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# Non-pharmacological interventions for managing delirium in hospitalised patients (Protocol)

Teale EA, Siddiqi N, Clegg A, Todd OM, Young J

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[Intervention Protocol]

# Non-pharmacological interventions for managing delirium in hospitalised patients

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## ABSTRACT

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

To determine the effectiveness of single or multicomponent non-pharmacological interventions in reducing the symptoms, duration or severity of an established episode of delirium in hospitalised people outside intensive care settings.

## BACKGROUND

Delirium is a common cause and complication of hospitalisation in older people (Ryan 2013; Siddiqi 2006). Estimates of delirium occurrence vary depending on the setting. In a recent Italian point prevalence study in older hospital inpatients, 21.2% of patients on general medical wards, 24.7% on geriatric wards, 20.6% on orthopaedic wards and 14% of those in rehabilitation beds were delirious (Bellelli 2016). Occurrence rates of greater than 50% have been reported in those at particularly high risk (co-incident dementia, older age, severe illness or perioperatively) (Inouye 2014; Ryan 2013). Prevention of delirium is possible through non-pharmacological means. A meta-analysis of randomised controlled trials (RCTs) showed that multicomponent interventions reduce incident delirium by about 30% (Siddiqi 2016). However, once established, delirium confers a poor prognosis, with evidence to suggest development, or progression, of lasting cognitive impairment (Gross 2012; MacLullich 2009; McCusker 2001); increased mortality (Witlox 2010), especially in the context of frailty (Eeles 2012); and increased risk of institutionalisation (O'Keefe 1997; Pendlebury 2015). Delirium is a deeply unpleasant experience for patients and may result in lasting psychological sequelae (Morandi 2015; O'Malley 2008). There are no established treatments for delirium; UK best practice guidelines advise judicious use of antipsychotic medications at low doses aimed at reducing the symptoms of agitation and psychiatric symptoms of hyperactive delirium (NICE 2010). However, there is little trial evidence to suggest this approach either reduces the severity or duration of delirium, or improves outcomes. It is also not known whether interventions aimed at modifying the risk factors for delirium can attenuate or shorten a delirium episode.

### Description of the condition

Delirium is a syndrome with diverse and multiple aetiologies. Although several risk factors have been identified, its pathophysiology remains uncertain. A number of brain neural networks and

pathways have been implicated (MacLullich 2013), but mechanisms remain poorly understood. Delirium is characterised by rapid onset of fluctuating impairments in consciousness (arousal or attention) and cognition (memory, language, orientation, visuospatial ability, perception). Hallucinations and disturbance of the sleep/wake cycle are common. People with delirium often exhibit behavioural disturbances in keeping with hypo- and hyperactive delirium subtypes (39% and 21% of delirium episodes respectively). Fluctuation in symptoms is an important feature of delirium, and commonly people will switch between motor behaviours resulting in a third subtype: 'mixed' delirium (27% of delirium episodes). Approximately 14% of patients exhibit no motor symptoms (Bellelli 2016). The degree to which individual delirium features are present for an individual is variable and determines delirium severity. There may be profound disturbances of attention, awareness and cognition, or these may be present in a mild form that can be difficult to detect. Fluctuation of delirium severity within an individual is a key feature of delirium.

Diagnosis of delirium remains clinical and depends on meeting diagnostic criteria outlined in the Diagnostic and Statistical Manual for Mental Disorders (DSM-V; APA 2013). Delirium can only be diagnosed if the neurocognitive disturbance is due to a physiological consequence of a medical condition, substance withdrawal, toxicity or secondary to multiple aetiologies. Previous iterations of these diagnostic criteria have been operationalised into delirium assessment tools, such as the Confusion Assessment Method (CAM) (Inouye 2000), and the Delirium Rating Scale - Revised 1998 (DRS-R-98) (Trzepacz 1988; Trzepacz 2001). Delirium assessment tools may underestimate symptoms of hypoactive delirium. Detection of delirium with these instruments is operator-dependent and relies on adequate training.

Delirium duration is very variable and episodes may last from a few days to several months. Persistence of delirium beyond hospital discharge is common; meta-analysis of available prevalence estimates and different time points revealed 44.7% of patients still had evidence of delirium at hospital discharge, and about half of these had recovered by three months post discharge (Cole 2009). Up to 1 in 5 patients still had features of delirium at six months post hospital discharge and the relationship with more longer-lasting cognitive decline is poorly understood. People with pre-existing dementia are more likely to develop persistent delirium and their outcomes are particularly poor (Cole 2009).

A number of factors predispose to delirium and some of these cannot be modified. In some circumstances therefore, e.g. at the end of life or advanced frailty, delirium may be all but inevitable in the presence of a physiological stressor. Identification of effective treatment strategies that lessen symptoms or shorten the duration of delirium remain important.

## Description of the intervention

Treatment of delirium may be pharmacological or non-pharmacological. A Cochrane Review found some evidence to support the use of antipsychotic medication for the treatment of delirium (Lonergan 2007). Attention to the factors contributing to an episode of delirium may also be an effective treatment strategy. This Cochrane Review therefore aims to determine whether non-pharmacological interventions aimed at modification of delirium risk factors can attenuate established delirium.

Non-pharmacological interventions for the treatment of delirium may be targeted at ward level, e.g. modification of the ward environment or educational interventions to enable nurses and clinicians better to identify and manage delirium (Cole 2002; Milisen 2001; Naughton 2005; NICE 2010). Interventions could also be personalised to identify and attenuate risk factors specific to an individual, e.g. strategies to manage pain or improve hydration. Multicomponent interventions may attempt to target several risk factors simultaneously through the use of standardised protocols, staff and carer education, or systems redesign (e.g. proactive geriatric consultation) (Cole 2002; Milisen 2001; Pitkälä 2006); these may have components targeted at both a ward and individual level. An effective delirium treatment intervention may be aimed at relieving the distress that delirium causes, reducing associated harmful complications (such as falls) or attenuating delirium severity rather than resolution of the delirium episode.

## How the intervention might work

Reducing known precipitants of and risk factors for delirium will decrease the burden of factors contributing to (and possibly perpetuating) an episode of established delirium (NICE 2010). This may reduce the severity and duration of the episode. There is evidence that multicomponent interventions targeted at several risk factors concurrently are effective in prevention of delirium (reduction in incident delirium of about one-third) (Siddiqi 2016).

## Why it is important to do this review

Pharmacological treatment strategies for delirium are currently aimed at reducing symptoms of hyperactivity. Removing or modifying factors likely to be contributing to an episode of delirium is a common clinical treatment strategy but this approach is unsupported by the current evidence base: it is unclear whether an episode of established delirium can be attenuated through non-pharmacological strategies.

This Cochrane Review aims to establish the clinical effectiveness of non-pharmacological interventions for the treatment of established delirium, through examination of randomised and cluster-randomised trials. This will help to inform service design for the management of this distressing and harmful condition in older people.

## OBJECTIVES

To determine the effectiveness of single or multicomponent non-pharmacological interventions in reducing the symptoms, duration or severity of an established episode of delirium in hospitalised people outside intensive care settings.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

We will include all randomised controlled trials (RCTs), including cluster-RCTs.

#### Types of participants

We will include studies of patients with a diagnosis of delirium made either through fulfilment of the Diagnostic and Statistical Manual for Mental Disorders (DSM-V) (APA 2013), or the International Classification of Diseases (ICD10) criteria (WHO 2016), as assessed by a clinician or with a validated delirium assessment tool. We will include studies of delirium where the diagnosis is made at presentation (prevalent delirium) or during the course of hospital admission (incident delirium), but only where the intervention is aimed at treating established delirium.

We will include studies performed in patients aged 16 years or over, admitted to medical or surgical wards in general hospitals. We will exclude studies in intensive care unit settings, and studies of delirium associated with substance intoxication or withdrawal as the physiological stressors and population are different in these circumstances. We will consider studies of delirium in palliative care settings separately as delirium is a common complication of end of life care, where the focus of treatment is often control of symptoms (Hosker 2016).

#### Types of interventions

We will include trials that compare non-pharmacological interventions designed to treat delirium with usual care. Also we will include trials that compare an active control intervention. Trials of interventions aimed at single risk factors (e.g. medication review, hydration, re-orientation, occupational or physiotherapy interventions) or multicomponent interventions (combining one or more of these risk factors) will be eligible for inclusion. Interventions may be implemented at a ward or individual level. We will include studies of multicomponent interventions where one of the components is a pharmacological agent provided the drug is not the focus of the intervention. We will consider these types of interventions separately to interventions without a pharmacological component.

#### Types of outcome measures

We will include studies if they report any of the primary or secondary outcomes relating to the study of a multicomponent intervention. We will include studies that measure duration or severity of delirium through patient experience or patient-reported outcomes (e.g. relating to a reduction in delirium symptoms or improved quality of life).

##### Primary outcomes

- Duration of delirium, measured as either the number of days that delirium is detected using a validated delirium diagnostic method or the duration of the episode as reported by study authors. We will only include studies in which clinical experts (psychiatrists, old age psychiatrists, geriatricians) or clinical or research staff trained according to standardised training methods performed the delirium assessments.

##### Secondary outcomes

- Peak reported delirium severity measured by a validated instrument such as the Delirium Rating Scale Revised 1998 (DRS-R98) (Trzepacz 2001), Memorial Delirium Assessment Scale (MDAS) (Breibart 1997), or Delirium Rating Scale (Trzepacz 1988), by assessors trained using standardised methods.
- Length of hospital admission.
- New diagnosis of dementia made between 1 and 3 months, 6 and 12 months, and beyond 12 months from randomisation.
- Progression of existing dementia measured with a validated scale between 1 and 3 months, 6 and 12 months, and beyond 12 months from randomisation.
- Use of psychotropic medicines during admission.
- Delirium symptoms including cognitive, perceptual, psychotic, affective and behavioural disturbance during admission measured through objective or patient experience measures (e.g. Delirium Observation Screening Scale (Schuurmans 2003)).
- New move to institutional care facilities at discharge, between 1 and 3 months, 6 and 12 months, and beyond 12 months from randomisation.
- Activities of daily living between 1 and 3 months, 6 and 12 months, and beyond 12 months from randomisation.
- Quality of life (through validated patient reported measure) between 1 and 3 months, 6 and 12 months, and beyond 12 months from randomisation.

- Carer's quality of life (reported through validated carer-reported measure) between 1 and 3 months, 6 and 12 months, and beyond 12 months from randomisation.
- Direct costs of interventions.
- Cost-effectiveness of interventions.
- Withdrawal from protocol by participants.

#### Adverse events

- Readmission to acute hospital within 30 days of discharge.
- Falls.
- Pressure ulcers.
- Nosocomial infections.
- Mortality as an inpatient, between 1 and 3 months, 6 and 12 months, and beyond 12 months from randomisation

We will use GRADEpro Guideline Development Tool (GDT) software to determine the overall quality of the evidence and to generate a 'Summary of findings' table for the key primary and secondary outcomes of duration of delirium, peak reported delirium severity, length of hospital admission, new move to institutional care facilities at discharge, new diagnosis of dementia or progression of existing dementia, and the adverse event of mortality as an inpatient (GRADEpro 2014).

## Search methods for identification of studies

### Electronic searches

We will search the specialised register of the Cochrane Dementia and Cognitive Impairment Group (ALOIS) ( www.medicine.ox.ac.uk/alois). We will search for all RCTs or non-pharmacological interventions for treating delirium.
ALOIS contains records from all major healthcare databases. The Information Specialist of the Cochrane Dementia and Cognitive Impairment Group maintains ALOIS, which contains studies about dementia and cognitive impairment identified from the following.

- Monthly searches of a number of major healthcare databases: MEDLINE, Embase, CINAHL, PsychINFO and LILACs.
- Monthly searches of a number of trials registers: the metaRegister of Controlled Trials, the Umin Japan Trial Register, the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) portal (which covers ClinicalTrials.gov, ISRCTN Registry, the Chinese Clinical Trials Register, the German Clinical Trials Register, the Iranian Registry of Clinical Trials and The Netherlands Clinical Trials Register, plus others).
- Quarterly searches of the Cochrane Library's Central Register of Controlled Trials (CENTRAL).
- Monthly searches of a number of a grey literature sources: ISI Web of Knowledge Conference Proceedings, Index to Theses, and Australasian Digital Theses.

To view a list of all sources searched for ALOIS see About ALOIS on the ALOIS website (www.medicine.ox.ac.uk/alois).
Details of the search strategies run in healthcare bibliographic databases, used for the retrieval of reports of dementia, cognitive improvement and cognitive enhancement trials, can be viewed in the 'methods used in reviews' section within the editorial information about the Cochrane Dementia and Cognitive Improvement Group.
We will run additional searches in MEDLINE, Embase, PsycINFO, CINAHL, ClinicalTrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) portal to ensure that the searches for each suite of reviews are as comprehensive and as up-to-date as possible. We have presented the search strategy that we will use for the retrieval of reports of trials from MEDLINE (via the Ovid SP platform) in Appendix 1. There will be no time or language restraints on literature searches.

### Searching other resources

We will examine reference lists of retrieved articles and relevant reviews to identify any additional potential trials for inclusion. We will perform a search of the ClinicalTrials.gov database, to identify any relevant ongoing trials. We will compare the trials that meet the inclusion criteria of our review with the trials register to identify any trials where results are unpublished. We will contact the lead author of any unpublished trials and request results. We will examine published reports against their protocols to ensure per protocol analysis has occurred. The search for ongoing clinical trials will help to inform future updates of this Cochrane Review.

## Data collection and analysis

### Selection of studies

We will merge the results of the literature search into Covidence software (Covidence 2017). We will collate multiple reports of the same studies and we will remove duplicates. Two review authors with experience in conducting systematic reviews will independently screen the titles and abstracts of the articles identified from the literature searches and will exclude irrelevant titles. We will resolve any disagreement by consensus with a third review author. Two review authors will independently examine the full-text articles of potentially relevant studies against the stated eligibility criteria, and will resolve any disagreements by consensus with a third review author. If there is insufficient information in the full-text article, we will contact the study authors for clarification. We will

list all articles excluded after full-text assessment and their reasons for exclusion in a 'Characteristics of excluded studies' table. We will present the study selection process in a PRISMA diagram.

### Data extraction and management

Two review authors will extract data using a piloted data extraction tool. We will resolve any disagreements regarding data extraction by consensus with a third review author. We will produce 'Characteristics of included studies' tables, 'Characteristics of excluded studies' tables, 'Characteristics of ongoing trials' tables and a 'Summary of findings' tables using Review Manager 5 (RevMan 5) (Review Manager 2014), and GRADEpro GDT software (GRADEpro 2014). We will extract data from multiple reports of the same study directly into a single data extraction form.

### Assessment of risk of bias in included studies

Two review authors will independently determine the risk of bias as either high, low or unclear against the criteria identified in the *Cochrane Handbook of Systematic Reviews of Interventions* (Higgins 2011). We will resolve any disagreements through reaching a consensus with a third review author. We will assess included trials for adequacy of sequence generation, allocation concealment, blinding (of participants, personnel and of outcome assessors), incomplete outcome data, selective outcome reporting and other sources of bias. Cluster-RCTs are subject to additional biases: recruitment bias (recruitment of individual study participants after randomisation of clusters), chance between-cluster baseline imbalances due to a small number of clusters, loss of clusters (e.g. withdrawal of a study site), not accounting for clustering during the analysis (incorrect unit of analysis issues) or bias introduced through combining data from cluster- and individually-randomised trials in meta-analyses (risk of underestimation of treatment effects). We will generate summaries of risk of bias in RevMan 5 (Review Manager 2014). We will include additional rows in the 'Risk of bias' tables specifically to assess for the potential biases associated with cluster-RCTs.

### Measures of treatment effect

We anticipate that we will find a combination of continuous and dichotomous outcome measures across included studies. Where possible we will undertake meta-analysis of extracted data using RevMan 5 (Review Manager 2014). We will calculate between group (intervention vs control) mean differences in the continuous outcomes with 95% confidence intervals (CIs). The minimally important difference (MID) for the primary outcome of delirium duration will be one day. Where studies report the same outcome measured with different instruments, we will report standardised mean difference (SMD) values with 95% CIs. Where SMD are used, the MID will be based on detection of a small effect size (SMD of less than 0.4). For any dichotomous secondary outcome measure, we will calculate risk ratios (RRs) (intervention vs control) with 95% CIs. We will analyse time-to-event data with hazard ratios (HRs). If an included study does not report data to determine the primary outcomes, we will attempt to obtain data by contacting the study authors directly.

### Unit of analysis issues

We expect some included studies to use a cluster-randomised design. Where these studies have analysed data using statistical methods that account for clustering, we will extract the adjusted effect measures (RR or HR) and their 95% CIs. If an included study has performed unadjusted analyses we will approximate corrected analyses by extracting data on the number of clusters, mean size of each cluster, primary outcome data and estimates of intra-cluster correlation coefficient (ICC). If approximately corrected analyses are not possible, then we will extract the primary data and calculate RRs with 95% CIs.

### Dealing with missing data

We will assess missing outcome data due to attrition or exclusions for each included study. If available, we will report the reasons for incomplete outcomes data due to participants or clusters lost to follow-up. Where a study has not reported relevant data, we will try to obtain these data by contacting the study authors directly. We will perform available-case analysis and will only include cases where outcomes are known. We will report incomplete outcomes data in 'Risk of bias' tables and will include an assessment of the potential impact of missing data on the results.

### Assessment of heterogeneity

The nature of complex interventions for delirium treatment is likely to result in both clinical and methodological heterogeneity. We will complete an assessment of clinical heterogeneity among the treatments identified. Where synthesis is appropriate, we will estimate the extent of (combined) heterogeneity across studies included in the meta-analysis by using the $I^2$ statistic.

### Assessment of reporting biases

We will compare the studies included in our review against databases and international registries of clinical trials to identify trials with unpublished results. We will examine published studies against their protocols to ensure protocol adherence. A search for ongoing clinical trials will identify studies that should be included in future updates of this Cochrane Review.

### Data synthesis

We will perform meta-analyses using a random-effects inverse variance model. We will present pooled RRs with 95% CIs for dichotomous outcomes and pooled mean differences with 95% CIs for continuous outcomes (standardised if the included studies have used different instruments to measure the same outcome). We will synthesise outcomes from appropriately adjusted cluster-RCTs using generic inverse variance models. We will not synthesise data for meta-analysis if clinical heterogeneity is such that we cannot make valid outcome comparisons; instead we will undertake a narrative evidence synthesis.

### Subgroup analysis and investigation of heterogeneity

We will perform subgroup analyses for individuals in trials with and without a clinical diagnosis of dementia or frailty (measured with a validated instrument).

### Sensitivity analysis

We will perform sensitivity analyses where appropriate following our assessment of the risk of methodological bias in the included trials. This will include sensitivity analysis of studies where a pharmacological agents forms part of a multicomponent intervention.

## ACKNOWLEDGEMENTS

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* *Indicates the major publication for the study*

# APPENDICES

## Appendix 1. MEDLINE search strategy

1. Delirium/
2. deliri*.mp.
3. "acute confusion*".ti,ab.
4. "acute organic psychosyndrome".ti,ab.
5. "acute brain syndrome".ti,ab.
6. "metabolic encephalopathy".ti,ab.
7. "acute psycho-organic syndrome".ti,ab.
8. "clouded state".ti,ab.
9. "clouding of consciousness".ti,ab.
10. "exogenous psychosis".ti,ab.
11. "toxic psychosis".ti,ab.
12. "toxic confusion".ti,ab.
13. Delirium, Dementia, Amnestic, Cognitive Disorders/su [Surgery]
14. obnubilat*.ti,ab.
15. or/1-14
16. (coordinat* OR "co-ordinat*").ti,ab.
17. prevent*.mp.
18. reduc*.ti,ab.
19. stop*.ti,ab.
20. taper*.ti,ab.
21. avoid*.ti,ab.
22. "cut* down".ti,ab.
23. manag*.ti,ab.
24. prog*.ti,ab.
25. or/16-24
26. 15 and 25
27. randomized controlled trial.pt.
28. controlled clinical trial.pt.
29. randomi?ed.ab.
30. placebo.ab.
31. drug therapy.fs.
32. randomly.ab.
33. trial.ab.
34. groups.ab.
35. or/27-34
36. (animals not (humans and animals)).sh.
37. 35 not 36

## WHAT'S NEW

| Date | Event | Description |
|---|---|---|
| 6 April 2017 | New citation required and major changes | Change in scope. Change in author team. |

## CONTRIBUTIONS OF AUTHORS

ET designed, developed and drafted protocol, and co-ordinated contributions from the other protocol authors.

NS contributed to the design of the review methodology and drafted the manuscript.

AC contributed to designing and drafting the protocol and the review methodology.

OT contributed to review design and critical appraisal of the manuscript.

JY critically appraised the protocol manuscript.

All protocol authors approved the manuscript.

## DECLARATIONS OF INTEREST

ET has no known conflicts of interest.

NS has no known conflicts of interest.

AC has no known conflicts of interest.

OT has no known conflicts of interest.

JY has no known conflicts of interest.

## SOURCES OF SUPPORT

### Internal sources

- No sources of support supplied

### External sources

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