Elderly (>60 years) male hospitalised medical patients	SAA was taken on recruitment in both groups, and additional sample at delirium resolution in delirium group	Delirious group: 6.05 ± 2.97 nM atropine equivalents Controls (3.38 ± 2.49nM)
Flacker 1998[189]	67	Acutely ill older medical adults	CAM and SAA on second hospital day	Mean SAA: Nondelirious group: 0.7 ± 0.8 nM/200μL Delirious group: 1.8 ± 1.6 nM/200μL in

Study	n	Population	Timing of serum anticholinergic activity specimen	Mean serum anticholinergic activity ± Standard Deviation
Flacker and Lipsitz 1999[253]	22	Long-term care residents with fever (temperature of 100 degrees Fahrenheit or more)	Second morning following fever – CAM, DSI and SAA One month follow-up	Mean SAA : during febrile illness: 0.67 ± 0.63 nM/200 μL at 1 month follow-up 0.09 ± 0.13 nM/200 μL
Mussi 1999[273]	61	Elderly geriatric inpatients (cross-sectional cohort)	Within 24 hours of admission to geriatric inpatient unit	Delirious patients: 23.0 ± 15.5 ρmol/mL Non-delirious: 3.9 ± 8.4 ρmol/mL
Flacker and Wei 2001[231]	10	Elderly medical inpatients with no recent anticholinergic medication usage	Day 2 of hospital admission	Mean 0.69 (0.23 – 1.72) nmol/L per 200μL
Plaschke 2007[256]	37	Intensive care patients (17 with delirium, 20 without delirium)	SAA 48 hours after ICU admission	Delirious patients: mean SAA 2.8 (SD 2.5) pmol/ml Nondelirious patients: mean SAA 2.6 (SD 2.3) pmol/ml
Thomas 2008[265]	61	Elderly patients with acute medical illness over 80 years	Third day after admission within a 4-hour time window	mean 10.9 ± 7.1 pmol/ml
Other populations				
Tune 1980[241]	35	Psychiatric inpatients Schizophrenia and manic depression		Mean not reported. Level >3.5 pmol/ml: EPS seen in 20/32 Level <3.5 pmol/ml: EPS seen in 2/24
Tune 1982[274]	24	Chronic schizophrenia	Not clear	12.0 ± 2.5pmol/ml (range 0-38)
Mondimore 1983[275]	20	Major depression (DSM-III defined) and post ECT	Varied whether first – fourth ECT treatment. Pretreatment of 0.5mg of atropine 15 – 30 minutes prior to ECT Evaluation before, and at 1 and 5 hours ECT	Mean not reported SAA levels at 1 hour post ECT >15ng/ml: 8/12 had decline in MMSE SAA levels at 1 hour post ECT levels <15ng/ml: 1/8 had decline in MMSE
Rovner 1988[276]	22	Nursing home residents with dementia (cross-sectional cohort)	One measure, approximately 4 hours after medications given	Range presented: 0.0–9.95 pmol/ml Median 0.83 pmol/ml
Theinhaus 1990[277]	28	Psychogeriatric patients admitted for psychotropic (neuroleptics or antidepressant) initiation or dose adjustment n = 10 AD, and n = 18 no cognitive impairment	At baseline and at steady state of new medications (at least 7 days after last dose increment)	Baseline: Non-demented: 4.09 ± 4.83 μM, Demented: 3.50 ± 2.39 μM After psychotropic steady state: Non-demented: 6.66 ± 6.23 μM, Demented: 6.17 ± 4.47 μM

Study	n	Population	Timing of serum anticholinergic activity specimen	Mean serum anticholinergic activity ± Standard Deviation
Nebes 1997[278]	36	Elderly patient with DSM-IV major depression	One measure at same time as verbal learning test, before antidepressant commencement	In 19 patients mean SAA 0.28 ± 0.26 pmol/ml. 17 patient had no detectable SAA
Tracy 1998[279]	22	Chronic schizophrenia	After breakfast, and one hour after morning medication dose (clozapine or risperidone)	Mean SAA at recruitment: Clozapine group: 4.35 ± 2.38 pmol/ml Risperidone group: 0.27 ± 0.28 pmol/ml
Pollock 1998[280]	61	Elderly depressed patients, RCT of paroxetine versus nortripytlline	SAA at baseline and at 1, 4, and 6 weeks of treatment	Not presented (only mean changes)
Carnahan 2002[249]	96	Residents of rural long term facilities, not delirious	Day 14 of 1-month study period	Mean SAA 0.91 ± 0.51 ρmol/0.2mL
Mulsant 2003[281]	201	Community based cohort not delirious	Serum taken every 2 years at which the cognitive tests were also done	Mean 1.45 (range 0.05 –5.70) ρmol/ml
Mulsant 2004[282]	86	Patients with DSM-IV defined Dementia (Alzheimer's, vascular or mixed)	Baseline, Week 3 and Week 6	Only changes from baseline presented
Chew 2005[283]	35	Patients admitted to geropsychiatric unit for treatment of behavioural disturbances in dementia and participating in a clinical trial for agitation in dementia	Baseline, at entry to the clinical trial	Mean SAA was 1.06 (1.20) pmol/ml; (range: 0–3.70)
Nebes 2005[284]	134	134 community dwelling elderly (aged 65–80) with no history of neurological or psychiatric disease, or narcotic use A neuropsychological battery was administered to exclude participants with incipient dementia	One measure	Undetectable SAA (n = 35); moderate SAA (0.25 to 3.9 pmol/ml) (n = 69); high SAA (≥4.0 pmol/ml) (n = 30)
Brecht 2007[285]		Study 1: 5 healthy volunteers and four patients post cardiac surgery	4-hourly measures for 24 hours	Absolute SAA varied in a wide range from 1.2–14.5 atropine equivalents over 24 hours
Nebes 2007[286]	88	Community-dwelling elderly (aged 65–80) with no history of neurological or psychiatric disease, or sedative hypnotic, antidepressant or antipsychotic use	One measure before testing	Mean in low SAA group (n = 29) 0.36 (SD 0.34) pmol/ml. Mean in medium SAA group (n = 33) 1.36 (SD 0.31) pmol/ml. Mean in low SAA group (n = 26) 3.42 (SD 2.33) pmol/ml

AD – Alzheimer's disease; CAM – Confusion Assessment Method; DSI – Delirium Symptom Interview; DSM III – Diagnostic and Statistical Manual third edition; DSM-IV – Diagnostic and Statistical Manual of Mental Disorders, fourth edition; ECT – electroconvulsive therapy; EPS – extrapyramidal side effects; ICU – intensive care unit; MMSE – Mini-Mental State Examination; SAA – serum anticholinergic activity; SD – standard deviation

1.13 Impact of delirium

Several studies have shown an association between an episode of delirium in medical, geriatric and surgical populations and increased length of hospital stay, increased risk of institutionalisation, functional and cognitive decline, and mortality.[190 287-294] In Palliative populations studies have only explored impact on mortality. The morbidity associated with a delirium episode has mainly been described in terms of complications such as pressure ulcers, risk of pneumonia, increased length of hospital stay, and post-operative complications.[295] More recently, the focus has been on high levels of psychological morbidity experienced by patients, caregivers, or healthcare providers, again demonstrated in medical, surgical, geriatrics and palliative populations.[295] In particular higher rates of depression have been identified in those who have recovered from delirium after hip fracture, which cannot be explained by persistent delirium or cognitive impairment.[296]. It is possible that presence of psychological sequelae may not be brought to the attention of health professionals due to patients and caregivers not raising these symptoms or being asked about them.

1.13.1 Mortality

A systematic review of 24 studies in 2000 determined that cognitive impairment is a factor definitely associated with reduced survival in terminally ill cancer patients.[297] Seventeen studies were prospective cohorts, and 15 of these studies used multivariate analysis, but only six studies used Cox proportional hazard models. Cognitive impairment was assessed in seven studies using multivariate analyses and was significantly associated with reduced survival in six of those studies. Delirium has been assessed variably using DSM-IV criteria and CAM, and at varying time-points in these studies, and some studies have only assessed cognitive impairment (for example using the MMSE).[115 297 298] A case series including 100 patients identified prospectively, and 40 patients retrospectively with systemic cancer in acute care identified with delirium (using DSM-III-R criteria evaluated by a neurologist) identified 30-day and six-month mortality as 25% and 44% respectively.[104] Younger age was also significantly associated with the 30-day mortality rate.[104] Two studies have looked specifically at predictors of mortality in palliative care populations with delirium. The prospective cohort

study of advanced cancer patients (n = 113) admitted to a Canadian specialist acute inpatient palliative care unit described earlier also explored survival, and showed those with delirium had a significantly shorter survival ($p < 0.001$); for example at 50 days from admission 25% of the delirium group were alive compared to 75% of the non-delirium group.[38] The other study in an inpatient palliative care unit in Ireland[215] also described previously, screened patients using the CAM[148] to screen participants with a high likelihood of delirium, who then went on to have delirium confirmed by a research physician using DSM-IV-R criteria. The mean survival in days for the group with reversible delirium was 39.7 ± 69.8, compared with 16.8 ± 10.0 for the irreversible group. Independent negative predictors of survival (in days) from the time of delirium diagnosis in linear regression analysis were severe cognitive impairment on CTD ($p < 0.001$), greater age ($p = 0.01$), and organ failure ($p = 0.01$).[215]

Two prognostic scores have been published for use in advanced cancer. The palliative prognostic index, which includes delirium using DSM-IV criteria, had 80% sensitivity and 85% specificity in predicting survival in a population of advanced cancer patients in a palliative care unit.[299] The Palliative Prognostic Score (PaP) does not include cognitive function assessment; however, when a diagnosis of delirium using CAM criteria was combined with the PaP score it was an independent factor in predicting survival.[97] The median survival time was 21 days for delirious patients (CI 16–27) and 39 days (CI 33–49) for others.[300] This study only included patients with advanced solid tumours when cytotoxic chemotherapy was no longer considered viable, and excluded renal carcinoma, multiple myeloma and haematological malignancies.[300] Since then, the original authors have revised the PaP score to include delirium as an additional variable (D-PaP).[301] They used a retrospective cohort of 361 terminally ill cancer patients and used a validation by calibration approach using the original score, plus the new variable: delirium into a multivariate model.[301] The discriminating ability of the three-group prognostic classification obtained by the PaP score and D-PaP was assessed using a Kappa statistic. Patients are assigned into three different risk groups according to 30-day survival probability based on total score with risk group A having 30-day survival >70%, 4.4% in group B 30%–70%), and 6.2% for group C <30%. Delirium added significantly to the original PaP score ($p <$

0.0001, hazard ratio (HR) 1.6, CI 1.22–1.99).[301] The discriminating ability of D-PaP was 0.86 (CI 0.82–0.88), compared with 0.85 (CI 0.82–0.88 for PaP). When assessing patients with D-PaP, 4.7% switched to a less favourable prognosis, whereas 14.4% switched to a more favourable group.[301] Based on the HR of delirium and from 30-day survival estimates, it is estimated that survival differed for patients with or without delirium by 0.9% in risk group A (30-day survival >70%), 4.4% in group B (30-day survival 30%–70%), and 6.2% for group C (30-day survival <30%). Hence, the addition of delirium seems to better classify group C.[301]

These studies used delirium diagnosis at the single time-points of collection of prognostic score information, and did not include prior episodes of delirium or duration or severity parameters. The role an episode of delirium plays in planning future care, and communication of prognosis to the patient and family also needs to be defined.[90]

The NICE guidelines on delirium diagnosis, prevention, and management[28] summarises the evidence for increased mortality following delirium across all studies in medical, surgical, orthopaedic and intensive care reviewed as moderate quality (excluded the studies considered above), with in-hospital mortality OR 2.6 (CI 0.7–6.2) and mortality at one month 3.0 (1.1–8.4). It is interesting to compare the covariates used in cancer patients to those in the above listed populations[76 302 303], which have explored mortality. The illness severity (such as measured by APACHE II [c] scores[304]), comorbidity burden (such as measured by Charlson Comorbidity Index (CCI)) and dementia diagnosis were commonly used in the geriatric studies.[288] The studies in cancer prognostication have included clinical symptoms, physical signs and biological factors associated with advanced disease, for example CNS metastases, performance status, symptoms related to advanced cancer, and lymphocyte counts.[90 297] The diagnosis of dementia, was only present in 7% of patients with cancer and delirium, compared with 35%–50% in general

[c] Acute Physiology and Chronic Health Evaluation II. The point score is calculated from 12 routine physiological http://en.wikipedia.org/wiki/Physiology measurements, such as blood pressure, body temperature, heart rate, during the first 24 hours after admission, information about previous health status, and some information obtained at admission (such as age).

medical populations, illustrating one of the key differences in these populations.[192 305 306]

1.13.2 Patient and caregiver experience

Maintaining lucidity at the end of life has been identified by patients and their families as very important; however, it is less likely to be identified as important by their treating physicians (92% of patients versus 65% of physicians rated being mentally aware as very important at end of life, $p < 0.001$).[307 308] Patients rated pain control only slightly higher to mental awareness (mean rank difference 1.51), in comparison to physicians (mean rank difference 3.76, $p < 0.001$), and further study is needed to identify if this is because physicians would accept reduced lucidity for achieving better pain control.[307 308] It can be extrapolated that mental awareness is a crucial component in allowing patients to achieve the other goals at end of life identified as significant, such as communication with their physician regarding decision-making, achieving a sense of completion, and preparation for death.[307 308]

Vivid case anecdotes[309 310] and studies in the literature[311 312] show that recall of delirium experience is common. A review conducted in 2008 of eight qualitative studies interviewing patients post delirium in a range of settings including burns, surgery, orthopaedics and geriatrics described some key areas of the experience: the emotional feelings, perceptual and thought disturbances, and subjective perception of delirium.[312] The dominant emotions were fear, anxiety and feeling threatened; and it was often in response to these that the patient displayed aggressive behaviour.[313] Visual hallucinations were particularly of people or animals and often frightening, and misinterpretation of real sensory experiences occurred. Some people did describe hallucinations of relatives, both living and deceased, which were not frightening, but caused frustration due to an inability to communicate with them.[313] Threatening delusions and also paranoid beliefs (often from over interpretation of real events, e.g. an injection as being a threat to one's life) were common. The subjective perception of being delirious involved a sense of being trapped in a situation which was out of one's control and at the border between reality and imagination.[313] Distorted time perception and a dream-like experience were also common descriptions.[313] The difficulty in communicating

with others compounds the situation, and they seek clues to make sense of the situation from others. People could describe a sense of health professionals being irritated with them or lacking patience when trying to communicate with them while delirious.[314]

Two studies have specifically explored the delirium experience in cancer patients.[315 316] These studies have explored the association with delirium recall and distress slightly differently. The first study looked at associations with delirium characteristics and functional status rated by the clinician[295], whereas the second study looked at the symptomatology recalled by the patient themselves.[316] The first study was a prospective cohort study of 154 hospitalised cancer patients meeting DSM-IV criteria for delirium demonstrating that in the 101 patients with delirium resolution, 53.5% recalled their delirium experience.[295] Delirium symptoms and severity were characterised at onset by MDAS, with mild delirium defined as score ≤ 15, moderate 16–22, and severe 23–30. The 53 patients with lack of delirium resolution all died; however, it was not possible in this study to determine the level of distress of family and carers for this group. The experience of delirium was assessed using a questionnaire, the Delirium Experience Questionnaire (DEQ) designed to elucidate recall and degree of distress.[295] The DEQ has face validity but has not undergone psychometric evaluation, and asks six questions:

1. Do you remember being confused? (yes/no)
2. If no, are you distressed that you can't remember? (yes/no)
3. If yes, how distressed on a numerical rating scale from 0–4 with 0 being not at all and 4 extremely?
4. If you do remember being confused, was the experience distressing? (yes/no)
5. If yes, how distressed on a numerical rating scale from 0–4 with 0 being not at all and 4 extremely?
6. Can you describe the experience?[295]

Seventy-five also had caregivers available for the interview (spouses n = 68, adult children n = 5, and sibling or friend n = 3). The primary nurse for the 101 patients was also available for interview. The caregiver was asked a single question—how distressed were you during the patient's delirium on a numerical rating scale from 0–4 with 0 being not at all and 4 extremely? The nurse was asked, 'your patient was confused: did you find it distressing: can you rate it on a numerical rating scale from 0–4 with 0 being not at all and 4 extremely?'[295] Univariate and multivariate analyses were undertaken to determine clinical characteristics of delirium, which were the best predictors of recall and distress.[295] The mean age for the 101 patients was 58.3 years (SD 16.7, range 19–89), with 50% female and a diverse range of cancer diagnoses, with 78% with metastatic disease. Seventy-seven per cent received olanzapine (as they were participating in an open label study of this agent), and 17 a combination of haloperidol and olanzapine. The mean MDAS at diagnosis of delirium was 19.2 (SD 3.18, range 14–30), with 69% with moderate and 19% severe delirium. Severe short-term memory impairment and disorientation, delirium severity, reduced level of consciousness and the presence of perceptual disturbance were negatively associated with delirium recall.[295] The mean delirium distress levels were 3.2 for patients, 3.75 for spouse/caregivers and 3.09 for nurses (on a 0–4 scale, with 0 = not at all and 4 = extremely distressing).[295] The presence of delusions was the most significant predictor of patient distress, while Karnofsky Performance Status (measuring patient function on a scale of 0–100, with lower scores indicating poorer function) of the patient predicted spouse/caregiver distress, and perceptual disturbance predicted nurse distress.[295] Distress occurred for both hyperactive and hypoactive delirium, with 43% of patients with hypoactive subtype and 66% of hyperactive subtype recalling the experience.[295]

The other study evaluated 99 patients with advanced cancer who had completely recovered from their delirium episode and had a MDAS score of <13, and their caregivers.[316] This study also utilised the DEQ. The family caregiver and nursing staff were also asked to score the emotional distress for themselves associated with each delirium symptom on a scale from 0 to 4 (0 indicating no distress, 1 a little, 2 a fair amount, 3 very much and 4 extremely distressing).[316] Univariate and multivariate analyses were conducted to determine associations between average

distress scores, clinical and delirium variables. Seventy-three patients (74%) recalled the delirium episode, with recall similar in the hypoactive, hyperactive and mixed subtype groups. In relation to recall of specific delirium symptoms, 48 (66%) participants reported abnormal space orientation, 51 (70%) disorientation to time, 41 (56%) visual hallucinations, 11 (15%) tactile hallucinations, 14 (19%) auditory hallucinations, 28 (38%) delusional thoughts, and 45 (62%) psychomotor agitation.[316] In comparison, caregiver recall of specific delirium symptoms was much higher, with 75 (76%) participants reporting abnormal space orientation, 79 (80%) disorientation to time, 55 (56%) visual hallucinations, 25 (25%) tactile hallucinations, 82 (30%) auditory hallucinations (19%), 46 (46%) delusional thoughts, and 45 (83%) psychomotor agitation.[316] In the participants who recalled their delirium (n = 73) median distress level on the DEQ was 3 (25%–75% quartile, 1–4), which was significantly higher than those with no recollection of delirium episode (n = 26) who reported a median distress level of 2 (25%–75% quartile, 0–4) ($p = 0.03$).[316] The family caregivers mean distress score was 3 (2–4). For most symptoms, patients and family caregivers expressed a high level of distress (a median of 3 or 4 for most symptoms). The median overall distress scores associated with delivering care to delirious patients reported by the ward nurses was 0 (0–1) and specialist palliative care nurses 0 (0-1), both significantly lower than median distress scores reported by patient and family caregiver ($p = 0.0004$).[316] There were no significant associations between age, gender, duration of delirium episode, MDAS score, MMSE score or delirium subtype of patients' delirium distress. This study did not look at associations with specific MDAS items. On univariate analyses there were significant associations between patients reported delirium distress with patient recall of psychomotor agitation ($p < 0.05$), delusions ($p < 0.05$) and time ($p < 0.05$) and space orientation ($p < 0.05$).[316] In multivariate analyses the only significant predictor of patient distress was psychomotor agitation ($p < 0.0001$).[316]

Several studies in Japan have focussed on the experience of delirium from a bereaved caregiver perspective. An initial survey of 195 bereaved caregivers in Japan found that more than two thirds found all delirium symptoms other than somnolence distressing.[317] The symptoms families reported were physical restlessness and mood lability in 62%, hallucinations and delusions in 35%,

somnolence in 92% and cognitive symptoms in 72%.[317] This study, however, did not correlate the symptoms with an established clinical diagnosis of delirium, and hence symptoms described may relate to other aetiologies. It also asked bereaved family members to recollect the experience retrospectively, which may introduce bias.

A qualitative study of 20 bereaved family members whose loved one had experienced delirium in the last two weeks of life was conducted more recently (37 consented; however, 17 then denied that the person had experienced delirium so were not interviewed).[318] In this study, families reported decreased conscious levels, communication difficulty, inappropriate behaviour, hallucinations/delusions and unstable mood.[318] They also reported that the patient talked about events that actually occurred in the past, were distressed as they noticed that they were talking strangely, and talked about uncompleted life tasks.[318] Families' emotions included distress, guilt, anxiety and worry, difficulty coping with delirium, helplessness, exhaustion and being a burden on others.[318] Families perceived the delirium to have different meanings, including positive meanings (e.g. relief from real suffering), a part of the dying process, and misunderstanding of the causes of delirium (effects of drugs, mental weakness and pain).[318]

Illustrative quotes from two family members who participated in this study are as follows:

> The patient said he had been out having fun or met such and such people. Maybe, he forgot his pain and suffering while he was talking. He was relaxed, being able to talk like that. (Bereaved 4)[318]

> Without understanding the cause of hallucination, we wondered if the patient had lost her soul, and we simply stopped talking, not being able to talk any longer. We can talk to the doctor about pain, but we cannot consult with him about matters like hallucinations or the soul. (Bereaved 8)[318]

Recommendations made by these families for support measures specifically for delirium, in addition to information and general support, were to respect the patients' subjective world, treating patients as the same person as before,

facilitating preparations for the patients' death, and relieving family's physical and psychological burden.[318]

A multicentre survey of bereaved family members of cancer patients who had died in eight palliative care units in Japan and experienced delirium in the last two weeks of life (based on a retrospective chart review for DSM-IV-R criteria), asked them to rate frequency and level of distress for 12 delirium related symptoms.[319] This study selected caregivers who were aware of the patient's diagnosis of malignancy and who did not have serious psychological distress as determined by the primary treating palliative care physician. The caregivers were asked to provide their age, gender and relationship to the patient, whereas the treating clinician provided information about the patient's age, gender, cancer diagnosis, and delirium severity and subtype.[319] The questionnaire content was developed based on previous qualitative study by this group (described above) and a systematic literature review.[319] The caregiver was asked if they thought the person was delirious or not—'delirium' was defined for the caregiver in the questionnaire as:

> the rapid development of difficulty in concentration, forgetfulness, disorientation about time and place, hallucinations and delusions, incoherent speech, clouding of consciousness and difficulty in communicating, emotional instability, reversal of daytime and nighttime activities (drowsiness during the day and wakefulness during the night), and inconsistent behavior, with these conditions changing even within a day.[319]

The level of family-perceived distress was assessed by the question: 'How distressing was the patient's delirium for you?' rated on a 5-point scale from 1 no distress at all to 5 very distressing; and the necessity for improvement using the question: 'How much improvement do you think is necessary in the care for delirium,' rated on a 4-point scale (1 no need for improvement, 2 need for some improvement, 3 need for considerable improvement, and 4 need for much improvement.[319] To explore the families' emotions and interpretation of the meaning of delirium they were asked to rate their degree of agreement with 16 statements to describe their feelings on a 5-point Likert scale of 1 disagree to 5 strongly agree and to rate their degree of agreement with eight potential meanings of delirium also on a 5-point Likert scale of 1 disagree to 5 strongly agree.[319]

During the study period 984 patients died in the eight palliative care units, with 672 diagnosed with delirium in the final two weeks of life (68%) (range in the eight units was from 47–87%).[319] Nineteen patients had no adult caregiver and 40 bereaved family members were excluded due to serious psychological distress.[319] There was a 78% response rate with 427 out of the 550 returning the questionnaire (10 were undeliverable, nine did not participate and 16 had missing data). Responses to questions were from 242 participants as 160 families denied delirium episodes.[319] The delirium subtype experienced by the patients was hypoactive in 29% (n = 70), hyperactive in 48% (n = 117) and mixed in 20% (n = 48).[319] Delirium severity was rated mild in 39% (n = 95), moderate in 47% (n = 114) and severe in 11% (n = 26).[319] The caregivers reported that they were very distressed (32% of cases) and distressed (22%) about the experience of terminal delirium.[319] Caregivers reported emotions which fitted into seven categories: ambivalent wishes for the patient (>50%), guilt and self-blame (>50%), worry about staying with the patient (>50%), burden about proxy judgment (25–30%), burden to others (25–30%), acceptance (25–30%), helplessness (25–30%), and relief (<5%).[319] Half the respondents perceived delirium as a sign of approaching death, with views that this was associated with suffering or alternatively relief of suffering.[319] Caregivers with high-level distress were more likely to have experienced agitated behavior, incoherent speech, the patient talking about uncompleted life tasks, the patient appearing incoherent but talking about actual past events, and being distressed by noticing that they were talking strangely; more likely to interpret the causes of delirium as pain or physical discomfort, medication effects, psychosis/'getting crazy,' and mental weakness/death anxiety; less likely to report that the medical professionals were present with the family; and more likely to report the patient being physically restrained.[319]

Another study separately interviewed 37 caregivers and 34 patients who had recovered from their delirium.[320] Three patients whose caregiver consented declined to be interviewed. The patients' age ranged from 28–82 years, half had lung cancer, and more than half of the patients died within a month of being interviewed.[320] Of the caregivers, 21 were the spouse of the patient, five siblings, nine children and two parents. Thirty-two out of 34 patients remembered being confused, with the experience being distressing.[320] Patients and caregivers gave

consistent descriptions of the experience, including behaviours, hallucinations and confusion.[320] Caregivers expressed a concern about how best to help the patient, describing it as 'heartbreaking' to watch.[320] Most of the patients and caregivers were searching for a cause of the confusion, and commonly attributing it to pain or pain medication (wrong one, too high a dose, too many medications).[320] The other causes proposed were lack of sleep in hospital, toxins from the cancer, lack of control of their schedules.[320]

A cross-sectional survey of 200 caregivers of patients with cancer with a life expectancy of less than six months asked participants to complete the Stressful Caregiving Response to Experiences of Dying (SCARED) questionnaire, in particular the item which asks them to record how often they witnessed the patient being confused or delirious (0 never, 1 once or twice, 2 every week or more 3 every day).[321] The caregiver burden scale was used to measure stress of caregiving (a 16-point Likert scale measuring physical, emotional and instrumental tasks of caregiving and their level of demand/difficulty).[321] It was hoped that as the study excluded caregivers of patients who had chronic cognitive impairment this reflected caregiver experience of delirium.[321] The caregiver also underwent a structured clinical interview for DSM-IV (SCID) diagnoses of anxiety and/or depression. Nineteen per cent of caregivers reported seeing the patient 'confused, delirious' at least once per week in the month prior to the study.[321] There was a significant association between caregiver perceived delirium and caregiver burden ($p < 0.0001$)[321]; 3.5% ($n = 7$) of caregivers met criteria for generalised anxiety on SCID, and caregiver anxiety was significantly associated with caregiver perceived delirium, even after adjusting for caregiver burden (OR 9.99, $p = 0.04$).[321] A limitation of this study was the small number of events (namely on seven participants with generalised anxiety), no definitive diagnosis of delirium in the patients, and other risk factors for psychiatric disorders in caregivers were not measured in detail.

The crucial role of the caregiver is being recognised, with recent literature developing a brochure to inform caregivers of patients in palliative care what delirium is and how they can behave towards the person with delirium[322], a version of the CAM for the family caregiver to screen for delirium[323], and a delirium prevention program for hospitalised older adults with family

participation.[324] Families who had received the brochure[322] reported their knowledge of delirium improved, understood delirium was treatable and medication was not the sole cause, felt more confident about making the right decisions on the patient's behalf, and interestingly felt the brochure should be given to all families, even those who had not yet experienced delirium. The sensitivity and specificity of CAM completions by families utilising the FAM-CAM (family confusion assessment method) compared to researchers competing the original CAM algorithm in 52 patients was 88% sensitivity and 98% specificity.[323] The family delirium prevention intervention modified an intervention targeted at four modifiable risk factors for delirium (the Hospital Elder Life Programme (HELP) which intervenes to improve cognition, vision, hearing and mobility) and piloted this with 15 caregivers.[324] This pilot study demonstrated caregivers could complete the intervention 75% of the time. The early mobilisation intervention posed the biggest challenge, as caregivers were fearful about the patients' physical state and symptoms (pain, fatigue, breathlessness).

A hypothesis that has been raised is that the behaviours characteristic of delirium in the terminal phase are perceived by lay people to represent the mental suffering of dying.[325] This perception leads to the expectation for the contemporary 'good death' of absolutely normal mental health, which raises challenges for further research and clinical practice.[308 325 326] These challenges include a need to understand the pathophysiology of delirium and other causes of cognitive impairment in life-limiting illness, to understand the physiological processes involved in reduced lucidity in the terminal phase of illness, and judicious use of psychoactive medication in an evidence-based manner.

1.14 Delirium management in clinical practice

The previous sections have highlighted the phenomenological and epidemiological features of delirium important for the clinician to ensure delirium is detected. Equally, understanding of the risk factors for delirium assists in prevention. The following section outlines the evidence base that informs delirium management in the cancer setting.

The standard approach for management of delirium in cancer and palliative care includes the search for underlying causes and management, with concurrent management of delirium symptoms and without jeopardising other symptom control (e.g. analgesia is maintained).[211 214 327 328] The goals of management are multiple, and include maintaining patient and staff safety, aiming for reversal of delirium, managing distress due to the whole spectrum of symptoms, allowing the patient to obtain adequate rest and sleep, and achieving adequate management of other symptoms and pain related to their cancer.[211 214 327 328] This all needs to be balanced with managing the potential contribution of psychoactive medication to the delirium causation. In more advanced disease, where the patient is entering the terminal phase of illness (last weeks, days or hours of illness) the degree to which reversible causes are explored may be altered by the disease trajectory itself and the person's specific stated wishes and goals, or delirium may be deemed irreversible despite an attempt to reverse it.[214 327 328] Delirium in the advanced cancer patient itself presents a diagnostic challenge, as the person often presents as extremely unwell and may mistakenly be thought to be dying even when a reversible cause is present, or alternatively aggressive intervention may be undertaken when indeed the person is close to death.

1.14.1 Pharmacological treatment of delirium in palliative care and cancer populations

The open label studies evaluating antipsychotics and methylphenidate in cancer or palliative care populations[329-332] are outlined in Table 12. The predominant agent studied was olanzapine. All the studies confirm a decrease in the overall score on a delirium numerical rating scale (MDAS or DRS) over time. All these studies allowed clinicians to treat the underlying cause of delirium as clinically indicated. Only one study had a specified dosing schedule[331], with all the others allowing the clinician to titrate the dose of study medication to effect. Improvement may relate to the natural history of delirium to resolve over time as precipitants are treated and reversed. The populations were predominantly in acute cancer centre environments and hence may have had less advanced disease than those seen in palliative care inpatient populations[38 215], which may also support the hypothesis that the responses seen reflect the natural history of delirium in this population

being higher rates of reversibility. One of these studies has specifically explored hypoactive delirium and the use of methylphenidate.

The randomised controlled studies evaluating antipsychotics in cancer or palliative care populations are outlined in Table 13. Three studies that include a placebo comparison have also been included, although two were in a general medical population and one in critical care. The first study by Hu et al[333] with placebo comparator did not meet CONSORT[d] criteria for allocation concealment, the randomisation schedule was not clearly revealed and power for the primary outcome was not disclosed. Two studies were stopped early before sample size met, due to request of the pharmaceutical company in response to the Food and Drug Administration concerns of use of antipsychotics in the elderly in the case of Tahir et al study[334] and due to slow recruitment for Devlin et al.[335]

The other studies also have small sample sizes, and do not provide a power calculation for primary outcome so are assumed to be underpowered. There is a total sample of 34 cancer patients across all the trials. The studies all approach delirium outcome measurement as a total delirium numerical rating score reduction, and hence don't assess the specific aspects of delirium which may be more difficult to treat, namely hypoactive symptoms and cognitive change. Delirium numerical rating scores also include more hyperactive symptoms, so if treatment effect includes sedation this may lead to a reduction score with patient still being delirous but with a hypoactive spectrum of symptoms.

There are many unanswered questions relating to pharmacological treatment in the palliative setting:

1. Is treatment best targeted to symptoms or delirium syndrome as a whole?
2. Should treatment be provided upfront or as needed when distressing symptoms occur?
3. Is treatment altering pathophysiology?

[d] CONSORT is the Consolidated Standards of Reporting Trials, designed improve reporting of randomised controlled trials.

4. What is optimal initial dosing, titration and subsequent approach to withdraw therapy once response is seen?

5. What is the effect of treatment of patient experience and prognosis?

Current Australian and international clinical guidelines[e] are consistent in their recommendations for the targeted use of antipsychotics, cautious dosing and very close monitoring as the following excerpts highlight:

> Pharmacological therapy should only be considered in the delirious patient with severe behavioural or emotional disturbance where their behaviour threatens their own safety or safety of others, is causing significant distress and is likely to interfere with medical and nursing care (Clinical practice guidelines for the management of delirium in older people, Victorian Department of Health 2006).[336]
>
> If a delirious person is distressed or risk to themselves or others, and verbal and nonverbal de-escalation techniques are ineffective or inappropriate consider giving short term (usually one week or less) haloperidol or olanzapine. Start at the lowest clinically appropriate dose and titrate cautiously according to symptoms (NICE 2010).[28]

[e] Internationally the most current and well accepted guidelines is the National Institute for health and Clinical Excellence (NICE) Delirium: diagnosis, prevention and management (Clinical guideline (CG)103 2010; http://guidance.nice.org.uk/CG103/Guidance/pdf/English). In the Australian context clinical practice guidelines for the management of delirium in older people (Victorian Department of Health 2006) is the most current and accepted nationally available at: http://docs.health.vic.gov.au/docs/doc/Clinical-Practice-Guidelines-for-the-Management-of-Delirium-in-Older-People---October-2006. The British Geriatrics Society updated their guidelines for the prevention, diagnosis and management of delirium in older people in hospital in 2006 available at: (http://www.bgs.org.uk/index.php?option=com_content&view=article&id=170:clinguidedeliriumtreatment&catid=42:catclinguidelines&Itemid=107). The American Psychiatric Association practice guideline (http://psychiatryonline.org/guidelines.aspx) for the treatment of patients with delirium was published in 1999 and has not been updated to reflect current knowledge and practice.

Table 12 Open label studies of antipsychotics in cancer and palliative care populations

Study	Population (n)	Intervention	Primary outcome	Results	Comments
Breitbart et al 2002[330]	Advanced cancer with DSM-IV-R diagnosed delirium (n = 79) Mild delirium defined as MDAS 0–15, moderate 15–22, and severe 23–30	7-day treatment olanzapine Mean dose at baseline 3mg (SD 0.14, range 2.5–10) Mean dose at study end 6.3mg (SD0.52, 2.5–20) Route of administration not specified	MDAS Day 3 and 7 Resolution of delirium defined as MDAS ≤ 10 No power calculation presented	MDAS scores significant improved over time of the study Mean baseline MDAS 19.85 (SD 3.79) was significantly lower at Day 3 (12.73, SD 6.87) and Day 7 (10.78, SD 7.31) (p = 0.001) 45% (n = 36) had delirium resolution at Day 3 and 76% (n = 57) at Day 7 Only 9 of 18 (50%) patients with severe delirium responded, compared to 100% of those with mild delirium (n = 13) and 35 out of 48 with moderate delirium (73%)	Patients with central nervous system involvement, hypoactive subtype and age >70 had poorer response 30% reported sedation at both Day 3 and 7 Olanzapine dose reduced due to sedation in 8 participants 2 patients had olanzapine stopped due to worsening of delirium
Kim et al 2001[332]	Medical patients with delirium in Korea (n = 20). Over half had leukaemia (n = 11)	Olanzapine mean initial dose 4.6mg (±0.9) per day Mean maximal dose was 8.8mg (±2.2). Overall mean dose was 5.9 (±1.5). Mean duration of administration was 6.6 (±1.7) days Route of administration not specified	DRS on day of maximal response No power calculation presented	DRS at baseline were 20.0 ± 3.6, and reduced significantly on day of maximal response to olanzapine to 9.3 ± 4.6 (p < 0.01) The 11 leukaemia patients showed decreased scores of 50% or more	One patient discontinued due to adverse effects 2 patients had mild sedation
Elsayem et al 2010[331]	Advanced cancer (n = 24) with agitated delirium defined as ≥ RASS +1 who had not responded to 10mg or higher of parenteral haloperidol over 34 hours	Subcutaneous olanzapine 5mg every 8 hours for 3 days (n = 9), and haloperidol for breakthrough agitation (2mg intravenously). Patients who required greater than 8mg of rescue haloperidol had olanzapine increased to 10mg every eight hours (n = 8, 6 increased on Day 2, and 2 after Day 2)	Toxicity rate Secondary outcome RASS < +1 at 72 hours No power calculation presented	25 consented but one patient improved prior to olanzapine being given. 24 patients received at least one olanzapine dose and 15 completed the study Efficacy in 9 patients (37.5%)	Adverse events in 4 patients (hypotension <90/50 mmHg, paradoxical agitation, seizure, diabetes insipidus)

Study	Population (n)	Intervention	Primary outcome	Results	Comments
Boettger et al 2011[329]	Case matched patients with cancer and DSM-IV-R delirium treated with aripiprazole (n = 21) and haloperidol (n = 21)	Mean initial aripiprazole dose was 15.2 mg and at study end 18.3mg. Mean initial haloperidol dose was 4.9 mg and at study end 5.5mg.	MDAS at Day 3 and 7 Resolution of delirium defined as MDAS ≤ 10 No power calculation presented	In aripiprazole group MDAS scores declined from 18.1 at baseline to 10.8 at Day 3 and 8.3 at Day 7 ($p < 0.001$). In haloperidol group MDAS scores declined from 19.9 at baseline to 9.9 at Day 3 and 6.8 at Day 7 ($p < 0.001$). No significant differences in MDAS scores at Day 3 and 7 for aripiprazole and haloperidol groups.	Haloperidol group more EPS toxicity (19% parkinsonism, 9% dystonia) Treatment results did not differ between delirium subtype
Gagnon et al 2005[337]	Advanced cancer with hypoactive delirium and cognitive failure (abnormal MMSE). Excluded if perceptual disturbance or reversible cause of delirium (n = 14)	Methylphenidate 10mg orally at 8am and midday. Doses were increased in 5mg increments titrated to effect and maximal tolerated dose. Most patients were on 20 – 50mg	MMSE at stable dose of methylphenidate (time not specified)	The median pre-treatment MMSE was 21 (mean 20.9, SD 4.9), which improved to a median of 28 (mean 27.89, SD 4.7) at a stable dose of methylphenidate	Proposed mechanism of action was correction of phasic tonic imbalance in mesolimbic dopamine system by blocking dopamine reuptake.

DSM-IV-R – DSM-IV-R – Diagnostic and Statistical Manual of Mental Disorders, fourth edition – revised; DRS R98 – Delirium Rating Scale Revised 98; DRS – Delirium Rating Scale; EPS – Extraypyramidal side effects; MDAS - Memorial Delirium Assessment Scale; MMSE – Mini-Mental State Examination; SD – standard deviation; RASS – Richmond Agitation Sedation Scale

Table 13 Randomised controlled studies of antipsychotics in cancer and palliative care populations

Study	Population	Intervention (n)	Comparator	Primary outcome	Results	Comments
Breitbart et al 1996[338]	Terminally ill AIDS patients	Haloperidol (n = 11) over 6 days Dose titration every hour if DRS >13. Once patient had achieved score on DRS <12 a maintenance dose twice daily was started (half of first 24 hour dose) Haloperidol dose within first 24 hours of treatment was 28mg (SD 2.4, range 0.8–6.3) and at maintenance dose 1.4 mg (SD 1.2, range 0.4–3.6)	Chlorpromazine (n = 11) vs Lorazepam (n = 11) Dose titration as per haloperidol arm Chlorpromazine dose within first 24 hours of treatment was 50mg (SD 23.1, range 10–70) and at maintenance dose 36mg (SD 18.4, range 10–80) Lorazepam dose within first 24 hours of treatment was 3mg (SD 3.6, range 0.5 - 10) and at maintenance dose 4.6mg (SD 4.7, range 1.3–7.9)	DRS Days 2 and 6	DRS improved in both haloperidol and chlorpromazine arms ($p < 0.05$), but not for lorazepam group ($p < 0.63$). Mean DRS scores at baseline, Day 2 and Day 6 respectively were: Haloperidol (20.45 (SD 3.45), 12.45 (SD 5.87) and 11.64 (SD 6.1); Chlorpromazine (20.62 (SD3.88), 12.08 (SD 6.5), 11.85 (SD6.74); and lorazepam (18.33 (SD 2.58), 17.33 (SD 5.18), 17 (SD 4.98) Most improvement was seen by Day 2 with little further improvement up to Day 6	Lorazepam arm discontinued due to sedation No EPS were seen in chlorpromazine or haloperidol arms
Hu et al 2004[333]	Hospitalised patients	Olanzapine mean dose 4.52 ± 4mg per day(n = 75) vs IM haloperidol mean dose 7.08 ± 2.26 mg (n = 72) over 7 days	Oral placebo (n = 29)	DRS	DRS significantly reduced in olanzapine and haloperidol group compared to placebo (72%, 70%, 29%, $p < 0.01$) Higher rates of dry mouth among haloperidol compared with olanzapine arm (haloperidol, 16.7%; olanzapine, 2.7%; $p < 0.01$). EPS more frequent in haloperidol than olanzapine arm(haloperidol, 31.9%; olanzapine 2.7%; $p < 0.01$)	Intramuscular haloperidol unblinded the study Randomisation approach not described and unequal distribution in arms not explained

Study	Population	Intervention (n)	Comparator	Primary outcome	Results	Comments
Kim et al 2010[339]	Mostly oncology patients Risperidone (n = 17) vs Olanzapine (n = 15) over 7 days	Risperidone mean starting does 0.6mg (SD 0.2) to last observation dose 0.9 (SD 0.6)	Olanzapine 1.8mg (SD 0.6) to last observation dose 2.4 (SD 1.7)	DRS-R98	Both groups improved with no difference between arms	No differences seen in safety profiles
Han et al 2004[340]	General medical patients (one cancer patient in each arm)	Haloperidol (n = 12) over 7 days. Starting dose 0.75mg twice daily, titrated to clinical effect. Mean dose at Day 7, 1.71 mg (SD 0.84, range 1–3)	Risperidone (n = 12) Starting dose 0.5mg twice daily, titrated to clinical effect. Mean dose at Day 7, 1.02mg (SD -0.41, range 0.5–2)	DRS MDAS	Both groups improved with no difference between arms. Mean DRS scores for the haloperidol group at baseline was 21.83 SD 4.43) and the risperidone group 23.50 (SD 4.19). MDAS scores of each group decreased significantly ($p < 0.05$)	No differences seen in safety profiles
Tahir et al[334]	General medical patients Quetiapine (n = 21), placebo (n = 21) over 10 days	Quetiapine 25mg oral once daily - dose titration 25mg/day up to maximum 175mg in divided doses. Clinician decision for titration based on lack of improvement in DRS R98	Matching placebo	DRS-R98	Quetiapine group improved 82.7% faster (p=0.026) than placebo group. On day 3 mean (SE) was 11.98 (3.11) in quetiapine group compared to 14.3 (2.63) in placebo group	Underpowered, as 95% power to detect five-point difference in DRS-R98 needed 34 participants in each arm. Only 16 completed in Quetiapine arm and 13 in placebo Excluded pre-existing cognitive impairment

Study	Population	Intervention (n)	Comparator	Primary outcome	Results	Comments
Devlin et al 2010[335]	Intensive care (n = 36)	Quetiapine intravenously 50mg every 12 hours, increased by 50mg every 24 hours if more than one dose of rescue haloperidol (1 – 2mg every 2 hours allowed)	Placebo	First time ICDSC was ≤ 3	Quetiapine was associated with a shorter time to first resolution of delirium – 1 day (IQR 0.5–3) vs 4.5 (IQR 2.0–7.0) p = 0.001; reduced duration of delirium 36 hours (IQR 12 – 87) vs 120 (IQR 60–195) p = 0.006; and reduced duration of agitation 6 hours (IQR 0–38) vs 36 (IQR 11–66)	Underpowered, as 24 participants in each arm were needed to have >80% power to detect a 50% rate of delirium resolution in quetiapine group versus 10% in placebo. QT_c interval measured every 12 hours

DRS – Delirium Rating Scale; DRS- R98 – Delirium Rating Scale Revised 98; EPS – Extraypyramidal side effects; ICDSC – Intensive Care Delirium Screening Checklist; IQR – Interquartile range; MDAS – Memorial Delirium Assessment Scale; SD – standard deviation, SE – Standard error; QT_c – measure of time between start of q wave and end of T wave in hearts electrical cycle

1.14.2 Management of pain in the patient with delirium and the role of opioid rotation

Following the discussion by researchers that opioids may increase the risk of delirium, and may be a precipitating factor, there has been consideration of the clinical strategies to reduce this risk or to improve delirium once it occurs.[179] The general principles have included re-evaluating the cause of pain and the options for non-opioid analgesia, assessing hydration status, and considering changes in physiological parameters which may have altered the pharmacokinetics and/or pharmacodynamics of the medication.[179 341 342] As most delirium episodes have more than one cause, it is important not to only consider opioids as the sole contributing factor.[179] Opioid induced cognitive dysfunction includes a spectrum of presentations from subtle cognitive deficits (e.g delayed recall, reduced reaction times, word recall and recognition), to delirium.[342] In some patients with opioid toxicity and delirium other features may be present such as myoclonus, pin point pupils, hyperalgesia and respiratory depression.[342]

One strategy that has received attention is opioid rotation or switching.[179]

'Opioid rotation' or switching is a term used to describe substituting one strong opioid with another, a strategy proposed as useful when a satisfactory balance between pain relief and adverse effects is not achieved with the first opioid.[343] The biological mechanisms underpinning why better pain relief and reduced adverse effects has been seen in some clinical observations when switching from one μ-opioid receptor agonist to another is not fully understood[343]; however, it is considered an approach when delirium related to opioid adverse effects has occurred. Further exploration is needed to determine if it is actually uncontrolled pain mediating the increased delirium risk in patients with uncontrolled pain on opioids where it has been assumed delirium has been precipitated by the opioid, given data in uncontrolled post operative pain showing association with increased risk of delirium.[206,205]

The evidence for opioid rotation in the context of delirium is limited to small case series where the diagnosis of delirium is described by clinician report, apart from one case. The first series undertook opioid rotation to transdermal (n = 9) or

parenteral (n = 11) fentanyl if morphine was thought to be involved in delirium aetiology (n = 21), and delirium severity was monitored utilising the MDAS.[344] Treatment success was defined as delirium resolution (MDAS score below 10), with good pain control (pain score of 2 or less); this occurred in 13 patients on Day 3 and 18 patients by Day 7.[344] This was achieved with a median increase of 42% in opioid dose (converting fentanyl dose to the oral morphine equivalent).[344]

Another case series of 20 terminal cancer patients rotated them to methadone due to persistent delirium and uncontrolled pain, with pain control improved in 15 patients and significant cognitive improvement in nine.[345]

A third prospective study (n = 13)[346] included cancer patients who had acute delirium, thought to relate to morphine. Conversion to subcutaneous (SC) oxycodone occurred using a conversion ratio of 0.7:1, with subsequent dose modification dependent on pain response. Nineteen patients consented, but six participants were not included as they pulled their SC line out, had already been changed to another opioid, or deteriorated rapidly. The outcome measured was presence of change in cognition and level of consciousness as reported by the bedside nurse, and scores were recorded at 24 hours of oxycodone and at Day 6. This study reported an improvement in cognition and level of consciousness. However, substantive methodological flaws include a lack of validated delirium assessments, primary outcome measurements by clinical nurses who may have low recognition of delirium symptoms, no aetiological checklist for delirium precipitants (as it is well established that there is often more than one precipitant, and the opioid may not be the only cause), and no discussion on what other interventions to reverse delirium precipitants also occurred (e.g. treatment of infection, metabolic disturbance).

1.14.3 Non-pharmacological management of delirium

Non-pharmacological interventions have focused on multicomponent interventions in the hospital setting (Table 14). The studies include geriatrician and nurse led components, proactive approaches to identify those with delirium and targeted interventions to improve orientation, mobility and the environment in which the person with delirium is cared for. Of the non-randomised studies only one had the data assessors blinded to outcome measure results in the control

group. The assessment of the quality of the design of the three RCTs is outlined in Table 14. Overall, these studies demonstrate that it is more difficult to achieve definitive outcomes in terms of mortality or reduced institutionalisation, although trends indicate more rapid improved cognition and reduced duration of delirium.

Table 14 Non-pharmacological therapy for delirium

Study	Population and design	Intervention	Comparator	Results
Cole 1994[347]	n = 88 RCT General medical patients over 65 years screened for delirium (CAM) and those with prevalent or incident delirium recruited Allocation concealment not stated Outcome assessors were blinded Intention to treat	Geriatric specialist initial assessment and intervention nurse follow-up who assessment mental status of patient, assessed compliance with consultant and followed up on management problems, assisted with improving environment to assist with orientation, mobility, and clear communication with patient	Usual care, and usual method to obtain geriatric consultation	There was a small improvement in cognition seen in intervention group at 2 weeks; however, this effect was lost by 8 weeks There was no statistically significant difference between the groups in use of restraints, length of hospital stay, discharge to a setting providing more care than was needed before admission or mortality rate
Cole 2002[348]	n = 227 RCT Population as above Independent allocation but full details of randomisation not stated Outcome assessors were blinded Intention to treat	As above but more intensive follow-up Geriatric specialist initial assessment and individualised follow-up Intervention nurse reviewed 5 days per week	Usual care, and usual method to obtain geriatric consultation	The time to improvement in cognitive status did not differ between groups. No difference in length of stay, improvement in delirium index, or discharge rate back to community
Pitkala 2006[349]	n = 174 RCT Adequate allocation concealment Unknown if outcome assessors were blinded Intention to treat	Comprehensive geriatric assessment and treatment The primary endpoint was the sum of those deceased individuals and the patients permanently institutionalised Secondary endpoints included the number of days in hospitals and other institutions, delirium intensity, and cognition	Usual care	60.9% in intervention group and 64.4% controls died or were institutionalised by one year (p = 0.64) The intervention group spent a mean of 126 days in institutions, and the control group 140 days (p = 0.7) Delirium was, however, alleviated more rapidly during hospitalisation, and cognition improved significantly at 6 months in the intervention group

Study	Population and design	Intervention	Comparator	Results
Milisen 2001[350]	n = 120 Before and after sequential design Older hip-fracture patients	(1) Education of nursing staff, (2) systematic cognitive screening, (3) consultative services by a delirium resource nurse, a geriatric nurse specialist, or a psychogeriatrician, and (4) use of a scheduled pain protocol	Usual care	No significant effect on the incidence of delirium (23.3% in control group, 20.0% in intervention cohort; p = 0.82) Duration of delirium was shorter (p = 0.03) and severity of delirium was less (p = 0.005) in the intervention Higher cognitive functioning and a trend toward decreased length of stay postoperatively No effect on improvement in activities of daily living
Rahkonen 2001[351]	n = 102 over 65 with delirium Before and after intervention cohort	Nurse specialist support who provided counselling and support, and advocated for patient's needs Structured rehabilitation with mobility Follow-up into community setting	Age and gender matched patients admitted to the same hospital for delirium	There was no difference in short term hospitalisation between the groups Higher duration of care in community for intervention group (p = 0.025)
Naughton 2005[352]	n = 374 Pre and post-test design (2 cohorts post intervention at 4 and 9 months). Emergency department and acute geriatrics units (3 cohorts)	Intervention to improve delirium detection in emergency department by education, improved medication management and focus on non-pharmacological strategies	Pre-intervention period	Length of stay reduced by 3.3 days following each episode of delirium Improved triage of patients with delirium to acute geriatrics unit Prevalence of delirium in the cohorts reduced from 40.9% at baseline, 22.7% (4 months, p < 0.002) and 19.1% at 9 months) p < 0.02)

CAM – Confusion Assessment Method; RCT – randomised controlled study

1.14.4 Delirium prevention

The recently published National Institute for Health and Clinical Excellence (NICE) guideline provides a comprehensive review of strategies for delirium prevention in hospital.[28] Despite the significance of delirium in cancer settings, there were no studies in cancer available to inform specific guidance for patients with cancer. Pharmacological strategies have included anticholinesterases, atypical (risperidone) and typical (haloperidol) antipsychotics compared with placebo or in one study proactive geriatric consultation, all exploring prevention in the post-operative setting with no agent showing definite promise.[28] Methodological issues in these studies included incomplete follow-up, delirium case identification not clearly described (with likelihood of missing delirium episodes), younger patient population so not representative of the population at highest risk of delirium, and *a priori* sample size calculation for only three trials.[28] Only one study showed a modest reduction in incidence (risperidone); another reduced severity (haloperidol).[28]

Non-pharmacological strategies have been explored in 3 RCTs (2 out of 3 with delirium incidence as primary outcome), 2 non-randomised prospective studies and 3 historical controlled trials (all with delirium incidence as primary outcome), none of which were in cancer populations or could be blinded due to the nature of the intervention.[28] The interventions included multicomponent interventions targeting risk factors (e.g. the Hospital Elder Life Programme (HELP)[353]), nursing interventions, proactive geriatric consultation (which may include review of medications and pharmacological strategies) and education.[28] Only one of the RCTs had an *a priori* sample size powered to detect a highly ambitious reduction of delirium incidence of 33%, and one used the mini-mental assessment to diagnose delirium, which is inadequate for delirium diagnosis. Taking into account the methodological limitations the two multicomponent interventions demonstrated a reduction in delirium incidence (relative risk of approximately 0.66 (95% CI 0.46 to 0.95)).[306 354]

There are significant issues in translating multicomponent interventions into practice as they require substantive national and health administrative changes[355], as well as comprehensive and ongoing education needed for clinicians, and upfront additional costs of the intervention per patient in the order of US$600 per patient, although in the long run there is associated reduction of costs due to delirium prevented of US$800.[356] Equally, multicomponent interventions include cognitive and exercise components that may not be feasible for patients with advanced cancer suffering from fatigue or functional decline, and sustaining the intervention over time is unlikely as cancer progresses, which is the period that most corresponds to increasing delirium risk. A less challenging multicomponent intervention which targeted cancer patients in the terminal phase failed to demonstrate a difference in the incidence of delirium between two palliative care centres' that received the intervention and seven that did not.[357] A recent Cochrane review affirmed the urgent need for well designed trials of delirium prevention due to the limited research evidence on effectiveness to date.[358]

1.14.5 Challenges of delirium detection and management in practice

Several studies demonstrate that delirium is poorly detected and managed in a way disparate to available clinical practice guidelines and evidence. For example, a survey of 784 trainee general physicians in the United Kingdom (UK) working in 34 hospitals, demonstrated many underestimated the prevalence and poor outcomes related to delirium.[359] Equally, studies exploring a cohort of nurses who provide care for older patients, demonstrated that their knowledge of delirium was inadequate.[360] Studies demonstrate that these signs of delirium often go unrecognised by bedside nurses.[361-365] In relation to pharmacological approaches, the European Delirium Association (EDA)[366] and the American Geriatric Society[367] surveyed their members and found a wide variation in pharmacological approaches.

Studies also demonstrate that to change practice in delirium prevention and management requires high intensity and ongoing strategies to alter processes and outcomes for the care of the person with delirium.[368] HELP is an example of a multicomponent strategy using a quality improvement framework that can reduce delirium episodes in the 'at risk' older person in hospital. The HELP intervention

involves standardised protocols for the daily management of six risk factors for delirium: cognitive impairment, sleep deprivation, immobility, visual impairment, hearing impairment, and dehydration.[306] The initial study used a prospective individual matching strategy where intervention (n = 452) and control (n = 452) patients were matched according to age, gender, baseline risk of delirium (utilising a predefined validated prediction model with variables being visual impairment, severe illness, cognitive impairment and high BUN to creatinine).[306] Delirium occurrence was defined according to CAM and was assessed daily. Adherence to the intervention occurred in 87%. In the intervention group, 9.9% developed delirium compared to 15% in the control group, (matched OR, 0.60; CI, 0.39 to 0.92). The total number of days with delirium (105 vs 161, p = 0.02) and the total number of episodes (62 vs 90, p = 0.03) were significantly lower in the intervention group.[306] Delirium severity and rate of delirium recurrence were not significantly different.[306] The intervention is designed to be mediated by a team of volunteers, geriatric nurse specialists, and geriatricians, working closely with the primary nursing and medical team with two interdisciplinary rounds per week.[353] In the initial study of 852 participants HELP saved an average of $US831 per intervention participant in acute hospital costs, and $US9446 per participant in long-term institutional (nursing home) costs.[356 369]

Other authors propose that the development of specific delirium units within hospitals, which provide a secure environment, and concentrated health professional expertise with specific training in either geriatric and/or delirium care, is what is required. Although trends in data from audits and retrospective data report a benefit from a delirium unit, it has been harder to evaluate this approach in a randomised control trial. A recent study randomised 600 participants who were confused and over the age of 65 years to either care in a specialised medical and mental health unit or standard care (geriatric or general medical ward). The study found improvements in patient and caregiver experiences, but the location did not impact on hospital length of stay or mortality.[370] This study had the limitation that geriatricians in the specialised units also provided care in the general wards (so intervention may not have been exclusive), and there were a larger number of nursing home residents and patients with dementia in the intervention unit arm.

1.15 Summary

Delirium is common in palliative settings, and includes the full spectrum of presentations from SSD, FSD and persistent delirium (often with irreversible cause). Delirium remains reversible in a large number of people, even in advanced disease. The significant impact of delirium on patients and caregivers in the cancer and palliative setting has been well described. Despite the degree of distress, less is known about the risk factors to identify those most at risk and approaches to pharmacological and non-pharmacological management which will provide the best chance of reversal of delirium, relief of symptoms and improved longer term outcomes.

1.16 Outline of thesis content

The remaining chapters are ordered as follows:

Chapter 2 reports the findings of a survey of the current practice of geriatricians, aged care psychiatrists, medical oncologists, and palliative medicine specialists, with regard to the pharmacological and non-pharmacological management of delirium in patients with advanced cancer.

Chapter 3 describes a qualitative exploration to understand and contrast the approaches that nurses use to assess and manage delirium when caring for people with cancer, the elderly, or older people requiring psychiatric care in an inpatient setting.

Chapter 4 describes a study quantifying the anticholinergic load of medications for comorbid disease, symptom control, or medications that may be used for either indication in a palliative care population followed longitudinally as death approaches. This study also aims to evaluate how anticholinergic load from medications contributes to symptom burden, changes in function, health-service utilisation and survival.

Chapter 5 describes a prospective cohort study that explores the relationship of serum AA, anticholinergic load of medications, and other clinical and investigational factors. In particular, it explores these variables' correlation with delirium in the palliative care inpatient population with advanced cancer.

Chapter 6 outlines the protocol and results to date for a RCT of risperidone versus haloperidol versus placebo in the management of delirium in palliative care, and discusses the pertinent issues to consider in a delirium clinical trial design in this population.

Chapter 7 presents the final conclusions and implications of the research.

Chapter 2: Delirium management by medical specialists in advanced cancer

This chapter reports the findings of a survey of the current practice of geriatricians, aged care psychiatrists, medical oncologists, and palliative medicine specialists, with regard to the pharmacological and non-pharmacological management of delirium in patients with advanced cancer. The aim of the study was to document and compare the assessment and management practices for each specialist medical group in the treatment of delirium, in the context of two vignettes.

2.1 Current delirium practices

Delirium assessment and management is complex, and clinicians who are trained and competent are crucial in improving delirium outcomes.[28] Current practice in delirium management is driven by a limited (but growing) evidence base and expert opinion, summarised in several clinical practice guidelines. Individual approaches are also influenced by training and experience, clinical presentations frequently seen in practice, and 'borrowing' evidence from related fields (such as management of behavioural and psychological symptoms in dementia).[338 371-373] Hence, the current management of delirium practice relies heavily on expert opinion, both at the individual clinician level within a specialty group, and more broadly within clinical guidelines. High intensity efforts are needed to translate clinical guidelines into changes in processes and outcomes for the care of the person with delirium, and hence a disparity may exist between the best emerging evidence and clinician practice at the 'coal face'.[368]

Delirium is a clinical syndrome that is not limited to one area of medical specialty. Indeed, clinicians in all settings may see patients presenting with delirium. However, the four sub-specialties of geriatrics[f], aged care psychiatry (ACP)[g], oncology and palliative medicine provide care for populations where delirium is frequent and has a substantial impact on patient outcomes.

[f] In Australia geriatrics is also referred to as aged care, and is the equivalent of geriatric medicine
[g] In Australia aged care psychiatry is the equivalent of geriatric psychiatry or old aged psychiatry

In ACP a key group of people with delirium are those with dementia.[374] The prevalence of delirium in people with dementia varies from 22% to 89%, with figures reported in studies varying dependent on whether the sample population was hospitalised (higher prevalence) or in the community (lower prevalence).[374] Studies using retrospective and cross-sectional cohorts also report lower rates; likely due to incident cases being missed.[374] The older person in hospital, whether admitted due to a medical or surgical problem, also has a high risk of delirium.

Forty-two cohort studies of delirium prevalence and incidence were identified for inclusion in this review, with the majority of the studies based on cohorts of older hospitalised patients.[375] The prevalence of delirium at admission in these studies ranged from 10% to 31%, the incidence of new delirium during admission was 3%–29%. Studies of occurrence rates for the overall admission (incidence and prevalence) cited rates of 11%–42%.[375] These studies also show that the older population in residential aged care is also at risk. After adjusting for dementia, functional status (defined as Katz activity of daily living (ADL) score less than or equal to 4), hearing impairment, and the presence of systemic inflammatory response syndrome[h] in older patients aged 65 years and over (n = 341) residing in nursing homes was independently associated with delirium presentation to emergency departments.[376]

Delirium is a frequent complication during cancer treatment, and its prevalence increases in advanced cancer with older people being particularly susceptible.[39 185 214 377 378] A study in an Australian inpatient oncology setting found an 18% delirium rate, with advanced age, metastatic disease and haematological malignancy being independent risk factors.[185] Gender, CNS tumour involvement, prior confusional state, alcohol abuse, corticosteroid use, cytotoxic chemotherapy, dehydration, abnormal liver function, hypercalcaemia and sensory impairment were not found to be risk factors in the oncology setting, however this may be due to the limited sample size not providing adequate power for the large number of risk factors studied.[185]

[h] Systemic inflammatory response syndrome was used as a surrogate marker of severe illness and was defined as presence of two or more of the following: tachycardia, hypothermia or hyperthermia, increased respiratory rate and leukocytosis.

As death approaches, prevalence figures in the days before death are as high as 88%.[38 82] A review of delirium prevalence and incidence in inpatient palliative care included eight prospective studies, and found prevalence on admission ranged between 13% and 42%, with the incidence during admission being 26%–62%, increasing to 59%–88% in the weeks to hours preceding death.[101] Clinical decisions are impacted by the need to utilise a range of psychoactive medications in supportive cancer care, which have a high propensity to precipitate delirium.[197 211] The intensity of the oncological treatment is also an important consideration, with rates in haematopoietic stem cell transplant of over 50% documented.[44] Oncology and palliative care literature has predominantly considered the impact of delirium on symptoms, distress of the patient and caregiver, and quality of life.[379] The impact of delirium and delirium recall on patients and caregivers is well described in cancer populations.[315 316]

The specialities of geriatrics and ACP specifically focus on syndromes impacting the older person, with delirium considered a 'geriatric syndrome'.[380] Delirium care could be assumed to be a core competency for clinicians in this field. The negative outcomes of delirium in the older person are well described, including medical complications, falls[381], institutionalisation, functional and cognitive decline and accelerated death.[302 375 382]

The standard approach to the management of delirium in the medically ill includes correcting underlying causes and specific interventions to control symptoms.[28] Non-pharmacological interventions are highlighted as important, with the mainstay of pharmacological treatment being antipsychotic medication, and occasionally benzodiazepines.[28] Antipsychotic medications are usually utilised to manage behavioural and perceptual disturbance[383], and benzodiazepines are occasionally indicated when delirium symptoms are refractory at the end of life; behavioural disturbance is severe and safety of patient or staff is of concern needing more immediate acting medication; or if associated anxiety is severe and nonresponsive to antipsychotics.[327 328] All aspects of delirium management are integral to medical practice, including diagnosis (and considering differential diagnoses for reversible underlying precipitants), organising appropriate investigations, prescribing treatment and monitoring outcomes. However, the decision-making processes of medical practitioners caring for a delirious patient

or how they identify delirium in practice are less well described than those of nurses. The variance in decision-making by clinicians in different health settings and between different clinicians have not been explored in depth. It is known that variations can occur within a specialty group[367], so it would be fair to assume that similar or greater variations may also occur between different specialty groups. These include the approach(es) clinicians use in determining which symptoms require pharmacological management, their opinions about the predicted response to therapy[384], or the ideal location of care for delirious patients.[384] The studies that have explored delirium care specifically from a medical perspective, and their deficiencies, are outlined below.

The four sub-specialties of geriatrics, ACP, oncology and palliative medicine see different populations, despite the high prevalence of delirium in their patients, as illustrated in Table 15.

Table 15 Differences in patient populations by specialty

	Aged care psychiatry	**Geriatrics**	**Medical oncology**	**Palliative medicine**
Age (years)	usually over 65	usually over 65	Wide range	Wide range
Comorbidity	Psychiatric comorbidity (depression, psychosis) Medical comorbidity Dementia	Medical comorbidity Dementia	Wide range Some patients do not have other comorbid illness	Wide range Some patients do not have other comorbid illness
Treatment			Anticancer therapies	Psychoactive medications for symptom control

Geriatric populations are usually over 65 years in age, with mean age over 75 years in inpatient settings[385 386] with multiple comorbidities and a high rate of dementia.[371,372] Aged care psychiatry has a wider age range in their population (some studies citing more than half the patients being aged 65 – 70, whereas other units having mean age of 80) often with multiple psychiatric (predominantly dementia, depression, psychosis) and medical comorbidities.[387 388] In both these specialties a specific diagnostic challenge is to differentiate delirium from

dementia, or to identify delirium on a background of dementia. The patient populations that palliative medicine and oncology populations see include patients from a wider age range, including the older person with multiple comorbidities. Advanced cancer patients may be exposed to anticancer therapies with significant toxicities including CNS toxicities, may have direct CNS involvement from a tumour, and receive psychoactive medications for symptom control. A particular challenge in advanced cancer is the dichotomy of delirium populations, with eminently reversible delirium and delirium as part of the physiological process of dying being seen.[38] This brings with it the specific challenge of when an aggressive clinical approach to reverse potential aetiologies should occur compared with symptom management as the only intervention[38 215], as delirium has been demonstrated to be an independent predictor of mortality.[97]

Carnes et al undertook to ascertain the variations in strategies for managing delirium by physicians with expertise in geriatrics, by sampling members of the American Geriatrics Society.[367] A cross-sectional mail survey utilising a two-part clinical vignette was performed. It requested management choices for an older woman hospitalised with a hip fracture who developed mild delirium initially, and subsequently developed more severe delirium.[367] At least a third of the respondents selected diagnostic tests deemed unnecessary for mild delirium in clinical guidelines (e.g. lumbar puncture); more than half chose doses of haloperidol higher than recommended for geriatric patients (above 1mg in 24 hours); and a third selected lorazepam as the agent of choice (alone or in combination with haloperidol).[367]

Delirium remains under-detected and hence under-managed. This is often assumed to be related to a lack of clinician knowledge or experience, particularly at the junior medical officer level.[389] A survey of 784 trainee general physicians in the UK working in 34 hospitals, also sheds light on the barriers to delirium care from the medical perspective.[359] In this survey, a significant proportion of the physicians underestimated the prevalence and the poor outcomes of delirium; most did not recognise inattention as a core diagnostic feature; and more than one third opted for doses of haloperidol of 2.5mg or more.[359] Reassuringly, over 80% of respondents agreed that delirium knowledge was essential, considered delirium as treatable and thought that responsibility for diagnosis did not primarily lie with

psychiatrists.[359] Less than a third believed that they had a good knowledge of delirium diagnostic criteria and had confidence in delirium management.[359] Experience in geriatric medicine provided slightly more confidence in the diagnostic criteria and more appropriate starting doses of haloperidol; however, this was not associated with better actual knowledge of the diagnostic criteria.[359] A study exploring under-detection within general hospital wards determined that for patients with delirium in five UK general district hospitals, only 50% of the medical notes had a record of delirium diagnosis.[368] However, it was not made clear whether the poor documentation was at junior medical officer level or also at more senior levels.[368] It is important to recognise that under-detection relates to cognitive disorders more generally, with delirium being just one specific diagnostic group.[390]

Another area of medical practice that has received attention is the role of prescribing in delirium, both in the prescribing practices that may lead to delirium unnecessarily[187], and the treatment approaches when delirium occurs.[391 392] Australian acute care hospitals demonstrate a range of prescribing practices. Less than a quarter of patients started on antipsychotics for delirium commenced on a low dose, and the majority of hospitals do not have evidence of regular reviews.[391] A similar retrospective study in cancer patients also demonstrated a range of antipsychotic dosing, with the administered dose (summarised as haloperidol equivalent daily doses for all antipsychotics) associated more with health professional distress than frequency of hallucinations (scored from 0 - not present to 4 symptom present most of the time).[392] The survey of trainee doctors described previously also illustrates higher than recommended doses of antipsychotics being chosen by the majority.[359]

Delirium in emergency departments and intensive care has had recent attention, with under-detection or lack of recognition of the importance of delirium.[393-395] Education in delirium care is often only superficially covered in undergraduate medical curricula[396], but educational strategies in the clinical and undergraduate environment are being explored to improve this.[397 398] One study[399] in the UK explored the use of a one hour group education session which included group discussion to medical and nursing staff on a medical unit, with concurrent written management guidelines. This was followed up by regular small group and one-to-

one sessions discussing challenging cases. The intervention medical unit was compared to another medical unit (control ward) in the same hospital for the same year. Delirium diagnosis on a single assessment by an aged care psychiatrist was compared to recognition of delirium in the medical notes by ward staff but the time-point when this assessment occurred was not clear. 122 patients were assessed in the intervention ward and 128 patients in the control ward. This case control study showed a lower point prevalence of delirium 9.8% compared to 19.5%, $p < 0.05$). In the intervention ward medical staff recognized 8 out of 12 cases of delirium diagnosed by the aged care psychiatrist, compare to 6 out of 23 on control ward ($p < 0.01$). Boston University School of Medicine compared online delirium curriculum (case based interactive curriculum using videos and text) compared to a one hour live delirium lecture delivered to fourth year medical students.[398] This was evaluated using a pre- and post-education short answer test with two cases with a 2 point improvement out of 34 maximum score seen, with no difference between the groups. This demonstrates that though the online curriculum was equivalent to the live lecture, the degree of knowledge increase was minimal.

It is also important to consider whether one specialty group (geriatrics being the key contender) provides better delirium care. The specific approach to delirium management within geriatrics has usually been evaluated in the context of multidisciplinary team-based care or a specialised 'delirium unit', which makes it difficult to discern the relative contribution of the geriatric specialist.[400 401] One reported intervention was proactive geriatric consultation after hip fracture, where a geriatrician undertook daily reviews for the duration of the hospitalisation and provided targeted recommendations based on a structured protocol. This approach successfully reduced delirium rates if there was adherence to the recommendations by the orthopaedic team.[354] There was a mean of ten recommendations made throughout hospitalization, with 77% adherence (range 45% - 100%) by the orthopaedics team. Delirium occurred in 32% (20/62) compared with 50% (32/64) in usual care patients, representing a relative risk of 0.64 (95% CI 0.37 – 0.98) for the geriatric consultation group ($p = 0.04$). This relative risk is equivalent to a number needed to treat of 5.6 patients receiving

geriatric consultation to prevent one case of delirium, in the context of on average, three quarters of recommendations being adhered to.

The HELP is another example of a targeted intervention that can reduce delirium episodes in the 'at risk' older person in hospital (described in more detail in section 1.14.4). This intervention was designed to be mediated by a team of volunteers, geriatric nurse specialists, and geriatricians, working closely with the primary nursing and medical team with two interdisciplinary rounds per week.[353] In summary, the initial prospective study comparing admissions to the intervention and control units (using case matchin for case and control) showed 9.9% developed delirium in the intervention group compared to 15% in the control group, (matched OR, 0.60; CI, 0.39 to 0.92). The total number of days with delirium (105 vs 161, p = 0.02) and the total number of episodes (62 vs 90, p = 0.03) were significantly lower in the intervention group.[306] In the Australian context, a modification of this intervention for patients already under geriatric care utilising trained volunteers and assistants in nursing (AIN) to mediate the core domains of the daily intervention (reorientation, therapeutic activities, feeding assistance, hydration assistance and vision/hearing protocols) showed delirium incidence could be further reduced once patients were already under geriatric care (as long as the full complement of medical, nursing and allied health staff was maintained).[402] This before and after controlled study with 21 patients receiving usual care compared to 16 patients receiving the intervention showed lower delirium incidence (6.3% in intervention compared to 38% in control, p = 0.032) and a trend to reduced duration in days of delirium (5.0 compared to 12.5, p=0.64).[402]

Understanding staff skills, decision-making and attitudes is pivotal to improving care for patients with delirium.[403] [404] Delirium is one of the most common preventable adverse events, is integrally related to processes of care, including medication usage, and is a marker of quality of care and patient safety.[405] To my knowledge, there has not been detailed exploration of clinician decision-making at the specialist level than the current study, as detailed in the remainder of this chapter. This study aimed to explore the decision making of four specialty groups and compare choices in location of care, investigations, pharmacological and nonpharmacological therapies, and assessment of treatment effectiveness.

2.2 Methods

2.2.1 Participants

Four specialist groups with clinical experience in the management of delirium were included in the current study. The survey questionnaire was sent to palliative medicine specialists, medical oncologists, geriatricians and aged care psychiatrists in Australia and New Zealand. Respondents who advised they were not currently in active clinical practice were excluded from the analysis. Those who replied were deemed to have provided informed consent to participate (Appendix 1).

The study included palliative medicine specialists as they see patients with advanced disease where delirium is prevalent. Palliative medicine specialists provide care for patients with life limiting illness who often have complex physical symptoms or psychosocial needs. Specialist palliative care is provided in the community, ambulatory settings, acute care hospitals (usually on consultative basis), residential aged care, and as an inpatient (usually in specialist palliative care units, but sometimes in acute care hospitals).

Medical oncologists were included as they provide acute medical care for patients with advanced cancer in whom delirium is a common cause for admission. Medical oncologists provide care and anticancer treatments for people with solid tumours and solid haematological malignancies in inpatient and ambulatory settings, for both early and advanced disease.

The final two groups for inclusion were aged care psychiatrists and geriatricians, as they provide care for the older person who is at higher risk of delirium, including those with coexisting dementia. Other medical and surgical teams also often call these specialists to provide advice and assistance in the care of the delirious patient. In Australia and New Zealand, aged care psychiatrists provide diagnosis, treatment and clinical psychiatric care to the older person, and work to prevent psychiatric morbidity in older people in inpatient, community and residential aged care settings. Geriatricians provide medical care, convalescent and rehabilitative care for the older person within the inpatient setting, and ambulatory and community services (including consultation) in residential aged care settings. There is an overlap between ACP and geriatrics; they need to work

closely together in the care of the older person with complex combinations of physical and mental ill health. Regional variations in service availability may lead to crossover of patient populations, and both provide specialist care for people with dementia.

Permission was obtained to distribute the survey to mailing lists of the Royal Australian and New Zealand College of Psychiatrists (Faculty of Psychiatry of Old Age), Australian and New Zealand Society of Palliative Medicine, Australian and New Zealand Society of Geriatric Medicine, Medical Oncology Group of Australia (Royal Australasian College of Physicians), and Australasian Chapter of Palliative Medicine (Royal Australasian College of Physicians). There is no comparative group consisting of purely medical oncology (MO) specialists in New Zealand.

A stamped self-addressed envelope was included with the survey for reply, and confidentiality was assured, as the survey did not seek any identifying information. The names and addresses of participants were not released to the investigator, with all mail outs performed by college/specialist society staff.

The questionnaires were numbered, and the colleges/special societies were asked to link the numbers to their mailing list, with this linkage not revealed to the investigator so ensuring the investigator had no identifying information about the respondent. A list of the survey numbers not received after six weeks was forwarded to the colleges/special societies, which sent reminders to the non-respondents without the investigator being able to identify participants. The colleges/special societies also abided by their own privacy regulations and did not send out material to persons who had not given permission for them to do so.

The most recent workforce demographic surveys for each speciality group were also obtained to compare its demographic characteristics with respondents to my sample. Clinicians who were on the mailing list, but replied that they were retired or not in active clinical practice were excluded from the analysis. Respondents who did not reply were deemed to have not consented to participate.

2.2.2 Aims

The specific aims of the study were to compare specialty groups and responses to two vignettes (Table 16) in relation to the:

1. total number of investigations and the specific choice of investigations
2. usefulness and frequency of routine use of non-pharmacological strategies (according to a provided list of options derived from the literature)
3. usefulness of antipsychotic and benzodiazepine medications for specific symptoms
4. respondent choice of the agent they would commonly use to manage delirium, including
    a. the dose ranges for commencing dose, increments, and maximum dose
    b. the frequency and severity of side effects
5. clinical indicators used by respondents to determine success of treatment
6. respondents' views on the predictors of poor outcomes in delirium.

2.2.3 Questionnaire

A questionnaire was designed to identify demographic variables of age, gender, specialty area of practice, years of practice in this speciality field, and frequency of caring for patients with delirium (Appendix 2). These variables were chosen as they may influence both exposure to delirium and the approach used to manage delirium. The number of patients seen with delirium per week and years of practice in the specialty field were asked in categories as it was felt respondents were more likely to be able to recall a range not a specific number.

The questions were posed in relation to two contrasting vignettes of delirium outlined in Table 16—delirium in the setting of good functional status and high likelihood of reversibility in comparison with delirium superimposed on the last days of life.

Table 16 Two contrasting vignettes of delirium

Vignette 1: delirium in the setting of good functional status
62-year-old woman with metastatic breast cancer, involving multiple bone sites, and single lung metastasis, usually ambulant, living at home with her very supportive family. She is currently receiving hormonal therapy, and no other medication. Routine visit by community nurse identifies a three-day history of increased confusion with no other symptoms. She is afebrile, haemodynamically stable, with no neurological deficits.
Vignette 2: delirium superimposed on the last days of life
84-year-old man with metastatic small cell lung cancer, with liver and brain metastases, where chemotherapy and radiotherapy are not treatment options, develops progressive agitation and confusion due to delirium in the terminal phase of his disease. His prognosis is thought to be days rather than weeks.

The questionnaire asked respondents for the location in which they would provide care for these patients; the usual assessment and investigations for reversible components of delirium; the usefulness of non-pharmacological measures; the symptomatology of delirium requiring treatment; the pharmacological treatment of choice and dosing schedule used. The questionnaire was piloted with 10 specialists to identify any omissions or problems with its design.

2.2.4 Ethical approval

Approval of St Vincent's Hospital, Sydney (New South Wales, Australia) Human Research Ethics Committee was obtained (Appendix 3).

2.2.5 Statistical analysis

Fisher's exact test was used to compare dichotomous outcomes between the specialist groups: (choice of location of care, care at home or not); agent of choice (antipsychotic or benzodiazepine); pre-emptive treatments prior to delirium aetiology being known; and initial investigations (basic blood tests—electrolytes, full blood count, liver function tests and calcium—or not, chest X-ray or not, urinalysis or not). Each specialist group was compared to the pooled data for the other three. Fisher's exact test was chosen to allow for small numbers of observations in some categories. Bonferroni's correction for four analyses was applied.

Logistic regression was used to explore the association between other factors and the dichotomous outcomes if enough observations were available. In addition to the specialist groups, independent variables included specialist demographics

(gender, number of patients seen with delirium per week—more than five versus five or fewer, number of years in clinical practice—less than 10 years versus more than 10, and place of predominant practice—community versus hospital-based practice).

The Kruskal-Wallis test was used to compare total numbers of investigations between specialist groups. This was because the groups being examined were likely to be of unequal size and to be non-normally distributed. If significant, this was followed up by the Mann-Whitney U test to identify the source of the difference from the specialist groups. Analyses were performed using SPSS version 11.1.4 for Mac OS X (2002, SPSS Inc, Chicago, Illinois, USA). Reporting of the study context, rationale for the survey tool, sample selection, and analysis is according to good practice in the conduct and reporting of survey research.[406]

2.3 Results

2.3.1 Piloting of survey

No changes to the survey were required after the initial piloting.

2.3.2 Response rate

The response rates for the four specialist groups were MO n = 62 (24%); palliative medicine (PM) n = 79 (38%); geriatrics (G) n = 88 (33%); and ACP n = 41 (26%). Three respondents sent the questionnaire back blank or sent a letter, reporting that they were not actively in clinical practice; one was an aged care psychiatrist, however, what specialty group the other two belonged to was not clear. The overall response rate was 270 out of 918, or 30%. The initial response rate was 202 respondents (22%) with the remainder providing the additional 68 responses following a reminder from the society/college. There was a similar response across the four groups from all states within Australia and from New Zealand, where applicable.

2.3.3 Demographics of respondents

Seventy per cent of specialists had a predominantly urban practice, and 13% rural. The balance was made up of metropolitan practitioners providing some rural outreach services. The percentage of male and female specialists in each group

was approximately 50%, except for aged care psychiatrists, with 71% male and only 29% female specialists responding. Fifty-seven per cent of specialists had been in practice for more than 10 years, with no significant differences between specialty groups.

There were three significant practice differences between speciality disciplines. First, medical oncologists reported no community-based practice compared with over 51% of other specialists ($p < 0.01$). Second, fewer palliative medicine specialists (67%) conduct some of their practice in acute care inpatient settings compared with 90% of other specialists ($p < 0.01$). Third, 51% of geriatricians saw more than five patients per week with delirium, whereas only 18% of other specialists saw this number ($p < 0.01$). There were no significant differences between specialities in consultative, private or outpatient practices.

2.3.4 Location of care

Table 17 illustrates that only 35% of medical oncologists considered care at home an option for a patient with delirium in the setting of good functional status (Vignette 1) compared with 66% of other specialists ($p < 0.01$).

Table 17 Percentage of specialists cross-tabulated for choices in care (Vignette 1)

Management choice		Aged care psychiatry (n = 41)	Geriatrics (n = 88)	Medical oncology (n = 62)	Palliative medicine (n = 79)	p-value
Location of care (n, %)[a]	Would consider care at home	28 72%	21 35%	21 35%	54 69%	< 0.01
	Would not consider care at home	11 28%	34 39%	39 65%	24 31%	
	Total number of respondents[b]	39 (95%)	55 (63%)	60 (97%)	78 (99%)	
Investigative approach: Choice of initial investigations (n, %)[a]	Basic blood tests[c]	35 90%	75 85%	55 92%	60 77%	NS
	Urine culture	36 92%	82 93%	51 85%	59 76%	< 0.05
	Oxygen saturations	17 44%	54 61%	46 77%	43 55%	< 0.05
	Thyroid function	16 41%	25 28%	8 13%	6 8%	< 0.05
	CT head	7 18%	33 38%	27 49%	8 10%	< 0.01
	Chest X ray	21 54%	59 67%	33 55%	10 13%	< 0.01
	Total number of respondents[b]	39 (95%)	82 (93%)	60 (97%)	78 (99%)	

Management choice		Aged care psychiatry (n = 41)	Geriatrics (n = 88)	Medical oncology (n = 62)	Palliative medicine (n = 79)	p-value
Pre-emptive therapy: Use of pre-emptive therapies prior to aetiology of delirium being identified. (n, %)[a]	Antibiotics	1 3%	4 5%	10 16%	3 4%	< 0.05
	Intravenous fluids	1 3%	24 27%	24 39%	8 10%	< 0.01
	Oxygen	1 3%	14 16%	24 39%	9 12%	< 0.01
	Pharmacological management	17 44%	26 30%	19 31%	60 77%	< 0.01
	Non-pharmacological management	38 97%	80 90%	37 62%	66 85%	NS
	Total number of respondents[b]	39 (95%)	82 (93%)	60 (97%)	78 (99%)	
Symptom control: Choice of agent for management of delirium symptoms	Antipsychotic treatment of choice	35 95%	85 98%	45 79%	76 97%	NS
	Benzodiazepine treatment of choice	2 5%	2 2%	12 21%	3 3%	< 0.01
	Total number of respondents[b]	37 (90%)	87 (99%)	57 (92%)	79 (100%)	

[a] (n, %) = number of respondents and % for each specialty (out of total respondents in that specialty for the question)

[b] n(%) = number of respondents in specialty (% out of specialty group respondents overall)

[c] Electrolytes, full blood count, calcium and liver function tests ; NS = not significant; CT – Computerised Tomography

Logistic regression demonstrated medical oncologists were less likely (OR 0.43, CI 0.19 to 0.97) to choose care at home (Table 18). There were no other significant associations between choice of care at home for vignette 1 and gender, years of practice, and number of patients seen with delirium.

Table 18 Logistic regression analysis of predictors of choice of care at home (Vignette 1)

Specialist demographics	**Odds Ratio (CI)**	**p-value**
Geriatrics vs palliative care	0.75 (0.37 to 1.53)	0.42
Aged care psychiatry vs palliative care	1.07 (0.42 to 2.73)	0.89
Medical oncologist vs palliative care	0.43 (0.19 to 0.97)	0.043
Specialist with community based practice	2.07 (1.10 to 3.92)	0.025
First 10 years of practice	0.77 (0.43 to 1.37)	0.37
More than five patients with delirium seen each week	1.68 (0.86 to 3.28)	0.13
Specialist gender female	1.11 (0.63 to 1.95)	0.72

CI – 95% Confidence Interval, Reference categories are palliative medicine for specialist discipline, noncommunity practice for location of practice, more than 10 years of practice for duration of practice, fewer than five patients per week with delirium and male for gender.

For Vignette 2, there were no significant differences between specialties for options for location of care (home, hospital or palliative care unit, see Table 19).

Table 19 Percentage of specialists cross-tabulated for choices in care (Vignette 2)

Management choice		Aged care psychiatry (n = 41)	Geriatrics (n = 88)	Medical oncology (n = 62)	Palliative medicine (n = 79)	p-value
Location of care (n, %)[a]	Would consider care at home	20 56%	58 67%	30 50%	54 69%	NS
	Would not consider care at home	16 44%	29 33%	30 50%	24 31%	
	Total number of respondents[b]	36 (89%)	87 (99%)	60 (97%)	78 (99%)	
Investigative approach: Choice of initial investigations (n, %)[a]	No investigations	19 54%	41 47%	28 47%	32 41%	NS
	Basic blood tests[c]	2 6%	13 15%	12 20%	12 15%	NS
	Urine culture	12 34%	24 28%	15 25%	17 22%	NS
	Oxygen saturations	10 29%	25 29%	20 33%	29 37%	NS
	Thyroid function	0	2 2%	0	0	NS
	CT head	0	0	1 2%	0	NS

Management choice		Aged care psychiatry (n = 41)	Geriatrics (n = 88)	Medical oncology (n = 62)	Palliative medicine (n = 79)	p-value
	Chest X ray	1 3%	7 8%	3 5%	0	NS
	Total number of respondents[b]	36 (89%)	87 (99%)	60 (97%)	78 (99%)	
Symptom control: Choice of agent for management of delirium symptoms (n, %)[a]	Antipsychotic	23 72%	57 69%	13 23%	48 62%	
	Benzodiazepine or opioid	9 28%	26 31%	43 77%	30 38%	< 0.01
	Total number of respondents[b]	32 (78%)	83 (94%)	56 (90%)	78 (99%)	

[a] (n, %)* = number of respondents and percentage for each discipline (out of total respondents in that discipline for the question)

[b] n(%) = number of respondents in specialty (% out of specialty group respondents overall)

[c] Electrolytes, full blood count, calcium and liver function tests

NS = not significant

CT – Computerised Tomography

2.3.5 Investigative approaches

For Vignette 1, significant differences between groups were seen in the median number of first line investigations ordered by palliative medicine specialists (median = 5) compared to other specialists (median = 7; $p < 0.001$; Table 17). There were no significant differences between specialist groups prepared to order blood assays with 85% ordering electrolytes, full blood count, calcium and liver function tests.

Seventy-seven per cent of medical oncologists ordered oxygen saturations compared with 56% of other specialists ($p < 0.05$). A Computerised Tomography (CT) head scan was ordered by 46% of medical oncologists compared with only 23% of other specialists ($p < 0.01$).

Only 13% of palliative medicine specialists ordered a chest X-ray to investigate potentially reversible delirium compared with 60% of other specialists ($p < 0.01$). Only 76% of palliative medicine specialists ordered a urine analysis compared with 90% of other specialists ($p < 0.05$).

Forty-one per cent of aged care psychiatrists ordered thyroid function tests compared with 17% of other specialists ($p < 0.05$).

For Vignette 2, no significant differences were seen in first line investigations between any speciality groups (median = 1). There were no differences between each specialty group with 15% of respondents ordering the same blood tests as in Vignette 1. More than 40% of all specialists undertook no investigations for Vignette 2, with no differences between specialties.

No specialists considered lumbar puncture, EEG or arterial blood gas as routine initial investigations in either Vignette 1 or 2. Logistic regression exploring other factors of interest was not conducted due to the small number of observations in some cells.

2.3.6 Management approaches

2.3.6.1 Pre-emptive treatments prior to delirium aetiology being known

For Vignette 1, medical oncologists were significantly more likely than the other three specialties to use pre-emptive antibiotics prior to the aetiology being defined (16% versus 4%, $p < 0.05$), intravenous fluids (39% versus 16%, $p < 0.01$), and oxygen (39% versus 12%, $p < 0.01$) (see Table 17).

2.3.6.2 Pharmacological management

For Vignette 1, symptomatic pharmacological measures were more likely to be used by palliative medicine specialists (77%) as initial management compared with only 33% of other specialists ($p < 0.01$) (see Table 17). Twenty-one per cent of medical oncologists used a benzodiazepine as agent of choice for Vignette 1 compared with 3% of other specialists ($p < 0.01$).

For Vignette 2, a benzodiazepine was given as the agent of choice by 77% of medical oncologists compared with 34% of other specialists ($p < 0.01$) (see Table 19). Overall, the usage of benzodiazepines by all specialty groups was higher for delirium in the terminal stages (43%) than for reversible delirium (7%). It is also interesting to note that 9.4% of aged care psychiatrists and 4.8% of geriatricians nominated that they would use an opioid as agent of choice to manage 'terminal delirium' symptoms, despite this not being provided as a choice in the questionnaire (respondents created another tick box spontaneously to put forward this choice).

Age, severity of symptoms and level of sedation were the predominant factors considered by the respondents affecting dose, regardless of agent. The key side effects of interest for antipsychotics were sedation, falls, confusion, postural hypotension and Parkinsonian effects. For benzodiazepines the side effects were falls, sedation and confusion.

2.3.6.3 Choice of pharmacological agent by symptom

Table 20 provides details of the agent different specialists recommended for particular symptoms of delirium for Vignette 1, with some specific differences in management of particular symptoms that warrant highlighting. Twenty three per

cent of medical oncologists (n = 14 out of the 60 medical oncologists who responded to that question) recommended benzodiazepines or a combination of benzodiazepine and an antipsychotic to manage hallucinations compared to 5% of other specialists ($p < 0.01$). Medical oncologists were more likely to use a benzodiazepine alone to manage agitation (30%; n = 18 out of the 60 medical oncologists who responded to that question) compared to 10% (n = 19) of other specialists ($p < 0.05$), and disruptive behaviour (18% compared to 3%; $p < 0.01$).

Significantly more palliative medicine specialists compared to other specialists recommended an antipsychotic to manage disorientation (57%; n = 44 of the palliative medicine respondents for that question) compared to 16.7% of other specialists (n = 29; $p < 0.01$); decreased activity (36%; n = 28) compared to 3% of other specialists (n = 5; $p < 0.01$), impaired concentration (31%; n = 24) compared to 9% of other specialists (n = 16; $p < 0.01$); and cognitive impairment (47%; n = 36) compared to 7% of other specialists (n = 14; $p < 0.01$).

There were no significant differences in the use of benzodiazepines to manage sleep/wake cycle alterations between palliative care (34%) and other specialists (31%) ($p > 0.05$).

Table 20 Choices of pharmacological agents by symptom and specialty (Vignette 1)

Symptom	Specialty	None n (%*)	Antipsychotic n (%[a])	Benzodiazepine n (%*)	Both n (%*)
Anxiety	ACP	5 (13%)	6 (16%)	***16 (42%)***	11 (29%)
	G	12 (14%)	6 (7%)	***38 (45%)***	27 (32%)
	MO	2 (3%)	0	***47 (78%)***	11 (18%)
	PM	1 (1%)	2 (3%)	***58 (75%)***	16 (21%)
Cognitive impairment	ACP	***35 (92%)***	3 (8%)	0	0
	G	***78 (94%)***	5 (6%)	0	0
	MO	***49 (82%)***	6 (10%)	3 (5%)	2 (3%)
	PM	***40 (52%)***	***36 (47%)***	1 (1%)	0
Hallucinations	ACP	1 (3%)	***35 (92%)***	1 (3%)	1 (3%)
	G	3 (4%)	***78 (94%)***	1 (1%)	1 (1%)
	MO	4 (7%)	***42 (70%)***	4 (6%)	10 (17%)
	PM	0	***71 (92%)***	0	6 (8%)
Delusions	ACP	2 (5%)	***34 (90%)***	1 (3%)	1 (3%)
	G	3 (4%)	***76 (92%)***	1 (1.2%)	3 (4%)
	MO	4 (7%)	***49 (82%)***	2 (3%)	5 (8%)
	PM	0	***74 (96%)***	0	3 (4%)
Disorientation	ACP	***33 (87%)***	5 (13%)	0	0
	G	***74 (89%)***	8 (10%)	0	1 (1%)
	MO	***39 (66%)***	16 (27%)	2 (3%)	2 (3%)
	PM	30 (39%)	***44 (57%)***	1 (1%)	2 (3%)
Disruptive behaviour	ACP	0	***27 (71%)***	2 (5%)	9 (24%)
	G	7 (8%)	***49 (59%)***	0	27 (33%)
	MO	6 (10%)	16 (27%)	11 (18%)	***27 (45%)***
	PM	1 (1%)	26 (34%)	4 (5%)	***46 (60%)***
Agitation	ACP	2 (5%)	***21 (55%)***	2 (5%)	13 (34%)
	G	3 (4%)	***35 (42%)***	6 (7%)	39 (47%)
	MO	3 (5%)	6 (10%)	18 (30%)	***33 (55%)***
	PM	1 (1%)	10 (13%)	11 (14%)	***55 (71%***

Symptom	Specialty	None n (%*)	Antipsychotic n (%[a])	Benzodiazepine n (%*)	Both n (%*)
Decreased activity	ACP	***38 (100%)***	0	0	0
	G	***81 (98%)***	1 (1%)	1 (1%)	0
	MO	***56 (93%)***	4 (7%)	0	0
	PM	***49 (64%)***	28 (36%)	0	0
Impaired concentration	ACP	***33 (87%)***	5 (13%)	0	0
	G	***78 (94%)***	5 (6%)	0	0
	MO	***51 (86%)***	6 (10%)	2 (3%)	0
	PM	***53 (69%)***	24 (31%)	0	0
Mood lability	ACP	***16 (42%)***	***16 (42%)***	0	6 (16%)
	G	***58 (70%)***	18 (22%)	2 (2%)	5 (6%)
	MO	***30 (50%)***	18 (30%)	7 (12%)	5 (8%)
	PM	29 (38%)	***33 (43%)***	11 (14%)	4 (5%)
Sleep wake alteration	ACP	6 (16%)	7 (18%)	***12 (32%)***	***12 (32%)***
	G	***27 (33%)***	13 (16%)	19 (23%)	24 (29%)
	MO	12 (20%)	11 (18%)	***26 (43%)***	11 (18%)
	PM	12 (16%)	19 (25%)	***26 (34%)***	20 (26%)

ACP – aged care psychiatry; G – geriatrics; MO – medical oncology; PM – palliative medicine

Note: not all respondents provided an answer for each symptom (non-responders ACP n = 4, G n = 5, MO n = 2, PC n = 2)

[a] per cent is out of the total number of respondents who answered the question for that symptom in that specialty group

The bold italic figures are the highest n, % for the symptom and are of interest

Table 21 details the ratings each specialty gave to specific agents in the management of delirium symptoms. Aged care psychiatrists' rated the usefulness of agents to manage delirium symptoms as follows: 87% rated haloperidol as moderately to very useful, approximately two thirds rated olanzapine and risperidone as moderately to very useful, and approximately half quetiapine as moderately to very useful. The majority never used levomepromazine; and midazolam and diazepam were not used by one third.

Geriatricians showed a preference for haloperidol and risperidone, with 96% rating haloperidol as moderately to very useful, 85% rating risperidone as moderately to very useful, 58% rated olanzapine as moderately to very useful. The majority never used levomepromazine, and lorazepam and quetiapine were not used by a third.

Eighty-six per cent of medical oncologists rated haloperidol as moderately to very useful as an agent to manage delirium symptoms, with a lower preference for atypical antipsychotics. Forty-five per cent rated olanzapine as moderately to very useful, and 32% rated risperidone as moderately to very useful. The majority never used levomepromazine and quetiapine, and risperidone was not used by two thirds. All of the individual benzodiazepines were rated moderately to very useful by 20%–30% of medical oncologists.

Palliative medicine ratings of usefulness of agents to manage delirium symptoms were as follows: 99% rated haloperidol as moderately to very useful, 76% rated olanzapine and risperidone as moderately to very useful, and 47% rated levomepromazine as moderately to very useful. The majority never used quetiapine, and risperidone was not used by two thirds of respondents. All of the individual benzodiazepines received a rating of moderately useful by 22%–26% of palliative medicine specialists.

Table 21 Usefulness of specific agents to manage delirium symptoms by specialty group

Specific agent		Aged care psychiatry	Geriatrics	Medical 0ncology	Palliative medicine
Haloperidol (n, %)[a]	Never used	1 (3%)	0	0	0
	Slightly useful[b]	3 (8%)	3 (4%)	8 (13%)	1 (1%)
	Moderately useful	12 (32%)	23 (28%)	17 (28%)	4 (5%)
	Very useful[c]	22 (58%)	57 (68%)	35 (58%)	72 (94%)
Olanzapine (n, %)[a]	Never used	2 (5%)	1 (1%)	31 (52%)	18 (23%)
	Slightly useful	13 (34%)	18 (22%)	2 (3%)	1 (1%)
	Moderately useful	11 (29%)	24 (30%)	9 (15%)	9 (12%)
	Very useful	12 (32%)	40 (28%)	18 (30%)	49 (64%)
Risperidone (n, %)[a]	Never used	2 (5%)	1 (1%)	39 (65%)	17 (22%)
	Slightly useful	10 (26%)	11 (13%)	2 (3%)	2 (3%)
	Moderately useful	8 (21%)	25 (30%)	7 (12%)	16 (21%)
	Very useful	18 (47%)	46 (55%)	12 (20%)	42 (55%)
Levomepromazine (n, %)[a]	Never used	34 (90%)	73 (88%)	57 (95%)	34 (44%)
	Slightly useful	3 (8%)	7 (8%)	1 (2%)	7 (9%)
	Moderately useful	1 (3%)	2 (2%)	0	9 (12%)
	Very useful	0	1 (1%)	2	27 (35%)
Quetiapine (n, %)[a]	Never used	7 (18%)	23 (28%)	58 (97%)	65 (84%)
	Slightly useful	11 (29%)	25 (30%)	1 (2%)	5 (6%)
	Moderately useful	8 (21%)	18 (22%)	0	2 (3%)
	Very useful	12 (32%)	17 (20%)	1 (2%)	5 (6%)
Lorazepam (n, %)[a]	Never used	7 (18%)	23 (28%)	7 (12%)	6 (8%)
	Slightly useful	12 (32%)	32 (39%)	21 (35%)	41 (53%)
	Moderately useful	9 (24%)	19 (23%)	16 (27%)	20 (26%)
	Very useful	10 (26%)	9 (11%)	16 (27%)	10 (13%)

Specific agent		Aged care psychiatry	Geriatrics	Medical 0ncology	Palliative medicine
Midazolam (n, %)[a]	Never used	13 (34%)	14 (17%)	5 (8%)	0
	Slightly useful	15 (39%)	38 (47%)	18 (30%)	26 (34%)
	Moderately useful	6 (16%)	10 (12%)	15 (25%)	17 (22%)
	Very useful	4 (11%)	21 (25%)	22 (37%)	34 (44%)
Clonazepam (n, %)[a]	Never used	11 (30%)	24 (30%)	9 (15%)	3 (4%)
	Slightly useful	19 (50%)	39 (47%)	18 (30%)	26 (34%)
	Moderately useful	7 (18%)	10 (12%)	16 (27%)	21 (27%)
	Very useful	1 (3%)	10 (12%)	17 (28%)	27 (35%)
Diazepam (n, %)[a]	Never used	3 (8%)	11 (13%)	6 (10%)	11 (14%)
	Slightly useful	20 (53%)	39 (47%)	27 (45%)	35 (45%)
	Moderately useful	7 (18%)	17 (21%)	12 (20%)	17 (22%)
	Very useful	8 (21%)	6 (7%)	15 (25%)	4 (5%)
	Total number of respondents (% of specialty group respondents overall)	38 (93%)	83 (94%)	60 (97%)	77 (97%)

[a] n, % = number of respondents, and per cent of overall respondents for this question in the specialty group
[b] combination of not useful, rarely useful and slightly useful categories
[c] Combination of very and extremely useful categories

2.3.6.4 Dosing of pharmacological agents

The dosing schedules proposed for specific agents demonstrated a range of choice of dose, increments for titration, and ceiling doses. The dosing ranges are compared between agent and specialty group are outlined in Table 22 for Vignette 1, and Table 23 for Vignette. For example, when you consider responses for both Vignette 1 and 2, doses of haloperidol recommended to be commenced orally or subcutaneously differed 20-fold in a 24-hour period (0.25mg to 5mg), with increments varying 40-fold (0.25mg–10mg), and maximum doses varying 240-fold (0.5mg to 120 mg). For midazolam, commencing doses ranged between 0.5 and 30mg per 24 hours, with increments of 0.5–10mg per 24 hours, and maximum doses of 2–150mg per 24 hours.

Table 22 illustrates that for Vignette 1 the dosing utilised by ACP was on the lower end of the range, and no midazolam was used. Most aged care psychiatrists used haloperidol. Medical oncologists and palliative medicine specialists used two–three times the mean doses of haloperidol for commencing, increment and maximum doses. Interestingly, no palliative medicine specialists or aged care psychiatrists used midazolam as the agent of choice. For both Vignette 1 and 2 the highest maximum doses for haloperidol and midazolam for medical oncologists and palliative medicine specialists were also 10-fold higher than aged care psychiatry and geriatric specialists. Very few medical oncologists and palliative medicine specialists used olanzapine and risperidone. Logistic regression exploring other factors of interest was not conducted due to the small number of observations in some cells.

Table 22 Dosing ranges by agent and specialty group for Vignette 1

Agent	Specialty group (n)	Starting dose (mg) mean (range)	Magnitude of difference mean starting dose[a]	Increment (mg) mean (range)	increment mean dose difference magnitude[a]	Maximum dose (mg) mean (range)
Haloperidol	ACP (24)	0.5 (0.25–3)	-	0.5 (0.25–1)	-	7 (0.2–20)
	G (61)	0.5 (0.25–2.5)	ND	0.6 (0.25–2.5)	MD	5 (0.5–10)
	MO (40)	1.2 (0.5–5)	Two fold	1.4 (0.5–5)	Three fold	11 (1.5–100)
	PM (72)	1.2 (0.25–5)	Two fold	1.5 (0.5–20)	Three fold	15 (1–120)
	Overall	1 (0.25–5)		1 (0.25–20)		10 (0.5–120)
Risperidone	ACP (6)	0.5 (0.25–1)	-	0.5 (0.25–1)	-	0.75 (0.5–3)
	G (11)	0.4 (0.25–0.5)	MD	0.5 (0.25–2.5)	ND	2.5 (1–5)
	MO (1)	0.5 (0.5)	ND	0.5 (0.5)	ND	4 (4)
	PM (3)	0.4 (0.25–0.5)	MD	0.5 (0.5)	ND	3 (2–6)
	Overall	0.5 (0.25–1)		0.5 (0.5–2.5)		3 (1–6)
Olanzapine	ACP (3)	5 (2.5–10)		3.75 (1.25–5)		10 (2.5–20)
	G (6)	2.5 (2.5)	half	2.5 (2.5)	Two thirds	10.5 (10–12.5)
	MO (2)	1.75 (1–2.5)	third	3 (1–5)	Eight tenths	12.5 (5–20)
	PM (1)	2.5 (2.5)	half	2.5 (2.5)	Two thirds	20 (20)
	Overall	3 (1-10)		2.5 (1-5)		16.5 (2.5-20)
Midazolam (24-hour dose)	ACP (0)	-	-	-	-	-
	G (1)	2.5 (2.5)	-	1 (1)	-	10 (10)
	MO (5)	1.5 (0.5-2.5)	Two thirds	2 (1-7.5)	half	22 (10-30)
	PM (0)	-	-	-	-	-
	Overall	0.5 (0.5 – 2.5)		2.5 (1-7.5)		17 (10-30)

[a]Comparator for magnitude of differences in mean doses is ACP group for antipsychotics geriatrics for midazolam and is approximate factor for the difference

ACP – aged care psychiatry; G – geriatrics; MO – medical oncology; PM – palliative medicine ND – no difference, MD – minimal difference

Note not all respondents provided an answer for each symptom (non-responders ACP n = 5, G n = 4, MO n = 1, PM n = 2)

Table 23 Dosing ranges by agent and specialty group for Vignette 2

Agent	Specialty group	Starting dose mg mean (range)	Magnitude of difference mean starting dose[a]	Increment mg mean (range)	Magnitude of difference in increment mean dose[a]	Maximum dose mg mean (range)
Haloperidol	ACP (11)	0.4 (0.25–0.5)	-	0.8 (0.25–5)	-	9 (2–20)
	G (47)	0.6 (0.25–2.5)	MD	0.7 (0.25–2.5)	MD	4.5 (2–20)
	MO (13)	1.8 (0.5–5)	Four fold	1.3 (0.5–5)	Two fold	20.5 (1.5–100)
	PM (41)	1.4 (0.5–5)	Three fold	1.2 (0.5–5)	MD	(5–120)
	Overall	1 (0.25–10)		1 (0.25–5)		13 (1.5–120)
Risperidone	ACP (4)	0.4 (0.25–0.5)	-	0.4 (0.25–0.5)	-	2.75 (2–4)
	G (5)	0.45 (0.25–0.5)	MD	0.45 (0.25–0.5)	MD	1.7 (1–2)
	MO (0)	-	-	-	-	-
	PM (0)	-	-	-	-	-
	Overall	0.5 (0.25–5)		0.65 (0.25–2.5)		3 (1–10)
Olanzapine	ACP (1)	5 (5)	-	5 (5)	-	60 (60)
	G (1)	2.5 (2.5)	Half	2.5 (2.5)	half	10 (10)
	MO (0)	-	-	-	-	-
	PM (0)	-	-	-	-	-
	Overall	3.75 (2.5 -10)		3.8 (2.5–5)		35 (10–60)
Midazolam	ACP (3)	3 (1–5)	-	2 (1–2.5)	-	8 (5–10)
	G (10)	2 (0.5–5)	Two third	2(0.5–5)	MD	4 (2–10)
	MO (30)	4 (0.5–10)	MD	3.5 (0.5–10)	Two fold	24 (10–100)
	PM (26)	6.5 (10–20)	Two fold	5 (0.5–10)	Two fold	59 (15–150)
	Overall	4.75 (0.5–20)		3.75 (0.5–10)		46 (2–150)

[a]Comparator for magnitude of differences in mean doses is ACP group and is approximate factor for the difference

ACP – aged care psychiatry; G – geriatrics; MO – medical oncology; PM – palliative medicine ND – no difference, MD – minimal difference

Note not all respondents provided an answer for each symptom (non-responders ACP n = 15, G n = 10, MO n = 11, PM n = 3)

2.3.6.5 Non-pharmacological approaches

No significant differences were identified in the rating of the usefulness of several non-pharmacological measures. Respondents rated the following as useful:

- quiet well-lit room 62% (n = 167) of specialists for Vignette 1 and 44% (n = 118) for Vignette 2
- a visible clock/calendar 37% (n = 99) for Vignette 1 and 18% (n = 48) for Vignette 2
- familiar items from home 41% (n = 110) for Vignette 1 and 32% (n = 86) for Vignette 2
- family able to sit with patient 61% (n = 164) for Vignette 1 and 60% (n = 162) for Vignette 2
- reorientation 46% (n = 124) for Vignette 1 and 21% (n = 57) for Vignette 2
- one-to-one nursing 28% (n = 67) for Vignette 1 and 25% (n = 67) for Vignette 2.

Having family sit with the patient was the one measure rated by two thirds of of all specialists as very useful in both Vignettes 1 and 2. The percentage rating the other strategies as useful were lower.

The non-pharmacological strategies that required the patient to be more alert were rated as less useful in delirium superimposed on the last days of life (for example a clock and calendar, well-lit room, and reorientation). However, in practice, initial management using non-pharmacological measures was significantly more likely to be used by aged care psychiatrists for Vignette 1 ($p < 0.01$) (Table 17).

2.3.6.6 How do we know treatment has been successful?

2.3.6.6.1 Clinical outcomes in delirium in the setting of good functional status

The percentage of specialists utilising the following outcomes measures to determine treatment success varied as follows: delirium resolution (57%–82%), decreased severity (62%–96%), improved symptoms (52%–92%), improved cognition (30%–58%), and sedation (18% - 28%). Table 24 outlines the specific response by specialist group. The key features are a focus on delirium resolution

and minimal sedation. Functional impairment received almost no responses as a measure of treatment impact.

Table 24 Treatment response used by each specialty in Vignette 1

n, %	Aged care psychiatry	Geriatrics	Medical oncology	Palliative medicine
Delirium resolution	21 (57%)	51 (61%)	42 (72%)	63 (82%)
Reduced delirium severity	23 (62%	65 (78%)	47 (81%)	74 (96%)
Reduction in delirium duration	21 (57%)	37 (45%)	21 (36%)	39 (51%)
Improvement in targeted symptom	34 (92%)	75 (90%)	30 (52%)	50 (65%)
Improvement in cognitive impairment	16 (43%)	25 (30%)	27 (47%)	45 (59%)
sedation	8 (22%)	15 (18%)	16 (28%)	20 (26%)
Family comfort	0	1 (1%)	1 (2%)	0
Improvement in function	0	2 (3%)	0	0

2.3.6.6.2 Clinical outcomes in delirium superimposed on the last days of life

The percentage of specialists utilising the following outcome measures to determine treatment success for Vignette 2 varied as follows: delirium resolution (27% - 42%), reduced severity (54–77%), improved symptoms (61%–90%), improved cognition (12% - 25%), and sedation (41%–68%). Table 25 outlines the specific response by specialist group for Vignette 2. The key differences between Vignette 2 and Vignette 1 are the shift to focusing on improved severity, reduced symptoms and sedation.

Table 25 Clinical indicators of treatment success used by each specialty in Vignette 2

	Aged care psychiatry	Geriatrics	Medical oncology	Palliative medicine
Delirium resolution	11 (37%)	21 (27%)	18 (32%)	32 (42%)
Improvement in delirium severity	19 (63%)	51 (65%)	31 (54%)	59 (77%)
Reduction in delirium duration	10 (33%)	26 (33%)	7 (12%)	20 (26%)
Improvement in targeted symptom	27 (90%)	67 (85%)	35 (61%)	54 (70%)
Improvement in cognitive impairment	7 (23%)	10 (13%)	14 (25%)	17 (22%)
Sedation	14 (47%)	32 (41%)	35 (61%)	52 (68%)
Family comfort	0	0	0	3 (4%)
Reduction in distress	0	7 (9%)	2 (3%)	3 (4%)
Death	1 (3%)	0	0	0

2.3.6.6.3 Frequency of reversible component to delirium

Two thirds of geriatricians and medical oncologists identified that a reversible cause would be present in greater than half of their patients, and another 25% in a third to half of their patients. Forty per cent of aged care psychiatrists and 20% of palliative medicine specialists would identify that their patients have a reversible cause in greater than half of their patients, and a further 40% in a third to a half of their patients (Table 26).

Table 26 Frequency of reversible component to delirium

	Aged care psychiatry	Geriatrics	Medical oncology	Palliative medicine
Never	0	0	0	0
Less than 10% of times	2 (5%)	1 (1%)	1 (2%)	2 (3%)
11–30%	6 (16%)	8 (10%)	5 (8%)	30 (39%)
31–50%	15 (40%)	24 (29%)	13 (22%)	30 (39%)
>50%	15 (40%)	50 (60%)	41 (68%)	15 (20%)

2.3.6.6.4 Indicators of a poor outcome

Table 27 outlines the views of respondents on predictors of a poor outcome for a delirium episode. The most dominant factors are irreversible aetiology, multiple comorbidities, poor performance status and prior cognitive impairment. Hypoactive delirium was believed to have poorer outcomes than hyperactive delirium.

Table 27 Predictors of poor outcome used by each specialty

n, %	Aged care psychiatry	Geriatrics	Medical oncology	Palliative medicine
Delirium severity	12 (32%)	43 (52%)	21 (36%)	40 (52%)
Duration of delirium	28 (76%)	68 (82%)	32 (55%)	48 (62%)
Hypoactive delirium	13 (35%)	30 (36%)	14 (24%)	17 (22%)
Hyperactive delirium	1 (3%)	4 (5%)	4 (7%)	12 (16%)
Performance status	3 (8%)	38 (46%)	40 (70%)	55 (71%)
Number of comorbidities	32 (87%)	67 (81%)	40 (69%)	56 (73%)
Extent of malignancy	26 (70%)	37 (45%)	39 (67%)	42 (55%)
Brain metastases	26 (70%)	52 (63%)	42 (72%)	49 (64%)
Previous episode of delirium	12 (32%)	34 (41%)	24 (42%)	27 (35%)
Degree of prior cognitive impairment	28 (76%)	67 (81%)	46 (80%)	43 (56%)
Age	19 (51%)	38 (46%)	25 (43%)	28 (36%)
Irreversible aetiology	28 (76%)	65 (78%)	44 (76%)	64 (83%)
Dehydration	1 (3%)	0	1 (2%)	0
Failure to make diagnosis of delirium	0	1 (1%)	0	0
Chronic alcohol use	0	1 (11%)	0	0
Malnutrition/ deconditioning	0	1 (1%)	0	0
Sensory impairment	0	1 (1%)	0	0
Unresolved psychosocial/spiritual issues	0	0	1 (2%)	1 (1%)
Rate of onset	0	0	0	1 (1%)

2.3.6.7 Reported routine use of a delirium or cognitive assessment

Thirty per cent of aged care psychiatrists, 55% of geriatricians, 3% of medical oncologists and 20% of palliative medicine specialists reported using a cognitive function or delirium scale routinely in their practice. The most common scales used were the MMSE and the CAM.

2.4 Discussion

2.4.1 Key findings

This current study explored baseline patterns of clinical care for people with advanced cancer who develop delirium from the perspective of different specialties. The study builds on prior work exploring barriers to delirium care from a medical perspective[359], variations in practice from a geriatric perspective[367], and patterns of antipsychotic prescribing.[391 392] These data provide insights into clinical decisions around location of care, routine clinical assessments, pre-emptive treatments, and therapy (both from a pharmacological and non-pharmacological perspective). It also provides the ability to contrast care for delirium patients with cancer in the setting of good functional status with the delirium being experienced in the last days of life.

The major differences between specialties identified in the study relate to:

- the perceived appropriateness of care for patients with reversible delirium in community settings
- the use of more specialised investigations such as CT of the brain or thyroid function
- the frequency of use of evidence-based nonpharmacological strategies
- the use of benzodiazepines for symptom control
- wide dosing ranges for antipsychotics and benzodiazepines
- the use of pre-emptive treatments (intravenous fluids, oxygen, antibiotics)
- the treatment of hypoactive cognitive symptoms
- the use of opioids in the terminal phase.

There was agreement between the specialties on other decisions such as flexibility in choice of location of care and minimising investigations for delirium in the

terminal phase of care, basic investigations for reversible causes of delirium and ratings of non-pharmacological measures. In terms of the goals of treatment, in delirium with reversible components the focus of respondents was on maximising delirium resolution and minimising sedation. In delirium in the terminal phase with reversible components, respondents shifted their focus to reducing symptoms and their severity, with sedation being the preferred option. Reversible delirium was more commonly reported in oncology and geriatric practices. More than 60% of medical oncologists and geriatricians reported that reversible components of delirium were present in over 50% of their patients, compared to less than 50% of specialists in ACP and palliative care.

The dominant factors cited by respondents to be associated with poor outcomes from a delirium episode were consistent with the literature. Factors in studies exploring the variables associated with poor outcomes are the same confounding variables adjusted for in studies exploring the outcomes relating to delirium itself.[375 407] The belief that hypoactive subtypes also did more poorly is consistent with some literature[61 408], but not all.[409 410] Kiely et al found that the hypoactive subtype had the highest mortality risk for one year mortality in 457 hospitalised older people with delirium.[408] Marcantonio et al found the opposite, with the hypoactive type having less severe delirium and better outcomes (nursing home placement or death at one month 32% in hypoactive group versus 79% in hyperactive group, $p = 0.003$) in 122 older patients with delirium post hip-fracture surgery.[409] Despite functional impairment being a feature of a poor outcome[411] from a delirium episode, maintainence of function was not mentioned as a marker of treatment success.

2.4.2 What do these data support or refute?

2.4.2.1 Location of care

Many studies demonstrate that an episode of delirium has a significant impact on morbidity and mortality.[190 287-294] It has been established that environmental components influence the occurrence of delirium, and indeed the NICE Guidelines for delirium diagnosis, prevention and management provide specific recommendations about environment.[412] These include recommendations that the person is cared for by a team who is familiar with the patient, that they avoid

moving the patient within or between wards or rooms if possible, and that appropriate lighting and signage is provided.[412]

More interesting is the emerging evidence that both the occurrence of delirium and possibly delirium outcomes may be influenced by the location of care.[413] This work explored the post-acute care setting and new episodes of delirium; however, there are no data yet exploring the acute management of delirium at home. A randomised control trial of a 'hospital in the home' intervention for patients referred for geriatric rehabilitation demonstrated that the home group had lower odds of developing delirium (assessed by CAM) during rehabilitation.[413] This study randomised inpatients (n = 104) referred for geriatric rehabilitation who could transfer independently and mobilise sufficiently to toilet themselves, and who were expected to return home and live independently, to home rehabilitation by a multidisciplinary team versus inpatient rehabilitation in the geriatric rehabilitation ward. The patients undertook assessment for delirium using the CAM on alternate days, and during the rehabilitation phase there were significantly lower rates of delirium in the home rehabilitation group (0.6% versus 3.2%, absolute risk reduction of 2.6%, p = 0.0029). A previous study of the management of acute illness with the same intervention indicated a lower incidence of confusion in hospital compared to the home group; however, this was ascertained from the medical record, rather than with formal delirium assessment.[414] The exact mechanism by which this benefit is mediated is not clear, but it could be related to the avoidance of adverse effects associated with hospitals (e.g. nosocomial infection) or the environmental benefits of being in the most familiar and least disruptive environment.

It may not be the place of care that influences outcomes, but rather the quality of care in relation to delirium prevention and management received in that location which may be more important. Some literature discusses the need for specialist multidisciplinary management of delirium in relation to the role of specialised delirium units.[415-419] A delirium unit aims to provide a secure environment, and concentrated health professional expertise with specific training in either geriatric and/or delirium care. Although trends in data from audits and retrospective data report a benefit from a delirium unit, it is harder to evaluate this approach in a randomised control trial. A recent study randomised 600 participants who were

confused and over the age of 65 years to either care in a specialised medical and mental health unit or standard care (geriatric or general medical ward). The study found improvements in patient and caregiver experiences, but the location did not impact on hospital length of stay or mortality.[370] This study had the limitation that geriatricians in the specialised units also provided care in the general wards (so intervention may not have been exclusive), and there were a larger number of nursing home residents and patients with dementia in the intervention unit arm.

The qualification and skills of the medical officer making the assessment is also crucial. For example, a junior medical officer assessment in the acute care setting of a cognitively impaired patient compared to a home or hospital assessment by a specialist interdisciplinary team experienced in delirium assessment may also lead to differential outcomes.[353] Equally a palliative care or cancer care community service may not be resourced sufficiently to provide comprehensive investigational and interventional management of potentially reversible delirium in the home setting. In the home setting the assessment may be conducted by community nurses, who equally may under-recognise delirium and may not refer for further medical assessment (see Chapter 3).

The other mediator may be the change in care location. People with advanced cancer may have complex care needs requiring care in multiple settings, and in the management of delirium it may be important to focus on not only the site of care but also the care transitions (even within a single institution), which may be a point of particular vulnerability in this population. It is not clear whether a comprehensive plan of care being in place within the first 24 to 48 hours of the delirium episode is in place also alters outcomes.[420] One study including 423 cancer patients reported more than half had more than one site of care in the last month of life.[421] Another study in Canada demonstrated that, out of 5903 patients registered with a comprehensive palliative care program, over 40% experienced one transition in care location, 31% experienced two or more, and 6.3% five or more changes in location or service providing care.[422 423]

It is well documented that delirium detection in the emergency department is poor, in particular hypoactive delirium which is the more common presentation in

patients with advanced cancer[80 424] and is a setting where 'palliative' patients may be under-investigated for reversible conditions.[425]

2.4.2.2 Investigative approaches

This current survey demonstrates broad agreement with the first line investigations for geriatricians, aged care psychiatrists and medical oncologists, with key differences being a lower median number of investigations being ordered by palliative medicine specialists (mainly due to less ordering of chest X-rays and urinalysis. The other key difference was the higher frequency of brain imaging by medical oncologists and thyroid function by aged care psychiatrists, reflective of the important differential diagnoses that may have a specific management approach in the populations these specialists care for. Current guidelines exist to guide clinicians in the investigational approaches in patients with delirium; however, the recommendations are based on expert opinion or low levels of evidence, and predominantly relate to the older population without cancer.[371 372 426] The British Geriatric Society and American Psychiatric Association guidelines suggest first line investigations should include full blood count, electrolytes, calcium and liver function; thyroid function tests; oxygen saturations; chest X-ray; electrocardiogram; blood cultures; and urinalysis. The Australian clinical practice guidelines for the management of delirium in older people[336] suggest the following investigations will screen for common causes of delirium: urinalysis and urine culture (if urinalysis is abnormal); full blood examination, urea and cardiac enzymes electrolytes, glucose, calcium, liver function tests; chest X-ray; and electrocardiogram; with further investigations based on clinical features. The Australian guidelines also highlight aetiologies titled 'critical management issues': hypoxaemia, hypotension, hypoglycaemia, infection, alcohol withdrawal, constipation, faecal impaction, urinary retention and potential medication precipitants. A CT of the brain is recommended if there are focal neurological signs, a history of falls, or use of anticoagulation. The recommendation that CT of the head is not useful to investigate delirium if there are no clinical pointers to neurological condition or injury, is based on a small descriptive study, and was not specific for the oncology setting.[427] The NICE delirium clinical guidelines suggest assessing for infection, hypoxaemia and undertaking a medication review; but does not provide a prescriptive list of proposed investigations.[412] In no

guideline is EEG or lumbar puncture considered first line investigations, consistent with the views of the respondents to this current survey.

The EDA recently conducted a survey of its members (n = 200)[366], and the investigations routinely used or recommended in delirium workup were laboratory analyses (58%), brain CT (25%), brain magnetic resonance imaging 11%, EEG (10%) and lumbar puncture (6%). This survey also highlighted the higher rate of brain imaging (36%), than would be expected if practice followed clinical guidelines. Another survey of members of the American Geriatric Society (n = 282, response rate of 65%) provided a clinical scenario of delirium in an older patient after hip-fracture surgery with no clinical or laboratory indications of infection, metabolic disturbance or hypoxaemia, and no history of alcohol or substance abuse. For this case 'best practice' had been selected *a priori*, which was proceeding to brain imaging. Lumbar puncture or EEG were not required in mild delirium, and hence the 50 respondents (18%) who selected one or more of these investigations were deemed to have selected an unnecessary diagnostic test. The rationale was based on 'current expert recommendations' that neuroimaging does not necessarily contribute to diagnosis and may worsen confusion when the patient is placed in CT or MRI apparatus, and in particular if sedation is needed to achieve the imaging in the first place. This also highlights that those who are in specialist practice, due to their clinical exposure to more unusual clinical scenarios, may have a tendency to look for these diagnoses more frequently, and earlier in the diagnostic pathway.

A recent review of delirium in palliative care settings highlights the controversy that exists in the extent of diagnostic workup in patients with life-limiting illness.[214] A prospective study of 113 people with advanced cancer admitted to an acute palliative care unit in Canada demonstrated that delirium is potentially reversible in 50% of patients in this setting, with hypoxaemia and non-respiratory infection independently associated with irreversibility in multivariate analyses.[38] [428] Another study of 121 palliative inpatients in Ireland with delirium demonstrated that 27% recovered from delirium.[215] In this cohort delirium with more aetiologies, in older age, more severe cognitive disturbance and related to organ failure, was more likely to be irreversible.[215] This supports this current survey's findings of the clinicians' perceptions of reversibility in the palliative

care population, where only 20% of palliative medicine specialists reported greater than half of their patients to have reversible cause, whereas 40% reported reversibility in a third to a half of their patients.

Choice of initial investigations may be influenced by practical considerations such as care in the home setting.[428] For example, palliative medicine specialists practicing in community settings may be less likely to order an initial chest X-ray. Differences in the patient populations seen by each specialty may also account for the differences seen, with aged care psychiatrists and palliative medicine specialists seeing patients in the post-acute care setting more commonly, when reversible causes already have been considered.

2.4.2.3 Symptom control differences: pharmacological and non-pharmacological approaches

This current survey demonstrates differences in both the frequency of use of pharmacological strategies—with palliative medicine specialists more likely to use medication to control delirium symptoms—but also in choice of agent, both for overall management of delirium and for specific target symptoms.

This survey was unique in terms of asking clinicians to specify which symptoms of delirium they are treating or think warrant treatment, rather than simply specifying subtype. This is an important distinction as motoric subtype definitions evolve[65 429], and also individual clinicians may operationalise the subtype definitions differently.[56] This methodology was able to identify that the higher use of benzodiazepines by medical oncologists was for target symptoms of hallucinations, agitation and disruptive behaviour. It was also able to identify that palliative medicine specialists also treat hypoactive symptoms (disorientation, impaired concentration, decreased activity, and cognitive impairment) pharmacologically. The frequency of hypoactive presentations is much higher in palliative populations, and hence the impetus to offer symptomatic treatments may be higher, especially since patients report maintaining lucidity as important.[80 307 430]

The EDA survey[366] similarly found variability in the pharmacological management of delirium, and in particular explored hypoactive delirium. Sixty per cent of respondents would use a combined pharmacological and non-

pharmacological approach, with only 9% using a pharmacological approach alone. The agents of choice for hyperactive delirium were haloperidol (49%), risperidone (10%) quetiapine (3%), and other drugs in (16%). Sixty per cent would utilise an electrocardiogram before starting treatment to evaluate for prolonged QT_c [i] interval. In hypoactive delirium, 29% would use a combined pharmacological and non-pharmacological approach, and 3% a pharmacological approach alone, with 9% using haloperidol, 16% rivastigmine, 6% quetiapine, and 13% other drugs. The survey of the American Geriatric Society by Carnes et al[367] found that for mild delirium 74% would prefer to observe and have a bedside attendant, whereas 17% (n = 47) intervened pharmacologically (30 chose haloperidol, 11 lorazepam, and five chose another drug). In severe delirium only 12% chose to treat with no medication, 180 chose haloperidol (64%), seven (2%) risperidone, 55 (20%) chose lorazepam, and 23 (8%) chose haloperidol in combination with lorazepam.[367] The rates of pharmacological management of hypoactive symptoms were much higher in this current Australian survey for palliative care specialists, compared to that found by Carnes et al.[367] The EDA survey rates of pharmacological treatment of hypoactive delirium, albeit in conjunction with non-pharmacological strategies, were comparable with rates of treatment of decreased activity, and impaired concentration by palliative medicine specialists, but again much higher than the other specialists.[366]

In terms of dosing, the Carnes et al survey of the American Geriatric Society[367] found that of the 180 participants selecting haloperidol alone, the initial dose was less than 1mg for 39% (n = 70), 1mg for 42% (n = 75), 2mg for 17% (n = 30), and 5mg for 3% (n = 5), with no respondents choosing a 10mg dose. Sixty-six per cent (n = 117) of respondents delivered haloperidol by the intramuscular route, 16% (n = 29) intravenously, and 18% (n = 32) orally. For lorazepam as a single agent, 54% (n = 27) chose less than 1mg, 42% (n = 21) chose 1mg, and 4% (n = 2) chose 2mg.

Similarly a pre-survey of participants at an educational workshop on delirium pharmacotherapy (n=66) demonstrated that there was variable beliefs about the role of antipsychotic medication (median frequency of use by the respondents was

[i] QT interval, corrected for heart (a measure of time between start of Q wave and end of T wave

60%).[431] Antipsychotic use was less when respondents perceived there to be less supporting evidence (p=0.02). The principle mechanism of action was considered to be sedative (38%) and antipsychotic (33%), rather than a specific action on delirium neuropathophysiology.[431] The key side effects of concern cited were sedation (32%), extrapyramidal (52%), cerebrovascular (30%) and metabolic (8%).[431]

A structured audit conducted in a general medical and orthopaedic unit of a tertiary hospital in Australia of all patients older than 65 who had an ICD-10 code for delirium coded on discharge over a one-year period, reviewed 174 episodes of care.[391] For 102 episodes with severe symptoms, 66% (n = 67) were newly prescribed antipsychotics, with over half (n = 45/79, 57%) prescribed one and 43% (n = 34) more than one.[391] The antipsychotic prescribed included haloperidol (n = 50), olanzapine (n = 49), risperidone (n = 17), quetiapine (n = 2) and droperidol (n = 5).[391] Eighteen per cent (n = 12) of those with severe symptoms were already taking antipsychotic agents on admission and were prescribed another antipsychotic type additionally. In the majority, the commencement dose of antipsychotics was higher than recommended in the Australian guidelines (75%, n = 59/79), and many were prescribed at least one as a required dose of antipsychotic medication (80%, 63/79). Thirty per cent (52/174) were newly prescribed sedative or hypnotic medications, with 39 of those patients having severe delirium symptoms. Seventeen per cent of patients were admitted on benzodiazepines, with these ceased or given intermittently in 72%. Benzodiazepines were newly prescribed before antipsychotics in 37% (n = 11), prescribed in combination with antipsychotics on the same day in 27% (n = 8) and after the antipsychotics in 37% (n = 11).[391] This audit demonstrated higher doses than recommended, commonly prescribing multiple antipsychotics, high frequency of new benzodiazepine prescribing, very few patients with adequate documentation of a medication management plan or regular medication review once antipsychotic medications have been prescribed and high numbers of statum doses ordered.[391]

Another audit focussed on 99 patients with advanced cancer in a large cancer centre. Seventy-two per cent (n = 71) received haloperidol, 17% (n = 17) olanzapine, 12% (n = 12) chlorpromazine, 14% (n = 14) lorazepam, and 2% (n =

2) midazolam.[392] Eighteen per cent received no antipsychotic or benzodiazepine.[392] Chlorpromazine, lorazepam and midazolam were preferentially given to patients with hyperactive delirium (p = 0.01, p = 0.016, p = 0.016 respectively). Patients with hyperactive delirium were also more likely to receive haloperidol in combination with another antipsychotic (p = 0.03) and benzodiazepines (p = 0.004). The median average total haloperidol daily dose was 1.3mg (0–3.2mg).

These survey data and prior published survey and audit data verify wide variation in agent and dosing, including higher use of benzodiazepines than recommended in guidelines in current clinical practice. The audit data provide insight into what actually happens in practice, in comparison to survey data which is self report. These survey data also highlight that the increments used in titration are relatively large, with total daily dosing at a relatively high level as well. As doses are titrated, the prior audits have also demonstrated that monitoring and review is suboptimal, which is also a cause for concern. Of note is that the standard ampoule size for antipsychotics such as haloperidol and olanzapine of 5mg may also encourage the use of higher doses of parenteral administration than recommended or required.

Current evidence for pharmacological management of delirium is limited with no pharmacological agent approved by the United States Food and Drug Administration or similar international bodies for a delirium indication.[333 334 338-340 432] The randomised placebo controlled trials reported to date include one where allocation concealment was not maintained and the allocation between arms was uneven with the randomisation schedule unclear (n = 176).[333] A study of quetiapine versus a placebo was stopped early (due to feasibility issues) and underpowered[334], and the only other study was in a population of terminally ill patients with AIDS (n = 30).[338] The other studies compared two antipsychotics: risperidone and olanzapine (n = 32)[339], and risperidone and haloperidol (n = 28).[340] The studies reported to date in people with cancer have been open label designs: olanzapine in advanced cancer (n = 79)[330], quetiapine in a population predominantly with leukaemia (n = 12)[433], olanzapine in advanced cancer (n = 24)[331], and case matched control comparision of aripiprazole and haloperidol in patients with cancer (n = 41).[434] The mean doses seen across the open label

studies vary between 2.5mg and 20mg for olanzapine, 93.75mg for quetiapine, 15.2mg and 18.3mg for aripiprazole, and 4.9 and 5.5mg for haloperidol. In the randomised studies the mean doses were usually lower but still varied, with mean doses of 1.4–7mg of haloperidol, 36mg of chlorpromazine, 4.6 mg of lorazepam, 1.8–4.5 mg of olanzapine, and 0.6 mg of risperidone. As treatment response was measured by delirium numerical rating scores which include more hyperactive symptoms, a reduction score may also occur due to sedative effects with the patient still being delirous but with a hypoactive spectrum of symptoms. This adds to the difficulty in interpreting these trial findings.

The only randomised control trial evidence of benzodiazepines in delirium showed worsening delirium compared to haloperidol, however this study only had a sample size of 30 with six in the lorazepam arm, and was in a specific population (terminally ill AIDS patients).[338] It has been previously demonstrated that the use of benzodiazepines in palliative care settings is high, with up to 58% of patients being prescribed a benzodiazepine in the last three weeks of life in an inpatient palliative care setting, for non-specific distress, especially for younger patients, and those concurrently on antipsychotics or opioids.[435] These survey data also highlight that the use of benzodiazepines extends to the oncology setting, potentially earlier in the disease trajectory.

The only study which specifically explored hypoactive symptoms explored the use of methylphenidate in 14 participants[436], but this was not included as an option in the survey due to restrictions in its use and the minimal data available at present informing its role.

These open label and randomised studies also only looked at efficacy in terms of overall delirium score reduction, and do not help in informing decisions relating to targeting specific symptoms seen with delirium. There are also limited adverse event data especially in relation to worsening confusion, extrapyramidal toxicity, drug interactions and falls risk. This is particularly pertinent given the higher use of antipsychotics by palliative medicine specialists for multiple symptoms including cognitive impairment, and hypoactive delirium symptoms, and the use of benzodiazepines for agitation and disruptive behaviour by medical oncologists.

Another interesting finding in prescribing practice in the current study was that up to 10% of aged care psychiatrists and geriatricians nominated an opioid to manage delirium in the terminal stages of illness. This may reflect the difficulty in distinguishing pain and delirium in the person who is both cognitively impaired and potentially also non-communicative. The impetus to ensure someone is pain free in the terminal phase may be a stronger driver for clinical decisions, with clinicians responding with analgesia at a lower signal threshold for pain or distress. Equally, it is unknown whether delirium causes neuro-pathological changes in pain pathways. One hypothesis is of an interrelationship mediated by alternation of the circadian rhythm, with abnormalities seen in both pain and delirium.[207-210] There is also an increasing body of literature describing the role analgesia (including opioids) may have in improving severe behavioural and psychological symptoms in advanced dementia, which may also influence this prescribing.[437-439]

There are currently no specific pain assessment tools for use in delirium. Pain assessment in cognitive impairment scales have been developed for use in dementia and rely on behavioural, verbal, facial and/or physiological domains, all of which may be abnormal in delirium.[177 178] A recent study of 124 cognitively impaired long-term care residents compared six observational pain measures (ADD, CNPI, NOPPAIN, PADE, PAINAD, and PACSLAC), and investigated the impact when the delirium related items of agitation, restlessness, increased mental confusion, fear and anxiety, calling out, changes in sleep, and incoherent language were eliminated.[177] The number of items that needed to be deleted varied between the scales: four out of five for ADD, one of six for CNPI, one of eight for NOPPAIN, 22 of 60 for PACSLAC, four of 14 for PADE, and three of 15 for PAINAD.[177] Hence the remaining items which are not likely to be influenced by the presence of delirium were quite variable, with some scales losing most of their items rendering the tool unhelpful in delirium. To assess these scales' ability to identify pain, with and without the items which overlap with delirium, the participants were video recorded during three pain conditions—baseline, during influenza vaccination and during movement-exacerbated pain.[177] All measures were able to differentiate between pain and baseline states, and when items that

overlap with delirium were not included the measures' ability to identify pain persisted (apart from ADD).[177]

Differences seen in prescribing in the current population may include a desire to reduce risks of polypharmacy leading to a conservative approach to pharmacotherapy.[440 441] Training differences may help to explain some of the variations in practice encountered in this current study. Likewise, extrapolation of evidence from other related fields (e.g. behavioural disturbance in dementia) might also be a key influence. A recent survey of 4000 physicians in the US highlighted only 7.4% of antipsychotic prescribing was for delirium and dementia, with the predominant use for psychiatric conditions.[442] The ability to actively improve symptoms and the underlying disease simultaneously may have driven the pattern of practice for MO. Differences in the patterns of delirium symptoms seen by each specialist group may vary due to differences of severity, number of acute insults and baseline vulnerability of the patient population in their practice setting. The specialists' perceptions of the distress of the symptom complexes may also influence differing pharmacological approaches.

In terms of non-pharmacological therapies, these were likely to be first line strategies for aged care psychiatrists but were highly valued by most specialists. This is similar to the findings from the qualitative work exploring the nursing perspective from the same respective disciplines (Chapter 3). The EDA's recent survey of its members (n = 200)[366] also explored this aspect of care with pharmacological interventions prescribed regularly by the respondents. These included uninterrupted sleep and minimising noise (58%), pain evaluation and treatment (80%), assessing constipation and urinary retention (78%), minimising physical restraints and urinary catheters (6%), patient reorientation and cognitive stimulation (63%), ensuring family member presence (62%), aids for sensory impairment (spectacles, hearing aids), and early mobilisation (67%). The views that pain evaluation and treatment were important, also aligns with the approach of utilising analgesia for Vignette 2 in this current survey.

The use of delirium and cognitive assessments was routinely low in our survey, and included common use of MMSE which is not specific for delirium, has copyright issues, and often is difficult to complete fully in the patient with

delirium. By contrast, in the EDA's recent survey[366], 52% reported using the CAM, 30% the delirium observation scale, 10% the DRS-R98 and 13% the CAM-ICU. This EDA survey participants, however, is one of international experts in delirium with a specific interest from a clinical and research perspective around delirium detection. Routine introduction of delirium screening has been shown to improve detection; however, it needs to be associated with substantial training and education for sensitivity and specificity to reach levels seen when the same tools are used in the research setting.[443-445]

2.4.3 Limitations of the study

There were several limitations to this study. First, the response rate was relatively low. To interpret the data, a comparison was made between the survey respondents and the demographics obtained from the most recent available workforce surveys of the respective specialist colleges membership. The sample surveyed are broadly representative in terms of demographics (age, gender and location of practice).[446-449] This suggests that the findings of this survey are applicable and valid within the Australian and New Zealand context. In other healthcare settings it is quite likely interdisciplinary variation may occur; however, further research to determine specific areas of difference is needed and, due to variations in cancer care, these may not be the same issues found in this survey. The survey length may also have impacted on response rate.

Second, the survey methodology of using vignettes cannot capture the complexity of delirium management in clinical practice, only identifying what clinicians self-report rather than what actually is done in practice. However, the survey is an important first step in understanding and contrasting the management of delirium across the four key disciplines that encounter this syndrome as part of specialist practice. A survey with the topic specified as 'delirium', is not going to capture under-detection of delirium, nor how this varies by specialty. A recent study looking at hospital episode statistics in the UK showed that reporting of delirium did vary by specialty, demonstrating higher rates of reporting in general medicine and geriatrics when compared to trauma and orthopaedics.[450]

Equally, as the vignettes were centred around people with cancer, the third limitation is generalisability. The key area of difference is the higher frequency of

hypoactive presentations[71 80], and the challenges of determining the intensity of investigation and treatment which is warranted in far advanced disease.[327] The aetiologies that may precipitate delirium in cancer are not hugely different, apart from the higher prevalence of intracranial disease.[38 104 185 327] Many people still have reversible delirium, even in the setting of advanced disease, and from the survey results the clinicians clearly identified that this was so for Vignette 1.[38] The current open label studies of the pharmacological treatment of delirium in cancer populations support the recommendations for low dose pharmacological management, and hence do not support the wide range of pharmacological approaches suggested by the respondents in this survey.[330 332 434]

2.4.4 Implications for practice

It is important to define variations in practice in relation to factors that may be relevant to improving delirium outcomes, and to assist in developing better evidence for care pathways and translating this evidence into clinical practice. In response to specific case scenarios, divergent views about key clinical decisions were seen across four specialist disciplines with experience in the care of patients with delirium and cancer. These variations in patterns of care reflect many factors, but some of the variations may lead to less-than-ideal outcomes for the person with delirium.

Efforts need to continue to improve the recognition of delirium, including assessment of reversible causes. Another area that deserves attention is the development of assessment tools, which can more reliably determine the presence of pain when someone is delirious, considering the item selection to avoid those that overlap with delirium features.

Based on the current evidence for the location of care that offers the best outcomes for delirium care, it is not clear that hospital necessarily offers advantages over home care, but the consideration of the level of intervention and supportive care needed and the ability to provide, supervise and monitor this care in the home setting is crucial. This may depend on severity of symptoms, in particular the hyperactive component.

Further work is needed in the area of delirium in cancer to determine the sensitivity of brain imaging and the role for more routine use in delirium assessment. There are few data providing guidance on the yield of imaging, and its impact on outcomes, in the setting where no clinical symptoms or signs apart from the delirium itself are present. Given delirium is usually multifactorial in aetiology, if other causes are found, does brain imaging still have a role to play? It is reassuring that clinicians place value on non-pharmacological strategies and healthcare systems need assistance to embed these into routine care.

The biggest variation from clinical practice guidelines is in pharmacological management. These variations include the higher use of benzodiazepines, larger dose ranges for antipsychotics, and choice by at least some practitioners in two specialties of opioids in the setting of delirium superimposed on the last days of life. This is consistent with the literature findings, regardless of whether you look at junior medical officer or specialist prescribing, and whether you ask for clinician's self-report of prescribing practice or undertake medication chart audits. Wide variation in prescribing is seen with large deviation from clinical practice guidelines.[366 367 391 392]

Future studies also need to consider clinical decision making in the context of the other pharmacological therapies used commonly in the palliative patient population. This includes opioids, corticosteroids and benzodiazepines. In some instances the patient will also already be taking antipsychotic medications for management of nausea.

The key is to determine what are the known barriers to knowledge about delirium care and why clinical practice guidelines are not being taken up. Specific challenges include lack of education or knowledge about delirium and its consequences at an individual and organisational level, competing needs for screening for other health conditions (e.g. falls risk, pain), the common mistake of misdiagnosing delirium as dementia, and delirium as an 'orphan condition' not belonging to a specific specialty (and hence lacking clinical or research champions).[451] A division of roles is also perceived as a problem, with it being unclear whether delirium is best managed by mental health professionals or general clinicians, and also the views of health professionals who see geriatrics as

'unchallenging' or not their responsibility.[451] More recently a qualitative study explored the views of health professionals working in acute care settings, and also demonstrated an issue of lack of 'ownership' and negative attitudes towards confused patients and lack of awareness of how frightened the person with delirium in hospital is.[452] The survey of junior medical officers identified that though they were aware of the high prevalence and significance of delirium, they lacked knowledge in diagnosis and management even when they had had experience in geriatric medicine.[359]

Another challenge is the use of informal words and phrases to describe delirium, which leads to both diagnostic ambivalence and imprecision.[453] Delirium is a challenging condition due to heterogeneity in presenting symptoms, aetiology, and the need to carefully and individually combine pharmacological and non-pharmacological management approaches.[453] The nuances of how clinicians balance these factors in clinical practice are difficult to ascertain from a survey approach.

2.4.5 Implications for research

Further research is needed to delineate the best location of care, and to investigate if differences relate to staff skill, intensity of monitoring or other factors. The experience in stroke units was that the care provided is not transferable to general medical wards.[454 455] An evidence-based strategy is needed to allow clinicians to balance burdens of excessive investigation, compared with investigations that may define potential reversibility or improve symptoms in the population with advanced cancer. The variables measured in this current survey did not identify very strong specialist demographic predictors relating to key decision-making in care of cancer patients with delirium, which suggests decision-making may be more variable than first considered. This study also raises significant implications for the approach to training of medical specialists with the need to obtain a core body of knowledge in delirium management that drives management decisions irrespective of type of medical specialty[359 398], partnered with management pertinent to the specific patient populations seen.[389]

Delirium care, by nature of the interventions needed for prevention and management, is multidisciplinary. In intensive care settings, the use of formal

delirium screening is seen as a useful mechanism for communication between nurses and physicians.[456] It also raises the question of who should drive practice change, with literature emerging demonstrating nurse-led interventions or those delivered by trained volunteers are effective.[350 353]

There is an urgent need for studies exploring efficacy of pharmacological management of delirium in advanced cancer—given that this is the area of care in which the most substantial variations in practice were seen—and to focus particularly on effectiveness of managing targeted symptoms, adverse events profiles as well outcomes that are meaningful to patients and their families, such as improved cognition.

2.5 Conclusion

There is significant variability in the investigation and management of delirium in people with advanced cancer, both in the setting of good functional status, and also in the terminal phase of illness. It builds on prior work that has demonstrated variability in delirium care in other medical settings. Major differences were seen in the perceived appropriateness of care at home for someone with potentially reversible delirium, use of more specialised interventions such as CT, and wide variation in pharmacological therapies. Future research needs to focus on areas where the evidence base is sparse, and on strategies to reduce the evidence/practice gap so as to ensure that interventions that can impact on outcomes are taken up into practice in a more timely and systematic way.

Chapter 3: Making decisions about delirium—a nursing perspective

This chapter describes a qualitative exploration to understand and contrast the approaches that nurses use to assess and manage delirium when caring for people with cancer, the elderly, or older people requiring psychiatric care in an inpatient setting.

3.1 Background

Delirium is a frequent phenomenon in people with cancer and in older people, regardless of the healthcare setting.[38 211 457-460] Nurses caring for the hospitalised elderly will have approximately a quarter to two thirds of their patients with delirium at any one time[461], and the prevalence in inpatients with dementia or with advanced illness such as cancer is up to 90%.[38 82 214 374] In oncology settings the prevalence varies from 20% to 60%, dependent upon the number of elderly oncology or advanced cancer patients admitted to the service and the acuity of care, (e.g. patients undergoing bone marrow transplant have very high rates of delirium).[182 183 185 211 462-466]

Delirium impacts significantly on nursing practice. Nurses need to make sense of the manifestations of delirium and come to a diagnosis, formulate management strategies, and deal with family distress, all while maintaining patient and staff safety.[467 468] Delirium is referred to as the 'silent unspoken piece of nursing practice', and as such has significant workload implications.[467 468] In particular, nurses need to deal with the unpredictable and fluctuating presentation of patients with delirium.[469 470] The presence of a confused patient is often deemed a signal of impending 'chaos' on the shift if not effectively managed.[469 470] The person with delirium becomes difficult to engage or predict, and nurses describe this as causing ambivalence, doubt, and sometimes even irritation and frustration.[471] Studies report that, although nurses generally find it hard to manage the delirious patient, they do seek to assess the situation and intervene. The choice of intervention and the outcomes being pursued, however, vary—both by nursing group as well as by the values or beliefs of the individual nurse.[471]

Equally the role of nurses significantly impacts upon the outcomes for the person with delirium.[471] Bedside nurses are in an optimal position to detect symptoms that fluctuate over time due to their more continuous presence with the patient during a shift; however, it has been repeatedly demonstrated that these signs often go unrecognised.[361-365] If symptoms are detected, they are more usually unusual behavior or communication, which relates to the nature of nursing interaction and tasks.[86] Delirium is often under-identified, unrecognised and undertreated, being associated with poorer outcomes such as increased medical complications, longer length of stay, nursing home placement, and death.[355 472] The support and explanation provided to families through this period will shape their perceptions and experiences of delirium, and is also important, as witnessing delirium symptoms is associated with risk of significant anxiety in caregivers.[317 321]

Operationalising the DSM-IV-R criteria to make a diagnosis of delirium relies on recognition of changes in cognition developing over a short period of time, and their fluctuation, with a temporal relationship to a precipitant general medical condition.[473] Several explanations have been given for the continued under-detection of delirium. These include a lack of knowledge of the criteria for delirium diagnosis, poor awareness of screening assessments for delirium, ineffective communication of detected symptoms at onset to other team members, lack of thorough observations of patient behaviours, incorrect interpretation of witnessed patient behaviours, not undertaking further cognitive assessment for fear of offending patients, 'making excuses for patients' and consequently minimising the significance of their symptoms, and a lack of confidence in performing a cognitive assessment.[469 474-479]

In inpatient settings, particularly in oncology and palliative care, patients with advanced and progressive disease may be significantly medically unwell. In the elderly, pre-existing cognitive impairment is common. These factors amplify the challenge of noticing clues to delirium that include subtle cognitive changes or new precipitant medical problems.

Once a delirium episode has been identified, nurses need to have the capabilities to navigate through the various pharmacological and non-pharmacological management strategies of delirium, which may either be physician prescribed or

nurse initiated. 'As required' medications may be available giving the nurse choices in responding to the individual symptoms prior to a definitive physician diagnosis of delirium.[391 480] Nurses also need to attend to other care needs that may exacerbate delirium symptoms including urinary retention, constipation, sensory deprivation (hearing and vision impairment) and pain. It is also crucial that nurses communicate the symptoms they have identified (and hopefully also alert that they suspect a delirium diagnosis) to other health professionals caring for the patient, including to medical colleagues, so that all aspects of management are attended to.

There is limited literature about the experience of nurses caring for confused patients in surgical, acute medical and palliative care settings.[467 469 481 482]

A qualitative study of orthopaedic nurses (n = 48) demonstrated that the nurses found it difficult to interpret the confused patient's reality. Interaction sometimes had a calming effect, but also could worsen aggressive behaviour, and the nurses needed to 'take over the patients' responsibilities'.[482]

Another qualitative study of graduate nursing students (n = 4) in adult medical surgical acute-care settings described early cues for delirium that the nurses recognised as lack of concentration, irritability, exaggerated body language and gestures, difference in expression in visual cues, little eye contact, or differences in behaviour.[469] The nurses described other conditions such as pain and emotional reactions to disease that could give these same cues, and that knowing the patient also helped detect small changes in behaviour.[469] Continued observation or asking a family member to inform the nurse when any changes occurred were the most common nursing actions reported by this sample.[469] Few described consideration or checking of medication or physiological risk factors of the patient.[469] Caring for delirious patients was described as stressful due to the unanticipated nature of delirium and increased nurses' workload; needing to balance care of the delirious patient with other patient needs. These nurses considered this care 'hard work both mentally and physically'.[469] This study had the methodological problems that theoretical saturation was not reached and only relatively junior (1.5 and four years of clinical experience) female nurses were interviewed.[469]

Palliative care nurses working in inpatient and home care settings experience multiple challenges in caring for delirious patients.[481] A qualitative study, in which five inpatient and four home care palliative care nurses described such challenges, included witnessing the distress experienced by these patients and their loved ones, and the difficulty in achieving a 'peaceful' death.[481] The nurses identified the importance of their presence to calm and comfort a delirious patient and the importance of teamwork to deal with these difficult situations. These nurses were concerned about a lack of ability to provide continuity of care to these patients and their level of knowledge and education about delirium.[481]

In summary, these prior studies of nurses' experiences identified that the care of the confused patient is often stressful and distressing.[467 469 481 482] The focus of care was often on 'controlling the situation'.[467 482] Nurses understood the value of their 'presence' to patients, as well as the need to keep an eye on the patient.[467 482] They articulated reliance on behavioural symptoms as a clue to delirium being present.[467 482] These studies provided an overview of how nurses approach delirium, but did not provide an in-depth understanding of their approaches to assessment or management. There are also no studies that articulate and compare the experiences of nurses in oncology, geriatrics or ACP settings. The aim of this current qualitative study was to explore and contrast nurses' assessment and management of delirium when caring for people with cancer, the elderly or older people requiring psychiatric care in an inpatient setting.

3.2 Methods

3.2.1 Design

Semi-structured interviews explored nurses' views and thoughts about defining, diagnosing and managing delirium, the perceived aetiology of distress for patients and their caregivers, and their level of confidence in managing delirium symptoms. The question route was structured to allow for a thorough exploration of the issues identified from the literature. Human Research Ethics approval was obtained from South West Sydney Human Research Ethics Committee and Hope Healthcare Human Research Ethics Committee (Appendix 4), as well as approval from the management of the inpatient units in which the study was conducted.

3.2.2 Theoretical framework for the methodology

As very few studies have explored the experience of nurses caring for someone with delirium, in particular within the context of the decisions nurses make and how they experience this component of nursing work, it was not possible to test pre-existing theory.[483] The purpose of this current study was to develop substantive theory (a theory about a particular situation or group) to better understand and interpret how nurses in a variety of clinical settings with a high prevalence of delirium, work with patients with delirium. Hence, a grounded theory methodological approach was utilised.[484] This allowed the analysis of the phenomenon of nurses caring for patients with delirium considering 'why, how, where, when and under what conditions and with what consequences' (symbolic interactionism and social constructionist perspective), which would allow a theoretical model which could inform nursing practice and education.[483]

3.2.3 Setting

3.2.3.1 Characteristics of the inpatient units

South West Sydney Local Health District includes Liverpool hospital, Camden and Campbelltown hospitals, and Braeside hospital. The network provides care for patients within a 3245-square kilometre area from Fairfield to Bowral (local government areas of Bankstown, Camden, Fairfield, Liverpool and Wollondilly), serving over 800,000 people. The included departments were the geriatric units at Liverpool and Camden hospitals, the oncology unit at Liverpool hospital, the ACP unit at Braeside hospital, and palliative care units at Braeside and Camden hospitals.

The geriatric units provide acute medical care and some convalescent/rehabilitation care to older people. The ACP unit provides psychiatric care to the elderly, and require acute medical conditions to be stable prior to admission. The oncology inpatient unit provides care for medical and radiation oncology patients and those with haematological malignancies, who require acute care for medical problems associated with their malignancies or its treatment, and can include those with both early and advanced disease. The specialist palliative care inpatient units provide inpatient care for those patients with life-limiting illness who have complex physical symptoms or psychosocial

needs, with the aim of stabilising them to enable discharge, but also in some cases terminal end of life care.

The nursing allocation (skill mix) for shifts in the oncology and ACP settings and in the palliative care unit at Camden hospital included half to two thirds of nursing staff on a shift being registered nurses, supported by a one third to half of staff who were enrolled nurses. In the acute geriatric units and one of the palliative care units (Braeside hospital), the registered nursing workforce (also comprising half to two thirds of nurses per shift), was augmented with one care assistant who assisted with personal care, rather than enrolled nurses alone. In general, there were fewer staff in total, and less registered nurses, on night shifts within the units at the time the study was undertaken.

3.2.3.2 Rationale for choice of inpatient settings

These clinical areas were chosen as they were most likely to provide data and experiences regarding the phenomenon of interest[483 485], namely nurses caring for people with delirium in the setting of complex or advanced disease, and nurses' experiences in the setting of advanced disease, cancer, and cognitive impairment. Settings were thus selected where complex or advanced medical problems were concurrent with a high prevalence of delirium. They were also the clinical settings where physician management of delirium had been explored (Chapter 2), and hence this would allow some comparisons to be drawn between medical and nursing practice.

3.2.4 Participants

Nurses working in the defined public hospital dedicated inpatient units in palliative care, geriatrics, ACP and oncology in South West Sydney were eligible to participate in this study. These nurses had to be working predominantly in their respective inpatient specialty area for at least six months and for a minimum of 15 hours per week in that setting. Purposive sampling was used to ensure adequate representation of nurses, including variables such as shifts worked, work experience in the respective inpatient settings, and qualification level, both undergraduate (registered nurses, enrolled nurses and AIN) and postgraduate qualifications in their specialist field.[485]

The participants were initially approached by the relevant nurse unit manager of the unit, who provided a written information sheet to all eligible nurses within the unit. The participant information outlined the rationale for the study and the research team conducting it, and those who indicated interest to the nurse unit manager were then contacted face-to-face or via telephone to discuss the study further. All participants provided written informed consent (Appendix 5).

The demographic variables for participants collected were age, gender, the shift type they worked predominantly (day, night or both), duration of work in the inpatient unit (months), total years in nursing and postgraduate qualifications in their respective inpatient specialty area.

3.2.5 Semi-structured interviews

3.2.5.1 Characteristics of the interviewers

Two female research nurses, both registered nurses with several years of clinical palliative care and general nursing experience, conducted the semi-structured interviews in person. They were specifically selected as they were not in a direct management role for any of the potential participants, nor had they worked clinically in any of the inpatient unit settings. The research nurses had experience and training in conducting such interviews, and were familiar with the clinical issues of delirium as they had been involved in a number of studies relating to delirium.

As a service director of the one of the inpatient units and senior medical practitioner within South West Sydney, I did not conduct the interviews as it was deemed that the participants may have been hesitant to freely voice their views to someone in a senior management role, and may have perceived that their answers would be used in relation to their work performance.

The interviews were conducted at a convenient location for the participant, which was usually a meeting room specifically booked for the interview in their hospital workplace but not within their ward. The interviews were conducted in person, audiotaped, saved as a digital recording in de-identified format and then transcribed to ensure all issues were identified. The research nurses also

documented notes immediately after each interview if there was a specific theme or observation in the interview to augment the transcripts.

3.2.5.2 Characteristics of the interview

The question route was structured to allow for a thorough exploration of the issues of interest identified both from clinical experience and from the literature, with the interviewers provided with a set of open-ended questions and prompts to guide the interview. The goal of the interviews was to explore the participants' opinions in relation to:

1. symptomatology of reversible delirium and irreversible delirium including delirium in the last days of life;
2. the aetiology of distress to patients and their caregivers;
3. the aspects of delirium that require management;
4. views regarding reversibility of symptoms and/or delirium;
5. choices and thresholds used for non-pharmacological and pharmacological management of delirium and its symptoms; and
6. methods of assessing the response to those interventions.

The semi-structured interview format is outlined in Appendix 6. The first five interviews were utilised to pilot the interview format, which did not lead to any changes to the interview structure, questions or prompts. Further interviews were conducted until no additional topics were raised.

3.2.5.3 Analysis

The transcribed material was analysed using thematic content analysis, using a constant comparative method (viz. themes from the initial interviews were tested on further interviews) to assist conceptualisation and categorisation.[483 486 487] Individual points were identified in the transcripts and organised into mutually exclusive themes. NVivo 8 (QSR International 2008) was used to organise the data. A process of deviant case analysis was also undertaken to ensure every component of the transcripts was accounted for within the themes (comprehensive data treatment).[487]

A process of independent review and peer consensus was used to validate the findings. Each transcript with accompanying research nurse notes was read

independently and coded by myself, and by one other researcher who discussed their coding to derive the initial coding tree (inter-coder agreement). All coders kept notes of their rationale for theme choice and the approach they took to the analysis (auditability). The initial coding tree was discussed with a third researcher, who read and coded 10% of the total transcripts selected at random to reach consensus of the established themes, again with notes kept to record discussions and explain rationale. The themes that emerged from the interviews were fed back to the interview participants in a written aggregated summary of themes and subthemes (rather than individual transcripts), and they were provided with the opportunity to further comment (respondent validation). Reporting of the context of the study, research team description and reflexivity, study design and methodology, and analysis and findings are assessed according to the consolidated criteria for reporting qualitative research (COREQ).[488]

3.3 Findings

3.3.1 Demographics of participants

Sixty-five nurses were approached and 40 agreed to participate. The researchers did not have contact with those who did not agree to participate, so reasons for non-participation could not be ascertained. The demographic characteristics for the 40 participants are outlined in Table 28. Consistent with purposive sampling there was a wide range in duration of work in the clinical area, which varied from six months to 37 years. The oncology nurse participants were the most highly qualified. They were all registered nurses with Bachelor of Nursing degrees and additional postgraduate qualifications in an oncology-related field or palliative care, but they had the shortest nursing experience (mean five years). In contrast, only three of the ACP nurses had Bachelor of Nursing and only one had additional qualifications relevant to the discipline; however, they had the most years of nursing experience (mean 13 years). Representation of nurses who worked night shift was achieved in all specialties except geriatrics. The interviews ranged in duration from 15–60 minutes, and all participants were interviewed once.

Table 28 Demographics of the participants

	Palliative care	Oncology	Geriatrics	Aged care psychiatry
Number of participants	10	10	10	10
Age in years: median (mean, range)	51 (50, 25–59)	40 (42, 24–66)	49 (49, 42–62)	54 (45, 21–60)
Duration of work in clinical area in years: median (mean, range)	6 (7, 0.5–15)	11 (5, 0.75–17)	11 (10, 2–17)	5 (13, 4–37)
Primary nursing qualification (n)	Bachelor of Nursing: n = 2 RN: n = 3 Diploma in nursing: n = 2 EEN: n = 3	Bachelor of Nursing: n = 5 RN: n = 5	RN: n = 6 AIN: n = 1 EEN: n = 1 Unkn: n = 2	RN: n = 2 Bachelor of Nursing: n = 1 EEN: n = 3 AIN: n = 2 TEN: n = 1
Total shift hours/week	35 (24–60) (n = 10)	37 (24–40) (n = 10)	36 (24–40) (n = 10)	35 (16–40) (n = 10)
Morning shift hours/week	20 (8–45) (n = 9)	25 (16–40) (n = 8)	20 (8–40) (n = 8)	18 (8–40) (n = 10)
Afternoon shift hours/week	15 (8–28) (n = 7)	18 (8–40) (n = 6)	22 (8–40) (n = 6)	19 (8–40) (n = 9)
Night shift hours/week (mean, range. n)	18 (8–28.5) (n = 3)	10 (6–20) (n = 2)	16 (8–24) (n = 2)	0
Time working in an inpatient setting in years: median (mean, range)	20 (16, 8–36)	13 (16.9, 2–45)	24 (22.4, 4–45)	4 (6.4, 0.75–20)

	Palliative care	Oncology	Geriatrics	Aged care psychiatry
Postgraduate study in clinical area	Grad diploma in palliative care (n = 1) Grad cert in palliative care (n = 1) Oncology certificate (n = 1)	Grad cert oncology (n = 4) Grad cert palliative care (n = 2) Master of palliative care (n = 1) Post graduate studies in cancer services (n = 1) Grad cert in chemotherapy (n = 1) Grad cert in cancer nursing (n = 1)	nil	Grad cert gerontology & grad diploma in mental health nursing (n = 1)

AIN – assistant in nursing; EEN – endorsed enrolled nurse; RN – registered nurse; TEN – trainee enrolled nurse; unkn – unknown

3.3.2 Themes

The analysis revealed four broad analytical themes:

1. superficial recognition and understanding of delirium as a syndrome
2. nursing assessment— use of an investigative compared to a problem solving approach
3. management—importance of maintaining dignity and minimising chaos
4. distress from delirium and its effect on others.

Table 29 outlines the coding tree, including main themes and sub-themes. Data saturation was achieved for all four themes over the 40 participants. Within each specialty group within the management theme (theme 3), saturation of the specific management strategies was not reached. Supporting participant quotes are identified by specialty group, with P being palliative care, AP aged care psychiatry, G geriatrics and O oncology.

Table 29 Outline of themes and subthemes

Theme	Subtheme
Superficial recognition and understanding of delirium as a syndrome	Limited definitions
	Behavioural and cognitive symptoms
	Symptoms infrequently identified
	Lack of understanding of acute onset
Nursing assessment— use of an investigative compared to a problem-solving approach	Precipitants relating to specialty area
	Concept of reversibility and irreversibility
	Investigative assessment compared to assessment of a shortlist of problems
	Continuous assessment of risk
Management— importance of maintaining dignity and minimising chaos	High levels of confidence in delirium management in the face of limited understanding of delirium
	Multiple decisions and actions
	Variable views on medication choices: • medications are not the solution for everything and can make the situation worse. • varying views about antipsychotic and benzodiazepine use. • variable confidence about *pro re nata* (as required) medication
	Diverse non-pharmacological strategies are highly valued
	Conflicting opinions about physical restraints
	Experiential learning and senior role models guide management
Distress and the effect on others	Specific situations related to patient distress
	Family distress
	Distress of other patients in the unit
	Staff frustration of barriers to quality care
	Staff distress and exhaustion

The following sections describe in detail the themes and their subthemes.

3.3.2.1 Superficial recognition and understanding of delirium as a syndrome

3.3.2.1.1 Limited definitions

The description of delirium across the specialty groups varied from 'confusion' to a limited but incomplete list of clinical signs. Many included the likely medical precipitant in the definition, such as pyrexia, urinary tract infection, medication or hypoxia. The definition often included the core feature of 'experiencing something outside reality'. The words used to describe this included, 'they are not actually in this day to day setting' (participant P7), 'they are not able to reason properly within their framework' (participant P3), or, 'being out of the ordinary for them and experiencing things you can't necessarily see' (participant O10) and, 'not in their reality' (participant AP3).

No participant referred to recognised international delirium diagnostic criteria in their definition. For example, no participant included all of the DSM-IV-R delirium criteria (the major components of the DSM-IV-R classification being disturbance of consciousness, a change in cognition, short and fluctuating chronology, and presence of an underlying medical condition[473]), or ICD-10 criteria (impaired consciousness or attention, global disturbance in cognition, psychomotor sleep and emotional disturbance[5]). Some participants were unable to provide any definition or explanation of what delirium actually meant.

> It's basically patients seeing things … out of themselves they're [they are] hearing everything that's not in the world and their surroundings. Basically they're [they are] very confused or they don't know where they are (participant G1).

> I guess delirium in most cases is when a patient is being out of their ordinary … for them … and when they're [they are] experiencing things that you can't necessarily see and they can't put into words. It's just unusual and different for them. Some of them are pleasantly confused and others get aggressive or get very distressed (participant O10).

> I think confusion in a way. I'm not quite sure but to me, confused (participant AP4).

3.3.2.1.2 Behavioural and cognitive symptoms

The main clinical manifestations identified were cognitive change or behavioural signs, with many recognising signs worsening at night and sleep – wake alteration. Participants in all specialty groups referred to cognitive changes related to disorientation in time, person and place, or experiencing something outside reality. Participants mentioned patients' not recognising family, but often orientation to self was maintained. Poor attention span was also mentioned. Cognitive symptoms described include the following:

> Symptoms of a confused patient … a classic one would be not realising exactly where they are. Um … not knowing where they are, not knowing the time of the day thinking that it's morning when it's actually afternoon or vice versa. They forget that you've just been in there just to be with them so their attention span is shortened (participant O4).

> They could be confused as to you know, date, time, who they are, where they are um they often lose direction, they can be shown and say for instance where the toilet is but then within a short time they can't remember ... (participant G4).

Tasks that needed planning or were related to specific times of the day were most affected by cognitive change.

> … even with ADLs [activities of daily living] … with showering, sometimes they want to have shower at night time even if it's not appropriate for them to have it and with clothing as well (participant AP6).

The majority described hyperactive behavioural change such as agitation, wandering, verbal aggression or calling out, climbing out of bed, pulling out intravenous cannulae or indwelling catheters, aggression, and other inappropriate behaviours. Some examples of descriptions of behavioural symptoms are:

> I could say that the restlessness has *[sic]* a sign of ongoing pacing between the ward or within the room and couldn't just sit down for even one minute; has to be followed by a nurse at all times and just totally unable to even follow instructions … (participant AP9).

> They're [they are] calling and making a big disturbance which is upsetting to everyone, including their family and themselves and the potential for them to do harm to themselves. Like, perhaps they've got oxygen … they keep

> ripping them off … it's just worsening the situation, or they have an IV and they're [they are] going to have blood and they try to pull it out … or a catheter and they pull it out and cause trauma … (participant P5).

Few participants described hypoactive behaviours in the context of a spectrum of behavioural changes. Affective components and perceptual disturbances were rarely described. Hypoactive symptoms were described in terms of the person being 'very quiet', refusal to allow care, not conversing, and being withdrawn from the environment.

> They would be restless … saying things, incoherently, sometimes they lash out to staff. They may not eat, they may not drink, refuse to do things, may be very drowsy (participant A8).

3.3.2.1.3 Symptoms infrequently identified

Very few participants identified the core feature of delirium being a time frame of rapid or acute onset. Perceptual disturbances and sleep wake disturbances were infrequently described. A small number of participants distinguished delirium as a different condition from dementia due to acuity of onset, or an alteration from usual patterns of cognition.

> With delirium it's usually quite abrupt. Yeah it's quick (participant P1).

> … some of them are confused and they're [they are] pleasantly confused, they're [they are] seeing people who aren't there or we've had people who've had fairies floating around the ceiling and they're [they are] happy; constantly got a smile and they're [they are] pleasantly confused and not distressed at all, where you've got other people who feel like they've got ants crawling on them. They scratch and they itch and they pluck at the air all the time (participant 010).

> … if they stay awake all night they're [they are] going to be asleep all day, so it's the same as a baby (participant G5).

3.3.2.2 Nursing assessment—use of an investigative compared to a problem solving approach

3.3.2.2.1 Precipitants related to specialty area

The main aetiologies suggested across all the specialty groups and levels of nursing were urinary tract infection, urinary retention or constipation. There were,

however, some differences depending on the clinical area with regard to the depth of understanding of the nature of delirium precipitants. Participants working in oncology and palliative care more frequently mentioned hypoxia, cerebrovascular accidents, polypharmacy and pre-existing medications (in particular opioid toxicity), nutritional status, hydration and specific metabolic disturbances (hypercalcaemia, liver and/or renal dysfunction), and brain metastases. No-one identified baseline vulnerability factors that increase the risk of developing a delirium, such as visual, hearing or cognitive impairment. Several participants did not give any suggested aetiologies or precipitants, or show understanding of the concept of reversibility.

> I think a lot of our patients … being in acute crisis like tumour lysis syndrome, high calcium and that sort of stuff. They tend to get a different type of confusion and we use a lot of morphine and stuff, not that we get a lot of patients who are confused with the morphine because they tend to pick it up fairly quickly so it doesn't happen. But more with the renal function or infection. The confusion is different than somebody who has got like a brain tumour, which you also get, but the confusion are different and you can usually orientate somebody back who has got a urinary tract infection or whatever, where the brain tumours you can't orientate them back. Basically I would look to see if there was any source of infection because in our patients, infection tends to be one of the bigger things. So look to see if they're [they are] febrile, if their white cell counts are going up; look at their UEC [urea, electrolytes and creatinine] see what they're [they are] like. Sometimes they're [they are] hypercalcaemic, which happens a lot in our patients, and they become very confused very quickly … where the brain tumours tend to be slower and little things just inappropriate to start with, losing things, misplacing things and then works its way around. Unless they've stopped the Dex [dexamethasone]; if they've stopped the steroids or their treatment then their confusion tends to become quicker (participant O10).

> The thing in aged care psych [psychiatry] … is most of these confusion … could be secondary to a delirious state where a patient could be constipated or suffering from an infection like a urinal *[sic]* infection (participant AP9).

3.3.2.2.2 Concept of reversibility and irreversibility

Assessment of reversibility was linked to the suggested aetiologies where the participant listed precipitants, and in general these were provided by registered nurse participants. Reversibility was commonly mentioned relating to urinary tract infections; however, drug toxicity, medication, hypoxia, metabolic abnormalities or electrolyte imbalance (with hypercalcaemia specifically mentioned by palliative care and oncology nurses such as participant 01 cited above) were also mentioned. Some participants discussed the possibility that even if a cause were found it may not reverse despite intervention, and were specific about which were less likely to improve. In geriatrics and ACP the participants described that it was also important to identify if the confusion was new or different from baseline, a concept which was understood by participants at all levels of nursing from AIN to registered nurses.

> Delirium is a condition or a symptom that's related to somebody's condition, usually a medical condition. It's reversible and it causes confusion, changes in emotion, sleep disturbances, hallucinations, things like this. So a classic example of something that would cause that would be hypoxia … or if their liver function's out of whack. So that's reversible. But if they've got cancer metastases spread to the brain, that would cause delirium, but that's not necessary reversible. You've got to treat it, though (participant P5).

Constipation, urinary retention and pain were clinical issues associated with confusion or thought to be aetiologically related to delirium by some participants, a feature identified by all levels of nursing participants. In this context nurse driven management to improved bowel care and pain relief were thought to be able to assist reversal of an 'acute confusional state'. Several participants only mentioned bowel and bladder problems as aetiologies, with no other medical precipitants discussed, such as the following example:

> … I guess if it's confusion it may be due to just a full bladder because of that, if you do assess that and you actually maybe put in a IDC [indwelling catheter], or offer that patient a bottle to pass urine or a bed pan, once they've done that you know you find that they settle. And if it's constipation, once that is attended to you find they settle. Um sometimes it can be confusion maybe due to increased medication and if that medication is

> stopped you find that the confusion also settles as well. So in a way I'll say yeah sometimes it's reversible (participant P3).

In relation to drug toxicity, opioids were mentioned as a reversible aetiology by one participant, with the use of naloxone mentioned as a management strategy.

> Well sometimes it is if it's drug related confusion yes, we just stop the drug or if its morphine related one … give them Narcan [naloxone] and change them to hydromorphone (participant O6).

Irreversibility was associated with progressive disease affecting the brain, the patient who was at the end of life, and for geriatrics it was associated with underlying dementia. Some linked irreversibility to a situation where symptoms could only be 'managed'; whereas others deemed the clinical situation where symptoms were controlled with medication as 'reversible'. Some linked medical complications of delirium or injury sustained while delirious as factors impeding recovery.

3.3.2.2.3 Investigative assessment compared to assessment of a shortlist of problems

Many nurses discussed often carrying out a baseline assessment, including a full set of observations (temperature, blood pressure and pulse); with some extending to oxygen saturations, ward urinalysis, blood sugar level, bowel care, urinary retention (bladder scanning), hydration levels, and pupil function. Some provided rationale for these observations, whereas others discussed them in terms of being routine prior to calling the doctor to review the person. In general, baseline assessments and a more investigative focus were provided by registered nurse participants. The investigative and problem-solving approaches were present in participants across the specialty groups.

A problem-solving approach used a shortlist of potential problems, mainly bowel or urinary problems. Some participants only focused on making sure the patient and staff were not in danger. The problem-solving approach was one identified by all levels of nursing, from AIN to registered nurses.

> … reversible, I can't say, I've seen, um yeah I suppose um sometimes when patients become very constipated. Then as soon as you fix them up you can't believe they're [they are] the same person. Yeah sometimes if they're [they

are] oxygen sat's [*saturations*] are down. Um yeah, those two things mainly (participant G5).

Well you just identify safety issues about whether the patient is in any danger, or whether the staff are in any danger, and really that's all you can do (participant P9).

Other participants described undertaking a more investigative approach comparing new information with baseline, and information in the medical record and coming to their own diagnoses; an example of this is:

… just to try and get information for myself and then once I've tried to do everything that I can, then I document all that, confer with the doctors, and then if everything's clear like if they're [they are] not anxious … they're [they are] not febrile if everything's kind of been ruled out they're [they are] not retaining urine, not constipated then the doctors they take their bloods and they go from there kind of thing so. Yeah I just try to rule out as much as I can and just do what I can to try and determine the confusion what's going on (participant P1).

3.3.2.2.4 Continuous assessment of risk

There was an awareness of the constant threat of risk of harm, or absconding, and the need to constantly be on the watch:

There are times when you do actually have to be very quick to make sure that they're [they are] safe and you actually, you can talk with them while you're doing what you're doing, but you have to do what you have to do so they don't put their head through a plate of glass or, you know, wrap a leg around something and break it or cause other people harm. So it's … so there's lots of risks for them for self-harm and disturbing everybody's general peace. Mainly the nurses and, you know, hurting themselves trying to climb out of bed and stuff like that. It's a big worry (participant P4).

They need quite a bit of watching. I think mostly you just need to frequently check on them (participant O9).

3.3.2.3 Distress and the effect on others

3.3.2.3.1 Specific situations related to patient distress

Participants delineated two types of delirium, one associated with patient distress, contrasting with episodes that did not cause distress. There were some respondents who felt the patient was unaware of the experience. Participants related patient distress to the patients not understanding why they had to remain in hospital, feeling frightened, awareness that they were not acting as their usual self (especially during times when lucid) or frustration in communicating their needs.

> For patients I think it's distressing because a lot of times if when I've observed confusion they sometimes seem to be in and out of it, and when they're [they are], when they are not confused they seem to recall when they were confused and they feel very embarrassed and upset about it, and you know obviously not having any control is a scary situation for anybody (participant P9).

3.3.2.3.2 Family distress

Distress for families was related to not knowing the cause of the person's confusion or the context in which it was happening, and seeing their loved one not being their usual self or unsettled. Having their loved one not recognise them was a particular source of family distress. Poor prognosis and the inevitability of the situation getting worse for a cancer or dementia diagnosis were mentioned by geriatrics and oncology participants.

> The families I think are the ones that suffer the most actually when their loved one is confused, because they have that, you know, if they walk in and their loved one doesn't know who they are or forgets who they are or you know, because we have had in the past a patient who got confused and I remember the son walked in and said dad, do you know who I am? And his dad didn't know who he was and it was sad because the son just burst into tears because the day before, he knew who he was, and it was due to his condition. But that's what the patient's family see, and I think sometimes they hang onto this hope that today they might be confused but tomorrow they'll be alright and maybe we … you know, this is just a small part of their treatment (participant O1).

3.3.2.3.3 Distress of other patients in the unit

The predominant cause of a patient with delirium affecting others was wandering behaviours, or patients who were calling out. It is interesting that these were not features mentioned by oncology or palliative care participants, suggesting wandering and vocalisation may be more frequent in geriatrics and ACP settings.

> If they're [they are] wandering and they wander into another room and the patients in that room don't want them in there … relatives coming and constantly telling you 'Can't you keep that person quiet cause it's upsetting my mother?' (participant G9).

3.3.2.3.4 Staff frustration of barriers to quality care

Participants were distressed trying to provide quality care in the context of time pressures, budget restrictions, staffing mix, inadequate environment and the high acuity of the care. The participants described the challenges of balancing the confused patient's care needs, with all the other patients needs on the ward.

> ... but I think these days with the way the hospital system's becoming … is that the focus is more about a number and not necessarily the patient or what's actually wrong with the patient. So you know, if I can use an example, which is we're a 26-bed ward, so as long as we've got 25 patients, then you know, the hospital's happy. But what if we've got 26 confused patients? (participant O1).

3.3.2.3.5 Staff distress and exhaustion

Patients who were physically or verbally aggressive and/or resistive to care also caused distress. Witnessing the symptoms delirium patients experienced was distressing and exhausting, and in palliative care and oncology impeded achieving a 'dignified death'.

> I find it very draining looking after demented and confused people. I go home exhausted mentally sometimes. It's always about time; having time for everybody and fitting in everything you have to do. I don't know, I find, I find that one of the hardest aspects of nursing. You can be run off your feet and not be as tired as what you experience from the mental drain from caring for someone with confusion (participant G9).

Conflict of opinion on the level of interventions (especially if multiple medical teams were involved) and also the reluctance of junior doctors to prescribe medication were other challenges that added to participants' distress.

3.3.2.4 Management—maintaining dignity and minimising chaos

3.3.2.4.1 High levels of confidence in delirium management in the face of limited understanding of delirium

Overall participants' degree of confidence was disproportionately high to the degree of understanding of delirium and its management. Some felt they had senior level experience and could provide advice to other staff.

> Well I think I could say I'm quite excellent in that because I have a big, a long experience with that one to the point that I even sometimes alert the doctors that, I suggest what we could do (participant AP9).

> Confident managing symptoms, er, yeah I feel confident in that if you know we do have good prn [*pro re nata*] medications that are you know first choice medication for confusion, anxiety and confusion. Second choice medication if that doesn't work. So you know it's written there (participant P7).

3.3.2.4.2 Multiple decisions and actions

The participants described involvement in multiple decisions including choices about management of safety and distress, managing the underlying aetiology of the delirium requiring a nursing intervention (e.g. urinary retention), deciding when to refer to the medical team and planning the patient's physical care. For the most part, participants across the specialty groups and at all levels of nursing provided their opinion of the effectiveness or otherwise of various management options, both pharmacological and non-pharmacological. Those who were less qualified (AIN or enrolled nurses) provided examples of what they had seen done, but still often had an opinion about effectiveness. The choice not to intervene was also mentioned with some participants suggesting that 'being pleasantly confused' did not require intervention.

> There's a difference between being pleasantly confused and frightening type of confusion. So I guess in that situation it's really up to the doctor to decide whether there's going to be any medication that's going to help with that to, to address the agitation and try and keep the patient more relaxed, happily confused, then there is not really any need for any intervention other than just ensuring safety that … not wander off the ward and get lost (participant P9).

All specialty groups were very aware of the safety implications of delirium with wandering, falls and self-injury identified as risks to the patient but also risks to staff and other people on the ward. To ensure safety constant vigilance was required.

> The main symptom that would require intervention is the patient's safety so if you feel that they are going to fall out of bed or try and escape through the rails then that's obviously the reason that they would need supervision. When they are just confused but they're [they are] staying in their bed, they're [they are], maybe just messing up their sheets or talking to themselves or something like that then they're [they are] not really needing something (participant O2).

3.3.2.4.3 Variable views on medication choices

Medications are not the solution for everything: Medication played a major role in the participants' management of patients' with delirium; however, participants generally acknowledged that medication was not the solution for all symptoms or situations. In particular, the need for caution was suggested by several participants as sedation from medication could contribute to worsening confusion, and described the decision as a tradeoff. Several participants preferred to observe closely and only resorted to medications for symptoms causing distress, physical restlessness or aggression, or for insomnia.

> But when it is because they are only confused and they are misery *[sic]* and disorientated, no we do nursing intervention rather than going into medication (participant AP9).

> Some people that are confused can be very afraid, it can make them very frightened or very aggravated, agitated, you know it's not pleasant. There's a difference between being pleasantly confused and frightening type of confusion. So I guess in that situation it's really up to the doctor to decide whether there's going to be any medication that's going to help with that to, to address the agitation and try and keep the patient more relaxed, happily confused … if this is not the case then no not really any need for any intervention other than just ensuring safety that they're [they are] … not going to wander off the ward and get lost (participant P9).

Varying views about medications: Participants' preference for an antipsychotic or benzodiazepine, as first line medication management varied, with both sequential and combination use described. In relation to choice of antipsychotic medications or benzodiazepines as first line therapy there were varying views, with some specifying the rationale for their preference or giving a case example to illustrate. Several participants used antipsychotics and benzodiazepines in combination or sequentially, often citing different types of target symptoms for these approaches.

> Haloperidol's always my first line and I usually give that a good hour to see if that's getting rid of the symptoms, if that's helping, settling them down. If that doesn't help I find that, on the chart, they've got midazolam there. But if it is helping I let it go a little bit longer, it just depends on the patient. If it's had moderate effects then I might, and they need it again maybe say next two hours get a little bit again, I still might use haloperidol again because it has good effects and sometimes the second lot has done the trick (participant P1).

The choice of medication varied according to clinical specialty. Haloperidol, midazolam and clonazepam were agents more often discussed in oncology and palliative care, and often in the context of regular and frequent dosing; whereas in geriatrics and aged psychiatry reference was made to atypical antipsychotics, diazepam and temazepam—often at night-time. Oncology participants discussed increased doses of dexamethasone in the context of cerebral metastases to stabilise confusion, while levomepromazine as an agent to control delirium symptoms was only mentioned by palliative care participants. Sodium valproate and donepezil were agents participants from ACP mentioned they 'had seen used', however it was difficult to ascertain whether this was in the context of management of co-existing dementia or that the participants had interpreted the indication for use was for delirium symptoms.

Most participants described the desired medication response as occurring within a 30 minute timeframe. Effective medication resulted in the patient being more settled, calm, comfortable, peaceful, and/or less anxious, with improved sleep and night-time symptoms. A process of 'trial and error' was required for tailoring the right dose and drug. Sedation was mentioned in two contexts dependent on the

situation: first if that was the desired medication effect, and second as a potential side effect to avoid the need to monitor for over-sedation.

Variable confidence about as required medication: The more confident participants (predominantly registered nurse or endorsed enrolled nurse participants) discussed in detail nurse initiated as required medication administration whereas others only mentioned what they observed being prescribed.

> I know patients written up for Seroquel [*quetiapine*] here … 25mg nocte if needed. That's quite a good one that's working for one of the patients at the moment … valium [*diazepam*], like a prn [*pro re nata, as required*] valium order is always quite good … regular doses are usually always around probably about the 6 o'clock mark of the night time. In others it's just prn's like we have um like a lot of our clients here have been on temazepam you know all their adult life … and we find sometimes with some patients that they might have a prn dose of Valium ordered but need to go on a tds [*ter die sumendus*, taken three times daily], we find that works really well (participant G1).

> It depends on how big the patients are. It depends on how they react with the medications and what other medications are actually written up there. Sometimes you get written up for haloperidol or you can actually get the variable dose between 0.25 to 0.5 milligrams so if the patients quite big we try to give them the maximum dose. And if we are about to suggest something we normally start with a very low dose and then the space of time intervals would be at least every four hours … so it's not as if we're trying to suggest to other doctors … for haloperidol first, if that haloperidol hasn't touched them or hasn't done anything and if there is some midaz [*midazolam*] written up you go first to midaz if you knew that the patient hasn't had midaz before you give the smaller dose. And if the midaz doesn't work in a low dose of 2.5 milligrams we gradually increase because normally they give us a bit of a fluctuating dose we can actually pick what dose we can like 2.5 milligrams to 5 milligrams so we can just use that and in the span of every two hours (participant O6).

> When I first started it was really overwhelming, all those prn drugs on the back of the chart. They're [they are] very helpful though. So once I got my

> head around all those drugs, with confusion the first line I always use even if they're [they are] on haloperidol say BD [*bis die*, taken twice a day], I'll always use haloperidol first … if I find that they're [they are] confused but the haloperidol has kind of worked but they're [they are] anxious, starting to see a bit of anxious, anxiety I'll go for lorazepam, and then if that—a lot of the time that has actually helped. If I haven't seen any anxiety so much and I don't feel lorazepam's the choice I'll go to midazolam but dependent on the patient because it's so different sometimes I do ring up the consultant and I've been ordered some levo [levomepromazine], levo sometimes helps as well. So it really just depends on um, yeah, depends on the assessment, after the hour of haloperidol (participant P1).

3.3.2.4.4 Diverse non-pharmacological strategies are highly valued

Non-pharmacological interventions were highly valued approaches to delirium management, regardless of the level of nursing and specialty group. Participants provided a wide range of suggested non-pharmacological strategies. Some participants expressed that despite their preference for non-pharmacological approaches, limitations of time or appropriate expertise often meant resorting to medication. Attention to physical care needs was also important.

There was a strong view about the attitude and manner of interaction with the person as having a settling or aggravating effect:

> I mean you never raise your voice to somebody that's already confused. You have to talk nicely and calmly to them (participant AP10).

A safe environment without clutter, having the light on in the room, familiar objects, regular verbal reorientation to the persons' environment, reducing stimulation, and structured routine were environmental strategies thought to be helpful. The presence of family was thought to be extremely useful; however, the participants were aware this was often distressing for family, and sometimes the family dynamics could worsen agitation. Confused patients were often moved to a single room or in view of nurses. Relocation also was reported to worsen disorientation in some cases due to the new and unfamiliar environment.

> Not having too much stimulation, have one person looking after that person. Yeah just don't have too many people intervening, rushing around and

> interfering, just keeping the whole environment as calm as possible, and yeah reduce stimulation, not too much noise and lights and everything (participant P9).

> Place a patient in sight, you know in a room where we can actually sight them so we know that we can keep an eye on them … move them to a room where we can assess them from the nurse's station so we know that we're … keep them in close view (participant P2).

> Try to like talk to them a bit more and you know, listen to them because like you know even though they tell you the same thing like you know in a five-minute conversation, it's the same thing over and over again, but like to them what they're [they are] saying is for the first time (participant G4).

'Specials' (one on one nursing) were thought to be an ideal strategy by some, but others felt it only addressed safety, since the presence of the special nurse did not serve to reduce the level of confusion. An issue was the nurses allocated to 'special' the patient did not have the authority or scope of practice to provide medications. Special nurses, even though they gave an extra pair of hands, did raise concern that more senior skills in assessment, communication with the patient and the ability to administer medication was required for confused patients. By contrast, 'specials' are usually junior nurses or AIN from agency services.

> …one on one nurses are very limited in what they can do, and they're [they are] very inexperienced … so whilst that one person might help the nursing staff with that confused patient, that nursing staff member still has to deal with everything around that patient, like medications, treatment … (participant O1).

Overall, consistency of staffing needed to be balanced with the high acuity of delirium care, and nurses needing to have a break from the complexity of caring for a patient with delirium.

> Just kind of re-orientate them every now and again. To who they are, who you are and try and get familiar faces but they usually only help, it happens—the familiar faces with the nurses only happens with when you have the special nurse because a lot of the time there's just too many swap over shifts and you can't get the same nurses there and I think maybe it's a

> selfish thing but with the nurses, especially confused patients it takes a lot out of you and sometimes we have like an agreement like oh look I've been over this side for two days now and she's really, you know, doing my head in. Do you mind taking care of this patient so even though it's probably in the patient's best interest that we all kind of—they have a familiar nurse all the time, it's it gets hard on the nurses so we do kind of swap around a bit too (participant P1).

3.3.2.4.5 Conflicting opinions about physical restraints

The use of physical restraints was a controversial topic, with some participants stating that it was unethical to physically restrain a patient by any means and that restraints reduce the patient's dignity. Some felt physical restraints were a last resort if there was significant risk the person would hurt themselves. Others felt they made the confusion worse not better. In geriatrics, consideration of a lap table was felt to be an option in some situations. Personal alarms were used in geriatrics but were not considered highly successful. Bed rails were sometimes helpful, but could be a hazard, especially if the patients climbed over them. Several participants mentioned a need for specific changes in practice, such as that medication should be used more proactively and physical restraints used infrequently.

> If the person is severely at risk of hurting themselves then physical restraints um…they're [they are] helpful as well. But we prefer to use them as a sort of last resort (participant O4).

> Well they're [they are] backing off from restraints so we don't use them, physical restraints at all. Sometimes we put a lap tray on but that's only at meal times. That's not really a restraint (participant G9).

> I don't think that in my experience that restraining somebody is um very helpful. Quite often even though people are confused they know you are restraining them and they get even more confused (participant O9).

3.3.2.4.6 Experiential learning and senior role models guide management

Participants identified senior staff and clinical experience 'on the job' as their main sources of delirium knowledge, while a smaller proportion cited investing in their own continuing professional development through reading and in-service

education. The areas identified for further education were variable and individual, and included alternatives to medication, a better approach to assessment, diversional therapy approaches, understanding aetiologies and pathophysiology, and cultural implications/interpretations of confusion.

> Just being exposed to it and other nurses learning from others. It came into our Mental Health Studies um we did do a lot, well not a lot, but a bit on delirium and that but I still felt that I was confused about confusion and the difference. We usually have a continuing in-service about different illnesses that have a direct link to confusion … but also I think my own experience in nursing because I graduated since 1970, and I think it's more or less combining the two … time and time again (participant G9).
>
> … just regular work with confused patients you sort of pick up how to look after them, medications, your staff, what your doctors, what the nurses are doing so you learn from each other (participant P10).

3.4 Discussion

This study has explored the views of nurses in a range of inpatient settings where delirium is prevalent in order to provide understanding of the clinical processes involved and the challenges posed by delirium detection and care, when delirium detection is crucial to improve delirium care. The participants had varying understanding of delirium, predominantly based on behavioural and cognitive cues. The concept of baseline vulnerability and hence delirium risk was not raised by any of the participants. The participants varied in approach from investigative assessment to a more problem solving approach, but some participants did not identify an assessment approach at all. All specialty groups at all levels of nursing valued non-pharmacological strategies. There was a wide range of approaches outlined for the use of antipsychotics and benzodiazepines, with both single agent and combinations suggested. The precipitants discussed as being the most common precipitants related to the specific clinical areas and common causes in the settings in which they practiced. Some key points of difference between specialty groups included identification of wandering behaviours and calling out in ACP and geriatrics, and the importance of control of delirium symptoms in achieving a 'good death' for patients at the end of life by oncology and palliative care nurses.

3.4.1 Recognising delirium

The participants in this study predominantly had a 'snapshot' of delirium within the clinical context in which they work. This is consistent with prior studies demonstrating that under-recognition of delirium is common[489 490]; awareness of cardinal features of delirium represented in the major international diagnostic systems for a delirium diagnosis was limited; and reliance for recognition was on very overt behavioural and cognitive cues.[472 473] Perceptual disturbance, hypoactive symptoms, and more fundamentally, the acute onset over a short time, were not features explicitly identified by most participants across all specialty groups, even in the registered nurse group.

In most instances participant descriptions did not meet criteria within a screening instrument for delirium, such as the commonly used instrument, the CAM, designed to aid nurses in the recognition of delirium.[491] Screening instruments rely on observable behaviours rather than features elicited on specific testing, and hence are aimed to assist nurses articulate the features of delirium observed in a patient. The CAM relies on identification of the presence of acute onset and fluctuation, inattention, disorganised thinking, memory impairment, perceptual disturbance, psychomotor agitation or retardation, and altered sleep – wake cycle.[477] Prior studies using the CAM for screening by bedside nurses also demonstrate the particular difficulty in identifying the features of acute onset, fluctuation of symptoms and altered level of consciousness.[477] In the setting of chronic cognitive change, the need to observe acuteness of change is more important; and if cognitive symptoms are predominantly being used as the delirium triggers, subtle acute changes may be missed.[492] The lack of oncology or palliative care nurses describing wandering or calling out behaviours is consistent with the higher prevalence of hypoactive presentations in those with advanced cancer, and the prevalence of dementia in geriatric and ACP settings.[39 44 78-81]

Once delirium symptoms are detected, they need to be communicated effectively to other members of the multidisciplinary team. In this context delirium could be considered as another 'vital sign'.[493] Inter-shift handover and doctor/nurse handover are high risk times, where identified delirium symptoms may be miscommunicated or forgotten.[472] Other studies have identified the issue of non-

responsiveness in clinical teams, where a clinician who repeatedly attempts to escalate symptoms suggesting delirium to other members of the team (e.g. junior to more senior nurse, nurse to doctor), will eventually no longer raise the issue when it is repeatedly ignored or not taken seriously.[360]

3.4.2 Baseline vulnerability and precipitants

The concept of baseline vulnerability (for example sensory impairment, prior cognitive impairment, sleep deprivation and dehydration) in conjunction with a medical precipitant (a concept essential to delirium prevention or risk assessment)[92 336] was not raised by the participants. This is a crucial omission given the largest impact in delirium care can be made by risk modification and prevention, with many of the areas to intervene pertinent to nursing practice. It is an area covered in depth in available clinical practice guidelines.[92 306 336 353 494] HELP has successfully reduced delirium rates in the hospitalised elderly by utilising targeted interventions on patients who have any of six risk factors present (cognitive impairment, sleep deprivation, immobility, dehydration, vision or hearing impairment) but required significant education, collaboration and involvement of ward based nurses.[353]

Reassuringly, those participants who had an understanding of medical precipitants knew the most common precipitants related to clinical areas and common causes in the settings in which they practiced. Oncology nurses showed a high level of understanding of oncological medical or emergency problems, which may be due to the high level of specialty training and all of those interviewed being registered nurses, but this did not translate into similar knowledge of delirium. Aetiologies such as urinary retention, pain and constipation were described as single precipitants for delirium, which are important factors that may contribute to it along with other aetiological factors, particularly in the frail or cognitively impaired older person. However, an understanding that these factors were more likely to aggravate symptoms, or are one of several precipitating medical factors, was not demonstrated. There also was not a strong understanding of the likelihood of the presence of more than one delirium precipitant in most people given that most studies describe an average of three precipitants.[38 215]

3.4.3 Assessment

In general, there were two approaches to assessment identified by the participants across all specialty groups in this study. The first approach was investigative, utilising a comprehensive assessment of the patient, collateral history from the family and a review of the patient's medical record. Registered nurse participants predominantly took this approach. The other approach was based more on problem solving, and consisted of a short checklist of common problems, with safety being a key issue. There were also a few participants who utilised limited or no assessment, which included AIN and hence is likely related to level of training. The problem-solving approach was described in a prior qualitative study exploring how nurses care for hospitalised older adults at risk for delirium, revealing that nurses care for older adults by, 'Taking a quick look, keeping an eye on them, and controlling the situation'.[467] Another study of graduate nursing students in adult medical surgical acute care settings found the common nursing response to delirium symptoms was continued observation or asking a family member to inform the nurse of further changes, with few considering checking medication or physiological risk factors of the patient.[469] Another study of 18 nurses similarly came to the conclusion that nurses 'positioned themselves to give care typified by the continuous surveillance of patients and actions to contain them'.[495]

The challenge of assessing pain in the distressed patient with delirium, and deciding on the appropriateness of analgesia if pain was contributing, was an area identified as both important and a challenge for practice.

3.4.4 Impact of delirium

The impact of delirium on family, other patients and their families and the nurses themselves was clearly identified in this study, supporting prior findings. Caring for delirious patients in acute medical and surgical settings has been described by junior nurses as stressful due to the unanticipated nature of delirium and the need to balance the care of the person with delirium with the needs of other patients.[469] A study of palliative care nurses describes witnessing the distress experienced by these patients and their loved ones, and the associated difficulty in achieving a peaceful death.[481] Other studies identify that nurses find it difficult to reach and

understand the patient experience in settings where delirium creates a lack of trust and unpredictable patient behaviour.[496]

One group has developed a preliminary tool to measure the subjective strain on nurses caring for delirious patients by asking nurses to rate the difficulty of coping with a variety of patient behaviours.[497] Preliminary validation in a sample of 190 nurses of a 20-item questionnaire demonstrated construct and content validity, and internal consistency.[497] Further development of such tools will allow research to quantify the degree of impact of delirium on nurses and other disciplines, the possible long-term implications of ongoing levels of staff distress in a field with high delirium prevalence, and the impact of related interventions (e.g. specific staff support mechanisms, education strategies) in response. Further, utilising the awareness of nurses of the level of distress and the lived experience of delirium could help to both critically reflect on what makes care of the delirious person challenging, and also foster skills in building relationships with the person with delirium and individualising interventions.[471]

It is interesting to note that the participants felt confident they could classify delirium symptoms into two groups: those that were causing distress to the participant, compared to those that were not. This is contrary to the emerging literature on widespread patient distress relating to the broad range of delirium presentations when recollecting a delirium episode.[312 315 316] It is possible that there was under-identification of patient distress in this participant group, in particular as there was a consistent lack of identification of perceptual disturbance, which is predictive of patient distress if they are able to recall a delirium episode.[315 316] In cancer patients it has been clearly identified that if delirium resolution occurs, a large number recall the experience (50% in one study and 80% in the other), with 'hypoactive' delirium just as distressing as 'hyperactive' delirium.[315 316] The descriptions of the participants of the patient being 'pleasantly confused' suggests the participants do not identify hypoactive delirium as distressing.

Similarly, several qualitative studies in geriatric, medical, surgical (interviews post delirium) and burns (interviews daily during delirium) patients have shown that recall is very common, and the experience is described as distressing by

patients both during and after delirium.[312-314 498-503] These studies demonstrate the following breadth of distressing experiences: emotions (fear, anxiety, sense of being trapped, loss of control or feeling threatened); visual hallucinations; misinterpretation of real sensory experiences (e.g. busy ward perceived as the other patients having wild parties); threatening delusions; distorted time perception; and a lack of ability to communicate or make sense of their situation.

3.4.5 Non-pharmacological strategies

Non-pharmacological strategies were highly valued across all clinical areas with a range of interventions suggested, including the value of one-on-one nursing. This is an area of nursing practice that can be validated due to the effectiveness of the systematic introduction of non-pharmacological measures.[504 505] Non-pharmacological strategies were one area where the participants' approach was more consistent with clinical practice guidelines (though the participants did not refer to a guideline as source of their recommendations). There was an awareness that a one-on-one nurse needed expertise in care of the confused patient, and of the usefulness of reorientation strategies and maintaining a stable environment.[336] Participants identified that using these strategies increased professional satisfaction that high quality care had been provided. Given that the care of patients with delirium is perceived as highly stressful and that it increases workload (both factors potentially associated with health professional burnout), strategies which provide positive impacts on staff could be important, while also positively impacting on patient care by reducing reliance on pharmacological measures. To foster non-pharmacological approaches to delirium will require healthcare systems that value these environments, and senior leadership positively supporting such initiatives.[472] HELP, which focuses on delirium prevention with practical non-pharmacological risk reduction strategies, is an excellent example where system change in acute care hospitals has been possible, including all members of the multidisciplinary team, by using quality improvement feedback mechanisms, adherence monitoring and outcome monitoring.[353 506]

The view on restraints that the participants held demonstrated evolution over time, and is consistent with changes in current hospital policies of minimising restraint use.[507] There remained some participants who still considered some specific

scenarios where they thought restraints were the last resort. A key to changing views on restraint use has been identified as having clear alternate strategies[507], which would require a better understanding of delirium and its management.

3.4.6 Pharmacological strategies

Pharmacological strategies were varied and consistent with similar variability demonstrated in two recent surveys of medical professionals, also conducted in the Australian context, regarding use of medications to manage delirium.[391 480] The approaches bore little resemblance to each other and were not related to the comprehensive clinical practice guidelines available.[336 372 508] The participants in this current study seemed unaware of the relative roles of antipsychotics and benzodiazepines, the evidence underpinning their use, and also the adverse effect profiles, especially in the elderly, despite several guidelines available within the Australian context.[336] More alarmingly, the perceived intent of medication was sedation, with descriptions of the effect being 'settled, calm, peaceful, relaxed' without much recognition that this had to be done cautiously to be safe. Palliative care and oncology nurses more commonly mentioned midazolam and clonazepam as pharmacological strategies, but ACP and geriatric nurses also mentioned benzodiazepines. The more senior nurses demonstrated significant confidence in administering and choosing 'as required' medications if available, or even suggesting their prescription to junior medical staff. The views on as required medication, including indications, medication of choice and dose, dose escalation and combination therapies, seemed to be predominantly based on the participant's personal view, informed by the local culture, with little reference to local delirium policies or clinical guidelines. The specific pharmacological agents discussed also varied by specialty group. For example, the choice of specific benzodiazepines (midazolam and clonazepam) was only mentioned in oncology and palliative care, diazepam and temazepam was referred to by ACP and geriatrics, antipsychotics (levomepromazine) were only mentioned by palliative care, and atypical antipsychotics referred to by ACP and geriatrics.

'As required' medications are often charted in acute care or specialist in patient settings pre-emptively for problems that may occur, or for symptoms that are intermittent. The situations where they are prescribed are often complex clinical

problems, for example, pain, psychosis and delirium, which require a balance of comprehensive assessment, the need for the medication beneficial effects balanced against the risk of its side effects, plus monitoring of its effect once administered.[509 510] In particular, given the philosophy of palliative care to have management plans that cover future potential problems, and also to immediately be able to respond to symptoms and distress, the administration of 'as required' medication is a significant component of nursing practice, especially in the inpatient setting and is an autonomous nursing role. Despite this the nursing literature has little research on this important area of practice in particular in palliative care, oncology or geriatric practice.

'As required' medication has been explored in psychiatric practice, in particular related to the management of acute psychosis. These studies found a significant variation in the attitudes of medical and nursing professionals for the use of as required medication.[511-513] There are variations in beliefs regarding indication, efficacy, chosen routes and agent of choice.[511 512] Lack of clarity surrounding psychotropic 'as required' medication administration practices, confusion surrounding decision-making processes related to this intervention, and poor documentation practices (in relation to observed benefit and unwanted side effects) also have been demonstrated.[514-517]

In post-operative settings variation in the way nurses use 'as required' analgesic medication compared to the intended approach by the prescriber has been demonstrated, in particular in relation to the amount of patient information collected prior to administration.[518] Another study explored 'as required' use of medications with psychoactive side effects, namely anti-cholinergics, analgesics, and antipsychotics in the orthopaedic hip fracture and elective arthroplasty setting for post-operative nausea, pain and agitation. This research demonstrates a wide range of prescribed 'as required' medication choices available to the nursing staff in these three classes, with doses delivered to patients including approximately 20% receiving a antipsychotic, 50% receiving a benzodiazepine and over 90% receiving an opioid.[509] The retrospective chart review design of this study, however, limits any further conclusions.

3.4.7 Reported confidence and knowledge

Despite the objective evidence that delirium recognition and assessment was limited for many participants, the majority described being confident in the management of the confused patient and said they had gained that knowledge from clinical experience. This is contrary to prior studies in the hospital setting which demonstrate that nurses' knowledge of delirium was generally inadequate,[360] although one ward which had had in-service education had attained better knowledge levels.[519] Knowledge of what delirium is compared to what they recognise in their patients may be different. It has been hypothesised that although nurses recognise the confused patient in distress who is exhibiting inappropriate behaviour, the logical next step of identifying a delirium syndrome is unlikely to occur without a framework in which to put these symptoms into context.[472] This seemed to be the case in this sample with clear identification of symptoms without a delirium definitional framework leading to responses and management associated with a high degree of unjustified confidence.

3.4.8 Decision-making in nursing practice

Critical examination of the processes by which nurses judge and reach clinical decisions is important. It facilitates the maintenance and refinement of good standards of nursing care and the pinpointing of areas where improvement is needed.[520] For example, clinical reasoning may be altered by views on ageing, and those with a 'decline perspective' may assume cognitive impairment is inevitable.[521] This perspective has also been found in postoperative settings, where nurses link the common occurrence of delirium with normalcy that hence does not require fixing.[360] It could be hypothesised that this perspective may also occur in palliative care settings where cognitive decline or confusional states are assumed to be part of normal 'dying' for many people.

Several theories of decision-making in professional nursing practice are described in the literature, emphasising responsibility, autonomy, and accountability as foundations for high quality nursing care.[521-531] The pragmatic view describes nurses' decisions as being informed by research and tested theories, practice and nursing theories, and common sense or everyday life experience.[532] The systematic viewpoint looks at decision-making as a series of definable

processes—recognition, formulation, alternative generation, information search, judgement or choice, action and feedback, and is similar to clinical decision-making in medical practice.[532] The theory of diagnostic reasoning (hypothetico-deductive model) depends on four components: attending to available cues, generating tentative hypotheses, gathering data to rule hypotheses in or out, and then decision of the diagnoses.[532] This approach was seen in participants who showed an investigative approach to delirium assessment and management. Clinical decision-making in terms of intuition includes a number of techniques including 'gut feeling', pattern recognition, know how, and tacit knowledge.[532] It is argued that there is not a dichotomy between intuition and rational decision-making, however it can be difficult for health professionals to value the intuitive element of their practice within health systems driven by objective measures of quality and accountability.[523 532] It is also argued that more than one method of decision-making may be used in clinical reasoning[523] and indeed, may need to be used.

One study using a factorial survey with vignettes has explored the social, behavioural, and medical characteristics that affect nurses' clinical decision-making regarding the recognition of, and intervention for, patient confusion.[530] Each vignette contained a combination of seven independent patient variables (age, gender, patient affect, type, seriousness, time of occurrence and medical diagnosis).[530] This study used an interactionist framework, which predicted that response to confusion will vary by the context of the situation, including patient, nurse and organisational factors. The hypothesis was that nurses are more likely to recognise patients as confused when the patients are unable to interact with the person or the person is difficult socially. The factors associated with increased likelihood of being identified as confused (and also identified as needing restraints) were exhibition of verbal or unpleasant behaviours, being an older patient, symptomatology occurring on night and evening shifts, and having diagnoses that require an explanation such as falls.[530] This suggests preconceived ideas about causes of confusion that may influence detection, and this may be derived from clinical experiences rather than standardised assessment. One limitation of the study by Ludwick et al was that the vignettes provided limited

information and did not reflect the true complexity of confusion in real life, and importantly only one choice of intervention (restraints) was presented.

Another study using dimensional analysis explored detection of confusion in older adults by nurses caring for hospitalised older adults.[521 531] This study describes three distinct perspectives or personal philosophies that the nurses may adopt—decline, vulnerable and healthful perspectives. This influenced their interpretation of confusion. For example, nurses who had a decline perspective generally did not differentiate acute and chronic confusion, were usually not alarmed by episodes of confusion, and acted only when it posed potential threats to the safety of staff or patient. This is in contrast to those with a healthful perspective who were adamant that all episodes of confusion were cause for concern, and would only entertain a chronic aetiology when all other possibilities had been ruled out.[521 531]

Some initial work has been done to try to identify critical nursing behaviours in the care of the dying, which could be useful in defining expert nursing practice in palliative care.[533] One qualitative study of 10 senior palliative care nurses and 10 nurse educators explored the behaviours they associated with the positive and negative aspects of care of the dying.[533] The behaviours included responding to patients in the terminal phase, including providing a sense of calm, maintaining physical comfort, responding to family anger, ability for personal growth in their role, providing emotional support to colleagues, enhancing quality of life during dying, and responding to the families' need for information and care. It would be important to consider how these key components of practice play a role in how palliative care nurses respond to delirium, both when delirium is irreversible and part of the terminal phase of illness, but also when potentially reversible. The expert skills in supporting families would directly extrapolate to meeting the needs of a family who has a loved one with delirium, as would approaches which aim to provide calm, responding to family emotions such as anger and improve comfort.[533] The challenge may be ensuring that adequate assessment of reversible causes is part of the approach aimed at improving delirium symptoms.[38]

3.4.9 Strengths of this study

This study interviewed a wide range of nurses with a wide range of qualifications and experience, covering issues of definition, assessment and management as well

as levels of confidence and education. Thus, it has provided an in-depth understanding of how these issues interact across a variety of inpatient settings. It has provided insight into the breadth of the decision tasks nurses face when caring for someone with delirium, demonstrating the spectrum of decision-making strategies and use of analytical, intuitive and combined approaches.[534] Thematic saturation was achieved across the whole sample, however not within each specialty group for all of the themes described. Further studies are needed to explore each subspecialty in more depth.

3.4.10 Limitations of this study

An interview methodology will only provide information about what a health professional says they do, which may not directly reflect their practice. However it is unlikely that their practice is more comprehensive than their stated responses. The term delirium and confusion were used in the interview questions so may have provided a prompt to participants. The purposive sampling approach did not achieve representation from enrolled nurses working in oncology, or night nurses working in geriatrics, which are limitations of the sample. Thematic saturation was not achieved for some themes within the specific specialty groups, though it was achieved in the total sample.

3.4.11 Future directions for practice

It will be important for clinicians in a multidisciplinary team to understand a nursing perspective of this challenging area of care, as quality delirium care requires building team approaches to management. Managers and executive teams need to consider the distress health professionals experience when they witness patients with delirium, and ensure that this experience is validated and adequate support mechanisms exist. Further research needs to consider whether the reasons for under-detection and under-management of delirium are similar in other disciplines, and how individual discipline factors inter-relate to compound the problem.

Any educational strategy to improve screening assessment for delirium needs to be multipronged, involving education about delirium features to increase awareness and skill in recognition of core delirium features. To make an impact,

education will require concurrent system changes and leadership.[361 397 399 535] This study has demonstrated that nursing practice in key areas of delirium management is divergent from currently available clinical practice guidelines, and prior work has demonstrated that without associated high intensity training, guidelines of themselves are unable to improve process or outcomes of delirium care.[368]

Focus is also needed to assist nurses in choosing decision strategies which match the complex nature of delirium care and the multiple tasks at hand, and which require a balance of knowledge, more intuitive 'cue' recognition and context-related experience. Nursing and medical practice do not occur in isolation, and any nursing strategies need to be matched by strategies to improve delirium assessment and management within the medical workforce. Equally, in physicians a comprehensive and sequential intervention (including both didactic components but also small group sessions and practical case discussions) improved confidence and knowledge.[536] This suggests that it takes multiple and reinforced modes of education to influence health professional behaviour when considering delirium management. This study has provided a more detailed insight into where difficulties in delirium assessment and management lie, which will inform educational and healthcare services in delirium management.

3.4.12 Future directions for research

Research approaches that verify interview findings with direct observation will assist in understanding the differences between what nurses 'say' they do,compared to what is observed in practice. More in-depth work is needed to understand the differences or similarities in patient delirium experience, related to the nature of the illness to assist health professionals working in specialist settings (e.g. traumatic circumstances such as severe burns, compared to terminal cancer).[312] The impact of the stress on nursing professionals who work in areas with a high prevalence of delirium also needs further exploration. In particular, its association with burnout, and the impact on educational and support strategies on professionals' wellbeing, as well as the quality of patient care that is delivered.

The findings of this study need to be replicated in studies of nurses working in similar inpatient units in other settings not only within Australia but also internationally. The utilisation and decision-making processes of as required

medications needs to be explored in palliative, oncology and geriatrics settings as it is identified as an area where the most divergence from clinical practice guidelines can occur. Any educational or health service intervention needs corresponding research to evaluate outcomes so determine which methods are most effective in closing the evidence-practice gap.

3.4.13 Comparison of findings from nursing practice to medical specialist practice

Chapter 2 outlines the findings of a survey of current practice of geriatricians, aged care psychiatrists, medical oncologists, and palliative medicine specialists, with regard to the pharmacological and non-pharmacological management of two contrasting vignettes of delirium in a patient with advanced cancer. It is possible to compare some key results between nursing and medical approaches in the specialty groups of ACP, geriatrics, oncology and palliative care.

Notably, a wide range of dosing and approaches of use for antipsychotics and benzodiazepines was seen in both nursing and medical practice. Benzodiazepines were more commonly discussed in oncology and palliative care nursing practice, consistent with the findings in Chapter 2 that medical oncologists also used benzodiazepines more frequently. Most physicians utilised improvements in targeted symptoms as an indicator of treatment success, whereas the nursing participants perceived sedation as the intended outcome of pharmacological therapy. The specific choice of agents within a class of medication also seems to vary between specialist groups, both medical and nursing. For example, midazolam and clonazepam are restricted to MO and palliative care practice; atypical antipsychotic is more common in ACP and geriatric practice, and levomepromazine is restricted to palliative care practice. The interaction of delirium and pain was a concept identified at both nursing and medical levels. Medical precipitants of delirium, and hence approaches for investigation, seem to relate to commonly seen aetiologies. For example brain metastases were identified quite clearly by the medical oncologists choosing to undertake CT head scans, with their nursing counterparts describing brain metastases as a cause of delirium and the use of dexamethasone as a therapeutic strategy. Non-pharmacological approaches were highly valued by both nursing and medical participants.

It is not possible to compare views on location of care as this was not raised with the nursing participants, nor delirium definitions/diagnoses, as this was assumed knowledge in the way the survey of medical specialists was constructed (an assumption which should be tested in future work).

Chapter 4: Anticholinergic load from regular prescribed medications in palliative care

Medications for symptom control and comorbid disease both contribute to the cumulative number of prescribed medications in palliative care.[537 538] Recent studies of palliative care populations in acute care, specialist inpatient palliative care and community settings show that each patient on average takes five medications.[537 538] The total medication number increases as the person is closer to death, predominantly due to the addition of medications for control of symptoms. Previous research has not described the contribution of anticholinergic medication in the palliative population. This chapter describes a study quantifying the anticholinergic load of medications for comorbid disease, symptom control, or medications that may be used for either indication in a palliative care population followed longitudinally as death approaches. This study also aimed to evaluate how anticholinergic load from medications contributed to symptom burden, changes in function, health-service utilisation and survival.

4.1 Methods to assess the potential for adverse medication effects

It is important to consider how adverse effects from medications occur, as well as the methods reported in the literature to assess them, to apply research findings in the context of anticholinergic medication more specifically. Many adverse symptoms can be attributed to side effects of a single medication. The prevalence or risk of side effects for each individual medication may vary depending on the underlying illness, comorbid disease, and other physiological changes.[539]

The cumulative effect of medications is also crucial. This area has received little attention in prescribing for people with life-limiting illness where pharmacological interventions are mostly administered in combinations, targeting both single and multiple symptoms.[538 540] There are cumulative or synergistic effects of multiple medications, especially for those with psychoactive effects.[182 183 197 342] The adverse effects of medication may be mediated by drug duplication (cumulative effects of more than one drug in a therapeutic class), drug – drug interactions (multiple psychoactive medications) and drug – disease interactions

(which can be with the underlying progressive life-limiting illness and/or other comorbid or inter-current disease, examples include non-steroidal anti-inflammatory drugs with peptic ulcer disease and beta blockers with chronic obstructive pulmonary disease).[541 542]

Another approach to evaluating the risk of medication toxicities is utilising consensus criteria that rate the propensity of a medication to cause adverse effects. Medications which are listed have been named 'potentially inappropriate' or inappropriate. These aim to highlight specific class effects, drug – disease interactions, drug – drug interactions, or problems associated with a long duration of therapy or cumulative effects. These correspond to a high rate of adverse effects, often in a particular population of interest (e.g. nursing home residents or people over 65 years).[543] Anticholinergic medication contributes highly to all the available lists of criteria for adverse outcomes relating to prescribed medications. To affect prescribing, these criteria need to be considered in conjunction with the therapeutic aim of the medication (for primary, secondary or tertiary prevention, or active treatment of a condition and/or symptomatic management), and the alternative options available. The prescribing response may include cessation, change to alternate agent, reduction in dose or duration of exposure, or addition of another medication to manage side effects.[544]

The available lists of criteria include:

- Potentially Inappropriate Medications (PIMs) or drug interactions leading to adverse effects;
- the Beers criteria (a classification to identify PIM use in older adults over 65 years);
- the Screening Tool of Older Persons' potentially inappropriate Prescriptions (STOPP)[545-548], the DBI[239]; and
- the Improved Prescribing in the Elderly Tool.[441 549]

One of the issues is the currency of these lists, with the STOPP criteria adding newer medications that are now in widespread use. STOPP has an emphasis on

drug – drug interactions and duplication of drug class prescription. Similar to Beers criteria, STOPP emphasises the risks of using long-acting benzodiazepines, tricyclic antidepressants, anticholinergic drugs, and non-cyclooxygenase 2-selective non-steroidal anti-inflammatory drugs.[550] The DBI includes medications with anticholinergic or sedative effects, and also considers the number of medications, as identified by *Mosby's Drug Consult*[551] and the *Physicians desk reference*.[552] The DBI makes the assumption that cumulative effects would be linear and additive, and takes into account daily dose.[239] In this schema, an agent that is both anticholinergic and sedative is classified as an anticholinergic.[239]

4.2 Clinical utility of methods to assess potential for adverse medication effects

The main use of these criterion-based approaches is to provide prescribing guidance for older adults; predominantly to alert clinicians to medications where caution is required. Beers criteria has recently been extended to provide lists of preferred medications with no effects on the CNS for older adults (positive Beers criteria) and also to include an approach to alert clinicians to appropriate treatment, called Screening Tool to Alert doctors to Right Treatment (START).[441 546 553-557] In particular, START aims to alert clinicians to medications where the predicted adverse effect is likely to be severe in the patient population of interest, and hence encourage alternative medication choices.[441] Several medications with anticholinergic properties, mainly those with marked activity (e.g. amitriptyline, doxepin, and the antihistamines which have potent anticholinergic properties) are rated as 'high risk' on Beers criteria predominantly due to high propensity to cause CNS side effects.[441]

Studies demonstrate the prevalence of inappropriate prescribing in the elderly, with rates ranging from 14%–40% seen in elderly patients (regardless of whether the person is in the acute, community or nursing home setting) when defined as receiving at least one inappropriate medication by either the initial Beers list of 20 inappropriate medications[558], or various modified versions of the Beers list. Some studies exclude those agents that are only inappropriate if used for the wrong duration or too high a dose, others add one or two select medications (e.g. diphenhydramine, gastrointestinal antispasmodic agents, reserpine, clorazepate,

antihypertensive agents) or exclude specific medications (e.g. isoxsuprine (a beta-adrenergic agonist), cyclandelate (direct acting smooth muscle relaxant) both which cause peripheral vasodilation).[553 558-561] Inappropriate prescribing is higher in specific populations, such as those with neuropathic pain where up to 50% were prescribed an inappropriate medication.[562] Equally, since the introduction of prescribing criteria, there has been some reduction in inappropriate prescribing. For example, from 1995–1999 in an American cohort of community dwelling elderly (n = 7628), there was a reduction in rates for those taking more than one medication of risk on Beers criteria from 24% to 21%.[563] At the same time, however, there was no decrease in the prevalence of people taking one medication of risk.[563] In relation to specific patterns of anticholinergic use, a study of ambulatory older adults in the Netherlands (the sample population ranged from 18,030 to 29,605 per year, for the five years between 1997 and 2001) amitriptyline was one of the most frequently prescribed 'inappropriate' medications.[564] In the US study[563] an annual exposure to amitriptyline of 2.7% was cited and had not changed over time. A potential explanation may be the focus on chronic pain in the elderly, in particular neuropathic pain, which may be the targeted symptom that has evidence supporting the use of amitriptyline.[564 565] Similarly, the potential for drug reactions has been quantified, with one outpatient service demonstrating that out of 372 people with advanced cancer there were 250 potential drug interactions identified in 115 patients (31%, CI 26%–36%), with most rated at moderate severity.[566]

Intervention strategies focus on reducing inappropriate prescribing with varying levels of success.[567 568] For example, a randomised trial that demonstrated education interventions can reduce inappropriate prescribing without adversely affecting the behaviours or level of function of nursing home residents (i.e. there was no loss of therapeutic benefit of the persons' medication regime with a reduction in the inappropriate medication), did not explore whether it also reduced adverse outcomes attributable to medication.[568]

The challenge is that the use of medications deemed 'inappropriate' or high risk in older adults has not been consistently associated with poorer health outcomes, such as hip fracture, increased rate of hospitalisation, increased length of stay and/or mortality. Some studies demonstrate an association of 'inappropriate'

medications with these poor outcomes[541 569-575], others demonstrate 'medication attributable' adverse effects[554 574 576], while others do not show poor outcomes of adverse effects.[541 554 569 570 577-580] The variability in results may be partly due to:

- selection of the measures used to calculate inappropriate medication use;
- whether the study explored multiple groups of high risk medications versus a single medication or class of medications;[571-573]
- the method used to attribute outcome as a drug-related problem;[554 574 576]
- the degree and sophistication with which the analysis accounts for factors which may mediate medication effects, such as dose, duration of use, and disease burden;[576 581]
- confounders of analyses that have not yet been identified and hence not controlled for in these studies;
- methodological issues such as unrepresentative samples, inadequate sample size or retrospective methodologies; and
- accuracy of the approach to measure actual medication use, for example use of databases where medication prescribed or dispensed may not completely correlate with medications actually taken by the person.

A similar approach has not been explored in other vulnerable populations, such as palliative populations who may not necessarily be 'elderly' but may be equally frail.

4.3 The importance of medication with anticholinergic action

Medications with anticholinergic action are an important group of medications to consider. Their side-effect profile leads to their propensity to cause significant morbidity, and should be avoided or used with caution if use is unavoidable in the elderly or frail.[441] Simultaneous use of medications with anticholinergic action puts the person at risk of cumulative anticholinergic effects both from the medication itself, and in some cases active metabolites.[232] Medications in this

class range from having minimal to marked AA, which also may vary with dose and duration of use.[186] Apart from adverse effects directly mediated by anti-muscarinic activity such as dry mouth, dry eyes, urinary retention and constipation[582], medications with anticholinergic properties are associated with delirium[247 259 266 583-588]; falls, reduced functional status and impaired motor performance[239 276 589-591]; and poor cognitive outcomes (particularly in those with prior cognitive deficits).[239 269 277 591-596]

The 'anticholinergic' burden that an individual is exposed to can be defined as the anticholinergic load generated by all of the medications (and their metabolites if relevant) with anticholinergic properties as well as endogenous anticholinergic substances (dynorphin A, MBP, protamine), that some evidence suggests are produced in acute illness.[230 231] There is evidence that many medications have anticholinergic properties, in addition to those traditionally labelled as anti-muscarinic medications, including commonly used medications such as warfarin, ranitidine, digoxin, codeine and diazepam.[232 233] Importantly, many of these medications are continued or commenced during the end-of-life care period. Understanding the cumulative anticholinergic load and how this changes as a result of prescribing at the end of life is crucial, due the significant morbidity, and even premature mortality, potentially associated with this spectrum of unwanted effects. This understanding will also assist clinicians by generating a more coherent framework in which to make decisions about discontinuation of medications no longer contributing a therapeutic benefit, or substitution of medication with lower anticholinergic effects but the same or similar therapeutic benefit, and interpretation of the potential contribution of medications with anticholinergic action to the patient's symptoms.

4.4 What is known about the potential risk of adverse medication effects in palliative care?

Out of the medications for symptom control being taken at referral to a specialist palliative care service, one-third meet Beers criteria as inappropriate, and over time this percentage increases to almost 50% as death approaches.[537] Medications being taken for comorbid disease reduce in number slightly as death approaches; however, this group of medications continue to contribute to high-risk medication

with approximately 15% meeting Beers criteria at any time-point after referral to specialist palliative care.[537]

The anticholinergic medication load in palliative care patients has not been quantified in the literature in either cross-sectional or longitudinal analyses, and to date there has been no study of people with advanced cancer exploring the association between anticholinergic medication load and health-service utilisation or survival outcomes.[541 569 570] The study described in this chapter quantified the use of medications with anticholinergic action and described their associations. An understanding of anticholinergic load due to medication in the palliative population will guide future prospective studies by determining if strategies to reduce anticholinergic load may be able to improve patient function and comfort at the end of life without compromising symptom control.

The primary aim of the main study was to undertake a secondary analysis to quantify the anticholinergic load of medications for comorbid disease, symptom control, or medications that may be used for either indication in a palliative care population followed longitudinally as death approaches.

The secondary aims of the sub-study were to explore associations between the total anticholinergic load of medications for comorbid disease and symptom control and:

1. quality of life (measured by the McGill Quality of Life scale)
2. performance status—measured by the Australia-modified Karnofsky Performance Scale AKPS)
3. specific symptoms (measured on the Memorial Symptom Assessment Scale (MSAS), namely dry mouth, constipation, hallucinations and confusion)
4. health-service utilisation (defined as number of days spent as an inpatient) and survival (in the sub-group with advanced cancer only).

The primary null hypothesis of the main study was that total anticholinergic load of medications for comorbid disease and symptom control remains unchanged as death approaches.

The secondary null hypotheses of the sub-study were that total anticholinergic load of medications for comorbid disease and symptom control is not associated with:

1. changes in quality of life
2. changes in performance status
3. specific symptoms (dry mouth, constipation, hallucinations or confusion)
4. changes in health-service utilisation in the sub-group with advanced cancer
5. changes in survival in the sub-group with advanced cancer.

4.5 Methods

4.5.1 Setting

The participants for the study were patients referred for specialist palliative care in Adelaide, South Australia. Southern Adelaide Palliative Services (SAPS) consists of specialist services including a 15-bed stand-alone inpatient palliative care unit, medical outpatient clinics, acute-care medical and nursing consultations, and a community service which provides visits by nursing, social work, specialist pharmacy and medical health professionals (including visits into residential aged care). Similar to other specialist palliative care services in Australia, it has a dedicated volunteer and bereavement service, but uniquely it also has practitioners who provide complementary care (e.g. massage and relaxation therapy). The service also provides consultative in-reach and inpatient care to private hospitals within the region it serves. Community, consultative and ambulatory services are provided in conjunction with the person's attending physician or GP and community nursing services. Direct care is available within the inpatient unit and also in select number of beds in acute care.

The geographic area that SAPS covers is an area of more than 750 km^2 that serves an estimated population of more than 350,000 people, with approximately 1000 new referrals per year at the time of the study.

4.5.2 Study design

The main study and sub-study are secondary analyses of participants in the Palliative Care Trial (PCT).[597-599]

4.5.2.1 Methodology of the Palliative Care Trial

The PCT was a prospective unblinded cluster RCT of three interventions in people receiving palliative care. The study had three randomisations, creating a 2 x 2 x 2 factorial design.[597-599] Patients and their GPs were randomised three times at the same time-point to:

1. GP educational outreach visiting versus usual care (1:1 randomisation)
2. structured patient and caregiver educational outreach visiting versus usual care (1:1 randomisation)
3. a coordinated palliative care model of case conferencing versus the standard model of palliative care in Adelaide, South Australia (3:1 randomisation).[597-599]

The three alternative primary hypotheses of the PCT were that, compared to routine palliative care:

1. GP educational outreach visiting leads to decreased patient-reported pain intensity (on a numeric rating scale).
2. Structured patient and caregiver educational outreach visiting leads to decreased patient reported pain intensity.
3. Case conferencing leads to increased time with maintenance of independent physical function (measured by the AKPS).[597-599]

The inclusion criteria for the main study were patients referred to SAPS with any form of pain in the three months preceding the trial. Exclusion criteria included the place of residence being outside the geographic area served by SAPS, patients where death was expected within 48 hours of referral, and cognitive impairment (defined as MMSE score ≤ 24[127] at baseline assessment, unless there was a healthcare proxy who could provide consent. Once the patient had consented,

their GP was also invited to participate. Consent of both patient and GP was required to proceed to randomisation.

4.5.2.2 Methodology of the main study and sub-study

The main study and sub-study were nested in the PCT study, and required supplementary measures taken at the same time-points, namely at initial referral, bi-weekly for two months, and then at least monthly until death.

4.5.2.2.1 Participants for the main study

All participants of the PCT who had a known date of death were included in the primary analysis quantifying medications with anticholinergic action (total anticholinergic score) longitudinally over time.

4.5.2.2.2 Participants for the sub-study

Participants for secondary analyses exploring health-service utilisation and survival included a subset of PCT participants who met the following inclusion criteria:

1. a diagnosis of cancer;
2. known date of death at the end of the study period;
3. AKPS score at initial assessment of 60 or above; and
4. AKPS score fell to below 60 at some time-point during longitudinal follow-up.

A cancer-only group was chosen as the relationships of function and survival in advanced cancer differ from non-cancer life-limiting illness.[600] The pattern of functional decline as death approaches in someone with advanced cancer is typically a period of relatively slow functional decline followed by more rapid decline occurring at an identifiable time-point within weeks to days before death.[600] Performance status has a definite correlation with survival in cancer with deterioration in performance status associated with worsening survival.[601]

The AKPS is a functional scale where 100 equates with full function, a score less than 70 requires increasing support from other people, less than 30 is totally

dependent on others' help, and 0 is dead (Appendix 9).[602] In order to standardise a common starting point for the calculation of survival in this population, only people whose AKPS score was 60 or above at initial assessment were included in the analyses. The baseline time-point for this substudy was defined as the first visit at which AKPS score was below 60. This gave a homogenous starting point from prospectively collected data for subsequent health-service utilisation and survival trajectories to be considered, given the widely varying time-points at which referral to specialist palliative care services occurs before death. AKPS of 60 also corresponds to the functional level where people start requiring assistance.

4.5.3 Ethics approval

This PCT was approved by 12 Human and Research Ethics committees. It was also approved by the Australian Department of Veteran Affairs and Health Insurance Commission, Canberra, Australia. The trial was registered with the international standard RCT number register (ISRCTN) clinical trials registry (ISRCTN81117481).[603]

4.5.4 Assessments

All participants enrolled in the PCT trial underwent community-based or inpatient reviews for the study at initial referral, every two weeks for following two months, and then at least monthly until death.

4.5.5 Data collection

4.5.5.1 Demographic and baseline clinical data

Demographic data collected at baseline included age, gender, primary diagnosis, comorbid diseases, and date of referral to the service.

4.5.5.2 Medication use

A list of medications used regularly was recorded at each visit, documenting generic drug name, dose, route of administration, indication, frequency, and pattern of use. Medications used on an as-needed basis, short-course medications such as antibiotics, intravenous chemotherapy, and agents with no Australian Therapeutics Code (complementary or alternative therapies given wide variation in formulation and labelling) were excluded from data collection.[537]

Medications were divided into three categories under ‘reason for prescription’:

1. those used for comorbid disease
2. those used for symptom control of life-limiting illness
3. those medications that may fulfill both roles.

The latter group included tricyclic antidepressants and some anti-epileptics that are also utilised for neuropathic pain. This approach allowed the relative contribution of medications used for comorbidities to be distinguished from the symptom-control medications added at the end of life.

A subtotal anticholinergic score was calculated for each of the three medication categories, and a total score was obtained by summing subtotals at each time-point.

4.5.5.3 Medications with anticholinergic action

The most comprehensive method currently available is the CRAS-M[246 247], which gives medication one of four ratings:

- Level 0 (no known anticholinergic properties)
- Level 1 (potentially anticholinergic as demonstrated by receptor binding studies)
- Level 2 (clinically significant anticholinergic effects are sometimes seen, usually at excessive doses)
- Level 3 (marked anticholinergic effects).

This allows calculation of a total anticholinergic score at each time-point for each participant.[246 247] The approaches available to measure anticholinergic load are covered in Chapter 1, Section 1.11.2, including the strengths and weaknesses of the CRAS-M.

4.5.5.4 Quality of life

Quality of life was measured using the MQOL questionnaire—a 16-item tool which has been developed, validated and extensively used in both cancer and non-

cancer palliative settings—comprised of an item measuring physical wellbeing and four subscales: physical symptoms, psychological symptoms, existential wellbeing, and support.[604-606] Each domain is scored as a separate subscale and can be summed to give an overall score.[607] The MQOL was designed as a patient self-report measure that can be self-completed or read aloud to the patient by a staff member—the mode of administration does not affect scores.[607]

MQOL differs from other quality of life scales by making the physical domain less dominant, including an existential domain, and measuring positive contributors to quality of life to reflect the aspects which play a role in quality of life in people with advanced disease.[608 609] This instrument is designed to be brief, but applicable to a large range of patients, and includes a section where the respondent can list the three symptoms which are most problematic, rather than present a long list of symptoms.[610] Internal consistency of the MQOL is good, with a Cronbach alpha for the total score of 0.83.[608] The internal consistency for the physical symptoms subscales was 0.62; however, this is likely due to the three most troublesome physical symptoms named by the patient often being unrelated.[607] The test-retest reliability of the MQOL has been tested in oncology patients seen by a palliative care service, with an intra-class coefficient of the total score of 0.75, which is in the medium range.[607 611] The MQOL demonstrates responsiveness to change, with the total score and its subscales (except for the support domain) able to detect change between the days on which oncology patients self-rate as good, average, and bad.[611]

4.5.5.5 Performance status

Functional assessment was made at each review using the AKPS.[602] The AKPS is a modification of the Karnofsky Performance Scale (KPS) (which links performance status levels much more to determinations of where care should be provided) for use in palliative care settings, in particular in the community. AKPS has been shown to be equally predictive of survival as the KPS, has longitudinal test-retest reliability and excellent correlation with the original KPS; but has the benefit of better face validity with palliative care clinicians.[602]

4.5.5.6 Symptom assessment

At each visit, the presence or absence of symptoms including dry mouth, constipation, hallucinations and confusion was recorded using clinical assessment and the MSAS.[612 613] This scale is a patient-rated instrument, which has been shown to be reliable and valid in measuring symptom experience in both cancer and non-cancer palliative populations.[612 613] It assesses 32 psychological and physical symptoms, in three dimensions (intensity, frequency and distress).[614]

4.5.5.7 Health-service utilisation

Health-service utilisation can be measured from the perspective of the patient or the health service, with the patient perspective captured by self-report and the health-service perspective utilising an administrative database or chart audit data.[615] Patient self-report has the advantage of being inclusive of all sources of healthcare; however, studies demonstrate that patients tend to under-report their health-service utilisation when compared to provider records, with reporting error related to the patient characteristics—which may also drive higher health-service uptake or use (e.g. age, education, income, health status).[616] Where the patient uses several providers, data need to be sourced from several databases or medical records.[616] Chart entries may be difficult to decipher, and some visits may not be clearly documented; computerised data sources mostly have the primary aim of tracking patient billing rather than following medical histories.[616]

The choice of inpatient hospitalisation as an outcome for health-service utilisation, was to capture events related to medication use that were significant enough to require inpatient care (and length of admission will be related to the seriousness of the event). It was also a requirement that the use of the health-service was confirmed with hospital database records to ensure accuracy. This is also an outcome of clinical significance, as avoiding unnecessary hospitalisation is a key goal of community palliative care, and has been used in studies exploring health-service utilisation outcomes in the elderly.[541 569 578]

The location of the patient was determined at each follow-up visit, by patient, family or community palliative care nurse report. The length of admission was determined from the hospital information systems (to determine accurate date of

admission and discharge). Emergency department only presentations were not collected in this study.

Health-service utilisation was obtained by summing all length-of-stay times (in days) that occurred after the baseline time-point. For descriptive purposes, health-service utilisation was divided by time from baseline to death for each participant to give the proportion of time spent as an inpatient.

4.5.5.8 Survival

Survival was calculated as the number of weeks from the baseline time-point (crossing AKPS score of 60 as functional decline occurred) until death.

4.5.6 Data analysis

4.5.6.1 Quality of life, performance status and symptoms

Time was anchored at death, given the various reasons for referral to a specialist palliative care service and hence variation in time of referral. Time trends in total anticholinergic score were examined using generalised linear models, with a gamma error distribution and logarithmic link function (log-gamma model).[617] This type of model is useful for positively skewed outcomes that take non-negative values. Non-independence of observations within subjects was allowed for by using a clustered Huber-White variance estimator.[618] This method was chosen due to complex correlation patterns (correlation of scores for the same 'reason for prescription' category at different time-points, correlation between different 'reason for prescription' category at the same time-point, and correlation between different 'reason for prescription' categories at different time-points) giving unbiased results regardless of the within-subject correlation pattern.[618]

Time before death was categorised into 0–1 month, >1–3 months, >3–6 months, and >6 months, and was entered into models as a categorical variable. These groups were determined to ensure even distribution of data in each category and, as the shape of association of key variables over time was not known, time could not be used as a continuous variable. The possibility of different time trends for the three 'reason for prescription' categories (comorbid, symptom-specific, mixed) was examined by fitting a log-gamma model with total anticholinergic

score as the dependent variable, and independent variables of time before death, drug class, and the time X drug class interaction.

Associations between total anticholinergic score and quality of life, AKPS, and side-effect scores were examined using separate random intercepts for each subject in ordinal logistic regression[619], with total anticholinergic score as the independent variable. In order to ensure adequate adjustment of estimates for time before death, time before death was included as a categorical variable with seven levels. As the aim was to adjust for time before death, not to estimate its effect, the seven categories are divided into relatively small categories (<0.8, 0.8–1.8, 1.8–2.8, 2.8–4.3, 4.3–6.4, 6.4–8.9, >8.9 months). To ensure any association seen was not an artifact of deteriorating quality of life as death approaches, the time categories were as short as possible, while still maintaining enough participants in each category, so that within each time category there was little association between quality of life and time to death. As it was not known what the shape of the relationship between total anticholinergic score and time was, time was considered as a categorical variable rather than continuous. This allowed the relationship of total anticholinergic score to be detected if linear or nonlinear, and also if it changed direction of effect over time.

The generalised linear latent and mixed models (gllamm) module was used to fit the random intercept ordinal regression models.[619]

4.5.6.2 Health-service utilisation and survival

Demographic data of subjects who were included in this sub-study and those who were not, were compared by the chi-square test for categorical data or the Mann-Whitney U-test for continuous and ordinal data.

To explore the association of total anticholinergic score and health-service utilisation and survival, total anticholinergic score at baseline (i.e. when AKPS was 60) was divided into three strata from summed scores with approximately equal numbers of patients: 0–2, 3–5, and 6–9. The three strata of anticholinergic scores were entered into models as categorical variables, to ensure equal distribution of participants. These stata also equally distribute degree of anticholinergic exposure.

Length of survival is a dominant factor affecting health-service utilisation measured as time as an inpatient. For descriptive analyses, health-service utilisation (total length of stay) in days was divided by survival time in days. This gives a figure, which ranged from 0 to 1, representing the proportion of time that a patient spent as an inpatient. For inferential analyses, a log-gamma model was used to determine 'health-service utilisation per week of survival', with a logarithm of survival time included as an offset.

Analysis of service utilisation was performed using generalised linear models, with a gamma error distribution and logarithmic link function. The dependent variable was the number of days spent as an inpatient. Kaplan Meier survival curves were compared using a logrank test.

Analyses were conducted using the software package Stata version 10 (Stata Corporation, College Station, Texas USA 2007).

4.6 Results

4.6.1 Participants of the Palliative Care Trial

The PCT enrolled 461 people, with their corresponding GP (50% males, n = 232/461) with an average age of 71 (SD 12). Of the participants, 63% (n = 282/461) were married or in a *de facto* relationship, 90% (n = 410/461) were residing in their own home, and 91% (n = 420/461) had cancer as their life-limiting illness (Table 30). At study entry, the median AKPS was 60.

Baseline entry to the study was a mean 107 days before death (SD 103 days; median 93; range 11–752). The mean time from the last assessment until death was 23 days (SD 23 days; median 16 days; range 1–241 days), and the assessment before this was a mean of 29 days earlier (SD 22; median 25). The mean number of study assessments between referral and death per patient was 4.8 (SD 4.18; median 3, range 1–24).

Table 30 Baseline demographic and clinical characteristics for all Palliative Care Trial patient participants

Characteristic		**n = 461**
Age	Mean (SD)	71 (12)
Gender	Male	232 (50%)
Marital status	Married/ *De facto*	282 (63%)
	Widowed	107 (24%)
	Divorced/ Separated	45 (10%)
	Never Married	17 (4%)
Educational level	Didn't complete high school	262 (64%)
	Completed high school	146 (36%)
MMSE[127]	Mean (SD)	28.7 (2.3)
Caregiver status	Has caregiver	394 (94%)
	No caregiver	27 (6%)
Accommodation	Private residence	410 (90%)
	Aged care facility	30 (7%)
	Hospital	14 (3%)
Living arrangement	Lived alone	102 (24%)
	Lived with spouse/ Partner only	257 (60%)
	Additional person(s) in household	68 (16%)
Life-limiting illness	Cancer	420 (91%)
Performance status (AKPS) [602]	Mean (SD)	61.0 (13.8)
	Median (range)	60 (20–90)
	AKPS < 70%	236 (59%)
Phase[j] of palliative care[620]	Stable	224 (55%)
McGill Quality of Life	Mean (SD)	6.0 (2.0)

Note: For each characteristic, percentages reflect percent of non-missing totals.

AKPS – Australia – modified Karnofsky Performance Status; MMSE – Mini-Mental State Examination; QOL – Quality of life; SD – standard deviation

[j]Palliative Care 'Stable' Phase is defined as patient problems and symptoms are adequately controlled by established plan or care and further interventions to maintain symptom control and quality of life have been planned and family/carer situation is relatively stable with no new issues apparent (Palliative Care Outcomes Collaborative)

4.6.2 Comparison of the Palliative Care Trial patient population with Southern Adelaide Palliative Services referrals during the same time period

Patient participants in the RCT did not differ in age, gender, marital status, or level of education from the whole population referred to the palliative care service during the same period (data not shown). They did, however, more commonly have cancer (study 91% vs whole of service 85%), and lived longer from the time of referral to palliative care (median, study 87 days, range 1–833, vs whole service 48 days, range 0–1642). This longer survival is consistent with the exclusion of patients expected to die within 48 hours of enrolment.

GP participants numbered 230, and 105 GP practices participated, with a median of one participant in the study per GP (range 1–7) and three participants per GP practice (range 3–23).

4.6.3 Participants in the main study

All the participants in the RCT were included in the analysis if their date of death was known (n = 304). Figure 2 illustrates the flow of participants (using CONSORT[k] criteria[621 622]) in the main study and the sub-study.

[k] Consolidated Standards of Reporting Trials

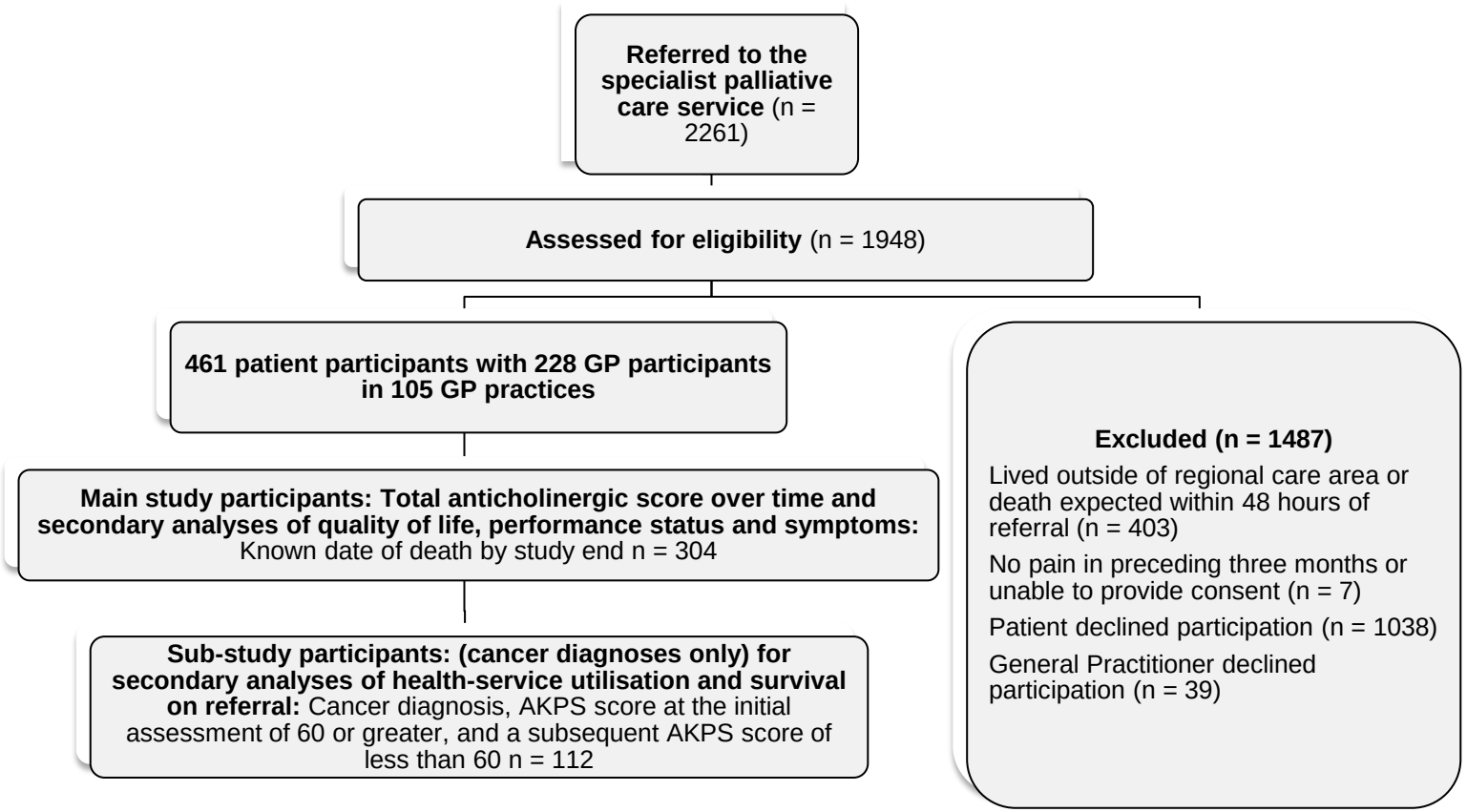


Figure 2 Patient flow for all participants of the main study and sub-study

4.6.4 Participants in the sub-study

For the analysis of health-service utilisation and survival, a specific sub-group of the RCT population (n = 112) was used as described in Section 3.2.2.2. In this group (n = 112), the median AKPS scale was 60. Table 31 illustrates that the sub-study participants were similar to the whole cohort, apart from:

- all having a diagnosis of cancer (as a specific inclusion criterion)
- having a higher AKPS at referral (mean AKPS of 64.8 for all participants in RCT with cancer vs 69.2 for eligible participants for this sub-study at entry to main RCT; $p < 0.001$)
- a higher percentage of people in the stable phase[1] [623] (58% n = 217 out of 434 RCT participants with cancer vs 69% n = 74 out of 112 eligible participants for this sub-study at entry to main RCT; $p = 0.006$), consistent with better performance status.

[1] Palliative Care 'Stable' Phase is defined as patient problems and symptoms are adequately controlled by established plan or care and further interventions to maintain symptom control and quality of life have been planned and family/carer situation is relatively stable with no new issues apparent (Palliative Care Outcomes Collaborative)

Table 31 Baseline demographic and clinical characteristics for Palliative Care Trial participants with cancer and sub-study participants

Characteristic		n = 434[a] (all participants in RCT with cancer diagnosis)	n = 322 (not in sub-study)	n = 112 (sub-study participants)	P value (two previous columns)
Age	Mean (SD)	71 (12)	71 (12)	72 (12)	0.22
Gender	Male	216 (50%)	162 (50%)	54 (48%)	0.70
Marital status	Married/ De facto	264 (63%)	191 (61%)	73 (66%)	0.36
	Widowed	98 (23%)	71 (23%)	27 (25%)	
	Divorced/ Separated	45 (11%)	39 (13%)	6 (5%)	
	Never Married	15 (4%)	11 (4%)	4 (4%)	
Educational level	Didn't complete high school				
	Completed high school	75 (20%)	58 (21%)	17 (17%)	0.45
Mini-Mental Status Exam[127]	Mean (SD)	28.8 (2.2)	28.7 (2.3)	29.0 (1.9)	0.12
Caregiver status	Has caregiver	350 (93%)	259 (93%)	91 (95%)	0.45
	No caregiver				
Accommodation	Private residence	387 (91%)	285 (90%)	102 (94%)	0.26
	Aged care facility	25 (6%)	20 (6%)	5 (5%)	
	Hospital	13 (3%)	12 (4%)	1 (1%)	

Characteristic		n = 434[a] (all participants in RCT with cancer diagnosis)	n = 322 (not in sub-study)	n = 112 (sub-study participants)	P value (two previous columns)
Living arrangement	Lived alone	88 (23%)	70 (24%)	18 (19%)	0.56
	Lived with spouse/ Partner only	234 (61%)	173 (60%)	61 (66%)	
	Other person in household	61 (16%)	47 (16%)	14 (15%)	
Performance status (AKPS)[602]	Mean (SD)	64.8 (13.9)	63.4 (14.2)	69.2 (12.2)	< 0.001
	Median (range)	70 (20-90)	60 (20-90)	70 (50-90)	
	AKPS < 70%	215 (50%)	174 (54%)	41 (37%)	
Phase of palliative care[624]	Stable	217 (58%)	143 (54%)	74 (69%)	0.006
McGill Quality of life[604]	Mean (SD)	6.1 (2.0)	6.0 (2.0)	6.3 (1.9)	0.17

[a] this table represents participants with cancer only
AKPS = Australian – modified Karnofsky Performance Status

The 6% with non-cancer life-limiting illness excluded in this sub-study had predominately cardio-respiratory diseases.

In comparison to the main RCT, baseline entry to the sub-study of health-service utilisation and survival was a mean 62 ± 81 days (median 37, range 1–591) before death (survival). The mean time from last the assessment until death was 23 days (SD 23 days; median 16 days; range 1–241 days), and the assessment before this was a mean of 29 days earlier (SD 22; median 25). The mean length of follow-up after the first assessment was 109 days (SD 124, range 1–159). The mean number of study assessments between referral and death was 4.8 per participant (SD 4.18, median 3, range 1–24).

The participant flow for the larger RCT, and how this sub-group was derived, was shown previously in Figure 2. There were 434 participants with cancer out of the 461 participants (94% of sample). Out of the 304 participants with a known date of death, 112 participants met all four criteria of diagnosis of cancer, AKPS score at initial assessment of 60 or greater, and an AKPS score that fell to less than 60 at some time-point.

4.6.4.1 Total anticholinergic score as death approaches

Figure 3 shows the mean total anticholinergic score over the four time periods. Although there appears to be a slight increase as death approaches, analysis using a clustered gamma-log model showed no statistically significant variation in total anticholinergic score over the four time categories ($p = 0.21$). The model had adequate power to detect a difference of 23% between the highest and lowest total anticholinergic scores. The smallest amount of change in total anticholinergic score that would still be clinically relevant has not yet been defined, so the clinical relevance of the differences between groups is awaited.

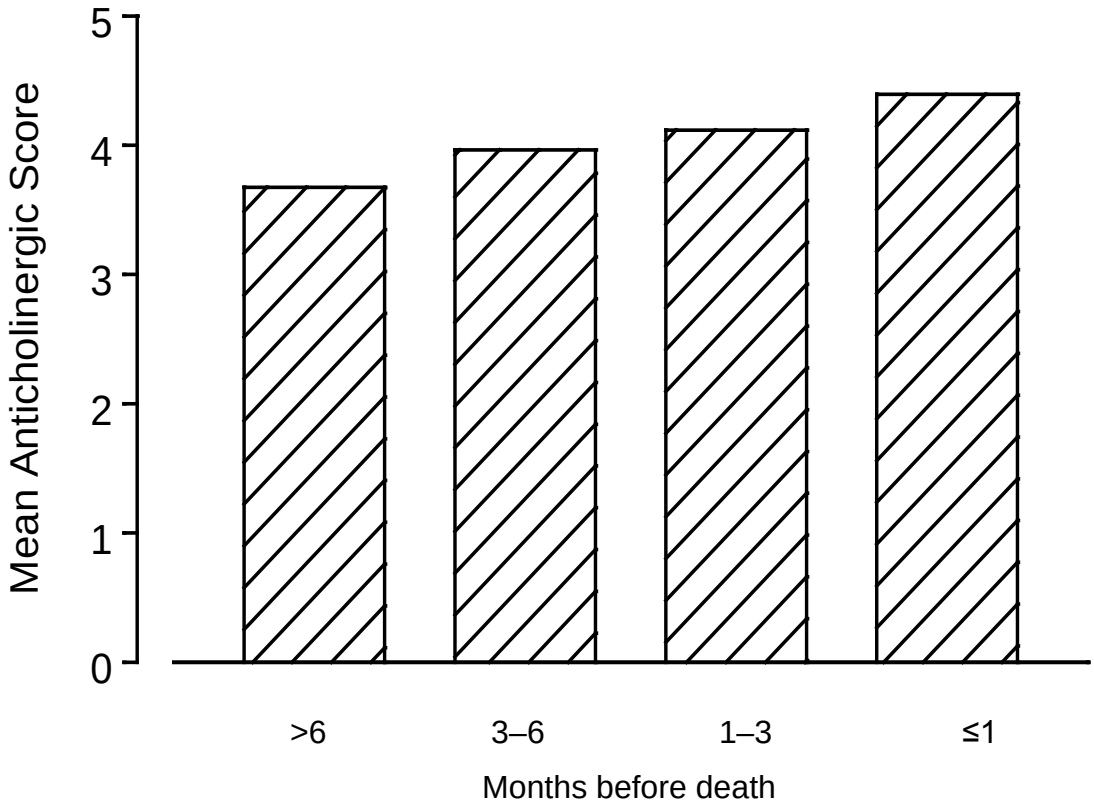
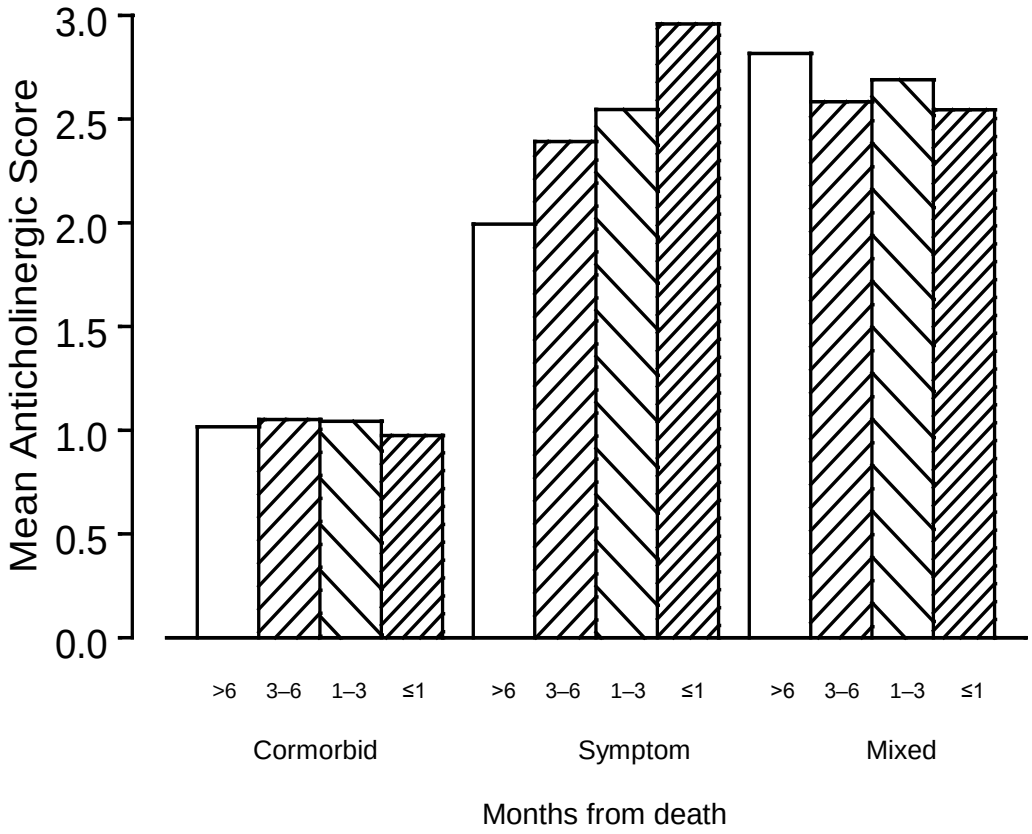


Figure 3 Mean total calculated anticholinergic score at time-points leading to death

4.6.4.2 Total anticholinergic score classified by 'reason for prescription' as death approaches

When analysed in terms of the contribution of different drug classes, there was a significant ($p < 0.001$) difference in time trends among classes. The total anticholinergic score due to comorbid and mixed 'reason for prescription' categories remained relatively constant over time, while load due to symptom-specific medications increased as death approached (Figure 4).



Mean anticholinergic score = Mean total calculated anticholinergic score; Comorbid = medications for comorbid disease; Symptom = symptom specific medication; Mixed = medication for both comorbid disease and symptoms

Figure 4 Mean total calculated anticholinergic score by three categories of prescribed medications at time-points leading to death

The contributions of the symptom-specific category and medications for comorbid disease to anticholinergic load at the time of the last assessment are listed in rank order in Tables 33 and 34.

Table 33 Contribution of symptom specific drugs to anticholinergic load at last assessment[a]

Medication	Anticholinergic contribution	Clinician rated anticholinergic score – modified version
Oxycodone (immediate and slow release)	220	1
Morphine (all routes)	214	1
Dexamethasone	142	1
Temazepam	72	1
Fentanyl	65	1
Clonazepam	48	1
Hyoscine butylbromide	30	3
Paracetamol codeine	27	2

Table 34 Contribution of medication for comorbid disease to anticholinergic load at last assessment[a]

Medication	Anticholinergic contribution	Clinician rated anticholinergic score – modified version	Clinical implication (Possible substitution of agent with no anticholinergic effects or cessation)
Frusemide	66	1	Cessation may be possible dependent on clinical indication.
Ranitidine	62	2	Substitution with proton pump inhibitor may be possible depending on indication
Prednisolone	27	1	Consider minimum effective dose and/or cessation.
Warfarin	22	1	Low molecular weight heparin
Digoxin	20	1	Alternative agent for rate/rhythm control control or cessation (amiodarone, beta blocker)
Sertraline	11	1	Regular review of efficacy for depression and attention to non-pharmacological strategies.
Diltiazem	7	1	Cessation may be possible dependent on clinical indication.

[a] The table is presented in rank order of anticholinergic contribution (from highest to lowest) = number of patients receiving medication x anticholinergic score of the medication

4.6.4.3 Association of total anticholinergic score with Australia – modified Karnofsky Performance Scale and quality of life

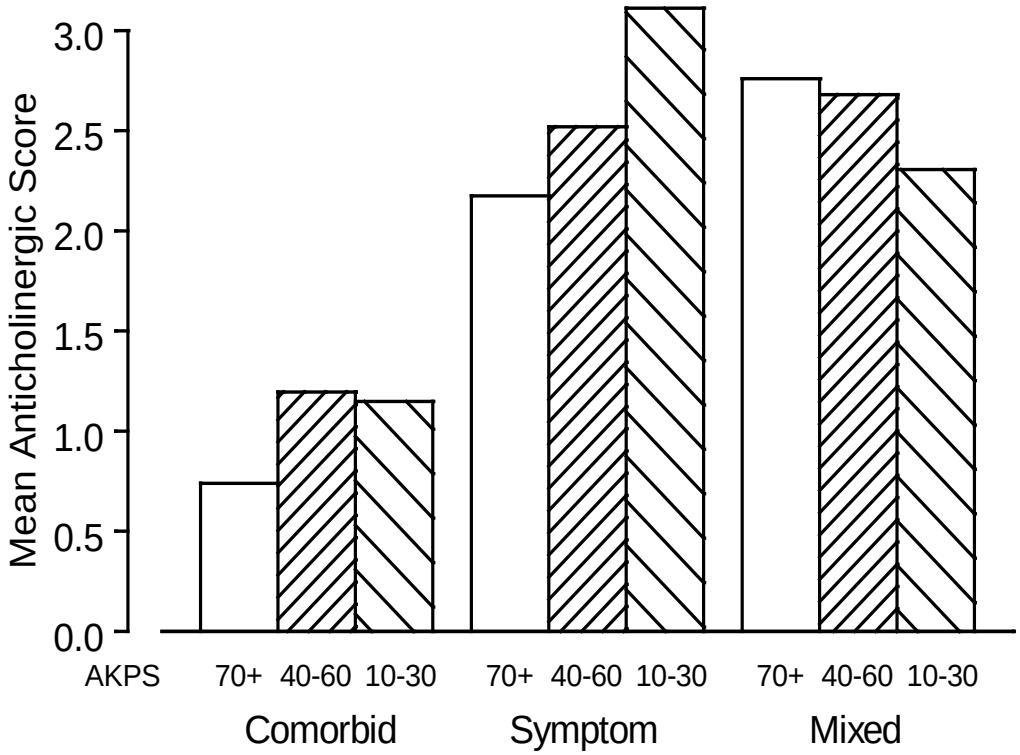
Table 35 illustrates that there were significant inverse associations between the total anticholinergic score and the AKPS after adjustment for time before death (OR 0.85, CI 0.81–0.90, per unit of total anticholinergic score) and quality of life (OR 0.90, CI 0.85–0.95). An increase in total anticholinergic load of one unit is associated with an increase in the odds of being in a lower AKPS category by a factor of 1.18 (CI 1.11–1.23), after adjustment for time before death.

Table 35 Associations with total anticholinergic load: functional status, quality of life and symptoms

Side-effect	Adjusted OR per unit of anticholinergic score (CI)
Australian modified Karnofsky performance status	0.85 (0.81 to 0.90)[a]
Quality of life	0.90 (0.85 to 0.95)[a]
Weight loss	0.99 (0.93 to 1.06)
Anorexia	0.97 (0.91 to 1.03)
Dry mouth	1.11 (1.03 to 1.20)[a]
Constipation	1.05 (0.98 to 1.12)
Difficulty concentrating	1.22 (1.12 to 1.33)[a]
Confusion	1.09 (0.98 to 1.21)
Hallucinations	1.12 (0.92 to 1.35)

CI – 95% Confidence Interval OR – odds ratio
[a] Statistically significant

Figure 5 shows that the total anticholinergic load due to comorbid and mixed drug 'reason for prescription' categories were not significantly different when compared between participants in the different AKPS score categories; however, anticholinergic load due to symptom specific medications was higher in the groups with lower AKPS scores.



Comorbid = medications for comorbid disease; Symptom = symptom specific medication; Mixed = medication for both comorbid disease and symptoms

Figure 5 Associations with mean anticholinergic load and functional status by three categories of prescribed medications

4.6.4.4 Total anticholinergic score and symptoms

The total anticholinergic load was significantly associated with difficulty in concentrating (OR 1.22, CI 1.12–1.33) and dry mouth (OR 1.11, CI 1.03–1.20, per unit of anticholinergic score). Total anticholinergic load was not significantly associated with weight loss, anorexia, constipation, confusion, or hallucinations (all $p > 0.05$) after adjustment for time before death.

4.6.4.5 Baseline Australia-modified Karnofsky Performance Scale and total anticholinergic score at first visit

Table 36 shows the distribution of AKPS at the initial assessment (enrolment in study) and anticholinergic score at the baseline time-point for this sub-study (defined as the first visit at which the AKPS score was below 60).

Table 36 Baseline total anticholinergic score and Australian-modified Karnofsky Performance Status at first visit where status was less than 60

	Score	n	Percentage (%)
AKPS	10	5	4.5
	20	8	7.1
	30	9	8.0
	40	16	14.3
	50	74	66.1
Total anticholinergic score	0–2	32	28.6
	3–5	47	42.0
	6–9	33	29.5

AKPS – Australia – modified Kamofsky Performance Scale

4.6.4.6 Association between health-service utilisation and total anticholinergic scores

Patients spent a mean of 22% (range 0–100%) of their time as an inpatient. The distribution of total length of stay is shown in Figure 6.

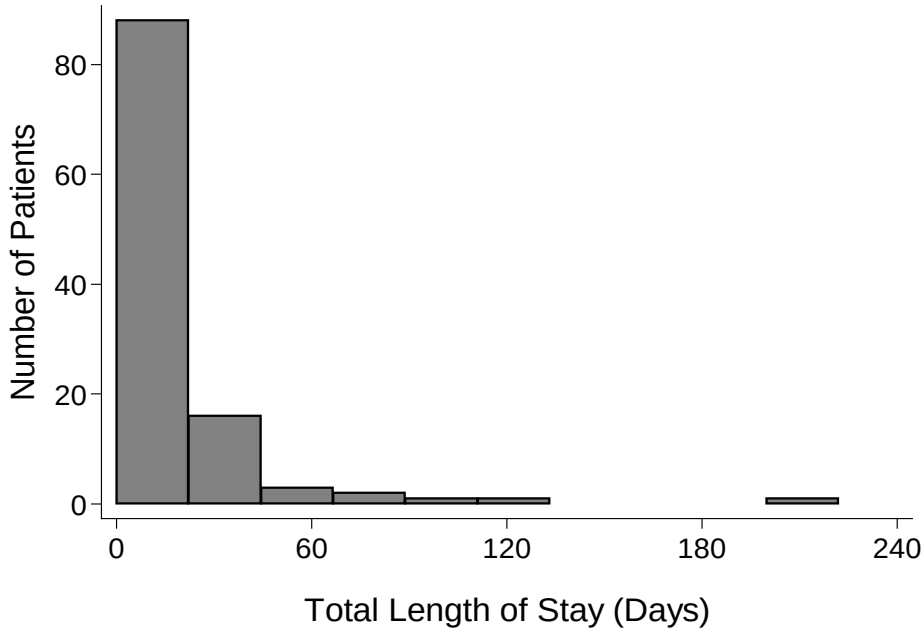


Figure 6 Distribution of total length of inpatient stays[a] (n = 112)

[a] 51/112 participants had no inpatient stay

Analysis using an unadjusted log-gamma model (scaled for survival time) did not show a significant association between total anticholinergic score and time spent as an inpatient (p = 0.94) (Figure 7).

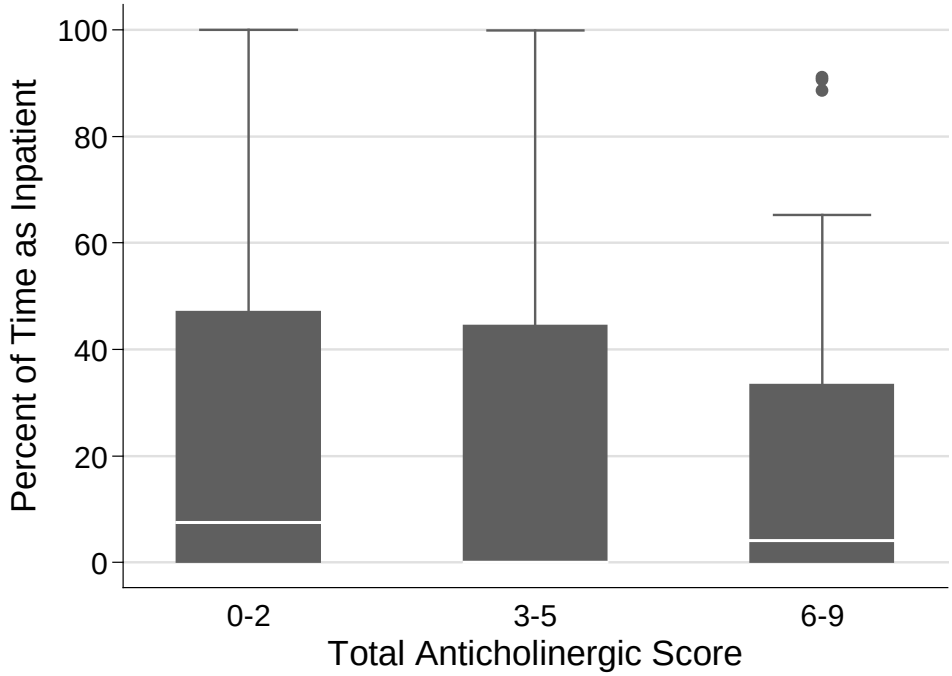


Figure 7 Association between health-service utilisation (n = 112 participants)

4.6.4.7 Survival times

The mean survival time for the 112 participants was 8.9 weeks (SD 11.6, median 5.3, range 0.2–84.4).

Association of total anticholinergic score with survival: Figure 8 presents a Kaplan-Meier plot showing survival for the three categories of total anticholinergic scores. A log-rank test demonstrated there was no evidence that survival differed between the three groups. The median survival times were approximately five weeks in each group.

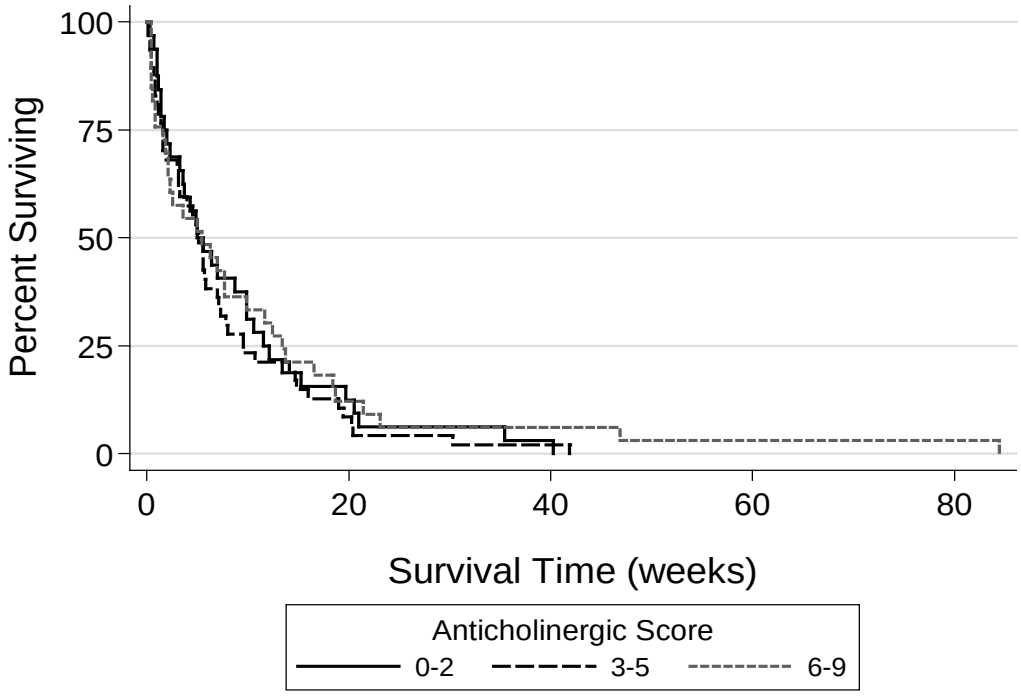


Figure 8 Kaplan-Meier plot showing survival for the three categories of total anticholinergic score

4.7 Discussion

Prior studies in palliative care populations demonstrate that the number of medications used in the palliative care population is high[537] [538], and more importantly, the total number of medications prescribed increases due to the addition of medications aimed to control disease-related symptoms.[537] At the same time, as diseases progress a slight reduction in medications prescribed for comorbid disease is seen; however, this occurs very late in the illness trajectory, and doesn't balance out the increase in symptom medications.[537]

4.7.1 New findings from this study

This study has mapped longitudinally over time the anticholinergic burden associated with medications used in a palliative care population from the time of referral to an Australian specialist palliative care service until death. These data demonstrate that the biggest contributor to anticholinergic load in a palliative care population is from symptom-specific medications. Higher anticholinergic load was associated with proximity to death and lower performance status.

Performance status and quality of life as measured by AKPS and MQOL decreased after adjusting for time from death, as the total anticholinergic load increased. This association does not demonstrate causality; however, it is of concern that the anticholinergic load is associated with worsening function and quality of life independent of prognosis. There are several hypotheses that could explain this finding. First, increasing the anticholinergic load may directly worsen symptoms and function by means of an anticholinergic effect at a level substantial enough to account for these findings. This may be mediated by cognitive changes that would require more detailed cognitive and neuropsychological testing to detect. Second, it is possible that people who are less well, either from their primary life-limiting illness or due to several comorbidities or intercurrent illnesses, have more symptoms or symptoms which are more severe and require more medications in order to optimise their symptom control and/or function, which leads to a higher anticholinergic score mediated by the addition of symptom-specific medications. A third explanation is that increasing anticholinergic load may contribute directly to worsening symptoms; which then leads to a prescribing cascade with the addition of medications to control the medication side effects which are clinically interpreted as new or worsening symptoms, thus increasing anticholinergic load further, and so on. This is compounded by the clinical difficulties in the palliative population of separating the effects of one or multiple medications, in the context of multiple, fluctuating and often complex symptoms due to advanced illness and multiple comorbidities. It may be possible that specific medications are more prone to anticholinergic effects, adverse effects only occur in patients with a particular life-limiting illness or comorbidity clearance is delayed, endogenous anticholinergic substances[625 626] accentuate the effect, and/or endogenous anticholinergic substances are generated in higher frequency in certain diseases. It also is not known whether the burden of numerous medications itself (both number and frequency) has an impact on quality of life.

In the CRAS - M utilised in this study, opioids contribute to the anticholinergic load with codeine alone, paracetamol – codeine combinations, topical fentanyl, morphine, oxycodone, and methadone all having a score of 1. Interestingly, hydromorphone and buprenorphine have a score of 0; it may be that specific

clinical or laboratory studies to confirm AA have yet to be conducted, as they are newer opioid agents (the current lists of AA is based on earlier published data, and clinician opinion). Corticosteroids and benzodiazepines also contribute with dexamethasone, prednisolone, prednisone, diazepam, lorazepam, clonazepam, temazepam, midazolam, and oxazepam all having scores of 1. In this patient cohort the number on only non-opioid medications with anticholinergic action were too few to further separate or to differentiate opioid versus non-opioid anticholinergic effects.

The total anticholinergic load was significantly associated with difficulty in concentrating and dry mouth, both symptoms which could be mediated by anticholinergic pathways. However, total anticholinergic load was not significantly associated with weight loss, anorexia, constipation, confusion, or hallucinations after adjustment for time before death.

No association was demonstrated between anticholinergic load and changes in survival or health-service utilisation measured as time as an inpatient (both in a specialist inpatient palliative care unit or acute care hospital) in the population referred to a specialist palliative service with advanced cancer.

It is also important to note that for the medications where anticholinergic pathways are not the sole mechanism of action, associations with quality of life and function may be mediated by non-anticholinergic pathways. There were not enough participants on opioids scoring 1 nor scoring 0 to undertake a separate comparison.

4.7.2 What other data do these findings support or refute?

Several other studies have explored the clinical adverse outcomes of anticholinergic medications. Anticholinergic medications have been associated with risk of falls, reduced functional status, and impaired motor performance, mainly in ambulatory patients in the community over the age of 65.[239 250 276 589-591] There is also a link with poor cognitive outcomes, especially in the group with existing cognitive impairment.[239 269 277 591-596] A recent systematic review of 27 studies that systematically measured AA (SAA assay or clinician-rated list of drugs with known anticholinergic effects) correlating it with standardised

measures of cognitive performance (acute effects on cognition (delirium), mild cognitive impairment (MCI) or dementia), demonstrated a negative impact on cognition.[195] This review included cross sectional, case control, retrospective or prospective cohort studies, and 17 utilised serum anticholinergic assay to determine AA. There have only been a few studies that have explored the long-term effect over a 12-month duration. These studies are explored in more detail below.

4.7.2.1 Association with physical and cognitive function impairments

In a cross-sectional study of 932 moderately to severely disabled women (self-reported disability in self-care, function or complex tasks) residing in the community, aged 65 years and over, anticholinergic drug burden was independently associated with greater difficulty in several measures of physical function, after adjustment for age, education and comorbidities.[591] Medications that were listed in *Mosby's Drug Consult* as having anticholinergic effects were included in the calculation of anticholinergic drug burden—with 22 categories of medications with anticholinergic action.[627] A dose response model (utilising recommended dose regimen, actual dose and frequency of drug taken) was used to calculate drug load. Using this method, drug load equalled the daily dose divided by the sum of daily dose and minimum recommended daily dose. The individual drug loads were summated to provide total drug burden.[591] This method included some medications not traditionally labelled as anticholinergic, and assumed anticholinergic drug burden is simply additive, and not related in some other way. The adjusted ORs were 4.9 (2.0–12.0) for balance difficulty; 4.2 (2.0–8.7) for chair stands difficulty; 3.6 (1.6–8.0) for slow gait; 3.4 (1.7–6.9) for difficulty in ADL; 3.2 (1.5–6.9) for mobility difficulty; 2.7 (1.3–5.4) for upper extremity limitations; 2.4 (1.1–5.3) for weak grip strength; and 2.4 (CI, 1.1–5.1) for poor performance on the MMSE.[591] In this study 11.6% of participants had cancer, 10% had cardiac failure; and 28.4% had pulmonary disease. The most frequently used medications with anticholinergic properties in this study were antihistamines and tricyclic antidepressants.[591] The cross-sectional design also limited the ability to determine cause and effect relationships or the contribution of exposure over time. The ability to apply these findings to a palliative care population is limited by the heterogeneity of comorbid illness, and the lack of assessment of severity of

illness to determine those with advanced disease and no measure of global functional status, and hence a palliative diagnosis.

Another study of well-functioning community-dwelling elderly (n = 3075) showed use of anticholinergic medications was associated with poorer physical performance score (Health ABC performance score) (2.08 vs 2.21, $p < .001$) and cognitive performance on the Digit Symbol Substitution Test (anticholinergic exposure, 34.5 vs 35.5, $p = .045$), after adjustment for socio-demographic factors and comorbidities.[239] These differences are clinically meaningful, as the physical performance score differences are similar in magnitude to differences seen in individuals with or without diabetes mellitus; and differences of this magnitude have predictive nursing home admission, disability and mortality[239]. Similarly, this study classed anticholinergic medications based on listing in *Mosby's Drug Consult*. This study focused on high-functioning community-dwelling adults, with a mean number of comorbidities of two, hence generalisability to a more medically unwell (and potentially younger) palliative population is not known.[239]

The Eugeria Longitudinal study of cognitive ageing recruited 372 participants in southern France aged over 60 years without baseline cognitive deficits, from 63 randomly selected general practices.[628] This study demonstrated 9.2% of participants continuously used anticholinergic medications for the year prior to the cognitive assessment undertaken in the study.[628] Medications with known AA measured by SAA, was supplemented by a review of each participants' records by a pharmacologist, physician and biologist in order to classify each medication from 0 (no anticholinergic drugs used), 1 (drugs used with no likely effect), 2 (drugs with low effect), and 3 (drugs used with high effect).[628] It is not clear whether this process developed an identical list and scoring to the CRAS-M, developed by a similar process. Computerised neuro-psychometric examinations were performed annually to assess primary memory, verbal and visuo-spatial secondary memory, language skills (word and syntax comprehension, naming, verbal fluency), visuo-spatial performance (ideational, ideo-motor and constructive apraxia), functional and semantic categorisation of visual data (visual reasoning and form perception), and focused and divided attention (visual and auditory modalities.[628] A neurologist also carried out a standardised neurological examination for the DSM-III-R) criteria for neuropsychiatric disorders, without

knowledge of the cognitive testing (which was also conducted eight years later). Of the 372 participants, 51 (14%) were taking at least one medication with AA at the start of the study.[628] The study found an increased risk of MCI at the one-year follow-up based on criteria established by the Stockholm consensus group.[629] The participants who used anticholinergic drugs had significantly poorer performance on psychomotor speed, primary and secondary visuo-spatial memory, narrative recall, and visuo-spatial construction, after adjustment for other risk factors for cognitive impairment (age, gender, education, untreated depression and treated hypertension) than non-users.[628] These deficits are similar to those found in young adults if administered scopolamine.[628] No significant difference for implicit memory or logical reasoning ability was found. At the eight-years follow-up there was not an increased risk in the diagnosis of dementia (DSM-III) between consistent users of anticholinergic (16%) and nonusers (14%), so it is not clear if there is long-term impact of these changes.

The Australian Imaging, Biomarkers and Lifestyle (AIBL) study of ageing is a multidisciplinary longitudinal study of aging, exploring neuroimaging, biomarkers, clinical, and neuropsychological research. Participants in this study were over 60 years, fluent in English, on stable medication (e.g. controlled hypertension). This study included three cohorts: 211 people with AD, 133 people with MCI and 768 healthy controls (HC).[630] The association between anticholinergic load and cognitive function was examined for each diagnostic group (AD, MCI, HC). The AIBL cognitive battery includes the California Verbal Learning Test, 2nd edition (CVLT-II) and logical memory I and II (story A) to evaluate memory and learning; the CogState computerised battery (www.cogstate.com), digit symbol coding and digit span-WAIS III for working memory, attention/concentration and processing speed; the Delis-Kaplan Executive Function System for letter fluency, category fluency and category switching; the 30-item Boston Naming Test for language skills; and the Rey Complex Figure and the Stroop (Victorian version) to measure visuo-spatial capacity and executive functioning.[630] The MMSE was also employed as a global cognitive task. Clinical diagnostic allocation was determined by a clinical panel who reviewed these cognitive tests.[630] Anticholinergic load was calculated by combining the clinician-rated scores and SAA for specific medications used in

prior studies (including the Eugeria longitudinal study).[628 631] The medication usage was calculated at baseline and, of the participants taking medication, 27.7% were taking medications with anticholinergic action. In the HC group a high anticholinergic load was only associated with significantly slower response speeds for the Stroop color and incongruent trials.[630] This study, contrary to others, demonstrated only modest effects of anticholinergic drugs on psychomotor speed and executive function, but not on other areas of cognition in healthy older adults. No significant associations were observed between anticholinergic load and cognitive measures in the MCI and AD groups ($p > 0.05$). The authors thought this could potentially be due to co-treatment with cholinesterase inhibitors in this group, and because the measurement of subtle changes was confounded by the pre-existing cognitive deficits in this group.[630]

4.7.2.2 Associations when anticholinergic load is considered in conjunction with sedative medication

When anticholinergic and sedative medications are considered in combination, utilising the DBI, association with the risk of falls in residential aged care is seen.[632 633] However, it is not possible to determine whether this is mediated by the anticholinergic medication alone.[632 633]

A study exploring fall rates in residential aged care followed a cohort of residents aged over 70 years, who were still ambulant and had a prognosis for dying thought to be over 12 months.[633] After adjusting for age, gender, history of falling, cognitive impairment, depression, use of a walking aid, comorbidities, polypharmacy, and incontinence, the incident rate ratio for falls was 1.61 (CI = 1.17–2.23) for residents with low DBI and 1.90 (CI = 1.30–2.78) for those with a high DBI.

4.7.2.3 Association with self-reported symptoms

The association with difficulty concentrating and dry mouth is consistent with the known effects of medications with anticholinergic action.[239 582 591 592] A study of cognitively intact community-dwelling patients over 65 years (n = 532) demonstrates anticholinergic use in 27% of participants (classified by the anticholinergic medications included in the modified Beers criteria and also a geriatric pharmacology reference text[634]), with a prevalence of self-reported

symptoms of dry mouth and constipation (on the elderly symptom assessment scale) significantly higher in the group utilising anticholinergic drugs. However, it found no association with self-reported confusion.[582] It should be noted that not all patients would have insight or awareness of cognitive issues to self-report, so under-reporting of confusion was likely to have occurred. It is interesting that no association with patient self-report of constipation was found in this study, as this is a commonly listed adverse effect of medications with anticholinergic action.

A more recent study demonstrates that the total anticholinergic score, utilising the same method as my current study, was significantly associated with the prescription of a single laxative (OR 1.4, CI 1.0–2.0) and two or more laxatives (OR 1.8, CI 1.3–2.5) for each unit increase in anticholinergic score.[635] Multiple ordinal logistic regressions showed prescription of one laxative was significantly associated with oral morphine-equivalent dose, total anticholinergic load (OR 1.4, CI = 1.0–2.0), disease progression to terminal phase and death (OR 0.1, CI = 0.0–0.3), and length of time in a palliative care phase.[635] (OR 1.1, CI = 1.0–1.2).

Although no association was found with self-reported confusion or hallucinations, without a formal delirium assessment it is not possible to determine the association with incident delirium. It is also possible that more subtle cognitive deficits detected in other studies were missed, due to lack of comprehensive cognitive testing.[582 591 592]

4.7.2.4 Association with delirium

A study of medical inpatients 65 years and older (n = 278) with a diagnosed incident or prevalent delirium and a range of underlying illnesses showed an increase in delirium severity was significantly associated with anticholinergic medication exposure (CRAS-M) on the previous day, adjusting for dementia, baseline delirium severity, length of follow-up, and number of medications rated as not having anticholinergic load.[247] The common agents included in the most frequently used anticholinergic medication listing in this delirium cohort[247] (which was also found in this study, refer to Table 3) were morphine, fentanyl, and codeine. Interestingly, in this current study the benzodiazepines commonly contributing were clonazepam and temazepam, whereas in the Han et al. delirium cohort it was diazepam.[247] This study did not undertake to analyse opioids,

benzodiazepines separately, without counting them as contributing to anticholinergic load. This is important as it is not known the degree of contribution of the anticholinergic effects of opioids and benzodiazepines in comparison to their action on other neurotransmitter pathways (e.g. GABA, opioid receptors) which are the psychoactive effects likely to be predominate.

These data suggest that reduction of anticholinergic load is a potentially modifiable precipitating factor of delirium, in some clinical situations. This is of crucial importance in palliative care patients who have incident and prevalent delirium rates as high as 40%.[95] In prior studies of hospitalised cancer patients' exposure to opioids (in particular over 90mg SC morphine equivalent per 24 hours), corticosteroids (over 15mg dexamethasone equivalent per 24 hours) and benzodiazepines (over 2mg oral lorazepam equivalent per 24 hours) increased the longitudinal risk of delirium.[182 183] In the clinical context, these doses are high for all three classes of drug, and the need for larger doses may be in the patient cohort with more complex symptoms and potentially more unstable or complex health status. These studies also explored medications with anticholinergic action and did not find an association; however, they included only a limited number of medications in the list deemed to have anticholinergic effects.[182 183] Interestingly this study did not include benzodiazepines and opioids as medications with anticholinergic effect supporting that the mechanism by which the mediate derlirium risk is predominantly via other neurotransmitter pathways. It is also possible that the opioid, benzodiazepine and corticosteroid contributions to delirium occurrence are partly mediated by their AA.

4.7.2.5 Association with health-service utilisation and mortality

Despite repeated studies demonstrating the prevalence of high-risk prescribing in the elderly, it has been more difficult to establish clear relationships between inappropriate prescribing and increased health-service utilisation or increased mortality. Some studies looking at high-risk medications in the older person have demonstrated poor outcomes (increased hospitalisation, increased length of stay, adverse drug reactions, risk of institutionalisation, mortality) but others have not.[541 554 569 570 577-579]

The 1996 national survey of the non-institutionalised US population, which annually obtains household and medical provider data from computer assisted in-person interviews, was utilised to explore the group who were both 65 years and over and taking psychotropic medications to examine their prevalence, correlates and associated healthcare outcomes.[553] The types of potentially inappropriate psychotropic medications in this population were antidepressants (amitriptyline, doxepin, and use of tricyclic antidepressants in people with arrhythmias), which were present in 25% of the cohort, or anti-anxiety or sedative/hypnotics, which occurred in 17% of cases.[553] The healthcare utilisation outcomes of interest were the total annual number of outpatient visits, all hospital-based discharges, all emergency department visits and home health days (days during the year that involved home healthcare services).[553] Regression analysis showed that the use of potentially inappropriate psychotropic medications after controlling for age, gender, race, education, region, income, insurance, general and mental health status (predisposing, enabling and need factors for healthcare utilisation) was not associated with differences in healthcare utilisation.[553] The limitations of this study are the cross sectional determination of medication usage, which does not address dose response relationships, and also that it did not explore more specific health outcomes such as falls or fracture.[553]

A study which undertook a secondary analysis of participants from the 'Duke Established populations for epidemiologic studies in the elderly (Duke EPESE[m])' (n = 3165) showed an association with inappropriate medications according to Beers criteria (after adjusting for three categories of confounding variables, namely socio-demographic, health status and access to healthcare) with reduced time to hospitalisation (adjusted HR 1.2, CI 1.04–139); but not with outpatient visits of nursing home placement.[578] When the analysis was repeated utilising drugs identified as inappropriate by an alternative method, particularly focusing on drug – drug and drug – disease interactions by drug utilisation review, only an association with increased outpatient visits demonstrated.[578]

[m] Duke EPESE study aims to describe and identify predictors of mortality, hospitalization, and placement in long-term care facilities, and study risk factors for chronic diseases and loss of functioning.

Another study explored the impact of inappropriate drug use in patients who were already hospitalised (n = 5152).[579] This study utilised the revised 2002 Beers criteria, with 28.6% of the study population receiving one or more inappropriate drugs. After adjusting for potential confounders (age, gender, cognitive impairment, ADL disability, CCI, ischaemic heart disease, congestive heart failure, hypertension, diabetes, cerebrovascular disease, chronic obstructive pulmonary disease, liver disease, number of drugs used during hospital stay, and year of survey), the use of inappropriate drugs was not associated significantly with mortality (OR 1.05; CI: 0.75–1.48), adverse drug reactions during hospital stay (defined by the study physician utilising the Naranjo algorithm (OR 1.20; CI: 0.89–1.61), or length of stay 13 days or more (highest tertile) (OR 1.09; CI: 0.95–1.25).[579] There have been other studies with equally conflicting results.[554 569 576 636]

A recently completed two-year longitudinal study (Medical Research Council (MRC) Cognitive functioning and ageing study)[637] of 1304 participants over the age of 65 years explored decline in cognition measured by decline in MMSE at two years. In this study medications with anticholinergic action were quantified using the ACB scale.[251] The ACB was developed from a Medline database, including studies from 1966 to 2007 that measured the AA of a medication and evaluated the association with cognitive function in older adults.[251] These studies were utilised to determine a list of medications with anticholinergic activities that were associated with negative cognitive effects, including delirium, MCI, dementia or cognitive decline. This list was examined by an expert interdisciplinary team that included geriatricians, geriatric pharmacists, geriatric psychiatrists, general physicians, geriatric nurses and aging-brain researchers who categorised the medications into three classes of mild, moderate and severe cognitive anticholinergic negative effects.[251] Medications with possible anticholinergic effects (as demonstrated by SAA or the *in vitro* affinity to muscarinic receptors but with no clinically relevant negative cognitive effects) were given a score of 1; medications with established and clinically relevant cognitive anticholinergic effects were given a score of either 2 or 3 (based on the drug blood-brain barrier permeability and its association with the development of delirium); and all other drugs with no anticholinergic effects had a score of zero. These scores were added for the different drugs taken by the patient to calculate

the accumulative ACB.[251] The ACB differs from the CRAS-M utilised in my current study with the ACB only listing medications with identified cognitive effects, so may underestimate other anticholinergic effects.[251]

In the MRC study, 47% of the participants were taking a medication with possible anticholinergic properties, and 4% a medication with definite anticholinergic effects, as classified by ACB.[637] The MRC study demonstrated that the use of medications with definite anticholinergic effects at baseline based on the ACB was associated with a 0.33 greater decline in MMSE score at two years (CI 0.03–0.64, $p = 0.03$) than when not taking anticholinergic medications (after adjusting for age, gender, education level, social class, number of non-anticholinergic medications, number of comorbid health conditions, and cognitive performance at baseline).[637] The mortality at two years was greater for those taking definite (OR = 1.68; CI = 1.30–2.16; $p < 0.001$) and possible (OR = 1.56; CI = 1.36–1.79; $p < 0.001$) anticholinergic medications.[637] Mortality information was derived from the UK Office of National Statistics National Health Service Central Register, in which the study participants had been flagged.[637] The strengths of this study are its large sample size, detailed assessment of medications, and comprehensive socio-demographic factor documentation, health related factors documentation and cognitive assessment, which allowed the potential confounding variables to be considered in the analysis. Its limitations are that the medications with anticholinergic actions were taken at baseline, and it is unknown if participants continued to take these over the two-year period. Analysis of the ACB in 6685 participants showed that ACB scores were stable over that time, with 21% who weren't taking anticholinergics at baseline subsequently utilising one, and 17% were no longer using one.[637] This study also could not address dosing, nor duration of use.[637]

The Drugs and Evidence-based Medicine in the Elderly study followed 400 community-dwelling older people aged between 75 and 90 years with stable cardiovascular disease.[638] The cohort was classified as taking medication with anticholinergic properties (n = 295) or not (n = 105) utilising a list of 31 potential medications with anticholinergic properties. Taking medications with anticholinergic properties was not a significant predictor of mortality after adjustment for age, gender and CCI. The mean number of hospital days was

higher in the group taking medications with anticholinergic properties (14.9 ± 32.5) compared with those who were not (5.2 ± 12.3) ($p < 0.001$).[638]

A study in residential aged care in Finland explored the prevalence and determinants of anticholinergic medication use, and the association with mortality.[639] The ARS, a ranked categorical list of commonly prescribed medications with anticholinergic potential, was used to determined anticholinergic medication use.[250] Among the 1004 residents recruited to the study from 53 facilities, 455 (45%) were non-users of anticholinergic drugs, 363 (36%) had a mild anticholinergic load, and 186 (19%) had a high anticholinergic load.[639] One-year all-cause mortality rates were 28%, 29%, and 27%, respectively. Higher ARS scores were not associated with mortality (ARS score 1–2, HR 1.08; CI 0.84–1.41; ARS score ≥ 3: HR 1.05; CI 0.75–1.46).

Anticholinergic medications can precipitate delirium and intensify pre-existing delirium, another mechanism by which they can mediate adverse outcomes including increased need for health services or mortality.[247 259 266 582-588] An episode of delirium is linked to significant morbidity and mortality, and is associated with increased length of hospital stay, institutionalisation, irreversible functional and cognitive decline, and mortality in the elderly.[190 287-294] My study did not include prevalent delirium, and the occurrence of incident delirium was not formally assessed. It is also unlikely that the study was sufficiently powered to explore survival and hospital length of stay for the incident delirium group separately.

The studies described illustrate the complex contributing factors to health-service utilisation and survival requiring careful definition of covariates, and that the way that the anticholinergic effects of medication may be classified and health-service utilisation is defined or collected (e.g. self-report vs database collection) and how these can affect the associations with outcomes seen. Medications with anticholinergic action contributed, often quite substantially, to the inappropriate medication use quantified; however, in most studies were not considered separately in relation to analysis of health-service utilisation or mortality. A recent systematic review identified multiple factors which had a significant influence on length of stay, namely functional status, illness severity, cognitive score, poor

nutrition, comorbidity score, diagnosis or presenting illness, polypharmacy, age and gender.[640]

4.7.3 What are the implications for prescribing?

When making decisions about prescribing, clinicians need to account for medications used intermittently, and complementary and alternative medication use[641], and the contribution of dose and duration of use. These factors also are important when considering the implications of anticholinergic-related medical effects. The number of medications with a documented anticholinergic effect is over 200, which is difficult for a clinician to consider unless specific computerised systems can provide this information or feedback about a particular patients' medication list in real time.[642] For example a cluster randomised study, which utilised the DBI and communicated this to the GP by letter or phone call to prompt reduction or cessation of anticholinergic or sedative medication, had a minimal effect in changing prescribing.[567] This study also presented the data in rank order (refer to Table 3) of anticholinergic contribution, providing the clinician with an indication of the medications contributing at the greatest frequency in their population—similar to the ranking provided by Han et al[247] in providing the most frequently used anticholinergic medications in patients with delirium.

Since this current study was conducted, the ARS has been developed, which follows a similar approach in development to the CRAS-M, allocating 1–3 points depending on anticholinergic effects.[250] Similarly, this scale includes 50 medications which makes it to difficult to rate within the context of each clinical encounter.

Recent discussions highlight that current systems alerting clinicians to the potential risks of a specific medication or group of medications prescribed to an individual patient have two problems. First, sensitivity is not adequate and serious risks remain undetected. Second, there are problems with specificity where the clinician receives so many alerts of less serious risks that they don't take action when serious medication issues occur or could occur.[642] There also has been focus on including patient reporting of adverse events to increase capture of events and to understand the actual impact on quality of life of these events.[643 644]

Equally, the clinician is still faced with the dilemma of choosing an efficacious medication for the symptom or condition the patient is experiencing, and needs to have alternative medication choices, or in most cases will still need to prescribe the high-risk medication. In the palliative population complex symptoms may continue to require prescribing of high risk or so called 'inappropriate' medications. This highlights the need to consider the degree that a medication is 'avoidable' or 'unavoidable' after considering efficacy, risk and alternatives. Specific mechanisms to assist a clinician classify or attribute the chance of a particular observed symptom to the medication are also helpful, such as utilising the Naranjo algorithm.[645]

Research to date also has not explored whether the underuse of medications for appropriate indications has an association with poorer outcomes. Clinicians are asked to focus on inappropriate prescribing and are often audited or monitored for this, which possibly may lead to hesitation in prescribing even in appropriate situations. The clinician may take an approach predominantly focused on reducing or minimising medications purely in terms of the absolute number of medications, without critically thinking about the specific clinical situations that a certain medication (despite having a particular high-risk-to-benefit ratio) may lead to an improvement of outcomes. Utilising 'potential' risk of a medication being appropriate, may differ from the actual risk in any given individual, and also does not account for the potential benefit that a medication offers for the condition for which it is prescribed.

The population of people with advanced cancer, and other progressive life-limiting illnesses, may differ to aged care populations in age (with at least one third of the palliative population being under 65 years), more marked cachexia[646] (although levels of sarcopaenia may be similar), and hence may have different susceptibilities to long-term treatment-related effects. Similiarities include polypharmacy[537 538], comorbidities and progressive functional impairment. Hence when considering generalisability, the palliative population is one with advanced medical illness, which may include a proportion of the elderly population, but is not exclusive to it. Equally, the studies in the ambulant community-dwelling elderly, which dominate our understanding of outcomes of medications with

anticholinergic properties, may not be entirely applicable to the palliative population.

4.7.4 Strengths of this study

Unlike many other studies that have looked at anticholinergic load[8,18,19], my current study reports changes longitudinally over a clinically meaningful period of time rather than at a single time-point. These data were also prospectively collected at the point of care. Separating medications into those needed for symptom control and comorbid disease provides some initial data to aid clinical decisions, in particular consideration of reducing baseline anticholinergic load by substitution or cessation of medication for comorbid disease depending on the current indication. This study has also provided the rank order of anticholinergic contribution, to allow clinicians to understand the medications that contribute in the largest number of patients in the population of interest (refer to Table 3).

4.7.5 Innovations in this analysis

By anchoring the sub-study population using prospectively collected data for the time at which a predetermined threshold of functional status was reached in order to define inclusion, this sub-study allows the analysis of survival in a palliative population despite widely varying times before death at which referral to the specialist service occurs. The threshold use of AKPS of 60 is also clinically relevant as it corresponds to when people start requiring some assistance. This includes the spectrum of people who have earlier stage disease with significant symptoms to those who are in the terminal phase of illness. Referral also is dependent on the services admission criteria, local clinician practice, and service resources or capacity.

By doing this, Kaplan Meier curves can be generated in a population with advanced disease. This is an important evolution in analysis, moving away from death as the only anchor point to standardise palliative care analyses that can be used in palliative care studies. Such a process can be employed with different thresholds of functional status on any prospectively collected data.

4.7.6 Limitations of this study

4.7.6.1 Limitations of the sample

Not everyone with life-limiting cancer is referred to a specialist palliative care service and, in general, people with more complex needs are the people referred.[647] Patients with cognitive impairment were excluded from the study and, as such, the sub-group that may be most vulnerable to anticholinergic effects. Also people with prevalent delirium possibly resulting from high anticholinergic load, would have been excluded from entering the study. Incident delirium also may not have been comprehensively detected due to reliance of self-reported symptom assessment, with confusion or difficulty concentrating being the only cognitive symptoms collected. Such a process fails to meet screening or diagnostic requirements to detect delirium therefore underestimate impacy.

Exclusion of people with delirium or prior cognitive impairment will also impact on the assessment of health-service utilisation and survival in the sub-group with advanced cancer, in particular as delirium in the majority of cases precipitates admission to hospital and is also an independent predictor of survival in palliative populations.[601] Incident delirium following a previously resolved delirium occurs in up to 30% of people with advanced cancer. Resolution of the second episode of delirium is less likely and has poorer outcomes including increased mortality.[88 95]

The main RCT inclusion criteria specified that participants needed to have recent pain, so this sample had an over-representation of patients who had cancer (91%) compared to the usual referral pattern to this service where 15% of people did not have cancer as their life-limiting illness. This means that people in the study were potentially more likely to be on medications for pain (in particular opioids, antidepressants for neuropathic pain (for example amitriptyline) and corticosteroids), which may lead to an estimate of anticholinergic load that does not reflect the whole palliative care population. It was also not possible to do a secondary analysis of a group on non-opioid medications with anticholinergic actions alone due to very small numbers in this category.

The sub-group size used for the secondary analysis of health-service utilisation and survival in the advanced cancer patients only was small, and hence was exploratory in nature. It was not adequately powered to detect differences in

health-service utilisation or survival, but of note, the trends seen make it unlikely that any difference found in a much larger study are likely to be clinically significant. It was also not adjusted for the intervention received (case conference, GP educational outreach, patient and caregiver educational outreach). This would not impact on the survival analysis, as the survival was similar in all randomised groups regardless of cohort, with overlapping Kaplan-Meier curves.[599] The log rank tests for equality were p = 0.1824 (case conference vs control), p = 0.04878 (GP education vs control) and p = 0.2672 (patient education vs control).[599] Participants who had a case conference had a significantly reduced number of hospitalisations ('least squares' means hospitalisation per patient of 1.26 vs 1.7 in control, that is, a difference of 0.5 hospitalisations per patient), but no significant associations were seen with GP/patient/caregiver education.[599] However, this sub-study utilised time as an inpatient, rather than purely the number of hospitalisations.

The choice of AKPS as the threshold for the entry to the health-service utilisation and survival analysis was not entirely arbitrary. This choice needed to balance the number of people who would be eligible across the disease trajectory (a very low AKPS) with the longest possible time for follow-up after entry to the study (a high AKPS). As such, crossing the threshold of 60 was chosen as the compromise between these two extremes. The inclusion of only 112 out of 434 participants suggests that almost three out of four people had significant functional impairment at the time of referral to this specialist palliative care service.

4.7.6.2 Limitations of the measures

Medications used intermittently were not included. These may contribute to acute exacerbations of a number of symptoms associated with anticholinergic load including acute delirium.

Defining anticholinergic load requires medication usage data. There were at least four potential sources of this: the prescriber, the dispenser, the patient, or the study nurse who recorded the patient's current medication on each contact. An arbitrary decision was made to use the latter source. Overall, any difference between sources is unlikely to systematically influence the pattern of medications reported in this paper.

The medications for symptom control were not detailed to the level of specific symptom, and hence specific differences in anticholinergic load contribution for pain, dyspnea or nausea control cannot be determined. Equally, medications used for more than one symptom indication could not be separately analysed (for example opioids for pain and dyspnoea).

The benefits of using the CRAS-M[246 247] (see Chapter 1 section 1.11.2) is that it characterises medications based on anticholinergic potency, instead of dichotomously into having AA or not, and includes any medication with AA, not just those most easily identified as having AA.[186] It is a method of classification that could be easily applied into a clinical setting. There are several limitations of the CRAS-M, including lack of dose weighting, assumption of anticholinergic effects being additive (not synergistic or exponential) and linear (that is, one medication with score of 3 is equivalent to three medications each with score of 1). The relative central nervous system effect of an anticholinergic medication allocated the same score on CRAS –M may also vary, as well as the degree of specific interactions with pathways implicated in delirium pathophysiology. Though an assay for SAA exists with the potential of correlating this directly with medications actually taken by the participant, this is not a gold standard measure as the degree of correlation is low.[249] (see Chapter 5).

The measures of side effects that could be attributed to anticholinergic load were collected prospectively. The instruments are, however, not particularly sensitive to detecting early signs of delirium for example, and also do not differentiate side effects due to single or multiple medications. This may therefore underestimate the subjective impact of anticholinergic load experienced by patients, or attribute side effects to medications with anticholinergic action that may be due to an opioid, other psychoactive medication or non-medication aetiology.

There are limitations of using length of inpatient stay(s) as a measure of health-service utilisation. Access to health services also is continually changing, which may also influence hospitalisation rates. For example, the development of medical assessment units, and aged care assessment teams in emergency departments, may increase the number of people who are stabilised and then discharged from emergency departments, whereas in other health services they may actually get

admitted. Combining health-service utilisation from acute care inpatient days and also specialist palliative care bed days, may also influence associations, and future studies should be powered to detect differences in specific types of health-service usage separately. This includes understanding unplanned contact with health services such as out-of-hours general practice calls or visits to the emergency department. Once admitted, the duration of inpatient stay may also be in part related to non-clinical factors such as the availability of community-based services, the care system in place at home, the discharge approaches of the admitting hospital, as well as clinical factors unrelated to medication adverse effects (e.g. the specific care needs of the patient related to their underlying illness).[648] The relevant contribution of these non-clinical factors was not measured in this study, so the influence on inpatient stay is unknown. This study was also not able to capture emergency department presentations without admission, also a substantial health-service usage. Emergency department, outpatient and GP presentations potentially may be needed when a serious medication related adverse effect is first brought to medical attention, and should be included in future studies. However, if in the case of medications causing a serious adverse effect (for example fall and a fracture, delirium), it is reasonable to assume admission would be required for someone with advanced disease, and hospitalisation will capture this.

4.7.7 Generalisability

Specialist palliative care is a referral dependent service, and there is a tendency for patients to have more complex needs than the whole of the population at the end of life.[647] This would potentially over-estimate the effect of anticholinergic load for all people with life-limiting illnesses. This population, because of an inclusion criteria based on prognostication, also excluded participants believed to have a short prognosis, and did not provide direct data on those in the terminal phase of their illness at referral. This could systematically under-estimate the effect on anticholinergic load especially in the terminal stages of a life-limiting illness where data may need to be collected more frequently. With these caveats, the sample is a large cohort derived from a regional palliative care service spanning inpatient, outpatient and community care, reflecting a cohort typical of

many similar services in developed countries with universally subsidised healthcare.

4.7.8 Future directions for research, practice and policy

This study has demonstrated that prescribing patterns in palliative care cannot be ignored, and may have significant implications for function and quality of life. Whether it is possible to reduce the intensity of some of these side effects by decreasing total anticholinergic load and the degree they are solely attributable to anticholinergic effects of medications, requires further study.

Subsequent studies need to first determine the degree of causality for a relationship between anticholinergic load and functional decline and quality of life in prospective studies, independent of other medication effects, physiological variables such as renal and hepatic function, body mass index, the presence of cachexia and illness status. These studies will also need to consider broader categorisation of medication inappropriateness, with the available measures in older people modified to be more suited to palliative populations, as the adverse effects of medications with anticholinergic action may be different when taken in association with other high-risk medications. It is also important to separate out the relative contribution of opioids, and to explore whether type of opioid differentially contributes to outcomes.

This needs to be followed by randomised studies that are adequately powered for specific interventions that both reduce the use of medications of interest and provide alternatives to the clinician to maintain symptom control. Such randomised studies will need to consider, medication classification systems that focus on avoidable prescribing in the palliative population. This will allow study results to more definitively inform mechanisms of clinician feedback of the risk of medications for a particular patient and clinician decision aids relating to safer prescribing. Safer prescribing has the aims to both reduce the inappropriateness or medication use with maintenance of excellent symptom control, utilising approaches which can be integrated and change clinician practice at the point of care.

The term ‘inappropriate medications’ assumes a simple clinician decision to not use these medications in the population at risk. However, in many clinical scenarios cessation, or even dose reduction, may not be possible. This may occur when an alternate agent cannot achieve similar efficacy, the only active agents are from within a same class, or the alternative agents also have similar adverse effect profiles. Hence a better terminology may be to use ‘avoidable’ or ‘unavoidable’, with future systems guiding clinicians on such medications in the context of specific clinical scenarios and evidence base for each therapy.

A range of outcomes needs to be considered, which are broader than just quantifying inappropriate medication use. They should include specific clinical syndromes highly associated with medication adverse effects such as delirium and falls, symptom control of the primary symptoms of the person’s illness, new onset of symptoms and their attribution to medications, survival (adjusted for known prognostic variables in palliative populations), and health-service utilisation (including community, primary care and emergency utilisation, rather than acute care alone).

Chapter 5: Serum anticholinergic activity and delirium in advanced cancer

This chapter outlines a prospective cohort study that explores the relationship of SAA, anticholinergic load of medications, and other clinical and investigational factors. In particular, it explores the correlation of these variables with delirium in the palliative care inpatient population with advanced cancer.

5.1 Pathophysiological abnormalities in delirium

Delirium is a disorder which affects arousal, attention, sleep and cognition; all aspects where central cholinergic transmission is integrally involved.[649 650] The pathophysiology of delirium is complex, with involvement of dopamine and cholinergic pathways in conjunction with many other neurotransmitter and neurobiological pathways (e.g. serotonin, noradrenalin, gamma – aminobutyric acid (GABA), cortisol, cytokines and oxygen free radicals).[223 224 228 651 652] Central abnormalities in cholinergic and dopaminergic pathways are implicated in many patients with delirium, however there has been evolution from the hypothesis that cholinergic deficiency and dopaminergic excess, either absolute or relative to each other is the sole pathophysiology in all cases of delirium.[189 223 228 253 625 653] For example, the cholinergic mechanisms may be more critical when delirium is due to anticholinergic medication, whereas this relationship has not been clearly established in delirium due to infection.

These changes may be mediated by direct brain insults that compromise brain function by causing local energy deprivation (e.g. thrombosis, haemorrhage, hypotension, hypoxia), metabolic abnormalities (hypo- and hypernatraemia, hypercalcaemia), trauma, CNS infection or tumour, or direct medication-induced neurotransmitter changes.[224] Equally, cholinergic, dopaminergic and noradrenergic neurotransmitter systems, may be altered through overstimulation by aberrant stress responses, the other major category in delirium pathophysiology.[224] This includes an increased and/or inappropriately sustained inflammatory or stress response, and/or an exaggerated response of the target tissue to normal inflammatory signals.[224]

Some of the specific medications implicated in precipitating delirium include cholinergic antagonists, dopamine agonists, corticosteroids, opioids and GABA agonists.[224] It has been proposed that drug-induced delirium may result from transient thalamic dysfunction caused by exposure to medications that interfere with central glutamatergic, GABA-ergic, dopaminergic and cholinergic pathways at critical sites of action (Figure 9).[654] Some specific examples include anticholinergic medications exerting an inhibitory action on striatal cholinergic neurons, opioids indirectly increasing activity of ventral tegmental area (VTA), dopamine neurons via mu opioid receptors inhibiting VTA GABA neurons—which then have less effect in inhibiting dopaminergic neurons—and corticosteroids stimulating VTA dopaminergic neurons.[654]

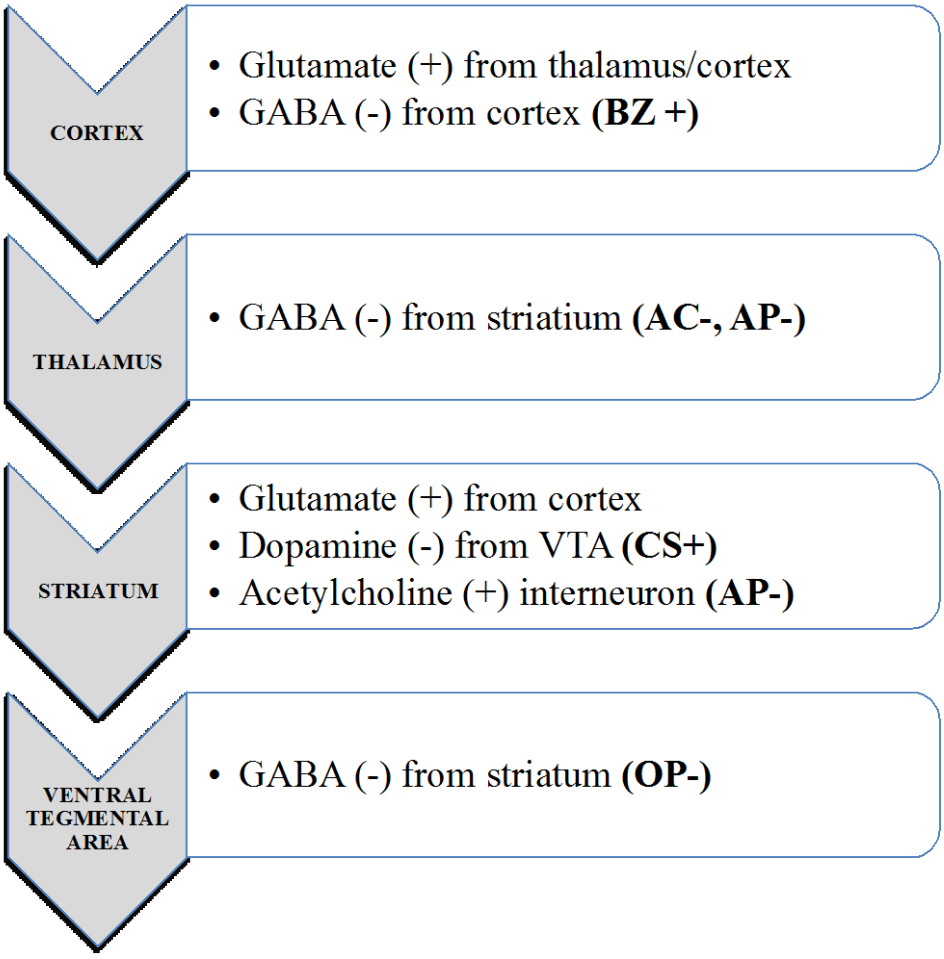


Figure 9 Schematic diagram of levels of central nervous system where glutamatergic, GABAergic, dopaminergic and cholinergic pathways interact and where psychoactive medications effects are potentially mediated (by medication class)

(derived from Gaudreau et al 2005)[654]

AP – antipsychotics; BZ – benzodiazepines; CS – corticosteroids; GABA – gamma-aminobutyric acid; OP – opioids
_- signifies where the pathway has an inhibitory effect and + an excitatory effect

Impairment of the central cholinergic system also occurs in ageing and dementia, both predisposing factors for delirium.[1 242 270] Measuring abnormalities in the central neurotransmission in the clinical setting is not yet possible, and a surrogate marker of cholinergic abnormality due to medication, and other yet to be identified pathophysiological processes, could be clinically useful. Currently, the literature describes three methods to identify anticholinergic burden[265 655]:

- determining a drug's affinity for muscarinic receptors with an antagonist profile in-vitro
- SAA measured by radio-receptor assay
- the presence of typical anti-muscarinic adverse drug reactions, such as dry mouth and constipation, in patient studies or clinical trials.[655]

When combining the first and third methods as a summary of current clinical and pharmacological knowledge about a specific medication, a score can be assigned to medication to quantify the degree of AA.[265 655] Chapter 1, Section 1.11.2 describes these three approaches in more detail.

5.1.1 Serum marker of anticholinergic activity

A serum anticholinergic radio-receptor assay is available to quantify SAA.[241 242] Activity measured reflects the effects of medication and other ingested exogenous substances, as well as endogenous substances such as dynorphin A, MBP, protamine and cortisol present in acute illness.[231 252 253 656] The advantage of SAA is the ability to assess cumulative effects of multiple medications, as well as pharmacologically active metabolites.[242] It thus provides one continuous variable to estimate AA that an individual is being exposed to at a given time, posing an alternative to more complex calculations derived from medication regimens.[244]

5.1.2 Serum anticholinergic activity and delirium

There have been a number of studies in various clinical settings to determine whether SAA can be a reliable predictor of cognitive impairment and/or delirium. A recent systematic review[255] of 27 studies which objectively measured AA correlated with standard measurements of cognitive function, demonstrates an

association between AA of medications and either delirium, cognitive impairment or dementia, in all but two of the studies reviewed.[256] [257] SAA has been significantly associated with the presence and severity of delirium in post-cardiotomy, geriatric medical, post-electroconvulsive therapy and in intensive care settings.[242] [261-264] There have been two negative studies, with no association seen in the frail elderly[265] and intensive care patients.[256] Delirium resolution has also been associated with a fall in SAA when observed longitudinally.[242] In elderly medical patients, multivariate analysis demonstrated SAA was independently associated with delirium, using the variables impairment in ADL, narcotic use, neuroleptic use, nursing home residence, prior cognitive impairment, admission diagnosis of infection and SAA.[189] A similar study in geriatric medical patients showed an association of high SAA with the development of delirium following hospital admission.[264] These studies are critically evaluated in Chapter 1, Section 1.12.

5.1.3 Calculated anticholinergic load of medication

Several methods of calculating anticholinergic drug burden is suggested in the literature, including the ADL developed by Tune in 1992[240], Summer's initial classification in 1978, and more recently the Anticholinergic Burden Scale (ACB) in 2002, and in 2001, the CRAS (initial and modified versions).[234-238] These are discussed in more detail in Chapter 1, Sections 1.11. The CRAS-M gives medication a rating as follows: Level 0 (no known anticholinergic properties), Level 1 (potentially anticholinergic as demonstrated by receptor binding studies), Level 2 (clinically significant anticholinergic effects are sometimes seen, usually at excessive doses), and Level 3 (marked anticholinergic effects).[234] [657]

5.1.4 Correlation of serum anticholinergic activity with calculated anticholinergic load of medication

There has been limited exploration of the correlation of SAA with calculated approaches. The CRAS-M scores were correlated with SAA in elderly nursing home residents, though only a small amount of variance was explained.[249] Several factors may explain this, including the effect of different dosages, pharmacokinetic differences between individuals, the likelihood that medications

given the same scores may not be identical, the effect of multiple medications may not be simply additive, and the presence of unmeasured endogenous factors.

5.2 Aims

SAA has not been measured in a population of advanced cancer patients, nor has the association of SAA with delirium in this population been explored. The aim of this study is to evaluate if SAA measured at admission to inpatient palliative care is predictive of either prevalent delirium at admission or future development of delirium in advanced cancer (incident delirium), after consideration of other aetiological or risk factors for delirium. This will provide insight into delirium pathophysiological mechanisms, and may provide information about whether interventions which reduce anticholinergic load may have impact on delirium occurrence.

Secondarily the study aims to explore whether an association between SAA and the CRAS-M existed, so as to determine if it is possible to predict SAA noninvasively, an important consideration for end-of-life populations where investigations may be burdensome.

The primary null hypothesis is high SAA is not independently associated with the presence and/or future development of delirium in advanced cancer patients.

The secondary null hypotheses is there is no relationship between ratings on the CRAS-M and SAA.

5.3 Objectives and methods

5.3.1 Primary objective

The primary objective of this study is to determine if an association exists between SAA on admission to an inpatient unit with the presence of delirium on admission (prevalent delirium) and subsequent occurrence of delirium (incident delirium) in palliative care patients with advanced cancer, after consideration of other aetiological factors for delirium including patient characteristics. This will be considered in two ways, utilising MDAS scores as a continuous variable and also utilising different MDAS thresholds to define delirium diagnosis.

5.3.2 Secondary objectives

The secondary objectives of this study are to determine:

- the relationship between ratings on the CRAS-M and SAA
- sensitivities and specificities for scores for SAA for the occurrence of incident and prevalent delirium

5.3.3 Exploratory objectives

- other clinical and investigational factors correlated with delirium in the palliative care inpatient population with advanced cancer. In particular to determine if baseline CRAS-M, Cumulative Illness Rating Scale (CIRS), CCI, presence of brain metastases, level of function—measured by the AKPS, oral morphine equivalents, oral dexamethasone equivalents, oral diazepam equivalents and presence of fever) are able to predict MDAS scores over time
- other clinical factors associated with SAA (in particular baseline AKPS, brain metastases, oral morphine equivalents, oral diazepam equivalents, number of medications, presence of fever, CIRS and CCI)
- outcomes and complications of a delirium episode
- association of SAA with survival.

5.3.4 Study design

A prospective, consecutive cohort of inpatients with advanced cancer from two metropolitan specialist inpatient palliative units was compared with all inpatients in the palliative care unit, and with the patients referred to the corresponding palliative care services using three key descriptors (age, gender, cancer or non-cancer primary diagnosis).

5.3.5 Study setting

The specialist palliative care inpatient units provide free inpatient care for patients with life-limiting illness who have complex physical symptoms or psychosocial needs, with the aim of stabilising these to enable discharge, but also in some cases to provide ongoing inpatient care for terminal care for people in the last days of life. Both the units have links to specialist community palliative care teams.

Braeside hospital provides specialist inpatient palliative care for patients within a 3245 km^2 area from Fairfield to Bowral (local government areas of Bankstown, Fairfield, and Liverpool), serving over 800,000 people in South West Sydney, Australia. The Braeside palliative care unit has 20 inpatient beds, approximately 480 admissions each year and is staffed by specialist nurses, doctors and allied health practitioners. There is no emergency department on campus, but access to general medical beds and the emergency department is from Fairfield Hospital on an adjacent campus. There were approximately 90% cancer diagnoses versus 10% non-cancer diagnoses, and 48% male versus 52% female patients in the inpatient population at the time of this study.

Sacred Heart Palliative Care Service provides specialist inpatient palliative care for patients within the metropolitan areas of Sydney, Australia, directly to the east and south east of the central business district of Sydney (108 km^2), as part of the South Eastern Local Health District. This area services a population of approximately 230,700 people, which covers the areas between Pyrmont, Vaucluse, La Perouse and Botany (local government areas of Woollhara, Waverley, Randwick, Botany, City of Sydney). Sacred Heart hospice has 50 inpatient beds, approximately 585 admissions each year and is staffed by specialist nurses, doctors and allied health practitioners. There is an emergency department and general medical beds on the hospital campus. There were approximately 85% cancer diagnoses versus 15% non-cancer diagnoses, and 55 % male versus 45% female patients in the inpatient population at the time of this study.

5.3.6 Patient population

The patient population consisted of palliative care inpatients with advanced cancer in the palliative care inpatient units at Braeside Hospital, Prairiewood and Sacred Heart Palliative Care Services, Darlinghurst, both in Sydney, New South Wales, Australia.

5.3.6.1 Inclusion criteria

1. Admission to a palliative care inpatient unit within the previous 72 hours.
2. Advanced cancer (defined as metastatic or advanced locoregional disease).
3. Clinician predicted survival of greater than seven days.

4. Age greater or equal to 18 years.
5. Informed consent from patient if able OR person responsible for consent if the person lacks capacity to provide his or her own consent due to prevalent delirium (see Section 5.3.7 for detailed consent procedures).
6. If participant provided their own consent, availability of a 'proxy' who was eligible to and willing to act as the 'person responsible' (in the event the participant developed delirium during study period).
7. English speaking.

5.3.6.2 Exclusion criteria

1. Significant communication problems such that the participant was unable to perform assessments (e.g. aphasia, severe hearing impairment, tracheostomy).
2. Previously participated in this study during a prior admission (only one admission captured for each participant).

5.3.7 Consent procedures

This study includes recruitment of cognitively impaired participants[658]; specifically those who have delirium on enrolment or participants who subsequently develop delirium during the study period. It also may include participants with prior cognitive impairment from other causes, as this is a risk factor for delirium development. The degree of cognitive impairment is variable and fluctuating in delirium. Informed consent was possible in many patients at enrolment; if not possible person responsible for consent was used.

The capacity to make informed decisions about participating in clinical research requires a factual understanding of the issues involved in the decision, evidence of understanding the research in question, and the risks and benefits of participation or non-participation.[659 660] Ability to give informed consent in the context of cognitive impairment is context specific and is possible in many patients. To determine the capacity of the cognitively impaired participant to provide consent, the researcher needs to establish that the participant has a rational ability to manipulate the relevant information, an appreciation of the nature of their situation and how the research impacts on this, and both consistency in their interpretation and view of the information, and evidence that this is an active choice.[659]

A proxy in Australia is defined as the 'person responsible' (a statutory concept), and is not necessarily the patient's next of kin. This is the person who is able to make decisions for children, and adults who have a disability and who are incapable of consenting to treatment, and is defined slightly differently in state or territory legislation. In New South Wales (NSW), the site of this study, the 'person responsible' definition is defined in section 33A, *Guardianship Act 1987*[661] according to the following hierarchy:

1. a guardian (including an enduring guardian) who has the function of consenting to medical, dental and healthcare treatments
2. the most recent spouse or *de facto* spouse with whom the person has a close, continuing relationship. '*De facto* spouse' includes same sex partners
3. an unpaid carer who is now providing support to the person or provided this support before the person entered residential care
4. a relative or friend who has a close personal relationship with the person
5. if there is no person identified, individual applications can be made to the NSW Guardianship Tribunal.

Advanced consent is defined as the consent of subjects prior to a predictable or potential loss of capacity.[662] This is particularly the case when the event under study is likely to occur at a time when capacity is lost, and therefore it will be difficult or impossible to have a conversation about trial participation or difficult to otherwise organise participation in the trial. Informed consent takes place before the onset of cognitive decline (in this study due to delirium) to allow information that is relevant and salient to the condition of interest to be discussed.[662] Advanced consent to participate in a study of delirium has been used in previous studies, and also has been used in other studies in palliative care, namely treatment of conditions seen in the terminal phase of patients' illness.[264 338 663] In this study advanced consent was obtained from the participant to ensure they had provided consent continued participation in the study in the event they developed delirium.

The participant was asked to nominate a person whom they deem is their proxy or person responsible (as per above definitions) during the study period to further safeguard the participant. The proxy's role was to act on the participant's behalf

for periods when lack of capacity occured (and make decisions such as reviewing the risks and benefits of continued participation, and to withdraw the person from the study if they believed this to be in best interests of the participant). The nominated person also provided written informed consent at the same time as the potential participant on enrolment to the study, confirming that they understood the study and were willing to act in this role if required. No information collected for this study was released to the proxy, except within the clinical context or that required for them to make decisions on the persons' behalf.

The major component of this study was documenting routine clinical management and assessment with validated standardised tools. The only additional component to the study is the serum sample for SAA. On Human Research Ethics Committee review and consultation with the New South Wales Guardianship Tribunal, the approval of the Guardianship Tribunal (under Part 5 of the *Guardianship Act 1987*)[664] was not required as this study did not meet the definition of a clinical trial of a drug or intervention technique that involves giving medical treatment to the trial participant. The study was approved by the St Vincents Hospital and Hope Healthcare ethics committees (Appendix 7 and 8). The study was also registered on the Australian New Zealand Clinical Trials Registry (ACTRN012605000044628).

5.3.8 Study procedures

The following baseline demographic and clinical parameters were recorded (see Table 39 for time schedule and Figure 11 for study flow diagram):

- age
- gender
- cancer diagnosis, stage and site of metastases (in particular presence or absence of cerebral metastases)
- reason for admission to palliative care unit, from three categories (symptom control respite or terminal care)
- presence of cognitive impairment
- visual impairment (defined as requiring glasses)
- hearing impairment (defined as requiring a hearing aid).

5.3.8.1 Performance status and functional status

5.3.8.1.1 Australia-Modified Karnofsky Performance Status

The AKPS (Appendix 9) has been developed for use to assess function in palliative care populations using descriptors more suited to palliative care populations (psychometric properties outlined in section 4.5.5.5).[602] A score of 0 to 100 (in increments of 10) is assigned to patients based on their ability to undertake a range of daily tasks. The tool was used in this study to provide a global measure of level of functional impairment.

5.3.8.1.2 Barthel Index

The Barthel Index (Appendix 10) was used to assess impairment of ADL, to further delineate functional domains affected by delirium, the cancer itself or both.[665] It has established psychometric properties, with construct validity established with factor analysis and good inter-rated reliability.[666-669] It evaluates 10 ADL grouped into self care (feeding, grooming, bathing, dressing, bowel and bladder care, and toilet use) and mobility (ambulation, transfers and stair climbing).[665] Five-point increments are used in scoring with a maximum score of 100 delineating full independence in physical functioning and 0 totally dependent bed-fast state.[665] The values assigned for each item are based on the time and amount of actual physical assistance required if the patient is unable to perform the activity independently.

5.3.8.2 Assessment of comorbidities

A scale for measuring comorbid illness to attempt to quantify the body systems involved and its severity is also crucial in a study of delirium. CIRS and CCI were calculated on admission and weekly (see Appendices 11 and 12) during the admission.

5.3.8.2.1 The Cumulative Illness Rating Scale

The CIRS rates 13 conceptually valid body systems on a five-point pathophysiologic severity scale, and is valid and reliable.[670] Inter-rater reliability has been established with intra-class coefficient of 0.81 (0.70–0.89).[671] It was developed as a measure of multi-morbidity, and takes into account the number of medical problems and weights them according to their severity.[671] The organs or

systems in the CIRS are cardiac; hypertension; vascular; respiratory; ear, eye, nose and throat; upper gastrointestinal; hepatic; renal; other genitourinary; musculoskeletal; neurological; endocrine metabolic; psychiatric; and behavioural. The scores are from one (no impairment to that system), two (impairment does not interfere with normal activity), three (moderate, impairment interferes with normal activity), four (severe, impairment is disabling with treatment urgently needed and prognosis guarded), and five (extremely severe, impairment is life threatening and prognosis is grave). It is scored based on clinical judgment, and was studied in populations including cancer patients.[670] CIRS does not require invasive physiological measures such as arterial pH or oxygenation, making it suitable for this study.

5.3.8.2.2 Charlson Comorbidity index

The CCI, a valid and reliable tool showing relationships with mortality, disability and length of stay, was also calculated.[670 672] This tool is a weighted index that takes into account the seriousness of a comorbid disease, with adjusted relative risks of one-year mortality employed as weights for different comorbid illness.[673] It was developed in a cohort of 559 medical patients and then tested in another cohort of 685 patients for its ability to predict risk of death in a 10-year follow-up.[673] Only conditions with one-year relative risks of mortality above 1.2 from the development cohort were included in the final index.[673] The index encompasses 19 medical conditions weighted 1–6 with total scores ranging from 0–37. A weight of 1 is equivalent to a relative risk of 9 RR ≥1.2 <1.5, weight 2 RR ≥1.5 <2.5 and weight 3 RR, ≥2.5 <3.5 and weight 6 for two conditions (metastatic solid tumour and AIDS).

5.3.8.3 Medication assessment and clinician rated anticholinergic scale calculation

A list of medications used regularly was recorded daily (generic drug name, dose, route of administration, indication, frequency and pattern of use). Medications used on an as-needed basis were only recorded if a dose was administered in the preceding 24 hours. Agents with no Australian Therapeutics Code (complementary or alternative therapies given wide variation in labelling and contents) were excluded from data collection. Daily alterations to medications were noted. The total number of medications per day was recorded.

All current medications were documented, and scored on the CRAS-M (described in detail in Chapter 1 Section 1.11).[234 248] The total number of medications having a score of 1 or more on the CRAS-M was recorded for each day.

Opioid dose was calculated using oral morphine equivalents for each 24 hours, according to the conversions outlined in Table 37 derived from the cancer treatments online opioid conversion calculator (EviQ cancer treatments online opioid dose calculator).[674]

Table 37 Conversion factors to oral morphine equivalents

Opioid	route	Conversion factor to oral morphine equivalents (milligrams)
Oxycodone	subcutaneous	X 2.5 [674]
Oxycodone	oral	X 1.5 [674]
Morphine	subcutaneous	X 2.5 [674]
Hydromorphone	oral	X 6 [674]
Hydromorphone	subcutaneous	X 15 [674]
Codeine	oral	X 0.125 [674]
Fentanyl	topical transdermal patch	12mcg/hour patch = 43.2mg [674]
Methadone (in steady state)[675]	oral	X 3 [675]

Corticosteroid dose was converted to oral dexamethasone equivalents, as in prior work by Gaudreau et al.[182 676] Prednisolone 5mg and prednisone 5mg, and 20mg hydrocortisone, is equivalent to 0.75 mg oral dexamethasone.[676] Benzodiazepine dose was converted to oral diazepam equivalents utilising the conversions cited by Drug and Alcohol Services South Australia[677] and the Tasmanian Adult Palliative Care Formulary[678] (see Table 38).

Table 38 Conversion factors for oral diazepam equivalents

Benzodiazepine	Dose (mg)	Oral diazepam equivalent (mg)
Temazepam	10.0	5
Clonazepam	0.5	5
Lorazepam	1.0	5
Oxazepam	30	5
Nitrazepam	5.0	5
Alprazolam	1.0	5
Zolpidem	1.0	5
Midazolam	5.0	5

5.3.9 Serum anticholinergic level assay

Ten millilitres of venous blood was collected, kept at 4°C for up to one hour until centrifuged (3000rpm, 10 minutes). The serum was transferred to polypropylene tubes (cryotubes) and stored at –80°C until SAA was determined. Storage in a frozen state does not affect SAA.[241] Specimens were collected at a standard time of 10am daily to avoid any problem with diurnal variation. Blood was collected on admission, at Day 7 for non-delirious patients, and at development of delirium if this occurred.

SAA was performed in triplicate, utilising 200µl aliquots of serum, according to the protocol originally described by Tune and Coyle (described below)[241], at the laboratory of Professor Juergen Kopitz, Institute of Molecular Pathology, University of Heidelberg. This laboratory was chosen as assay precision is well established and no Australian Laboratories are currently undertaking SAA or could establish it within the study timeframe and budget.

The patient's serum is added to a membrane preparation from rat forebrain and striatum containing muscarinic antagonist, tritiated quinuclidinyl benzilate (3H-QNB) (radioactively labelled).[241] 3H-QNB binds specifically and avidly to muscarinic cholinergic receptors.[241] The incubation mixture consists of 200µl of serum, 200µl of the rat-brain preparation, 0.6 pmol of 3H-QNB (in 200µl), and volume made up to 2ml with phosphate buffer (50nM, pH 7.7).[241] Two hundred µl was chosen as this had the lowest amount of serum protein (which also binds to 3H-QNB) yet at concentrations sufficient to detect anticholinergic medication.

Incubation is for 60 minutes at 22°C.[241] The assay is terminated by an isolation of ligand receptor complex by aspiration over glass fibre filters, and the receptor bound radioactivity is measured by liquid scintillation spectrometry.[241] Samples are compared with known concentrations of atropine (the internal standard), and the amount of QNB inhibition that would have been caused by the known standard amount of atropine, with the displacement of 3H-QNB used to quantify SAA (atropine equivalents) in comparison to an atropine standard curve (the amounts of atropine used for standard curve were 0, 0.5, 1, 5, 10, 25, and 50nM). The standard curves account for the presence of 200μl of serum. It does not measure protein-bound drugs as serum proteins are not denatured and precipitated.[241] Anticholinergic medications included in the CRAS-M which are highly protein bound, and hence may not be totally accounted for in SAA, include diphenhydramine, digoxin, and frusemide[679], depending on proportion of unbound fraction. Other highly bound proteins have a score of 0 on the CRAS-M (e.g. glipizide, indomethacin, doxycycline, phenytoin, spironolactone), so will not alter associations seen with SAA.

Hence the potency of anticholinergic substances in a serum sample that bind to the muscarinic acetylcholine receptor present in the rat forebrain/striatum homogenate is determined by measuring its ability to inhibit the binding of 3H-QNB to the receptor (Figure 10). The ability of the anticholinergics to compete with 3H-QNB for binding sites is dependent on both the affinity of the anticholinergics for the muscarinic receptors, the concentration of 3H-QNB, and the affinity of 3H-QNB for the receptors. The assay measures activity at all muscarinic receptor subtypes.[242]

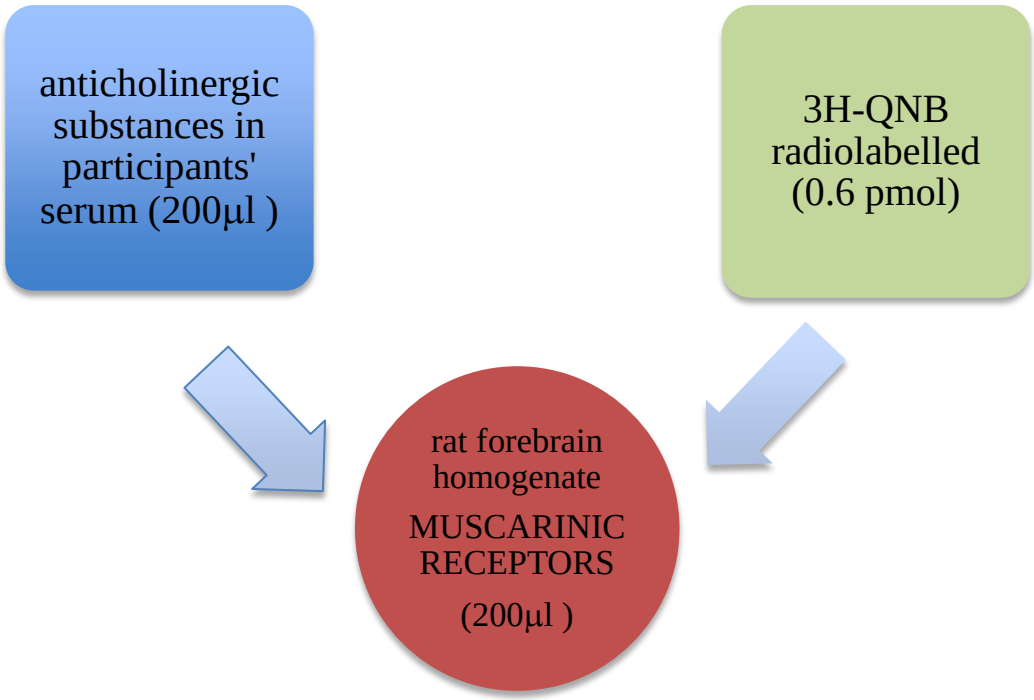


Figure 10 Serum anticholinergic activity competitive binding

The specimens were shipped on dry ice, to ensure the samples stayed frozen for a minimum of 48 hours. The detection limit of SAA in the Heidelberg lab is 0.5 nM (i.e. serum levels less than 0.5nM of atropine equivalents are below the detection level of the assay), intra-assay accuracy is between 93% and 100%, and intra-assay precision was always better than 9%.[265] 3H-QNB was obtained from Perkin ElmerLife Sciences: Specific activity 1,56TBq/mmol. The samples were run as one batch. The results are calculated as the amount of atropine, which would provide the identical degree of inhibition of 3H-QNB.

5.3.10 Delirium diagnosis – Memorial Delirium Assessment Scale

Several delirium evaluation instruments exist; however, for the purpose of this study, a tool that allowed repeated regular assessments and measured change in severity over time was needed.[26 40] The MDAS is a brief, valid and reliable tool for assessing delirium severity in advanced cancer patients, and is easy to use for repeated assessment (Appendix 13).[39 40]

It is a continuous severity measure, and hence can identify sub-syndromal delirium, which also has been associated with poorer outcomes.[76] MDAS has been validated in cancer populations. It allows repeated assessments; necessary in this

study.[40] MDAS is primarily used as a continuous outcome variable in this study. However, a cut-off for a second serum specimen of MDAS total score of 10 was used (96.7% sensitivity and 95.7% specificity)[138], to ensure this was a specimen taken while the person definitely had delirium.

The MDAS can classify hypoactive and hyperactive delirium using item 9 'decreased or increased psychomotor activity', and each is rated on severity from 0 – mild to 3 – severe.[76] Differentiation between hyperactive and hypoactive subtypes has shown positive correlation between delirium severity and functional outcome so is important to include.[76]

MDAS was performed daily in conjunction with information provided by treating medical and nursing teams, at a standardised time between 8am and 12 midday by the research nurses or author who were trained in its use (because of known variation of delirium symptoms within a 24-hour period.) An initial and several follow-up training sessions during the course of the study were conducted for the clinical staff so the observations that were required from them to contribute to scoring were understood. Daily MDAS were ceased if the patient remained an inpatient longer than three weeks (20 days after baseline day) of being on the study without an episode of delirium, as continuing daily MDAS would have been unduly burdensome and most episodes (apart from terminal delirium in last days of life) would be captured. The researchers continued to review the patient's file and reassessed with MDAS if any indications of acute confusion were found.

Cognition was not tested separately as MDAS includes items to assess cognition, and repeated MMSE were not deemed suitable for this study due to the length of this test, and previous study showing 25% of palliative care inpatients were unable to complete the MMSE due to fatigue.[111] Only English speaking participants were recruited as the MDAS only has a validated version available in Italian and Spanish; however, this has not been validated for use with a healthcare interpreter and Italian and English speakers are not the predominant community for whom English was not the first language in the study setting. Further confirmation of a diagnosis of delirium using SCID was not conducted as this was out of scope of the research staff and would be burdensome for participants if conducted daily.

5.3.11 Aetiological factors

Routine measurement of these parameters was not a requirement of this protocol, as in the palliative care setting the level of intervention and investigation will vary depending on the clinical scenario, and the patient's wishes and prognosis, and this study aims to describe a predictive model with relevance in this clinical framework. Presence or absence of fever on admission, cognitive, visual and hearing impairment were recorded for all participants.

5.3.12 Outcomes

Functional capacity measured by AKPS and Barthel Index, and occurrence of medical complications (falls, pressure ulceration, incontinence) were measures weekly. The following were record if they occurred:

1. discharge destination (home, residential aged care, acute care bed, died in palliative care unit, other)
2. length of stay (days)
3. death, with mortality data collected for up to 12 months from the medical record or palliative care service databases.

Figure 11 illustrates the flow of the study.

5.3.13 Study flow

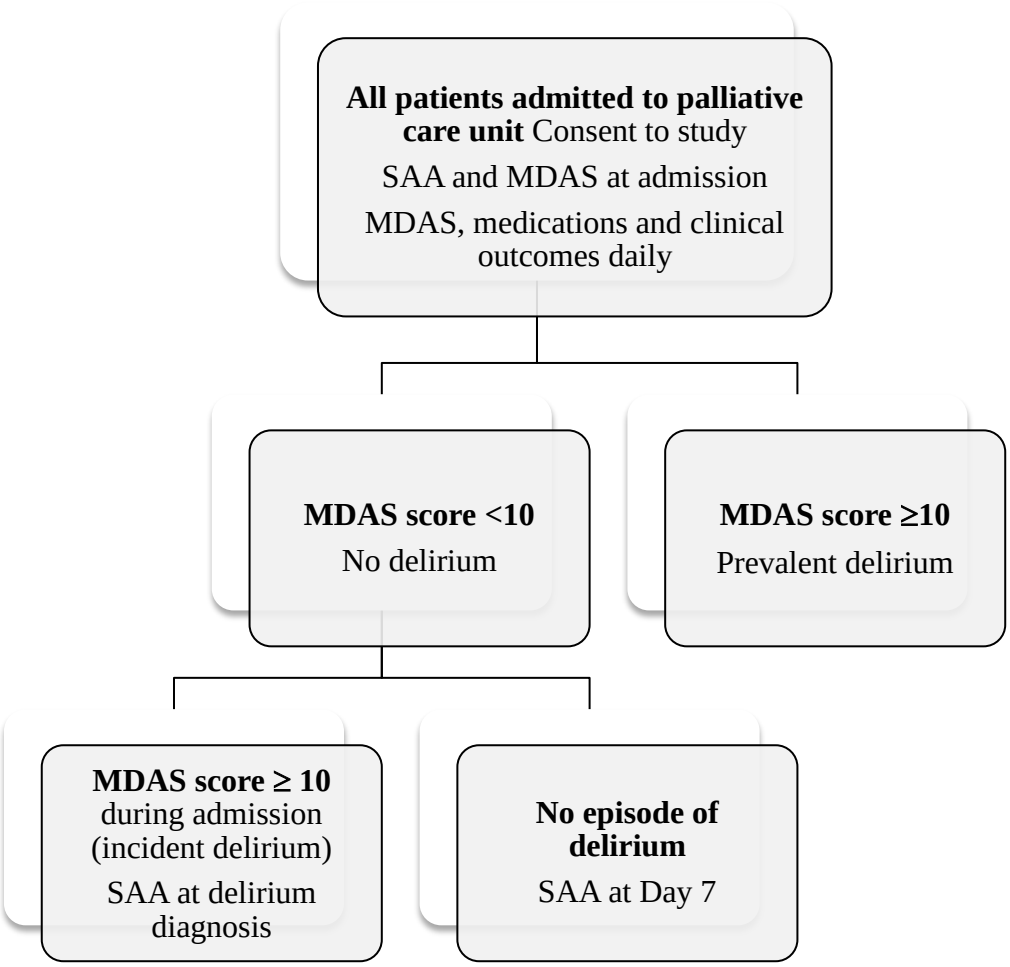


Figure 11 Study flow diagram

MDAS – Memorial Delirium Assessment Scale; SAA serum anticholinergic activity

5.3.14 Data collection schedule

Table 39 outlines the key variables and time-point for collection.

Table 39 Data collection schedule

Variable	On admission	Daily	Weekly	At delirium episode (within 24 hours)
Demographics	✓			
Main clinical diagnosis	✓			
Function (AKPS and Barthel Index)	✓		✓	✓
Comorbidities (CIRS and CCI)	✓	✓		✓
Investigations and interventions	✓	✓[b]		
MDAS	✓	✓[b]		✓
Medications	✓	✓[b]		✓
CRAS-M, oral dexamethasone, morphine and diazepam equivalents				✓
SAA[a]	✓		[b]	✓
Reason for admission	✓			
Delirium outcomes		✓		✓

[a] At delirium episode or Day 7 if no delirium episode
[b] At 3 weeks the participant will be followed by review of the medical record. If an episode of delirium that is clinically identified occurs, daily MDAS and medication record recommenced.
AKPS – Australia-modified Karnofsky Performance Scale; CCI – Charlson Comorbidity Index; CIRS – Cumulative Illness Rating Scale; CRAS-M – Clinician rated Anticholinergic Scale – modified version; MDAS – Memorial Delirium Assessment Scale; SAA – serum anticholinergic activity

5.4 Statistical considerations

5.4.1 Sample size

An estimate for regression analysis is that 10 participants are needed for each variable (if the factors outlined were to be included) in the random effects regression analysis; hence an estimate was that 130 patients were needed. The power to detect an association between calculated anticholinergic load and delirium score depends on the number of observations obtained on each patient, and the magnitude of the correlation between daily scores of a patient. The minimum power occurs when the correlation coefficient is 1 (in which case the number of days of observation is irrelevant). In this worst case scenario, using the method of Hsieh et al[680], 130 patients will provide 80% power to detect an association, at a type 1 error of 0.05, if a change of 1 SD unit in calculated anticholinergic load is associated with a change of at least 0.24 SD units in delirium score (MDAS).

If additional predictors are included in the model, power will be reduced to an extent, which depends on the squared multiple correlation coefficient between calculated anticholinergic load and the other predictors. For example, for an R^2 of 0.3, the minimum detectable change in delirium score at 80% power is increased to 0.35. As these correlation coefficients are not known prior to data collection, an exact calculation cannot be made. Due to the conservative nature of assumptions involved, actual power is expected to be greater than that given above.

5.4.2 Descriptive statistics

The data were summarised by descriptive statistics. Frequency counts and percentages were used for categorical variables, and mean, range, interquartile range and CI of mean for continuous variables. Outcomes and complications were summarised for the delirium and non-delirium groups.

5.4.3 Univariate analyses

Box plots were performed to describe the data for SAA and MDAS at baseline, with age, gender and AKPS.

5.4.4 Correlation between serum anticholinergic activity at baseline

Scatterplots and Lowess curves were performed for SAA at baseline and MDAS, CRAS-M, oral diazepam equivalents, oral morphine equivalents and oral dexamethasone equivalents at baseline, and Spearman's rank correlation (Spearmans rho) calculated. If an association was seen then the receiver operator curve (ROC) were plotted to determine the best (optimum sensitivity and specificity) cut-off score.

5.4.4.1 Linear mixed models: longitudinal analysis over time of association between serum anticholinergic activity and Memorial Delirium Assessment Scale

Analysis was conducted using GEE, with a gamma distribution, logarithmic link function, and exchangeable correlation structure. Standard errors (SE) of estimates were based on the Huber-White sandwich estimator of variance.[681]

Use of the logarithmic link function means that effects are considered to be multiplicative; a 1-unit change in SAA will be associated with a certain percentage change in MDAS, rather than a change of a fixed number of units, because for patients who already have a low MDAS, there is no scope for a large decrease in the MDAS score.

The gamma distribution[617] is a positively skewed distribution, which does not take negative values (in contrast to a normal distribution which does), thus it is more appropriate for MDAS, which does not include negative values.

Observations within patients are likely to be correlated. The model allows for such correlation, but assumes that all observations within a patient are equally correlated (exchangeable correlation structure).[617] While this may be only an approximation to the real correlation pattern, it is difficult to estimate the true pattern. In unbalanced data sets (number of observations in each cell formed by factors in the analysis are not the same), models with more complex correlation structures often do not converge well. The main source of imbalance in this data set is that not all participants would have a MDAS score for all 21 days included in analysis due to discharge, death or inability to assess the score. Hence the

analysis uses the robust estimate of variance, which gives unbiased SEs even if the correlation pattern is mis-specified.

It was assumed that if there is an association between MDAS (on Days 0–20) and SAA on Day 0, this association would diminish over time. Therefore, the model included an SAA x TIME interaction. If an SAA x DAY interaction was used, this would result in a model with a large number of parameters. To simplify the model, an alternative function of time was used. It was assumed that any association between SAA and MDAS would decline rapidly at first, then either disappear or decline at a lower rate. Therefore, the 21-day time span was divided into five periods, as follows:

Period 1	Day 0
Period 2	Days 1–2
Period 3	Days 3–6
Period 4	Days 7–13
Period 5	Days 14–20

The model assumes that within each period, there will not be much change in the association between SAA and MDAS, and so it is reasonable to estimate an averaged association within each period. However, the strength of the association may differ between periods. Due to the diminishing numbers of patients contributing data, data up to Day 20 only were included in this analysis (i.e. three weeks of data). Adjustment for potential confounding factors was conducted by including the interaction between SAA, time period and the confounding factor. This was conducted separately for the possible confounding factors of site (Braeside Hospital vs Sacred Heart Palliative Services), age (three categories (≤67 years, 68–77 years, ≥78 years), gender, and AKPS (three categories 20 and 30, 40 and 50, 60 and 70). Missing data in MDAS was assessed to determine if they were missing completely at random or whether non-random drop out occurred. If one or more items contributing to MDAS was not scored, MDAS was not calculated.

5.4.5 Logistic regression and receiver operator curve for predictive ability of baseline serum anticholinergic activity and delirium occurrence

Logistic regression was performed using baseline SAA and occurrence of delirium, defined as any MDAS score of 10 or greater from Days 0–20. Logistic regression was also performed using baseline SAA and a lower cut-off to 'define' a delirium of score of 7 or greater. The ROC was plotted for SAA and the occurrence of delirium to determine the best (optimum sensitivity and specificity) cut-off score that predicts for delirium. Sensitivities and specificities for levels for SAA were calculated.

5.4.6 Generalised estimating equations to determine clinical variables at baseline which were predictive of Memorial Delirium Assessment Scale scores during admission

GEE were performed using the following variables (as measured on admission), with the outcome measure being the MDAS score (continuous variable) in each patient:

- age (continuous)
- AKPS (three categories)
- cerebral metastases (categorical – present or absent)
- CRAS-M (continuous)
- CIRS (continuous)
- CCI (continuous)
- opioid dose (oral morphine equivalent)
- fever on admission (categorical – present or absent)
- dexamethasone equivalents on admission (continuous)
- diazepam equivalents on admission (continuous).

This analysis aimed to determine the ability of each variable at admission to predict for delirium occurrence. The variables of age, opioid dose, dexamethasone equivalents, diazepam equivalents were chosen based on prior work demonstrating their association with delirium.[183 197 682] CIRS was utilised as a measure of severity of illness. Fever as a marker of infection was also thought to be important, as it may lead to MDAS levels being high for longer periods of time, as infection is associated with less reversible delirium in palliative and

cancer populations.[38 305] The variables chosen are also those that can be measured noninvasively, so as to provide information on the ability of clinical predictors available in all palliative patients (without the need for blood tests) to predict MDAS scores. GEE were chosen to allow for multiplicative (rather than additive) effects and allowed for the positively skewed MDAS data.

The model was initially fitted utilising MDAS as an outcome, with variables of interest, time period, and time period x variable of interest interaction. Then an assessment of the significance of time period x variable of interest interaction was made. If the time period by variable of interest interaction was a non-significant fit, then a model of time period and variable of interest only was used.

5.4.7 Surrogate markers of serum anticholinergic activity

Regression analysis (ordinary least squares regression analyses) was performed with the following potential marker variables at baseline, and SAA at baseline as an outcome measure (continuous variable):

- age
- AKPS (three categories)
- cerebral metastases
- opioid dose (oral morphine equivalent)
- benzodiazepine dose (oral diazepam equivalents)
- medication burden – total number of medications (baseline)
- fever at baseline
- CIRS
- CCI.

5.4.8 Survival time and serum anticholinergic activity

Survival time and Kaplan Meier curves were calculated from baseline. At the time of analysis, 10 participants were still alive and eight participants had an unknown date of death. The effective sample size for the survival analysis is all participants who had died. Unadjusted survival was calculated for AKPS, age and SAA. Survival by SAA was also calculated with adjustment for age and AKPS.

5.4.9 Summary of analyses

Table 40 summarises the bivariate analyses, and Table 41 summarises the multivariate analyses.

Table 40 Summary of bivariate analyses

	SAA at baseline	MDAS at baseline	Total number of medications
Age	*Descriptive statistics and Box plot*	*Descriptive statistics and Box plot*	
Gender	*Descriptive statistics and Box plot*	*Descriptive statistics and Box plot*	
AKPS	*Descriptive statistics and Box plot*	*Descriptive statistics and Box plot*	
CRAS-M	*Scatter plot and Lowess curve* *Spearman's rank correlation*		*Descriptive statistics*
Oral morphine equivalents	*Scatter plot and Lowess curve* *Spearman's rank correlation*		
Oral diazepam equivalents	*Scatter plot and Lowess curve* *Spearman's rank correlation*		
Oral dexamethasone equivalents	*Scatter plot and Lowess curve* *Spearman's rank correlation*		
SAA at baseline		*Scatter plot and Lowess curve* *Spearman's rank correlation Logistic regression* *ROC*	

Shaded cells indicate comparisons undertaken
AKPS – Australia-modified Karnofsky Performance Scale; CRAS – Clinician Rated Anticholinergic Scale – modified version; ROC – receiver operator curve SAA – serum anticholinergic activity

Table 41 Summary of multivariate analyses

Model	Objective	Outcome	Variables at baseline (on admission)
Generalised estimating equations	association of baseline SAA with MDAS over time	MDAS (continuous)	SAA at baseline Time (divided into 5 time periods)
Generalised estimating equations	clinical variables at baseline which were predictive of MDAS scores over time during admission	MDAS (continuous)	Age (continuous) AKPS Cerebral metastases CRAS-M CIRS CCI Opioid dose (Oral morphine equivalent) Fever Dexamethasone equivalents Diazepam equivalents
Ordinary least squares regression analysis	clinical variables at baseline that predict SAA	SAA at baseline	Age AKPS (3 categories) Cerebral metastases Opioid dose Benzodiazepine dose Medication burden – total number of medications (baseline) Fever CIRS CCI

AKPS – Australia-modified Karnofsky Performance Scale; CCI – Charlson Comorbidity Index; CIRS – Cumulative Illness Rating Scale; CRAS – Clinician Rated Anticholinergic Scale – modified version score ; MDAS – Memorial Delirium Assessment Scale; SAA – serum anticholinergic activity

5.5 Results

5.5.1 Participants

The study recruited 126 participants over a three-year period from May 2006 until March 2009. There were 69 participants recruited from Braeside Palliative Care unit and 57 from Sacred Heart Hospice. Overall, 52% of the sample was female, with more females (35) recruited from Sacred Heart Hospice (61%). Table 42 outlines the demographic and clinical characteristics of the 126 participants, and Table 10 outlines their characteristics by delirium category.

The flow of participants is illustrated in Figure 12. Participants did not differ in mean age (mean age for inpatients in Sacred Heart Hospice 71 years, and 68 years for Braeside for study period) or range of cancer diagnoses (data not shown) from the whole population with cancer referred to the two palliative care services during the same period (data not shown). However, the participants were more frequently female (61%) from Sacred Heart Hospice than the population with cancer referred to that inpatient palliative care service (45% female) during the same period.

Table 42 Baseline demographics and clinical characteristics of all participants (n = 126)

Characteristic		Braeside Hospital (n = 69)	Sacred Heart Palliative Services (n = 57)	n = 126
Age	Mean (SD)	72.3 (10.1)	71.0 (11.6)	71.7 (10.7)
Gender	Male	38 (55%)	22 (39%)	60 (48%)
	Female	31 (45%)	35 (61%)	66 (52%)
Performance status (AKPS)[602]	20	9 (13%)	6 (11%)	15 (12%)
	30	8 (12%)	3 (5%)	11 (9%)
	40	17 (25%)	9 (16%)	26 (21%)
	50	15 (22%)	13 (23%)	28 (22%)
	60	19 (27%)	20 (35%)	39 (31%)
	70	1 (1%)	6 (10%)	7 (5%)
Performance status (ECOG)	2	22 (32%)	17 (30%)	39 (31%)
	3	33 (48%)	32 (56%)	65 (52%)
	4	14 (20%)	8 (14%)	22 (17%)
Cancer primary site	Lung	16	12	28 (22%)
	Breast	5	9	14 (11%)
	Colorectal	7	6	13 (10%)
	Prostate	5	8	13 (10%)
	Upper gastrointestinal	8	3	11 (9%)
	Head and neck	2	0	2 (2%)
	Pancreas	9	1	10 (8%)
	Unknown primary	6	4	10 (8%)
	Other	7	9	16 (13%)
	Gynaecological	1	3	4 (3%)
	Melanoma	3	1	4 (3%)
	Brain	0	1	1 (1%)
Neurological or psychiatric diagnosis	Brain metastases	8	6	14 (11%)
	Psychiatric diagnosis	14	11	25 (20%)
	Prior cognitive impairment	13	14	27 (21%)
Barthel Index total score	Mean (SD)	51.3 (32)	57.7 (29.3)	54 (31)
Charlson Comorbidity Index	Mean (SD)	8.0 (2.2)	6.9 (1.9)	7.6 (2.1)
Clinician Rated Anticholinergic Scale –modified score	Mean (SD)	2.06 (1.38)	2.25 (1.33)	2.14 (1.35)
Oral morphine equivalent	Mean (SD)	92.3 (153)	140 (177)	114 (165)
Oral diazepam equivalents	Mean (SD)	1.76 (3.4)	2.1 (4.09)	1.92 (3.72)
Oral dexamethasone equivalents	Mean (SD)	2.02 (3.05)	1.92 (3.57)	1.98 (3.28)

AKPS – Australia-modified Karnofsky Performance Scale; ECOG – European Cooperative Oncology Group; SD – standard deviation

Table 43 Baseline clinical characteristics of participants by delirium category

Clinical characteristics	No delirium (MDAS always <10)	Prevalent delirium **(MDAS ≥10 at** baseline)	Incident delirium **(MDAS ≥10 during** admission)
SAA baseline (mean, range, SD)	19.3 (1.8–65.2, 13)	14 (4.6–28.3, 7.2)	28.3 (10.3–62.5, 21.7)
CRAS-M (mean, range, SD)	2.1 (0–6, 1.34)	2.3 (0–5, 1.4)	2.2 (0–6,1.6)
Oral morphine equivalents (mean, range, SD)	121 (0–750, 169)	93.4(0–600, 157)	85 (0–500,149)
Oral diazepam equivalents (mean, range, SD)	1.55 (0–10,2.7)	3.7 (0–25, 6.5)	2.5 (0–15, 5.4)
Oral dexamethasone equivalents (mean, range, SD)	2.0 (0–14. 3.1)	2.5 (0–16, 4.8)	1 (0–4, 1.7)
AKPS (mean, range, SD)	49.9 (20–70,13)	29.4 (20–50, 9.9)	49 (20–60, 12.9)
CIRS (mean, range, SD)	25.7 (17–38,4.3)	28.8 (21–47,6.3)	28.9 (19–36, 5.2)
CCI (mean, range, SD)	7.5 (2–14,2.1)	7.4 (4–13, 2.1)	8.3 (6–12, 2.2)
Barthel Index (mean, range, SD)	61.2 (0–120, 27.3)	13.3 (0–50, 16.6)	59.5 (20–95, 28.1)
Prior cognitive impairment (n, % of delirium category)	6 (6%)	3 (16%)	1 (10%)
Brain metastases (n, %)	7 (7%)	6 (33%)	1 (10%)

AKPS – Australia-modified Karnofsky Performance Scale; CIRS – Cumulative Illness Rating Scale; CCI – Charlson Comorbidity Index; CRAS-M – Clinician Rated Anticholinergic Scale – modified version; MDAS – Memorial Delirium Assessment Scale ;SAA – serum anticholinergic activity; SD – standard deviation

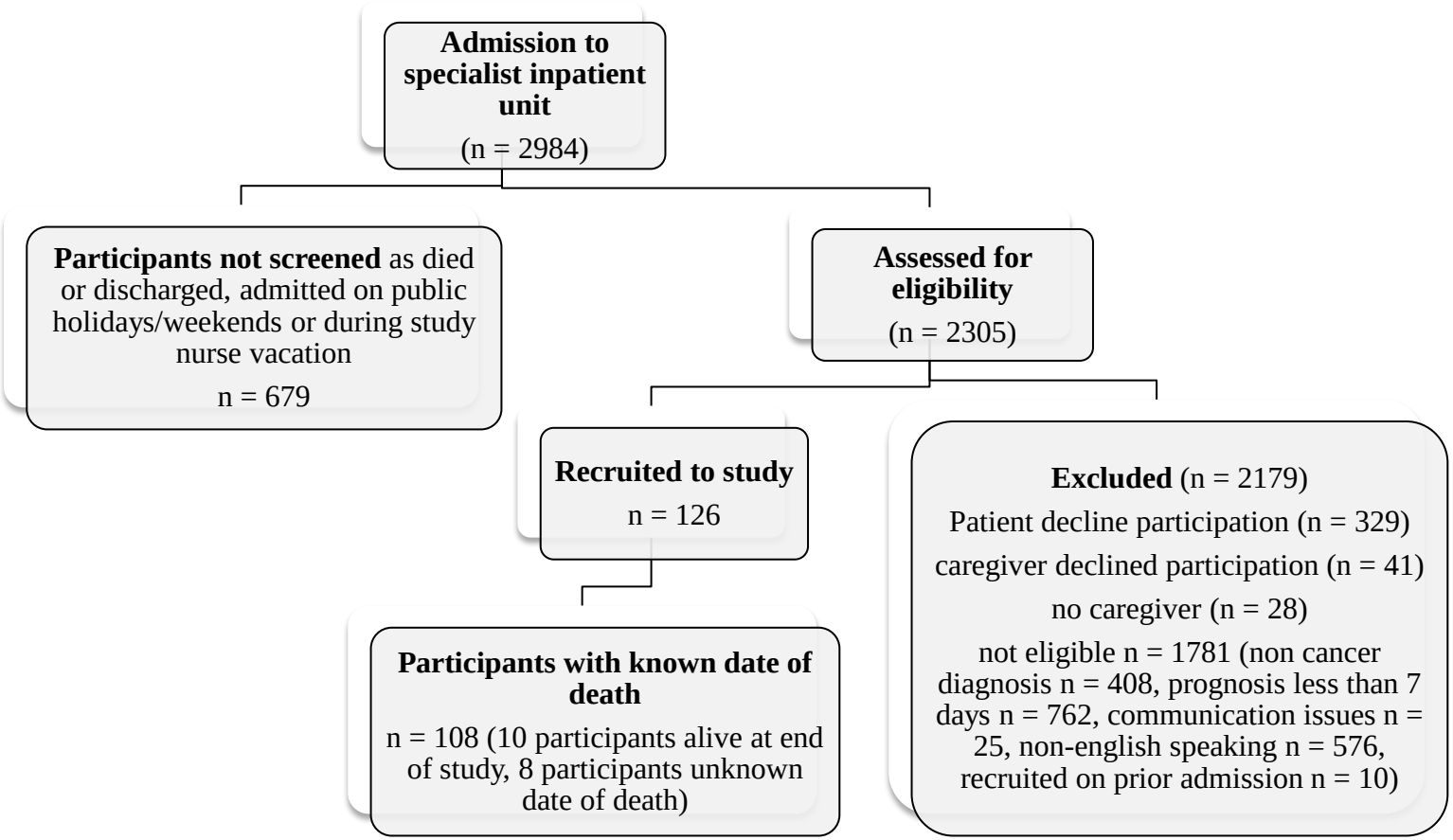


Figure 12 Flow of participants from admission to palliative unit to participation in study

5.5.2 *Memorial Delirium Assessment Scale total score at baseline*

The mean MDAS score at baseline was 5 (median 4, range 0–22, SD 4.6). At baseline, 19 participants (15%) had a MDAS score above 10. MDAS baseline score was not associated with age or gender. There was a strong association between baseline performance status (measured by AKPS) and MDAS (Figure 13).

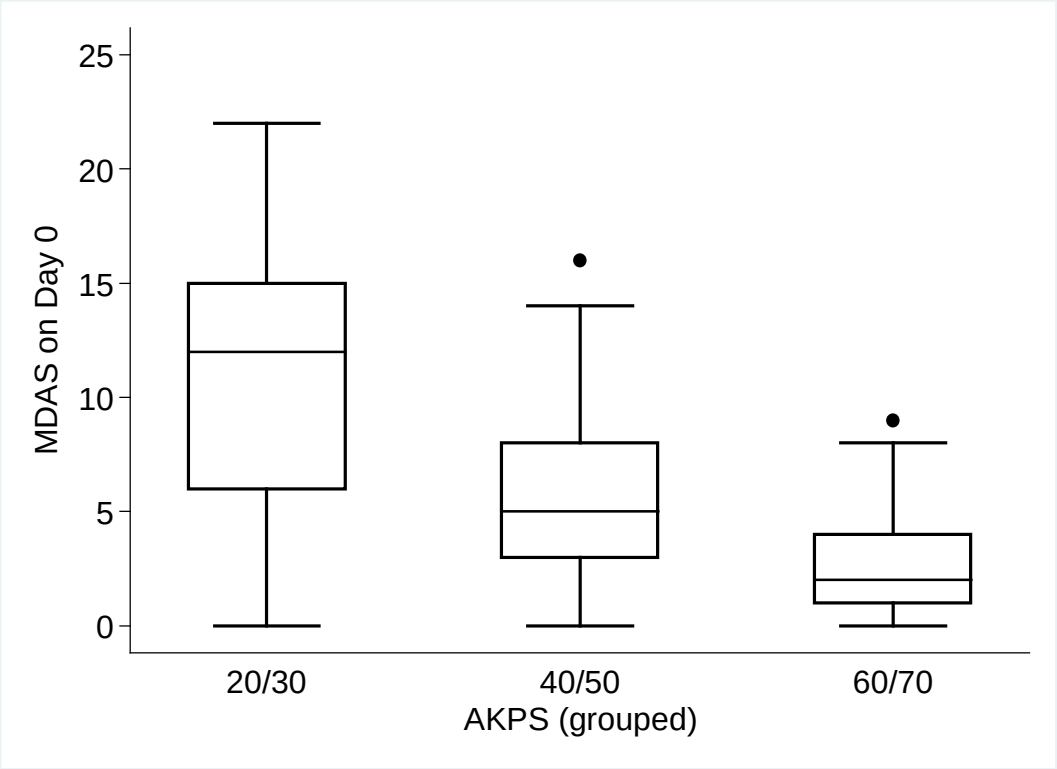


Figure 13 Box plot showing Memorial Delirium Assessment Scale total score on Day 0 by Australia-modified Karnofsky Performance Scale by three categories (n = 126)

5.5.3 *Serum anticholinergic activity at baseline*

The mean SAA at baseline was 19.2 pmol/ml (n = 121, median 16.3, range 1.8–65.2, SD 13.4). A baseline SAA was not available for five participants. There was no association of baseline SAA with AKPS or gender. There was a trend towards lower SAA in older patients (Figure 14).

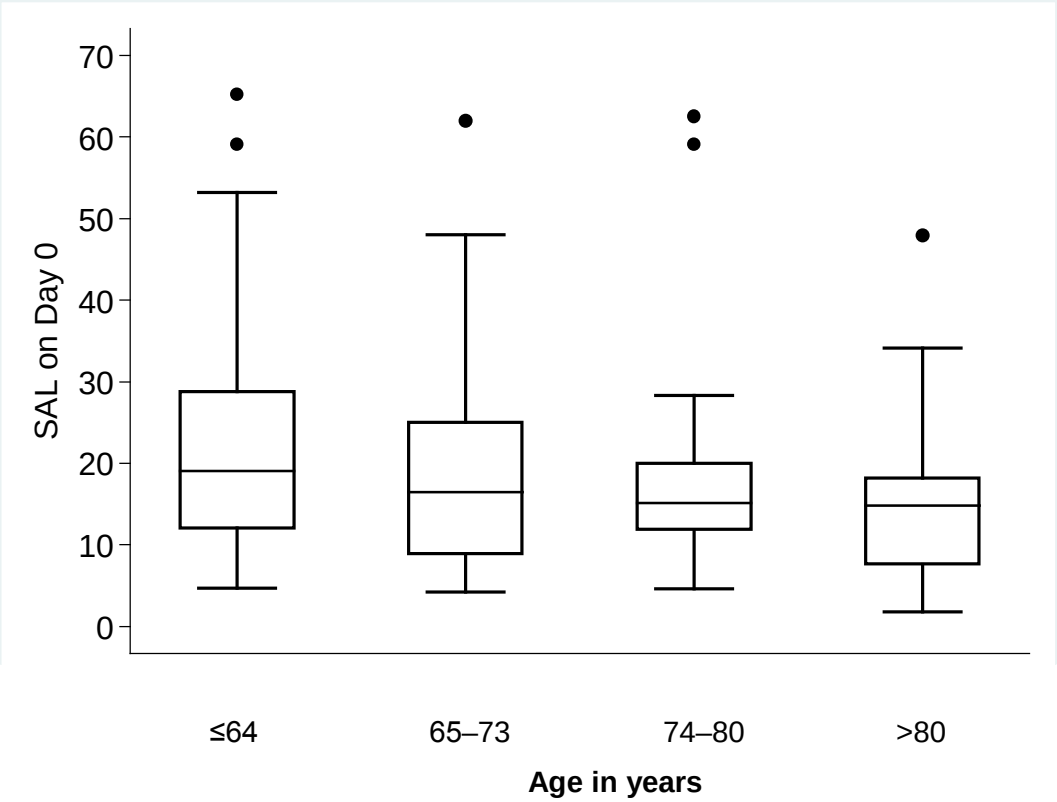


Figure 14 Box plot showing serum anticholinergic activity on Day 0 by age group

5.5.4 Association between serum anticholinergic activity and Clinician Rated Anticholinergic Scale-modified version at baseline

The mean CRAS-M score at baseline was 2.14 (median 2, range 0–6, SD 1.35). There is poor correlation between SAA and CRAS-M score at baseline (Figure 15), indicating no association (Spearman's rho = 0.14, p = 0.12). SAA was not correlated with the number of anticholinergic medications (Spearman's rho = 0.11, p = 0.24). A Lowess curve has not been fitted as there is no relationship between SAA and CRAS-M. The CI of the correlation coefficient was calculated using the bootstrap approach, which was –0.03 to +0.03 supporting that sample size has provided adequate power sufficient to show CRAS-M is not useful to predict SAA.

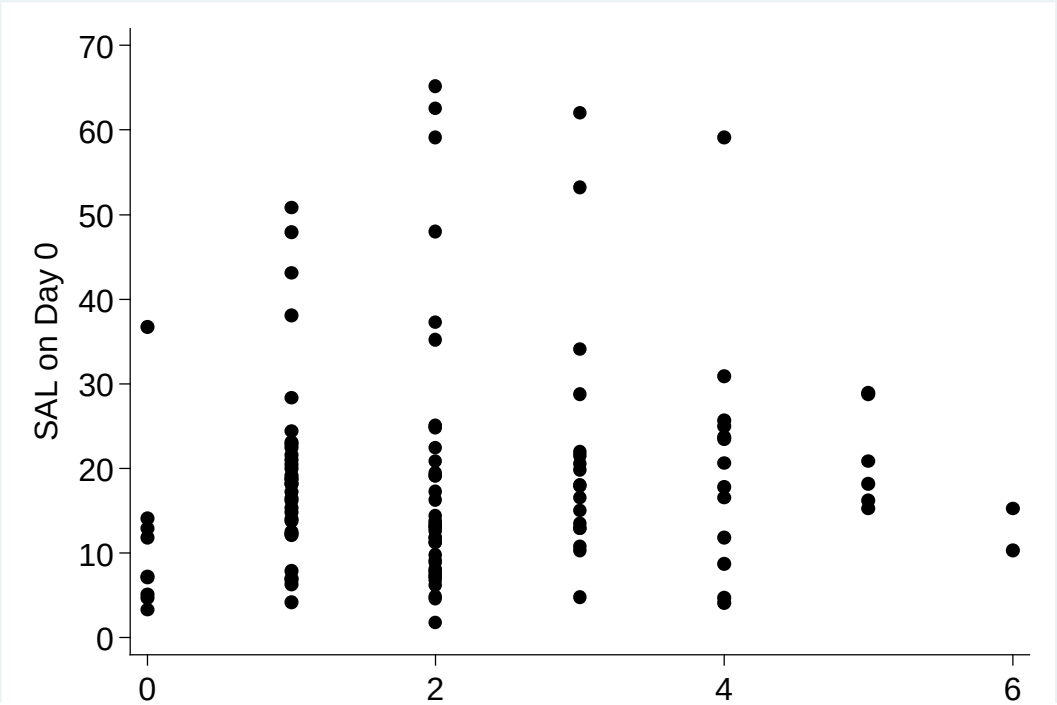


Figure 15 Scatterplot of serum anticholinergic activity versus clinician rated anticholinergic load at baseline

CRAS-M at baseline, as expected was strongly correlated with the number of anticholinergic medications (Spearman's r = 0.85, p < 0.001).

5.5.5 Association of serum anticholinergic activity and Memorial Delirium Assessment Scale at baseline

There is weak negative correlation between SAA (n = 121) and MDAS at baseline, which is not statistically significant (Spearman's rho = –0.16, p = 0.081) (Figure 16). This is predominantly due to increasing SAA associated with decreasing MDAS in the group with AKPS of 20 or 30, but was still not statistically significant (Spearman's rho = –0.32, p = 0.12). The CI of the correlation coefficient was calculated using the bootstrap approach, which was –0.33 to 0.01 supporting that sample size has provided adequate power sufficient to show SAA is not useful to predict baseline MDAS (as most of the CI is in negative region).

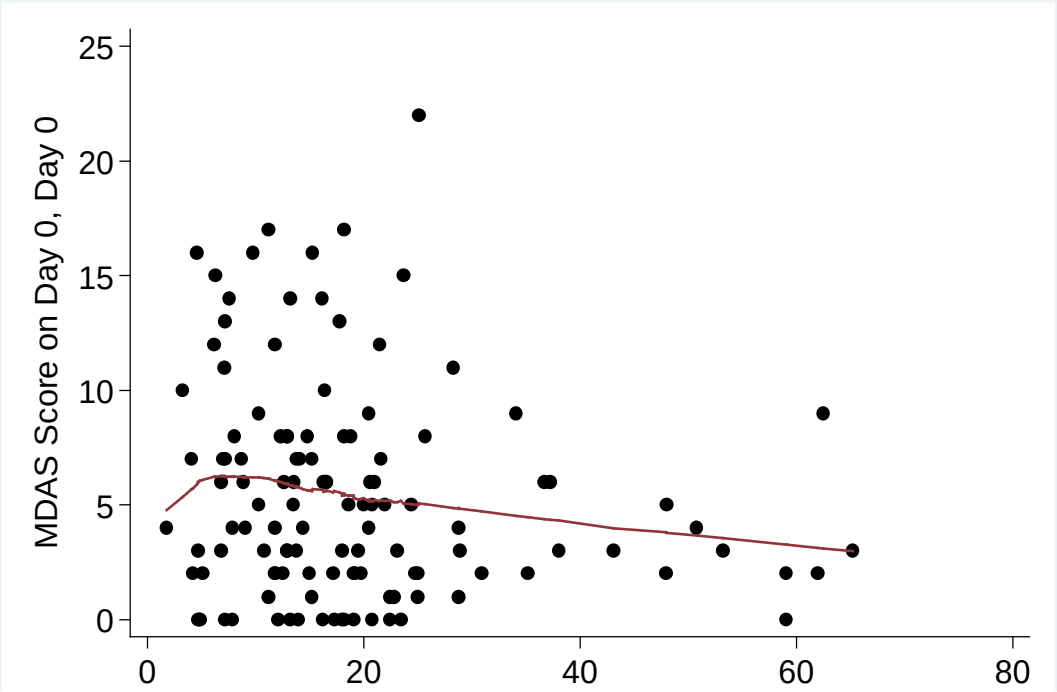


Figure 16 Scatterplot and Lowess curve of Memorial Symptom Assessment Scale versus serum anticholinergic activity at baseline (Day 0)

The fitted line is a non-parametric Lowess curve, intended to reveal the shape of any relationship

5.5.6 Association between serum anticholinergic activity and oral morphine equivalents, oral diazepam equivalents, oral morphine equivalents at baseline

There was no significant correlation between oral morphine equivalents (n = 120, Spearman's rho = 0.18, p = 0.05), oral diazepam equivalents (n = 119, Spearman's rho = 0.17, p = 0.06), and oral dexamethasone equivalents (n = 120, Spearman's rho = 0.002, p = 0.97) (Figures 17a, 17b, 17c).

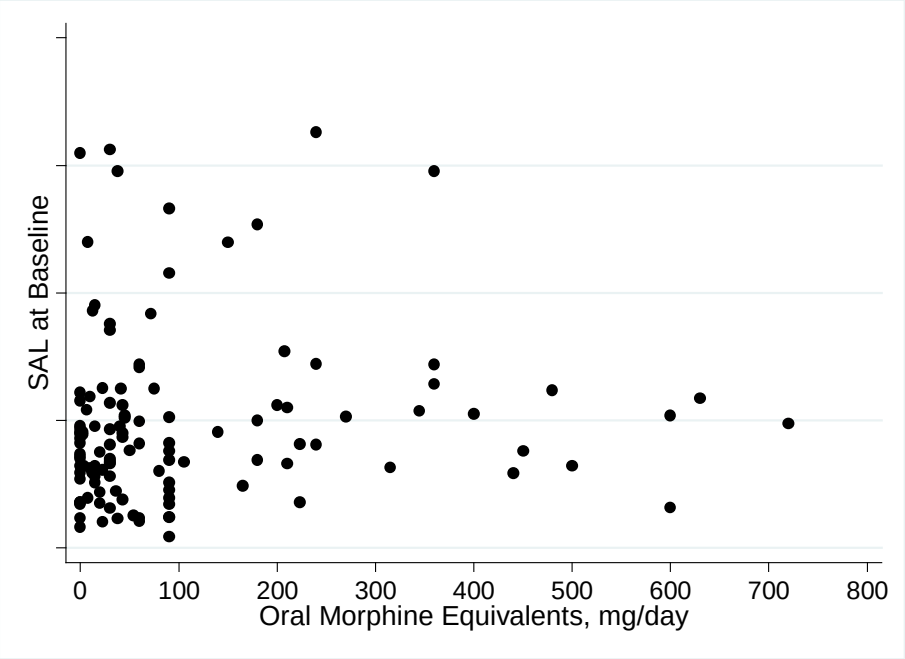


Figure 17a Scatter plot of serum anticholinergic activity and oral morphine equivalents at baseline (Day 0) (p=0.05)

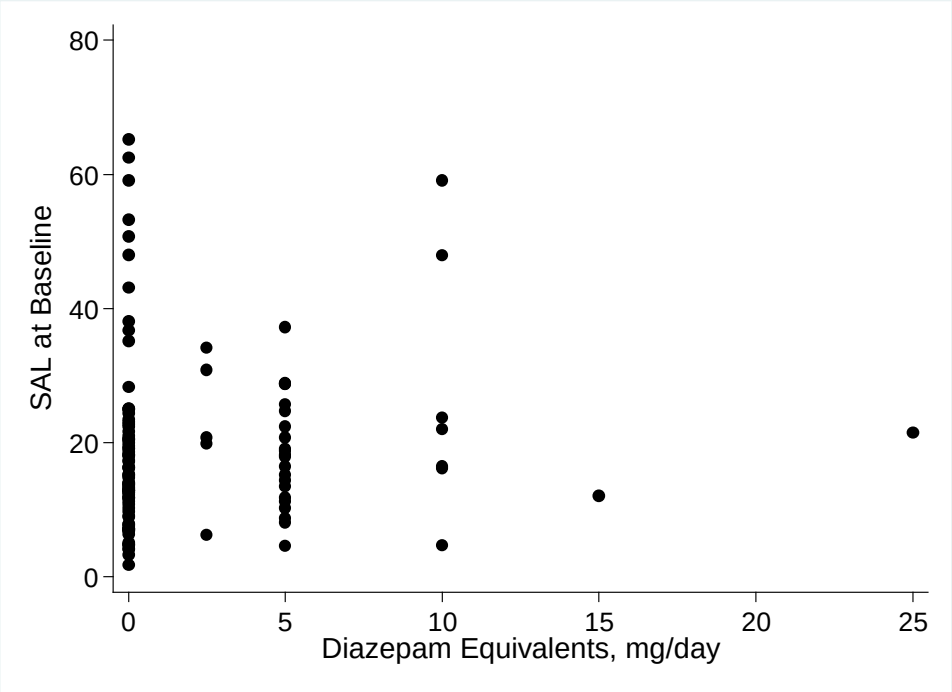


Figure 17b Scatter plot of serum anticholinergic activity and oral diazepam equivalents at baseline (p=0.06)

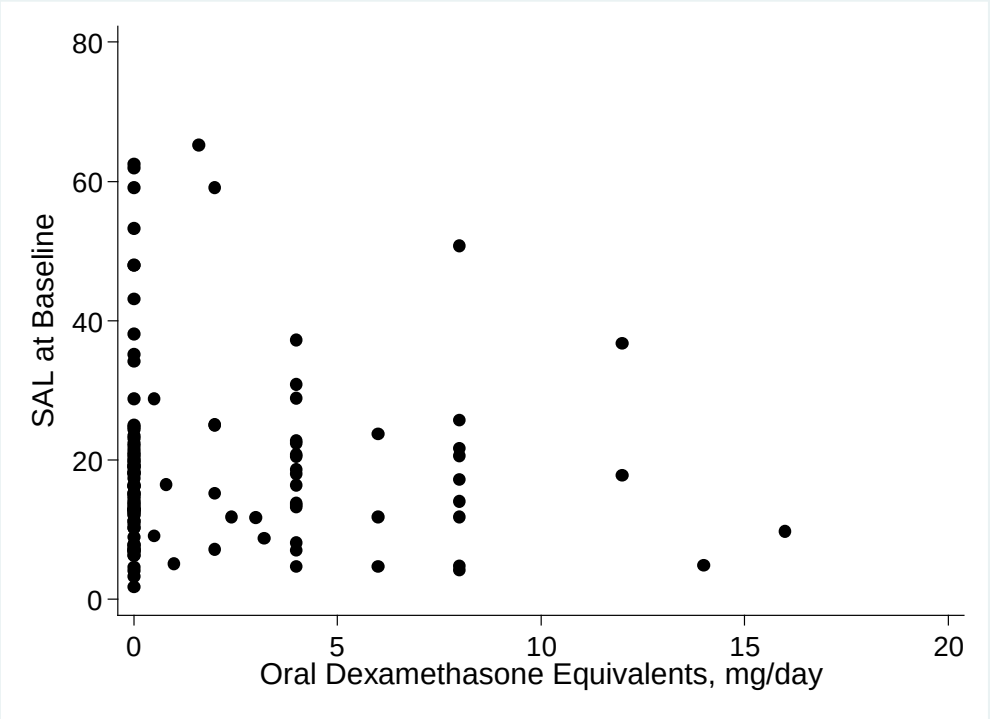


Figure 17c Scatter plot of serum anticholinergic activity and oral dexamethasone equivalents at baseline (p=0.97)

5.5.7 Memorial Delirium Assessment Scale scores over time

The following graphs (Figures 18 and 19) show the mean MDAS item scores over time, with baseline, Day 7, Day 14 and Day 20 graphed. Figure 18 is for all participants with and without delirium, whereas Figure 19 only includes participants with delirium. In patients with delirium disorientation, memory, attention and digit span are the items most affected (higher mean scores, and larger number of participants with abnormality in these items). The limitation of this method is changes in item mean scores could be due to participant drop out rather than change in the mean score; however, the general picture is of stability in symptom profile. For Figure 11 at Day 0 there are 37 participants, Day 7 has 19 participants, Day 14 has seven participants and Day 20 has one participant.

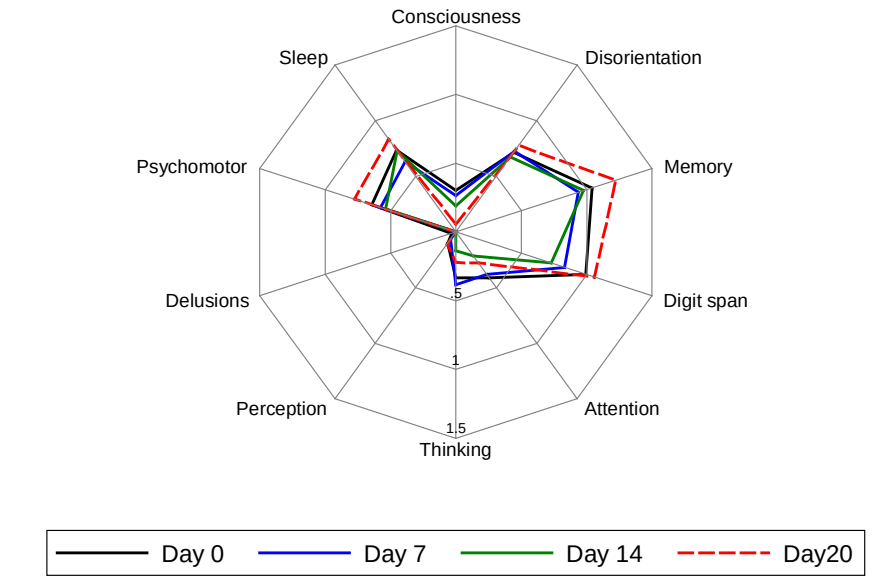


Figure 18 Radar graph of mean Memorial Delirium Assessment Scale scores over 20 days for all participants

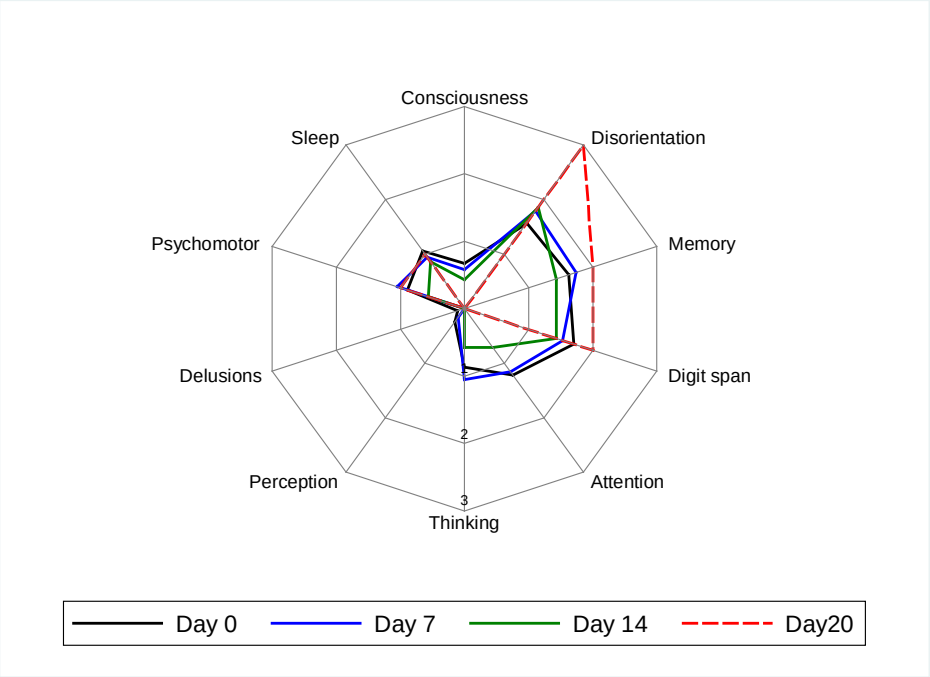


Figure 19 Radar graph of mean Memorial Delirium Assessment Scale scores over 20 days for participants who had either incident or prevalent delirium

5.5.8 Longitudinal association between serum anticholinergic activity and Memorial Delirium Assessment Scale

Patterns of missing MDAS items over the study duration were initially explored, and the rate was low overall. Out of 10,640 total MDAS items (item scores) only 1258 (11.8%) were missing. The proportion of missing values for each MDAS item was similar, ranging from 11.6%–12.1%, as the main reason for missing items was when a subject could not be scored on all items. In participants who could be scored on some items, item 2 (disorientation), item 3 (short term memory impairment), item 4 (impaired digit span), item 5 (attention) and item 6 (disorganised thinking) have the highest proportion of missing values, and are all items which are assessed on interview with the participant; however, the differences are small (0.5% difference). Item 9 (psychomotor activity) had no missing values as it is determined by observation. There is no evidence that AKPS has affected 'missingness'; patients with an AKPS of 20 have around 12% missing scores, about the same as patients with an AKPS of 70. Hence it does not seem that patients with low AKPS have more difficulty in completing items.

The time period x SAA interaction was not statistically significant ($p = 0.096$). However, it was included in the model as association between SAA and MDAS

may not remain constant over the 21 days. The model was also run using days instead of the pre-specified time periods, and there was no consistent difference in predicted in MDAS among days within periods.

The results of the log – gamma model shows that there is an association between SAA and MDAS, and this was statistically significant (p = 0.0047).

The multiplicative change in MDAS for a one-unit increase in SAA for Periods 2–5, and significance levels is shown in Table 44, and graphically in Figure 20. The association between Day 0 SAA and MDAS is statistically significant only in Period 1 (ie Day 0). The simplest interpretation of the model is there is a negative association between SAA and MDAS on Day 0, but this does not persist for the subsequent days' MDAS scores.

Table 44 Predicted multiplicative changes in Memorial Delirium Assessment Scale score for a one-unit increase in serum anticholinergic activity

	Period 1	Period 2	Period 3	Period 4	Period 5
Change in MDAS	0.988	0.997	1.002	0.993	0.993
p-value	0.0260	0.620	0.760	0.230	0.260

MDAS – Memorial Delirium Assessment Scale

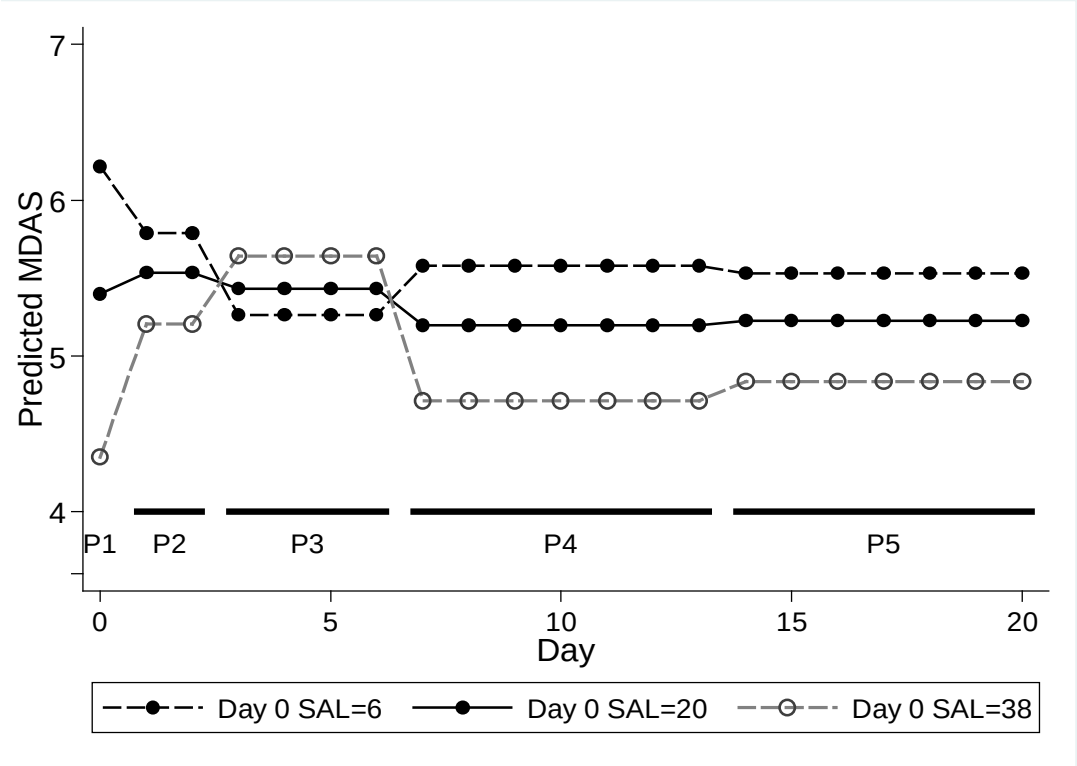


Figure 20 Predicted Memorial Delirium Assessment Scale values for model

Key: The text ‘P1’, ‘P2’, etc denote the different periods. The three lines denote an average patient with Day 0 SAL of 6, an average patient with Day 0 SAL of 20, and an average patient with Day 0 SAL of 38 respectively. SAL = serum anticholinergic level and is synonymous with serum anticholinergic acticity

However, as this study was a longitudinal cohort results can be distorted by non-random dropout, with duration of participation of patients in the study being associated with Day 0 SAA or MDAS. The mean MDAS for each period showed evidence of a trend to reduced mean MDAS scores over time (mean MDAS Day 0: 5.6, Days 1–2: 5.9, Days 3–6: 5.1, Days 7–13: 4.8 and Days 14–20: 4.2). This suggests that in part, the patients with higher mean MDAS scores may be dropping out earlier.

Adjustment for site of care (Braeside/Sacred Heart), age and gender made no difference to the model (Table 45). However, after adjustment for AKPS, the exponentiated coefficient of SAA became closer to 1, and no longer made a significant contribution to the model.

Table 45 Effect of including possible confounding factors as main effects in the model

	Exponentiated coefficients after adjustment for:				
	Unadjusted	Site of care	Age	Gender	AKPS
SAA	0.988	0.991	0.988	0.988	0.995
Period 2 SAA	1.009	1.008	1.009	1.009	1.006
Period 3 SAA	1.014	1.013	1.014	1.014	1.012
Period 4 SAA	1.006	1.004	1.006	1.005	1.005
Period 5 SAA	1.005	1.004	1.005	1.005	1.001
Overall SAA p-value	0.005	0.013	0.014	0.005	0.200
Adjusting factor p-value	n/a	0.070	0.880	0.390	< 0.001

AKPS – Australia-modified Karnofsky Performance Scale; SAA – serum anticholinergic activity

The AKPS x SAA X time period interaction was statistically significant (p = 0.006). The model was repeated using subsets of data based on AKPS (group 1 AKPS 20 and 30, group 2 AKPS 40 and 50, group 3 AKPS 60 and 70). The time period x SAA interaction is significant only for patient group with AKPS of 20 or 30. Thus there is only evidence for an association between MDAS and baseline SAA in patients with AKPS of 20 or 30. The predictive values for the three models by AKPS group, is shown in Figures 13a, 13b and 13c. Overall, predicted MDAS scores are much lower in the group with AKPS 40–50 and AKPS 60–70, than in AKPS 20–30.

Figures 21a, 21b and 21c show the predicted MDAS values (logarithmic scale) for the statistical model fitted separately to subsets of patients defined by AKPS. In the raw data for Period 1 (Day 0) mean MDAS of patients with AKPS = 20 and 30 in the lowest SAA category (SAA <13) is 1.35 times greater that that in the highest SAA category, compared to 1.20 times and 1.03 times in patients with AKPS of 40 and 50; and 60 and 70 respectively.

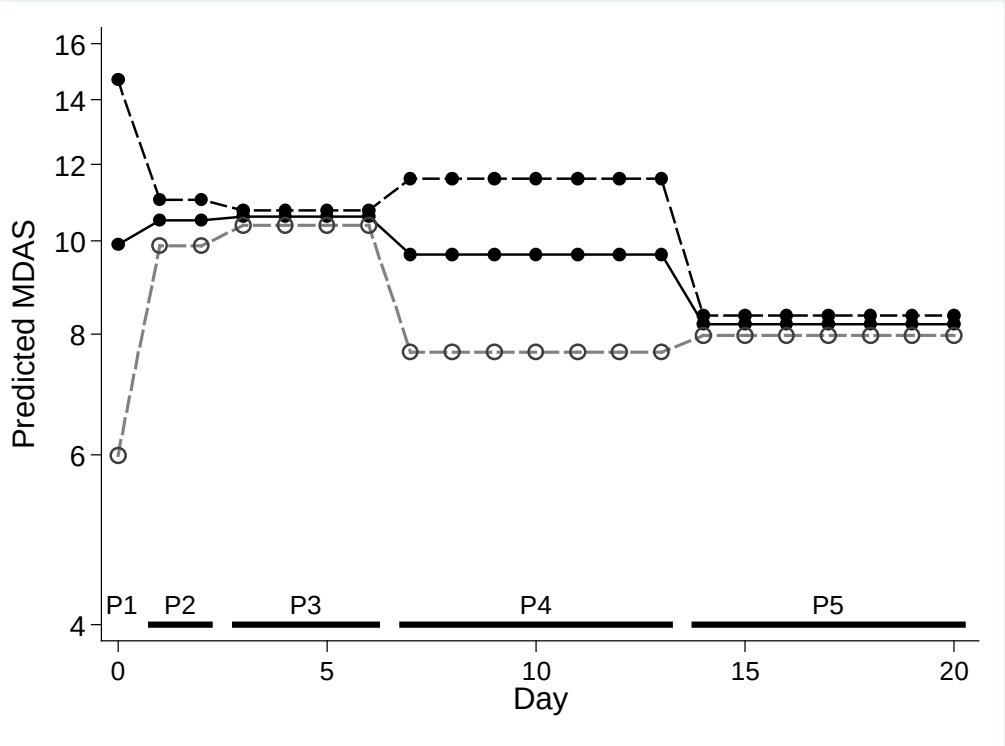


Figure 21a Australia-modified Karnofsky Performance Scale 20 and 30

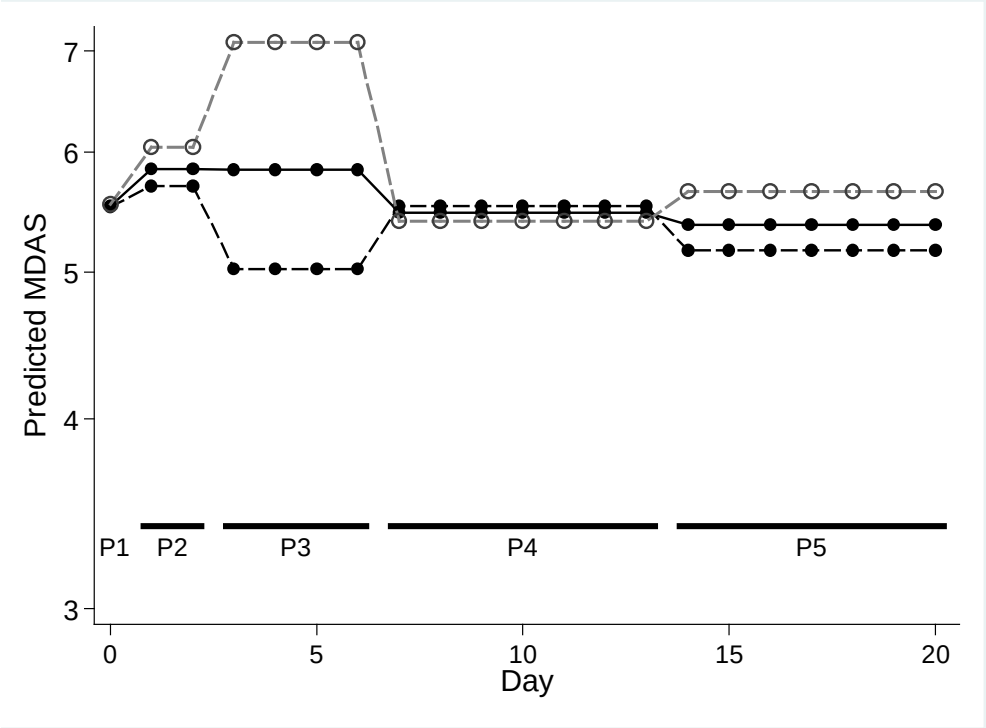


Figure 21b Australia-modified Karnofsky Performance Scale 40 and 50

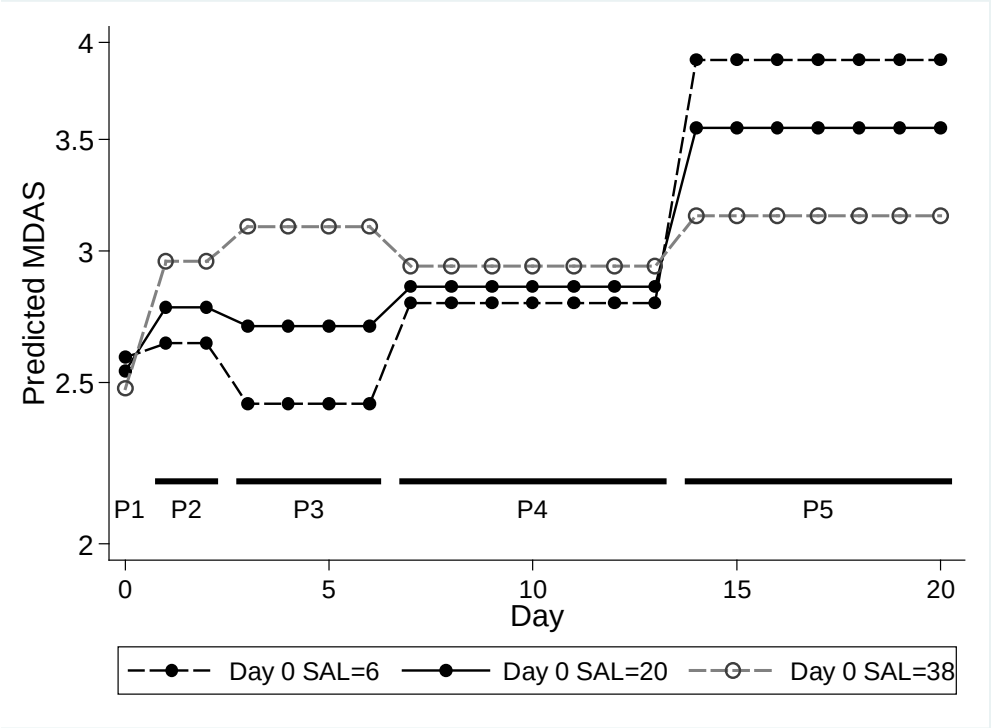


Figure 21c Australia-modified Karnofsky Performance Scale 60 and 70

Key: The graphs for each AKPS category have different y axis scales. The text 'P1', 'P2', etc denote the different periods. The three lines denote an average patient with Day 0 SAL of 6, an average patient with Day 0 SAL of 20, and an average patient with Day 0 SAL of 38 respectively. SAL = serum anticholinergic level and is synonymous with SAA

To assess this further, Spearman's correlation between SAA and MDAS at baseline (Day 0) was calculated, and was much higher (more negative) in patients with AKPS of 20 or 30 than in other patients; however, was not statistically significant (Table 46).

Table 46 Spearman correlations on Day 0, by Australia-modified Karnofsky Performance Scale

AKPS (n in the subgroup)	Spearman's correlation between SAA and MDAS on Day 0 (p-value)
20 and 30 (n = 25)	–0.32 (0.12)
40 and 50 (n = 51)	–0.06 (0.68)
60 and 70 (n = 45)	0.01 (0.93)

AKPS – Australia-modified Karnofsky Performance Scale; MDAS – Memorial Delirium Assessment Scale; SAA – serum anticholinergic activity

5.5.9 Episodes of delirium

The distribution of MDAS scores at baseline and at Day 7 are outlined in Table 47.

Table 47 Distribution of Memorial Delirium Assessment Scale scores at baseline and at Day 7

MDAS score	Baseline (n, %)	Day 7 (n, %)
MDAS <7	86 (68%)	52 (69%)
MDAS 7–9	21 (17%)	13 (17%)
MDAS ≥10	19 (15%)	10 (13%)
Total:	126	75

MDAS – Memorial Delirium Assessment Scale

Prevalent delirium (defined as MDAS ≥10) was present in 19 participants (15%), as seen in Table 47. Incident delirium (defined as MDAS score ≥10 on any day after baseline) occurred in 18 participants (14%), and day of occurrence ranged from Day 1 to Day 13 from baseline. No delirium occurred in 89 participants (defined as MDAS score <10 for whole study period).

5.5.10 Serum anticholinergic activity at baseline compared to delirium occurrence

Figures 22a and 22b illustrates the SAA levels for the three groups of no, prevalent or incident delirium; utilising an MDAS cut-off of 10 and 7 respectively. SAA did not differ significantly between the three groups.

Figure 22a shows the Box plot of SAA at baseline with three groups (utilising MDAS cut-off for delirium of 10): prevalent delirium (MDAS ≥10 at baseline), incident delirium (MDAS ≥10 at any time point after baseline) and no delirium (MDAS never over 10):

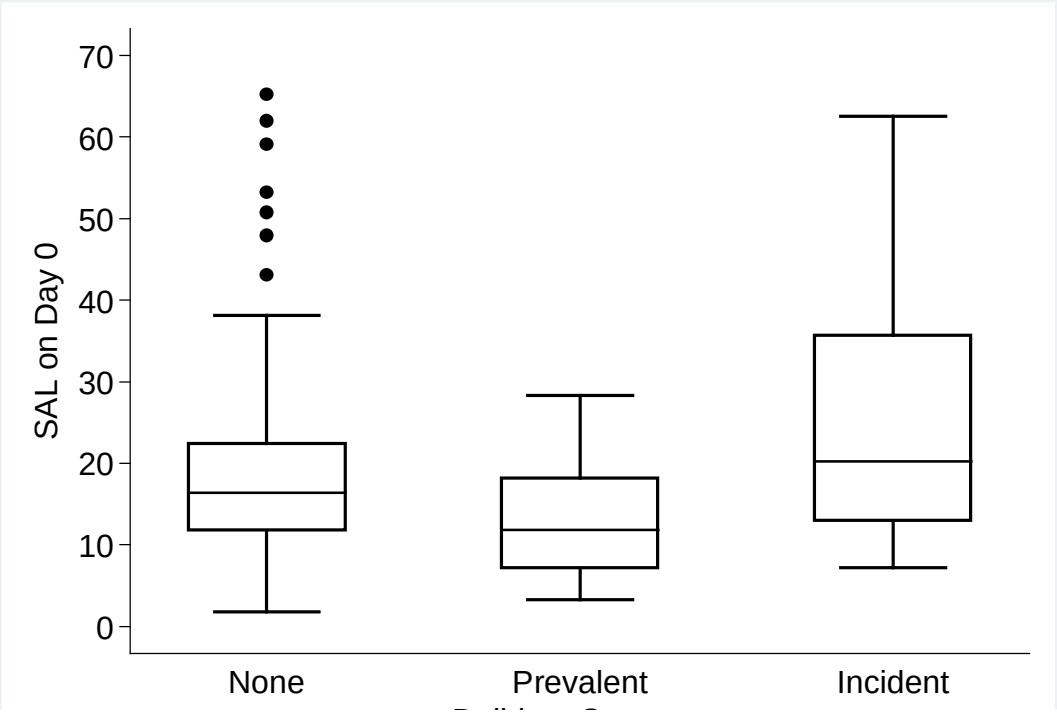


Figure 22 a Memorial Delirium Assessment Scale cut-off for delirium of 10

Figure 22b shows the Box plot of SAA at baseline with three groups (utilising MDAS cut-off for delirium of 7): prevalent delirium (MDAS ≥7 at baseline), incident delirium (MDAS ≥7 at any time point after baseline) and no delirium (MDAS never over 7):

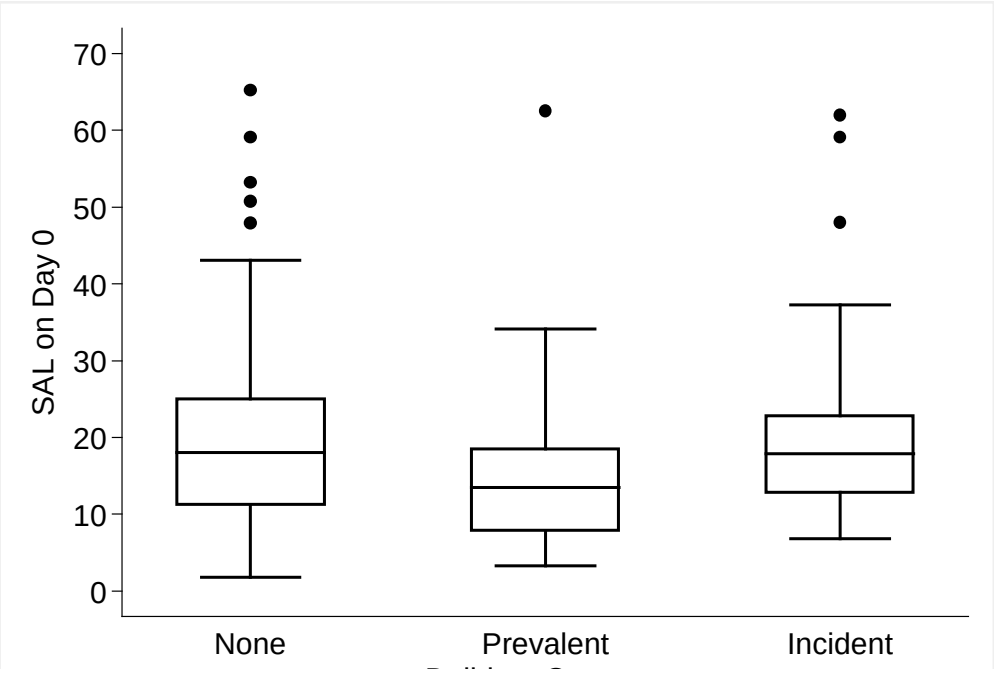


Figure 22 b Memorial Delirium Assessment Scale cut-off for delirium of 7

5.5.11 Predictive ability of serum anticholinergic activity for occurrence of delirium

Previous analyses have considered MDAS as a continuous variable. In this logistic regression analysis a cut-off of ≥10 was used to define delirium occurrence. Thirty-seven out of 126 (29%) participants had a delirium episode between Day 0 and Day 21. Logistic regression shows no significant predictive ability for SAA at baseline for delirium defined as MDAS score of 10 or greater ($p = 0.9$).

A similar logistic regression utilising a cut-off of 7 or greater also showed no predictive ability of SAA at baseline for delirium (at baseline or during 20 days of admission). This is supported further by the ROC examining all possible cut-off scores (Figure 23) that shows there is no cut-off with good sensitivity or specificity.

Only seven participants had a second SAA measure at the time of delirium, with a mean level of 25.5 pmol/ml (median 21, SD 20.4, range 8.4–69.2). Another 68 participants had an SAA measure at or around Day 7 (ranged from day 6 to 9), with mean level of 15.3 (median 15.3, SD 10.6). Hence in total, 75 participants had a second SAA with a mean level of 16 (median 18.2, SD 11.9).

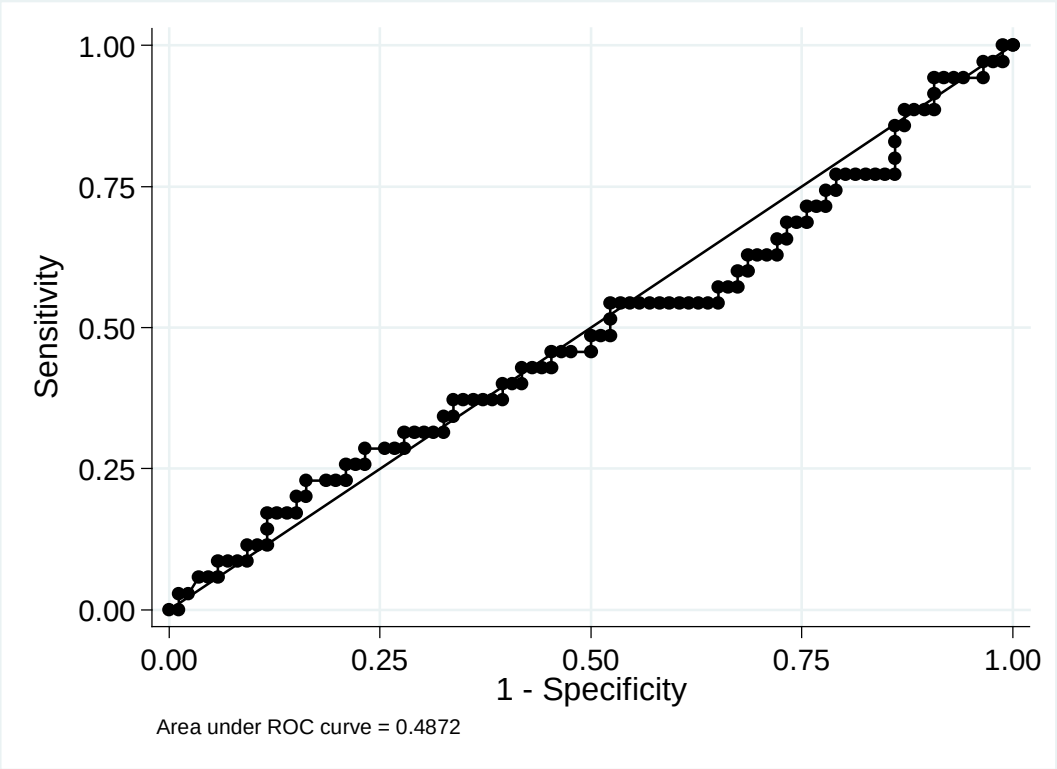


Figure 23 Receiver operator curve assessing predictive ability of baseline serum anticholinergic activity and occurrence of delirium

The area under the ROC is 0.49 indicating no worthwhile predictive value (an area of 0.5 corresponds to no predictive value).

5.5.11.1 Regression analyses with Memorial Delirium Assessment Scale as a continuous outcome

The ability of clinical variables at admission to predict for MDAS score was explored using random effects regression analysis.

Table 48 Baseline clinical variables and association with Memorial Delirium Assessment Scale score over time

Predictor variable (at baseline)	Overall model Overall model p value[a]	Predictor variable x time PERIOD interaction (p value)[b]	Main effect of main effect of predictor (p value)[c]
Age	0.71	0.79	0.26
AKPS (3 categories)	<0.001	0.17	<0.001*
Brain metastases	0.015	0.27	0.002*
CRAS-M	0.65	0.29	0.99
CIRS	0.006	0.81	<0.001*
CCI	0.09	0.13	0.20
Oral morphine equivalent	0.072	0.30	0.10
Fever	<0.001	0.77	0.15
Oral dexamethasone equivalents	0.85	0.68	0.63
Oral diazepam equivalents	0.13	0.31	0.014[d]

[a] Model fitted utilising MDAS as outcome, with variables of interest, time period, time period x variable of interest interaction
[b] Assess the significance of time period x variable of interest interaction
[c] If time period x variable of interest interaction is non-significant fit a model of time period and variable of interest only.
[d] significant
AKPS – Australia-modified Karnofsky Performance Scale; CCI – Charlson Comorbidity Index; CIRS – Cumulative Illness Rating Scale; CRAS-M – Clinician Rated Anticholinergic Scale – modified version

Age, CRAS-M, CCI score, oral morphine equivalents and oral dexamethasone equivalents showed no evidence of association with MDAS. The influence of AKPS on MDAS is displayed previously Figure 21.

The presence of cerebral metastases was associated with a 1.63 fold (CI 1.20–2.22) increase in MDAS, with no evidence that this factor varied over Days 0 to 20. CIRS was associated with MDAS; a one-unit increase in CIRS was associated with an increase in MDAS by a factor of 1.055 units (CI 1.028–1.082). There was no evidence that this factor varied over Days 0 to 20.

Oral diazepam equivalents showed some evidence of association with MDAS. An increase in diazepam equivalents of 1 mg was associated with an increase in MDAS by a factor of 1.04 (CI 1.01–1.07).

5.5.12 Potential clinical factors which could act as surrogate markers of serum anticholinergic activity

Ordinary least squares regression results with SAA at baseline as outcome and the clinical variables of interest at baseline are outlined in Table 49.

Table 49 Ordinary least squares regression serum anticholinergic activity and clinical variables at baseline

Predictor variable (at baseline)	p value
Age	0.007[a]
AKPS (3 categories)	0.092
Brain metastases	0.420
Oral morphine equivalents	0.280
Oral diazepam equivalents	0.300
Total number of medications	0.780
Presence of fever	0.940
CIRS	0.570
CCI	0.220

[a] significant
AKPS – Australia-modified Karnofsky Performance Scale; CIRS – Cumulative Illness Rating Scale; CCI – Charlson Comorbidity Index

Only age was associated with SAA. A one-year increase in age was associated with a 0.305pmol/ml (95% CI 0.085–0.526) unit decrease in SAA. The association was not strong, with a Spearman's correlation coefficient being –0.24.

5.5.13 Survival

Participants (n = 108) with known dates of death were included in the analyses. Baseline SAA and age were divided into three equal sized categories for the analysis Patients with AKPS survived substantially longer; those with AKPS 60 slightly longer than participants with lower AKPS (see Figure 24).

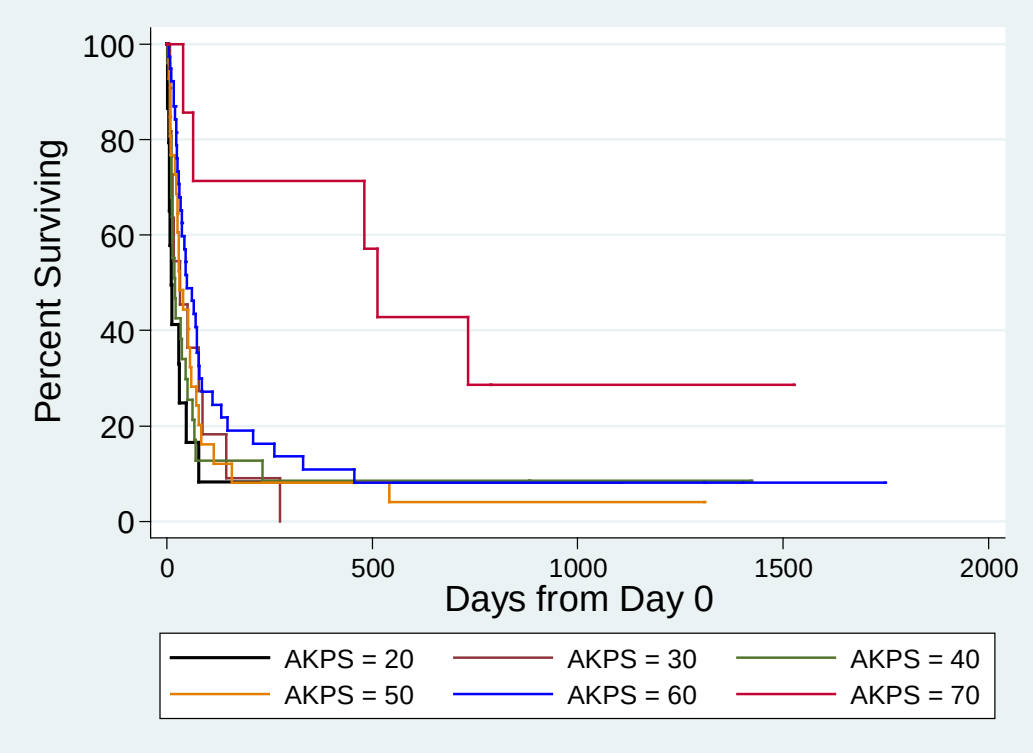


Figure 24 Kaplan Meier plot showing survival by AKPS

Figure 25 shows that younger participants have longer survival times.

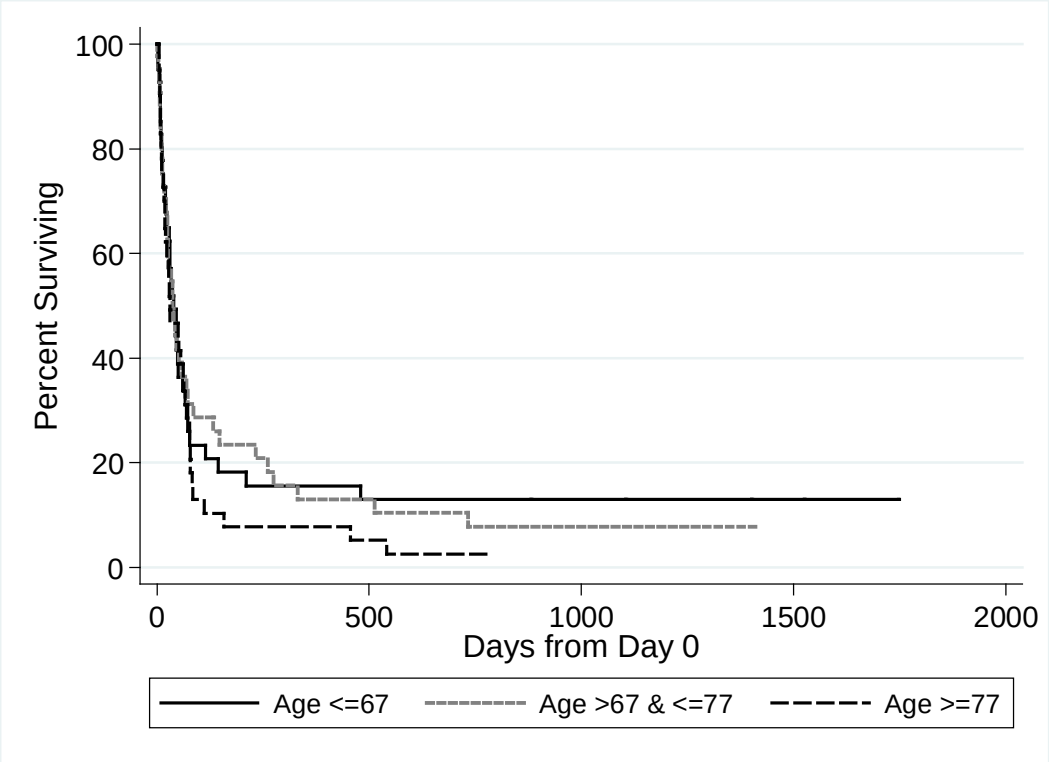


Figure 25 Kaplan Meier plot showing survival by age

Figure 26 shows unadjusted survival by SAA at baseline. The median survival time overall is 37 days (95% CI 28–50 days). Median survival times are 30, 45 and 40 days in the low, medium and high SAL categories respectively. Patients with SAA ≤13 seem to be at a lower risk of dying during most of the first year, but the difference is small. Cox regression without adjustment for potential risk factors (age, AKPS) shows no significant heterogeneity in hazard of dying in the three categories of baseline SAA (low ≤ 13, medium >13 and <20.8, and high ≥20.8 categories) (p = 0.99). After adjustment for age and AKPS, SAA at baseline still has no significant effect on survival (p = 0.956). Patients with AKPS of 70, and to a lesser extent AKPS of 60, have significantly longer survival than do those with AKPS of 20 (p = 0.002 and 0.031 respectively).

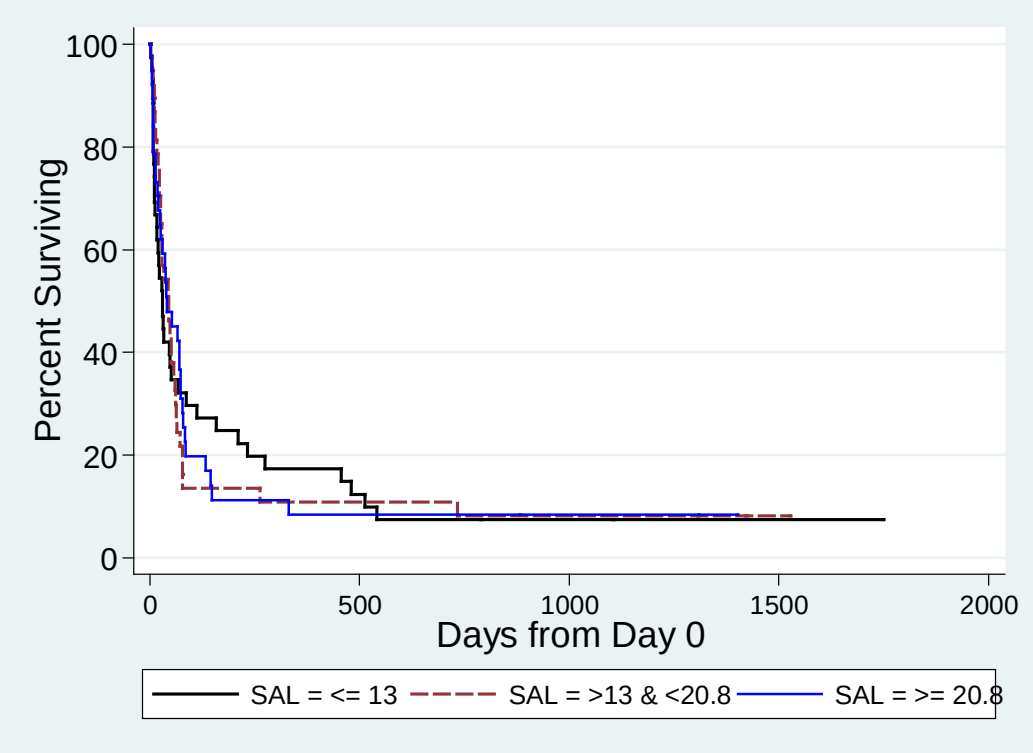


Figure 26 Kaplan Meier plot showing survival by serum anticholinergic activity (p=0.99)

5.5.14 Outcomes

Seven falls occurred (two in patients with incident delirium), 20 participants developed new onset incontinence (five with incident delirium, and five with prevalent delirium), seven participants developed new pressure areas (two with incident delirium) and one participant who did not experience delirium was discharged to residential aged care. As the number of events of interest was small no further analyses were conducted. Twelve participants (9.5%) had a MDAS that was ≥10 for the whole admission. The range of duration of delirium for the 37 participants with prevalent or incident delirium (defined as consecutive days with MDAS ≥10) was 1–11 days. Thirty-four participants (26.9%) died during the index admission (20 participants from Braeside Hospital and 14 participants from Sacred Heart Hospice). Thirty-five per cent of those participants who died had delirium during the course of the index admission. Of those who died, seven had prevalent delirium (5.5% of total sample; 20.5% of those who died during the admission) and five had incident delirium (3.9% of total sample; 14.7% of those who died during the admission). The mean length of admission to discharge or

death for participants from Braeside Hospital was 10.3 days (range 1–34) with 722 days of data. The mean length of admission to discharge or death for participants from Sacred Heart Hospice was 15.9 days (range 1–80) with 892 days of data. The mean length of stay for patients with prevalent delirium (n = 19) was 8.8 days (range 1–17), and for incident delirium (n = 18) 4.2 days (range 2–27). Interestingly there was an increase in dose of opioids, corticosteroids and diazepam prescribed over time. Day 7 oral morphine equivalents were a mean of 126 (median 55, SD 190, range 0–1080), oral dexamethasone equivalents were mean 2.83 (median 0, SD 4.83, range 0–24) and oral diazepam equivalents were mean 2.84 (median 0, SD 6.37, range 0–50).

5.5.15 Other analyses

Given that the analyses thus far have not shown any predictive value of SAA, further analyses to explore SAA and CRAS-M were not performed.

5.6 Discussion

This study has found the rates of prevalent delirium in an Australian specialist inpatient palliative care setting to be 15 % (n = 19), incident delirium 14% (n = 18), with no delirium occurring in 29% of the sample (n = 37). Higher MDAS scores at baseline were associated with lower AKPS. The overall pattern of item scores remains reasonably stable over time consistent with the findings of Meagher et al[72], albeit this needs to be interpreted with caution due to the diminishing number of participants at time-points further from admission.

5.6.1 Results of primary analysis

This is the first study to report SAA in a cohort of advanced cancer patients requiring inpatient palliative care, with mean SAA at baseline, was 19.2 pmol/ml (SD 13.4, 1.8–65.2). The mean SAA at baseline for the group who had prevalent delirium was 14pmol/ml (SD 7.2, range 4.6–28.3), and for those subsequently developed delirium (incident delirium) was 28.3pmol/ml (SD 21.7, range 10.3–62.5). For those participants with SAA taken in proximity to delirium episode the mean was 25.5 pmol/ml (SD 20.4, range 8.4–69.2). Contrary to other studies we did not find an increase at delirium episode.

SAA showed a weak negative correlation with MDAS score at baseline (Spearman's r = –0.16, p = 0.08). When broken down by AKPS, only participants with AKPS of 20 or 30 showed any evidence of association between SAA and MDAS, but this was still not statistically significant (Spearman's r = –0.32, p = 0.12). The ability to achieve statistical significance may be poor due to the small numbers in these subsets of participants.

The first model utilised generalised estimating equations to explore the predictive ability of SAA at baseline to predict subsequent MDAS scores over time. The log-gamma model showed evidence of association, but only at baseline (p = 0.0047). Equally when MDAS was considered categorically, with MDAS cut-off of 10 and above to denote delirium, logistic regression analysis did not show any predictive ability for SAA and delirium (p = 0.9).

Further analysis found AKPS to be the only risk factor of interest. The association between SAA and MDAS could be explained entirely on the basis that in patients with AKPS of 20 or 30, SAA and MDAS are negatively associated on Day 1 (i.e. higher SAA is associated with lower MDAS).

This finding suggests that the SAA levels seen in cancer patients are higher (20-50% higher then levels seen in medical inpatient cohorts), and the association of SAA and MDAS within the group with lower performance status (AKPS 20 and 30) suggests there may be contributing intrinsic factors associated with the dying process. The findings that SAA does not predict future occurrence of delirium is contrary to other studies where an association has been seen, however it is difficult to make direct comparisons as there have been divergent methodologies in terms of timing of SAA in relationship to delirium, including SAA at time of delirium, prior to anticholinergic premedication before anaesthetic, and SAA before and after of precipitants highlighted associated with delirium (surgery).

In relation to secondary objectives, SAA and CRAS-M score or number of anticholinergic medications at baseline showed no association.

5.6.2 Results of exploratory analyses

The second model explored the association of clinical factors at baseline and MDAS scores during admission. The random effects regression analysis demonstrated that the presence of cerebral metastases was associated with a 1.63-fold (CI 1.20–2.22) increase in MDAS. CIRS was associated with MDAS; a one-unit increase in CIRS was associated with an increase in MDAS by a factor of 1.055 units (CI 1.028–1.082). Oral diazepam equivalents showed some evidence of association with MDAS. An increase in diazepam equivalents of 1mg was associated with an increase in MDAS by a factor of 1.04 (CI 1.01–1.07).

Age, AKPS, CRAS-M score, CCI, presence of fever, oral dexamethasone equivalents, oral morphine equivalents and oral diazepam equivalents showed no association with MDAS scores over time. Only age was weakly associated with SAA, with a one-year increase in age associated with a 0.305 pmol/ml decrease in SAA. After adjustment for age and AKPS, SAA at baseline has no significant effect on survival ($p = 0.956$). A third of the patients with delirium died during the index admission.

5.6.3 What other data do these findings support or refute?

5.6.3.1 How does serum anticholinergic activity levels in advanced cancer compare with levels reported in the literature

A comparison of SAA levels in different populations is outlined in Chapter 1 Table 11. SAA levels reported in the literature measured with comparable methodology, demonstrate divergent levels, partly due to the studies including different populations and utilising different times of measurement. Time-points for SAA in studies conducted longitudinally have included SAA timed at time of delirium versus prior to delirium occuring, SAA prior and after anticholinergic premedication being given, and SAA before and after of precipitants highlighted associated with delirium (surgery). Cross-sectional studies have taken one SAA and delirium categorised as presence or absence so duration of delirium prior to SAA is not accounted for. All studies of delirium populations had small samples sizes, with total numbers under 70 participants. This poses some difficulty in comparisons of SAA between studies.

With the above stated limitations in mind, an initial comparison to make is the mean SAA levels seen in prior studies and how this compares with this advanced cancer cohort. Similar mean levels were found by Mussi et al[683], but only in the cohort of elderly geriatric inpatients who had delirium within 24 hours of admission (mean of 23.0 ± 15.5 pmol/ml). In general levels 20%–50% of the mean level seen at baseline in this cohort of advanced cancer have been seen in prior studies of medical inpatients[263 265 684] The only study which has shown substantially higher levels was of elderly pre-surgical patients receiving preoperative intramuscular scopolamine where mean SAA was 121.1 ± 85.5 pmol/ml. Levels have been shown to be higher in acute febrile illness (both with or without delirium) with levels decreasing as acute problems resolve.[253] In this cohort 14 nursing home residents with febrile illness and who did not have delirium had SAA levels of 0.65 ± 0.51 during acute illness, which had reduced to 0.08 ± 0.12 one month later. The eight residents who had delirium with febrile illness had similar levels, 0.69 ± 0.85, then 0.1 ± 0.16 at one month follow-up.[253] Medication changes did not seem to have a relationship. It is possible that acute illness changes SAA levels seen with similar medication regimens during periods when the person is well. The higher overall levels in this inpatient palliative care population is interesting, particularly as admissions are often for symptom control, and may not necessarily be for acute illness. This points to the underlying advanced cancer diagnosis being a key contributor.

Equally, we have not shown an association with SAA level with the presence of fever. It may be that the presence or absence of fever and SAA was at the same time-point, thus may miss a reactive increase in SAA in the ensuing time period, whereas Flacker et al collected SAA on the second morning following the temperature elevation in 24 participants.[253] Another explanation may be that fever itself may not be all that is required to alter SAA, with the aetiology, high endogenous cortisol levels and/or reactive inflammatory response being more predictive. Flacker et al 1998[189] found an association with elevated white cell count and an admission diagnosis of infection in 67 acutely ill older medical patients.

This finding suggests that the SAA levels seen in cancer patients are higher, and the association of SAA and MDAS within the group with lower performance status (AKPS 20 and 30) suggests there may be contributing intrinsic factors associated with the dying process.

5.6.3.2 Comparison with recent studies exploring the association of serum anticholinergic activity with delirium

The following section outlines the studies that have been recently completed which also explore SAA and delirium, and their results will be compared to the findings in our study.

Van Munster et al explored the association of SAA longitudinally with delirium and other risk factors in 142 elderly patients admitted for hip-fracture surgery.[685] This study collected data for several patient characteristics, age, gender, pre-admission cognitive impairment, CCI, CRAS-M, fracture characteristics and duration of hospital stay. SAA for their study was conducted in the same laboratory in Heidelberg as for the study reported in this chapter. In the Van Munster study the mean CRAS-M was 0 (range 0–1) in both delirium and no delirium groups, with a CCI of 6 (5–7), compared to higher values seen in our study: mean CRAS-M of 2.14 (SD 1.35) and CCI of 7.6 (SD 2.1). In the Van Munster study[685], prior cognitive impairment was seen in 67% of the delirium group compared to 16% in those with no delirium; the delirium group was also more functionally impaired with Katz ADL scores of 8 compared to 3 for the non-delirium group. In the 51% who developed delirium (n = 72), SAA was higher in the delirium group (4.2 vs 3.4 pmol/ml.[685] When the authors modelled a rate of change in SAA, SAA levels rise at a time-point that coincides with the operation and a 25% increase is also seen at delirium onset.[685] However, when matching SAA samples for time point from operation the delirium and no delirium groups were no longer statistically significant.[685] However, using mixed modelling only interleukin 6, cortisol, pre-existing functional deficits and prior cognitive impairment remain significant in influencing SAA rise, and onset of delirium no longer explains SAA increase.[685] Anticholinergic medication burden showed no association with the temporal changes in SAA.[685] Thier study shows, similar to the results in our cohort of cancer patients, a relationship with functional impairment, and no relationship with anticholinergic medication. The associations

with interleukin 6 and cortisol and SAA need to be explored further in the cancer population, in particular in those with poorer performance status.

Mangoni et al also explored SAA in 71 older hospitalised patients awaiting surgical repair of hip fracture.[686] SAA was collected the day before or on day of surgery prior to transfer to theatre. Their approach was to take the SAA prior to the potential precipitant of delirium (surgery). Medication exposure within 24 hours of SAA was collected, and anticholinergic medication load was determined utilising four methods: ARS[250], CRAS-M[687], Anticholinergic Burden Index[255], and anticholinergic component of the DBI.[239] CCI, IQCODE-short form and the Katz ADL score was also collected. The median SAA was 2.8 (range 1.1–4.9) pmol/ml. Age, pre-admission cognitive impairment, in-hospital delirium, Katz ADL score, and the number of non-anticholinergic drugs, were associated with SAA.[686] Similar to the results of our study with CRAS-M not associated with SAA, the four anticholinergic drug-scoring systems were not associated with SAA. Delirium was assessed for daily by psychiatric examination (DSM IV) and delirium observation screening scale.[686] SAA was not predictive of mortality, but ARS, cognitive impairment, in-hospital delirium, length of hospital stay, and previously living at home predicted all-cause mortality in this group.[686] This study confirms the findings in our study of no association with SAA and the CRAS-M, but also with three other methods of calculating anticholinergic burden. Equally, a similar association with pre-existing functional impairment was seen, but no association with survival. The strength of Mangoni et al's study are SAA levels prior to the precipitant exposure (surgery).

There have also been two negative studies. Thomas et al undertook extensive clinical and neuropsychological evaluation of 61 acutely hospitalised elderly in a cross sectional study on the third hospital day after admission within a four hour time frame.[265] SAA was taken one hour prior to a quantitative EEG. Fifteen participants had dementia and delirium, 31 had dementia alone, and 15 were cognitively unimpaired. This categorisation was done by a consensus panel of a geriatric psychiatrist, geriatrician and neurologist on Day three of admission, and thus the exact duration since delirium onset for the SAA sample timing is not known, with it being possible delirium was present since admission. The

participants were on a mean of 5.4 ± 2.5 SD (range 1–12) medications with 1.9 ± 1.3 SD (range 0–5) that were deemed delirogenic. CIRS scores were mean 29.9 ± 4.9 and Barthel Index on admission 43.9 ± 27.2. These are similar values to seen in our study, where the mean CIRS score was 28.9 (range 19–36, SD 5.2) and Barthel Index 59.5 (20–95, SD 28). SAA was detectable in all but one patient (mean 10.9 ± 7.1 pmol/ml).[265] Two patients showed extremely high SAA levels (>2 SD): one female with delirium due to amitriptyline with a level of 47 pmol/ml, and 87-year-old male with pneumonia on 10 medications, four which were anticholinergic (level 33pmol/ml). EEG correlates with delirium included occipital slowing, peak power and alpha increase, delta and theta power increase, and slow wave ratio increase.[265] SAA levels did not correlate with any of the EEG parameters, age, prior cognitive impairment (IQCODE), medication amount, delirogenic medication, delirium severity (DI) and overall delirium severity (CIRS) (Pearson correlation coefficient).[265] This analysis remained unchanged when the two participants with extremely high values were removed. The authors concluded that significant SAA levels indicated that there is an anticholinergic burden detectable in older adults with acute medical conditions, hypothesised to be due to stress and fever related endogenous AA operating in the periphery[268 688-690], but this does not seem to relate to delirium or dementia diagnoses. The authors propose that SAA is unable to measure central anticholinergic effects, including EEG changes, which are associated with scopolamine. Delirium diagnoses in other studies[683 684] which have shown associations were done with screening instruments only, so the strength of the negative study by Thomas et al was that it was a formal psychiatric evaluation. This study had several limitations, namely small sample size, no delirium sample without prior cognitive decline and the depth of neuropsychological testing was limited. The authors also propose that cerebrospinal fluid SAA also may show stronger correlations.

A prospective study by the same team explored SAA and quantitative EEG done at 48 hours of 37 ICU patients with delirium.[256] ICU patients were followed daily and assessment with the CAM-ICU, and patients then categorised as delirious or non-delirious for the purposes of this study. The mean SAA was 2.9 (SD 2.5) pmol/ml for delirious patients and 2.6 (SD 2.3) for non-delirious patients, which was not significantly different.[256]

Since completion of this current study several studies have been published exploring SAA in other clinical settings other than delirium.[691-694]

SAA and the severity of clinical symptoms in AD were studied in 76 participants.[691] Twenty-six of the 76 participants had SAA detected (mean SAA 4.14 ±2.7nM) and 50 were negative; cognitive and psychiatric symptoms were compared in the two groups.[691] The group showing SAA had significantly lower scores on MMSE, and higher scores on the Functional Assessment Staging and the Behavioural Pathology in Alzheimer's Disease Rating Scale ($p < 0.05$).[691] Interestingly, the SAA group also had more antipsychotics prescribed; this may be either in response to the symptom profile or may actually contribute to SAA, which then leads to the higher symptom prevalence.[691]

A study in 152 normal elderly community volunteers showed modest slowing in information processing time, only in those individuals who had low levels of serum paraxanthine (a caffeine metabolite).[693]

5.6.4 Hypotheses of contributing factors to measured serum anticholinergic activity and reasons for lack of association with calculated anticholinergic load

Medications that do not cross the blood-brain barrier will contribute to SAA without necessarily having a corresponding cerebral effect. This is supported by studies that show delirium not to be correlated with overall anticholinergic medication burden.[192 253 695] These studies vary in how comprehensively the list is used to codify medications with anticholinergic effects. For example Marcantonio et al[695] define anticholinergic exposure as antihistamines, tricyclic antidepressants, anti-emetics, and certain neuroleptics. Future studies may need to separate out participants with exposure to centrally active medication versus those without, including psychoactive medications, which mediate their effects by alternative pathways rather than being anti-cholinergic.[696] A further modification of CRAS-M could include dividing the medications into those who cross the blood brain barrier and those that do not, based on current literature.

CRAS-M score does not account for dose of the medication, or duration of exposure. It also cannot account for the different time-to-peak levels and clearance mechanisms, which may influence the given contribution of a

medication at SAA taken at a specific time-point. A small study of 10 participants who had not had any anticholinergic medication exposure in the previous week showed detectable SAA levels on Day two of admission for acute illness.[231] Anticholinergic medication was categorised for the purposes of this study to include those with well documented in vivo anticholinergic effects, demonstrated in vitro AA or belonged to a class of medication where a member of that class has demonstrated in vitro AA.[231] Participants were also excluded if on more than six medication, had receive an investigational medication or blood transfusion in week prior to SAA.[231]

In vitro studies have demonstrated AA in vitro. Dynorphin A and MBP have been shown to inhibit binding at muscarinic receptors by alteration of receptor conformation in rat heart and cerebral cortex using radioligand receptor binding assays.[697] The two basic peptides inhibit the binding of the muscarinic ligand (3H)-N-methylscopolamine, altering the kinetics of the ligand dissociation in an allosteric manner.[697] Protamine (an endogenous polycationic peptide) also inhibits binding at muscarinic receptors with a similar mechanism proposed[698], where protamine binds to the secondary domain of muscarinic receptor to influence allosterically, inhibiting the interaction of ligands at the primary binding site.[699 700] A naturally occurring low molecular weight inhibitor of antagonist binding has been identified in the 100,000xg supernatant fraction of brains of patients with AD.[701] Prevention of inhibition of muscarinic receptor by this low molecular weight inhibitor has been demonstrated with glutathione, arachdonic acid, pyrophosphate analogues, bioflavonoids and other antioxidants.[702-704] Similarly, an endogenous inhibitor of muscarinic receptors was found in the soluble fraction of ileal muscle of the guinea pig.[705] Muscarinic catecholamine secretion has been shown to be inhibited by cortisol and aldosterone, but not dexamethasone in the guinea pig.[706] A recent study in 30 cognitively unimpaired men scheduled for urological surgery compared SAA and cortisol levels in blood and CSF one day before surgery and conducted neuropsychological testing.[694] A significant linear correlation was detected between SAA and cortisol levels ($r = 0.614$, $p = 0.003$).[694] Interestingly, this study also showed that SAA was associated with two times the number of anticholinergic medications but not with age, medical history (American Society of Anaesthesiologists classification) or impaired cognition.[694]

The association with SAA and lower functional status is interesting. AKPS 20 and 30 corresponds to a group that is predominantly or completely bed-fast and corresponds to more advanced cancer stage. This association could be related to an increase in endogenous anticholinergic substances associated intrinsically with the dying process. MBP has been identified in the CSF of patients with brain tumours.[707] Abnormalities in cortisol circadian rhythm have been seen in cancer patients, and flatter diurnal rhythm associated with early mortality.[708-710] It is also not possible to determine whether these endogenous anticholinergic substances predominantly act in the periphery or have centrally mediated actions.

5.6.5 Strengths of this study

The study was adequately powered to determine if an association with SAA and MDAS exists. Patients with cognitive impairment were not excluded from the study and, as such, the subgroup that may be most vulnerable to anticholinergic effects and also people with prevalent delirium resulting from high anticholinergic load were included in this study. Sample size was determined to provide the power to undertake the multivariate analyses discussed. The analysis of the association with delirium was undertaken from two perspectives: one considered delirium as a dichotomous outcome, with a cut-off determining the presence or absence of delirium; the other considered that delirium symptoms present on a continuum, which also accounts for sub-syndromal presentations.

5.6.6 Limitations of this study

Not everyone with life-limiting cancer is referred to a specialist palliative care service and, in general, people with more complex needs are the people referred and more likely to require inpatient admission.[647] Participants who were within the last seven days of life were excluded; however, there were still participants who deteriorated and died unpredictably in the cohort, and one quarter of the participants died during the index admission so those within the terminal phase were represented in the cohort. Non-english speaking participants were also excluded, and it could be possible that they have a different profile of endogenous contributors to SAA due to genetic or other factors. The exclusion of non-english speaking participants and those within the last seven days of life may have contributed to the prevalence and incidence of delirium in this study being lower

than seen in some prior studies.[103] This study was not powered to explore relationship of individual MDAS items with SAA, and this will be important future work in understand specific symptom impacts. Inflammatory markers were not measured and these will be crucial in future work given evolving understanding in the role of delirium, but also due to associations in cancer anorexia cachexia may help understand the associations seen in people with lower functional status. The exploratory analyses were not adjusted for multiple comparisons, however were undertaken to be hypothesis generating.

5.6.6.1 Limitations of the assay

The serum was taken at a set time point (10am), which may not account for different peak levels from medications, medications which are given at different times-points in the day (may be capturing peak levels for some medications and troughs for others) and also endogenous substances, which may also have circadian patterns of release (e.g. cortisol). Considering 'duration of exposure' to both exogenous and endogenous contributors has not been accounted for in the current studies using SAA. Factors influencing pharmacokinetics of anticholinergic medication included CYP2D6 and CYP3A activity (and presence of inhibitors).[655] For example tricyclic antidepressants and phenothiazines are mainly metabolised by CYP2D6.[655] Little is currently known on the pharmacogenetic variations on anticholinergic pharmacokinetics.[655]

The serum was also taken at the time of delirium, for both incident and prevalent cases. The change in SAA may have occurred at a time-point prior to this if contributing to the delirium occurrence. In prevalent delirium cases, delirium symptoms prior to arrival in hospital were not taken into account, hence SAA may have been taken well into the delirium episode if admission did not mark the commencement of that delirium episode. Equally, SAA at baseline may not be temporally related enough to the episode of incident delirium to be predictive. Hence the timing of SAA to be used for predictive purposes may not be at the time of delirium occurrence.

No normative data for SAA exists in health individuals, and hence it is unclear whether detectable SAA can occur in absence of illness and medications with anticholinergic properties. Prior studies suggest a cut-off of 4pmol/ml for raised

anticholinergic load.[267 711] Hence, the hypothesis that circulating endogenous anticholinergic substances are only present in illness has not been tested.

More recently, it has been proposed to avoid contribution of serum protein binding of QNB, that filtering plasma should occur, so that only molecules larger than 50KD are retained.[712] This, however, does not avoid the issue of serum protein-bound medications not being included in the assay measurement.

5.6.6.2 Limitations of methods and sample

There are several limitations of the CRAS-M, which include lack of dose weighting, assumption of anticholinergic effects being additive (not synergistic or exponential), that all have CNS effects and linear (that is, one medication with score of 3 is equivalent to three medications each with score of 1). However, this is a step forward from prior studies exploring anticholinergic medication that omitted potentially anticholinergic medications and did not provide any hierarchy of degree of anticholinergic effects. The variables adjusted for in the models did not control for all possible aetiological factors of delirium, with over 25 possible aetiological risk factors described in the literature.[713 714] Equally, those variables definitively predictive of delirium in cancer are less well described but were the variables chosen in this study.[38 183 185 197 305 696 715]

The anticholinergic effects of complementary and alternative medicines may have contributed to SAA however use was not documented. This may be important given that at least two thirds of Australian cancer patients use a complementar or alternative medicine at some point in their cancer trajectory.[716]

Several variables were considered in a cross sectional manner and many variables which mediate delirium may be time and “dose” of exposure dependent. There is also an interaction between when these predictors occur in relationship to one an another.[717]

The sample is potentially biased to a cohort which is less unwell, as patients identified as imminently dying on admission were not recruited in most instances. Delirium diagnosis was purely based on MDAS score, not SCID criteria and hence delirium diagnosis may have been inaccurate in some cases.

5.6.7 Generalisability

Specialist palliative care is a referral dependent service, and there is a tendency for patients to have more complex needs than the whole of the population at the end of life.[647] Equally those who are admitted for specialist inpatient palliative care have a degree of complexity again, or are admitted for terminal care. This would potentially over-estimate the effect of anticholinergic load for all people with advanced cancer. The study also has not explored delirium in patients with non-cancer life-limiting illness.

5.6.8 Future directions for research, practice and policy

Further understanding of SAA in advanced cancer may be determined from longitudinal measures, correlated with levels of putative endogenous substances where assays are available. Consideration of more sophisticated SAA methods, which filter serum components, and measure protein bound medication are also needed. Further work exploring SAA in CSF and characterising the endogenous compounds that can interact with central anticholinergic systems is crucial. One approach suggested is to further develop imaging approaches targeted for central muscarinic receptors and cholinergic pathways.[655] More recently, rodent models have allowed specific pathophysiological hypotheses of delirium to be tested.[227] [718] Anticholinergic medication burden calculation needs to account for dose and duration of exposure, and in some situations the degree of anticholinergic effect of medications requires clarification with further studies in patient population measuring anticholinergic adverse effects systematically. More sophisticated SAA measurement may also assist in determining relative anticholinergic contribution of specific medication.

The anticholinergic hypothesis cannot be considered in isolation, with other putative pathways being demonstrated. Further pathophysiological studies will need to consider an array of approaches to piecemeal together a unifying understanding of delirium neuropathology.[224] Further work is required to understand the role of benzodiazepines in delirium risk in this population, and to determine if reducing benzodiazepine exposure (dose or duration) can change risk profiles. The lack of association with opioids and corticosteroids is contrary to prior work, and further work is needed to explore this further. A more detailed

exploration of cumulative exposure over time to a class of medication, relationship with other psychoactive medications and change in dose need to be modeled with temporal occurrence of delirium, its severity and resolution in more sophisticated ways. The palliative patient with comorbid illness and cerebral metastases require specific screening for delirium on a regular basis, as their chance of developing delirium is high. Finally, SAA may be measuring processes intrinsic to the dying process in advanced cancer, unrelated to delirium that warrants further exploration.

Chapter 6: Risperidone and haloperidol for delirium

This chapter describes the protocol and study participants to date for an RCT of oral risperidone, oral haloperidol, and oral placebo with rescue SC midazolam in the management of delirium in palliative care inpatients[n]. It discusses the optimal design approaches for RCTs of pharmacological therapies for delirium in the palliative setting.

6.1 Background and rationale

6.1.1 Pathophysiological abnormalities in delirium and rationale for intervention

Delirium is conceptualised as a disorder of 'arousal and cognition'; however, its pathophysiology is poorly defined.[649 650] One of the dominant theories is of central neurotransmission abnormality with cholinergic deficiency, serotonin deficiency and/or dopaminergic excess, either absolute or relative to each other (covered in detail in Chapter 1 Section 1.10).[189 223 228 253 625 653 719]

Antipsychotics have become the pharmacological agent most widely used for delirium management. The initial use of antipsychotics was extrapolated from the evidence that dopamine and serotonin antagonists reduce psychotic symptoms in other disorders such as schizophrenia.[720] Haloperidol is thought to block positive psychotic symptoms (hallucinations, delusions) by blocking dopaminergic D_2 activity in the mesolimbic pathway; however, this same action in the nigrostriatal pathway results in extrapyramidal symptoms.[721] haloperidol also blocks cholinergic (muscarinic), histamine (H_1) and noradrenergic (α_1) receptors leading to other adverse effects (sedation, blurred vision, dry mouth, orthostatic hypotension, dizziness).[721] The atypical antipsychotics (in particular risperidone, olanzapine, and quetiapine) have gained popularity given their specific pharmacological property of serotonin$_{2A}$-dopamine$_2$ ($5HT_{2A}D_2$) antagonism, a property that theoretically leads to less toxicity, in particular extra-pyramidal side effects.[720 721]

[n] This trial has been registered on the Australian and New Zealand Clinical Trials Registry with number ACTRN12607000562471

Table 50 Comparative receptor antagonism of haloperidol and risperidone

Receptor	Haloperidol	Risperidone
D_1 Dopamine	++	+
D_2 Dopamine	+++	+++
D_3 Dopamine	+++	+
D_4 Dopamine	+	+
Muscarinic	+	+
Histamine 1 (H_1)	+	++
α_1 adrenergic	+++	++
α_2 adrenergic	+	+++
Serotonin type 2 ($5\text{-}HT_{2A}$)	++	+++

+ = degree affinity with +++ highest affinity[722]

6.1.2 Existing evidence for pharmacological management of delirium

Antipsychotics are considered by most clinicians as first line pharmaco-therapeutic agents for delirium, despite limited randomised double blind controlled evidence for management of delirium in any healthcare setting, including palliative care.[723] The current evidence for pharmacological management in cancer and palliative populations have been outlined in Chapter 1 Section 1.14.1. As discussed, these open label and randomised controlled studies explored post-treatment efficacy simplistically, in relation to total delirium score reduction. There has been limited systematic evaluation of the toxicity profile in relation to delirium management with typical or atypical antipsychotics, with most study designs relying on clinical reports of toxicities rather than daily assessments with a validated measure or structured clinical examination. These studies also were not adequately powered to detect predetermined efficacy outcomes.

The studies that compare one antipsychotic with another showed a reduction in mean total scores in the delirium scale utilised in the study over time. However, participants were receiving treatments to reverse the aetiology of their delirium and it is not possible to delineate whether improvement was due to the improvement in aetiological factors, and whether the antipsychotic treatments offer further improvement in either the rate or degree of delirium resolution above this, or hinders improvement. One randomised study[333] with a placebo arm had

significant methodological issues, with the randomisation schedule not specified, and allocation concealment flawed due to one agent being given by the intramuscular route, hence unblinding the study. The other two placebo controlled studies[334 724] were stopped early due to slow recruitment in one study and because the pharmaceutical company providing study drug withdrew due to concerns on the use of antipsychotics in the elderly, and although both these studies showed a faster improvement with quetiapine than placebo they were substantially underpowered.

6.1.3 Studies of risperidone for delirium

There has only been one randomised double-blind trial of risperidone versus haloperidol, in 28 oncology, general medical and intensive care patients in Korea with DSM-IIIR defined delirium.[432] There was one cancer patient in each arm of the study. Patients were screened using the CAM and the DRS, and then diagnosis of delirium was confirmed using structured clinical examination for DSM-III-R structured clinical interview criteria to determine inclusion in the study.[432] Patients who had already received antipsychotics or benzodiazepines in the emergency department were excluded. A consulting psychiatrist who was not an investigator undertook the randomisation. The haloperidol and risperidone tablets were not identical looking; however, patients and caregivers were not provided with the name of the medication. The patients were assessed daily using the MDAS for seven days, and the definition of response was a MDAS score <13; however, no power calculation was presented. The starting dose of haloperidol was 0.75mg BD, titrated to clinical effect. The mean dose in the haloperidol arm at Day seven was 1.71 mg (SD 0.84, range 1–3).[432] Risperidone was started at 0.5 mg BD, and also titrated to clinical effect. The mean dose in the risperidone arm at Day seven was 1.02mg (SD 0.41, range 0.5–2).[432] Two patients in the haloperidol arm withdrew, one due to worsening of the medical condition on the second day, and one with severe sedation on the third day. In the risperidone arm one patient refused participation on Day two and one had a tracheostomy on Day four. Twelve patients in each arm completed the study to Day 7, and these were the only participants included in the analysis (not intention to treat). The mean age was 66.5 years with 58% female in the haloperidol group, and 65.6 years with 50% female in the risperidone group. There was a reduction in the MDAS total

scores in both groups (n = 24), with no significant difference in mean scores between groups ($p < 0.05$).[432] The group-by-time effect was not significant; (n = 24, Fishers exact test = 1.66, $p = 0.14$).[432] One patient had severe sedation with haloperidol, and one patient mild akathisia.[432] The average time to response was 4.22 days in the haloperidol arm, and 4.17 days in the risperidone arm.[432] The frequency of response was not different between the two groups: 75% in the haloperidol group (responders n = 9/12) and 42% in the risperidone group (responders n = 5/12) ($p = 0.11$). This study did not rigorously assess for adverse events relying on clinical reports, or assess more complex outcomes such as health-service utilisation.[432] It also relied on clinicians to titrate to effect, and there may have been different approaches as to how this was done between clinicians. The other methodological issues were the tablets were not identical with potential for unblinding, inadequate power to determine response, the randomisation schedule is not described, and intention to treat analyses were not done. The risperidone arm may also have not had equivalent dosing, as published data suggests haloperidol and risperidone are equal in antipsychotic effects when cited as chlorpromazine equivalents.[725] This study does not definitely answer whether either antipsychotic has added further improvement in delirium resolution, above the natural history of resolution related to improvement in the underlying precipitant.

There have been several case reports, three open label prospective studies, and one retrospective study exploring the role of risperidone in delirium in palliative care patients (Table 50).[726-731] These studies provide support for risperidone having potential for controlling delirium symptoms with less extrapyramidal side effects (EPS). They vary in the population studied, and dosing approaches varied from a standard protocol versus clinicians determining the dose titration, making comparisons difficult. Horikawa et al report the use of oral risperidone in 10 medical and surgical inpatients (0.5mg/day titrated by 0.5 mg/day until DRS score 50% of baseline). The average dose used in this study was 1.7mg/day; and in eight of the 10 patients moderate to marked improvement in DRS score was reported.[732] Mittal et al conducted a similar study using risperidone 0.5 mg BD, and used a fixed titration schedule until DRS score <12, and demonstrated that DRS scores improved from Day 1 and remained improved up to Day 6, with mean

ESRS scores low and decreased by Day 6.[729] A larger study of 64 hospitalised medical patients with DSM-IVR defined delirium used mean daily doses of 2.6mg (± 1.3mg), had 90% of participants achieved DRS scores less than 13 within 72 hours of treatment, with two patients experiencing drowsiness.[733]

A more recent prospective open-label flexible-dose study (n = 10) measured plasma concentrations of risperidone, 30 minutes after administration of the first 0.5mg dose of risperidone oral solution.[734] The plasma concentrations varied between 0.3–14.60 ng/ml. The two patients who had the highest concentrations experienced daytime somnolence, whereas the patient with the lowest plasma level did not achieve remission of delirium symptoms (defined as DRS-Japanese version score less than 12). This study provides preliminary evidence of ojective correlation between clinical response and plasma concentrations, which needs to be further defined in future work. This study, however, did not measure steady state concentrations.

A recent randomised trial added bright light therapy to risperidone treatment compared to risperidone only arm, which also showed DRS reduced over time in the risperidone arm (Table 51).

Table 51 Studies exploring risperidone for the management of delirium

Study	Population (n) and design	Risperidone dosing and comparator (if applicable)	Primary outcome	Results	Comments
Horikawa et al 2003[735]	n = 10 Open label Medical and surgical inpatients referred to psychiatrist (the number of days from onset of delirium to psychiatry referral was 13.2 days (SD 13.3, range 5–50) DSM IV defined delirium Excluded 6 patients who could not swallow oral medications, and 8 who were deemed delirium was going to resolve spontaneously	Risperidone started at 0.5mg daily in evening. No other psychotropic medications used Several patients had been on haloperidol prior to study commencing (0.75mg–5mg day) and this had been ceased prior to first assessment for eligibility for this study. Dose increased by 0.5mg increments 2 to 3 times per week until DRS score <50% of baseline (if adverse effects profile permitted), then continued for 1 week Study was stopped when absence of a marked change in symptoms	DRS two to three times per week. Time to maximum effect was time to minimum DRS score The period to onset of effect was from start of risperidone to any reduction in DRS from baseline Marked improvement was defined as DRS <50% of baseline, moderate response 21–50%, and no improvement 0–20% change. DIEPSS was used to evaluate adverse effects	Observation period was a mean 19.4 days (SD 6.0, 10–28) At the study end 5 patients (50%) showed a marked, 3 (30%) moderate, and 2 (20%) showed no improvements respectively The average DRS scores before and after treatment were 20.0 (SD = 5.0, range 12–29) and 10.6 (SD = 5.5, range = 5–20), respectively	Excluded those with reversible delirium, and on average only started on the study a mean 19.4 days after delirium onset
Mittal et al 2004[736]	n = 10 Open label Medical and surgery inpatients DSM IV defined delirium and DRS ≥13	Risperidone 0.5mg twice daily Additional doses permitted on Day 1 for target symptoms Total Day 1 dose was given daily until DRS ≤12. Dosage was then decreased by 50% as maintenance dose and continued until Day 6	DRS, CTD, modified ERS, KPS, CIRS at baseline and Day 6	Mean CTD scores improved to day maintenance dose was commenced (CTD score 7.1 ± 2.0, $p < 0.0005$) and remained improved at Day 6 (CTD score 16.9 ± 3.0) $p = 0.0078$). Mean DRS scores similarly improved to maintenance dose (DRS score 25.2 ± 0.9) $p < 0.0001$, and Day 6 (11.3 ± 1.5) $p < 0.0001$)	Excluded patients with dementia or terminal illness, those with alcohol or benzodiazepine withdrawals and those already on antipsychotics

Study	Population (n) and design	Risperidone dosing and comparator (if applicable)	Primary outcome	Results	Comments
Parellada et al 2004[737]	n = 64 Open label Medical patients with DSM IV defined delirium Exclude delirium in terminal phase, delirium due to drug intoxication or withdrawal, and those needing physical restraint	Oral risperidone liquid 1.25mg daily for patients ≥65 and 2.5 mg for those <65 years in two divided doses per day, and adjusted to clinical response Mean dose at Day 3 was 2.6mg ± 1.7 per day, decreasing to 1.5mg±0.8 at Day 7	DRS (response defined as DRS <12), positive subscale of PANSS, MMSE, CGIS[a,738], UKU Side Effect Rating Scale[739] (unwanted side effects of psychotropics) daily for 7 days	58/64 participants responded (90%) Mean DRS was 22.5 ± 4.6 at baseline, 12.3 ± 7.3 at Day 3 and 6.8±7.0 at Day 7 ($p < 0.05$). There were similar improvements on PANSS, MMSE and CGIS 2 patients experienced sedation and one nausea No EPS were seen	Validated assessments for side effects
Liu 2004[728]	n = 41 Retrospective Patients with delirium referred to consultative psychiatric service	41 patients who received risperidone mean dose of 1.17 (range 0.5–4) treated for 3–18 days. 36 patients who received haloperidol mean dose of 4.25mg (range 1–10) treated for for 2–19 days	Global severity determined from medical record by psychiatrist rating 0 for none to 10 for extremely severe symptoms.	9% of patients in risperidone group recovered from delirium, and 100% in haloperidol group Less extrapyramidal toxicity reported in risperidone group	No side-effect ratings Retrospective design Concurrent benzodiazepines in 36% of risperidone group and 31% in haloperidol group
Han et al 2004[340]	n = 28 RCT General medical patients	Risperidone (n = 12) Starting dose 0.5mg twice daily titrated to clinical effect. Mean dose at Day 7, 1.02mg (SD –0.41, range 0.5–2) Haloperidol (n = 12) over 7 days. Starting dose 0.75mg twice daily titrated to clinical effect. Mean dose at Day 7, 1.71 mg (SD 0.84, range 1–3)	DRS and MDAS daily	MDAS scores of each group decreased significantly during the study period ($p < 0.05$), but no difference between the groups.	MDAS scores not cited (graphically presented only). Blinding compromised by non-identical tablets.Power calculation not provided Not intention to treat as only 24 participants included in final analyses
Toda 2005[734]	n = 10 Open label flexible dosing study Mainly post-surgical patients with delirium	0.5 mg risperidone per day with subsequent titration based on clinical judgment	DRS daily (Japanese version) Plasma concentrations of risperidone 30 minutes after first 0.5 mg dose	Negative correlation between plasma levels and durations of treatment until remission ($r = –0.861$, $p = 0.0095$) Mean DRS score was 19.6 ± SD 3.2 at baseline and 11.3 ± SD 5.5 at Day 7	Small sample size Correlates with plasma levels will inform the ideal dosing

Study	Population (n) and design	Risperidone dosing and comparator (if applicable)	Primary outcome	Results	Comments
Yang et al 2012[740]	n = 36 RCT Patients with delirium referred to psychiatry services	The patients were randomised to risperidone (n = 16) or risperidone with LT (10000 lux by a light box) (n = 20) Risperidone was given as 0.5 mg initial dose and increased until DRS <12 or 50% reduction from baseline	DRS and MDAS daily until Day 5	Risperidone with LT showed a significantly greater decrease in the DRS score than the risperidone-only group (p=0.025). MDAS score was not significantly different between the groups There was a significant improvement in total sleep time (p = 0.037) and sleep efficiency (p = 0.029) in the risperidone with LT than in the risperidone-only group	No power calculation Psychiatrist who undertook assessments was blinded to allocation
Grover et al 2012[741]	n = 64 Single blind RCT Medical and surgical patients with delirium referred to consultant liaison psychiatry Participants with QT_c interval over 500ms, dementia, Parkinsons disease, history of NMS, aphasia, visual loss, terminal illness excluded	Haloperidol (n = 20) Olanzapine (n = 23) Risperidone (n = 21) A flexible dose regimen was allowed with adjustment by clinical judgment daily. The ranges allowed were haloperidol 0.25 to 10mg; risperidone 0.25 to 4mg; olanzapine 1.25 to 20mg Allowed pareneteral haloperidol and olanzapine as rescue in those arms respectively In risperidone arm allowed intravenous haloperidol or lorazepam as rescue	DRS-R98 MMSE	Reduction in DRS-R98 scores and improvement in MMSE scores over the period of 6 days was seen, but there was no difference between the three groups	Proxy consent used Excluded patients with dementia and terminal illness Single blind (assessor who did delirium measures was blinded) Underpowered

[a] The Clinical Global Impression rating scales (CGIS) are commonly used measures of symptom severity, treatment response and the efficacy of treatments in treatment studies of patients with mental disorders
CIRS – Cumulative Illness Rating Scale; CTD – Cognitive Test for Delirium; DRS – Delirium Rating Scale; DRS-R98 – Delirium Rating Scale Revised 98; DIEPSS – Drug Induced Extra-Pyramidal Symptoms Scale; EPS – extrapyramidal side effects; ERS – Extrapyramidal Symptom Rating Scale; KPS – Karnofsky Performance Status; LT – light therapy; MDAS – Memorial Delirium Assessment Scale; MMSE – Mini-Mental Status Examination; NMS – neuroleptic malignant syndrome; PANSS – Positive and Negative Syndrome Subscale; QT_c –QT interval corrected for heart rate; RCT – randomised controlled trial; SD – standard deviation, UKU – The Udvalg for Kliniske Undersøgelser Side Effect Rating Scale

6.1.4 Aims

Delirium is a significant clinical problem in palliative care, from both a clinical and consumer perspective. There is currently limited evidence in the understanding of the pathophysiological processes involved and no adequately powered placebo controlled randomised evidence to guide pharmaco-therapeutic options. Following review of the data available from clinical trials it was concluded that additional data are required in order to justify the use of either risperidone or haloperidol in the treatment of delirium in the palliative care setting. Risperidone is currently not approved for use for this indication internationally, despite current clinical use. Indeed, there are currently no medications approved for the treatment of delirium across the world. The most appropriate study design is to compare risperidone and haloperidol against a placebo.

A placebo-controlled arm can be justified as there is no 'gold standard' pharmacological therapy and available evidence supports clinical equipoise with uncertainty existing about the relative efficacy and toxicity of the choices of antipsychotic therapy and the alternative choice of managing delirium by reversing underlying precipitant and nonpharmacological strategies to minimise symptoms as delirium resolves. First, there is no currently approved medication; second, there are short- and long-term side effects of medications in both active arms that may outweigh any benefit of the study medications if the clinical benefits are marginal; and third, there are accepted non-pharmacological approaches to mild delirium that may be of equal or greater benefit than medications. The current available data does not provide support that antipsychotics provide additional benefit above the current rates of delirium resolution (rate and degree of improvement of delirium) attributable to the natural history of resolution as delirium precipitants are treated and resolve. A comparison is needed between the natural history delirium which is to trend toward resolution in many people, with or without pharmacological treatment.

The haloperidol arm has been included in this study as it is currently in wide clinical use for this symptom. There are sparse outcome data for this medication in the treatment of delirium, although there are clinical practice guidelines

suggesting that it may be of some use. The extent of benefit has not been quantified, nor the population most likely to benefit from this intervention.

Therefore, the primary aim of this study is to compare the efficacy of regular oral risperidone solution and oral placebo solution, for the treatment of delirium, and the incidence of adverse effects, in particular EPS.

The secondary aims are to compare the efficacy of regular oral haloperidol solution and oral placebo solution; and haloperidol with risperidone for treatment of delirium, including the incidence of adverse effects, in particular EPS.

The other secondary aims are to consider the economic implications; patient, caregiver and health professional-rated distress in relation to delirium episodes; and to explore pathophysiological correlates of delirium management.

6.2 Study objectives and hypothesis

6.2.1 Primary objective

The primary objective of the study is to compare the efficacy of oral risperidone solution and control (oral placebo solution with SC midazolam rescue) in control of targeted delirium symptoms at 72 hours from treatment commencement.

6.2.2 Secondary objectives

6.2.2.1 Efficacy

The first secondary objective is efficacy:

1. to compare the efficacy of oral haloperidol solution and control (oral placebo solution with SC midazolam rescue); in control of targeted delirium symptoms at 72 hours from treatment commencement
2. to compare the efficacy of oral haloperidol solution and oral risperidone solution; in control of targeted delirium symptoms at 72 hours from treatment commencement
3. to describe the time-profile of delirium in the three treatment arms (delirium duration, severity, subtype, cognitive impairment and resolution)
4. to describe
    - patient-reported distress on delirium resolution;

- caregiver and health professional rated distress;
- improvement in cognition;
- requirement for usage of rescue midazolam protocol; and
- dosage and length of administration.

6.2.2.2 Toxicity

The second secondary objective is to compare the toxicity of oral risperidone solution and oral haloperidol solution versus control (oral placebo solution and SC midazolam rescue), in terms of EPS and sedation.

6.2.2.3 Pathophysiology

The third secondary objective is to explore the pathophysiological correlates (serum marker of neuronal apoptosis (S100 calcium binding protein B (S100B) and other serum markers) over time in patients treated with oral risperidone solution, oral haloperidol solution and oral placebo solution with rescue midazolam, and compare associations with outcomes.

6.2.2.4 Health outcomes and health services utilisation

The fourth and final secondary outcome is to compare the incremental effectiveness and costs of risperidone in comparison to placebo, and haloperidol in comparison to placebo, in terms of:

- age care facility admissions;
- medical complications (pressure ulceration, thromboembolism, pneumonia, falls, incontinence—while an inpatient);
- usage of AIN (hours);
- persistent cognitive impairment;
- functional decline;
- survival (time as a total);
- survival time outside of institutional care;
- acute care hospital or palliative care unit admissions;
- readmission for second episode of delirium;
- inpatient medication use;
- GP use; and
- quality of life.

6.2.3 Primary null hypothesis

There null hypothesis is that there is no difference between oral risperidone (delivered in oral solution with dose titrated to effect—dose range of 0.5 mg/24 hours to 4mg/24 hours) and oral placebo solution in the management of targeted delirium symptoms at 72 hours from treatment commencement.

6.2.4 Secondary null hypotheses

1. The secondary null hypothesis is that there is no difference between oral haloperidol (delivered in oral solution with dose titrated to effect—dose range of 0.5 mg/24 hours to 4mg/24 hours) and oral placebo solution in the management of targeted delirium symptoms at 72 hours from treatment commencement.
2. The secondary null hypothesis is that there is no difference between oral risperidone (delivered in oral solution with dose titrated to effect—dose range of 0.5 mg/24 hours to 4mg/24 hours) and oral haloperidol solution (delivered in oral solution with dose titrated to effect—dose range of 0.5 mg/24 hours to 4mg/24 hours) in the management of targeted delirium symptoms at 72 hours from treatment commencement.

6.3 Study population

Palliative care inpatients in both acute care hospitals or specialist palliative care inpatient units with incident or prevalent delirium as defined by DSM IVR criteria for diagnosis of delirium and MDAS score ≥7.

6.3.1 Inclusion criteria

The inclusion criteria for the study are:

- diagnosis of delirium as defined by DSM-IVR criteria for delirium and MDAS score ≥7;
- score on NuDesc (Appendix 14) Item 2 (inappropriate behaviour), and/or Item 3 (inappropriate communication), and/or Item 4 (illusions/hallucinations) ≥1;
- age ≥18 years;
- English speaking or access to healthcare interpreter;

- proxy written informed consent;
- cancer or non-cancer life limiting illness; and
- able to take oral medication in solution formulation.

6.3.2 Exclusion criteria

The exclusion criteria are:

- delirium due to alcohol or other withdrawal syndrome where more specific treatment is indicated;
- current or past history of neuroleptic malignant syndrome;
- regular antipsychotic use within past 48 hours. A single 'as required' dose of haloperidol prochlorperazine or levomepromazine is allowed if administered more than 24 hours previously, the dose was at or below study dose for the age group, and prescribed for a non-delirium indication;
- maintenance on antipsychotic required for other diagnosis;
- previous adverse reaction to any of the study medications;
- established Parkinson's disease or other extrapyramidal disorder;
- documented prolonged QT syndrome (greater than 0.43 seconds for males, 0.45 seconds for females);
- clinician predicted survival less than seven days;
- cerebrovascular accident within the last month;
- seizure within the last month; and
- pregnant or breastfeeding.

6.4 Study methods

6.4.1 Overall study design

The study design is a randomised double-blind placebo-controlled phase III study to compare the effectiveness and adverse events of oral risperidone, oral haloperidol, and oral placebo with rescue midazolam in the management of palliative care patients with cancer or non-cancer life-limiting illness with DSM-IVR defined delirium and MDAS ≥7; and who develop specific target symptoms as defined by a score of on ≥1 on NuDesc (Appendix 14) Item 2 (inappropriate behaviour), and/or Item 3 (inappropriate communication), and/or Item 4 (illusions/hallucinations).

6.4.2 Treatment arms

Arm I risperidone: Risperidone oral solution with rescue protocol for 72 hours

Arm II: haloperidol: Haloperidol oral solution with rescue protocol for 72 hours

Arm III: control: Placebo oral solution with rescue protocol for 72 hours

All participants in the three arms of the study will receive active non-medication measures for management of delirium (including assessment and interventions for potentially reversible precipitants where clinically indicated; and non-pharmacological measures such as attention to hydration, sensory deprivation (vision and hearing aids), presence of familiar family and reorientation). Due to the individual nature of precipitants the non-medication management will be decided by the treating clinician.

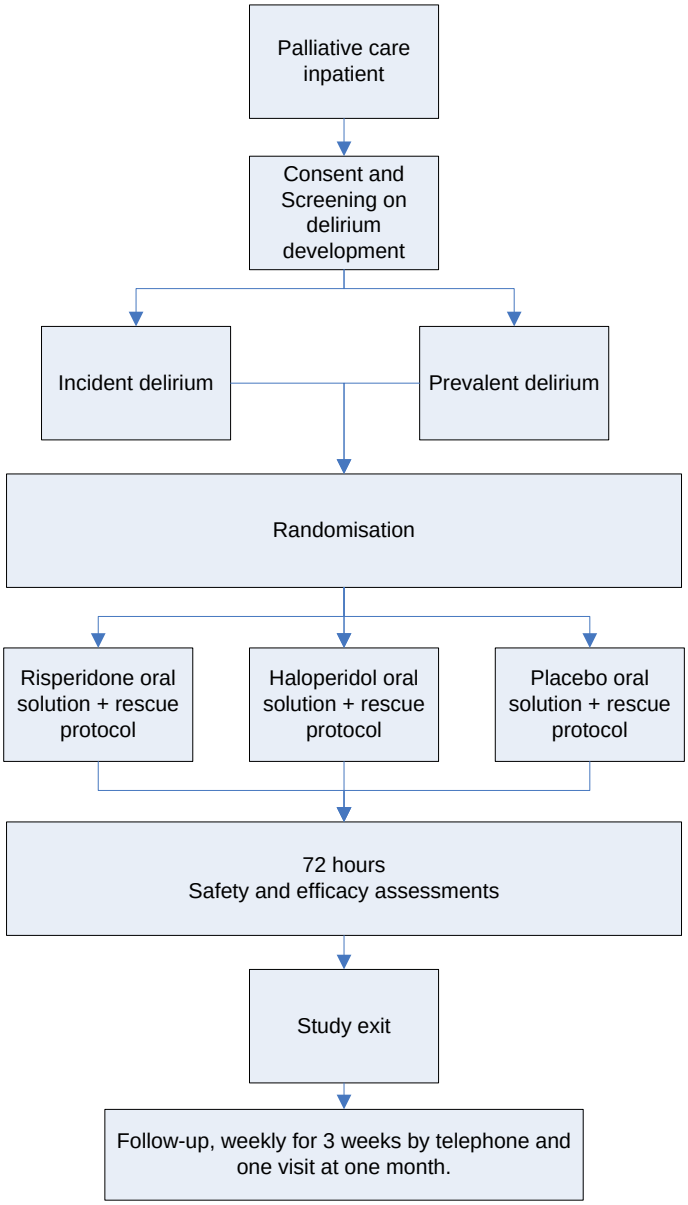


Figure 27 Study diagram

6.4.3 Study medication

1. Oral risperidone solution 1mg/4 ml (twenty ml of risperidone oral solution 1mg/ml diluted with 60ml of placebo solution) containing lactic acid B.P[o], compound hydroxybenzoate solution A.P.F[p], sodium hydroxide 2% and water for irrigation
2. Oral haloperidol solution 1mg/4 ml (ten ml of haloperidol oral solution 2mg/ml diluted with 70ml of placebo solution) containing lactic acid B.P,

[o] B.P stands for British Pharmacopoeia and denotes the formula utilised to manufacture the solution

[p] A.F.P stands for Australian Pharmaceutical Formulary formula utilised to manufacture the solution

compound hydroxybenzoate solution A.P.F, sodium hydroxide 2% and water for irrigation

3. Oral placebo solution (manufactured in 100ml batches) containing lactic acid B.P 1.1g compound hydroxybenzoate solution A.P.F 1ml, sodium hydroxide 2% for pH adjustment and water for irrigation to a volume of 100ml
4. midazolam for SC injection.

6.4.4 Dosing schedule

If 65 years or less, participants will be given a loading dose of 0.5mg together with the first dose of 0.5mg (total dose 1.0mg), then 12 hours later commence on maintenance dose (first dose level 0.5mg every 12 hours). The dose will be adjusted in increments of 0.25mg (every 12 hours for the first 24 hours) after assessment at 8am and 5pm each day. The dose can be titrated from first 12-hourly dose. After 24 hours if symptoms persist dose can be adjusted by increments of 0.5 mg every 12 hours.

If over 65 years, participants will be given a loading dose of 0.25mg together with the first dose of 0.25mg (total dose 0.5mg), then 12 hours later commence on maintenance dose (first dose level 0.25mg every 12 hours). The dose will be adjusted in increments of 0.25mg (every 12 hours for first 24 hours) after assessment at 8am and 5pm each day. The dose can be titrated from first 12-hourly dose. After 24 hours if symptoms persist dose can be adjusted by increments of 0.5 mg every 12 hours.

Dose titration only occurs based on the NuDesc score. At any time-point if the NuDesc score is <1 on Items 2, 3, or 4 no titration will occur and patient will remain on prior dose level unless there is evidence of adverse events or symptoms in which case the dose can be reduced to the previous dose. If the NuDesc score on Item 2 (inappropriate behaviour), and/or Item 3 (inappropriate communication), and/or Item 4 (illusions/hallucinations) is ≥1 the dose can be titrated up according to the following tables.

Standard dosing times will be 8am and 8pm. NuDesc scores will be taken at the end of each nursing shift (eight-hourly intervals). The 8am dose will be determined by the 8am NuDesc score and the 8pm dose determined by 4pm

NuDesc score; however, if there is a change in the patient condition between the time of the afternoon NuDesc score and the evening study dose, the NuDesc is to be repeated. If at this point, the NuDesc indicates a change in the patient condition, the site investigator is to be called so that the evening study dose can be reviewed.

The maximum duration of treatment will be 72 hours (or 12 hours after the 6th dose). Patients who show a response and or side effects can increase or decrease the dose from one dose to the next at the same incremental levels as described above.

6.4.5 Dose schedule timeline

Table 52 details the dosing schedule for patients under 65 years, and Table 53 details the schedule for those over 65 years. A dosing calculator is utilized which ensures study investigators and research nurses can calculate accurately the dose at each time-point using the variables of age, time-point and NuDesc score.

Table 52 Dosing for participants under 65 years

	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	
Time-point	0	12 hrs	24 hrs	36 hrs	48 hrs	60 hrs	72 hrs
Maximum dose possible at that time-point[a]	1mg (loading dose and first dose)	0.75	1.25	1.75	2.0	2.0	-
Data point	Baseline		Visit 1		Visit 2		Visit 3

[a]dose titration only occurs based on NuDesc score. At any time-point if NuDesc score <1 on Items 2, 3, 4 no titration will occur and patient will remain on prior dose level unless there are adverse events

Table 53 Dosing for participants over 65 years

	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	
Time-point	0	12 hrs	24 hrs	36 hrs	48 hrs	60 hrs	72 hrs
Maximum dose possible at that time-point[a]	0.5mg (loading dose and first dose)	0.5	0.75	1.0	1.0	1.0	-
Data point	Baseline		Visit 1		Visit 2		Visit 3

[a] dose titration only occurs based on NuDesc score. At any time-point if NuDesc score <1 on Items 2, 3, 4 no titration will occur and patient will remain on prior dose level unless there are adverse events

6.4.6 Method of assigning participants to treatment groups

Over the course of the study, participants will be allocated a series of identification numbers (ID). A two-digit study number, a two-digit site number, and a sequential three-digit screening number will be allocated on referral to the study. This ID number will be used for all subsequent study documentation for that participant. In addition, a three-digit randomisation number will be allocated on randomisation of the participant. The full number sequence will be unique to that participant and will not be reassigned.

Randomisation schedules will be developed for each site using random number tables, generated at an independent centre (central registry). Treatment for each patient will be allocated according to a block randomisation (blocks of six) schedule held by the central registry in a 1:1:1 ratio. Block randomisation will ensure even allocation to each code in each site. There is a central registry that supplies the schedule tables to each site pharmacy.

The pharmacist at each site will allocate the next lowest code available according to the supplied schedule and prepare the active or inactive drug delivered in a labelled opaque screw top bottle. The participant ID, allocation code, dates of request, preparation, and dispensing will be recorded in a log maintained by the pharmacist.

At all times, from eligibility screening to completion of the study, all study staff will be unaware of the treatment allocation. Allocation is concealed from the investigator at the time of the participant inclusion in the trial; the allocation is determined by contacting the lead investigator following the unblinding procedures.

6.4.7 Blinding

All medication bottles will be prepared by the site clinical trial pharmacist according to the randomisation schedule. Each bottle will be numbered according to the pre-determined allocation code and labelled as 002/07 study – risperidone (1mg/4ml containing 80ml) / haloperidol (1mg/4ml containing 80ml) / placebo (80ml) oral solution. All opaque bottles will look identical in volume and colour,

and smell and taste the same, to preserve the blinding irrespective of the contents. The 80ml volume will contain the entire study drug needs for the patient over the study timeframe of 72 hours, allowing for the maximum allowable doses. Treatment allocation will not be disclosed to the patient and their proxy, study staff, treating clinicians or investigators. The code will only be broken in cases of extreme emergency. Such situations only include where knowledge of the code will have consequences for clinical decision-making.

6.4.8 Method of administration

The pharmacist will locate the appropriate solution according to the randomisation schedule immediately prior to dispensing the study medication. All medications must be prepared in the pharmacy and dispensed as an 80ml volume in a screw top, opaque bottle. The intervention will be delivered as oral solution. At each dose, the individually labelled bottle will be opened and the prescribed dose drawn into a 5 or 10ml terumo or BD syringe (dependant on the dose to be administered) in order to accurately check the dose volume for administration to the patient. The clinical nurse will observe the participant while the participant drinks the entire contents of the syringe, and then record the administration in the medication record.

6.4.9 Drug accountability

All active drugs must be stored undiluted in a locked drug cabinet at or below 25°C within the site pharmacy. The pharmacy will maintain accountability records in addition to the study allocation records. On dispensing to the inpatient unit, the drug will be stored within a locked drug cabinet appropriate to state regulations. The drugs will be checked and recorded by an appropriately qualified nurse on administration to the patient.

6.4.10 Drug supply

All study drugs will be manufactured by an external facility (Pharmaceutical Packing Professionals, Adelaide, South Australia) and supplied to each site pharmacy in pre-prepared opaque screwed top coded bottle to required concentrations as an 80ml volume. Once manufactured, an expiry date of 28 days will apply. This volume will enable accurate measurement of the regular (0.5mg)

and incremental doses (0.25mg to 0.5mg) with a maximum dose available to the participant of 2mg every 12 hours (8ml volume). Allowing for slight measurement differences, this will make a maximum of 80mls available to the participant over the total six doses assuming the maximal titration rate. Once manufactured, an expiry date of 28 days will apply.

6.4.11 Drug destruction

Unused syrup in the ward/inpatient unit, as well as any empty bottles, will be delivered back to the pharmacy, using the established practice within the hospital. All unused syrup and empty bottles returned to pharmacy will be stored until study monitoring and then destroyed in a manner consistent with the applicable regulations governing destruction in each state. The pharmacy Standard Operating Procedures and state regulations are to be referred to and adhered to at all times.

6.4.12 Concurrent treatments

Trial patients are to continue their current medication regimen. Any changes in concomitant medications will be documented daily. Benzodiazepines for sleep disturbance, dyspnoea or seizure control are allowed as the clinician prescribes and will be calculated as diazepam dose equivalents. No other antipsychotics are allowed.

6.4.13 Rescue medications

Rescue medications are available for administration throughout the 72-hour intervention period. The medication can be initiated at the time of first treatment if the indications indicated in Figure 28 are met.

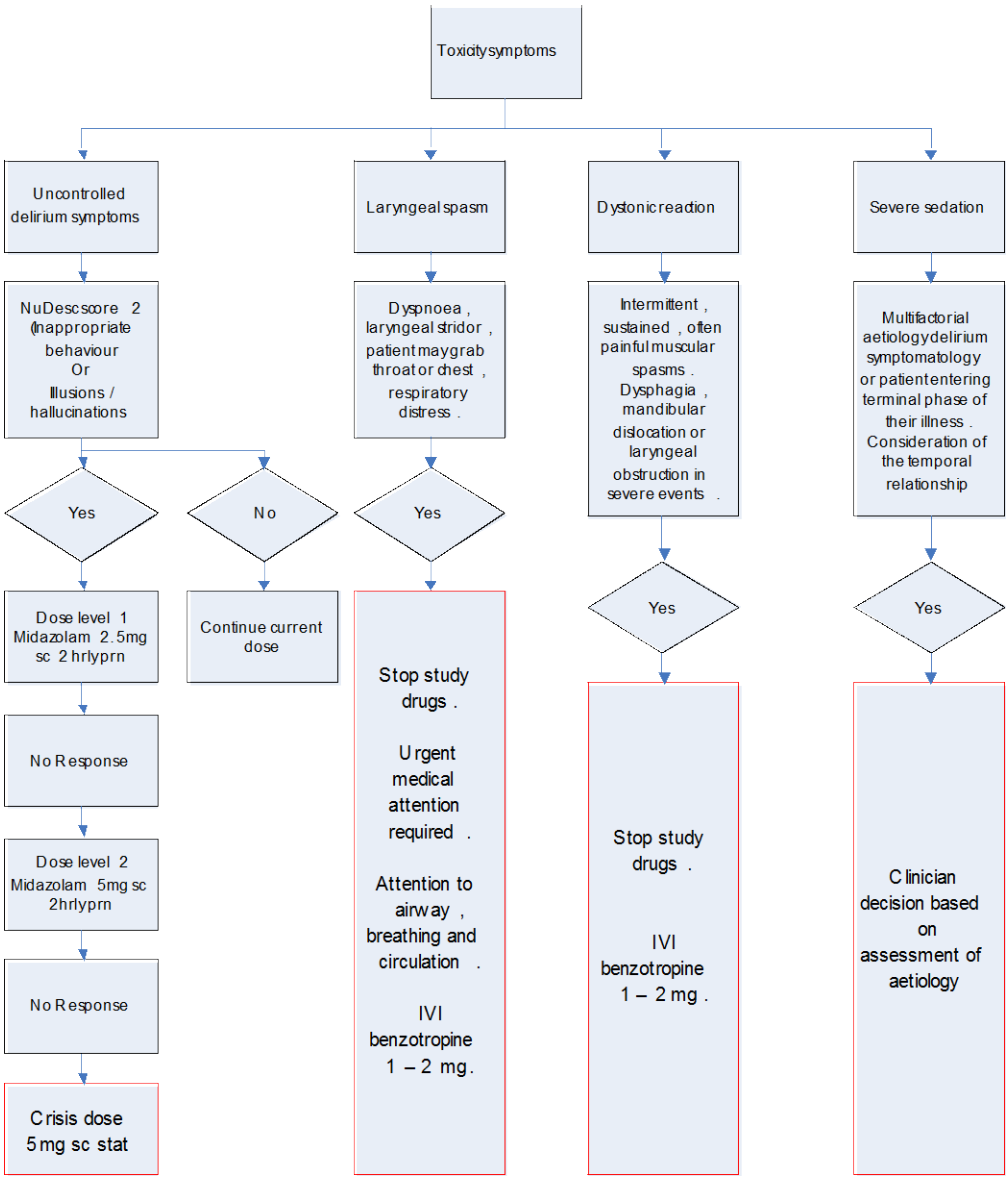


Figure 28 Rescue dose diagram

6.4.14 Uncontrolled delirium symptoms

Any NuDesc scores of 2 on one or more of the items listed below that requires immediate intervention for patient and or staff safety, or due to patient distress, can result in the rescue midazolam doses listed in Table 54 in consultation with the investigator:

1. inappropriate behaviour (behaviour inappropriate to place and/or for the person e.g. pulling at tubes or dressings, attempting to get out of bed when that is contraindicated and the like)

2. illusions and/or hallucinations (seeing or hearing things that are not there, distortion of visual objects).

Table 54 Dosing of rescue medication for targeted symptoms

Dose level of intervention	Dosing of midazolam rescue	Frequency
Dose Level 1	2.5mg subcutaneous	Q2h prn
Dose level 2[a]	5mg subcutaneous	Q2h prn
Crisis dose	5mg subcutaneous	stat

[a] increase to Level 2 if no response to dose Level 1 on two repeated doses
prn – *pro re nata*, as required or as needed

In event of non-response to crisis dose, further therapy is at the discretion of the treating physician. Midazolam administered for symptoms other than delirium symptoms is to be ordered separately on the prescription orders, clearly prescribing the indication for administration.

6.4.15 Specific adverse effects

Laryngeal spasm and dystonic reactions require immediate cessation of study drugs. Urgent medical attention is required and attention given to airway, breathing and circulation. Intravenous benzotropine 1–2mg may be required as per clinical review. Severe sedation is defined as a RASS of –3 to –5. Consideration is required of multifactorial aetiology of sedation in this setting given fluctuating levels of consciousness may be part of delirium symptomatology or patient entering terminal phase of their illness. Consideration of the temporal relationship to dose titration is important. The clinician's decision on whether drug cessation or dose reduction is required will be dependent on individual clinical circumstances.

6.4.16 Dose modification

The study drug dose can be increased or decreased according to participant response. If there are adverse effects the clinician can choose to reduce the dose by 0.25mg. If delirium resolution (defined as MDAS score <7 for 48 hours) reduces by 0.25mg and if symptoms recur at the dose level that symptoms reappear, the clinician can increase the does by 0.25mg (reducing the dose again when definition for delirium resolution next met). If symptoms resolve, defined as NuDesc Items 2 (inappropriate behaviour), and Item 3 (inappropriate

communication), and Item 4 (illusions/hallucinations), <1 for 48 hours a similar dose reduction can occur as per delirium resolution. If no improvement at 72 hours, clinicians can choose to continue on blinded medication up to a maximum of five days.

6.4.17 Treatment failure

Treatment will be deemed to have failed if:

- adverse events related to the study drug are unacceptable to participant/carer or clinician in charge; and/or
- treatment is deemed ineffective by the treating clinician, who wishes to use alternative therapy.

6.4.18 Cessation for reasons other than treatment failure

Cessation will also occur if:

- participants who are not well enough to continue the study drug;
- it is inappropriate to continue the study drug for whatever reason; or
- the participant or proxy withdraws their consent, with or without consent to use already collected data.

6.4.19 Post study treatments

After 72 hours, participants will enter the follow-up phase of the study. The treating clinician can choose the treatment depending on the scenarios outlined in Table 55.

Table 55 Post study treatments

		Response (MDAS and NuDesc)	
		Complete response	Lack of efficacy
Ability to swallow	Can swallow	Continue on study protocol with dose reductions as specified for symptom or delirium resolution	Further therapy decided by treating clinician (can continue on blinded medications for maximum of five days only)
	Can't swallow	Further therapy decided by treating clinician	Further therapy decided by treating clinician

In the event of lack of efficacy at 72 hours, clinicians may continue the current dose of study medication for five days if the patient can swallow; or may choose

to add an additional agent on a regular or as required basis; or change to an agent of clinician choice and cease the study drug. (The clinician remains blinded to whether patient received active antipsychotic or not and will institute new agent with re-titration as will not have information of whether active agent was received and its dose level). Rapid re-titration within 24 hours is possible with appropriate access to as-required doses.

6.5 Outcomes and measures

The outcome measures are listed in Sections 6.5.1 and 6.5.2 and more detailed discussion of choice of measure follows in Sections 6.6.5 onwards.

6.5.1 Primary outcome and measure

The measure of the primary outcome will be the sum of the scores on NuDesc Item 2 (inappropriate behaviour), Item 3 (inappropriate communication), and Item 4 (illusions/hallucinations) at 72 hours.

6.5.2 Secondary outcomes

6.5.2.1 Efficacy outcomes

Efficacy outcomes will be measured by:

- time to discontinuation of therapy (hours);
  - lack of efficacy following an appropriate titration protocol; or
  - lack of tolerability – extrapyramidal toxicity or other toxicity (global measure of effectiveness—integrated outcome of clinician, participant and caregiver efficacy, safety and tolerability)
- time to first rescue midazolam dose (hours);
- number/total dosage of midazolam rescue usage;
- MDAS score <7 at 72 hours;
- percentage of participants who did not require rescue dosage within 72 hours;
- percentage of participants who have delirium recurrence after 48 hours of MDAS <7;
- time profile using linear mixed models of MDAS scores, adjusted for baseline covariates: performance status, prior cognitive impairment; comorbidity burden—CCI and CIRS scores, presence or absence of brain

metastases, opioid dose in morphine equivalents, benzodiazepine dosage, CRAS;

- participant-reported recall after delirium resolution (48 hours after MDAS <7);
- participant, caregiver and nursing staff-rated distress after delirium resolution using the DEQ for patients, caregivers and nursing staff respectively.

6.5.2.2 Toxicity outcomes

Toxicity outcomes will be measured by:

- extrapyramidal toxicity—ESRS score >75th percentile of worst ESRS score (worst ESRS score in first 72 hours);
- sedation—worst score on sedation subscale of RASS over seven days;
- adverse events—adverse events and serious adverse events will be elicited by direct questioning and observation by the investigator and their delegates. The adverse events will be reported using National Cancer Institute Common Terminology Criteria for adverse events version 4.0. Specific adverse events include reporting of neuroleptic malignant syndrome, cerebrovascular accidents, laryngeal spasm and acute dystonia.

6.5.3 Health-service utilisation and long-term outcomes

Health-service utilisation and long-term outcomes will be measured by:

- medical complications during admission (falls, pressure ulceration, thromboembolism, pneumonia, incontinence);
- death;
- cognitive impairment (defined as abbreviated short mental status score ≤7), after delirium resolution and at last follow-up;
- functional decline;
- usage of AIN (hours) during delirium episode;
- nursing home placement;
- length of admission in palliative care unit (days);
- survival outside of institutional care (days).

6.5.4 Serum apoptosis marker levels

Marker levels will include:

1. S100B;
2. Cytochrome C;
3. Caspase 3;
4. Neuron specific enolase.

6.5.5 Laboratory measures

6.5.5.1 Metabolic factors

Liver function tests, serum electrolytes, and full blood count will be taken on eligibility (or within previous three days) and on delirium resolution to assess precipitating factors of delirium according to the definitions described below.

6.5.5.2 Serum apoptosis markers

The longer-term pathophysiological sequelae of delirium are uncertain; however, direct neuronal injury is likely in some cases, and may be related to the long-term clinical outcomes seen.[719] Serum markers that detect neuronal injury may be relevant in delirium onset, delirium persistence and adverse cognitive sequelae and have been studied in situations of direct neuronal injury (stroke, head trauma, subarachnoid haemorrhage, post cardiac surgery) where relationships to degree of damage sustained have been seen.[719 742] These markers also may provide an indicator for the impact of pharmacological therapies on pathophysiological mechanisms, and hence determine if these therapies have potential to improve/impact long-term outcomes. S100 calcium binding protein B (S100B) is a serum protein that can be assayed using enzyme-linked immunosorbent assay methods using arterial or venous serum.[719 743] The role of protein S100B is not yet fully understood; however, it seems to have intracellular and extracellular neurotropic as well as neurotoxic function.[743] At nanomolar levels, S100B stimulates neurite outgrowth and enhances survival of neurons.[743] However, at micromolar levels it stimulates the expression of inflammatory cytokines and induces apoptosis.[743] Other markers that have been studied include Cytochrome C, Caspase 3 and Neuron Specific Enolase, and these also have a role in neuronal cell death.[744-747] S100B, caspase 3 and Neuron Specific Enolase are serum proteins that can be assayed using Enzyme-Linked Immunosorbent Assay (ELISA) methods through venous blood sampling.[719 743] Ten ml of blood will be collected from a consenting subset of participants, and dispatched to the

Department of Cell Biology, University of New South Wales. Serum will be stored at –80°C and analysed in batches. Assays will apply ELISA analysis initially for the S100B serum marker, and subsequently a selected series of potential delirium serum indicators (Cytochrome C, Caspase 3 and Neuron Specific Enolase).

6.5.6 Medical and physical measurements

The study assessments are tabulated in Table 56. The study period will be for 72 hours from randomisation. The follow-up phase will be weekly for one month. If the patient is discharged, follow-up will be weekly for three weeks by telephone, then a face-to-face visit at one month. Date of death will be collected for all patients. Though some studies have demonstrated mean time for delirium resolution is an average of four days, this study has outcomes of targeted symptom control. The time period of 72 hours was determined as the clinically significant time period in which target symptom resolution should occur for these therapies to be effective, especially in a palliative care population where rapid control of distressing symptoms is important, even in the setting where delirium resolution does not occur.

Table 56 Summary of study measures

	Eligibility	Baseline	Day 1-3	Cessation	Resolution/ withdrawal	Discharge	Follow up
Investigations							
Liver function	*				*		
Electrolytes	*				*		
Full blood count	*				*		
Serum markers		*			*		
Medical file review							
Demographics	*						
Diagnosis	*						
Barthel Index		*	*		*	*	*
Con meds		*	*		*		*
Rescue medications			*				*
Anticholinergic scale		*	*		*		*
Admission data		*					
Complications							
Patient measures							
Vision	*						
Hearing	*						
AKPS		*		*	*	*	*
MMSE		*		*		*	
Pulse oximetry		*	*		*		
Patient rated distress					*		Week 4
EORTC QLQ					*		
FACIT – PAL					*		
Medical assessment	*		*				*

	Eligibility	Baseline	Day 1-3	Cessation	Resolution/ withdrawal	Discharge	Follow up
Clinician assessed measures							
Toxicity		*	*		*		
CIRS		*			*		
CCI		*			*		
Sedation		*	*				
ESRS		*	*				
MDAS	*		*		*		Week 4
NuDesc	*	*	* shift				
IQCODE		*					
Nursing rated distress		*		*	*		
Caregiver distress		*		*	*		Week 4
Supportive measures		*	*		*		*
Survival							*
Date of death							*
GP visits							*

AKPS – Australia-modified Karnofsky Performance Status; CIRS – Cumulative Illness Rating Scale; CCI – Charlson Comorbidity Index; ESRS – Extrapyramidal Symptom Rating Scale; EORTC QLQ – European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – core 30 questions; FACIT-PAL – Functional Assessment of Chronic Illness Therapy-Palliative care; GP – General Practitioner; IQCODE – Informant Questionnaire on Cognitive Decline in the elderly; MDAS – Memorial Delirium Assessment Scale; MMSE – Mini-Mental Status Examination, NuDesc – Nursing Delirium Screening Scale

6.5.7 Demographics and clinical information

Demographic details include age, gender, availability of primary caregiver, Aboriginal or Torres Strait Islander status, language spoken at home and post code. The main life-limiting illness will be documented, and for cancer diagnosis, most recent staging and sites of metastases including the presence of brain metastases.

6.5.7.1 Performance status

The AKPS was developed for use in palliative care populations, and is designed to use descriptors more suited to palliative care populations. Preliminary data has shown this provides a measure that is more applicable to palliative care patients, in comparison to the standard KPS measure in palliative care.[748] This objective measure has high inter-rater reliability and is sensitive to changes in function over time. A score of 0 to 100 (in increments of 10) is assigned to patients based on their ability to undertake a range of daily tasks. The score gives an indication of the patient condition (in terms of physical ability) and can assist in prognostication. The tool will be used in this study to provide a global measure of level of impairment.

6.5.7.2 Barthel Index

The Barthel Index will be used to assess impairment of ADL, to further delineate functional domains affected by delirium. It has established psychometric properties.[666-668] This tool will be used in this study to provide a measure of specific impairment.

6.5.7.3 Comorbidity burden

The comorbidity burden is a scale for measuring comorbid illness is also crucial in a study of delirium, to attempt to quantify the body systems involved and the severity.

The Cumulative Illness Rating Scale: The CIRS rates 13 conceptually valid body systems on a five point pathophysiologic severity scale, and is valid and reliable.[670] It is useful in the palliative care setting as it is structured relating to body systems and gives a clinical severity rating, both of which correspond well

with clinical practice.[670] It is scored based on clinical judgment, and has been studied in populations including cancer patients.[670] CIRS does not require invasive physiological measures such as arterial pH or oxygenation, which are not appropriate to perform routinely in many patients with advanced cancer.

The Charlson Comorbidity Index: The CCI will also be calculated, which is a valid and reliable tool, and has shown relationships with mortality, disability and length of stay.[670 672]

6.5.7.4 Vulnerability factors

A series of factors will be recorded in order to describe the study population in terms of delirium vulnerability. If possible, visual acuity will be assessed and documented by whether or not the participant requires reading glasses or glasses for vision at all times; hearing impairment will be defined as the wearing of a hearing aid, or participant/caregiver assessment of a hearing impairment and presence of a serum albumin level less than 30 g/L occurring during hospitalisation; and the IQCODE will be used to define the presence or absence of prior cognitive impairment.

6.5.7.5 Precipitating factors

The following factors will be assessed according to the protocol used by Lawlor et al[38] which evaluated each potential precipitating factor for delirium for:

1. evidence of presence from specific clinical, laboratory, or radiological findings
2. temporal association with the course of delirium consistent with a potential precipitating role
3. changes in the severity of delirium in association with similar changes in the precipitating factor.

Reversibility will be assessed in view of delirium improvement (at least a 25% reduction in MDAS score) or reversal corresponding to evidence of improvement or resolution of the precipitating factor as previously defined by Lawlor et al.[38] If MDAS scores fail to decrease or even increase with clinical or other evidence of unsuccessful treatment or progression of the putative precipitating factor, this will be defined as irreversible as previously defined by Lawlor et al.[38]

The specific factors that will be considered are: infection (presence of intercurrent infection: pneumonia, urinary tract infection, or wound infection); psychoactive medication (patient received a psychoactive medication known to cause delirium; and delirium improvement or reversal occurs after at least 25% reduction in dose; or drug cessation); hypoxia (oxygen saturation <90% on room air, or requiring an oxygen flow of 2l/min or more) and metabolic factors:

- persistent creatinine level of greater than 150 µmol/L (1.70 mg/dL) (renal insufficiency)
- glucose level of less than 4 mmol/L (72.0 mg/dL) (hypoglycemia); magnesium level of less than 0.7 mmol/L (1.75 mg/dL) (hypomagnesemia)
- aspartate aminotransferase levels of greater than 40 U/L
- alanine aminotransferase levels of greater than 50 U/L
- bilirubin levels of greater than 20,000 µmol/L (1169.6 mg/dL) (hepatic impairment)
- hypercalcemia was recorded if calcium levels (corrected for albumin level) were greater than 2.6 mmol/L (10.4 mg/dL).

Cessation or reduction of nicotine or alcohol intake: nicotine intake will be documented as cigarettes per day, and duration (days) or reduced or ceased intake recorded. Whether or not nicotine replacement therapy is needed will be recorded. Alcohol intake will be documented in standard drinks per day and duration (days) or reduced or ceased intake recorded. Whether or not alcohol withdrawal needed benzodiazepine therapy will be recorded.

6.5.7.6 Medication

Opioid dose equivalents: daily opioid dose will be calculated using oral morphine equivalents/24 hours, according to pre-specified conversion (see Table 37 Chapter 5).[749]

Benzodiazepine usage: daily benzodiazepine dose will be calculated as oral diazepam/24 hours, according to the conversion table. Benzodiazepines for sleep disturbance, dyspnoea and/or seizure control are allowed as the clinician prescribes and will be calculated as diazepam dose equivalents. Benzodiazepine usage for delirium is as per benzodiazepine rescue protocol.

Rescue midazolam usage: daily rescue midazolam usage will be calculated and the time for first rescue, and time between rescue doses recorded.

Number of medications added: the number of medications added to the participant's medication regimen will be calculated for each 24-hour period.

Clinician Rated Anticholinergic Scale – modified version: All current medications will be documented, and scored on the CRAS - M (see Chapter 1 Section 1.11.2), which is the best available measure for calculating AA of medication.[186 234 248] Daily alteration to medication regimes will be noted. As required (*pro re nata* or prn) medication will be included only if a dose has been administered within 24 hours.

6.5.8 Nursing Delirium Screening Scale

As a continuous assessment measure to assess delirium fluctuation, and to measure targeted delirium symptoms as the primary outcome over 24 hours, the NuDesc will be used.[78] The NuDesc is an observational five-item scale that can be completed quickly. The psychometric properties were studied in 146 consecutive hospitalised patients from a prospective cohort study, and compared NuDesc assessment by bedside nurses with 59 blinded CAM ratings made by research nurses and psychiatrists.[78] DSM-IV criteria and the MDAS were rated along with CAM assessments. Analysis of these data show that the NuDESC is psychometrically valid and has a sensitivity and specificity of 85.7% and 86.8%, respectively.[78] These values are comparable to those of the MDAS.

The NuDesc will be administered in order to determine the dose titration, and will be obtained and recorded at 8am, 4pm and 12 midnight daily; and be scored based on the prior eight hours. The 4pm score will be obtained by the study nurse and will be discussed with the site investigator in order to determine the study drug dose for that evening.

The investigators recognise that delirium often becomes more apparent later in the day and into the evening. An increase in the symptoms of delirium may potentially occur after the NuDesc score at 4pm, and before the evening study dose. To avoid mistakes with the study protocol, study dose prescribing has been

kept within working hours when the investigator and study nurse are both still on site. The NuDesc score is an assessment of the presence and intensity of symptoms since the last recording so all fluctuations during that period will be captured. If there is a change in the patient condition between the time of the afternoon NuDesc score and the evening study dose, the NuDesc is to be repeated. If at this point, the NuDesc indicates a change in the patient condition, the site investigator is to be called so that the evening study dose can be reviewed. Whenever possible the overnight nurses will be requested to complete at the 12 midnight NuDesc.

6.5.9 Memorial Delirium Assessment Scale

Several delirium evaluation instruments exist, however, for the purpose of this study, a tool which allows repeated assessments and measured change in severity over time is needed.[26 40] The MDAS is a brief, valid and reliable tool for assessing delirium severity in advanced cancer patients, and is easy to use for repeated assessment [39 40] MDAS has been validated in cancer populations and it allows repeated assessments—necessary in this study.[40] A detailed discussion on the MDAS and its psychometric properties is in Chapter 1 Section 1.7.2.1. The MDAS will be performed at eligibility and daily in conjunction with information provided by the treating medical and nursing team, between 8am and 12 midday (because of known variation of delirium symptoms within a 24-hour period.) The MDAS will be scored based on the prior 24-hour period. An initial training session will occur for staff so observations required are known.

6.5.10 Extrapyramidal symptom rating scale

The ESRS was developed to assess the EPS of psychoactive medications[750], and has been widely used as a research tool in psychiatry and in pharmacological studies of psychoactive medications. The scale identifies four drug-induced movement disorders—Parkinsonism, akathisia, dystonia, and tardive dyskinesia. The incidence of these movement disorders in palliative care patients has not been described; however, the ESRS measurement of drug-induced EPS is valid and discriminative from psychiatric symptoms in other populations.[750] The scale consists of an objective (observational) component based on a standardised clinician neurological assessment, and a component of the subjective experience

of the symptoms, addressed with a few simple questions. In participants with a sedation score of –3 or less, only the objective measures will be used. In participants who are judged to be too unwell for the complete standardised examination, a minimal examination will be performed to assess muscle tone, facial movements, and presence or absence of dystonias or dyskinesias.

6.5.11 Sedation (Richmond Agitation Sedation Scale)

The three aspects of consciousness that need measurement are:

1. arousal (a state of responsiveness to sensory stimulation)
2. alertness (a condition of being mentally quick, active, and keenly aware of the environment, i.e. orientation and communication)
3. appropriate voluntary motor activity.[751]

The RASS has been validated in the intensive care setting in patients on mechanical ventilation.[752] [753] It is a 10-point scale using observation, verbal stimulation, and physical stimulation, the last used only to assess the two (out of five) deepest levels of sedation. It has been selected because it gives clear descriptors for assigning scores, differentiates between different potency of stimulation (verbal vs physical) and also looks at constructs related to delirium (inattention as measured duration of eye contact).[752] More recently, since commencement of the protocol, a modification has been developed (RASS-Palliative) which modifies the requirement for verbal or physical stimuli for scoring with an interclass correlation coefficient of 0.83–0.98 (equivalent to the RASS in the same population) supporting the psychometric properties of the RASS in the palliative population.[754] It has also more recently been used to monitor palliative sedation in the terminal phase.[755]

6.5.12 Prior cognition impairment – Informant Questionnaire on Cognitive Decline in the elderly

The IQCODE (Appendix 17) for caregivers has high reliability, and measures a single general factor of cognitive decline in the participant over time as reported by a family informant.[756-758] It has had its validity tested against conventional cognitive screening tests, predicts incident dementia, and correlates with a wide range of cognitive tests. It is relatively unaffected by education and pre-morbid ability or by proficiency in the culture's dominant language. Its disadvantages are

that is by informant characteristics (e.g. depression and anxiety in the informant) and the quality of the relationship between the informant and the subject. This instrument has been used in prior outcomes of studies of delirium in other populations to define prior cognitive impairment.[407 759] The introduction has been modified to make sure the caregiver understands it is in relation to the weeks prior to delirium episode as the comparator.

6.5.13 Mini-Mental Status Examination

The MMSE[127] is used in this study to determine higher cognitive function. A discussion of the psychometric properties of MMSE is found in Chapter 1 Section 1.7.1.

6.5.14 Patient, caregiver and nurse distress - Delirium Experience Questionnaire

The DEQ is a face-valid, brief instrument that assesses recall of the delirium experience and the degree of distress related to the delirium episode in patients, spouses/caregivers, and nurses.[295] It has been used to describe delirium experience in 154 hospitalised cancer patients; however, its psychometric properties have not been established. There is, however, no other available instrument to measure distress, hence it has been chosen for this study. The scale consists of several yes/no questions plus two 5-point Likert scale questions (for the patient), one Likert scale question for the carer and nurse versions, as well as an open question in each version to allow qualitative analysis of the experience. Participant distress and recall will be assessed at delirium resolution (MDAS <7 for 48 hours), at discharge, and at Week four. Nurse distress will be assessed at recruitment, and at 72 hours and delirium resolution if occurs. Caregiver distress will be assessed at recruitment and at 72 hours, at delirium resolution if it occurs, and at four weeks following discharge (study nurse visit).

6.5.15 Quality of life

Quality-of-life assessment will be undertaken in participants who have delirium resolution only. Quality of life of patients will be measured using the European Organisation for Research and Treatment of Cancer Quality of life Questionnaire – core 30 questions (EORTC QLQ-C30)[760] and in participants who are able with

the Functional Assessment of Chronic Illness Therapy – Palliative care (FACIT-Pal).[761 762] Both the FACIT-Pal and EORTC QLQ-C30 have been used in cancer and palliative populations, with EORTC QLQ-C30 the more widely used cancer-specific quality-of-life measure. Both instruments are valid for use in a wide variety of cancer populations, including patients undergoing palliative care.[762-766] A large amount of published data is available for comparison purposes.[763 766] A palliative-specific EORTC-QLQ[88,89] has been developed with only 15 key questions, recognising that palliative patients become fatigued quickly.[766-770] These 15 questions are included in the 30-question version, but we will shade the 15 questions; if it is clear that the patient is fatigued, the study nurse will administer the 15 shaded questions only, instead of the 30 questions. In addition, we intend to collect data for the validation of the FACIT-Pal, which shows promise as a palliative care-specific measure and includes items concerned with existential issues that are absent from the QLQ-C30. The FACIT-Pal will only be completed in patients who are not fatigued and have been able to complete EORTC QLQ (30 or 15 item) without problems.

6.5.16 Assessments for economic analysis

With limited healthcare resources, a new therapy must be shown not only to be effective but also to provide any benefits at a reasonable cost to the community. Consequently, information on economic outcomes is becoming necessary in the evaluation of any new treatment (the Australian Pharmaceutical Benefit Scheme requires such analyses for new submissions). The objective of the economic evaluation is to estimate and compare costs and consequences for oral risperidone, oral haloperidol and oral placebo in the management of delirium, in each case with midazolam rescue. The economic evaluation will utilise within-study data on treatment effectiveness and resource use in the three arms. The treatment effects will consider patient, family and carer psychosocial effects. The variables included will include delirium symptom duration/severity/resolution; patient reported distress on delirium resolution; medical complications (pressure areas, pneumonia, thromboembolism, new onset incontinence with index hospitalisation); utility from health-related quality of life; caregiver, family and health professional-rated distress; patient function measured by AKPS and Barthel's Index; and cognition. Additionally the economic analyses will consider

healthcare resource use, costs related to the medication in each treatment arm (preparation administration and need for rescue medication) and consequences (time in hospital, home, side effects). Resource use to be collected includes: days spent in hospital; palliative care, clinician and nursing time during index hospital admission (including need for one on one nursing, use of restraints, hoists); time to readmission (acute hospital or palliative care inpatient unit); requirement for residential aged care (nursing home); number of in-patient admissions to death; community support (GP visits, home care palliative care team review); and caregiver time (time taken in hands-on caregiving). At one site recruiting to the study, a full economic evaluation will be undertaken of the cost of risperidone and haloperidol purchase, preparation and delivery.

6.5.17 Consent process

6.5.17.1 Proxy consent

It is critically important to improve the evidence base for management of delirium in palliative care due to the significance patients and families place on maintaining lucidity at the end of life, and also due to the associated significant distress, morbidity and mortality attributable to delirium itself. By definition delirium is a disorder associated with cognitive impairment, though the severity of this can be variable and fluctuate.[771] Hence it is not possible to obtain written informed consent from the participant in this population.[771] Two consent processes have been utilised in delirium therapeutic trials, namely advanced[338] or proxy consent.[772] This study will utilise proxy consent. Obtaining consent for this study will be a process of information exchange between the study staff, the potential proxy and any other person the potential proxy believes should be included in the discussion. The information sheet will be used as a basis for the discussion, which will cover all procedures, benefits, burdens and side effects expected or possible during the study. The proxy will be given opportunity (in time and physical capacity) to consider the study and formulate questions, any questions will be addressed and answered fully. An actual time period is not specified as this will be determined in part by conditions at the time, but the proxy will be given the time to consult with others and to ask questions. The study nurse will specifically ask if the proxy has been given enough time and opportunity to consider the study.

Written informed proxy consent (Appendix 18) will be obtained from a 'person responsible'[q]. No information collected for this study will be released to the proxy consent person. In the states of New South Wales and Queensland, Australia, the Guardianship Tribunal (Guardianship Tribunal of New South Wales [r] and Queensland Civil and Administrative tribunal[s]) and also is required to review and approve clinical trials that require person responsible consent, after Human Research Ethics Approval has been obtained.

6.5.17.2 Consent for serum sample

Separate proxy consent will be obtained to participate in the serum marker study, so that participants who do not wish to have blood tests can still participate in the main study. If at the time of blood collection the patient refuses to have specimen collected they will be withdrawn from this sub-study.

6.5.17.3 Nurse and caregiver consent

Written informed consent will be obtained from nursing staff and the caregiver to participate in the study in relation to caregiver and nursing distress. If the caregiver or nurse does not wish to participate in rating distress, this does not exclude the participant from study participation.

6.5.17.4 Participant consent

Participant consent will be obtained at the time of symptom resolution in order to record participant recall of distress. Where possible this consent will be obtained within the presence of the person who gave the proxy consent for the study, and will be carefully scripted and practised by study staff in order to reduce burden and potential conflict over the initial consent. If the participant withdraws consent

[q] 'Person responsible' is a term used in Australian legislation to clearly define who can make medical decisions on behalf of some who lacks capacity. Each state and territory in Australia has specific legislation, outlining the hierarchy of people who may be deemed the 'person responsible'. The list includes spouse, de facto spouse, enduring guardian, close friend or adult relative, legally appointed guardian, with slightly different ordering and definitions between states and territories.

[r] The Guardianship Tribunal of New South Wales, an agency of the Government of New South Wales, is a specialist disability tribunal for people with cognitive incapacity, or disability. This includes review of clinical trials within these populations.

[s] Queensland Civil and Administrative tribunal is an agency of the Queensland Government and has roles to assess an adult's decision-making capacity, appoint a responsible adult to make some or all personal and health care decisions for the adult, and ensure their rights are protected. This includes review of clinical trials including for those who lack decision-making capacity.

for their participation in the main study when they regain capacity they will be withdrawn from the study intervention and will be asked specifically if data already collected can be retained.

6.6 Reporting of adverse events

All adverse events (AE) will be reported via an online reporting system to enable study-wide reporting in real-time. Severity of AEs will be assessed according to Good Clinical Practice guidelines.[773] Adverse events are defined as any untoward or unexpected occurrence in a patient or clinical investigation participant where the occurrence does not necessarily have a causal relationship with the study intervention. The site investigator will assess each event for relatedness or causality of the intervention and the event. Adverse events will be identified during each visit using criteria established by the National Cancer Institute Common Terminology Criteria for Adverse Events (V4.0); with participant symptoms will be graded accordingly. There are circumstances where AEs will not be reported, for example, signs or symptoms associated with the disease or disorder under study, unless they are more severe than expected, or social admission to hospital.

Serious adverse events (SAE) are any untoward medical occurrence that results in death, is life-threatening, results in attempted suicide, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, requires ongoing medical or professional attention and/or are judged to represent significant hazard.

In this study, a number of SAEs are expected. The expected study population have an underlying disease that is expected to significantly shorten life expectancy, they are already termed palliative and are expected to die within a short period of time. The conditions recognised as being excluded from SAE reporting are as follows:

- where participants are admitted as a planned admission due to respite, family or social issues, or for pre-planned treatment
- where participants are admitted due to a documented deterioration in their condition due to the underlying disease process

- where participants die due to a well-documented decline in their condition due to the underlying disease process.

In all other cases, SAEs will be reported according to the requirements of the local Hospital Ethics Committee.

Specifically for this study, the AEs of interest that may be related to the study intervention and/or condition under study (delirium) are anorexia, cardiac arrhythmia, tachycardia, cognitive disturbance, cerebral-vascular accident, constipation, diarrhea, dysphagia, dyspnea, oedema (peripheral), gait/walking, hypertension, hypotension, hyperthermia, hypoxia, insomnia, involuntary movement/tremor, laryngeal nerve dysfunction, nausea, neuroleptic malignant syndrome, mood alteration, agitation, anxiety, musculo-skeletal rigidity (lead pipe), prolonged QT_c interval, seizures, somnolence, sweating and vomiting.

Cessation of study intervention and an AE report in all cases (of any severity) will occur for neuroleptic malignant syndrome, laryngeal spasm, acute dystonia, prolonged QT interval and cerebrovascular accident. A grade of 3 or 4 will activate cessation of the study intervention, as well as an AE report for seizures, cardiac arrhythmia, tachycardia or hyperthermia.

6.6.1 Unblinding

In cases of medical need, where urgent medical decisions will be influenced by knowledge of the treatment assignment, the lead investigator will have access to the sealed unblinding envelopes and must be contacted in the first instance. Clinical staff will be able to discuss the clinical situation with the lead investigator to determine the urgency and need for unblinding, and will be informed by the lead investigator of the assignment based on these discussions.

6.6.2 Data Safety Monitoring Board

This study will have a contracted independent Data Safety Monitoring Board (DSMB) managed through the Mater Health Service, Brisbane, Australia. The primary role of the DSMB will be to monitor adverse and SAEs. All SAEs are be sent to the DSMB within seven days for review while AE reports will be reviewed at three-monthly intervals, as agreed by the DSMB. In addition, any emerging safety issues will be reviewed by the DSMB on an ad hoc basis if required. The

DSMB will consist of experts in the field, a clinical trials statistician, a trial pharmacist and an experienced palliative care physician. The DSMB will also receive an updated literature summary at each meeting, which will address new published literature that may have an impact on the study. Interim unblinded analysis is not planned for this study given the impact that this will have on the sample size calculation.

6.7 Analysis plan

6.7.1 Primary endpoint

The primary endpoint will be the sum of scores on NuDesc Item 2 (inappropriate behaviour), Item 3 (inappropriate communication), and Item 4 (illusions/hallucinations) at 72 hours.

6.7.2 Analysis of primary null hypothesis

The sum of NuDesc scores (Items 2, 3 and 4) at 72 hours (morning score by researcher) will be compared by analysis of variance. A linear contrast will be constructed to compare risperidone and control groups. The corresponding score at baseline will be used as a covariate. Intention to treat analysis will be used. For patients who die during the 72-hour period, the last recorded NuDesc score will be used in the analysis. The null hypothesis will be rejected if $p < 0.05$.

6.7.3 Analysis of secondary null hypotheses

Secondary null hypotheses will be tested by analysis of variance. Linear contrasts will be constructed comparing risperidone and haloperidol groups, and haloperidol and control groups.

6.7.4 Analysis of toxicity outcomes

The worst ESRS score during the treatment period will be determined for each patient. The 75^{th} percentile will be determined after pooling scores over all treatment groups. Proportions of patients with scores greater than or equal to the 75^{th} percentile will be compared by chi square tests.

6.7.5 Analysis of other efficacy outcomes

Proportions of patients with MDAS scores <7 at 72 hours, proportions who did not require rescue dosage within 72 hours, and proportions with delirium recurrence after 48 hours of MDAS <7 will be compared by chi square tests. The delirium episode for participants who die during the 72 hours and do not have a further MDAS score after baseline, will be classified as not resolved.

6.7.6 Time-to-event analysis

Time in hours to resolution of delirium or withdrawal due to toxicity will be analysed jointly using competing risks methodology. Patients withdrawn for reasons unrelated to treatment (e.g reaching end of study period) will be considered as censored. Gray's method will be used to compare crude cumulative incidences.[774] Time to first rescue medication will be analysed by Cox's proportional hazards regression. Should the proportional hazards assumption be violated, the treatment period will be divided into intervals within which the proportional hazards assumption holds.

6.7.7 Linear mixed models

Daily MDAS scores, daily NuDesc, and daily ESRS scores will be analysed using linear mixed models. Covariates will include baseline measurements of performance status (AKPS score), CRAS - M, opioid dose (oral morphine equivalents), benzodiazepine dosage (diazepam dose - equivalents), comorbidity burden (CCI and CIRS scores), brain metastases (present/absent), and prior cognitive impairment (yes/no).

6.7.8 Power and sample size

A total sample size of 165 completed patients (55 risperidone, 55 haloperidol, 55 control) will provide 80% power, at a 2-tailed type I error of 0.05, to detect a difference of 0.55 SD unit between any two treatment means.

6.7.9 Economic analyses

The main objective of the health economics study is to determine the costs and consequences of oral risperidone compared to haloperidol management; and both haloperidol/risperidone combined compared to placebo management of palliative

care patients with delirium. This will be accomplished by comparing these strategies:

1. Estimating the effectiveness of risperidone compared to haloperidol; and risperidone/haloperidol combined versus placebo in terms of reductions in delirium scores, increase in survival time and survival time out of institutional care (at home) and impact on family and carers.
2. Estimating the resource usage associated with risperidone compared to haloperidol and risperidone/haloperidol combined versus placebo, with particular reference to determining whether incremental study medication procurement, preparation and administration costs are somewhat offset by lower costs associated with any better management of delirium.
3. A within-trial analysis will estimate the incremental costs and improvement in delirium management with risperidone compared with haloperidol, and with risperidone/haloperidol combined over placebo control over a 72-hour follow-up period. This analysis will enable best evidence for an acute within study estimate of incremental cost per improvement in NuDesc (additional delirium symptom resolution) at 72 hours. Longer term incremental costs and consequences (time to delirium resolution, weeks of survival, weeks of survival out of institutional care at home, impacts on family and carers) will also be estimated based on data collected over a further three months of less intensive study follow. Sub-studies of medication use (dosage, preparation, and administration) and costs, distress in patients, families and carers and carer burden are also planned.

Sensitivity analysis will be undertaken on ranges of uncertainty of treatment effect observed within the trial follow-up period and extended for three months. The analysis will utilise a recently developed method (cost consequences), which enables joint consideration of evidence from multiple domains (e.g. functioning, delirium management, psychosocial support) and decision-making under uncertainty.[775 776] Data will be prospectively collected from patients in each arm of the study on costs and consequences of patient symptom relief, functioning, capabilities and psychosocial support in the defined palliative care population of interest. This patient-level data allows within-trial modelling using bootstrapping

methods[777] of replicates for costs and consequences of strategies with multiple outcomes, allowing for covariance between costs and effects.

6.8 Study progress and results to date

6.8.1 Ethical review

The process of achieving human research ethics approval across 11 sites in Australia was prolonged, and took 18 months to complete. There needed to be initial discussions with site investigators and clinicians about the study design, in particular about the placebo arm and proxy consent to ensure they were comfortable about the clinical approach being taken, confident about having discussions with a proxy in a clinical situation where decisions needed to be made relatively quickly, and they had an understanding that the current literature did not provide sufficient support for specific approach with known efficacy and toxicity (equipoise existed). Similar discussion were needed with the research and ward nurses.

In two states (New South Wales and Queensland) a specific application to the guardianship tribunal (outlined in section 6.6.16.1) was required. This specifically asked the investigators to address whether any treatments being tested had already been proven to be beneficial, that the study can only be conducted in those without decision-making capacity, the approach to consent for the trial, whether a placebo will be used, and whether the study would present material risk other than that which is associated with the existing health care participants would receive. The applications were reviewed by a lay person, a legal representative and a health professional, and in New South Wales required a formal presentation in person to a tribunal hearing. Key points which were covered were that the medications under study are currrently in use in clinical practice to manage the symptoms of delirium, without clear evidence for safety or efficacy and without registration in any international juridisction for a delirium indication. The study introduces a level of monitoring for safety and efficacy which exceed currently clinical practice, and is not introducing medications which are not already in use. The active measures which participants receive in all arms were clearly outlined, which include assessment and interventions for potentially reversible precipitants when it is clinically indicated, and non-pharmacological measures such as

attention to hydration, reducing sensory deprivation (making sure visual and hearing aids are available and used), presence of family and regular reorientation. The rescue medication protocol was also outlined, to reassure the tribunal that participants would not be left distressed or with safety at risk, and that the clinician could change to alternative therapy at anytime and withdraw the patient from the study due to nonresponse or toxicity. Both tribunals provided verbal feedback when approval was granted, that they were pleased that the issue of the poor evidence-base for delirium care was being addressed.

It is important to note that one site in Western Australia was unable to proceed, as the Human Research Ethics Committee was unable to make a final decision about approval. There was no tribunal in Western Australia which could deliberate on trials with proxy consent, and the committee chair did not feel comfortable reviewing the study from a ethical or scientific perspective. The study remained under review for 12 months, and there were multiple discussions with the committee chair, the site investigator and me to assist in their understanding of the issues for consideration, including presentation to the full committee. After 12 months it was decided to withdraw the application and not pursue the study at this site.

6.8.2 Recruitment and completion

At 21 January 2013, the study has been open since July 2008 at 11 sites across Australia, as part of the Palliative Care Clinical Studies Collaborative. Table 57 overviews the recruitment as of 21st January 2013. One thousand four hundred and thirty six participants have been referred to the study, 226 participants were eligible (16% of participants referred), 200 participants consented and were randomised (88% of eligible), 172 participants have completed day 1 (86% of those randomised), 152 completed day 2 (76% of those randomised) and 137 completed the study to day 3 (69%). Twenty eight further participants completing day 3 are required to complete the study, with projected completion based on current recruitment rates in December 2013. The predominant reasons for non-recruitment are informed consent not provided by proxy (30%), inability to swallow oral medications (35%), prior antipsychotic use (usually for nausea) (43%), target symptoms not present (20%) and short prognosis (25%). Some

participants had more than one of these reasons for not proceeding to randomisation.

There has been a a wide range in numbers of potential participants referred due to different screening approaches across the sites, with some sites having the lead investigator also the primary clinician at the site whereas other sites receive referrals more widely resulting in a higher number of ineligible patients referred due to unfamiliarity with the study inclusion criteria. The study overall process is for clinical staff to refer all people with delirium to study staff for further assessment. The reasons for not completing to day 3 include non-response (n = 2), toxicity (n = 4), unable to swallow study medication (n = 21), died on study unrelated to the study intervention (n = 3), patient deterioration (n = 28), and non-specified reasons (n = 5). As the study is blocked randomised a close to even distribution between the study arms is expected at this stage. Sites also vary in relation to the time they started recruiting to the study (receiving full ethics approval were staggered dependent on response to issues raised and meeting schedules, and need for internal scientific or guardianship tribunal review at some sites prior to ethics review. There is also a variation in the size of the units from stand alone palliative care units will 20 beds to services in large tertiary acute hospitals. Sites also vary in rates of eligible or randomised to day 3 completion, which may reflect the number of patients who are likely to develop inability to swallow or deterioration based on referral population patterns. It does not seem to reflect clinician practice, as withdrawals of participants due to non-response or toxicity have been minimal.

In 2010 protocol amendments occurred to tackle the mismatch between actual and projected recruitment which clearly indicated that continuing at the actual recruitment rate would not ensure study completion (Figure 29, noting this figure has adjusted predicted recruitment over an extended period where as intital predictions were over a three year period with a steeper slope). These amendments were made in conjunction with the investigator team, site investigators, Palliative Care Clinical Studies Collaborative Scientific Committee, the study statistician and ratified by all the relevant HREC's. The screening data were used to determine the main reasons for non-eligibility. These changes allowed a single 'as required' dose of antipsychotic to have been administered as

long as it was more than 24 hours prior to study entry and prescribed for a non-delirium indication without limiting eligibility. At the same time specific guidelines were provided to the site investigators to discuss the management of nausea with the recruiting clinical units, plus alternative options to haloperidol provided.

Following monitoring of participant study records and source documents a number of protocol violations were found, where the incorrect dose was administered at predominantly timepoints 2 and 3 and the dose calculator was introduced to minimise these errors. The dose calculator was developed in Microsoft Excel, to allow study staff to enter NuDesc item scores, prior dose, age of the patient and the time point in the study, and this would determine the required study medication dose for the next time point. Use of this dose calculator has been well received by study staff and at further monitoring shown to have substantially reduced the occurrence of this protocol violation type.

The study has been responsive to emerging literature on safety, and continue to ensure patient safety within the study daily blood glucose monitoring was introduced after a review in 2009, demonstrated risk of hyperglycaemia in older patients who receive antipsychotics.[778]

Collateral benefits of undertaking this RCT at a clinical site have been reported by site investigators and research staff, and include a greater recognition of delirium, a better understanding of the management of delirium by focus on precipitants and non-pharmacological strategies, and a higher level of confidence and increased frequency of explanation to caregivers of what delirium is.

Table 57 Summary of study recruitment

	Site 1	Site 2	Site 3	Site 4	Site 5	Site 6	Site 7	Site 8	Site 9	Site 10	Site 11	Total
referred to study (n)	31	112	115	182	180	194	315	5	71	48	183	1436
Eligible	28	12	22	40	22	24	35	0	3	15	25	226
(n, %[a])	90%	10%	19%	22%	12%	11%	11%	-	4%	31%	14%	16%
Consented and randomised (n, %[b])	28	11	20	26	18	20	34	0	3	15	25	200
	100%	92%	91%	65%	82%	83%	97%	-	100%	100%	100%	88%
Completed day 1	21	11	15	22	17	18	30	0	2	13	23	172
(n, %[c])	75%	100%	75%	84%	85%	90%	88%	-	66%	87%	92%	86%
Completed day 2	15	11	15	20	15	15	27	0	2	11	21	152
(n, %[c])	54%	90%	75%	77%	83%	75%	79%	-	67%	73%	84%	76%
Completed day 3	16	10	15	15	15	12	22	0	2	11	19	137
(n, %[c])	57%	90%	75%	58%	83%	60%	65%	-	67%	73%	76%	69%

	Site 1	Site 2	Site 3	Site 4	Site 5	Site 6	Site 7	Site 8	Site 9	Site 10	Site 11	Total
Completed day 3/eligible	16/28	10/12	15/22	15/40	15/22	12/20	22/34	0	2/3	11/15	19/25	137/226
(%)	57%	83%	68%	38%	68%	60%	64%	-	67%	73%	76%	67%
Completed day 3/randomised (%)	16/28	10/11	15/20	15/26	15/18	12/20	22/34	0	2/3	11/15	19/25	137/200
	57%	90%	75%	58%	83%	60%	64%	-	67%	73%	76%	69%

[a] percentage of participants who were referred, [b]percentage of participants who were eligible, [c] percentage of participants who were randomised

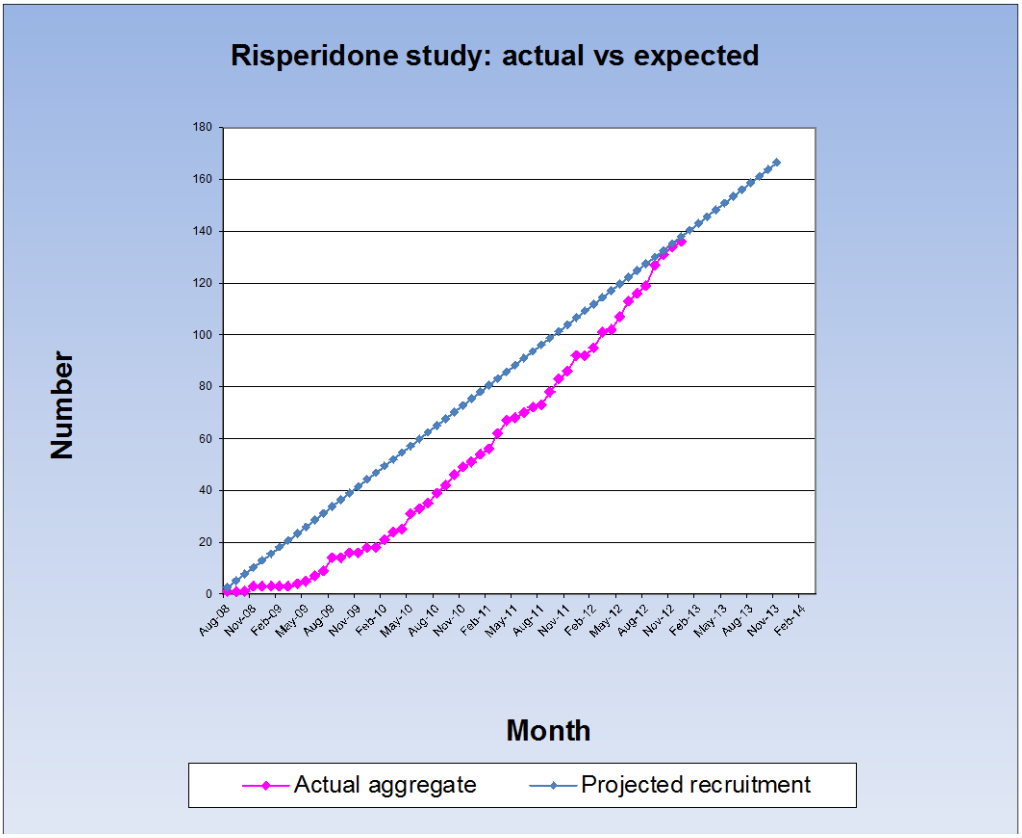


Figure 29 projected recruitment compared to actual recruitment

6.8.3 Participant characteristics at baseline

The baseline demographic and clinical characteristics of the 200 randomised participants are outlined in table 58. The predominant reason for admission was symptom control (74%, n=149). Terminal care admissions accounted for 8.5% (n=17). The remainder of admissions were for acute medical issues and respite. Ninety one and a half percent of the participants had a cancer life limiting illness, with predominant groups bein lung, urological (predominatly prostate), gastrointestinal (predominantly colorectal) and breast/gyaecological cancers. Only 1% (n = 2) had a primary brain tumour, and 3.5% (n = 7) had brain metastases, however 21% had prior cognitive impairment. The population is older, with low functional level and moderate levels of comorbid illness burden. Baseline cognitive function was also significantly impaired, consistent with delirium

diagnosis. Mean scores of presenting symptoms on NuDesc 2, suggesting that most participants had predominantly mild symptoms, or one severe symptom.

Table 58 Baseline characteristics of all randomised participants (n = 200)

Characteristic			n = 200
Age	Mean (SD)		74.6 (9.8)
Gender	n (%)	Male	106 (53%)
		Female	94 (47%)
Performance status (AKPS)[602]	n (%)	20	30 (15%)
		30	28 (14%)
		40	49 (24.5%)
		50	71 (35.5%)
		60	15 (7.5%)
		70	7 (3.5%)
Primary diagnosis	Cancer	-	183 (91.5%)
		Lung	54 (27%)
		Urological	40 (20%)
		Brain	2 (1%)
		Breast/gynaecological	23 (11.5%)
		Gastrointestinal	27 (13.5%)
		Haematological	12 (6%)
		Unknown primary/other	18 (3%)
	Non-cancer	-	17 (8.5%)
		Liver failure	3 (1.5%)
		Heart failure	3 (1.5%)
		Renal failure	4 (2%)
		Respiratory failure	1 (0.5%)
		Neurological	6 (3%)
MDAS	Mean (SD)		14.4 (5.4)
NuDesc	Mean (SD)		2.56 (1.76)
Prior cognitive impairment	n (%)		42 (21%)
Barthel Index total score		Mean (SD)	33 (25)
Charlson Comorbidity Index		Mean (SD)	6.6 (2.9)
CIRS		Mean (SD)	24 (6.4)
RASS	n (%)	-4	1 (0.5%)
		-3	6 (3%)
		-2	10 (5%)
		-1	45 (22%)
		0	58 (29%)
		1	57 (28%)
		2	13 (6%)
		3	5 (2.5%)
		4	5 (2.5%)
MMSE		Mean (SD)	13.5 (7.5)
Nursing reported distress (DEQ)		Mean (SD)	1.4 (1.2)
Caregiver reported distress (DEQ)		Mean (SD)	3 (1.1)

AKPS – Australia-modified Karnofsky Performance Status; CIRS – Cumulative Illness Rating Scale; CCI – Charlson Comorbidity Index; MDAS – Memorial Delirium Assessment Scale; MMSE – Mini-Mental Status Examination, NuDesc – Nursing Delirium Screening Scale, RASS - Richmond Agitation Sedation Scale

6.8.4 Serious adverse events

Five serious adverse events have occurred. Hypotension occurred in two participants on day 2 of study with one deemed unrelated and one possibly related to study medication. In both cases study medications were continued and the hypotension resolved. One patient experienced a fall, productive cough and atrial fibrillation one month after completion of study medication and required inpatient hospitalization, which was deemed unrelated and also resolved. Another participant experienced dramatic worsening in cognition and increased agitation which was deemed possibly related to study medication and the study medication was discontinued. Another participant had septicaemia which was deemed unrelated to study medication and the study medication was also stopped, and participant died one day later. All of the serious adverse events have been reviewed by the Data Safety Monitoring Board and have not warranted changes to the protocol or cessation of the study.

6.9 Discussion

The participant profile so far in this randomised study is predominantly an elderly cohort with advanced cancer, functional and cognitive impairment, presenting with mild to moderate delirium symptoms at baseline. This may lead to some limitations in general applicability of the study results due to the lower representation of people with more severe symptoms. It may also reflect clinicians being uncomfortable randomising participants with very overt symptoms with significant distress and safety issues to a placebo arm. The study also excludes those with regular antipsychotic use, so will not directly inform the management of those who develop delirium whilst being on antipsychotics previously.

The main barriers for randomisation of eligible patients have included the proxy not providing consent, current antipsychotic use predominantly for nausea, inability to swallow and the participant deemed to be imminently dying. These withdrawals are predicted at the population level in palliative care, however could not be predicted *a priori* at the individual participant level. The rates of deterioration on study highlight both the incidence of delirium in the last days of life but also the mortality rate associated with delirium. The main reasons for not

completing the 72 hours of study intervention have been inability to swallow and deterioration, which are inter-related.

It is reassuring to note that proxies have been able to refuse consent, which supports that they are being fully informed and making a decision based on their knowledge of the participant in a situation where the participant is very unwell and decisions need to be made quickly.

This protocol illustrates some key issues to be considered in optimal clinical trial design assessing pharmacological interventions to treat delirium[779] and these are discussed in more detail below.

6.9.1 Design considerations

6.9.1.1 Inclusion and exclusion criteria

The inclusion criteria were developed to outline the adult population of interest, namely those with delirium who had the targeted symptoms of inappropriate behavior, communication and/or presence of illusions or hallucinations. The informed consent criteria was based on the requirement for proxy consent in this study. It was decided to include both cancer and non-cancer life limiting illness, to ensure this is an effectiveness study with broad applicability of the results. This does limit applicability to those with less advanced disease, as it is not known how delirium pathophysiology or response to treatment varies between these populations. However, in medical and geriatric populations, large numbers of patients will also have advanced illness, in particular nonmalignant disease, which was another reason to include non-cancer patients.

As the study medications are in oral solution ability to take this was a key criteria. The exclusion criteria were based on ensuring people who should not be exposed to antipsychotic medications due to prior adverse reactions (neuroleptic malignant syndrome, previous adverse reaction, pregnant or breast feeding women), risk of serious adverse effects (Parkinson's disease where an atypical antipsychotic or alternative management not including an antipsychotic may be indicated, prolonged QT interval, and recent cerebrovascular events, recent seizures) and specific delirium aetiologies where specific treatment is indicated. The exclusion criteria were derived from the product information for haloperidol and

risperidone, and also current literature.[780,781] Antipsychotics can lead to increase confusion, obtundation, postural instability and falls, and worsen extrapyramidal symptoms in Parkinson's disease.[780,781] Risperidone and haloperidol prolong QT intervals and increase risk of arrhythmias, and potentially risk of sudden cardiac death.[782] Haloperidol can reduce seizure thresholds[780], and risperidone has not been extensively studied in those with seizure disorders so effect is unknown. Antipsychotic medication have been associated with increased risk of cerebrovascular accidents, in particular in those with longer term exposure and dementia.[783,784]

Those who required antipsychotics for another condition also were excluded, as adding in blinded study medication in this group may adversely affect the treatment of condition for which they were receiving antipsychotic treatment, expose them to more serious adverse effects from larger doses or of antipsychotics, and also make interpretation of results impossible due to their exposure to different dosing or combinations of antipsychotic medications (in comparison to the other study participants).

This study aimed to have a true placebo arm, and hence it was important to control for prior exposure to antipsychotics for both delirium and other indications. The feasibility assessments, including the audit data suggested that this will be a crucial issue in terms of ineligibility for this study so required careful consideration. The time period of 48 hours was determined based on the half life of haloperidol and risperidone, and the clinical practice of twice daily dosing for both agents in delirium suggest that effect wears off within 12 hours. For risperidone, peak plasma concentrations are seen within 1 – 2 hours of oral dosing, steady state reached within one day, and half life of 3 – 17 hours.[781] For haloperidol, peak plasma concentrations are seen within 2 – 6 hours of oral dosing, steady state reached within one day, and half life of 20 ± 4.6 hours.[780] This has had substantive impact on the trial recruitment rate, and an amendment to allow single doses if greater than 24 hours prior to commencing study was made as long as it was not for a non-delirium indication to relax this inclusion. This decision was made given the substantive problems with recruitment and on balance, was thought not to completely jeopardising the placebo arm as sufficient clearance of the medication would have occurred. No other adjustments to

exclusion were made, as the safety exclusions were considered to be as liberal as they could be without jeopardising participant safety.

6.9.1.2 Choice of primary outcome

Initial diagnosis needs to utilise recognised criteria, and in this study DSM-IV-R criteria for delirium have been used, consistent with approach taken in recent delirium studies.[785] This ensures the population included in the trial have delirium, according to current 'gold standard' criteria for diagnosis.

Within the trial a primary outcome measure that measures delirium symptoms overall or the targeted symptoms of interest is needed.[785] This study is exploring delirium care in the palliative population, which has a focus on improving the symptom experience for the person with a life limiting illness. The studies described in Chapter 2 and 3, outline that response to symptoms drives pharmacological management both by medical and nursing professionals in palliative care. In this clinical context and given current randomised or open label studies of delirium pharmacological management have not addressed the response of specific symptoms to antipsychotic medications, it was decided that this would be the focus and primary aim of this study. Hence a primary outcome that measures targeted delirium symptoms was required.

As delirium symptoms fluctuate it is also important that these target symptoms were measured shift-by-shift, and assess delirium symptoms at least daily at a minimum but ideally several times in a day. Prior studies of delirium pharmacological management have taken the approach of daily assessment utilising the longer delirium severity instruments and not undertaking an analysis of specific symptoms.[334 338 340 434]

The scale chosen for daily use needs to consider ease of use, burden of assessment and the training required for the person administering the scale. In particular scales which require ward nurses to be assessing the participant need to be brief, easily understood and reliable, and suited for repeated assessment during a 24 hour time period. In this study the NuDesc was chosen for this purpose.[361]

Instrument which have been developed for assessment of delirium several times across each 24 hour period at the ward nurse level, and these were the scales

considered for a primary outcome measures. These include the NuDesc and the CAM (psychometrics outlined in Table 6). The Delirium Observation Screening Scale was not considered due to the length (25 items).[786] The CAM was not appropriate as it does not rate the severity of symptoms, and is designed to determine probability of delirium as a 'true' screening instrument focusing on presence or absence of symptoms.[148] Two items on the NuDesc also did not capture the symptoms of interest, namely disorientation and psychomotor retardation.

Hence it was decided that for the primary endpoint the sum of scores on NuDesc Item 2 (inappropriate behaviour), Item 3 (inappropriate communication), and Item 4 (illusions/hallucinations) would be used. These items have face validity, with training can be accurately captured by ward nurses, and correspond to the issue of concern for family (assisting discussions about the study with the proxy providing consent). Since our study has commenced, a recently published clinical trial in the intensive care unit has used a similar approach.[724] Devlin at al explored the response of delirium symptoms in the intensive care unit, in a randomised control comparing quetiapine and placebo, with haloperidol rescue.[724] The primary end point used was time to score of 3 or less on the 10-item intensive care delirium screening checklist, which is was collected every 12 hours. Similar to the CAM, the CAM-ICU doesn't allow tracking delirium symptoms over time intensive care setting.

There are several delirium severity measures with excellent psychometrics in appropriately trained hands which are designed for repeated measures (in particular DRS-R98[169] and MDAS[139] which is being used in this study), and substantive open label and natural history cohorts that can inform choice of clinically meaningful changes and have been used in the prior clinical trials of pharmacological management of delirium. In this study the delirium severity measure (MDAS) was chosen as secondary outcome rather than the primary outcome (as discussed above due to the focus on the impact on target symptoms), but was measured daily to inform time profile and time to resolution of delirium.

The limitations of the choice of inclusion criteria of delirium with the targeted symptoms of inappropriate behavior, communication and/or presence of illusions

or hallucinations, and the use of selected items of the NuDesc are that the outcome measures is though this has strong face validity the NuDesc scale less well established psychometric properties, and the sum of individual items has had no validation testing. The other key limitation is hypoactive delirium is being systematically excluded on inclusion and due to choice of outcome measures, the impact on hypoactive symptoms will be only part of secondary analysis in this study. This is balanced with the benefits a higher capture rate of the symptoms of interest by eight-hourly measures, the ability to titrate to effect with the titration protocols for study medication in response to the symptom measure (which also has the benefit of reducing clinicians withdrawing participant early due to lack of effect as a clear protocol for how to adjust dosing exists), higher accuracy of ratings by clinical staff due to the ease of use without complex training requirements, and engagement of medical and nursing clinicians as the study is exploring outcomes aligned with current clinical practice.

All study staff were specifically trained in all outcome measures, in particular the primary outcome measure. Consistency amongst raters and inter-rater reliability assessment needs to be part of that training prior to enrolling the first participant on the trial.[785] This training needs to continue throughout the trial to maintain competencies.

In the palliative care setting it is important to consider the shortest timeframes to the primary outcome measure[779 787], whilst keeping the duration to effect predicted from the agent being studied. In this study 72 hours was chosen, as in the palliative setting control the indicator of success of the agent added to control delirium symptoms would be effectiveness within or in less than three days, with effects seen after a longer period deemed to be too long for a patient at the end of life with distressing symptoms.

6.9.1.3 Power and sample size

There is an urgent need for adequately powered trials, and with almost all trials to date failing to provide a power calculation for their primary outcome.[785 788] It is promising that more recent trials have tried to tackle this issue and provide data of net clinical effect.[191 789] There are a variety of approaches to explore in terms of an efficacy signal, and include a reduction in delirium events in prevention studies,

or reduced delirium scores, reduced target symptom scores, days free of delirium or reduced delirium duration. There also needs to be definition of a clinically meaningful difference. The placebo effect has not been clearly defined in delirium treatment, but it may be smaller than seen in other settings and hence can be taken to be the natural history of delirium resolution.[785]

This study has been powered such that a total sample size of 165 completed patients will provide 80% power, at a 2-tailed type I error of 0.05, to detect a difference of 0.55 SD unit between any two treatment means. The use of a standard deviation unit as effect size, was due to lack of information in the literature on standard deviations and variability of the NuDesc, and in particular items 2, 3 and 4.[361]

6.9.1.4 Choice of three arm study

The funding from the Commonwealth Department of Health and Ageing was in the context of work done previously on understanding Australian palliative medicine specialists views on the essential medications in palliative care and following work of an expert advisory committee and the Commonwealth Department of Health and Ageing to generate specific list of registered medications subsidized for a palliative indication on the Australian Pharmaceutical Benefits Scheme.[790] The medications of interest derived from this work where a registered indication was not available to pursue subsidy but clinicians felt they were essential, for the management of delirium in the palliative setting were risperidone and olanzapine. The Commonwealth Department of Health and Ageing funded the Palliative Care Clinical Studies Collaborative to develop a study protocols for several medications in this category, which would enable registration is the study was positive, with olanzapine and risperidone potential contenders for study development.

As a preliminary step, discussions were had with the respective pharmaceutical companies about their interest in taking data from this trial forward when completed to the Therapeutic Goods Administration (for registration of a delirium indication if the study was positive) and if registered Pharmaceutical Benefits Scheme (for subsidy) and interest was only obtained from the company for risperidone. The wide spread use of haloperidol and the recommendations in

clinical guidelines supported the use of a third arm. The distribution of two antipsychotic medications to one placebo arm also reassured clinicians that the percentage of participants exposed to placebo was lower yet these participants were contributing to a study which could answer questions about two agents, was helpful in increasing engagement to participate in this study. The primary comparison has been specified is the risperidone compared to placebo, and as such the significance levels have not been adjusted for multiple comparisons as the other hypotheses are secondary.

6.9.1.5 Study intervention and comparator

Choice of placebo arm

Currently it is still proposed that one of the arms in a delirium therapeutic trial needs to be a placebo[334 791], given there is no established efficacious medication which has been demonstrated to alter the natural history of delirium resolution and hence can act as an active comparator. The current evidence does not clearly delineate whether adding an antipsychotic in conjunction with assessment and management of the aetiological precipitant and evidence-based nursing measures improves the rate or degree of delirium resolution above what the natural history of resolution would be, and this is reflected internationally with no currently approved medication for a delirium indication.

The data in palliative care inpatients also support this premise with 30 – 50% of delirium being reversible.[38 215] Non-pharmacological approaches also offer improvements in time to resolution and reduced duration of delirium, however this has been more difficult to demonstrate (section 1.14.3).[28] The research nurses have received specific training in this study to provide clinical staff with the skills for regular orientation, minimising sensory deprivation to ensure hearing and visual aids are available, and that mobility and hydration are optimised. Site investigators also provide regular education to clinicians and nursing staff about the non-pharmacological approaches to delirium management.

Equally the fact that delirium identification is poor in routine clinical practice, means that being assigned to a placebo arm provides active identification of delirium and proactive management of reversible causes which in itself will

improve outcomes. It can also be argued that the placebo arm indeed may be at less risk of unknown or unmeasured side effects of the medication being tested, which was the case in the recent trial of rivastigmine versus placebo as adjunctive therapy to haloperidol in delirium in intensive care.[789] This study was stopped early by the DSMB at an interim analysis, due to mortality in the rivastigmine group (n = 12, 22%) being higher than in the placebo group (n = 4, 8%, p = 0.07) and the median duration of delirium being longer (five days) than in the placebo group (three days). This study also chose to have background haloperidol in both arms, and hence the additional morbidity and mortality seen may have been due to the synergistic or additive effects, rather than rivastigmine alone.

Route of administration and adequate blinding

Consideration of the route of administration is important given the formulations vary between agents (oral, subcutaneous, oral disintegrating wafer or tablet (also known as a quicklet), intramuscular, intravenous). In this study, we have found that the ability to swallow even a solution formulation can be problematic in the very unwell palliative patient with delirium. The manufacture of a matching placebo or a double-dummy approach also needs to be considered, as the parenteral or wafer route if available on study may reduce the number of participants who do not complete the study due to a change in swallowing ability and improve generalisability.

The lack of adequate blinding has been an issue in several randomised trials in delirium (one trial used different routes of administration—oral and intramuscular, and the other did not have matching oral tablets).[333 340] In this instance it was going to add significantly to the logistic challenges of the study.

Dosing regimens

Dosing regimens can be fixed, or have an initial titration period. In this study, step-wise titrations upwards were chosen for improved efficacy, with an allowance for downward titrating for addressing side effects, which mimics the approach taken in palliative care clinical practice.[779 785] The dosing schedule (initial dose, increments, and maximal doses) were developed from the available literature, understanding the pharmacokinetics of the medications under study,

and consensus from the investigating team. It was crucial to have broad representation in the investigating team from palliative medicine, clinical pharmacology, clinical pharmacy, geriatrics and aged care psychiatry to critically appraise the evidence and existing clinical guidelines. Achieving consensus in study design when there is a wide range of clinical opinion (as evidenced by the studies outlined in Chapters 2 and 3 where diverse approaches to pharmacological management of delirium was identified in both nursing and medical practice) can be difficult. These discussions are important to ensure all participating sites are comfortable with the final study design and dosing, and hence prepared to recruit and randomise participants, but also that it is aligned with evidence from current literature. We have found that the dosing regimens used here have been accepted and have been operationalised without difficulty in this trial, after robust discussion to reach initial consensus. A specific calculator has been developed to reduce protocol violations due to inaccurate titrations for each time-point and age group.

Rescue medication for symptoms causing distress or safety issues

A contingency plan is needed in trials of symptom relief medications for participants whose symptoms escalate and safety or distress is an issue, and also for those who do not respond to the agent in the doses (active or placebo) prescribed in the trial.[779 785] The challenge is that utilising antipsychotic rescue will alter treatment arms and render the placebo arm invalid, and hence impact on comparisons. In fact, as there is no licensed drug for delirium no evidence based choice could be made. In this case it was decided to utilise midazolam for severe distress and safety issues, as it is short acting and parenteral and is currently used inclinical practice within palliative care for this indication, though there is no evidence-base to support this decision. This decision was made with much deliberation, due to the potential benzodiazepines have to worsen delirium.[338] In practice, due to the ability to increment study treatment with the standardised algorithm, routine measurement of symptoms and degree of distress, the use of rescue midazolam has been rare in this study.

Failure to respond on-study should not be a criterion for unblinding. A specific criteria of a predefined response (reduction in symptom score by a certain per cent

or below a certain score) in a timeframe which has given the agent adequate time to work, is recommended.[785] Equally, clear guidance on how clinicians can treat patients off-study is important to avoid requests for unblinding unless it is required for patient wellbeing and safety.

6.9.1.6 Choice of secondary outcomes

Pre-specified secondary outcomes are needed, and cover aspects not addressed by the primary outcome measure such as delirium duration, medication safety and toxicity, patient functioning, patient and caregiver distress and long-term outcomes such as survival.[785] In this study patient, caregiver and nursing staff experience have been evaluated so as to compare how this varies between the treatment arms.

Another value add is the substudy exploring neuronal apoptosis to better delineate delirium pathophysiology in the context of standardised treatment, and this should be considered in all delirium treatment trials if it can be added without substantive burden to the participants and at marginal increase is costs across the whole study. In most cases participants will be undergoing venepuncture to assess metabolic causes of delirium, so the additional serum specimen can be collected simultaneously. The current recruitment is 42 participants (21% of randomised participants).

Prior randomised studies have relied on clinician report to detect toxicity, however extrapyramidal toxicity can be subtle and may not be picked up without formal examination. It is important that validated measures are used to assess toxicity if appropriate tools are available, in particular as one of the key clinical arguments for use of atypical antipsychotics in delirium rather than haloperidol has been the reduced risk of extrapyramidal toxicity. In the case of extrapyramidal toxicity well developed scales[792] exist to systematically assess for these signs and symptoms. It is also important to monitor cognition as evidence suggests antipsychotics may contribute to cognitive impairment in dementia, with potential for similar toxicity in patients with delirium.[793]

The cost of delirium has been well articulated in the literature[356 794-796], and treatment trials need to consider not only efficacy as measured by the primary

outcome but also net clinical benefit. Hence this study is undertaking a detailed health economic analysis of proposed treatments with a follow-up phase. This includes assessment of costs in a broad sense—to the patient, their caregiver and the health system.

6.9.1.7 Other considerations for the statistical analysis

Stratification needs to be considered for baseline factors that may influence delirium outcomes, and in geriatric populations it has been usual to consider prior cognitive impairment, age, and illness severity.[785] In the palliative population the specific baseline factors have not been robustly delineated (see Chapter 1 Section 1.8) so a decision was made not to stratify for specific factors in this study, but to consider these in secondary analyses using multivariate analyses. Stratification was undertaken by site, to ensure a balanced sample assigned to each arm within sites and the contribution of different patient populations referred to those services due to widely varying referral base and the inclusion of sites within acute care and also stand alone palliative care units. There are two different dosing schedules dependent on age of the participant.

Statistical methods need to account for the fluctuation of delirium symptoms and also daily measures which can be correlated over time.[797] Care also needs to be taken in utilising methods for missing data such as last observation carried forward (which was the method utilised in a trial comparing quetiapine and placebo[334 788]), as missing data in delirium outcomes may not be predictable from the data at hand.[797] Other ways proposed have been time to first delirium resolution, but this does not necessarily account that there is sustained resolution.[335 788]

In the participants to date in this study it is clear that there is a high rate of withdrawal due to deterioration or death unrelated to the intervention, but due to the primary life limiting illness or delirium itself. One approach for future studies, which has been recently described to address this issue where the proportion of withdrawals can cause a systematic bias, is the palliative – modified intention to treat analysis.[80 430 798] This suggests not including the data from participants who withdraw from the study where it is definitively due to disease progression and not a possible effect of the intervention and confirmed by an independent data

monitoring committee to be unrelated to study intervention, if the analysis is pre-specified in the original protocol and these participants are clearly identified when describing the study participants and who were included in the analysis and why.

6.9.1.8 Safety monitoring

Given the nature of the palliative care population under study, AEs related to progression of underlying disease and even death will be very common across the population. This study has undertaken to ensure reporting focuses on key toxicities of importance, with reporting not required for events related to documented disease progression so important toxicity signals are not lost in the volume of disease related AEs.[799]

It is also crucial that clinical trials in delirium have an independent data safety monitoring board to review all AEs, and indeed this was crucial in acting on stopping rules in the rivastgmine trial[789] described above. This study has a DSMB that includes a clinical trials statistician, a trial pharmacist and a palliative care physician, all who are independent and not currently or previously involved in the study conduct or design. The DSMB reviews all SAE's reported for this study, and also all recent literature that may have impact on the continuation of this study (adverse effects or emerging efficacy data). The DSMB can also be asked to review safety issues out of session if this is required.

A choice has been made to not have a interim analysis and stopping rules derived from this. The study is powered to a clinically meaningful effect and effect size, and will require the sample size to be met to make clear conclusions about effectiveness. There is a rescue protocol, which provides alternative treatment within the study for clinical issues of concern, namely safety and distress. The toxicities where are of concern have been seen with long term exposure to antipsychotics, and in particular in the population with Dementia and given the short term use within this study were not deemed to be of concern. The other toxicities (extrapyramidal side effects and sedation) are being measured and clinicians can respond by reducing dose, or stopping the study medication at an individual patient level. A limitation is that an interim blinded analysis can provide a better indication of the variance of the primary outcome and can allow

adjustment in sample size if the predictions underpinning sample size were not accurate.

6.9.2 Recruitment

Feasibility considerations are also important, to ensure the sample size for the power calculation can be reached. In this study a feasibility audit[800] was conducted across the planned participating sites, to map predicted accrual and to ensure sites who came on board to recruit to the study would be able to contribute participants.[800] Multi-site studies are crucial to ensure timely accrual to delirium studies.[785] Considering exclusion criteria to ensure that they are not overly restrictive whilst still maintaining participant safety is also important to ensue recruitment.[779]

6.9.2.1 Project recruitment

The projected recruitment was developed from a detailed audit of five symptoms (pain, delirium, bowel obstruction, anorexia, cholestatic itch) at six out of the eleven participating sites in this delirium RCT.[800] The audit (n = 468) covered all deaths in a 3-month period for people who were referred to the specialist palliative care service who had at least on inpatient admission between referral and death, regardless of when the person was referred to the service. For delirium, the audit was based around the inclusion and exclusion criteria for this study, and 5.8% of the medical records audited demonstrated that the person who have been eligible for this delirium RCT.[800] On admission 39/468 (8%) had evidence of presence of delirium, and 59/468 (12%) during admission. The number who had the symptom at any time was 73/468 (15%, noting this is less than the sum of the 'on admission' and 'during admission' figures, due to people who had delirium present on admission, had it resolve, and then developed delirium again during admission).[800] The dominant reason these 73 people would not have been eligible was difficulty swallowing (90%) and prior exposure to antipsychotic medications (37%), which equated to 5.8% of the audit participants meeting eligibility.[800] The audit is limited by the retrospective nature and that documentation of delirium symptoms in medical records can be non-specific; utilising words such as confusion, disorientation, agitation rather than delirium, and as such may have overestimated the delirium rate. The audit may also have not reflected the

percentage of people who had the specific targeted symptoms of interest, which relate to hyperactive presentations of delirium, and this is supported by the literature which suggests hypoactive presentations are more common in palliative care.[80 430]

6.9.2.2 Actual recruitment

Figure 29 illustrates that actual recruitment was significantly lower than projected recruitment from 2008 – 2011. The projected recruitment figures suggested the study could be completed within 3 years. The predominant reasons for ineligibility seen in the actual study key performance indicators, were similar to those seen in the audit data. The audit was not able to provide projections of the rate of declined consent, which contributes to the mismatch between actual and projected. The other issues contributing are that not all people with delirium are being referred to the study, due to some sites relying on clinician referral, delirium which occurs after hours and weekends may be treated with antipsychotics immediately prior to referral, and study sites with high levels of familiarity with the study protocol don't refer participants who are unable to swallow or on antipsychotics leading to a underestimation of the degree of impact on these criteria on eligibility.

The collection of key performance indicators and screening data have been crucial to the studies success. This has helped identify why recruitment was challenging despite delirium being a highly prevalent problem. This data directly informed the discussions and amendments undertaken in 2010 and focused brainstorming with all the sites to improve recruitment, which directly influence the improvement in the recruitment rate such that by 2012 the actual and projected lines are now tracking together. This improved recruitment rate is continuing and completion of the study in 2013 is predicted.

This study has demonstrated that the inability to swallow is a major issue in the population with life limiting illness and delirium. Inability to swallow is a reason for ineligibility at referral, but also contributes to withdrawal from the study before primary endpoint. Future studies where injectable formulations are available for the study medications should consider this option strongly. The difficulty in taking this approach in this study was the lack of availability of

parenteral risperidone. It is interesting to note there is a low withdrawal rate for toxicity and few serious adverse events (all which have been unrelated or only deemed possibly related to study intervention).

6.9.3 Consent

Delirium research presents the challenge of research in a population who essentially will have absent or fluctuating capacity to consent.[771 801] It is not possible to conduct effective research into delirium in a population of adults who have capacity to consent, as a comparative population to delirium does not exist and hence evidence cannot be extrapolated from other populations. The two approaches in this setting are advanced consent, which was used in the first randomised control treatment trial in delirium[338] from high-risk individuals, or proxy consent.

6.9.3.1 Advanced consent

The study utilising advanced consent approached 412 people, and 244 consented in advance (59%); however, only 30 participants eventually developed delirium (12%). Advanced consent hence is labour intensive, and also involves discussing delirium with someone who may never develop the condition. Advanced consent may be possible for those with prior delirium which has resolved in particular if they have recollection of the condition, and who are at high risk. In populations of older people it also has been impractical due to the high prevalence of dementia, which also affects capacity.[771] More recent delirium RCTs have utilised proxy consent.[789 802] In some studies it has been reported that patients have provided their own consent; however, mechanisms for the assessment of capacity were not cited[340] Another study obtained ethics approval to conduct the trial subject to relative's assent; however, it did not detail if this indeed was equivalent to obtaining informed consent from a proxy.[334]

6.9.3.2 Proxy consent

When a potential participant does not have decision-making capacity and hence cannot provide his or her own informed consent, a proxy or 'person responsible' can be used. A 'proxy' often is thought to equate to the person's 'next of kin', however this is not always the case. The definition of those who have authority to

act as proxy is usually defined in legislation, statutes, regulations or the equivalent that delineate the circumstances in which, and the process by which proxy consent can be given. The challenge is that there is much variation seen internationally in both definitions of a proxy and operationalising these definitions into practice.[658 803-809] For example, in the US a 'proxy' is defined as a 'Legally Authorised Representative' (LAR) in Federal Regulations as 'an individual or judicial or other body authorised under applicable law to consent on behalf of the prospective subject to the subject's participation in the procedure(s) involved in the research'.[810] The Federal Regulations are complemented by US state-based laws again outlining who can serve as a LAR, however these have often provided less clarity as to the circumstances under which an LAR can provide consent for research.[810] Similarly, the European Directive states that the vulnerable should 'be included in clinical trials only where there are grounds for expecting the administering of the medicinal product would be of direct benefit to the participant, thereby outweighing the risks'.[805] As with the US, practical difficulties remain, The European Directive is yet to be formally adopted in several European countries. Even in countries where sign off has occurred, this has been followed by individual legislative frameworks, which again define proxy consent and conditions slightly differently, or even worse are less clear than the original directive.[801]

In a setting where the participant may not have capacity to consent, it is important to consider whether the research question has sufficient merit and whether the risks involved are justified by the proposed benefits.[658 801] The thresholds for both risks and benefits of the research considered appropriate by Human Research Ethics Committees or Institutional Review Boards in the setting of a clinical trial with proxy consent, usually differ to trials where the participants can consent for themselves.[803 805 807] Review of such studies needs clear systems, which can objectively determine whether the population under study has capacity to provide consent (and in what situation), and consider the merits of the question (scientific validity, risks and benefits, and alternative study designs which could use a population with decision-making capacity). Institutional Review Boards or Human Research Ethics Committees need to be skilled in the deliberation of such issues or a specific independent tribunal established which reviews trials of this

nature.[811] The difficulty faced by the ethics committee in Western Australia highlights this point, where the study could not proceed. In contrast, the clear processes in Queensland and New South Wales allowed the study to be reviewed by highly expert professionals, who clearly understood the need for an evidence-base to guide delirium care, and were able to weigh up the issues at hand.

Some guidelines also include the principle that even when proxy consent is obtained the trial should continue if the participant expresses dissent.[662] The challenge remains to define 'dissent' or indeed 'assent', as these processes also may require understanding of key facts or risks.[662] However, in most situations, it is deemed inappropriate to continue to enroll a participant who is expressing adamant objection to the trial procedures.[662]

There also remains the need to ensure that if a person responsible or proxy is used, that the same principles for obtaining informed consent directly from the participant apply[812], namely:

1. the proxy of the potential participant is provided with objective information by the research without coercion or undue influence to consent for that person to participate
2. the researcher undertaking the discussion has the appropriate credentials and knowledge to provide information relevant to the proxy and address questions
3. discussion is had in an appropriate setting with adequate time allowed
4. ample opportunity is provided for the proxy to ask questions. Equally the research needs to establish that the proxy has a factual and contextual understanding of the issues involved in the decision, including understanding the research protocol and the risks and benefits of participation or non-participation for the person for whom they have capacity to make decisions.[801]

Proxy consent has been utilised in other clinical settings successfully and with high acceptability. For example in dementia research it has been shown to be acceptable to both participants and their proxies.[813]

Delirium research which is unable to utilise person responsible consent leads to participant populations that do not represent delirium patients as a whole (and

hence are difficult to apply in practice), or have led to the selection of designs other than randomised control trials.[771 814] Adamis et al[814] undertook a study where they randomly allocated potential participants to a study of the natural history of delirium to a process which required formal capacity assessment or an informal assessment of capacity and obtaining consent. This study confirmed that using a formal capacity assessment, recruitment favoured the younger, less dependent and more cognitively intact, which would not represent the population at greatest risk of delirium or its poor outcomes. Equally, requirements for serial capacity monitoring and consent processes has been a challenge in the interpretation of the Mental Capacity Act in the UK, however it is proposed in delirium research that this should only occur once capacity has been returned consistently or if the participant expresses a wish to withdraw, and needs to be considered in the context of the overall risk of the research.[771]

The other challenge in delirium research is its acute onset, requiring urgent recruitment.[771] The experience in this trial is that this has been possible, and even if the proxy does not go on to provide consent it has highlighted the importance of communication with families about what delirium is, the management plan in place and the interpretation of the symptoms which are occurring which are likely to be causing family distress. It also raises the question of similar consent being needed in routine clinical practice for off-label use[815] of antipsychotics which are currently not licensed for a delirium indication.

6.10 Conclusions

Well-designed and feasible RCTs can be conducted to evaluate delirium therapies, and this can also be achieved in the palliative population in an ethically defensible way. Legislative clarity is required to ensure consent can be undertaken ethically, however without undue restriction so as to halt the improvement of the evidence base to guide care for those with delirium. Working within a multi-centre collaborative with careful planning helps to ensure the trial can achieve an adequate sample for an adequately powered trial. Collaboration with all specialties with delirium expertise who care for the population of interest is crucial to achieve the most robust trial design, the results of which can directly inform clinical practice.

Chapter 7: Conclusion

The results presented have implications in four key areas in the palliative population: clinical decision-making in the care of the person with delirium, understanding the person at risk of delirium, prescribing, and clinical trial design of delirium therapies.

7.1 Clinical decision-making

Delirium assessment and management is complex, and clinicians who are trained and competent are crucial in improving delirium outcomes. The results presented in this thesis demonstrate that there are still substantive gaps in clinical practice which need to be addressed. There is significant variability in the investigation and management of delirium in people with advanced cancer (as an illustrative palliative diagnosis) at a medical specialist level, both in the setting of good functional status, and also in the terminal phase of illness. These results are consistent with variability in delirium care, which has been demonstrated in other medical settings, including in specialists with an interest in care of the older person and delirium. From the nursing perspective, most participants had a limited understanding of delirium based on behavioural and cognitive clues and aetiologies common in their setting. Nurses showed a wide variation in approaches from limited assessment to a highly investigative approach. Consistent with the findings from a medical perspective, there was wide range of views on appropriate pharmacological agents and dosing described by the nurse participants. Non-pharmacological strategies were highly valued by nursing and medical participants. Most physicians utilised improvements in targeted symptoms as an indicator of treatment success, whereas the nursing participants perceived sedation as the intended outcome of pharmacological therapy.

Future research needs to focus on areas where the evidence base is sparse. In particular there is an urgent need for studies exploring the efficacy of pharmacological management of delirium in advanced cancer—given that this is the area of care in which the most substantial variations in both medical and nursing practice were seen. This includes better understanding net clinical benefit, with adverse events measured systematically, and also exploring the ability of the

medication under study to improve a broad range of delirium symptoms including those which are bothersome to patients such as cognitive impairment.

Another specific area of delirium care in palliative settings where further evidence is needed is to consider approaches which can best inform clinicians balancing the burden of excessive investigations and treatment of delirium precipitants where the value add is minimal and harm to patient is high, whilst ensuring those patients who have potentially reversible delirium receive the appropriate clinical care in the location which can best deliver it.

Strategies are required that reduce the evidence – practice gap so as interventions that can impact on outcomes are taken up into practice. Any educational strategy to improve delirium recognition will need concurrent system changes with administrative and clinical leadership. Importantly, nursing and medical care do not occur in isolation, and good communication, mutual respect for the significant roles each discipline has to play in improving care, and validating the distress that caring for a patient with delirium brings to the health professional will all be crucial.

7.2 Anticholinergic mechanisms: implications for delirium risk and prescribing

The biggest contributor to anticholinergic load in a palliative care population is from symptom-specific medications. Higher anticholinergic load was associated with proximity to death and lower performance status. Anticholinergic load is associated with worsening function and quality of life independent of prognosis, and though this association does confirm causality, it is of concern. Anticholinergic load was significantly associated with difficulty in concentrating and dry mouth, both symptoms which could be mediated by anticholinergic pathways. No association was demonstrated between anticholinergic load and changes in survival or health-service utilisation consistent with prior studies in other populations, which have not demonstrated a clear relationship between anticholinergic medication and these outcomes.

In the Australian palliative care inpatient setting, those who were not imminently dying at admission, the rate of prevalent delirium was 15% and incident delirium

14%. Higher MDAS scores during the admission were associated with the presence of cerebral metastases, benzodiazepine dose and severity of comorbid illness on admission. Performance status, SAA, CRAS-M score, number of anticholinergic medications, opioids and corticosteroids at baseline showed no association with future development of delirium. SAA was 20%–50% higher in this cohort of advanced cancer than seen in other medical and surgical populations, and was associated with lower functional status, which may relate to an increase in endogenous anticholinergic substances associated with the dying process.

These results highlight that prescribing patterns in palliative care cannot be ignored, with potential impacts of anticholinergic medication on function, symptoms and quality of life, but no association with delirium in the population referred to specialist palliative care services. The degree these adverse effects are solely attributable to anticholinergic effects of medications, and whether they can be reversed or prevented by adjusting anticholinergic load, requires further study. From a clinical perspective the balancing act still requires choosing efficacious medication(s) for the symptom or condition the patient is experiencing, with the potential for adverse effects. In the palliative population complex symptoms may continue to require prescribing of high risk or so-called inappropriate medications. This highlights the need to have mechanisms to inform clinicians at the bedside of the degree that a medication is ‘avoidable’ or ‘unavoidable’ after considering efficacy, risk and alternatives. Future research needs to have a degree of sophistication in the methods of calculating medication exposure accounting for dose, duration of exposure, interaction with other medications and the known pharmacokinetics and pharmacodynamics of the medications in a population with advanced disease who have high prevalence of hepatic and renal dysfunction, cachexia and comorbidity.

The exploration of cholinergic mechanisms of delirium cannot be considered in isolation, and future pathophysiological studies will need to consider an array of approaches to piecemeal together a unifying understanding of delirium neuropathology. SAA may be a measure of other factors intrinsic to the dying process in advanced cancer, and longitudinal measures as death approaches may help understand this with concurrent measurement of putative endogenous

compounds which may have anticholinergic activity. Correlation with proposed pathways mediating anorexia cachexia syndromes would also be important. Methods which can more accurately reflect central cholinergic dysfunction will also be crucial, and may include SAA measures in CSF or neuro-imaging which can detect central muscarinic receptor activity and cholinergic pathways. These methods may also inform the degree of anticholinergic activity of opioids and benzodiazepines, in contrast to their effects on other neurotransmitter pathways.

Further work is required to understand the role of benzodiazepines in delirium risk in the palliative population, and to determine if reducing benzodiazepine exposure (dose or duration) can change risk profiles. The lack of association with opioids and corticosteroids is contrary to prior work, and further work is needed to explore this. In particular, studies need to consider cumulative exposure over time to medication(s) and change in dose with temporal relationships to delirium. It is unclear what governs whether medication exposure changes baseline vulnerability and/or is part of the aetiology precipitating the delirium episode. Vigilance is needed for the palliative patient with comorbid illness and cerebral metastases, as their chance of developing delirium is high. In clinical practice establishing routine screening for delirium will be important to improve outcomes in high risk groups.

7.3 Clinical trial design

Well-designed and feasible RCTs can be conducted to evaluate delirium therapies, and it has been demonstrated this can also be undertaken in the palliative population successfully. A RCT of oral risperidone, oral haloperidol and oral placebo with rescue sc midazolam in the management of delirium in palliative care inpatients will directly contribute to understanding the net clinical benefit of antipsychotics in management of delirium symptoms. This study has informed some key principles in optimal trial design for delirium interventions in palliative care.

International legislation needs to find a balance of protecting participants without decision-making capacity whilst allowing proxy consent to be obtained ethically and without restricting a sorely needed development in evidence base to guide care for those with delirium. Similar principles should guide current clinical

practice, where antipsychotics are used for delirium without it being approved for this use, internationally. Conducting a clinical trial of delirium therapy has highlighted the critical role of informing proxy decision makers of what delirium is, the likely outcomes (especially when prognosis can be guarded if delirium occurs in setting of advanced illness), the biological rationale and mechanism of action of treatment, and the potential side effects – whether this occurs in clinical practice or in the process of consent for a clinical trial. There is a skill required in having these conversations so the trial processes need to include careful scripting and training of research staff and clinicians at each site.

A multi-centre recruitment approach is critical and careful planning can ensure the trial can achieve an adequate sample for an adequately powered trial. This includes engaging clinicians at the site in education targeted at improving delirium recognition and assessment, and current status of the literature to provide the context and scientific basis for the question being answered. Collaboration also needs to include all specialties with delirium expertise who care for the population of interest is crucial to achieve the most robust trial design, the results of which can directly inform clinical practice. In this case, engagement outside palliative care was with aged care psychiatrists, geriatricians and pharmacists. A health economic perspective is fundamental to ensuring that the trial results can directly inform health care policy, as the impact of an episode of delirium is broad ranging including increased morbidity, mortality and health care costs.

The ethical principles governing clinical trials insists that a well designed scientifically valid study is needed to ensure every participants contribution will allow the question to be answered. Based on current available evidence, it is still proposed that the comparator arm in a delirium therapeutic trial needs to be a placebo. Standardising the non-pharmacological approaches offered to patients is important – a clear definition of what was offered as “best supportive care”, and this needs to be adhered to carefully in the intervention and comparator arms. The study needs to be powered for a clinically meaningful effect size in the primary endpoint, and care to adequately blind the study is needed. In the palliative setting there are two approaches to consider – whether the treatment under study is aiming to improve a target symptom or whether the impact is to reverse the delirium itself. Secondary outcomes to be considered include delirium duration,

safety and toxicity, function, patient and caregiver distress and long-term outcomes such as survival. Treatment algorithms for each study arm with step-wise titrations upwards to allow maximum efficacy to be achieved, and an allowance for downward titrating for addressing side effects, mimicking the approach taken in palliative care clinical practice, is ideal. In the palliative care setting it is important to consider short timeframes to the primary outcome measure whilst keeping the duration to effect predicted from the agent being studied; and given how unwell and unstable delirium populations are more generally, this applies in other health care settings as well. As the field rapidly evolves, it is hoped this will bring novel interventions which can better treat delirium through therapies designed to impact on pathophysiology, or protect patients who are at risk from developing delirium in the first place.

Appendices

Appendix 1 Participant information for survey participants

ST VINCENT'S HOSPITAL AND SACRED HEART PALLIATIVE CARE SERVICES.

INFORMATION STATEMENT FOR SURVEY PARTICIPANTS

Survey of Current Practice: Management of Delirium by Palliative Care, Psychogeriatric, Geriatrics and Oncology Specialists in Australia.

Dear Colleague,

You are invited to participate in a survey regarding "Current management of delirium" in palliative care and advanced cancer patients. The incidence of delirium in palliative care patients is high, yet the literature has limited definitive data to assist treatment. This survey is aimed to assist in developing guidelines for current best practice, which can be then evaluated prospectively.

We hope to learn from this survey about current practice in the Palliative care, Psychogeriatric, geriatric and Medical Oncology fields, with regard to symptomatology requiring treatment; non-pharmacological and pharmacological management of reversible and terminal delirium. We aim to obtain information to assist developing a protocol of Delirium Management that could be tested prospectively.

Any information that is obtained in the survey questionnaire is anonymous and confidential; with no identifying information requested. In any publication, information will be provided in such a way that you cannot be identified. Financial support to cover the costs of carrying out this study is being provided by Sacred Heart Palliative Care Services.

If you have any questions about your rights as a research participant, please contact, Executive Officer, St Vincent's Hospital Research Ethics Committee (phone 8382 2075, fax 8382 3667, email recclestone@stvincents.com.au).

If you decide to participate, please complete the questionnaire provided and return in the addressed stamped envelope provided. If you have any questions, please contact Dr Meera Agar, Clinical Research Fellow, Sacred Heart Palliative Care Services, 170 Darlinghurst Rd, Darlinghurst NSW 2010 (phone: 02 8382 9444).

Appendix 2 Survey Questionnaire

The incidence of delirium in Palliative care patients is high, yet the literature has limited definitive data to assist treatment. This survey is aimed to assist in developing guidelines for current best practice, which can be then evaluated prospectively.

Thank you for assisting this research by answering the questions relating to the two cases provided below.

1. a) What best defines your area of practice (tick as many that apply, but ∗ main field):

□ Age care psychiatry

□ Geriatrics

□ Medical Oncology

□ Radiation Oncology

□ Palliative Medicine

b) Describe Location of practice (tick as many that apply):

□ Hospital Inpatient care

□ Hospital Consultative/ liaison

□ Community

□ Private

□ Outpatient Clinic

□ Hospice/palliative care unit

c) Is your practice predominantly:

□ Urban

□ Rural

□ Both, outline percentage for each: urban __%, rural: __%.

d) What is your country (and state) of practice:

□ Australia. List state_____

□ New Zealand

e) Duration of practice in the main field identified above:

□ 0-5 years

□ 6-10 years

□ 11-20 years

□ > 21 years

2. Demographic data – please tick:

a) Gender:

□ Male

□ Female

b) Age:

□ 20- 30 years

□ 31 – 40 years

□ 41 – 50 years

□ 51 – 60 years

□ > 61

3. a) Estimate the number of patients with delirium you would see per week:

□ None

□ 0-5

□ 6-10

□ 11-20

□ 21-30

□ >30

b) How many patients would you see in total per week:

□ None

□ 0-20

□ >21-60

□ >61-100

□ >100

Vignette 1:

62 year old lady with metastatic breast cancer, involving multiple bone sites, and single lung metastasis, usually ambulant, living at home with her very supportive family. She is currently receiving hormonal therapy, and no other medication. Routine visit by community nurse identifies a three day history of increased confusion with no other symptoms. She is afebrile, haemodynamically stable, with no neurological deficits.

4. a) In what location would you consider appropriate for care of this patient (tick as many as apply):

□ Home

□ Hospital

□ Palliative care unit

b) In relation to case 1 indicate which tests you would routinely use as initial investigations if no clinical factors pointed to aetiology (tick one or more):

□ Electrolytes and renal function

- □ Full blood count
- □ Liver function
- □ Serum Calcium
- □ Computerised Tomography head
- □ Urine culture
- □ Blood culture
- □ Oxygen saturation
- □ Arterial blood gas
- □ EEG
- □ Chest X ray
- □ Lumbar puncture
- □ Thyroid function
- □ Drug assays
- □ Other: Please list:

_____

_____

c) In relation to case 1 indicate which second line tests you would you use if initial investigations did not point to an aetiology (tick one or more):

□ Electrolytes and renal function

- □ Full blood count
- □ Liver function
- □ Serum Calcium

- Computerised Tomography head
- Urine culture
- Blood culture
- Oxygen saturation
- Arterial blood gas
- EEG
- Chest X ray
- Lumbar puncture
- Thyroid function
- Drug assays
- Other: Please list:

_____

d) What measures would you institute to manage confusion prior to aetiology being identified (tick as many as apply):

- Antibiotics
- Intravenous fluids
- Oxygen
- Nonpharmacological measures
- Pharmacological measures
- Other (please list) _____

e) What factors do you use to make a diagnosis of delirium (tick as many as apply):

- Clinical observation
- Formal cognitive testing: List tool _____
- Formal delirium scale: List tool _____
- Other: please list: _____

f) Estimate how often a reversible component would be found in your patients with delirium?

- Never
- < 10% of times
- 11- 30%
- 31 -50%

□ >50%

5. Please indicate the usefulness of each of the following non-pharmacological measures, and also indicate if they are routinely used in your unit:

	not useful				very useful		routinely used
Quiet well lit room	0	1	2	3	4	5	□
Visible clock/calendar	0	1	2	3	4	5	□
Familiar items from home	0	1	2	3	4	5	□
Family able to sit with patient	0	1	2	3	4	5	□
Reorientation	0	1	2	3	4	5	□
One to one nursing	0	1	2	3	4	5	□

6. For each symptom indicate, in relation to pharmacological management, the agent (s) that are useful:

	none	antipsychotic	benzodiazepine	both
Anxiety	□	□	□	□
Cognitive impairment	□	□	□	□
Hallucinations	□	□	□	□
Delusions	□	□	□	□
Disorientation	□	□	□	□
Disruptive behaviour	□	□	□	□
Agitation	□	□	□	□
Decreased activity	□	□	□	□
Impaired concentration	□	□	□	□
Mood lability	□	□	□	□
Sleep wake alteration	□	□	□	□

7. Please rate the usefulness of the following agents in controlling delirium symptoms according to your clinical experience (circle):

	Not at all					extremely Useful	
Haloperidol	0	1	2	3	4	5	N/A*
Olanzapine	0	1	2	3	4	5	N/A

Risperidone	0	1	2	3	4	5	N/A
Levomepromazine	0	1	2	3	4	5	N/A
Quetiapine	0	1	2	3	4	5	N/A
Lorazepam	0	1	2	3	4	5	N/A
Midazolam	0	1	2	3	4	5	N/A
Clonazepam	0	1	2	3	4	5	N/A
Diazepam	0	1	2	3	4	5	N/A

*(N/A – not applicable, or never used agent)

8. In regard to the agent you would use most commonly use to manage delirium symptoms please answer the following:

a) Agent: ———————————

b) What is you commencing dose range?

_____

c) What increment range do you use to escalate dose?

_____

d) What is the maximum dose you would use?

_____

e) What factors affect dosage used (tick as many as apply):

□ Age

□ Renal function

□ Liver dysfunction

□ Severity of symptoms

□ Level of sedation

□ Comorbidities

□ Other (please list) _____

f) Please rate side effects, in your experience seen with this agent.

	mild	moderate	severe	rarely seen
Sedation	□	□	□	□
Parkinsonian effects	□	□	□	□
Nausea	□	□	□	□
Tardive dyskinesia	□	□	□	□
Akathisia	□	□	□	□
Neuroleptic malignant syndrome	□	□	□	□
Urinary retention	□	□	□	□
Respiratory suppression	□	□	□	□
Confusion	□	□	□	□
Agitation	□	□	□	□
Mood disturbance	□	□	□	□
Postural hypotension	□	□	□	□
Falls	□	□	□	□
Dysarthria	□	□	□	□
Hypersalivation	□	□	□	□

Other (please list) _____

g) What reasons would cause you to change to a different agent, and what agent would you choose?

□ Poor efficacy

□ New symptoms developed

□ Side effects

□ Other. Please list: _____

Agent: ———————

h) What reasons would cause you to add a different agent, and what agent would this be?

_____

_____

Agent: ———————

9. a) What clinical indicators do you use to determine success of pharmacological treatment (tick as many as apply)?

□ Delirium resolution

□ Improvement in delirium severity

□ Reduction in delirium duration

□ Improvement in targeted symptom

□ Improvement in cognitive impairment

□ Sedation

□ Other

b) What in your experience are predictors of poor outcome for delirium resolution (tick as many as applies):

□ Delirium severity

□ Duration of delirium

□ Hypoactive delirium

□ Hyperactive delirium

□ Performance status

□ Number of comorbidities

□ Extent of malignancy

□ Brain metastases

□ Previous episode of delirium

□ Degree of prior cognitive impairment

□ Age

□ Irreversible aetiology

□ Other (please specify): _____

c) Does your unit routinely use a delirium measurement and/or cognitive function tool or scale?

□ Yes

□ No

□ Sometimes

if yes, please list: _____

Vignette 2:

84 year old man with metastatic small cell lung cancer, with liver and brain metastases, where chemotherapy and radiotherapy are not treatment options, develops progressive agitation and confusion due to delirium in the terminal phase of his disease. His prognosis is thought to be days rather than weeks.

10. a) In what location would you consider appropriate for care of this patient (tick as many as apply):

    - ❑ Home
    - ❑ Hospital
    - ❑ Palliative care unit

b) In relation to terminal delirium (case 2) indicate which tests you would routinely use if no clinical factors pointed to aetiology (tick one or more):

- ☐ Electrolytes and renal function
- ☐ Full blood count
- ☐ Liver function
- ☐ Serum Calcium
- ☐ Computerised Tomography head
- ☐ Urine culture
- ☐ Blood culture
- ☐ Oxygen saturation
- ☐ Arterial blood gas
- ☐ EEG
- ☐ Chest X ray
- ☐ Lumbar puncture
- ☐ Thyroid function
- ☐ Drug assays
- ☐ nil
- ☐ Other: Please list:

_____

_____

11. Please indicate the usefulness of each of the following non-pharmacological measures in the management of terminal delirium, and also indicate if they are routinely used in your unit:

	not useful				very useful		routinely used
Quiet well lit room	0	1	2	3	4	5	□
Visible clock/calendar	0	1	2	3	4	5	□
Familiar items from home	0	1	2	3	4	5	□
Family able to sit with patient	0	1	2	3	4	5	□
Reorientation	0	1	2	3	4	5	□
One to one nursing	0	1	2	3	4	5	□

12. For each symptom indicate, in relation to pharmacological management of terminal delirium, the agent (s) that are useful:

	none	antipsychotic	benzodiazepine	both
Anxiety	□	□	□	□
Cognitive impairment	□	□	□	□
Hallucinations	□	□	□	□
Delusions	□	□	□	□
Disorientation	□	□	□	□
Disruptive behaviour	□	□	□	□
Agitation	□	□	□	□
Decreased activity	□	□	□	□
Impaired concentration	□	□	□	□

Mood lability	□	□	□	□
Sleep wake alteration	□	□	□	□

13. Please rate the usefulness of the following agents in controlling terminal delirium symptoms according to your clinical experience (circle):

	Not at all					extremely Useful	
Haloperidol	0	1	2	3	4	5	N/A*
Olanzapine	0	1	2	3	4	5	N/A
Risperidone	0	1	2	3	4	5	N/A
Levomepromazine	0	1	2	3	4	5	N/A
Quetiapine	0	1	2	3	4	5	N/A
Lorazepam	0	1	2	3	4	5	N/A
Midazolam	0	1	2	3	4	5	N/A
Clonazepam	0	1	2	3	4	5	N/A
Diazepam	0	1	2	3	4	5	N/A
Phenobarbitone	0	1	2	3	4	5	N/A

*(N/A – not applicable, or never used agent)

14. In regard to the agent you would use most commonly use to manage terminal delirium symptoms please answer the following:

a) Agent: ———————————

If same as for case 1, omit rest of question 14.

b) What is you commencing dose range?

_____

c) What increment range do you use to escalate dose?

_____

d) What is the maximum dose you would use?

_____

e) What factors affect dosage used (tick as many as apply):

□ Age

□ Renal function

□ Liver dysfunction

□ Severity of symptoms

□ Level of sedation

□ Comorbidities

□ Other (please list) _____

f) Please rate side effects seen with this agent, in your experience.

	mild	moderate	severe	rarely seen
Sedation	□	□	□	□
Parkinsonian effects	□	□	□	□
Nausea	□	□	□	□
Tardive dyskinesia	□	□	□	□
Akathisia	□	□	□	□
Neuroleptic malignant syndrome.	□	□	□	□
Urinary retention	□	□	□	□
Respiratory suppression	□	□	□	□

Confusion □ □ □ □

Agitation □ □ □ □

Mood disturbance □ □ □ □

Postural hypotension □ □ □ □

Falls □ □ □ □

Dysarthria □ □ □ □

Hypersalivation □ □ □ □

Other (please list) _____

g) What reasons would cause you to change to a different agent, and what agent would you choose?

□ Poor efficacy

□ New symptoms developed

□ Side effects

□ Other. Please list:

_____

Agent: _____

h) What reasons would cause you to add a different agent, and what agent would this be?

_____

_____

Agent: _____

15. What clinical indicators do you use to determine success of pharmacological treatment in terminal delirium (tick as many as apply)?

□ Delirium resolution

□ Improvement in delirium severity

□ Reduction in delirium duration

□ Improvement in targeted symptom

□ Improvement in cognitive impairment

□ Sedation

□ other (please list)_____

16. Comments: Please feel free to provide further comments regarding aspects of delirium management or research in this area

Appendix 3 Survey ethics approval

ST VINCENT'S HOSPITAL SYDNEY LIMITED
A.B.N. 77 054 038 872
UNDER THE CARE OF THE SISTERS OF CHARITY

September 13, 2004

Dr Meera Agar
Sacred Heart Hospice
170 Darlinghurst Road
Darlinghurst 2010

Dear Dr Agar

Re: Survey of current practice: Management of delirium by palliative care, psychogeriatric, geriatric, and oncology specialists in Australia.
St Vincent's Hospital Ref No: H04/068

Thank you for providing the additional information on this study as requested by the Human Research Ethics Committee.

I am pleased to inform you that APPROVAL has been given to commence this study. The St Vincent's Hospital Human Research Ethics Committee is constituted and operates in accordance with current NHMRC guidelines. The approved subject information statement and consent form is that submitted with the original application.

Under NO circumstances may you or your co-investigators depart from the approved protocol without the prior consent of the Committee.

Would you inform the Committee of any adverse effects or events occurring in association with your study.

Would you inform the Committee when the research is completed.

If you have any queries relating to the above, please contact me on (02) 8382 2075

Yours sincerely,

HEFraser

Helen Fraser
Executive Officer
Human Research Ethics Committee

Cc A/Prof Brian Draper.

Victoria Street Darlinghurst Sydney 2010 Australia
Tel: (02) 8382 1111 Fax: (02) 9332 4142 Internet: www.stvincents.com.au
NSW Hospitals also under the Care of the Sisters of Charity: St. Joseph's Hospital St. Vincent's Private Hospital.

Appendix 4 ethics approvals

SYDNEY SOUTH WEST
AREA HEALTH SERVICE
NSW HEALTH

Human Research Ethics Committee (Western Zone)
Locked Bag 7017, LIVERPOOL BC, NSW, 1871
Phone: 02 9612 0614
Facsimile: 02 9612 0611

July 7, 2008

Dr Meera Agar
Director of Palliative Care
Braeside Hospital
Locked Bag 82
WETHERILL PARK 2164

Dear Dr Agar,

Project No **2008/065 - Descriptive study of decision making by palliative care, aged care, aged care psychiatry and oncology nurses caring for confused patients in the inpatient are setting**

Thank you for submitting the above project which was first considered by the SSWAHS HREC (Western Zone) on 26th May, 2008 with further consideration of documentation at the meeting held on 23rd June, 2008. This HREC is constituted and operates in accordance with the National Health and Medical Research Council's *National Statement on Ethical Conduct in Research Involving Humans* and the *CPMP/ICH Note for Guidance on Good Clinical Practice*.

I am pleased to advise that the Committee has granted ethical approval of the above project.

The following documentation has been reviewed and approved by the HREC:

Participant Information Statement	V 1.2 230608
Consent Form	Version 1.2

Please note the following conditions of approval:

1. 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; and
   - unforeseen events that might affect continued ethical acceptability of the project.
2. The Principal Investigator will report proposed changes to the research protocol, conduct of the research, or length of HREC approval to the HREC in the specified format, for review.
3. The Principal Investigator will inform the HREC, giving reasons, if the project is discontinued before the expected date of completion.
4. The Principal Investigator will provide an annual report to the HREC and at completion of the study in the specified format.

HREC approval is valid for 12 months from last day of the month when the HREC met and a progress report will be required by 31st May, 2009.

Should you have any queries about your project please contact Mrs Jennie Grech, HREC Executive Officer on the telephone number listed above. The HREC Terms of Reference, Standard Operating Procedures, membership and standard forms are available from the SSWAHS website:

http://www.swsahs.nsw.gov.au/areaser/ethics/default.asp

Please quote 08/065 in all correspondence.

The HREC wishes you every success in your research

Yours faithfully

Professor Hugh Dickson
Chairperson
SSWAHS Human Research Ethics Committee

HOPE HEALTHCARE

Form # HHL 022

Human Research Ethics Committee

Certificate of Approval

This is to certify that

Project No: **2007-4-2**

Project Title: **Descriptive study of decision making by palliative care, aged care, aged care psychiatry and oncology nurses in inpatient settings.**

Chief Investigator: **Dr Meera Agar**

has been considered by the Human Research Ethics Committee and is **approved**.

Approval date: 19th April, 2007 **Expiry Date:** 19th April, 2010

It is the Chief Investigator's responsibility to ensure that all researchers associated with this project are aware of the conditions of approval and which documents have been approved.

The Chief Investigator is required to notify the Research Co-ordinator of the Human Research Ethics Committee immediately of:

- any significant change to the project and the reason for that change, including an indication of ethical implications (if any);
- serious adverse effects on participants and the action taken to address those effects;
- any other unforeseen events or unexpected developments that merit notification;
- the inability of the Chief Investigator to continue in that role, or any other change in research personnel involved in the project;
- a delay of more than 12 months in the commencement of the project, and,
- termination or closure of the project.

Additionally, the Chief Investigator is required to submit:

- a Progress Report every twelve months for the duration of the project;
- a Request for Extension of the project prior to the expiry date, if applicable; and
- a detailed Final Report at the conclusion of the project.

All research subject to Hope Healthcare Human Research Ethics Committee review must be conducted in accordance with the National Health and Medical Research Council (NHMRC) Statement on Ethical Conduct in Research Involving Humans (2001).

Special Conditions:
- Use of amended consent forms.

Signed _____ **Date** 26/4/07

Chair, HREC (or delegate)

Please quote Project number and title in all correspondence

M:\Windows\My Documents\Word Files\HREC\20070621\certificate agar2.doc

Appendix 5 Sample participant information for nurses

PARTICIPANT INFORMATION STATEMENT

Decision making of palliative care, aged care, aged care psychiatry and oncology nurses caring for confused patients in inpatient settings

You are invited to participate in a study that wants to explore the experience of nurses in caring for inpatients who have confusion. Confusion is a common clinical problem in inpatient settings in palliative care, aged care, aged care psychiatry and oncology. It has significant implications for nursing practice, and nurses significantly contribute to the care of these patients due to them being with the patient 24 hours a day, being able to facilitate early detection, communication with families, pharmacological and non-pharmacological management. We want to understand more about the decisions and challenges faced by nurses when caring for confused patients, and also the interventions which nurses feel are helpful in this setting.

This study is being conducted by Dr. Meera Agar, (Palliative Care Specialist), at Braeside Hospital, and Ms Janeane Harlum (Area Nurse Coordinator, SSW (west) Area Palliative Care Service. This study is a qualitative study, and we are asking you to participate in an interview that will take approximately one hour. You will be interviewed by of the investigator or research staff in person or over the phone. We will ask you questions about your experience and opinion about symptoms and their assessment, decision making around care for confused patients and also what informs these decisions. We are also asking if you would also complete a questionnaire in relation to two case vignettes, which is a validated tool that describes decision making framework that nurses use, based on decision making theories in the literature.

The discussion will be audio taped and then transcribed to allow us to analyse the interview in detail. All tapes and paper files will be identified only by a research ID number. Anything you say will be strictly confidential, only the investigators will have access to information on participants. The information we collect will not be identified by your name, to maintain confidentiality. Any information that is obtained in connection with this study and that can be identified with you will remain confidential and will be disclosed only with your permission or except as required by law.

If you give us your permission by signing this document, we plan to publish the results of this study in a medical journal. In any publication, information will be provided in such a way that you cannot be identified.

Participation in this study is entirely voluntary; you are in no way obliged to participate and, if you do participate, you can withdraw at any time. Your participation or non-participation will not affect your relationship with the hospital who employs you in any way. Only Dr Agar and Ms Harlum will be aware of your participation or non-participation.

We do not expect you to suffer any serious effects or injury from participating in this study. If during the interview there is a particular question you find difficult or do not wish to answer you can either stop the interview or omit that question. However if you have any concerns whatsoever while you are part of the study, please contact the researchers immediately.

When you have read the information Dr Agar will discuss it with you further and answer any questions you may have.

This study has been approved by the Sydney South West Area Health Service Ethics Committee. Should you wish to discuss the study with someone not directly involved, in particular in relation to matters concerning policies, information about the conduct of the study, or your rights as a participant, you may contact:

The Ethics secretariat (Western Zone), SSWAHS, Area Health Service, Locked Bag 7017, LIVERPOOL BC, NSW, 1871 (phone: 9612 0614, fax 9612 0611, email jennie.grech@sswahs.nsw.gov.au).

If you would like to know more at any stage please feel free to contact Dr Meera Agar on (02) 9616-8649.

This information sheet is for you to keep.

Appendix 6 Nurses interview questions

Demographics of interviewee:

1. How old are you? ___ years.

2. How many years have you been working in Palliative Care/Geriatrics/Aged Care Psychiatry/Oncology (circle one that is applicable) ?
   ____ Months/years.

1. What is/are your primary nursing qualification(s)?

2. How many years have you worked in an inpatient setting? _____ Months/years.

3. How many hours of clinical work do you do per week? _____/hours.

4. What shifts do you work?

Morning yes/no - _____hours per week.
Afternoon yes/no - _____hours per week.
Night yes/no - _____hours per week.

5. Have you done any postgraduate studies in palliative care/Geriatrics/Aged care psychiatry/Oncology (circle one that is applicable)? If yes please give details:

Interview format:

Thank you for sharing some of your experiences in relation to care of patients with confusion. Confusion is an important problem in the setting in which you work. Confusion has significant implications for nursing practice, and nurses have a significant and crucial role in its detection and management, and we want to explore and understand in more depth the issues that nurses feel are important, and the approach they take in managing this difficult clinical problem in a number of clinical settings. We have a few questions that explore areas of assessment and management of confusion, but also would like to encourage you to tell us any other aspects, which you feel are important. The interview will take approximately one hour, and will be audio-taped and later transcribed, however no identifying data will be stored.

Questions:

The semi-structured interview will be framed around the following general questions:

Symptomatology:

What does the term delirium mean to you?

What does the term terminal restlessness mean to you?

In your experience can you describe the symptoms or problems a confused patient in your *(insert Palliative Care/Geriatrics/Aged Care Psychiatry/Oncology as applicable)* inpatient setting may experience?

In your experience are these symptoms or problems reversible of irreversible, and how do you usually assess this?

Assessment:

In you own practice how do you assess a confused patient, in relation to symptoms/problems the person might be experiencing and the possible causes?

Over the last two weeks, can you think of a confused patient you looked after, and how you would assess the diagnosis and causes for this person?

How do you assess how the symptoms are affecting the patient?

In your experience what is it about confusion that is distressing to patients, families and staff?

How do you assess what the patient and family goals are in this setting?

Management and assessment of response:

Nurses frequently need to institute a plan of care for a confused patient in your *(insert Palliative Care/Geriatrics/Aged Care Psychiatry/Oncology as applicable)* inpatient setting.

Can you describe what kind of decisions you have had to make in this setting and aspects you include in your plan of care?

In your experience what are the symptoms that require intervention - and are there any symptoms that don't?

Prompts – think about both non-drug and drug interventions, communication.

Nurses often need to make decisions about medications to control confusion. Can you tell us your approach, especially when given a number of drug choices?

- How do you assess the medication has been effective?
- What medications do you feel are the most useful, and in what doses?
- If it hasn't worked what is your next step in management?

In relation to non-drug interventions – which ones in your experience are helpful how do you assess the response to these?

Are patients and their families involved in the decision-making or plan of care, and if yes can you describe this?

What challenges does managing confusion bring to your practice?

What barriers/problems do you face in optimally managing confusion in a *(insert Palliative Care/Geriatrics/Aged Care Psychiatry/Oncology as applicable)* inpatient setting?

(Prompts – think about knowledge of team, access to medication, safety, time?)

How would you describe your confidence and knowledge in managing delirium symptoms?

Knowledge:

What are the sources of knowledge and information that have informed your practice in managing confusion – *for example clinical experience, what you learnt in your initial degree, post graduate study, specific education/inservice/opinions of your team*?
What are some aspects of management of confusion that you feel you need to learn more about?

How confident are you in managing symptoms of confusion?

Has your approach to managing confusion changed at all during your time in clinical practice? - If so could you explain what were the influences of this?

Are there any other aspects that we have not asked you about that you feel are important and would like to comment on?

Thank you for your time.

Appendix 7 Ethics approval

HOPE HEALTHCARE

Form # HHL 022

Human Research Ethics Committee

Certificate of Approval

This is to certify that

Project No: 2005-08-1

Project Title: Prospective study of Predictors of the Diagnosis of Delirium or Future Development of Delerium: the Association between Serum Anticholinergic Levels and Diagnosis or Future Development of Delirium in Palliative Care Patients with Advanced Cancer.

Chief Investigator: Dr Meera Agar

has been considered by the Human Research Ethics Committee and is **approved**.

Approval date: 18th August, 2005 **Expiry Date**: 18th August, 2008

It is the Chief Investigator's responsibility to ensure that all researchers associated with this project are aware of the conditions of approval and which documents have been approved.

The Chief Investigator is required to notify the Research Co-ordinator of the Human Research Ethics Committee, via amendment or progress report, of

- Any significant change to the project and the reason for that change, including an indication of ethical implications (if any);
- Serious adverse effects on participants and the action taken to address those effects;
- Any other unforeseen events or unexpected developments that merit notification;
- The inability of the Chief Investigator to continue in that role, or any other change in research personnel involved in the project;
- A delay of more than 12 months in the commencement of the project, and,
- Termination or closure of the project.

Additionally, the Chief Investigator is required to submit:

- A Progress Report every six months for the duration of the project;
- A Request for Extension of the project prior to the expiry date, if applicable; and
- A detailed Final Report at the conclusion of the project.

All research subject to Hope Healthcare Human Research Ethics Committee review must be conducted in accordance with the National Health and Medical Research Council (NHMRC) Statement on Ethical Conduct in Research Involving Humans (1999).

Special Conditions:
The Committee wished to alert the researcher to their concern for whether the study was sufficiently powered for a multifactorial analysis.

Signed _____ **Date** 20th **August, 2005**

Chair, HREC (or delegate)

Please quote Project number and title in all correspondence

Appendix 8 Participant Information Sheet

SUBJECT INFORMATION STATEMENT AND CONSENT FORM

PREDICTORS OF DELIRIUM

You are invited to participate in a study that wants to identify factors, which predict for delirium. A simple definition of delirium is a medical condition that occurs when someone is unwell, and it can manifest with many symptoms of varying severity, some of these can be confusion, restlessness and disturbance in sleep pattern. Delirium is a common problem when people are unwell, and often is caused by many factors. A common cause you may be familiar with is when someone gets an infection. We hope to learn about the factors that predict delirium in cancer patients, and hence develop ways to prevent it occurring. To be able to do this we need to monitor patients like you who are admitted for other reasons, but may develop delirium. This study is being conducted by Dr Meera Agar (Palliative Care specialist) at Braeside Hospital.

If you decide to participate, we will be recording information about your medical condition and medication on a daily basis during your admission. Nursing and medical staff will be completing an assessment tool designed to be able to detect delirium.

We will also collect two blood samples, which will be analysed for a particular marker known to be associated with a wide range of medications. We can then determine if there are certain factors, including this blood test, which predict which patients have a tendency to develop delirium. This will hopefully benefit people in the future by giving us strategies to prevent delirium when people are unwell. This study will not affect your medical care during your admission.

The information we collect will not be identified by your name, to maintain confidentiality. Any information that is obtained in connection with this study and that can be identified with you will remain confidential and will be disclosed only with your permission or except as required by law. If you give us your permission by signing this document, we plan to publish the results of this study in a medical

journal. In any publication, information will be provided in such a way that you cannot be identified.

Participation in this study is entirely voluntary; you are in no way obliged to participate and, if you do participate, you can withdraw at any time. Whatever your decision, please be assured that it will not affect your medical treatment or your relationship with medical staff. Only Dr Agar will be aware of your participation or non-participation. This study has been approved by the Ethics Committee of Hope Health Care.

When you have read the information Dr Agar will discuss it with you further and answer any questions you may have.

If you have any questions about being a research participant you can contact the Chairperson of the Research Ethics Committee Dr Melanie Lovell (phone: 9903 8293, email: ethics@hopehealthcare.com.au). If you would like to know more at any stage please feel free to contact Dr Meera Agar on (02) 9616-8600. This information sheet is for you to keep.

Appendix 9 Australia –modified Karnofsky Performance Status

100 = Normal; no complaints; no evidence of disease.

90 = Able to carry on normal activity; minor signs or symptoms.

80 = Normal activity with effort; some signs or symptoms of disease.

70 = Cares for self; unable to carry on normal activity or to do active work.

60 = Requires occasional assistance but is able to care for most of his needs.

50 = Requires considerable assistance and frequent medical care

40 = In bed more than 50% of the time.

30 = Almost completely bedfast.

20 = Totally bedfast and requiring extensive nursing care by professionals and/or family.

10 = Comatose or barely rousable.

0 = Dead.

Appendix 10 Barthel Index

FEEDING

0	unable
5	needs help cutting, spreading butter, etc., or requires modified diet
10	independent

GROOMING

0	needs to help with personal care
5	independent face/hair/teeth/shaving (implements provided)

DRESSING

0	dependent
5	needs help but can do about half unaided
10	independent (including buttons, zips, laces,etc.)

BOWELS

0	incontinent (or needs to be given enemas)
5	occasional accident
10	continent

BLADDER

0	incontinent, or catheterized and unable to manage alone
5	occasional accident
10	continent

TOILET USE

0	dependent
5	needs some help, but can do something alone
10	independent (on and off, dressing, wiping)

TRANSFERS (BED TO CHAIR AND BACK)

0	unable, no sitting balance
5	major help (one or two people, physical), can sit
10	minor help (verbal or physical)
15	independent

MOBILITY (ON LEVEL SURFACES)

0	immobile or < 50 yards
5	wheelchair independent, including corners, > 50 yards
10	walks with help of one person (verbal or physical) > 50 yards
15	independent (but may use any aid; for example, stick) > 50 yards

STAIRS

0	unable
5	needs help (verbal, physical, carrying aid)
10	independent

TOTAL SCORE = _____

Appendix 11 Cumulative Illness Rating Scale

System	1	2	3	4	5
Cardiac (heart only)	☐	☐	☐	☐	☐
Hypertension (rating is based on severity; affected systems are rated separately).	☐	☐	☐	☐	☐
Vascular (blood, blood vessels and cells, marrow, spleen, lymphatics).	☐	☐	☐	☐	☐
Respiratory (lungs, bronchi, trachea below the larynx).	☐	☐	☐	☐	☐
EENT (eye, ear, nose, throat, larynx).	☐	☐	☐	☐	☐
Upper GI (esophagus, stomach, duodenum, biliary and pancreatic trees do no include diabetes).	☐	☐	☐	☐	☐
Lower GI (intestines, hernias).	☐	☐	☐	☐	☐
Hepatic (liver only).	☐	☐	☐	☐	☐
Renal (kidneys only).	☐	☐	☐	☐	☐
Other GU (ureters, bladder, urethra, prostate, genitals).	☐	☐	☐	☐	☐
Musculo-skeletal-integumentary (muscles, bone, skin)	☐	☐	☐	☐	☐
Neurological (brain, spinal cord, nerves; include dementia).	☐	☐	☐	☐	☐
Endocrine - Metabolic - breast (includes diabetes, diffuse infections, infections, toxicity	☐	☐	☐	☐	☐
Psychiatric/Behavioural (includes depression, anxiety, agitation, psychosis, not dementia).	☐	☐	☐	☐	☐

1. General principles:

Every single disease must be classified in the appropriate system. If there are several problems in the same system, only the most severe is rated. Example: for a patient suffering from well controlled angina (rated 2) and terminal heart failure (rated 4), only the higher rated condition would be scored in the Cardiac system (i.e. rating is 4).

The spread of a cancer may lead to rate the condition in more than one category. For example, a lung cancer with bone metastases treated with non-steroidal anti-inflammatory drugs is rated 4 in Respiratory and 2 in Musculoskeletal.

2. General rules for severity rating:

0 – No problem affecting that system.
1 – Current mild problem or past significant problem.
2 – Moderate disability or morbidity and/or requires first line therapy.
3 – Severe problem and/or constant and significant disability and/or hard to control chronic problems.
4 – Extremely severe problem and/or immediate treatment required and/or organ failure and/or severe functional impairment.

3. Detailed description of severity rating (examples in parenthesis):

Rated 0:

- no problem or healed minor injuries
- past childhood illnesses (chickenpox)
- minor surgery (carpal tunnel completely healed, caesarean)
- uncomplicated healed fractures
- other past problems healed without sequel (pneumonia)

Rated 1:

- current medical problem that causes mild discomfort or disability, or has occasional exacerbations (asthma controlled with PRN bronchodilators, occasional heartburn relieved with as needed antacids)
- minor impact on morbidity
- medical problems that are not currently active but were significant problems in the past (kidney stone, spontaneous pneumothorax 5 ago)
- major surgery (hysterectomy, cholecystectomy , appendectomy)

Rated 2:

- medical conditions that require daily treatment or first line therapy (asthma controlled with inhaled steroids, gastro-oesophageal reflux treated with daily medication).
- moderate disability or morbidity

Rated 3:

- chronic conditions that are not controlled with first line therapy (asthma needing continuous corticosteroid therapy, symptomatic angina despite medical regimes, current desensitization allergic rhinitis).
- constant significant disability
- severe problem

Rated 4

- extremely severe problem.
- any acute condition that requires immediate treatment (severe bronchospasm, unstable angina).
- organ failure (end-stage renal disease needing dialysis, oxygen dependent chronic airways disease, terminal heart failure)
- severe sensory impairment (almost complete blindness or deafness, being wheelchair bound).
- severely affected quality of life, severe impairment in function.

4. Rating malignancies:

Rated 1: cancer diagnosed in the remote past without evidence of recurrence or sequel in the past 10 years or skin cancer operated in the past without major sequel (other than melanoma).

Rated 2: no evidence of recurrence or sequel in the past five years.
Rated 3: required chemotherapy, radiation or hormonal therapy in the past five years.
Rated 4: recurrent malignancy or metastasis (other than to lymph glands) or palliative treatment stage.

Appendix 12 Charlson Comorbidity Index

Assigned weights for diseases	Conditions
1	Myocardial infarct Congestive cardiac failure Peripheral vascular disease Cerebrovascular disease Dementia Chronic pulmonary disease Connective tissue disease Ulcer disease Mild liver disease Diabetes
2	Hemiplegia Moderate or severe renal disease Diabetes with end organ damage Any tumour Leukaemia Lymphoma
3	Moderate or severe liver disease
6	Metastatic solid tumour AIDS

Assign weights for each condition and total equals the score

Appendix 13 Memorial Delirium Assessment Scale

MEMORIAL DELIRIUM ASSESSMENT SCALE

INSTRUCTIONS: Rate the severity of the following symptoms of delirium based on current interaction which subjects or assessment of his/ her behaviour or experience over past several hours (as indicated in each time.)

ITEM 1 – REDUCED LEVEL OF CONSCIOUSNESS (AWARENESS): Rate the current level of awareness of and the interaction with the environment (interviewer, other people / objects in the room; for example, ask patient to describe their surroundings)

☐ 0 = None	Patient spontaneously fully aware and interacts appropriately
☐ 1 = Mild	Patient is unaware of some elements in the environment, or not spontaneously interacting appropriately with the interviewer, becomes fully aware and appropriately interactive when prodded strongly: interview is prolonged but not seriously disrupted)
☐ 2 = Moderate	Patient is unaware of some or all elements in the environment, or not spontaneously interacting with the interviewer, becomes incompletely aware and inappropriately interactive when prodded strongly: interview is prolonged but not seriously disrupted
☐ 3 = Severe	Patient is unaware of all elements in the environment with no spontaneous interaction or awareness of the interviewer, so that the interview is difficult-to-impossible, even with maximal prodding.

ITEM 2 – DISORIENTATION: Rate current state by asking the following 10 orientation items: date, month, day, year, season, floor, and name of hospital, city, state and country.

☐ 0 = None	Patient knows 9-10 items
☐ 1 = Mild	Patient knows 7 - 8 items
☐ 2 = Moderate	Patient knows 5 - 6 items
☐ 3 = Severe	Patient knows more than 4 items

ITEM 3 – SHORT-TERM MEMORY IMPAIRMENT: Rate current state by using repetition and delay recall of 3 words (patient must immediately repeat and recall words 5 min later after an interviewing task. Us alternate sets of 3 words for successive evaluations (for example, apple, table, tomorrow, sky, cigar, justice).

☐ 0 = None	All 3 words repeated and recalled
☐ 1 = Mild	All 3 repeated, patient fails to recall 1
☐ 2 = Moderate	All 3 repeated, patient fails to recall 23
☐ 3 = Severe	Patient fails to repeat 1 or more words

ITEM 4 – IMPAIRED DIGIT SPAN: Rate current performance by asking subjects to repeat first 3, 4, the five digits forward and then 3, then 4 backwards, continue to the next step only if patient succeeds at the previous one.

☐ 0 = None	Patient can do at least 5 numbers forward and 4 backward
☐ 1 = Mild	Patient can do at least 5 numbers forward, 3 backward
☐ 2 = Moderate	Patient can do 4 – 5 numbers forward, cannot do 3 backward
☐ 3 = Severe	Patient can do no more than 3 numbers forward

ITEM 5 – REDUCE ABILITY TO MAINTAIN AND SHIFT ATTENTION: As indicated during the interview by questions needing to be rephrased and / repeated because patient's attention wandering, patient loses track, patient is distracted by outside stimuli, or over-absorbed in a task.

☐ 0 = None	None of the above, patient maintains and shifts attention normally
☐ 1 = Mild	Above attentional problems occur once or twice without prolonging the interview
☐ 2 = Moderate	Above attentional problems occur often, prolonging the interview without seriously disrupting it

☐ 3 = Severe	Above attentional problems occur constantly, disrupting and making the interview difficult-to-impossible

ITEM 6 – DISORGANIZED THINKING: As indicated during the interview by rambling, irrelevant or incoherent speech, or by tangential, circumstantial or faulty reasoning. Ask patient a somewhat complex question (for example, "Describe your current medical condition.")

☐ 0 = None	Patient's speech is coherent and goal directed
☐ 1 = Mild	Patient speech is slightly difficult to follow, responses to questions are slightly off target, but not by so much as to prolong the interview
☐ 2 = Moderate	Patient disorganized thoughts or speech are clearly present, such that the interview is prolonged but not disrupted
☐ 3 = Severe	Examination is very difficult or impossible due to disorganized thinking or speech

ITEM 7 – PERCEPTUAL DISTURBANCE: Misperceptions, illusions, hallucinations inferred from inappropriate behaviour during interview or admitted by subject, as well as those elicited from nurse/family/chart accounts of the past several hours or of the last time since examination.

☐ 0 = None	No misperceptions, illusions or hallucinations
☐ 1 = Mild	Misperceptions or illusions related to sleep, fleeting hallucinations on 1-2 occasions without inappropriate behaviour.
☐ 2 = Moderate	Hallucinations or frequent illusions on several occasions with minimal inappropriate behaviour that does not disrupt the interview
☐ 3 = Severe	Frequent or intense illusions or hallucinations with persistent inappropriate behaviour that disrupts the interview of interferes with medical care.

ITEM 8 – DELUSIONS: Rate delusions inferred from inappropriate behaviour during the interview or admitted by the patient, as well as delusions elicited from nurse/ family/chart accounts of the past several hours or of the time since the previous examination

☐ 0 = None	No evidence of misinterpretation or delusions
☐ 1 = Mild	Misinterpretations or suspiciousness without clear delusional ideas or inappropriate behaviour.
☐ 2 = Moderate	Delusions admitted by the patient or evidenced by his / her behaviour that do not or only marginally disrupt the interview or interfere with medical care
☐ 3 = Severe	Persistent and / or intense delusions resulting in inappropriate behaviour, disrupting the interview or seriously interfering with medical care.

ITEM 9 – DECREASED OR INCREASED PSYCHOMOTOR ACTIVITY: Rate activity over the past several hours, as well as during the interview, by circling (a) hypoactive, (b) hyperactive or (c) elements of both present.

☐ 0 = None	Normal psychomotor activity
☐ a b c 1 = Mild	Hypoactivity is barely noticeable, expressed as sightly slowing of movement. Hyperactivity is barely noticeable or appears as simple restlessness.
☐ a b c 2 = Moderate	Hypoactivity is undeniable, with marked reduction in the number of movements or marked slowness of movement, subject rarely spontaneously moves or speaks. Hyperactivity is undeniable, subject moves almost constantly, in both cases, exam is prolonged as a consequence
☐ a b c 3 = Severe	Hypoactivity is sever, does not move or speak without prodding or is catatonic. Hyperactivity is severe, patient is constantly moving, overreacts to stimuli, requires surveillance and / or restraint, getting through the exam is difficult or impossible.

ITEM 10 – SLEEP-WAKE CYCLE DISTURANCE (DISORDER OF AROUSAL): Rate patient's ability to either sleep or stay awake at the appropriate times. Utilise direct observation during the interview, as well as reports from nurses, family, patient or charts describing sleep-

wake cycle disturbance over the last several hours or since the last examination. Use observations of the previous night for morning evaluations only.

☐ 0 = None	At night, sleeps well; during the day, has no trouble staying awake.
☐ 1 = Mild	Mild deviation from appropriate sleepfulness and wakefulness states; at night, difficulty falling asleep or transient night awakenings, needs medication to sleep well; during the day, reports periods of drowsiness, or during interview, is drowsy but can easily fully awaken him / herself.
☐ 2 = Moderate	Moderate deviations from appropriate sleepfulness and wakefulness states: at night, repeated and prolonged night awakening; during the day, reports frequent and prolonged napping, or during interview, can only be roused to complete wakefulness by strong stimuli
☐ 3 = Severe	Severe deviations from appropriate sleepfulness and wakefulness states: at night, sleeplessness; during the day, patient spends most of the time sleeping, or during the interview, cannot be roused to full wakefulness by any stimuli.

Appendix 14 Nursing Delirium Screening Scale

Date today; _____/_____/_____ Day of study (circle one) 1 2 3

Features and descriptions	**SYMPTOM RATING 0 - 2**		
Symptom/time period	Midnight – 8am	8am – 4pm	4pm - midnight
DISORIENTATION: Verbal or behavioural of not being orientated to time or place or misperceiving persons in the environment			
INAPPROPRIATE BEHAVIOUR: Behaviour inappropriate to place and/or for the person e.g. pulling at tubes or dressings, attempting to get out of bed when that is contraindicated and the like			
INAPPROPRIATE COMMUNICATION: Communication inappropriate to place and/or for the person e.g. incoherence, non-communicativeness, nonsensical or unintelligible speech			
ILLUSIONS/HALLUCINATIONS: Seeing or hearing things that are not there, distortion of visual objects.			
PSYCHOMOTOR RETARDATION: Delayed responsiveness, few or no spontaneous actions/words e.g. when patient is prodded, reaction is deferred and/or the patient is unrousable			
TOTAL SCORE (out of 10)			

Guide to scoring:

0 = Behaviour **not present** during shift/assessment period.

1 = Behaviour **present at some time** during shift/assessment period, but **mild** (minimal interference with function, communication and/or care needs)

2 = Behaviour **present at some time** during shift/assessment period, and **pronounced** (interfering with function, communication and/or care needs).

Appendix 15 Extrapyramidal Symptom Rating Scale (ESRS)

Summary of the ESRS examination procedure.

1. Patient is asked to remove their shoes (omitted if judged clinically inappropriate or when patient hesitates, or delayed after patient has walked). The patient is asked to remove anything from their mouth (except dentures). The patient is asked to sit facing the examiner on a chair with no armrests.
2. Complete the questionnaire.
3. Observe facial expressiveness, speech and dyskinesia while completing the questionnaire and while completing items 4, 5, and 6 below.
4. Patient is asked to extend both arms forward, with palms down and eyes closed.
5. The patient is asked to carry out pronation and supination of both hands as fast as possible, and to perform rapid alternate movements of both wrists. Repeat as necessary.
6. While the patient sits facing the examiner on a chair with no armrests about 30cm from a table with upper body turned, the patient is asked to copy a spiral with each hand and to write the name of their town, state and country.
7. Patient is asked to walk a distance of 4-5 m away from and then back towards the examiner.
8. Patient is asked to stand erect with eyes open with feet slightly apart (1-2cm). The examiner gently pushes the patient on each shoulder, the back and pushes the chest or pulls from the back while asking the patient to keep their balance.
9. Examination of muscular tone of all four limbs.
10. In case of doubt score the lesser severity

A. ESRS Interview

	Absent	Mild	Moderate	Severe
	0	**1**	**2**	**3**
1. Impression of slowness or weakness, difficulty in carrying out routine tasks?	☐	☐	☐	☐
2. Difficulty walking or with balance?	☐	☐	☐	☐
3. Stiffness, stiff posture?	☐	☐	☐	☐
4. Restless, nervous, unable to keep still?	☐	☐	☐	☐
5. Tremors, shaking?	☐	☐	☐	☐
6. Oculogyric crisis (abnormal sustained posture)?	☐	☐	☐	☐
7. Abnormal involuntary movements of tongue, jaw lips, face, extremities or trunk?	☐	☐	☐	☐

B. ESRS Examination

	0	1	2	3	4	5	6
Tremor Right upper limb	☐	☐	☐	☐	☐	☐	☐
Tremor Left upper limb	☐	☐	☐	☐	☐	☐	☐
Tremor Right lower limb	☐	☐	☐	☐	☐	☐	☐
Tremor Left lower limb	☐	☐	☐	☐	☐	☐	☐

	0	1	2	3	4	5	6
Tremor Head	☐	☐	☐	☐	☐	☐	☐
Tremor Tongue	☐	☐	☐	☐	☐	☐	☐
Tremor Jaw/chin	☐	☐	☐	☐	☐	☐	☐
Tremor Lips	☐	☐	☐	☐	☐	☐	☐
Bradykinesia	☐	☐	☐	☐	☐	☐	☐
Gait and posture	☐	☐	☐	☐	☐	☐	☐
Postural stability	☐	☐	☐	☐	☐	☐	☐
Rigidity	☐	☐	☐	☐	☐	☐	☐
Expressivity	☐	☐	☐	☐	☐	☐	☐
Akathisia	☐	☐	☐	☐	☐	☐	☐
Dystonia Right upper limb	☐	☐	☐	☐	☐	☐	☐
Dystonia Left upper limb	☐	☐	☐	☐	☐	☐	☐
Dystonia Right lower limb	☐	☐	☐	☐	☐	☐	☐
Dystonia Left lower limb	☐	☐	☐	☐	☐	☐	☐
Dystonia Head	☐	☐	☐	☐	☐	☐	☐

	0	1	2	3	4	5	6
Dystonia Tongue	☐	☐	☐	☐	☐	☐	☐
Dystonia Jaw/chin	☐	☐	☐	☐	☐	☐	☐
Dystonia Eyes	☐	☐	☐	☐	☐	☐	☐
Dystonia Lips	☐	☐	☐	☐	☐	☐	☐
Dystonia Trunk	☐	☐	☐	☐	☐	☐	☐
Dyskinetic movement lingual	☐	☐	☐	☐	☐	☐	☐
Dyskinetic movement jaw	☐	☐	☐	☐	☐	☐	☐
Dyskinetic movement bucco-labial	☐	☐	☐	☐	☐	☐	☐
Dyskinetic movement truncal	☐	☐	☐	☐	☐	☐	☐
Dyskinetic movement upper limb	☐	☐	☐	☐	☐	☐	☐
Dyskinetic movement lower limb	☐	☐	☐	☐	☐	☐	☐
Dyskinetic movement	☐	☐	☐	☐	☐	☐	☐
Dyskinetic movement	☐	☐	☐	☐	☐	☐	☐
Other involuntary movement	☐	☐	☐	☐	☐	☐	☐

C. Clinical Global impression

	Absent	Borderline	Very mild	Mild	Moderate	Moderate-ly severe	Marked	Severe	Extremely severe
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Dyskinesia	☐	☐	☐	☐	☐	☐	☐	☐	☐
Parkinson-ism	☐	☐	☐	☐	☐	☐	☐	☐	☐
Dystonia	☐	☐	☐	☐	☐	☐	☐	☐	☐
Akathisia	☐	☐	☐	☐	☐	☐	☐	☐	☐

Scoring guide:

1. Tremor – (rhythmic oscillation along an axis, including pill rolling.)

Amplitude	Occasional	Frequent	Constant or almost so
None	0		
Borderline	1		
Small amplitude	2	3	4
Moderate amplitude	3	4	5
Large amplitude	4	5	6

2. Bradykinesia – (slowed voluntary movements) scoring guide.

    0 Normal
    1 global impression of slowness in movements
    2 definite slowness in movements
    3 very mild difficulty in initiating movements
    4 mild to moderate difficulty in initiating movements
    5 difficulty in starting or stopping any movement, or freezing on initiating voluntary act
    6 rare voluntary movement, almost completely immobile

3. Gait and posture – (decreased pendular movement, freezing on turning, stopped posture) scoring guide.

    0 Normal
    1 Mild decrease of pendular arm movement
    2 Moderate decrease of pendular arm movement, normal steps
    3 No pendular arm movement, head flexed, steps more or less normal
    4 Stiff posture (head and neck) small step (shuffling gait)
    5 More marked, festination of freezing on turning
    6 Triple flexion, barely able to walk

4. Postural stability (impaired balance)

    0 normal
    1 hesitation when pushed but no retropulsion
    2 retropulsion but recovers unaided
    3 exaggerated retropulsion without falling
    4 absence of postural response would fall if not caught by examiner
    5 unstable while standing, even without pushing
    6 unable to stand without assistance

5. Rigidity (resistance on passive movement (smooth resistance or cogwheeling – ratchet like jerks)

    0 normal muscle tone
    1 very mild, barely perceptible
    2 mild (some resistance to passive movements)
    3 moderate (definite difficulty to move the limb)
    4 moderately severe (moderate resistance but still easy to move limb)
    5 severe (marked resistance with definite difficulty to move the limb)
    6 extremely Severe (limb nearly frozen)

6. Expressive automatic movements (facial mask/speech) (smiling , blinking, spontaneous eye movements less frequent, due to rigidity and bradykiesia of facial muscles.)

    0 normal
    1 very mild decrease in facial expressiveness

2 mild decrease in facial expressiveness
3 rare spontaneous smile, decrease blinking, voice slightly monotonous
4 no spontaneous smile, staring gaze, low monotonous speech, mumbling
5 marked facial mask, unable to frown, slurred speech
6 extremely severe facial mask with unintelligible speech

7. Akathisia - subjective feelings of restlessness with urge to move and/or objective restless movements of extremity, fidgeting, changing positions, rocking while standing or sitting, lifting feet as if marching on one spot, crossing/uncrossing legs while sitting and inability to sit down for long periods with pacing back.

0 absent
1 looks restless, nervous, impatient, uncomfortable
2 needs to move at least on extremity
3 often needs to move one extremity or to change position
4 moves one extremity almost constantly if sitting, or stamps feet while standing
5 unable to site down for more than a short period of time
6 moves or walks constantly

8. Dystonia

0 absent
1 very mild
2 mild
3 moderate
4 moderately severe
5 severe
6 extremely severe

9. Dyskinesia

Lingual movements (slow, lateral or torsion movement of tongue)

Behaviour	Occasional	Frequent	Constant or almost so
None	0		
Borderline	1		
Clearly present within oral cavity	2	3	4
With occasional protusion	3	4	5
With complete protusion	4	5	6

Jaw movements (lateral movement, chewing, biting, clenching)

Behaviour	Occasional	Frequent	Constant or almost so
None	0		
Borderline	1		
Clearly present small amplitude	2	3	4
Moderate amplitude but without mouth opening,	3	4	5
large amplitude with mouth opening	4	5	6

Bucco-labial movements (puckering, pouting, smacking, etc)

Behaviour	Occasional	Frequent	Constant or almost so
None	0		
Borderline	1		
Clearly present small amplitude	2	3	4

Moderate amplitude forward movement of lips	3	4	5
large amplitude, marked, smacking of lips	4	5	6

Truncal movements (involuntary rocking, twisting, pelvic gyrations)

Behaviour	Occasional	Frequent	Constant or almost so
None	0		
Borderline	1		
Clearly present small amplitude	2	3	4
Moderate amplitude	3	4	5
Greater amplitude	4	5	6

Upper extremities (choreoathedoid movements only; arms, wrists, hands, fingers)

Behaviour	Occasional	Frequent	Constant or almost so
None	0		
Borderline	1		
Clearly present small amplitude, movement of one limb	2	3	4
Moderate amplitude, movement of one limb or movement of small amplitude involving two limbs	3	4	5
Greater amplitude, movement involving two limbs	4	5	6

Lower extremities (choreoathedoid movements only; legs, ankles, toes)

Behaviour	Occasional	Frequent	Constant or almost so
None	0		
Borderline	1		
Clearly present small amplitude, movement of one limb	2	3	4
Moderate amplitude, movement of one limb or movement of small amplitude involving two limbs	3	4	5
Greater amplitude, movement involving two limbs	4	5	6

Other involuntary movements (swallowing, irregular respiration, frowning, blinking, grimacing, sighing etc)

Behaviour	Occasional	Frequent	Constant or almost so
None	0		
Borderline	1		
Clearly present small amplitude	2	3	4
Moderate amplitude	3	4	5
Greater amplitude	4	5	6

Appendix 16 Richmond Agitation Sedation Scale

1. Observe patient.
    a. Patient is alert, restless or agitated to +4 Score 0

2. If not alert, state the patients name and say ‘open yours eyes and look at me’
    a. Awakens with sustained eye opening and eye contact Score -1
    b. Awakens with eye opening and contact, but not sustained Score -2
    c. Any movement in response, but no eye contact Score -3

3. When no response to verbal stimulation, physically stimulate by shaking shoulder and/or rubbing sternum
    a. Patient has any movement to stimulation Score -4
    b. Patient has no response to any stimulation Score -5

Combative	+4	☐
Very agitated	+3	☐
Agitated	+2	☐
Restless	+1	☐
Alert and calm	0	☐
Drowsy	-1	☐
Light sedation	-2	☐
Moderate sedation	-3	☐
Deep sedation	-4	☐
Unarousable	-5	☐

Appendix 17 IQCODE

Now we want you to remember what your friend or relative was like 10 years ago and to compare it with what he/she is like a few weeks ago, prior to this episode of confusion/before this acute episode. 10 years ago was in 19__. Below are situations where this person has to use his/her memory or intelligence and we want you to indicate whether this has improved, stayed the same or got worse in that situation over the past 10 years. Note the importance of comparing his/her present performance with 10 years ago. So if 10 years ago this person always forgot where he/she had left things, and he/she still does, then this would be considered "Hasn't changed much". Please indicate the changes you have observed by circling the appropriate answer.

Compared with 10 years ago how is this person at:

	1 Much improved	2 A bit improved	3 Not much change	4 A bit worse	5 Much worse
1. Remembering things about family and friends e.g. occupations, birthdays, addresses	☐	☐	☐	☐	☐
2. Remembering things that have happened recently	☐	☐	☐	☐	☐
3. Recalling conversations a few days later	☐	☐	☐	☐	☐
4. Remembering his/her address and telephone number	☐	☐	☐	☐	☐
5. Remembering what day and month it is	☐	☐	☐	☐	☐
6. Remembering where things are usually kept	☐	☐	☐	☐	☐
7. Remembering where to find things which have been put in a different place from usual	☐	☐	☐	☐	☐

	1	2	3	4	5
	Much improved	A bit improved	Not much change	A bit worse	Much worse
8. Knowing how to work familiar machines around the house	☐	☐	☐	☐	☐
9. Learning to use a new gadget or machine around the house	☐	☐	☐	☐	☐
10. Learning new things in general	☐	☐	☐	☐	☐
11. Following a story in a book or on TV	☐	☐	☐	☐	☐
12. Making decisions on everyday matters	☐	☐	☐	☐	☐
13. Handling money for shopping	☐	☐	☐	☐	☐
14. Handling financial matters e.g. the pension, dealing with the bank	☐	☐	☐	☐	☐
15. Handling other everyday arithmetic problems e.g. knowing how much food to buy, knowing how long between visits from family or friends	☐	☐	☐	☐	☐
16. Using his/her intelligence to understand what's going on and to reason things through	☐	☐	☐	☐	☐

Total score **_____**
Divide total score by 16
Result **_____/5**

Appendix 18 Sample participant information sheet for New South Wales Sites

PERSONAL RESPONSIBLE PARTICIPANT INFORMATION SHEET

Randomised double blind control trial of oral risperidone versus oral haloperidol versus oral placebo with rescue subcutaneous midazolam in the management of delirium in palliative care inpatients.

RISPERIDONE FOR DELIRIUM

Invitation:
You are being asked to consider giving consent for participation in a research study on behalf of the person for whom you have decision- making responsibilities. This study involves people who have developed delirium (which is a medical condition that can develop when someone is unwell) during their current admission to hospital.

You are being asked about this study as patients with delirium are unable to give consent to participate in any trial. The Guardianship Act 1987 identifies you as the recognised "person responsible" to provide consent. The "person responsible" is either 1) a guardian (including an enduring guardian); or if there is no guardian 2) the most recent spouse or de facto spouse (including same sex partners) with whom the person has a close continuing relationship; or if there is no spouse or de facto spouse 3) an unpaid carer who is now providing support to the person or provided this support before the person entered residential care; or if there is no carer 4) a relative or friend who has a close personal relationship with the person. The "person responsible" is not necessarily the patient's next of kin or caregiver. If the person identified as "person responsible" declines to exercise this function in writing, then the next person listed on the hierarchy is the "person responsible".

Before you decide whether or not you wish for the person for whom you have decision-making responsibilities to participate in this study, it is important for you to understand why the research is being done and what it will involve. Please take the time to read the following information carefully and discuss it with others if you wish. This information form may contain words that you do not understand. Please ask the research staff to explain any words or information that you do not clearly understand. It is important you understand why the research is being done and what it will involve for the person for whom you have decision-making responsibilities.

Who is conducting the study?
This national study is being conducted **at eleven Australian hospital sites** on behalf of the Palliative Care Clinical Studies Collaborative, Flinders University; and is funded by the Australian Government-Department of Health and Ageing.

What is the purpose of this study?
This study involves people who have developed delirium (which is a medical condition that can develop when someone is unwell) during their current admission to hospital. Delirium is a significant clinical problem in palliative care. There are many factors that can cause delirium. A common cause you may be familiar with is when someone gets a severe infection. Symptoms of delirium can be of varying severity, and may include confusion and disorientation, loss of memory, restlessness, agitation, disorders of perception (for example hallucinations (seeing or hearing objects which are not there) and illusions (mistaking objects)). Delirium can also affect a person's understanding and

awareness, as well as their ability to communicate and interact with their environment. We know symptoms of delirium can be very distressing for the patient and their family.

The purpose of the study is to improve the quality of life of palliative care patients who have developed delirium, regardless of cause, through better treatment and management of this disorder. There is currently limited evidence in the understanding of the physical process involved in delirium and no clear research results to advise the best medicines with which the condition should be managed. This research is being carried out to compare three different approaches to management: the use of two medicines for the treatment of delirium; or if using medications only when needed. This research study aims to compare using haloperidol regularly, using risperidone regularly, or using medication as required based on symptoms that occur.

Current practice for the management of delirium involves non-medication measures to control symptoms (for example reorientation and having a familiar person with them), and measures to reverse the medical cause of delirium, which need to be individualised for each patient (such as treating infection). All participants in this study will receive individualised non-medication measures and measures to manage the cause of the delirium as decided by the treating medical team.

In addition to the non-medication measures and management of the medical causes medications can be used. The medications that can be used come from a group of medicines called anti-psychotics, and both haloperidol and risperidone are from this group of medicines. These medications are used mainly to manage the symptoms of restlessness, agitation, hallucinations and delusions. Some clinicians use medications on a regular basis, however others use only non-medication measures with medication used only if needed to maintain patient or staff safety, or relieve patient distress. With this approach regular medication is not prescribed, however rescue medication (such as antipsychotic, or a benzodiazepine medication for example midazolam) can be used when the specific symptoms of delirium (agitation, restlessness, hallucinations, delusions) become severe.

This study will specifically provide information about these three approaches, in particular:
1. Whether adding regular medications reduce the severity of the specific delirium symptoms
2. Side effects of the three approaches, such as sedation, tremor, rigidity, and muscle spasms
3. Patient and caregiver perception of the level of distress from delirium symptoms, and whether the level of distress is more or less with each of the three approaches.
4. The effects on the participant's lucidity of the three approaches.

In order to meet these aims, the study requires 165 people to take part.

What if I don't want the person for whom I have decision-making responsibilities to take part in this study or if I want to withdraw them later?

Participation in the study is entirely voluntary, you can choose that the person for whom you have decision- making responsibilities does not take part in this study, or if you do provide consent you can stop their taking part at any time.

If you decide not to provide consent for the person for whom you have decision- making responsibilities to participate in this study or if you withdraw the person for whom you have decision making responsibility from the study, you may do this freely without

prejudice to any future treatment for that person at the [Name of Local Institute]; and you do not need to provide a reason.

New information about the treatment being studied may become available during the course of the study. You will be kept informed of any significant new findings that may affect your willingness to continue to provide consent for the person for whom you have decision making responsibilities in the study.

Consent from the patient

If the delirium resolves, the person for whom you have decision-making responsibilities will also be asked if they agree to continue participating in the study. They may well decide not to continue, and we will cease the study if this is their wish.

If they agree, we will continue the study, which will include asking them a number of questions after we have specifically obtained their permission. These questions relate to our interest in knowing how the three approaches affect the person's perception and memory of the delirium experience.

What are the alternatives to participating in this study?
Current practice for the management of persons with delirium involves both medication and non- medication measures, such as reorientation and having a familiar person with them. Measures to reverse the cause of delirium, such as treating infection, are used when possible.

Medications that are often used are anti-psychotics and benzodiazepine medications. These medications are used mainly to manage the symptoms of restlessness, agitation, hallucinations and illusions. There is some variation in clinical practice. Some clinicians use medications on a regular basis; other clinicians use non-medication measures, and only use so-called "rescue" medications if they are needed to maintain patient/staff safety, or to relieve patient distress.

These treatments are available to the person for whom you have decision making responsibility, even if you do not agree to their participation in this study. Please talk to the doctor about these and about the other options that may become available during the study.

What does the study involve?

Study treatments:
This study is a randomised trial, which is being conducted over three days. Sometimes doctors don't know the best way of treating patients with a particular condition so comparisons need to be made between different treatments. To do this, study participants are put into groups and given different treatments, and the results are compared to see whether one treatment is better. To ensure the groups are similar to start with, a computer allocates each study participant into a group randomly, like the flip of a coin. Neither the doctor nor the study participant can decide which treatment the participant receives. If in an emergency the doctor needs to know which treatment a person has received, this information will be provided. There is an equal chance of being placed in any of the treatment groups.

In this study each participant will be randomised into one of the following three treatment groups are to be given one of the following medications for three days.

Group 1: regular haloperidol syrup twice daily.

Group 2: regular risperidone syrup twice daily

Group 3: placebo syrup twice daily with medication used as required for symptoms.

The placebo syrup is a dummy treatment that contains no active ingredient, yet appears identical to the other two active treatments used. The reason for using placebo syrup is to reduce the chance of the study being biased due to knowing what group the participant is in. Only pharmacy staff will know what medication patients are given, as they will be responsible for making up the syrup based on the randomization. The research staff, doctors and nurses will not know which medication is being given to the person for whom you have decision making responsibilities

All groups will also be able to be given a medication, midazolam, at any time for distressing symptoms needing immediate treatment, throughout the three days of the study; which is given as an injection under the skin.

The researchers may take the patient off the study treatment early for reasons such as:

- The treatment does not work for the patient.
- The patient is unable to tolerate the study treatment.
- New information shows that the study treatment is no longer in the patient's best interest.
- Your doctor no longer feels this is the best treatment for the patient.
- The sponsor decides to stop the trial.

Assessments

If you agree to consent for participation by the person for whom you have decision-making responsibility, we will be recording information about their medical condition and medication on a daily basis during the three days of the study. Nursing and medical staff will be completing an assessment tool designed to be able to measure any changes in their delirium. Each of these visits to the participant will take about 25 minutes and can be stopped if the person becomes tired. The assessments will measure delirium using two assessment tools, one that is diagnostic of delirium, and one that is a short assessment of the specific symptoms of delirium that may need treatment. Some of the items of these questionnaires only require nurse or medical observations, whereas others need a few questions (mainly to test the participant's orientation and understanding).

The following assessments will also be performed and are usually part of routine assessment of a person who has delirium. These assessments include:

- pulse
- blood pressure,
- level of oxygen in the blood (using a small monitor clipped onto the finger)
- ability to conduct physical activities (such as walking, getting to the toilet, eating).

All of this information will be collected each day while the person for whom you have decision making responsibility is taking the study medicines (3 days).

Blood tests:

Samples of blood taken from a vein will be required. The amount of blood taken will be equivalent to 10 millilitres (2 teaspoons) taken on maximum of 2 occasions (at the start of the study and if the delirium resolves). These blood tests are to check for abnormalities in kidney function, liver function and levels of sodium and calcium in blood, which may contribute to delirium. An optional blood sample of 10 millilitres (2 teaspoons) will be taken at the same time, for a new marker of brain cell damage, which will help understanding of what may cause delirium. This additional test is being performed by a laboratory, at the University of New South Wales.

Some further information will come from observing the person, some will come from asking questions of the medical and nursing staff, some information will come from the medical notes (such as medication use and current medical conditions), and some information will come from the person who generally looks after the person for whom you have decision making responsibilities (this caregiver may be you, a close family member, neighbour, or friend, and will have their involvement explained separately).

Follow up

We will also make some follow-up visits so we can understand the long-term benefits and implications of these medications, and how people recover from delirium.

This will be once per week for three weeks (while an inpatient or if the person goes home we will telephone them at home), where we will ask about their medications, any other episodes of delirium, any admissions to hospital or visits to their general practitioner, and the use of any other health services. This telephone call at home or follow-up visit on the ward will take approximately fifteen minutes.

The study nurse will visit the person at four weeks at home (or on the ward if still in hospital) to obtain similar information and to ask about their quality of life, and ask some follow-up questions of the person providing care. This visit will take approximately thirty minutes.

How is this study being paid for?

This study is funded by the Australian Government - Department of Health and Ageing, and Flinders University, South Australia is the sponsor of the study. Each site receives payment for medicines and cost for conducting the study. All payments to the study sites will be deposited into a specific account and used for salaries of those hospital staff that are involved in this research, infrastructure costs and for funding further research projects. There will be no personal financial benefit to the investigator for the conduct of this research.

Are there risks in taking part in this study?

The risks and adverse effects that are likely to be experienced by the person you have responsibility for are described below. Since both medicines of this study, haloperidol and risperidone, are not currently approved for use in the treatment of delirium, and their use in this condition has not been extensively studied in this condition, not all the side effects are known at this time. Any new findings that might cause you to change your mind about participating in this study, will be reported to you immediately.

Physical Risk

If you provide consent for the person whom you have decision-making responsibilities to take part in this study, there may or may not be direct benefit to him/her other than the potential relief from symptoms of delirium. We cannot guarantee or promise that he/she will receive any benefits from this study, though we hope the information learned from this study will help other patients with delirium in the future.

The person for whom you are providing consent will be monitored regularly by both ward nurses and study nurses to make sure their symptoms and any side effects are controlled. All medical procedures involve some risk of injury. In addition, there may be risks associated with this study that are presently unknown or unforeseeable. In spite of all reasonable precautions, you might develop medical complications from participating in this study. The known risks of this study are:

1. Unrelieved delirium symptoms. This study is aiming to understand how often symptoms are relieved. During the study if unrelieved symptoms do occur rescue medication (midazolam by injection under the skin) can be given. The doctor in charge of the participants care will also assess this regularly and if delirium symptoms persist can change to alternative treatment.

2. Common (1 in 10)

   One side effect is sedation. It is most commonly mild and temporary. This can be variable with some people experiencing more severe sedation. It is also common for delirium itself to alter the person's level of consciousness, so sedation is often not due to medications alone. We will very carefully review the participant's past and current medical conditions to ensure the conditions or other medications that may increase risk of sedation are not present or are monitored depending on the individual circumstance. In this study the starting doses are low to also minimise this side effect. This side effect may require the study medication to be reduced or stopped.

3. Not very common (1 in 100):

   Another group of side effects are muscle rigidity, slowness of movement or tremor of arms or legs. In some people dizziness or low blood pressure especially on standing up can occur. These side effects may require the study medication to be reduced or stopped; which usually results in resolution of the symptoms. This group of side effects can be more common in people who have recently had a stroke, seizure or have Parkinson's disease. We will very carefully review the medical history prior to starting the study, and may not proceed with the study if the risk to the person is too high.

   A blood sample will be collected from a vein in the arm with a needle (venepuncture). Whenever a blood sample is taken, there is a very small risk of local irritation and pain, bruising, infection or feeling faint.

4. Rare (1 in 10 000):

   Rare side effects include severe muscle spasm (dystonia), severe muscle spasm involving the airway (laryngeal dystonia) and a syndrome called neuroleptic malignant syndrome (which is a cluster of symptoms which includes high temperatures, sweating, high levels of a muscle enzyme measured in the blood, reduce level of consciousness. These side-effects are usually managed by stopping the medication and supportive medical care. To manage severe muscle spasm, other drugs which work like an antidote to the study medication can be given as an intravenous injection. In the event of these rare side effects the study medicines will be stopped.

As both haloperidol and risperidone are still being tested for their use in the relief of delirium, there may be other side effects that are not known at this time. The study nurses and the doctors and nurses in the ward will be monitoring the person for whom you have decision making responsibility closely and will make sure they are looked after appropriately.

Psychological Risk

If the delirium resolves, we will ask the person for whom you have provided consent to complete some questionnaires about their quality of life. We will specifically explain the complete study to this person at this time, and obtain their specific consent to ask these questions. There is a small risk that answering these questions may cause them to reflect on their life and situation and cause them to be distressed. The study nurses will talk to them about these feelings and will stop the questionnaire if they feel unable or too upset to continue.

Social Risk
All procedures for this study are carefully designed to protect privacy. We will ensure that the privacy of yourself and the person for whom you are providing consent takes priority and that the information obtained during this study will not be passed on to others.

Legal risk
We do not know of any legal risks to you as part of this study. The state legislation regarding consent for participation in research studies have been carefully followed, and you are able to provide this consent at this time. We know of no legal risks to the person for whom you are providing consent.

Economic Risk
This study is being conducted while the person for whom you have decision-making responsibilities is in hospital, there should not be any economic risk for participating. The telephone calls and home visit after they leave hospital will be negotiated with the family so that they do not interfere with any work or social commitments.

Will the participant benefit from the study?
This study is aimed at determining if any of the currently used medicines have any documented benefit for the specific symptoms of delirium. There are not expected to be any direct benefits for those who participate in the study but there is a possibility that risperidone may have a lower frequency of side effects than haloperidol because it works in a slightly different way.

What happens if the participant suffers injury or complications as a result of the study?
If the person for whom you have decision-making responsibilities suffer any injuries or complications as a result of this study, you should contact the study doctor as soon as possible, who will assist you in arranging appropriate medical treatment.

The person for whom you have decision-making responsibilities may have a right to take legal action to obtain compensation for any injuries or complications resulting from the study. Compensation may be available if the injury or complication of the person for whom you have decision-making responsibilities is sufficiently serious and is caused by unsafe drugs or equipment, or by the negligence of one of the parties involved in the study (for example, the researcher, the hospital, or the treating doctor). If the person for whom you have decision-making responsibilities receive compensation that includes an amount for medical expenses, you will be required to pay for your medical treatment from those compensation monies. The person for whom you have decision-making responsibilities does not give up any legal rights to compensation by participating in this study.

If the person for whom you have decision-making responsibilities are not eligible for compensation for your injury or complication under the law, but are eligible for Medicare, then the person for whom you have decision-making responsibilities can receive any

medical treatment required for your injury or complication free of charge as a public patient in any Australian public hospital.

Will taking part in this study cost me, or the participant anything, and will I be paid?
Participation in this study will not cost you or the person for whom you have decision-making responsibilities anything. There will be no payment to you, or the person for whom you have decision-making responsibility as a result of participating in this study.

How will the participant's confidentiality be protected?
You should be aware that the results from this study may be processed by computer, but no names or identifying information of the person for whom you have decision-making responsibilities or yourself 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. Participants' and your identity will not be disclosed in the event of any publication arising from this study. It is possible that your personal 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. All recorded information will be stored for 15 years.

What happens with the results?
If you give us your permission for the person for whom you have decision-making responsibilities by signing the consent document, we plan to discuss/publish the results. This will include reports to the sponsor for monitoring purposes, the HREC for monitoring purposes, and publication in peer-reviewed journals, presentation at conferences or other professional forums.

In any publication, information will be provided in such a way that you or the the person for whom you have decision-making responsibilities cannot be identified. Results of the study will be provided to you and/or the person for whom you have decision-making responsibilities, if you/they wish. If you wish to receive the study results you should contact the site investigator [Insert name/title, and relevant contact details].

Notifying the Investigator and other Relevant Doctors
You should advise the study doctor if the person for whom you have decision-making responsibilities and are providing consent is participating in any other research studies. In the event that the person for whom you are providing consent needs elective or emergency or other medical care, you should inform the doctor looking after them that they are participating in this study.

What happens to the participant's treatment when the study is finished?
When the study finishes further treatment for delirium will be made in consultation between you and the treating doctor for the person for whom you have decision-making responsibilities about the most appropriate treatment for them at that time. This may include continuing medication such as haloperidol or risperidone, and/or rescue midazolam.

What should I do if I want to discuss this study further?
Should you or the person for whom you have decision-making responsibilities require further details about the study, either before, during or after the study, you may contact [Name], [Contact Number].

Who should I contact if I have concerns about the conduct of this study?

This study has been approved the Cancer Institute NSW Clinical Research Ethics Committee. Any person with concerns or complaints about the conduct of this study should contact the Ethics Coordinator who is the person nominated to receive complaints from research participants. You should contact them on 02 8374 5600 and quote [Risperidone for delirium study, Cancer Institute NSW *HREC reference number 2008C/05/055*].

You are also free to discuss any concerns about this trial, not only with the medical team, but also your family, friends, other health care professionals or legal advisors.

Thank you for taking the time to consider this study.
If you wish to take part in it, please sign the attached consent form.
This information sheet is for you to keep.

Appendix 19 Sample Ethics approval for New South Wales sites

Dr Meera Agar
Locked Bag 82
Wetherill Park NSW 2164

25 June 2009

Dear Dr Agar,

Cancer Institute NSW Clinical Research Ethics Committee

AU RED Reference: 08/CIC/33
Cancer Institute NSW reference number: 2008C/05/055

Project Title: "Randomised control trial of oral Risperidone versus oral haloperidol versus oral placebo with rescue subcutaneous midazolam in the management of delirium in palliative care inpatients."

Thank you for your correspondence dated 14 May 2009 requesting changes to the Case report forms for the above referenced study submitted to the Cancer Institute NSW Clinical Research Ethics Committee for single ethical and scientific review. The Committee reviewed your amendment at its meeting held on 3 June 2009, and I am pleased to advise that ethical approval for this amendment has been granted.

The Committee reviewed and approved the following forms:

- CI NSW Request for Amendment form dated 19 Feb 2009
- Minor changes to Case Report Forms to convert word documents to forms that correlate to online date entry requirements on Caresearch and correspond to assessment tools listed in Protocol V1.4.3 previously approved by the Committee on 11.09.2008.
    - Case report form, Eligibility form (Form A) 002/07, v1.7, April 09
    - Case report form, Baseline form (Form B1) 002/07, v1.8, April 09
    - Case report form, Day 2 Visit form (Form B2) 002/07, v1.8, April 09
    - Case report form, Day 3 Visit form (Form B3) 002/07, v1.8, April 09
    - Case report form, Day 4 Visit form (Form B4) 002/07, v1.8, April 09
    - Case report form, Day 5 Visit form (Form B5) 002/07, v1.8, April 09
    - Case report form, Day 6 Visit form (Form B6) 002/07, v1.8, April 09
    - Case report form, Treatment Cessation form (Form C) 002/07, v1.8, April 09
    - Case report form, Medical Review Discharge 002/07, v1.7, April 09
    - Case report form, Follow Up form (Form D1) 002/07, v1.7, April 09
    - Case report form, Follow Up form (Form D2) 002/07, v1.7, April 09
    - Case report form, Follow Up form (Form D3) 002/07, v1.7, April 09
    - Case report form, Follow Up form (Form D4) 002/07, v1.7, April 09
    - Case report form, Withdrawal form (Form E) 002/07, v1.7, April 09
    - Case report form, Delirium Resolution form (Form F) 002/07, v1.7, April 09
    - Case report form, Discharge form (Form G) 002/07, v1.7, April 09

Australian Technology Park, Biomedical Building, Suite 101, 1 Central Avenue, Eveleigh, NSW 2015
• PO Box 41, Alexandria, NSW 1435 •
T 02 8374 5600 • F 02 8374 5700 • www.cancerinstitute.org.au • ABN 48 538 442 594
Trim Record: E09/12165

- Case report form, Medical Daily Assessment form – Baseline 002/07, v1.7, April 09
- Case report form, Medical Assessment Eligibility form 002/07, v1.7, April 09
- Case report form, Medical Review form Day 2, 002/07, v1.7, April 09
- Case report form, Medical Review form Day 3, 002/07, v1.7, April 09
- Case report form, Medical Review form Day 4, 002/07, v1.7, April 09
- Case report form, Pre-Screen form, 002/07, v1.7, April 09
- Case report form, Medical Withdrawal form, 002/07, v1.7, April 09

This approval letter applies to the following sites:

- Calvary Mater Newcastle
- Royal Prince Alfred Hospital
- St Vincent's Hospital
- Concord Repatriation General Hospital
- Calvary Hospital
- Braeside Hospital
- Sydney Cancer Centre
- Sacred Heart Palliative Care Services

The Cancer Institute NSW Clinical Research Ethics Committee has been accredited by the NSW Department of Health to provide single ethical and scientific review of research proposals conducted within the NSW public health system. The Committee has been constituted and operates in accordance with the National Health and Medical Research Council's *National Statement on Ethical Conduct in Human Research (2007)* and the *CPMP/ICH Note for Guidance on Good Clinical Practice*.

For further information about the Cancer Institute NSW Clinical Research Ethics Committee please refer to our website www.cancerinstitute.org.au/research.

Should you have any queries about the ethical review of your research proposal please contact the Ethics Administration Support Officer Marion Marson on 02 8374 3562 or email ethics@cancerinstitute.org.au.

The Cancer Institute NSW Clinical Research Ethics Committee wishes you well in your research endeavours.

Yours sincerely,

Sharon Falleiro
Ethics Coordinator
Cancer Institute NSW
NSW Population & Health Services Research Ethics Committee

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Trim Record: E09/12165

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