BMJ Open

Delirium prevention and treatment in the emergency department (ED): a systematic review protocol

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To cite: Dahlstrom EB, Han JH, Healy H, *et al*. Delirium prevention and treatment in the emergency department (ED): a systematic review protocol. *BMJ Open* 2020;**10**:e037915. doi:10.1136/bmjopen-2020-037915

► Prepublication history and additional file for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2020-037915).

Received 21 February 2020
Revised 30 August 2020
Accepted 10 September 2020

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ABSTRACT

Introduction Delirium is a dangerous syndrome of acute brain dysfunction that is common in the emergency department (ED), especially among the geriatric population. Most systematic reviews of interventions for delirium prevention and treatment have focused on inpatient settings. Best practices of effective delirium care in ED settings have not been established. The primary objective of this study is to identify pharmacologic and non-pharmacologic interventions as applied by physicians, nursing staff, pharmacists and other ED personnel to prevent incident delirium and to shorten the severity and duration of prevalent delirium in a geriatric population within the ED.

Methods and analysis Searches using subject headings and keywords will be conducted from database inception through June 2020 in MEDLINE, EMBASE, Web of Science, PsychINFO, CINAHL, ProQuest Dissertations and Theses Global and Cochrane CENTRAL as well as grey literature. Database searches will not be limited by date or language. Two reviewers will identify studies describing any interventions for delirium prevention and/or treatment in the ED. Disagreements will be settled by a third reviewer. Pooled data analysis will be performed where possible using Review Manager. Risk ratios and weighted difference of means will be used for incidence of delirium and other binary outcomes related to delirium, delirium severity or duration of symptoms, along with 95% CIs. Heterogeneity will be measured by calculating I^2, and a forest plot will be created. If significant heterogeneity is identified, metaregression is planned using OpenMeta to identify possible sources of heterogeneity.

Ethics and dissemination This is a systematic review of previously conducted research; accordingly, it does not constitute human subjects research needing ethics review. This review will be prepared as a manuscript and submitted for publication to a peer-reviewed journal, and the results will be presented at conferences.

PROSPERO trial registration number CRD42020169654.

Strengths and limitations of this study

- This study will utilise three reviewers to analyse articles and resolve discrepancies of data collection.
- Study will be conducted with a well-defined search strategy including a search of unpublished and grey literature.
- Study will search a broad group of databases to identify studies produced by physicians, nurses, pharmacists and other researchers.
- There will be increased heterogeneity due to the large number of interventions included.
- Some outcomes, such as delirium duration, may be assessed differently in each study, limiting the analysis.

INTRODUCTION

Delirium is an acute confusional state characterised by declines in attention, awareness and cognition. Fluctuations of mental status over time are characteristic and necessary for diagnosis.[1 2] Delirium is common in the acute care setting including the emergency department (ED), and is particularly prevalent among adults older than 65 years. As many as 7%–17% of older adults who present to the ED meet diagnostic criteria for delirium.[3–9] ED providers miss delirium in up to 80% of cases.[6] ED delirium is associated with significantly increased in-hospital, 30-day and 6-month mortality, as well as loss of independence,[5 9–11] accelerated cognitive decline and post-traumatic stress disorder which are especially troubling to patients and their families.[11 12] Delirium can be characterised by motor subtypes—namely hypoactive (92%), hyperactive or mixed delirium (8%).[4] Our understanding of delirium prognosis is evolving through a growing body of literature exploring associations between classification of delirium aetiology, motor subtypes and severities of outcomes.[4 13 14]

Interventions aimed at reducing the incidence and severity of delirium have been studied in various settings, but our preliminary searches revealed a paucity of ED research.[15] Multicomponent prevention programmes in hospitalised patients showed a reduction in delirium incidence.[16 17] Several Cochrane reviews have been published since 2012, which reported the utility

of pharmacological agents,[18 19] delirium prevention programmes in hospital setting[16] and long-term care.[20] Thus, both pharmacologic and non-pharmacologic interventions applied by physicians, nursing staff, pharmacists and other ED personnel could have a role in reducing the incidence, severity or duration of delirium in the ED, as reported in the studies from other practice settings including inpatient medical, surgical and palliative care units and long-term care facilities.[16–19 21–24] The ED is a critical setting for delirium screening and preventative measures, since more than half of geriatric hospitalisations begin in the ED.[25]

Clearly identifying, preventing and treating delirium is critical for improved patient care. Recognising the importance of improved delirium evaluation, management and prevention, the American College of Emergency Physicians developed an electronic tool, the ADEPT tool, to help improve care provided of older adults with or at risk of delirium in the ED.[26] ADEPT stands for Assess, Diagnose, Evaluate, Prevent, and Treat, and is used as a checklist to aid in the care of the confused and agitated elderly patient. The purpose of this study is to better understand which delirium prevention or treatment strategies provide the most compelling evidence of effectiveness and feasibility in ED settings.

Objective of systematic review and meta-analysis

This review aims to identify pharmacologic and non-pharmacologic interventions as applied by physicians, nursing staff, pharmacists and other ED personnel to prevent incident delirium and to shorten the severity and duration of prevalent delirium in a geriatric population within the ED.

METHODS AND ANALYSIS

Protocol design and registration

The study is a systematic review and meta-analysis to summarise randomised controlled trials and quasi-experimental studies. The study protocol adheres to the Preferred Reporting Items for Systematic Reviews and Meta-analysis Protocols (PRISMA-P; see online supplemental table 1).[27]

Study characteristics

This review will consider quasi-experimental or randomised controlled trial designs that evaluate the effectiveness of a prevention or treatment intervention(s) for all forms of delirium (ie, hypoactive, hyperactive and mixed subtypes), evaluating incidence and severity of delirium as primary outcomes. This review will exclude studies solely focused on delirium tremens or emergence delirium, but will not exclude studies that include these diagnoses as part of a broader delirium definition. Published studies, studies that are pending publication, and unpublished studies will be included to reduce the bias of selective outcome reporting. Further inclusion and exclusion criteria are listed in table 1.

Types of participants

This systematic review will include studies where participants are aged 65 or older who present initially to the ED and are evaluated for delirium. We will include studies that use subjects under the age of 65 if they also report data on people over age 65.

Types of interventions

Interventions of interest are those aimed at prevention or treatment of delirium. Prevention will be defined as any

Table 1 Eligibility criteria

PICOS strategy	Inclusion criteria	Exclusion criteria
Population	Age 65 or older, initial presentation to the ED	None
Intervention	Multicomponent interventions, single component non-pharmacologic interventions performed by physicians, nursing staff and pharmacists, pharmacologic interventions performed by physicians, nursing staff and pharmacists	None
Comparator	Usual care	None
Outcomes	Primary outcomes: Incidence of delirium (prevention study) Severity of delirium (treatment study) Secondary outcomes (treatment study): Delirium duration In-hospital and long-term mortality, discharge to skilled nursing facility, long-term quality of life, functional status and long-term cognition	Absence of the use of validated delirium assessment tool for delirium diagnosis or severity
Study design	Randomised controlled trials, quasi-experimental studies	None

ADEPT, Assess, Diagnose, Evaluate, Prevent, Treat; DSM, Diagnostic and Statistical Manual of Mental Disorders; GRADE, Grades of Recommendation Assessment, Development and Evaluation; ICD, International Classification of DIsease; PICOS, Population, Intervention, Comparison, Output, Study.

method employed specifically to reduce the incidence of delirium. Treatment will be defined as any treatments aiming to reduce the severity or duration of diagnosed delirium. Both single-component and multicomponent non-pharmacologic interventions will be considered for this systematic review. All pharmacologic interventions such as typical and atypical antipsychotics, benzodiazepines, alpha-2 agonists, sedatives, opioids, cholinesterase inhibitors, melatonin and melatonin receptor agonists will be considered for inclusion. Single-component and multicomponent non-pharmacologic interventions as well as pharmacologic interventions will be included if performed by a physician, nurse, pharmacist or other ED staff.

Types of outcome measures

For all outcome measures, delirium should be defined and assessed in triage, ED or inpatient by a validated or acceptable diagnostic tool for delirium reported in the peer-reviewed journal, including Single Question to Identify Delirium, Ultrabrief two-item Bedside Test, Delirium Triage Screen, 4AT, brief Confusion Assessment Method, applicable diagnostic tools listed on the Delirium Severity Measures Summary Table developed by the Network for Investigation of Deliurium: Unifying Scientists (NIDUS), ICD 10 criteria and DSM IV/V diagnosis.[28 29] Delirium severity will be measured initially in triage or the ED using any of the existing tools defined in the Delirium Severity Measures Summary Table developed by NIDUS, or as defined in the specific study.[29] The primary outcomes will be incidence of delirium for any prevention study and severity of delirium for any treatment study.

Secondary outcomes for any treatment study will include delirium duration. Duration will be defined using each study's respective definition of duration, and or measured as first instance of multiple consecutive positive tests until time of first instance of multiple consecutive negative tests for studies that include such data. We will also include all-cause mortality, in-hospital mortality, level of care, discharge to skilled care facility, any type of fall, quality of life and long-term cognitive impairment. In-hospital mortality will be defined as any death while in the ED or during the initial admission. Level of care will be defined categorically as discharge to home, admission to a step-down unit, or admission to an intensive care unit. Discharge to a skilled care facility will be assessed as new placement in a skilled nursing home immediately following the initial ED visit and primary hospital admission, but not including home health nursing. Long-term quality of life, functional status, and long-term cognition will be included as a secondary outcome if assessed using a validated, non-disease specific tool (such as the Activities of Daily Living Questionnaire).

Types of studies

Both randomised controlled trials and quasi-experimental studies will be included.

Timing

We will use timing parameters that extend throughout the hospital stay and up to a 180-day follow-up.

Setting

This review will be restricted to studies where initial delirium assessment starts in the ED or in triage and subsequent intervention(s) starts in triage, the ED or inpatient wards. This is because more than 50% of older adults who required hospitalisation are admitted through the ED, and effective screening, treatment and delirium prevention programme can have a significant impact on the remainder of their hospital stay.[25]

Information sources

Strategies for searching the literature will be developed to locate studies relating to the concepts; delirium, ED, interventions and the geriatric population. The strategies will use subject headings and keywords. A librarian (HH) will conduct searches in MEDLINE (Ovid), EMBASE (Elsevier), Web of Science, PsycINFO (EBSCOhost), CINAHL, ProQuest Dissertations and Theses Global and Cochrane CENTRAL (Wiley). The search strategies will not be limited by language. Each database will be searched from database inception through June 2020. The team will supplement the electronic database searches by looking for trial protocols and ongoing studies through ClinicalTrials.gov and PROSPERO. Additional unpublished sources and conference abstracts will be sought out directly from conference proceedings and primary authors. For each included article, the reference list will be searched for additional relevant studies.

Search strategy

The specific search strategies for each database will be developed by a health sciences librarian (HH) trained in systematic review searching. The team will provide input on the terminology for the strategies, and the strategies will be peer reviewed, using the PRESS guideline, by another health sciences librarian.[30] A draft PubMed search strategy follows in online supplemental file.

Clinicaltrials.gov and PROSPERO will be searched for incomplete or recently completed studies. As the paucity of literature exists in the prevention and intervention of delirium in the ED, we will identify any preliminary or unpublished study through the content experts (JHH, MK, GA and JL).

Data management

Database search results will be transferred to EndNote and deduplicated using the published methodology for deduplication as laid out by Bramer, Giustini and de Jonge.[31] Citations will be stored and sorted using Endnote. Data will be compiled and meta-analysed using Review Manager (RevMan, V.5.3; The Nordic Cochrane Centre, The Cochrane Collaboration). OpenMeta (Analyst) (Center for Evidence-Based Medicine, Brown School of Public Health) will be used for regression with continuous covariates.

Selection process

This review will follow the PRISMA standards for reporting a systematic review and meta-analysis.[27] Studies identified via the search strategy and other methods will undergo an initial review by two independent reviewers who will review the title and abstract to determine whether the study meets the defined inclusion criteria. Studies where there is disagreement between the reviewers will be included in the secondary review.

Selected studies will subsequently be subjected to full-text review, again with two independent reviewers utilising inclusion and exclusion criteria. A third reviewer will settle disagreements. We will report the kappa to measure inter-rater reliability. This analysis will be documented in a PRISMA flow diagram, and the process will result in a final list of included articles.

Data collection

Reviewers will use a standardised data collection form to gather desired information (see online supplemental table 2). The form will be developed following the style outlined by 'Data collection form for intervention review—RCTs and non-RCTs' from the Cochrane Collaboration.[32] Data collection will be done independently. Calibration exercises will be used prior to conducting the review to ensure that each reviewer is consistent with their data collection. A third reviewer will check for discrepancies between data sheets for each given article and settle any disagreements. We will reach out to original study authors for details or data if any uncertainties arise.

Data items

We will collect data on the year of publication, study design, method of evaluating for delirium or delirium severity, and interventions for delirium prevention and/or treatment. We will extract data on outcomes, including incidence of delirium, duration of delirium, delirium severity, mortality (30-day and in-hospital), new admission to a skilled nursing facility after ED visit, admission to an intensive care unit, quality of life and persistent cognitive deficits for intervention and control groups.

Risk of bias assessment

The study will use the Cochrane risk of bias assessment tool for randomised clinical trials and New-Castle-Ottawa scale for quasi-experimental studies for quality assessments.[33–35] Direct quotes from each study will be used for all subsections of the tool in order to assess the risk of bias. Two independent reviewers will assess risk of bias, and the third reviewer will settle any discrepancy. We will report kappa to report the inter-rater agreement. The quality of evidence for an association between treatment, prevention and delirium-related outcomes will be evaluated in accordance with the GRADE system.[36] This system grades quality of evidence at four levels: high (4), moderate (3), low (2) and very low (1). For high evidence, the requirements are a randomised, double-blinded study design with no selection biases. We will assess publication bias using funnel plots.

Data synthesis

If the studies, or an adequate subset of the studies in the review have sufficiently homogeneous outcomes data, meta-analysis will be conducted. Data associated with primary and secondary outcomes will be analysed in aggregate. For dichotomous data, risk ratios will be calculated with 95% CIs. A weighted difference of means will be used for continuous data with 95% CIs. Heterogeneity will be assessed using demographic features (age, sex) as well as study design factors (such as treatment type), and an I^2 value will be calculated. A value of less than 50% will be considered sufficiently homogeneous.[37] Forest plots will be created using this data. Individual outcomes will be combined and calculated using RevMan V.5.3.[38]

Subgroup analysis

Subgroup analysis will be conducted based on type of intervention (pharmacologic and non-pharmacologic), delirium motor subtype (hyperactive, hypoactive, mixed), delirium severity, presumed delirium aetiology (phenotype) and whether incident or prevalent delirium was studied. Possible sources of heterogeneity tested includes age, antipsychotics, delirium subtype and study year. A linear meta-regression model weighted to reflect the variance of the individual studies will be used to model the data.

Patient and public involvement

Patients and the public were not directly involved in the development of the research question or the design of the study, however many of the outcome measures (including quality of life, level of care and functional status) were chosen specifically to study the impact of delirium prevention and treatment measures on the patient experience. This study was conducted without direct patient involvement and patients were not involved in patient recruitment or conduction of the study.

Amendments

Amendments to this protocol, particularly database searches, will be documented in PROSPERO.

ETHICS AND DISSEMINATION

There will be no human subject participants involved in this review. The results of this review will be submitted for publication to a peer-reviewed journal. Other dissemination may include presentations at conferences and seminars.

DISCUSSION

Delirium is common and serious geriatric syndrome for which prevention and treatment best practices have not been established in the ED setting.[39] One of the strengths of this study is that it will compile the relevant evidence for delirium prevention and intervention within the ED setting to identify any effective strategy. Another strength

Table 2 A list of Cochrane reviews examining delirium intervention since 2012

Study author/year	Main intervention	Setting*
Woodhouse *et al* (2019)[20]	Software-based identification of high-risk medication	Long-term care
Burry *et al* (2018)[40]	Antipsychotic agent	Non-ICU inpatient ward
Herling *et al* (2018)[41]	Delirium prevention study (pharmacological)	ICU
Yu *et al* (2018)[19]	Cholinesterase inhibitor	Non-ICU inpatient ward
Punjasawadwong *et al* (2018)[42]	Electroencephalogram	Perioperative
Siddiqi *et al* (2016)[16]	Delirium prevention study (pharmacological and non-pharmacological treatment)	Mixed setting (none ED)
Candy *et al* (2012)[18]	Pharmacological therapy	Delirium with AIDS in the palliative care

*We were unable to identify any review in the ED.
ED, emergency department; ICU, intensive care unit.

of this study is that it will be conducted using a well-defined search strategy. We will consult transdisciplinary delirium for grey literature, unpublished works and ongoing studies to minimise the risk of bias of selective outcome reporting.

The review will explore a new insight to prevention and treatment options to employ in the ED, which have become the main entrance for the majority of older adults to the hospital. The clinical care delivered in the ED influences downstream clinical care and therefore, may have a significant impact on outcomes. We are aware of a total of seven Cochrane reviews published since 2012 that examine the various delirium prevention and treatment interventions in varied clinical settings (table 2).[16 18–20 40–42]

One Cochrane review examined the effect of antipsychotic agents for delirium treatment in non-ICU hospitalised patients and found no impact on delirium severity or duration.[40] Due to limited research in the palliative care setting, evidence was deemed insufficient to assess the impact of pharmacologic therapies for the treatment of delirium in terminally ill patients.[18] Similarly, the data were deemed insufficient to evaluate the effect of cholinesterase inhibitors in the treatment of delirium in the non-ICU hospital setting. A review evaluating prevention strategies in long-term care settings found limited evidence on interventions for preventing delirium, but a software-based intervention to identify high-risk medications and a pharmacist-led medication review reduced the incidence of delirium.[20] There is strong evidence that a multicomponent delirium prevention programme reduces the incidence of delirium in the non-ICU hospital setting. Despite the ample number of systematic reviews, it is important to note that none of these focused on delirium interventions in the ED (table 2).

Our study protocol may have limitations, including increased heterogeneity due to the large number of different interventions being included. There may also be limitations to the statistical power of our findings depending on the quantity of literature in this setting. Although we set a comprehensive list of outcomes, it may not be possible to find any studies that list them, for example, quality of life.

The importance of delirium prevention and management in the ED setting is underscored by the inclusion of delirium recognition and management as a best practice in the Geriatric ED Guidelines,[43] a quality indicator for geriatric emergency care,[44] a core competency for emergency medicine residents[45] as well as by the recent dissemination of the ADEPT tool.[26] Although guidelines and core competencies reflect the expert consensus-based best practices in EM, high-quality research evidence to support ED delirium prevention and intervention approaches have been lacking. This review will address a critical need to synthesise research into delirium prevention and management in the ED setting to further improve the care of older ED patients with or at risk for delirium and create a roadmap for future researchers.[46 47]

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Contributors EBD is the first and SL is the corresponding author; EBD, CC and SL conceived and designed the study; HH designed the draft search strategy; SL, MK, JHH, JL, GA will acquire data; SL will analyse and interpret data; EBD and SL drafted the initial and final protocol; MK, JHH, JL, GA, CC, HH and SL performed critical revisions of the protocol. All authors approved the final version of the protocol.

Funding This study was supported by the departmental seed funding by the Department of Emergency Medicine at the University of Iowa Hospitals and Clinics. The protocol was not influenced by the funding source. Award/Grant number is not applicable.

Competing interests CC: conflicts include SAEM Board of Directors, Geriatric Emergency Care Applied Research Network investigator leading cognitive impairment core, Clinician-Scientists Transdisciplinary Aging Research Leadership Core, Academic Emergency Medicine Deputy Editor-in-Chief, Journal of the American Geriatrics Society Associate Editor, Schwartz-Reisman Emergency Medicine Institute International Advisory Board Chair, and American Board of Emergency Medicine MyEMCert Editor.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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