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Pharmacological interventions for the treatment of delirium in critically ill patients

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

Our primary objective is to assess the effects of pharmacological interventions on the duration of delirium in critically ill patients with confirmed or documented high risk of delirium.

Our secondary objectives are to assess: 1) the effects of pharmacological interventions on delirium-free and coma-free days, relapse, duration of mechanical ventilation, ICU and hospital length of stay, mortality, long-term outcomes (e.g. cognitive, discharge disposition, health-related quality of life); and 2) the safety of such delirium treatments in critically ill patients.

BACKGROUND

Description of the condition

Delirium is an acute brain dysfunction characterized by inattention, fluctuating mental status, altered level of consciousness, and

disorganized thinking (APA 2013). It is a non-specific but reversible manifestation of acute illness, and as such, is commonly associated with surgery, infection, or critical illness (Inouye 2014). Delirium is reported in 40% to 60% of non-ventilated, and 60% to 89% of mechanically ventilated patients in the intensive care unit (ICU) (Ely 2001a; Ely 2001b; Ely 2007; Hipp 2012; Inouye 2014). Delirium is challenging to detect as symptoms are highly

variable with either hyper- or hypoactivity, or a mixed picture, and symptoms fluctuate with periods of lucidness (Inouye 2014). The gold standard tool for detection is psychiatric assessment with the Diagnostic and Statistical Manual (DSM) (APA 2013). Several validated tools exist (Bergeron 2001; Ely 2001a; Neelon 1996), however their utility is predicated on the patient being awake and able to communicate. Additionally, sedatives and opioids impair level of consciousness and may make identification of delirium challenging (Patel 2014). Thus, previous drug exposure should be considered when assessing for delirium, and if possible, assessments should be co-ordinated with periods of drug interruption (Patel 2014).

We now have a greater understanding of the effects of delirium on patients, their families, and the healthcare system. Clinically important outcomes impacted by delirium in critically ill patients include increased mortality, prolonged durations of mechanical ventilation, ICU and hospital stay, long-term cognitive impairment, and increased likelihood of transfer to chronic care facilities (Black 2011; Ely 2001b; Ely 2004; Girard 2010b; Jackson 2004; Lin 2004; Milbrant 2004; Pisani 2009; Van den Boogaard 2012). The odds of a poor outcome with delirium are also increased by patient frailty (Andrew 2006; Inouye 2006), and factors such as advanced age (> 75 years), cognitive and functional impairments, comorbid illness, and visual and hearing impairments are considered predisposing risk factors in its development (Inouye 2006). Precipitating factors are also numerous and include, among others, medications (e.g. sedatives, anticholinergic agents), neurologic disease, environmental insults (e.g. physical restraint use, catheters, emotional distress, pain), and prolonged sleep deprivation (Inouye 2006; Zaal 2015).

Description of the intervention

At present, the pathophysiology of delirium is not fully understood (Gunther 2008; Reade 2014), and there are likely multiple contributory mechanisms. Hypotheses include abnormalities in cerebral oxidative metabolism, direct neurotoxic effects of inflammatory cytokines, such as those released during sepsis and septic shock, as well as alterations in neurotransmitters, especially cholinergic, dopaminergic, serotonergic, and gamma-aminobutyric acid (GABA) pathways (Cerejeira 2011; de Rooij 2007; Ebersoldt 2007; Flacker 1999; Gunther 2008; Inouye 2006a; Rudolph 2008; White 2002). These pathophysiological mechanisms are not thought to be mutually exclusive, and are likely to act in concert. Pharmacological interventions for delirium treatment have focused on alterations in neurotransmitter pathways, in particular dopaminergic and cholinergic pathways. Pharmacological strategies for delirium that have been investigated include alpha-2-agonists, antidepressants, antipsychotic drugs (either typical or atypical agents), benzodiazepines, cholinesterase inhibitors, melatonin and melatonin agonists, and opioids (Devlin 2010; Girard 2010a; Maldonado 2009; Ohta 2013; Reade 2009;

Rubino 2010; van Eijk 2010). It is important to note that current critical care guidelines recommend first and foremost the use of non-pharmacological strategies in both the prevention and management of delirium (Barr 2013). These non-pharmacological strategies include, but are not limited to, early mobilization and re-orientation of the patient, risk factor assessment (e.g. drug and medical devices), and normalization of the sleep-wake cycle (e.g. noise reduction, use of ear plugs) (Inouye 2006; Schweickert 2009). Guidelines suggest that when delirium is suspected or identified, patients be closely evaluated for identification of potential underlying cause(s), allowing for deficiencies to be corrected, or exposures to be removed, whenever possible; pharmacological interventions are to be used when non-drug methods have failed to control symptoms (Barr 2013; BGS 2006; Royal College of Psychiatrists 2006).

How the intervention might work

Given the multiple possible mechanisms resulting in the development of delirium, numerous pharmacological strategies have been investigated to target the suspected neurotransmitter imbalances. Current pharmacological interventions target neurotransmitter imbalances, or attempt to control distressing cognitive (e.g. hallucinations) or dangerous behavioural symptoms (e.g. attempting to climb out of bed or interfere with medical devices) when non-pharmacological interventions prove ineffective. Pharmacological strategies investigated target the dopaminergic pathway (e.g. antipsychotics), cholinergic pathway (e.g. cholinesterase inhibitors), GABA pathway (e.g. benzodiazepines), N-Methyl-D-Aspartate (NMDA) receptor antagonism (e.g. ketamine), serotonergic pathway (e.g. antidepressants), alpha-2 agonists (e.g. clonidine, dexmedetomidine), and improved pain control (e.g. opioids) or sleep (e.g. melatonin and melatonin agonists) (Devlin 2010; Girard 2010a; Maldonado 2009; Ohta 2013; Reade 2009; Rubino 2010; van Eijk 2010). The specific therapeutic effects of such agents are unknown, but effects may be mediated through their ability to affect anxiety, sedation, and psychotic symptoms. Despite the conflicting evidence for benefit of the various pharmacological interventions, many of these agents are routinely used to treat ICU delirium, or to at least manage its symptoms (e.g. agitation), and are often continued after hospital discharge (Bell 2007; Burry 2014; MacSweeney 2009). Of the available pharmacological strategies, antipsychotics represent the current treatment of choice for ICU delirium, despite limited evidence regarding their benefit, and studies in non-critically ill patients identifying significant adverse effects (e.g. sudden death) (Barr 2013; Briskman 2010; Burry 2014; Gill 2007; MacSweeney 2009; Tropea 2009; Wang 2005).

Given the wide spectrum of available pharmacological treatments, we will use a network meta-analysis to determine the comparative benefits and harms of available pharmacological interventions for treatment of delirium in ICU patients.

Why it is important to do this review

Delirium is reported in 40% to 89% of ICU patients and is associated with poor clinical outcomes (Ely 2001a; Ely 2001b; Ely 2007; Hipp 2012; Inouye 2014). ICU delirium initiates a cascade of events that can include functional decline, long-term cognitive impairment, and caregiver burden (Girard 2010b; Jackson 2004; Van den Boogaard 2012). It is associated with increased morbidity, prolonged duration of mechanical ventilation, ICU and hospital lengths of stay, and a three-fold increase in mortality (Ely 2001b; Ely 2004; Girard 2010b; Jackson 2004; Lin 2004; Milbrant 2004; Pisani 2009; Van den Boogaard 2012). Furthermore from the geriatric and oncology literature, we know the experience of delirium is traumatic for both patients and their family members, and can lead to long-term psychological sequelae (Bruera 2009; Morita 2004; Partridge 2013; Rosenbloom-Brunton 2010). The economic burden of delirium is also significant; each additional day spent in a delirious state is associated with a 20% increased risk of prolonged hospitalization, translating to an average of more than 10 additional days in hospital. The annual cost of delirium is estimated to be greater than USD 164 billion in the USA, and greater than EUR 182 billion in 18 European countries combined (Leslie 2008; OECD 2012; WHO Regional Office 2012). Delirium is now considered a substantial public health concern, has garnered the attention of patient safety institutes, and is included as an indicator of quality care in the elderly (IHI 2015; Saferhealth Care Now!).

Advances in detection of ICU delirium and a better understanding of its impact on patient outcomes has prompted a large number of trials comparing different treatment options (both pharmacological and non-pharmacological), either against each other or to placebo. However, there remains considerable uncertainty regarding the relative benefits and safety of pharmacological interventions, in particular on important clinical outcomes in the ICU population, and trials have shown either positive (Devlin 2010; Reade 2009; Pandharipande 2007), equipoise (Girard 2010a; Page 2013), or negative results (van Eijk 2010). A Cochrane review on antipsychotics for delirium, the drug class most commonly used to treat delirium in any hospital population, and endorsed by various international guidelines as agent of choice, did not address the ICU population specifically (Loneragan 2007). A recent systematic review of ICU delirium included both prevention and treatment studies (Al-Qadheeb 2014) and included randomized controlled trials (RCTs) evaluating sedation strategies where delirium was evaluated as a secondary endpoint (i.e. not specifically delirium intervention trials). As a Cochrane review by Greve and colleagues (Greve 2012) will provide data on delirium *prevention* trials in critically ill patients, our review focuses on delirium *treatment* trials. Given the plethora of strategies used to treat ICU delirium, and the existence of a large number of head-to-head trials yielding varied results, we will use a network meta-analysis (NMA) approach for evidence synthesis of pharmacological interventions for treatment of delirium. A network meta-analysis, also known as a mul-

tipale treatment comparison meta-analysis, allows interpretation of a broad base of evidence so that we can understand the relative merits of the multiple different interventions available. NMA is a statistical method used to assess the comparative effectiveness of multiple different interventions among similar patient populations that have not been compared directly in a RCT. In contrast to conventional pair-wise meta-analysis (e.g. RCTs comparing treatment A to treatment B), NMAs can provide estimates of relative efficacy between all interventions, even though some have never been compared head-to-head by using indirect evidence (i.e. comparing the results from two or more studies that have one treatment in common). NMAs are gaining popularity among clinicians and guideline committees as all treatment options need to be considered in context of each other, and not just in the traditional pair-wise format.

OBJECTIVES

Our primary objective is to assess the effects of pharmacological interventions on the duration of delirium in critically ill patients with confirmed or documented high risk of delirium.

Our secondary objectives are to assess: 1) the effects of pharmacological interventions on delirium-free and coma-free days, relapse, duration of mechanical ventilation, ICU and hospital length of stay, mortality, long-term outcomes (e.g. cognitive, discharge disposition, health-related quality of life); and 2) the safety of such delirium treatments in critically ill patients.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomized controlled trials (RCTs) and quasi-RCTs (i.e. when method of allocation is known but not strictly random, such as by alternation, date of birth, or case record number), including those using an open-label study design. Due to the potential for bias and the availability of RCTs, we will exclude non-RCTs.

Types of participants

We will include RCTs of critically ill adults treated for delirium. We define critically ill patients as those treated in a critical care or ICU of any specialty (e.g. burn, cardiac, medical, surgical, trauma)

or high acuity unit. The participant will have confirmed or documented high risk of delirium. As patients with subsyndromal delirium are considered to be at high risk of delirium, we will include RCTs that include this population. We will include studies that evaluated participants for delirium using the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria (APA 2013) by a trained individual (e.g. psychiatrist) or a validated delirium assessment tool (e.g. Confusion Assessment Method (CAM-ICU), Intensive Care Delirium Screening Checklist (ICDSC), Neelon and Champagne (NEECHAM) Confusion Scale, Delirium Rating Scale or Delirium Rating Scale-revised-98 (Bergeron 2001; Ely 2001b; Neelon 1996; Trzepacz 2001).

Types of interventions

We will include RCTs of any pharmacological (drug) treatment for delirium including alpha-2-agonists (e.g. dexmedetomidine,

clonidine), antidepressants (e.g. fluoxetine), antipsychotic drugs (either typical [e.g. haloperidol] or atypical agents [e.g. haloperidol]), benzodiazepines (e.g. lorazepam), cholinesterase inhibitors (e.g. rivastigmine), N-methyl-D-aspartate (NMDA) receptor antagonist (e.g. ketamine), melatonin and melatonin agonists (e.g. ramelteon), opioids (e.g. morphine), and propofol that are compared to either another active drug treatment, a placebo, or a non-pharmacological intervention (e.g. mobilization).

We will not apply restrictions in terms of drug dose, duration, or route of administration. Our network structure will be at the drug class level as shown in Figure 1. This figure illustrates a network diagram of 'nodes' (i.e. drug classes) and 'edges' (i.e. comparisons between the different drug classes from existing trials), thus describing a treatment network of all possible comparisons between classes. The extent to which there is available trial data along the 'edges' will depend upon the body of evidence found from our search.

Figure 1. Proposed network of interventions to be examined. The network of 'nodes' (i.e. drug classes) and 'edges' (i.e. comparisons between the different drug classes) describes the all of the possible comparisons between classes.

Types of outcome measures

Primary outcomes

1. Our primary outcome is the duration of delirium defined as the time from which it is first identified to when it is first resolved (i.e. screened negative as defined by the authors [e.g. first negative screen, two consecutive screenings]), measured in days.

Secondary outcomes

1. Delirium-free and coma-free days (e.g. 14-day, 21-day, 28-day).
2. Total duration of delirium, measured in days,
3. Relapse of delirium (reported as n %).
4. Duration of mechanical ventilation (reported in days).
5. Length of stay (ICU and hospital) (reported in days).
6. Mortality (e.g. 30-day, 60-day, 90-day, ICU, hospital, following hospital discharge, and one-year as reported by study authors).
7. Resolution of delirium symptoms (e.g. hallucinations, agitation).
8. Adverse drug events (e.g. sudden cardiac death, prolongation of the QT interval [QT interval measures the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle], seizures).
9. Use of physical restraint.
10. Hospital discharge disposition (e.g. rehabilitation, chronic care facility, home).
11. Long-term cognitive outcomes (e.g. change in Mini Mental Status Exam) (as reported by study authors).
12. Health-related quality of life (as reported by study authors).

Search methods for identification of studies

We aim to identify all eligible RCTs regardless of publication status (published, unpublished, or in progress). We will not impose any language restrictions.

Electronic searches

We will search the following electronic databases from their inception date: Ovid MEDLINE®, Ovid MEDLINE® In-Process & Other Non-Indexed Citations, Embase Classic+Embase, and PsycINFO using OVID platform. We will also search the Cochrane Library on Wiley, Prospero (<http://www.crd.york.ac.uk/PROSPERO/>), CINAHL, and Web of Science.

Our electronic search strategies have been developed and tested through an iterative process by an experienced medical information specialist in consultation with our team.

The search strategies will utilize a combination of controlled vocabulary (e.g. intensive care units, delirium) and keywords (e.g.

intensive care unit, acute brain dysfunction). We will use a validated randomized controlled trial filter to identify RCTs. We will adjust the vocabulary and syntax for each database.

We will perform a separate search for published systematic reviews to identify additional published or unpublished trials. The core strategy will be reviewed prior to execution by another senior information specialist using the Peer Review for Electronic Search Strategies (PRESS) template (Sampson 2009). We will perform a grey literature search of relevant databases and websites using resources listed in CADTH's *Grey Matters* (<http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters>). Specific details regarding our search strategies can be found in the appendices (Appendix 1; Appendix 2; Appendix 3; Appendix 4; Appendix 5; Appendix 6; Appendix 7; Appendix 8).

Searching other resources

We will handsearch the abstracts from the annual scientific meetings of the Society of Critical Care Medicine, European Society of Intensive Care Medicine, International Symposium on Intensive Care and Emergency Medicine, American Delirium Society, American Thoracic Society, Chest, and the Australian New Zealand Intensive Care Society for the past five years to identify studies not yet published in full. We will also search for unpublished and ongoing trials on the following websites using the term "delirium".

1. www.clinicaltrials.gov/.
2. www.who.int/trialsearch.

When required, we will contact the corresponding author(s) of eligible trials to obtain additional information to confirm study inclusion or exclusion. In addition, we will communicate with content experts in the field of critical care medicine to identify other potentially relevant studies. Lastly, we will handsearch the reference lists of all included studies and any reviews on the treatment of delirium in order to identify potential additional studies for inclusion.

Data collection and analysis

Selection of studies

Two review authors (LB, LR) have developed and pilot-tested the study screening form (Appendix 9). We have tested this form on a sample of five studies to ensure its accurate discrimination of studies to include and exclude. The same review authors (LB, LR) will independently examine each title and abstract that is retrieved from electronic and manual searches to identify potentially eligible studies by applying the inclusion and exclusion criteria outlines in the screening form. We (LB, LR) will independently examine full-text versions of articles selected based on title and abstract in their entirety to confirm inclusion. We will refer any disagreements on

to a third independent arbiter (EWE), if needed. We will organize references in the reference management software package EndNote (Endnote Version X6, Thomson Reuters, Carlsbad, CA, USA) and document the reasons for exclusion in the notes field. We will document a summary of the search and study selection process using the PRISMA flow diagram (Moher 2009).

Data extraction and management

We will perform data extraction using a standardized electronic data extraction form developed by two review authors (LB, LR) and pilot-tested on five studies to ensure it captures all relevant data. As we anticipate a large volume of trials for extraction, we will use four review authors working independently (SM, DW, NA, IE) to extract data. We will extract data related to key items, including patient demographics (e.g. age, gender, weight, severity of illness score (Acute Physiology and Chronic Health Evaluation (APACHE) or Sequential Organ Failure Assessment (SOFA), reasons for admission), interventions (e.g. drug, dose, frequency or mode of administration, how titrated (protocol or not), who administered or wrote the orders), delirium assessment tool and sedation scale used, any cointerventions that might alter length of stay or duration of mechanical ventilation (e.g. ventilator weaning strategies, type of sedative or analgesic), and outcomes as described above. Whenever necessary, we will attempt to contact the corresponding authors to clarify issues related to data reporting and/or to obtain further study details (LB). Data extractors will not be blind to the identity of study authors because of their familiarity with the literature on the topic. All data extraction will be confirmed (LB) and discrepancies between author pairs will be resolved by an arbiter (LR).

Assessment of risk of bias in included studies

Each data extractor will independently assess the risk of bias of included studies. Two review authors (LB, LR) will then verify assessment of risk of bias. These assessments will be done via a domain-based evaluation included in the aforementioned data extraction form, and as recommended by The Cochrane Collaboration (Higgins 2011). The domains are as follows.

1. Random sequence generation (i.e. selection bias).
2. Allocation concealment (i.e. selection bias).
3. Blinding of participants and personnel (i.e. performance bias).
4. Blinding of outcomes assessment (i.e. detection bias).
5. Incomplete outcome data (i.e. attrition bias).
6. Selective reporting.
7. Other bias (e.g. study source of funding).

For each domain, we will assess the risk of bias as 'low risk', 'high risk', or 'unclear'. Unclear will be assigned if insufficient detail is reported or if what happened in the study is known, but the risk of bias is unknown or unclear. Once we have agreed on 'Risk of bias' assessment, we will assign the studies into the following categories.

- Low risk: describes studies where all domains are considered to be at low risk of bias;
- High risk: describes studies where one or more domains are considered to be at high risk of bias; and
- Unclear risk: describes studies where one or more domain(s) have unclear risk of bias.

We will generate a risk of bias graph figure and risk of bias summary figure upon completion of assessment.

Measures of treatment effect

We will calculate the mean difference and associated 95% confidence interval (CI) and standard error for continuous outcomes. We will log transform data for endpoints that we anticipate will have skewed data, such as duration of delirium, mechanical ventilation and lengths of stay. The data we will analyse in Review Manager 5 (RevMan 2014) will be on the log scale, and we will report geometric means and ratios of geometric means. We will calculate pooled estimates using the Mantel-Haenszel random-effects model, allowing for adjustments that incorporate variation both within and between studies (DeMets 1987). We will consider two-sided P value < 0.05 to be significant. We will express findings for binary outcomes in terms of odds ratios (ORs) with 95% credible intervals.

Unit of analysis issues

We will use individual study participants in each trial arm as the unit of analysis. We anticipate that all included trials will be parallel-group design and therefore no adjustment is expected to be necessary for crossover or clustering.

Dealing with missing data

We will conduct meta-analyses based on the data available from our included studies. For missing standard deviations associated with continuous outcomes, we will first contact study authors to determine if the information can be provided; a maximum of three attempts will be made. If this fails, then we will use established methods to impute standard deviation values (Abrams 2005; Follmann 1992). For outcomes assessed using change scores in each intervention group (e.g. delirium severity score), we will impute standard deviations using a moderate correlation coefficient of 0.5. For outcomes where groups are compared based on average values at the end of study follow-up, we will impute standard deviations by using the average value of standard deviations from studies with available data. We will perform sensitivity analyses, excluding studies with imputed data.

Assessment of heterogeneity

Within a treatment network involving multiple interventions, heterogeneity can be the result of an uneven distribution of important clinical and methodological effect modifiers across studies or

across comparisons. We will assess the presence of statistical heterogeneity by visual inspection of forest plots and by calculation of the I^2 statistic (Higgins 2003) and the χ^2 test (P value < 0.10 will be deemed significant). If the I^2 statistic is > 50% we will assess the type and sources of heterogeneity (clinical and methodological). We will qualitatively assess clinical heterogeneity by examining delirium management strategies in each trial (e.g. treatment dose, use of rescue medications, use of physical restraints, non-drug treatment or prevention strategies such as noise reduction). We will also assess clinical heterogeneity by examining factors that may influence delirium and sedation practices, including the country of study origin, the year of study publication, ICU type, the number of study sites (i.e. single versus multicentre study), the type of sedatives and analgesic used as well as drugs known to increase the risk of delirium (e.g. corticosteroids, benzodiazepines).

Assessment of reporting biases

Reporting biases can occur due to an increased likelihood of positive trials (large or small) being published, compared to negative trials. For direct comparisons in the network where a minimum of 10 studies are available, we will review contour enhanced funnel plots to assess for possible publication bias.

Data synthesis

We will conduct conventional pair-wise meta-analyses for all outcomes and comparisons, provided that at least two studies are available, using a random-effects model (DerSimonian 1986). This will inform judgements about whether there is important heterogeneity within any comparisons in our treatment network of interest. Once homogeneity is established, we will then perform network meta-analyses.

Network meta-analysis is a method of synthesizing information from a network of trials addressing the same question, but involving multiple different interventions. In this particular network meta-analysis, pairs of both pharmacological and/or non-pharmacological intervention strategies will serve as comparators. Generally speaking, for a given comparison (e.g. A versus B), evidence will be provided by the studies identified that compare these two treatments directly. In addition, indirect evidence for this comparison will be provided by synthesizing studies that compare A versus C and B versus C (Caldwell 2005; Higgins 1996). Network meta-analysis combines direct and indirect evidence across a network of RCTs into a single effect size. Under certain assumptions it can increase the precision of estimates while randomization is respected.

We will follow established procedures to assess the validity of the assumptions of homogeneity, similarity and consistency (Donegan 2013). We will perform network meta-analyses within a Bayesian framework, assuming a common heterogeneity parameter across all comparisons, and accounting for correlations in multiarm studies (Lu 2006; Salanti 2011). Two review authors (BH,

DF) will perform the analysis with WinBUGS software (Lunn 2000 version 1.4.3, MRC Biostatistics Unit, Cambridge, UK) (<http://www.mrc-bsu.cam.ac.uk/bugs/winbugs/contents.shtml>) using well established methods. We will express findings for continuous outcomes in terms of mean differences and corresponding 95% credible intervals. We will express findings for binary outcomes in terms of ORs with 95% credible intervals (Dias 2011a; Dias 2011b; Dias 2013).

We will evaluate the adequacy of model fit by comparing the posterior deviance to the number of unconstrained data points (i.e. the total number of intervention arms across studies); adequate fit is present when these quantities are approximately equal. Both fixed-effect and random-effects consistency models will be fitted, and we will compare the fit of these models via comparison of the Deviance Information Criterion (DIC), which penalizes model fit for complexity (note, lower values indicate better models) (Spiegelhalter 2002). We will consider a difference of approximately five points or more indicative of an important difference. We will also fit inconsistency models and compare DIC values with those from consistency models to explore the presence of inconsistency. If detected, we will explore individual study characteristics as well as the need for additional statistical considerations, such as meta-regression, to address the inconsistency. We will assess model convergence using established methods including Gelman Rubin diagnostics and inspection of Monte Carlo errors (Dias 2011b).

Subgroup analysis and investigation of heterogeneity

We will explore subgroup analyses and/or meta-regression analyses to address the impact of covariates on our findings to establish their robustness. If we identify sufficient information in the trials, we will seek to determine if the efficacy and safety of the drug treatment options are influenced by:

1. age (< 65 years, $\geq$ 65 years);
2. different types of ICU populations (e.g. mixed, medical only, surgical only);
3. delirium subtype (e.g. hyperactive, hypoactive, mixed); or
4. use of cointerventions with non-drug approaches (e.g. noise reduction, music therapy).

Sensitivity analysis

We will also conduct a sensitivity analysis involving alternative geometries of the network. Reformulations of the network may include:

1. excluding studies with high risk of bias;
2. collapsing atypical and typical antipsychotics into one node;
3. splitting each node in Figure 1 into two nodes to reflect 'low dose' and 'high dose', based on the dose reported in the trials; and
4. splitting each node in Figure 1 into two nodes to reflect fixed regular dosing and PRN (*pro re nata* or as needed) only dosing.

'Summary of findings' table

We will present specific outcomes of the review using a 'Summary of findings' table as recommended by The Cochrane Collaboration (Schunemann 2011b). We will present: duration of delirium (first episode), mortality (ICU and hospital), delirium-free and coma-free days, duration of mechanical ventilation, length of ICU and hospital stay, and adverse drug events in the 'Summary of findings' table. We will present the SoF table for the direct estimates only and include an overall grading of the evidence for our chosen outcomes using the principles of the GRADE system (<http://tech.cochrane.org/revman/grade>; Schunemann 2011a). We will grade the quality of evidence as 'high', 'moderate', 'low', or 'very low', considering risk of bias, within-study directness of evidence, heterogeneity, precision of effect estimates, and risk of publication bias. The control event rates to be used in the calculation of absolute risks will be based on the number of events in

the included studies.

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- * Indicates the major publication for the study

APPENDICES

Appendix I. RCT Search Strategy: Ovid MEDLINE®, Ovid MEDLINE® In-Process & Other Non-Indexed Citations, Embase Classic+Embase, and PsycINFO

Databases:

Embase Classic+Embase

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)

PsycINFO

Search Strategy:

-
- 1 ((postoperati* or post-operati* or postsurg* or post-surg*) adj1 (“cognitive dysfunction” or “brain dysfunction”)).tw.
 - 2 Intensive Care Units/
 - 3 Burn Units/
 - 4 Coronary Care Units/
 - 5 Respiratory Care Units/
 - 6 exp Intensive Care Units, Pediatric/
 - 7 exp Critical Care/
 - 8 ((intensive or critical or acute) adj3 care).tw.
 - 9 (ICU or ICUs or NICU or NICUs or PICU or PICUs or SICU or SICUs or CCU or CCUs).tw.
 - 10 (burn\$1 adj3 (unit\$1 or centre\$1 or center\$1)).tw.
 - 11 ((cardiac or coronary or heart) adj3 (unit\$1 or centre\$1 or center\$1)).tw.
 - 12 (respiratory adj3 (unit\$1 or centre\$1 or center\$1)).tw.
 - 13 ((surgical or surger*) adj3 (unit\$1 or centre\$1 or center\$1)).tw.
 - 14 Postoperative Care/
 - 15 Postoperative Complications/
 - 16 (postoperati* or post-operati* or postsurg* or post-surg*).tw.
 - 17 Critical Illness/
 - 18 (critical* adj (ill or illness*)).tw.
 - 19 or/2-18
 - 20 Delirium/
 - 21 deliri*.tw.
 - 22 Psychoses, Substance-Induced/
 - 23 (psychos* adj3 (toxic* or exogenous* or chemical* or drug or drugs or medication* or substance*)).tw.

24 (acute brain adj (dysfunction* or failure* or syndrome*)).tw.
 25 (cloud* adj3 consciousness*).tw.
 26 clouded state*.tw.
 27 ((psycho-organic syndrome* or psychoorganic syndrome* or organic psychosyndrome* or organic psycho-syndrome*) adj3 acute).tw.
 28 exp Confusion/ci
 29 Hallucinations/
 30 hallucinat*.tw.
 31 or/20-30
 32 19 and 31
 33 1 or 32
 34 (controlled clinical trial or randomized controlled trial).pt.
 35 clinical trials as topic.sh.
 36 (randomi#ed or randomly or RCT\$1 or placebo*).tw.
 37 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw.
 38 trial.ti.
 39 or/34-38
 40 33 and 39
 41 exp Animals/ not (exp Animals/ and Humans/)
 42 40 not 41
 43 (comment or editorial or interview or letter or news).pt.
 44 42 not 43
 45 44 use prnz
 46 remove duplicates from 45 [MEDLINE RECORDS]
 47 postoperative delirium/
 48 postoperative cognitive dysfunction/
 49 ((postoperati* or post-operati* or postsurg* or post-surg*) adj1 ("cognitive dysfunction" or "brain dysfunction")).tw.
 50 intensive care psychosis/
 51 or/47-50
 52 intensive care unit/
 53 burn unit/
 54 coronary care unit/
 55 intensive care/
 56 ((intensive or critical or acute) adj3 care).tw.
 57 (ICU or ICUs or NICU or NICUs or PICU or PICUs or SICU or SICUs or CCU or CCUs).tw.
 58 (burn\$1 adj3 (unit\$1 or centre\$1 or center\$1)).tw.
 59 ((cardiac or coronary or heart) adj3 (unit\$1 or centre\$1 or center\$1)).tw.
 60 (respiratory adj3 (unit\$1 or centre\$1 or center\$1)).tw.
 61 ((surgical or surger*) adj3 (unit\$1 or centre\$1 or center\$1)).tw.
 62 postoperative care/
 63 postoperative complication/
 64 (postoperati* or post-operati* or postsurg* or post-surg*).tw.
 65 critical illness/
 66 (critical* adj (ill or illness*)).tw.
 67 or/52-66
 68 exp delirium/
 69 deliri*.tw.
 70 (psychos* adj3 (toxic* or exogenous* or chemical* or drug or drugs or medication* or substance*)).tw.
 71 (acute brain adj (dysfunction* or failure* or syndrome*)).tw.
 72 (cloud* adj3 consciousness*).tw.
 73 clouded state*.tw.
 74 ((psycho-organic syndrome* or psychoorganic syndrome* or organic psychosyndrome* or organic psycho-syndrome*) adj3 acute).tw.
 75 exp hallucination/
 76 hallucinat*.tw.

77 or/68-76
 78 67 and 77
 79 51 or 78
 80 randomized controlled trial/ or controlled clinical trial/
 81 exp "clinical trial (topic)"/
 82 (randomi#ed or randomly or RCT\$1 or placebo*).tw.
 83 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw.
 84 trial.ti.
 85 or/80-84
 86 79 and 85
 87 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/
 88 exp humans/ or exp human experimentation/ or exp human experiment/
 89 87 not 88
 90 86 not 89
 91 (editorial or letter).pt.
 92 90 not 91
 93 92 use emczd
 94 remove duplicates from 93 [EMBASE RECORDS]
 95 ((postoperati* or post-operati* or postsurg* or post surg*) adj1 ("cognitive dysfunction" or "brain dysfunction")).tw.
 96 exp intensive care/
 97 ((intensive or critical or acute) adj3 care).tw.
 98 (ICU or ICUs or NICU or NICUs or PICU or PICUs or SICU or SICUs or CCU or CCUs).tw.
 99 (burn\$1 adj3 (unit\$1 or centre\$1 or center\$1)).tw.
 100 ((cardiac or coronary or heart) adj3 (unit\$1 or centre\$1 or center\$1)).tw.
 101 (respiratory adj3 (unit\$1 or centre\$1 or center\$1)).tw.
 102 ((surgical or surger*) adj3 (unit\$1 or centre\$1 or center\$1)).tw.
 103 postsurgical complications/
 104 (postoperati* or post-operati* or postsurg* or post-surg*).tw.
 105 (critical* adj (ill or illness*)).tw.
 106 or/96-105
 107 delirium/
 108 deliri*.tw.
 109 (psychos* adj3 (toxic* or exogenous* or chemical* or drug or drugs or medication* or substance*)).tw.
 110 (acute brain adj (dysfunction* or failure* or syndrome*)).tw.
 111 (cloud* adj3 consciousness*).tw.
 112 clouded state*.tw.
 113 ((psycho-organic syndrome* or psychoorganic syndrome* or organic psychosyndrome* or organic psycho-syndrome*) adj3 acute).tw.
 114 mental confusion/
 115 exp Hallucinations/
 116 hallucinat*.tw.
 117 or/107-116
 118 106 and 117
 119 95 or 118
 120 clinical trials/
 121 (randomi#ed or randomly or RCT\$1 or placebo*).tw.
 122 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw.
 123 trial.ti.
 124 or/120-123
 125 119 and 124
 126 exp Animals/ not (exp Animals/ and Humans/)
 127 125 not 126
 128 127 use prnz

129 127 use emczd
 130 127 not (128 or 129) [PSYCINFO RECORDS]
 131 remove duplicates from 130
 132 46 or 94 or 131
 133 remove duplicates from 132 [TOTAL UNIQUE HITS]
 134 133 use prnz [MEDLINE UNIQUE HITS]
 135 133 use emczd [EMBASE UNIQUE HITS]
 136 133 not (134 or 135) [PSYCINFO UNIQUE HITS]

Appendix 2. RCT Search Strategy: CCTR, DSR, DARE, CENTRAL, HTA, and NHS SEED

ID - Search

#1 (postoperati* or (post next operati*) or postsurg* or (post next surg*)) next ("cognitive dysfunction" or "brain dysfunction"):ti,ab,kw
 #2 [mh "Intensive Care Units"]
 #3 [mh "Burn Units"]
 #4 [mh "Coronary Care Units"]
 #5 [mh "Respiratory Care Units"]
 #6 [mh "Intensive Care Units, Pediatric"]
 #7 [mh "Critical Care"]
 #8 ((intensive or critical or acute) near/4 care):ti,ab,kw
 #9 (ICU or ICUs or NICU or NICUs or PICU or PICUs or SICU or SICUs or CCU or CCUs):ti,ab,kw
 #10 (burn or burns) near/4 (unit or units or centre or centres or center or centers):ti,ab,kw
 #11 (cardiac or coronary or heart) near/4 (unit or units or centre or centres or center or centers):ti,ab,kw
 #12 respiratory near/4 (unit or units or centre or centres or center or centers):ti,ab,kw
 #13 (surgical or surger*) near/4 (unit or units or centre or centres or center or centers):ti,ab,kw
 #14 [mh "Postoperative Care"]
 #15 [mh "Postoperative Complications"]
 #16 postoperati* or (post next operati*) or postsurg* or (post next surg*):ti,ab,kw
 #17 [mh "Critical Illness"]
 #18 critical* next (ill or illness*):ti,ab,kw
 #19 {or #2-#18}
 #20 [mh Delirium]
 #21 deliri*:ti,ab,kw
 #22 [mh "Psychoses, Substance-Induced"]
 #23 psychos* near/4 (toxic* or exogenous* or chemical* or drug or drugs or medication* or substance*):ti,ab,kw
 #24 "acute brain" next (dysfunction* or failure* or syndrome*):ti,ab,kw
 #25 cloud* near/4 consciousness*:ti,ab,kw
 #26 clouded next state*:ti,ab,kw
 #27 ("psycho-organic" next syndrome*) or (psychoorganic next syndrome*) or (organic next psychosyndrome*) or (organic next psychosyndrome*) near/4 acute:ti,ab,kw
 #28 [mh Confusion/ci]
 #29 [mh Hallucinations]
 #30 hallucinat*:ti,ab,kw
 #31 {or #20-#30}
 #32 #19 and #31
 #33 #1 or #32
 DSR -
 DARE -
 CENTRAL
 HTA -
 NHS EED -

Appendix 3. RCT Search Strategy: CINAHL

#	Query	Limiters/Expanders
S42	S33 AND S40	Limiters - Exclude MEDLINE records Expanders - Apply related words Search modes - Boolean/Phrase
S41	S33 AND S40	Expanders - Apply related words Search modes - Boolean/Phrase
S40	s34 or s35 or s36 or s37 or s38 or s39	Expanders - Apply related words Search modes - Boolean/Phrase
S39	TI trial	Expanders - Apply related words Search modes - Boolean/Phrase
S38	TI ((singl* or doubl* or trebl* or tripl*) w1 (mask* or blind* or dumm*)) OR AB ((singl* or doubl* or trebl* or tripl*) w1 (mask* or blind* or dumm*))	Expanders - Apply related words Search modes - Boolean/Phrase
S37	TI (randomised or randomized or randomly or RCT or RCTs or placebo*) OR AB (randomised or randomized or randomly or RCT or RCTs or placebo*)	Expanders - Apply related words Search modes - Boolean/Phrase
S36	TI randomised or randomized or randomly or RCT or RCTs or placebo*	Expanders - Apply related words Search modes - Boolean/Phrase
S35	(MH "Clinical Trials+")	Expanders - Apply related words Search modes - Boolean/Phrase
S34	(MH "Randomized Controlled Trials")	Expanders - Apply related words Search modes - Boolean/Phrase
S33	S1 OR S32	Expanders - Apply related words Search modes - Boolean/Phrase
S32	S19 AND S31	Expanders - Apply related words Search modes - Boolean/Phrase
S31	S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30	Expanders - Apply related words Search modes - Boolean/Phrase
S30	TI hallucinat* OR AB hallucinat*	Expanders - Apply related words Search modes - Boolean/Phrase
S29	(MH "Hallucinations+")	Expanders - Apply related words Search modes - Boolean/Phrase
S28	(MH "Confusion+/CI")	Expanders - Apply related words Search modes - Boolean/Phrase

(Continued)

S27	TI (("psycho-organic" w1 syndrome*) or (psychoorganic w1 syndrome*) or (organic w1 psychosyndrome*) or "organic psycho-syndrome" or "organic psycho-syndromes") n3 acute) OR AB (("psycho-organic" w1 syndrome*) or (psychoorganic w1 syndrome*) or (organic w1 psychosyndrome*) or "organic psycho-syndrome" or "organic psycho-syndromes") n3 acute)	Expanders - Apply related words Search modes - Boolean/Phrase
S26	TI clouded w1 state* OR AB clouded w1 state*	Expanders - Apply related words Search modes - Boolean/Phrase
S25	TI cloud* n3 consciousness* OR AB cloud* n3 consciousness*	Expanders - Apply related words Search modes - Boolean/Phrase
S24	TI ("acute brain" n1 (dysfunction* or failure* or syndrome*)) OR AB ("acute brain" n1 (dysfunction* or failure* or syndrome*))	Expanders - Apply related words Search modes - Boolean/Phrase
S23	TI (psychos* n3 (toxic* or exogenous* or chemical* or drug or drugs or medication* or substance*)) OR AB (psychos* n3 (toxic* or exogenous* or chemical* or drug or drugs or medication* or substance*))	Expanders - Apply related words Search modes - Boolean/Phrase
S22	(MH "Psychoses, Substance-Induced")	Expanders - Apply related words Search modes - Boolean/Phrase
S21	TI deliri* OR AB deliri*	Expanders - Apply related words Search modes - Boolean/Phrase
S20	(MH "Delirium")	Expanders - Apply related words Search modes - Boolean/Phrase
S19	S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18	Expanders - Apply related words Search modes - Boolean/Phrase
S18	TI (critical* w1 (ill or illness*)) OR AB (critical* w1 (ill or illness*))	Expanders - Apply related words Search modes - Boolean/Phrase
S17	(MH "Critical Illness")	Expanders - Apply related words Search modes - Boolean/Phrase
S16	TI (postoperati* or post-operati* or postsurg* or post-surg*) OR AB (postoperati* or post-operati* or postsurg* or post-surg*)	Expanders - Apply related words Search modes - Boolean/Phrase
S15	(MH "Postoperative Complications+")	Expanders - Apply related words Search modes - Boolean/Phrase

(Continued)

S14	(MH "Postoperative Care+")	Expanders - Apply related words Search modes - Boolean/Phrase
S13	TI (((surgical or surger*) n3 (unit or units or centre or centres or center or centers))) OR AB (((surgical or surger*) n3 (unit or units or centre or centres or center or centers)))	Expanders - Apply related words Search modes - Boolean/Phrase
S12	TI (respiratory n3 (unit or units or centre or centres or center or centers)) OR AB (respiratory n3 (unit or units or centre or centres or center or centers))	Expanders - Apply related words Search modes - Boolean/Phrase
S11	TI ((cardiac or coronary or heart) n3 (unit or units or centre or centres or center or centers))) OR AB (((cardiac or coronary or heart) n3 (unit or units or centre or centres or center or centers)))	Expanders - Apply related words Search modes - Boolean/Phrase
S10	TI (((burn or burns) n3 (unit or units or centre or centres or center or centers))) OR AB (((burn or burns) n3 (unit or units or centre or centres or center or centers)))	Expanders - Apply related words Search modes - Boolean/Phrase
S9	TI ((ICU or ICUs or NICU or NICUs or PICU or PICUs or SICU or SICUs or CCU or CCUs)) OR AB ((ICU or ICUs or NICU or NICUs or PICU or PICUs or SICU or SICUs or CCU or CCUs))	Expanders - Apply related words Search modes - Boolean/Phrase
S8	TI (((intensive or critical or acute) n3 care)) OR AB (((intensive or critical or acute) n3 care))	Expanders - Apply related words Search modes - Boolean/Phrase
S7	(MH "Critical Care+")	Expanders - Apply related words Search modes - Boolean/Phrase
S6	(MH "Respiratory Care Units")	Expanders - Apply related words Search modes - Boolean/Phrase
S5	(MH "Coronary Care Units")	Expanders - Apply related words Search modes - Boolean/Phrase
S4	(MH "Burn Units")	Expanders - Apply related words Search modes - Boolean/Phrase
S3	(MH "Intensive Care Units, Neonatal") OR (MH "Intensive Care Units, Pediatric+")	Expanders - Apply related words Search modes - Boolean/Phrase
S2	(MH "Intensive Care Units+")	Expanders - Apply related words Search modes - Boolean/Phrase
S1	TI (((postoperati* or post-operati* or postsurg* or post-surg*) n1 ("cognitive dysfunction" or "brain dysfunction"))) OR AB (((postoperati* or post-operati* or postsurg* or post-surg*) n1	Expanders - Apply related words Search modes - Boolean/Phrase

(Continued)

	("cognitive dysfunction" or "brain dysfunction")))	
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Appendix 4. RCT Search Strategy: Web of Science

# 41	#39 NOT #40 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 40	(#39) AND DOCUMENT TYPES: (Editorial Material OR Letter OR News Item) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 39	#38 AND #31 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 38	#37 OR #36 OR #35 OR #34 OR #33 OR #32 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 37	TI=trial Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 36	TS=((singl* or doubl* or trebl* or tripl*) NEAR/1 (mask* or blind* or dumm*)) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 35	TS=(randomised or randomized or randomly or RCT or RCTs or placebo*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 34	TS="clinical trials as topic" Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 33	TS=("randomized controlled trial" or "randomised controlled trial") Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 32	TS="controlled clinical trial" Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 31	#30 OR #1 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 30	#29 AND #21 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 29	#28 OR #27 OR #26 OR #25 OR #24 OR #23 OR #22 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years

(Continued)

# 28	TS=hallucinat* Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 27	TS=(clouded near/1 state*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 26	TS=(cloud* NEAR/3 consciousness*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 25	TS=(“acute brain” NEAR/1 (dysfunction* or failure* or syndrome*)) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 24	TS=(psychos* NEAR/3 (toxic* or exogenous* or chemical* or drug or drugs or medication* or substance*)) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 23	TS=deliri* Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 22	TS=delirium Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 21	#20 OR #19 OR #18 OR #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 20	TS=(critical* NEAR/1 (ill or illness*)) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 19	TS=“Critical Illness” Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 18	TS=(postoperati* or post-operati* or postsurg* or post-surg*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 17	TS=“Postoperative Complications” Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 16	TS=“Postoperative Care” Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 15	TS=((surgical* or surger*) NEAR/3 (unit or units or centre or centres or center or centers)) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 14	TS=(respiratory NEAR/3 (unit or units or centre or centres or center or centers)) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years

(Continued)

# 13	TS=((cardiac or coronary or heart) NEAR/3 (unit or units or centre or centres or center or centers)) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 12	TS=((burn or burns) NEAR/3 (unit or units or centre or centres or center or centers)) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 11	TS=(ICU or ICUs or NICU or NICUs or PICU or PICUs or SICU or SICUs or CCU or CCUs) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 10	TS=((intensive or critical or acute) NEAR/3 care) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 9	TS="Intensive Care" Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 8	TS="Critical Care" Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 7	TS="Intensive Care Units, Neonatal" Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 6	TS="Intensive Care Units, Pediatric" Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 5	TS="Respiratory Care Units" Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 4	TS="Coronary Care Units" Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 3	TS="Burn Units" Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 2	TS="Intensive Care Units" Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 1	TS=((postoperati* or post-operati* or postsurg* or post-surg*) NEAR/1 ("cognitive dysfunction" or "brain dysfunction")) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years

Appendix 5. Review Article Search Strategy: Ovid MEDLINE®, Ovid MEDLINE® In-Process & Other Non-Indexed Citations, Embase Classic+Embase, and PsycINFO

Databases:

Embase Classic+Embase

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) (1946 to Present)

PsycINFO

Search Strategy:

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1 ((postoperati* or post-operati* or postsurg* or post-surg*) adj1 ("cognitive dysfunction" or "brain dysfunction")).tw.
2 Intensive Care Units/
3 Burn Units/
4 Coronary Care Units/
5 Respiratory Care Units/
6 exp Intensive Care Units, Pediatric/
7 exp Critical Care/
8 ((intensive or critical or acute) adj3 care).tw.
9 (ICU or ICUs or NICU or NICUs or PICU or PICUs or SICU or SICUs or CCU or CCUs).tw.
10 (burn$1 adj3 (unit$1 or centre$1 or center$1)).tw.
11 ((cardiac or coronary or heart) adj3 (unit$1 or centre$1 or center$1)).tw.
12 (respiratory adj3 (unit$1 or centre$1 or center$1)).tw.
13 ((surgical or surger*) adj3 (unit$1 or centre$1 or center$1)).tw.
14 Postoperative Care/
15 Postoperative Complications/
16 (postoperati* or post-operati* or postsurg* or post-surg*).tw.
17 Critical Illness/
18 (critical* adj (ill or illness*)).tw.
19 or/2-18
20 Delirium/
21 deliri*.tw.
22 Psychoses, Substance-Induced/
23 (psychos* adj3 (toxic* or exogenous* or chemical* or drug or drugs or medication* or substance*)).tw.
24 (acute brain adj (dysfunction* or failure* or syndrome*)).tw.
25 (cloud* adj3 consciousness*).tw.
26 clouded state*.tw.
27 ((psycho-organic syndrome* or psychoorganic syndrome* or organic psychosyndrome* or organic psycho-syndrome*) adj3 acute).tw.
28 exp Confusion/ci
29 Hallucinations/
30 hallucinat*.tw.
31 or/20-30
32 19 and 31
33 1 or 32
34 (controlled clinical trial or randomized controlled trial).pt.
35 clinical trials as topic.sh.
36 (randomi#ed or randomly or RCT$1 or placebo*).tw.
37 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw.
38 trial.ti.
39 or/34-38
40 33 and 39
41 exp Animals/ not (exp Animals/ and Humans/)
42 40 not 41
43 (comment or editorial or interview or letter or news).pt.
44 42 not 43

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45 limit 33 to systematic reviews [Limit not valid in Embase; records were retained]
 46 meta analysis.pt.
 47 exp meta-analysis as topic/
 48 (meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review*).tw.
 49 (systematic review* or systematic overview* or evidence-based review* or evidence-based overview* or (evidence adj3 (review* or overview*)) or meta-review* or meta-overview* or meta-synthes* or “review of reviews” or technology assessment* or HTA or HTAs).tw.
 50 exp Technology assessment, biomedical/
 51 (cochrane or health technology assessment or evidence report).jw.
 52 or/46-51
 53 33 and 52
 54 45 or 53
 55 54 not (41 or 43)
 56 55 not 44
 57 56 use prnz
 58 remove duplicates from 57 [MEDLINE HITS]
 59 postoperative delirium/
 60 postoperative cognitive dysfunction/
 61 ((postoperati* or post-operati* or postsurg* or post-surg*) adj1 (“cognitive dysfunction” or “brain dysfunction”).tw.
 62 intensive care psychosis/
 63 or/59-62
 64 intensive care unit/
 65 burn unit/
 66 coronary care unit/
 67 intensive care/
 68 ((intensive or critical or acute) adj3 care).tw.
 69 (ICU or ICUs or NICU or NICUs or PICU or PICUs or SICU or SICUs or CCU or CCUs).tw.
 70 (burn\$1 adj3 (unit\$1 or centre\$1 or center\$1)).tw.
 71 ((cardiac or coronary or heart) adj3 (unit\$1 or centre\$1 or center\$1)).tw.
 72 (respiratory adj3 (unit\$1 or centre\$1 or center\$1)).tw.
 73 ((surgical or surger*) adj3 (unit\$1 or centre\$1 or center\$1)).tw.
 74 postoperative care/
 75 postoperative complication/
 76 (postoperati* or post-operati* or postsurg* or post-surg*).tw.
 77 critical illness/
 78 (critical* adj (ill or illness*)).tw.
 79 or/64-78
 80 exp delirium/
 81 deliri*.tw.
 82 (psychos* adj3 (toxic* or exogenous* or chemical* or drug or drugs or medication* or substance*)).tw.
 83 (acute brain adj (dysfunction* or failure* or syndrome*)).tw.
 84 (cloud* adj3 consciousness*).tw.
 85 clouded state*.tw.
 86 ((psycho-organic syndrome* or psychoorganic syndrome* or organic psychosyndrome* or organic psycho-syndrome*) adj3 acute).tw.
 87 exp hallucination/
 88 hallucinat*.tw.
 89 or/80-88
 90 79 and 89
 91 63 or 90
 92 randomized controlled trial/ or controlled clinical trial/
 93 exp “clinical trial (topic)”/
 94 (randomi#ed or randomly or RCT\$1 or placebo*).tw.
 95 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw.

96 trial.ti.
 97 or/92-96
 98 91 and 97
 99 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/
 100 exp humans/ or exp human experimentation/ or exp human experiment/
 101 99 not 100
 102 98 not 101
 103 (editorial or letter).pt.
 104 102 not 103
 105 meta-analysis/
 106 "systematic review"/
 107 "meta analysis (topic)"/
 108 (meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or
 research integration or research overview* or collaborative review*).tw.
 109 (systematic review* or systematic overview* or evidence-based review* or evidence-based overview* or (evidence adj3 (review* or
 overview*)) or meta-review* or meta-overview* or meta-synthes* or "review of reviews" or technology assessment* or HTA or HTAs).tw.
 110 biomedical technology assessment/
 111 (cochrane or health technology assessment or evidence report).jw.
 112 or/105-111
 113 91 and 112
 114 113 not (101 or 103)
 115 114 not 104
 116 115 use emczd
 117 remove duplicates from 116 [EMBASE HITS]
 118 ((postoperati* or post-operati* or postsurg* or post surg*) adj1 ("cognitive dysfunction" or "brain dysfunction")).tw.
 119 exp intensive care/
 120 ((intensive or critical or acute) adj3 care).tw.
 121 (ICU or ICUs or NICU or NICUs or PICU or PICUs or SICU or SICUs or CCU or CCUs).tw.
 122 (burn\$1 adj3 (unit\$1 or centre\$1 or center\$1)).tw.
 123 ((cardiac or coronary or heart) adj3 (unit\$1 or centre\$1 or center\$1)).tw.
 124 (respiratory adj3 (unit\$1 or centre\$1 or center\$1)).tw.
 125 ((surgical or surger*) adj3 (unit\$1 or centre\$1 or center\$1)).tw.
 126 postsurgical complications/
 127 (postoperati* or post-operati* or postsurg* or post-surg*).tw.
 128 (critical* adj (ill or illness)).tw.
 129 or/119-128
 130 delirium/
 131 deliri*.tw.
 132 (psychos* adj3 (toxic* or exogenous* or chemical* or drug or drugs or medication* or substance*)).tw.
 133 (acute brain adj (dysfunction* or failure* or syndrome*)).tw.
 134 (cloud* adj3 consciousness*).tw.
 135 clouded state*.tw.
 136 ((psycho-organic syndrome* or psychoorganic syndrome* or organic psychosyndrome* or organic psycho-syndrome*) adj3
 acute).tw.
 137 mental confusion/
 138 exp Hallucinations/
 139 hallucinat*.tw.
 140 or/130-139
 141 129 and 140
 142 118 or 141
 143 clinical trials/
 144 (randomi#ed or randomly or RCT\$1 or placebo*).tw.
 145 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw.

146 trial.ti.
 147 or/143-146
 148 142 and 147
 149 exp Animals/ not (exp Animals/ and Humans/)
 150 148 not 149
 151 limit 142 to "0830 systematic review" [Limit not valid in Embase,Ovid MEDLINE(R),Ovid MEDLINE(R) In-Process; records were retained]
 152 meta analysis/
 153 (meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review*).tw.
 154 (systematic review* or systematic overview* or evidence-based review* or evidence-based overview* or (evidence adj3 (review* or overview*)) or meta-review* or meta-overview* or meta-synthes* or "review of reviews" or technology assessment* or HTA or HTAs).tw.
 155 or/152-154
 156 142 and 155
 157 151 or 156
 158 157 use prmz
 159 157 use emczd
 160 157 not (158 or 159)
 161 remove duplicates from 160 [PSYCINFO HITS]
 162 58 or 117 or 161
 163 remove duplicates from 162 [TOTAL UNIQUE HITS]
 164 163 use prmz [MEDLINE UNIQUE HITS]
 165 163 use emczd [EMBASE UNIQUE HITS]
 166 163 not (164 or 165) [PSYCINFO UNIQUE HITS]

Appendix 6. Review Article Search Strategy: CCTR, DSR, DARE, CENTRAL, HTA, and NHS SEED

ID - Search

#1 (postoperati* or (post next operati*) or postsurg* or (post next surg*)) next ("cognitive dysfunction" or "brain dysfunction"):ti,ab,kw
 #2 [mh ^"Intensive Care Units"]
 #3 [mh "Burn Units"]
 #4 [mh "Coronary Care Units"]
 #5 [mh "Respiratory Care Units"]
 #6 [mh "Intensive Care Units, Pediatric"]
 #7 [mh "Critical Care"]
 #8 ((intensive or critical or acute) near/4 care):ti,ab,kw
 #9 (ICU or ICUs or NICU or NICUs or PICU or PICUs or SICU or SICUs or CCU or CCUs):ti,ab,kw
 #10 (burn or burns) near/4 (unit or units or centre or centres or center or centers):ti,ab,kw
 #11 (cardiac or coronary or heart) near/4 (unit or units or centre or centres or center or centers):ti,ab,kw
 #12 respiratory near/4 (unit or units or centre or centres or center or centers):ti,ab,kw
 #13 (surgical or surger*) near/4 (unit or units or centre or centres or center or centers):ti,ab,kw
 #14 [mh "Postoperative Care"]
 #15 [mh "Postoperative Complications"]
 #16 postoperati* or (post next operati*) or postsurg* or (post next surg*):ti,ab,kw
 #17 [mh "Critical Illness"]
 #18 critical* next (ill or illness*):ti,ab,kw
 #19 {or #2-#18}
 #20 [mh Delirium]
 #21 deliri*:ti,ab,kw
 #22 [mh ^"Psychoses, Substance-Induced"]
 #23 psychos* near/4 (toxic* or exogenous* or chemical* or drug or drugs or medication* or substance*):ti,ab,kw
 #24 "acute brain" next (dysfunction* or failure* or syndrome*):ti,ab,kw

#25 cloud* near/4 consciousness*:ti,ab,kw
 #26 clouded next state*:ti,ab,kw
 #27 ("psycho-organic" next syndrome*) or (psychoorganic next syndrome*) or (organic next psychosyndrome*) or (organic next psychosyndrome*) near/4 acute:ti,ab,kw
 #28 [mh Confusion/ci]
 #29 [mh Hallucinations]
 #30 hallucinat*:ti,ab,kw
 #31 {or #20-#30}
 #32 #19 and #31
 #33 #1 or #32
 DSR -
 DARE -
 CENTRAL -
 HTA -
 NHS EED -

Appendix 7. Review Article Search Strategy: CINAHL

#	Query	Limiters/Expanders
S52	S50 NOT S41	Limiters - Exclude MEDLINE records Expanders - Apply related words Search modes - Boolean/Phrase
S51	S50 NOT S41	Expanders - Apply related words Search modes - Boolean/Phrase
S50	S33 AND S49	Expanders - Apply related words Search modes - Boolean/Phrase
S49	S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48	Expanders - Apply related words Search modes - Boolean/Phrase
S48	TI ((evidence N3 (review* or overview*)) or (meta w1 review*) or (meta w1 overview*) or (meta w1 synthes*) or "review of reviews" or (technology w1 assessment*) or HTA or HTAs) OR AB ((evidence N3 (review* or overview*)) or (meta w1 review*) or (meta w1 overview*) or (meta w1 synthes*) or "review of reviews" or (technology w1 assessment*) or HTA or HTAs)	Expanders - Apply related words Search modes - Boolean/Phrase
S47	TI ((systematic or "evidence-based") w1 (review* or overview*)) OR AB ((systematic or "evidence-based") w1 (review* or overview*))	Expanders - Apply related words Search modes - Boolean/Phrase
S46	TI ((research w1 integration) or (research w1 overview*) or (collaborative w1 review*)) OR AB ((research w1 integration) or (research w1 overview*) or (collaborative w1 review*))	Expanders - Apply related words Search modes - Boolean/Phrase

(Continued)

S45	TI (integrative w1 (research or review* or overview*)) OR AB (integrative w1 (research or review* or overview*))	Expanders - Apply related words Search modes - Boolean/Phrase
S44	TI ((meta w1 analy*) or metanaly* or metaanaly*) OR AB ((meta w1 analy*) or metanaly* or metaanaly*)	Expanders - Apply related words Search modes - Boolean/Phrase
S43	(MH "Meta Analysis") OR (MH "Meta Synthesis")	Expanders - Apply related words Search modes - Boolean/Phrase
S42	(MH "Systematic Review")	Expanders - Apply related words Search modes - Boolean/Phrase
S41	S33 AND S40	Expanders - Apply related words Search modes - Boolean/Phrase
S40	s34 or s35 or s36 or s37 or s38 or s39	Expanders - Apply related words Search modes - Boolean/Phrase
S39	TI trial	Expanders - Apply related words Search modes - Boolean/Phrase
S38	TI ((singl* or doubl* or trebl* or tripl*) w1 (mask* or blind* or dumm*)) OR AB ((singl* or doubl* or trebl* or tripl*) w1 (mask* or blind* or dumm*))	Expanders - Apply related words Search modes - Boolean/Phrase
S37	TI (randomised or randomized or randomly or RCT or RCTs or placebo*) OR AB (randomised or randomized or randomly or RCT or RCTs or placebo*)	Expanders - Apply related words Search modes - Boolean/Phrase
S36	TI randomised or randomized or randomly or RCT or RCTs or placebo*	Expanders - Apply related words Search modes - Boolean/Phrase
S35	(MH "Clinical Trials+")	Expanders - Apply related words Search modes - Boolean/Phrase
S34	(MH "Randomized Controlled Trials")	Expanders - Apply related words Search modes - Boolean/Phrase
S33	S1 OR S32	Expanders - Apply related words Search modes - Boolean/Phrase
S32	S19 AND S31	Expanders - Apply related words Search modes - Boolean/Phrase
S31	S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30	Expanders - Apply related words Search modes - Boolean/Phrase
S30	TI hallucinat* OR AB hallucinat*	Expanders - Apply related words Search modes - Boolean/Phrase

(Continued)

S29	(MH "Hallucinations+")	Expanders - Apply related words Search modes - Boolean/Phrase
S28	(MH "Confusion+/CI")	Expanders - Apply related words Search modes - Boolean/Phrase
S27	TI (("psycho-organic" w1 syndrome*) or (psychoorganic w1 syndrome*) or (organic w1 psychosyndrome*) or "organic psycho-syndrome" or "organic psycho-syndromes") n3 acute) OR AB (("psycho-organic" w1 syndrome*) or (psychoorganic w1 syndrome*) or (organic w1 psychosyndrome*) or "organic psycho-syndrome" or "organic psycho-syndromes") n3 acute)	Expanders - Apply related words Search modes - Boolean/Phrase
S26	TI clouded w1 state* OR AB clouded w1 state*	Expanders - Apply related words Search modes - Boolean/Phrase
S25	TI cloud* n3 consciousness* OR AB cloud* n3 consciousness*	Expanders - Apply related words Search modes - Boolean/Phrase
S24	TI ("acute brain" n1 (dysfunction* or failure* or syndrome*)) OR AB ("acute brain" n1 (dysfunction* or failure* or syndrome*))	Expanders - Apply related words Search modes - Boolean/Phrase
S23	TI (psychos* n3 (toxic* or exogenous* or chemical* or drug or drugs or medication* or substance*)) OR AB (psychos* n3 (toxic* or exogenous* or chemical* or drug or drugs or medication* or substance*))	Expanders - Apply related words Search modes - Boolean/Phrase
S22	(MH "Psychoses, Substance-Induced")	Expanders - Apply related words Search modes - Boolean/Phrase
S21	TI deliri* OR AB deliri*	Expanders - Apply related words Search modes - Boolean/Phrase
S20	(MH "Delirium")	Expanders - Apply related words Search modes - Boolean/Phrase
S19	S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18	Expanders - Apply related words Search modes - Boolean/Phrase
S18	TI (critical* w1 (ill or illness*)) OR AB (critical* w1 (ill or illness*))	Expanders - Apply related words Search modes - Boolean/Phrase
S17	(MH "Critical Illness")	Expanders - Apply related words Search modes - Boolean/Phrase
S16	TI (postoperati* or post-operati* or postsurg* or post-surg*) OR AB (postoperati* or post-operati* or postsurg* or post-	Expanders - Apply related words Search modes - Boolean/Phrase

(Continued)

	surg*)	
S15	(MH "Postoperative Complications+")	Expanders - Apply related words Search modes - Boolean/Phrase
S14	(MH "Postoperative Care+")	Expanders - Apply related words Search modes - Boolean/Phrase
S13	TI (((surgical or surger*) n3 (unit or units or centre or centres or center or centers))) OR AB (((surgical or surger*) n3 (unit or units or centre or centres or center or centers)))	Expanders - Apply related words Search modes - Boolean/Phrase
S12	TI (respiratory n3 (unit or units or centre or centres or center or centers)) OR AB (respiratory n3 (unit or units or centre or centres or center or centers))	Expanders - Apply related words Search modes - Boolean/Phrase
S11	TI ((cardiac or coronary or heart) n3 (unit or units or centre or centres or center or centers))) OR AB (((cardiac or coronary or heart) n3 (unit or units or centre or centres or center or centers)))	Expanders - Apply related words Search modes - Boolean/Phrase
S10	TI (((burn or burns) n3 (unit or units or centre or centres or center or centers))) OR AB (((burn or burns) n3 (unit or units or centre or centres or center or centers)))	Expanders - Apply related words Search modes - Boolean/Phrase
S9	TI ((ICU or ICUs or NICU or NICUs or PICU or PICUs or SICU or SICUs or CCU or CCUs)) OR AB ((ICU or ICUs or NICU or NICUs or PICU or PICUs or SICU or SICUs or CCU or CCUs))	Expanders - Apply related words Search modes - Boolean/Phrase
S8	TI (((intensive or critical or acute) n3 care)) OR AB (((intensive or critical or acute) n3 care))	Expanders - Apply related words Search modes - Boolean/Phrase
S7	(MH "Critical Care+")	Expanders - Apply related words Search modes - Boolean/Phrase
S6	(MH "Respiratory Care Units")	Expanders - Apply related words Search modes - Boolean/Phrase
S5	(MH "Coronary Care Units")	Expanders - Apply related words Search modes - Boolean/Phrase
S4	(MH "Burn Units")	Expanders - Apply related words Search modes - Boolean/Phrase
S3	(MH "Intensive Care Units, Neonatal") OR (MH "Intensive Care Units, Pediatric+")	Expanders - Apply related words Search modes - Boolean/Phrase
S2	(MH "Intensive Care Units+")	Expanders - Apply related words Search modes - Boolean/Phrase

(Continued)

S1	TI (((postoperati* or post-operati* or postsurg* or post-surg*) n1 ("cognitive dysfunction" or "brain dysfunction"))) OR AB (((postoperati* or post-operati* or postsurg* or post-surg*) n1 ("cognitive dysfunction" or "brain dysfunction"))))	Expanders - Apply related words Search modes - Boolean/Phrase
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Appendix 8. Review Article Search Strategy: Web of Science

# 46	#44 NOT #45 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 45	(#44) AND DOCUMENT TYPES: (Editorial Material OR Letter OR News Item) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 44	#43 NOT #39 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 43	#31 AND #42 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 42	TS=((meta NEAR/1 analy*) or metanaly* or metaanaly* or (met NEAR/1 analy*) or (systematic NEAR/1 review*) or (systematic NEAR/1 overview*) or ("evidence-based" NEAR/1 review*) or ("evidence-based" NEAR/1 overview*) or (technology NEAR/1 assessment*) or HTA or HTAs) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 41	#39 NOT #40 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 40	(#39) AND DOCUMENT TYPES: (Editorial Material OR Letter OR News Item) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 39	#38 AND #31 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 38	#37 OR #36 OR #35 OR #34 OR #33 OR #32 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 37	TI=trial Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 36	TS=((singl* or doubl* or trebl* or tripl*) NEAR/1 (mask* or blind* or dumm*)) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 35	TS=(randomised or randomized or randomly or RCT or RCTs or placebo*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years

(Continued)

# 34	TS="clinical trials as topic" Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 33	TS=("randomized controlled trial" or "randomised controlled trial") Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 32	TS="controlled clinical trial" Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 31	#30 OR #1 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 30	#29 AND #21 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 29	#28 OR #27 OR #26 OR #25 OR #24 OR #23 OR #22 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 28	TS=hallucinat* Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 27	TS=(clouded near/1 state*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 26	TS=(cloud* NEAR/3 consciousness*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 25	TS=("acute brain" NEAR/1 (dysfunction* or failure* or syndrome*)) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 24	TS=(psychos* NEAR/3 (toxic* or exogenous* or chemical* or drug or drugs or medication* or substance*)) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 23	TS=deliri* Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 22	TS=delirium Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 21	#20 OR #19 OR #18 OR #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 20	TS=(critical* NEAR/1 (ill or illness*)) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years

(Continued)

# 19	TS="Critical Illness" Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 18	TS=(postoperati* or post-operati* or postsurg* or post-surg*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 17	TS="Postoperative Complications" Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 16	TS="Postoperative Care" Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 15	TS=((surgical* or surger*) NEAR/3 (unit or units or centre or centres or center or centers)) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 14	TS=(respiratory NEAR/3 (unit or units or centre or centres or center or centers)) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 13	TS=((cardiac or coronary or heart) NEAR/3 (unit or units or centre or centres or center or centers)) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 12	TS=((burn or burns) NEAR/3 (unit or units or centre or centres or center or centers)) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 11	TS=(ICU or ICUs or NICU or NICUs or PICU or PICUs or SICU or SICUs or CCU or CCUs) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 10	TS=((intensive or critical or acute) NEAR/3 care) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 9	TS="Intensive Care" Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 8	TS="Critical Care" Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 7	TS="Intensive Care Units, Neonatal" Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 6	TS="Intensive Care Units, Pediatric" Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 5	TS="Respiratory Care Units" Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 4	TS="Coronary Care Units" Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years

(Continued)

# 3	TS="Burn Units" Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 2	TS="Intensive Care Units" Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
# 1	TS=((postoperati* or post-operati* or postsurg* or post-surg*) NEAR/1 ("cognitive dysfunction" or "brain dysfunction")) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years

Appendix 9. Screening form

Pharmacological interventions for the treatment of delirium in critically ill patients.

Reviewer Initials	Review Date: __ / __ / __ (dd/mm/yy)		
Primary Author			
Citation (title, journal, year, vol, pg)			
Level of Review	Title and Abstract	Full text	
STUDY SELECTION			
Study Type	RCT	Yes	No
Population	Study subjects are patients treated in a critical care unit.	Yes	No
	Study subjects assessed by a trained individual (e.g. psychiatrist, geriatrician) and diagnosed with delirium according to DSM-IV criteria or a validated delirium screening tool (e.g. CAM-ICU)	Yes	No
	Inclusion criteria do not include only patients with delirium secondary to alcohol or benzodiazepine withdrawal (i.e. focus of study cannot be management of delirium secondary to drug/alcohol withdrawal)	Yes	No
Intervention	Any pharmacological agent (typical or atypical antipsychotic, benzodiazepine, alpha-2 agonists, opioid, antidepressant, cholinesterase inhibitor) for the treatment of delirium	Yes	No
Comparison	Placebo, a non-pharmacological intervention to treat delirium (e.g. noise reduction, music therapy, mobilization), or any of the above mentioned pharmacological interventions	Yes	No

(Continued)

Decision	-- INCLUDE	-- EXCLUDE	-- UNSURE
Primary reason for exclusion	Study type		
	Population		
	Intervention		
	Comparison		
Additional comments:			

WHAT'S NEW

Date	Event	Description
3 January 2019	Amended	Editorial team changed to Cochrane Emergency and Critical Care

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Conceiving the review: LB, LR

Designing the review: LB, LR, DF, BH

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Organizing retrieval of papers: LB

Screening retrieved papers against inclusion criteria: LB, LR

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Writing to authors of papers for additional information: LB

Providing additional data about papers: LB

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Data management for the review: LB, LR

Review Manager statistical data: BH, DF, LB

Other statistical analysis not using RevMan: BH, DF

Statistical inferences: BH, DF

Interpretation of data: all

Writing the protocol and review: LB, LR

Guarantor for the review (one author): LB

Person responsible for reading and checking review before submission: LB

DECLARATIONS OF INTEREST

None to declare: Lisa Burry, Neill KJ Adhikari, Ingrid Egerod, Dean A Fergusson, Brian Hutton, Sangeeta Mehta, Louise Rose, and David R Williamson.

To declare: E. Wesley Ely is an author on two RCTs that will meet the inclusion criteria (i.e. [Girard 2010a](#); [Page 2013](#)). He is also supported by NIH funding, which is paid to Vanderbilt University. E. Wesley Ely received funds as honoraria for evidence-based teaching activities from Orion, Hospira and Abbott Laboratories education divisions. These companies do not produce or market drugs for delirium, as

there is no specific indication for the treatment of delirium at this time, but they do market dexmedetomidine, which Dr. Ely is currently studying as a co-investigator in an NIH sponsored clinical trial.

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External sources

- No sources of support supplied