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Does pain optimisation impact delirium outcomes in critically ill patients? A systematic review and meta-analysis protocol

Amanda Y. Leong ,[1,2,3] Lisa Burry,[4,5] Kirsten M. Fiest,[1,2,6] Christopher J. Doig ,[1,2,6] Daniel J. Niven[1,2,6]

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For numbered affiliations see end of article.

Correspondence to
Dr Daniel J. Niven;
daniel.niven@albertahealthservices.ca

ABSTRACT

Background Untreated pain is associated with short-term and long-term consequences, including post-traumatic stress disorder and insomnia. Side effects of some analgesic medications include dysphoria, hallucinations and delirium. Therefore, both untreated pain and analgesic medications may be risk factors for delirium. Delirium is associated with longer length of stay or cognitive impairment. Our systematic review and meta-analysis will examine the relationship between pain or analgesic medications with delirium occurrence, duration and severity among critically ill adults.

Methods and analysis MEDLINE, EMBASE, CINAHL, the Cochrane Central Register of controlled trials and a review of recent conference abstracts will be searched without restriction from inception to 15 May 2023. Study inclusion criteria are: (1) age≥18 years admitted to intensive care; (2) report a measure of pain, analgesic medications and delirium; (3) study design—randomised controlled trial, quasiexperimental designs and observational cohort and case–control studies excluding case reports. Study exclusion criteria are: (1) alcohol withdrawal delirium or delirium tremens; or (2) general anaesthetic emergence delirium; or (3) lab or animal studies. Risk of bias will be assessed with the Risk of Bias V.2 and risk of bias in non-randomised studies tools. There is no language restriction. Occurrence estimates will be transformed using the Freeman-Tukey double arcsine. Point estimates will be pooled using Hartung-Knapp Sidik-Jonkman random effects meta-analysis to estimate a pooled risk ratio. Statistical heterogeneity will be estimated with the I^2 statistic. Risk of small study effects will be assessed using funnel plots and Egger test. Studies will be analysed for time-varying and unmeasured confounding using E values.

Ethics and dissemination Ethical approval is not required as this is an analysis of published aggregated data. We will share our findings at conferences and in peer-reviewed journals.

PROSPERO registration number The finalised protocol was submitted to the International Prospective Register of Systematic Reviews (PROSPERO ID: CRD42022367715).

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study will employ rigorous design in accordance with published systematic review and meta-analytic methodologic guidelines.
⇒ There exists significant variability in the tools used to measure and report pain severity and delirium, in which the inherent differences in sensitivity and specificity will impact the clinical and statistical heterogeneity of pooled measures of association in a meta-analysis.
⇒ Study definitions for incident and prevalent delirium are not always consistent with strict epidemiologic principles. This study will pool incident or prevalent delirium into a single measure reporting delirium occurrence.

INTRODUCTION

Pain is experienced in 80% of intensive care unit (ICU) patients.[1] Suboptimally treated pain has short-term and long-term consequences. In the short-term, the stress response results in fluid retention, hypertension and impaired wound healing.[2] Long-term consequences of uncontrolled pain include post-traumatic stress disorder, anxiety, depression and insomnia.[2] Analgesic medications used to treat pain may have significant side effects. Medications commonly used to treat pain in the ICU include non-opioid analgesics such as acetaminophen or ketamine. Ketamine is associated with adverse events including tachycardia, hypertension, cerebral ischaemia, hallucinations and delirium.[3] Opioid analgesics are associated with reduced respiratory drive, sedation, dysphoria and hallucinations.[3] Pain is commonly considered to be a risk factor for delirium; however, the evidence that underpins this belief is limited.[1 4]

Delirium, characterised by an acute state of fluctuating confusion, attention deficit and behavioural disorganisation, is a common syndrome in critically ill patients.[5] Delirium is experienced in up to 45% of ICU patients and is associated with longer ICU lengths of stay, mechanical ventilation and cognitive

impairment.[1 5–7] Symptoms of delirium are primarily treated with a multimodal approach, often inclusive of analgesia.

There is conflicting evidence on the relationship between pain and the development of delirium. The postulated biologic mechanisms relating to pain and delirium are numerous, and include glucocorticoid surge associated with neuronal vulnerability via apoptosis and neuronal damage resulting from breakdown in the blood–brain barrier.[8] When both pain and delirium are present, studies demonstrate elevation in interleukins 8–10 and tumour necrosis factor-α, and a reduction in acetylcholine.[9 10] Duprey *et al* conducted a retrospective cohort study to evaluate the relationship between opioid use and delirium among critically ill patients.[11] Among 4075 critically ill patients, moderate, severe and peak pain were associated with lower odds of transition to delirium.[11] A Canadian prospective cohort study among 820 patients admitted to a medical–surgical ICU examined the risk factors and outcomes associated with delirium.[12] Pain scores per the numeric rating scale were small but significantly higher by 0.49 points in those with delirium than those without delirium (OR 0.87, 95% CI 0.80 to 0.97).[12] Collating current evidence may help to identify whether it is the presence of pain or its severity that contributes to the development of delirium.

Similarly, the evidence on the relationship between opioid or ketamine exposure and transition to delirium is conflicting. In delirium states, high and low levels of dopamine may be associated with delirium, resulting in a U-shaped association.[9] In response to acute pain, dopamine concentrations increase, and administration of opioids for pain relief acts as a positive salient stimulus, further increasing dopamine release.[13] Both longer exposure to opioids and chronic pain impair dopamine signalling, which may contribute to the development of delirium.[13] Ketamine reduces acetylcholine, increases dopamine and N-methyl-D-aspartic acid and may be associated with neuronal vulnerability via apoptosis, which may contribute to the development of delirium.[14 15] Duprey *et al* reported the odds of delirium increased for every 10 mg of morphine per day (OR 1.09, 95% CI 1.04 to 1.13) and log transformed 10 mg morphine-equivalent dose increase of synthetic opioids (OR 1.77, 95% CI 1.33 to 2.35) compared with those without opioid exposure.[11] Pandharipande *et al* identified that the opioid molecule may play a factor in the development of delirium.[16] In multivariable analysis, surgical patients had higher odds of developing delirium when exposed to the synthetic opioid fentanyl (OR 3.99, 95% CI 1.47 to 10.85), whereas trauma patients had lower odds of delirium when exposed to morphine (OR 0.22, 95% CI 0.06 to 0.82).[16] Perbet *et al* performed a randomised, parallel group, placebo-controlled, double-blind trial comparing low-dose (0.2 mg/kg/h) ketamine to placebo. They reported a higher incidence of delirium in ICU patients randomised to the placebo arm compared with ketamine (37% vs 21%, p=0.03).[17] In contrast, a secondary post hoc subgroup analysis of a cohort study identified that ketamine exposure was associated with a higher odds of delirium occurrence (adjusted OR 5.56, 95% CI 1.09 to 28.65).[18] A synthesis of current evidence may help elucidate the independent effect of opioids for the development of delirium. Our systematic review with meta-analysis will examine the relationship between pain or analgesic medications with delirium occurrence, duration and severity among critically ill adults.

METHODS AND ANALYSIS

The protocol was submitted to the International Prospective Register of Systematic Reviews (PROSPERO ID: CRD42022367715). This systematic review and meta-analysis protocol is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Protocols guidelines.[19] Amendments to the protocol will be depicted and dated in the PROSPERO record.

Definitions for exposure

Pain will be categorised per previous research as no clinically significant pain (Numeric Rating Scale 0–4, behavioural pain scale 3–4 or critical Care Pain Observation Tool (CPOT) 0–2), moderate pain (Numeric Rating Scale 5–6, Behavioural Pain Scale 5–7 or CPOT 3–4) or severe pain (Numeric Rating Scale≥7, Behavioural Pain Scale≥8 or CPOT≥5).[1 20] Opioid medication doses will be converted to morphine equivalents (MEQ) per Centres for Disease Control and Prevention (CDC) guidelines[21] and McPherson[22] (table 1).

Definitions for outcome

Delirium presence or absence is defined as Richmond Agitation Sedation Scale (RASS) −3 or higher and one of Intensive Care Delirium Screening Checklist (ICDSC)≥4 out of 8, or confusion assessment method in the ICU (CAM-ICU) with acute change in mental status (feature 1), and inattention (feature 2), and one of disorganised thinking (feature 3) or altered level of consciousness (feature 4).[16 23] Other tools that are validated in critically ill patients for the diagnosis of delirium will also be accepted, including: variations of the CAM-ICU (such as CAM-ICU-7 or CAM-Severity) the delirium detection score, cognitive test for delirium, abbreviated cognitive test for delirium and Neelon and Champagne Confusion Scale.[24 25]

Delirium severity is defined per the rating tool that is used; for ICDSC, delirium is absent (ICDSC: 0), subsyndromal (ICDSC 1–3) or present (ICDSC 4–8)[26]; for CAM-ICU-7, delirium is absent (CAM-ICU-7: 0–2), mild to moderate (CAM-ICU-7: 3–5) or severe (CAM-ICU-7: 6–7)[26]; for CAM-Severity, higher scores indicate more severe delirium (short form is scored out of 7, and long form is scored out of 19); for the Delirium Rating Scale Revised-98 (scored out of 36), higher scores indicate more severe delirium; for the Memorial Delirium Assessment Scale (scored out of 30), scores over 13 indicate

Table 1 Opioid conversion to morphine equivalents

Opioid	Parenteral equianalgesic conversion (to intravenous morphine equivalent)	Oral equianalgesic conversion (to intravenous morphine equivalent)
Morphine	Multiply by 1	Multiply by 0.4
Codeine	Multiply by 0.1	Multiply by 0.05
Fentanyl	Multiply by 100	n/a
Hydrocodone	n/a	Multiply by 0.4
Hydromorphone	Multiply by 5	Multiply by 2
Meperidine	Multiply by 0.1	Multiply by 0.03
Oxycodone	Multiply by 1	Multiply by 0.5
Oxymorphone	Multiply by 10	Multiply by 1
Tapentadol	n/a	Multiply by 0.1
Methadone	Methadone intravenous to morphine intravenous	Methadone oral to morphine intravenous
	1–7.4 mg/day: Multiply by 4	1–14.9 mg/day: Multiply by 2
	7.5–15 mg/day: Multiply by 8	15–30 mg/day: Multiply by 4
	> 15 mg/day: Multiply by 12	>30 mg/day: Multiply by 6

delirium is present and higher scores indicate more severe delirium. For studies reporting delirium severity using the Delirium Rating Scale the Memorial Delirium Assessment Scale or the CAM-Severity, these scores have been harmonised and will be presented as CAM-Severity.[27]

Delirium occurrence is defined as all delirium cases (numerator) over the study population, as persons (denominator).

Time frame

From database inception to 15 May 2023.

Search strategy

The initial search strategy will be created with medical librarian assistance and peer reviewed using the Peer Review of Electronic Search Strategies (PRESS) checklist with a second medical librarian. The following databases will be searched by the study authors: Ovid MEDLINE, Ovid EMBASE, Ebsco Cumulative Index to Nursing and Allied Health Literature, Ovid Cochrane Central Register of Controlled Trials and a manual search of bibliographies from included articles. There will be no restriction on language, relevant date or country of publication. Where the same cohort of subjects is reported in multiple publications, only unique findings will be presented grouped together such that data included in the final analysis will only be reported from one source.

There will be four search themes: (1) critical care, (2) delirium, (3) pain and (4) pain medications. Medical subject headers for each theme will be exploded, some of which will include 'Critical Care', 'Intensive Care Units', 'Analgesics', 'Opiate Alkaloids', 'Acetaminophen', 'Anti-Inflammatory Agents, Non-Steroidal', 'Pain', 'Delirium'. Author keyword and text phrases will be searched for related key phrases such as 'ICU', 'SICU', 'opiate*', 'acet?minophen*', 'paracetamol', 'NSAID*', 'visual analog* scale*', 'deliri*' or 'acute confusion*'. For medications, the medical subject heading entry terms will be used to generate author keyword and text phrase searches. The search terms under each theme will be combined with the Boolean operator, 'OR'. The pain and pain medication themes will be combined with the Boolean operator 'OR', then, the themes of (1) critical care, (2) pain OR pain medications and (3) delirium, will be combined with the Boolean operator, 'OR'. The proposed search strategy is found in online supplemental appendix A.

Authors will perform a hand search of five major critical care and delirium conference abstracts from 2020 to present: Society of Critical Care Medicine Annual Congress, American Thoracic Society International Conference, European Society of Intensive Medicine Annual Congress, the Canadian Critical Care Forum and the American Delirium Society Annual Conference. The timeline selected for conference abstract review was chosen after review of the reference list of the key study on pain and delirium in the ICU, Duprey *et al* and the most recently cited paper in their reference list was from 2020.[11] The proposed hand search strategy for conference abstracts is found in online supplemental appendix A.

Study selection process

Covidence (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org) will be used to screen titles and abstracts. Endnote will be used to maintain a repository of all screened studies and included studies and for full-text review of articles. Screening of titles, abstracts and full-text studies will be conducted independently and in duplicate by two investigators. At the title and abstract screening stage, if either reviewer deems a citation as potentially relevant, the study will proceed to the full-text review stage. Prior to the full-text review stage, the eligibility criteria will be pilot tested, with an interobserver reliability cut-off of at least κ=0.8. At the full-text review stage, disagreements will be resolved by discussion among the two reviewers, and if that fails, a third reviewer will resolve the disagreement. For studies not written in English, Google Translate will be used.[28] If the article is not comprehensible using this tool, a person fluent in the language will be used to translate the article. A PRISMA flowchart will be used to document steps in citation screening and final study inclusion. Table 2 outlines the inclusion and exclusion criteria.

Table 2 Inclusion and exclusion criteria

Inclusion	Exclusion
Randomised controlled trial, non-randomised quasiexperimental, cohort, case–control or secondary analyses of these designs	Non-original research (including review articles, editorials, commentaries), case reports or series
Adults (≥18 years)	Animal or laboratory studies
Admitted to an ICU of any type	Studies that only report alcohol withdrawal delirium, substance withdrawal delirium, delirium tremens or emergence delirium
Able to extract data on reports of pain or exposure to analgesics while admitted to ICU	Non-pharmacologic methods as primary method of pain management
Reports delirium incidence, prevalence or severity	

ICU, intensive care unit.

Data extraction

A data extraction tool will be created using Microsoft Excel for Microsoft 365 MSO V.2201 (Microsoft, Redmond, USA). Data will be extracted independently and in duplicate using this form. Missing or unreported data will be resolved by contacting the corresponding authors of the studies. Variables that will be extracted include: study year, date of publication, ICU type (ie, surgical, medical, trauma, mixed), admission diagnosis (eg, sepsis, pneumonia, trauma, etc), country, inclusion and exclusion criteria, number of patients (per arm), definition of pain optimisation and delirium, age (mean±SD), Acute Physiology and Chronic Health Evaluation Score (mean±SD), Sequential Organ Failure Assessment Score (mean±SD), Simplified Acute Physiology Score II Score (mean±SD), proportion female sex, opioids (drug, class, dose), non-opioid analgesics (drug, class, dose), pain scores (eg, CPOT, Numeric Rating Scale), delirium scores (eg, ICDSC, CAM-ICU), delirium duration and RASS scores. Specific pharmacologic covariates will be collected, including the presence or absence of benzodiazepines, steroids, antipsychotics and anticholinergics. If studies cannot be translated into English, these studies will be classified as 'awaiting classification', but will not be analysed in the current review.[29]

Risk-of-bias assessment

The quality of all included studies will be assessed with the Cochrane Collaborative Risk of Bias V.2 (ROB V.2) assessment tool for randomised controlled trials (ROB V.2 Tool from www.riskofbias.info), or Risk of Bias in Non-randomised Studies of Interventions (ROBINS-I) tool for cohort studies (ROBINS-I Tool from www.prisma-statement.org).[30–32] Risk of bias will be assessed independently by two investigators, with discrepancies resolved by discussion, and if that fails, a third researcher.

Certainty of bias assessment

Certainty of bias for will be assessed using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) framework for the primary outcomes,[33] which include: (1) odds of developing delirium with the presence or absence of pain; (2) odds of developing delirium with the presence of opioids; (3) odds of developing delirium with the presence of non-opioid analgesics. GRADE will only be performed if we are able to perform a meta-analysis of these outcomes.

Statistical analysis

For dichotomous outcomes, Hartung-Knapp-Sidik-Jonkmann random effects meta-analysis model with an inverse variance method will be used to estimate the pooled risk ratio and 95% CI for developing delirium. For measured outcomes, a random effects meta-analysis model using an inverse variance method will be conducted to estimate the standardised mean difference and 95% CI. Data on prevalence or incidence will be transformed using the Freeman-Tukey double arcsine prior to pooling using a random effects meta-analysis model. Online supplemental appendix A outlines the prespecified order in which outcomes will be analysed. Briefly, our primary analysis will focus on examining: (1) the association between delirium and pain (presence vs absence); (2) the association between delirium and opioids (presence vs absence) where opioids will be presented on aggregate as MEQ and (3) the association between delirium and non-opioid analgesics (presence vs absence) where non-opioids will be presented as an aggregate group.

Statistical heterogeneity will be estimated with the I^2 statistic. An I^2 less than 25% will be considered no heterogeneity, 25%–50% as low heterogeneity, 51%–75% as moderate heterogeneity and greater than 75% as high heterogeneity.[31] Publication bias will also be assessed visually using funnel plots and quantitatively using the Egger test.[34] We will identify which studies perform time-varying analyses. The E value for the point estimates of pain and delirium, or analgesics and delirium, will be calculated. The E value represents the minimum strength of association that an unmeasured confounder would need to have conditional on measured covariates, to fully explain away an association, in this case a relative risk.[35] Point estimates presented as hazard ratios or ORs will be converted to relative risk before calculating an E value.[35] All analyses will be performed using RStudio.

Analysis of subgroups

Pending availability of data, subgroups analyses will be used to explore sources of statistical and/or clinical heterogeneity. Sources of heterogeneity are anticipated to include differences among: patient diagnostic classification (medical vs surgical); methods for reporting pain (CPOT, Numeric Rating Scale, etc); opioid classification;

non-opioid classification; delirium assessment tools (ICDSC, CAM-ICU, etc); and GRADE class (low vs high risk of bias). Opioid subgroups will be developed on the basis of either: (1) chemical class, separating by phenylpiperidines (meperidine, fentanyl, sufentanil, alfentanil), phenanthrenes (codeine, hydromorphone, levorphanol, morphine, oxycodone, hydrocodone, pentazocine), phenylheptanes (methadone, propoxyphene), morphinan (levorphanol) and other (tramadol); or (2) alkaloid (morphine, codeine), semisynthetic (hydrocodone, hydromorphone, oxycodone, oxymorphone) and synthetic (levorphanol, meperidine, fentanyl, sufentanil, alfentanil, methadone, propoxyphene). Non-opioids will be divided according to class as: (1) acetaminophen; (2) non-steroidal anti-inflammatory drugs; (3) gabapentinoids; (4) ketamine; (5) lidocaine; (6) dexmedetomidine; (7) serotonin norepinephrine reuptake inhibitors and (8) amitriptyline.

Expected outcomes

The relationship between pain, analgesics and delirium will be described as follows:

Primary outcome:

1. Presence of ever/never pain with the occurrence of ever/never delirium.
2. Presence of opioid or non-opioid analgesic medications on delirium occurrence.

Secondary outcomes:

1. Presence of pain with delirium severity or duration.
2. Severity of pain with delirium occurrence, severity or duration.
3. Presence of non-opioid analgesics with delirium occurrence, severity or duration.
4. Presence of opioid analgesics with delirium occurrence, severity or duration.
5. Presence of pain and opioid or non-opioid analgesics with delirium occurrence, severity or duration.

Patient and public involvement

Patients were not involved in development of the methods for this systematic review and meta-analysis.

Ethics and dissemination

As this systematic review and meta-analysis will be performed on published studies containing aggregated data and relies on information that is in the public domain, ethics will not be sought for this study. We intend to disseminate our findings at critical care and delirium conferences worldwide. We will publish our findings in a peer-reviewed journal.

DISCUSSION

Our study aims to summarise available evidence on the effects of pain and analgesics on delirium among critically ill adults. Despite the inclusion of pain management as a key pillar in multimodal delirium management,[1] it remains unclear whether pain is a risk factor for delirium occurrence. Both delirium and pain have significant short-term and long-term consequences. Currently, there is no definitive pharmacologic treatment for delirium. Thus, the focus of delirium management is frequently on prevention. There may exist an optimal approach to pain management that reduces the risk of delirium development; however, this is not defined within current evidence. A key step towards improving delirium management is therefore a more complete understanding of two common, potentially modifiable risk factors such as pain and analgesic medications. Our systematic review with meta-analysis will employ rigorous methodology to review contemporary literature examining the effects of pain and/or analgesics on delirium among adult patients admitted to ICU.

This study has important strengths and limitations. We will apply rigorous methods that include a comprehensive, peer-reviewed search strategy including a hand search of recent conference abstracts. Each step of the review, from abstract screening to risk of bias assessment, will be completed in duplicate. Our review will also explore the impact of unmeasured confounding on calculated point estimates by calculating E values.

Strengths and limitations

Our study has three main limitations. First, the measures of pain and delirium reported in critical care literature are highly heterogenous, and not all scores have been harmonised into a single representative score. This introduces clinical and statistical heterogeneity in the identification of pain and delirium among studies, which will impact reported point estimates, and subsequently impact reported pooled estimates in a meta-analysis. We will attempt to address this heterogeneity by stratifying analyses of pain and delirium by the type of pain scoring tool used. Second, reported delirium occurrence is used in this meta-analysis due to the variability in reporting incident or prevalent delirium. Study definitions for incident and prevalent delirium are not always consistent with strict epidemiologic principles; further, not all critical care studies robustly exclude those with prevalent delirium from their cohort, especially if delirium is not consistently measured in patients transferred from hospital wards into the ICU. As such, we have pooled incident or prevalent delirium into a measure reporting delirium occurrence to allow us to collate findings across studies. Third, it is unlikely that we will be able to disentangle the extracted data to model analgesic medications as a mediator to the pain (exposure) and delirium (outcome) relationship.

Our review will present contemporary, high-quality evidence on the effects of pain and analgesics on the outcome of delirium in critically ill adults. This study forms the basis of a programme of research that will examine the effects of pain and analgesic medications on delirium in critically ill patients.

Author affiliations
[1]Department of Critical Care Medicine, University of Calgary Cumming School of Medicine, Calgary, Alberta, Canada
[2]Department of Community Health Sciences, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada
[3]Department of Pharmacy Services, Alberta Health Services, Calgary, Alberta, Canada
[4]Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Ontario, Canada
[5]Lunenfeld-Tanebaum Research Institute and Departments of Pharmacy and Medicine, Mount Sinai Hospital, Sinai Health, Toronto, Ontario, Canada
[6]O'Brien Institute for Public Health, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada

Twitter Amanda Y. Leong @ondanceatron

Contributors AL: Conception and design of the work, drafting the work and revising for critically important intellectual content, final approval of the version to be published, agree to be accountable for all aspects of the work. KF, LB and CJD: Conception and design of the work; drafting the work and revising for critically important intellectual content. DN: Conception and design of the work, drafting the work and revising for critically important intellectual content, final approval of the version to be published, agree to be accountable for all aspects of the work.

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ORCID iDs
Amanda Y. Leong http://orcid.org/0000-0002-2593-7911
Christopher J. Doig http://orcid.org/0000-0002-8576-9139

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