Understanding the biological and clinical correlates of delirium: Development of Reporting Essentials for Delirium bioMarker Studies (REDEEMS)

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Table of Contents

List of tables

List of figures

Abstract

Background

Delirium is a common, serious and complex neurocognitive condition that is associated with negative impacts for both the person with delirium and their family/carers. Despite the significant burden, the pathophysiology of delirium remains unclear. To improve our understanding of delirium pathophysiology, robust delirium biomarker studies with optimal reporting are urgently needed to ensure each of these studies contribute to accelerate our knowledge.

Aim

To evaluate and optimize the methodological approaches in research evaluating biological and clinical correlates of delirium and underlying conditions.

Design

A multiple methods project, involving three discreet but inter-related studies conducted over three stages.

Methods

Study 1 was a systematic review of the overlap of delirium and advanced cancer-related syndrome biomarkers as an 'examplar' of the potential for interaction between the underlying condition and delirium; Study 2a was a three-stage modified Delphi study with delirium researchers and study 2b was a follow-up consensus meeting to generate a reporting guideline specific to delirium biomarker studies (REDEEMS). Study 3 comprised a series of semi-structured interviews which sought delirium researchers' perceptions of the key challenges of conducting delirium biomarker studies.

Results

The systematic review identified considerable overlap of delirium and advanced cancer biomarkers, with 41 biomarkers that had been studied in relation to both delirium and either an advanced cancer-related syndrome or prognosis. It also revealed a significant gap in the consistency and reporting of delirium biomarker studies. Considering this unexpected finding of poor quality, a drive to improve the methods of reporting delirium biomarker studies was warranted. The international Delphi study and consensus meeting (study 2) revealed a total of nine items which were deemed critical elements by delirium researchers for inclusion in the REDEEMS guideline. Finally, the third qualitative study identified a range of factors that contribute to the challenges and overall quality of delirium biomarker research. Delirium researchers concurred that delirium biomarker research is both an extremely difficult and complex field. and that the quality of reporting delirium biomarker research is poor, which contribute to lack of progress in scientific understanding. Analysis revealed two major themes and ten sub-themes, outlining key considerations to advance the field of delirium biomarker research. The major themes were: 1) Practical and scientific challenges of delirium biomarker research: stagnation versus driving improved methods and reporting; and 2) Valuing delirium research through investment and collaboration.

Conclusion

The REDEEMS guideline is the first reporting guideline specific for delirium biomarker studies aligned with impacts of reporting guidelines in other research methods. It aims to guide improvements in consistency and transparency of reporting future biomarker studies in delirium, conceivably permitting accurate replication and synthesis, and improving scientific rigor in the field. A collaborative effort to increase

awareness of, and improve research funding for delirium is needed, along with increased education and training in delirium biomarker methodology. These advancements will lead to significant improvement of our understanding of delirium pathophysiology and ultimately improve outcomes for people with delirium.

Certificate of original authorship

I, Ingrid Kathrine Viktoria Amgarth-Duff declare that this thesis, is submitted in fulfilment of the requirements for the award of Doctor of Philosophy in faculty of health at the University of Technology Sydney.

This thesis is wholly my own work unless otherwise referenced or acknowledged. In addition, I certify that all information sources and literature used are indicated in the thesis. This document has not been submitted for qualifications at any other academic institution.

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Signature of candidate:

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Anthology of Publications and Presentations

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Amgarth-Duff, I., Hosie, AM., Caplan, G., Agar, M. Delirium researchers' perspectives of the challenges in delirium biomarker research: A qualitative study. *PLOS ONE*. 2021;16:4:e0243254.

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Other presentations

Amgarth-Duff, I. (2019). Defining Methodological and Best Practice for Studies of Biological and Clinical Correlates of Delirium in Advanced Cancer – An International Modified Delphi Study, *IMPACCT Summer School*, University of Technology Sydney

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Subsidiary Research Outputs

Peer-reviewed journal articles

Hosie, A., Siddiqi, N., Featherstone, I., Johnson, M., Lawlor, P.G., Bush, S.H., **Amgarth-Duff, I**., Edwards, L., Phillips, J., and Agar, M. (2019). Inclusion, characteristics and outcomes of people requiring palliative care in studies of non-pharmacological interventions for delirium: A systematic review. *Palliative Medicine, 33*(8).

Book chapter

Hosie, AM., **Amgarth-Duff, I.**, Agar, M. (2017). Delirium and Terminal Agitation. MacLeod, R & Van Den Block, L (Eds.) In *Textbook of palliative care.* Sydney, Australia: Springer.

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Abbreviations

ADA	Australasian Delirium Association
ADS	American Delirium Society
APA	American Psychiatric Association
BRISQ	Biospecimen Reporting for Improved Study Quality
CAM	Confusion Assessment Method
CNS	Central nervous system
CONSORT	CONsolidated Standards Of Reporting Trials
CSF	Cerebrospinal fluid
DSD	Delirium superimposed on dementia
DSM	Diagnostic and Statistical Manual of Mental Disorders
E&E	Explanation and Elaboration document
EDA	European Delirium Association
ELISA	Enzyme-Linked Immunosorbent Assay
EQUATOR	Enhancing the QUAlity and Transparency Of Reporting
HREC	Human Research Ethics Committee
ICD-10	International Classification of Disease, edition 10
LP	Lumbar puncture
N/A	Not applicable
POD	Post-operative delirium
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomised Controlled Trial
REDEEMS	Reporting Essentials for DElirium bioMarker Studies
REMARK	Reporting rEcommendations for tumour MARKer prognostic studies
SAGES	Successful Aging after Elective Surgery
SSD	Subsyndromal delirium
STARD	Standards for Reporting of Diagnostic Accuracy Studies
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
UK	United Kingdom
USA	United States of America

Glossary of terms

Advanced cancer	Inclusive of stage III cancer (locally advanced with spread to nearby tissues or lymph nodes) and Stage IV cancer (metastatic disease).[1]
Anorexia cachexia	A complex metabolic syndrome of involuntary weight loss associated with cancer and some other palliative conditions.[2]
Biomarker	A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease.[3]
Cancer prognosis	The likely outcome or course of the disease; the chance of recovery or recurrence. Cancer prognosis is assessed by cancer-specific survival, overall survival, progression free survival or relative survival.[4]
Cancer-related cognitive impairment	Cognitive impairment that is commonly experienced by cancer patients and those in remission. The cognitive domains most commonly affected are memory, concentration, information processing speed and executive function.[5]
Cancer-related fatigue	A distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer and/or cancer treatment that is not proportional to recent activity and interferes with usual functioning.[6]
Cancer-related pain	An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.[7]
Classical Delphi Methodology	A research methodology with an aim to achieve consensus on a research question, using an expert panel, in an iterative and controlled survey process.[8]
Delirium	A neurocognitive disorder, characterised by acute disturbance to attention, awareness and cognition, affecting memory, language, visuospatial ability, orientation and perception.[9]
e-Delphi	A Delphi research method that involves the distribution of a survey electronically to panellists via email.
Hyperactive delirium	Delirium subtype where the patient has an increased level of psychomotor activity. There may also be lability of mood, agitation and resistance to medical care.[9]
Hypoactive delirium	Delirium subtype where the patient has a decreased level of psychomotor activity, along a continuum from lethargy to stupor.[9]
Incidence	The occurrence of new cases of a disease in a population over a specified period of time.[10]
Mixed delirium	Delirium subtype where the patient has either a normal or fluctuating level of psychomotor activity.[9]
Modified Delphi	Describes any methodological variation of the Classical Delphi method described by Dalkey and Helmer (1962).[11]
Morbidity	Non-fatal event.
Mortality	Fatal event/death.
Multiple methods	The use of two or more research methods in one research project.[12]
Persistent delirium	Full syndromal delirium at the time of admission (or shortly after admission) that continues to meet the criteria for delirium at the time of discharge or beyond.[13]
Prevalence	The proportion of a persons in a population who have a particular disease or attribute at a specified point in time or over a specified period of time.[10]
Point prevalence	The proportion of persons with a particular disease or attribute at a particular point in time (on a particular date).[10]

Prodromal delirium	Manifestation of symptoms such as changes to concentration, mood (irritability, anxiety, depression), sleep patterns (including vivid dreaming), cognition (e.g. disorientation), tiredness or noise sensitivity, that can occur in the hours, days or weeks prior to full syndromal delirium.[14]
Qualitative research	A means for exploring and understanding the meaning of individuals or groups ascribed to a social or human problem.[15]
Quantitative research	A means for testing objective theories by examining the relationship among variables.[15]
Reporting guideline	A checklist, flow diagram, or explicit text to guide authors in reporting a specific type of research, developed using explicit methodology.[16]
Sickness behaviour	The coordinated set of behavioural changes that develop in sick individuals during the course of an infection. Sickness behavior is also seen in other illness including cancer.[17,18]
Sub-syndromal delirium	Presence of one or more symptoms of delirium, where the patient does not meet the criteria for delirium.[19] Termed 'attenuated delirium syndrome' by the DSM-5.[9]

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