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

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Table of contents

List of tables

Chapter 3

Chapter 4

Chapter 5

Chapter 6

List of figures

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.