Cholinesterase inhibitors for the treatment of delirium in non-ICU settings (Protocol)

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Cholinesterase inhibitors for the treatment of delirium in non-ICU settings

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Editorial group: Cochrane Dementia and Cognitive Improvement Group.


Abstract

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

To evaluate the effectiveness and safety of cholinesterase inhibitors for treating established delirium in people in a non-ICU setting.

Background

This is an update of a previous Cochrane Review, ‘Cholinesterase inhibitors for delirium’, which was first published in Issue 1, 2008 (Overshott 2008).

Description of the condition

Delirium, an acute confusional state, has been described as “a transient global disorder of cognition and attention” (Luxenberg 1996). The presence of delirium may not be recognised due to the transient and fluctuating nature of symptoms and diverse presentations, which include three subtypes according to the patterns of motor activity: hyperactive, hypoactive and mixed when both hypoactive and hyperactive features are present (O’Keeffe 1999). The fifth edition of American Psychiatric Association’s Diagnostic and Statistical Manual of Mental Disorders (DSM-V) and the 10th Revision of the International Classification of Diseases (ICD-10) provide the current reference diagnostic criteria (Inouye 2014). In clinical practice, it is important to screen at-risk people for delirium with validated instruments to help clarify the diagnosis. These validated instruments screen for key diagnostic features of delirium including an acute onset and fluctuating course of symptoms, inattention, impaired consciousness and disturbance of cognition (Schwartz 2016). More than 24 delirium instruments have been used in published studies (Inouye 2014). The Confusion Assessment Method (CAM) is probably the most frequently used diagnostic instrument worldwide and has excellent specificity (Steiner 2011).

The causes of delirium are multifactorial and include patient vulnerability factors (dementia or cognitive impairment, ageing, medical comorbidity, malnutrition, history of alcohol abuse and prescription opioid or benzodiazepine use, among others) and potentially modifiable factors (such as infections, dehydration, electrolyte abnormalities, polypharmacy, seizures and surgery)
Delirium is common in all hospital settings as many hospitalised people will have risk factors for delirium. The highest incidence rates are noted in intensive care unit (ICU) and in postoperative and palliative care settings. In the ICU, incidence rates of up to 80% are reported (Ely 2004; Ouimet 2007). The ICU is a complex environment, in which the patients appear to differ from other settings, for example they are younger than patients in other settings. Treatment priorities also tend to differ with medical treatment in the ICU focused on the management of life-threatening illness rather than the rehabilitative focus often needed for elderly people in medical and surgical wards. It is reasonable to suspect potential clinical heterogeneity between ICU and non-ICU settings. Since the Cochrane Anaesthesia, Critical and Emergency Care Group are investigating delirium in the ICU setting (Greve 2012), this review will cover delirium in non-ICU settings only. The incidence of postoperative delirium varies with different types of surgery, with reported rates, for example, of 12% to 50% after non-cardiac surgery (Brouquet 2010; Olin 2005; Shah 2012), up to 51% after cardiac surgery (Zhang 2015), and 12% to 61% after orthopaedic operations (Holmes 2000). The incidence of delirium in palliative care settings ranges from 3% to 45% (Perr 2013). In general medical and geriatric medicine wards, incidence rates range from 11% to 29% (Inouye 2014). The prevalence of delirium at admission to these wards is also high (18% to 35% in general medical wards, Inouye 2014); when combined with new incidences postadmission, the overall occurrence of delirium in these settings is relatively high. The epidemiology of delirium in the emergency department is not as well established (Vasilevsks 2012). Delirium is not exclusive to hospital settings and one study shows the incidence of delirium is 20% in nursing home residents who experience an acute illness (Flaherty 2013).

Delirious people experience increased mortality, postoperative complications (Raats 2015), readmissions (McKhann 2002), poorer functional outcomes (Inouye 1998), increased length of hospital stay (McCusker 2003), and higher healthcare expenditures (Leslie 2008).

How the intervention might work

The mechanisms of delirium are complex and unclear. Several theories have been proposed to explain the processes leading to the development of delirium (Maldonado 2008). One of the leading hypotheses is that delirium results from an impairment of central cholinergic transmission and is considered by some investigators to be ‘a common denominator’ in delirium (Blass 1981). Acetylcholine is the main neurotransmitter mediating learning and attention, and these functions are profoundly disturbed during delirium. Impaired cholinergic function is correlated with the cognitive and behavioural changes in delirium (Trzepacz 1996). Furthermore, drugs with anticholinergic effects may induce delirium, and cholinergic drugs can improve delirium induced by lithium and anticholinergic medication (Oldenbeuving 2008). Acetylcholinesterase inhibitors, by inhibiting the activity of the enzymes which metabolise acetylcholine, cause increased cholinergic activ-
ity at synapses. Therefore, by treating the presumed cholinergic deficiency in people with delirium, acetylcholinesterase inhibitors may have beneficial effects.

Why it is important to do this review
This review will update and replace the previous review “Cholinesterase inhibitors for delirium” which was published in 2008 (Overshott 2008). That review included only one trial (Liptzin 2005) comparing donepezil with placebo in the prevention and treatment of postoperative delirium in people over the age of 50 years without dementia who were undergoing elective total joint replacement. Since then, more studies have been conducted with various cholinesterase inhibitors in different settings. Hence, it is necessary to update this review. As noted above, delirium in people in ICU and its optimal management may be different from that in people in a non-ICU setting. Therefore, this update will focus on cholinesterase inhibitors for delirium in non-ICU settings.

OBJECTIVES
To evaluate the effectiveness and safety of cholinesterase inhibitors for treating established delirium in people in a non-ICU setting.

METHODS

Criteria for considering studies for this review

Types of studies
We will include randomised controlled trials, published or unpublished, reported in English and Chinese.

Types of participants
We will include participants over 16 years of age, of either gender, diagnosed with delirium by standardised diagnostic criteria (e.g. DSM-IV, DSM-V, ICD-10). If studies state that people had delirium but have not used standardised diagnostic criteria, then we will include these studies in our meta-analysis and conduct sensitivity analyses to test whether the inclusion criteria influence the results. We will include participants who experience any cause of delirium, such as medical illnesses and adverse effects from medication. We will exclude people with delirium due to alcohol/drug withdrawal. We will include studies conducted in either hospital or community settings, but will exclude ICU settings.

Types of interventions
We will include trials assessing the effect of any of the currently marketed cholinesterase inhibitors (e.g. donepezil, rivastigmine, galantamine, tacrine and physostigmine), administered at any dose and at any frequency, compared with placebo. We will also include head-to-head comparisons of a cholinesterase inhibitor with another drug intended to treat delirium (e.g. antipsychotic drugs, α2-adrenoceptor agonists, benzodiazepines, melatonin). Included trials may involve non-pharmacological management strategies if we can extract data from groups which differed only in exposure to cholinesterase inhibitor and placebo/comparator medication.

Types of outcome measures

Primary outcomes
- Response to treatment:
  - Duration of delirium;
  - Severity of delirium measure by validated scales (e.g. Memorial Delirium Assessment Scale (MDAS) (Breitbart 1997), Delirium Rating Scale (DRS) (Trzepacz 1988), or DRS-R-98 (Trzepacz 2001)).
- Adverse effects.

Secondary outcomes
- Use of rescue medications (e.g. one-off doses of antipsychotic drug).
- Persistent cognitive impairment (defined by original studies).
- Length of hospitalisation.
- Institutionalisation.
- Mortality.
- Cost of intervention (such as direct monetary cost of intervention to participants or healthcare services).
- Leaving the study early.
- Quality of life.

Search methods for identification of studies

Electronic searches
We will search ALOIS (www.medicine.ox.ac.uk/alois), which is the Cochrane Dementia and Cognitive Improvement Group’s Specialised Register. ALOIS is maintained by the Trials Search Co-ordinator and contains dementia and cognitive improvement studies identified from:
- quarterly search of the Cochrane Central Register of Controlled Trials (CENTRAL).
• monthly searches of major healthcare databases: MEDLINE, Embase, CINAHL, PsycINFO and LILACS,
• monthly searches of trial registers: metaRegister of Controlled Trials; Umin Japan Trial Register; World Health Organization portal (which covers ClinicalTrials.gov; ISRCTN; Chinese Clinical Trials Register; German Clinical Trials Register; Iranian Registry of Clinical Trials and the Netherlands National Trials Register, plus others).
• monthly searches of a grey literature source: ISI Web of Science Conference Proceedings.

To view a list of all sources searched for ALOIS see About ALOIS. We will run additional separate searches of many of the above sources to ensure that we retrieve the most up-to-date results. The search strategy that we will use for the retrieval of reports of trials from MEDLINE (via the OvidSP platform) is in Appendix 1.

Searching other resources
We will cross-check the reference lists of included studies to identify any potentially eligible trials.

Data collection and analysis

Selection of studies
Two review authors (AY and SW) will independently assess each abstract and title for relevance. We will obtain the full texts of citations that describe a potentially relevant randomised controlled trial for further assessment. Two review authors will independently determine eligibility of these trials for inclusion. We will resolve disagreements at any stage of study selection by discussion or by the involvement of a third review author (ZZ).

Data extraction and management
Two review authors (AY and SW) will independently extract data using prespecified data extraction forms. A pilot data extraction will be performed before the formal data extraction. We will resolve any discrepancy by discussion. We will collect the following information where possible:

Participants’ characteristics
• Age.
• Sex.
• Education.
• Diagnostic criteria of delirium.
• Severity of delirium.
• Underlying aetiology of delirium.
• Baseline comorbid dementia.

Intervention characteristics
• Types of cholinesterase inhibitors.
• Description of the comparator.
• Dose, route, frequency and duration of cholinesterase inhibitor and comparator.
• Duration of treatment.
• Any concomitant treatments.

Outcomes
• Outcomes as outlined in Types of outcome measures.
• Definition, instruments and measured time points of outcomes.

Methodological characteristics
• Sample size.
• Duration of follow-up.
• Information needed for risk of bias assessments.

For continuous data, we will extract the mean, standard deviation and number of participants for each treatment group at each time point if available. For dichotomous data, we will retrieve the number in each treatment group and numbers experiencing the outcome of interest where possible. If only treatment effects and their standard errors are reported, then we will extract these.

Assessment of risk of bias in included studies
Two review authors (AY and SW) will independently assess the risk of bias of each included study using the Cochrane ‘Risk of bias’ tool (Higgins 2011), which evaluates the following risk domains: random sequence generation; allocation concealment; blinding of participants, personnel and outcome assessors; incomplete outcome data; selective outcome reporting and other potential sources of bias (including source of financial support). We will use the criteria reported in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). The following judgements will be applied to each domain: low risk, high risk or unclear risk (either lack of information or uncertainty over the potential for bias). Review authors will resolve disagreements by consensus, and a third author (ZZ) will be consulted to resolve disagreements if necessary.
Measures of treatment effect
Where trials have used the same rating scale to assess outcome, we will calculate mean difference (MD) with a 95% confidence interval (CI). We will use the standardised mean difference (SMD) for continuous data if different rating scales were used to measure the same outcome. We will express the treatment effect for dichotomous outcomes as a risk ratio (RR) with a 95% CI.

Unit of analysis issues
For studies with multiple eligible treatment group, we will use one of the approaches described in Section 16.5.4 of the Cochrane Handbook for Systematic Reviews of Interventions to overcome the unit-of-analysis error (Higgins 2011). Our preferred approach will be to merge all relevant experimental intervention groups of the study into a single group, and to merge all relevant control intervention groups into a single control group. If this approach is not suitable, then we will include all relevant experimental groups and split the shared control group.

Dealing with missing data
For all outcomes, we will report on missing outcome data and will consider and discuss the potential impact of the missing data on results. In the case where attrition for a continuous outcome is between 0% and 50%, and data only from people who complete the study to that point are reported, we will reproduce these. We anticipate that some studies will use the method of last observation carried forward (LOCF) or other imputation methods. If less than 50% of the data has been imputed, we will present and use these data and report the imputation method used. For studies with more than 50% of imputed data, we will conduct a sensitivity analysis by excluding these studies to test the robustness of the result. If standard deviations are not reported, we will first try to obtain the missing values from the study authors. If this is not possible, then we will attempt to calculate standard deviations from statistics available in the study report according to the methods described in the Cochrane Handbook for Systemic Reviews of Interventions (Higgins 2011).

Assessment of reporting biases
We will assess the possibility that publication bias affected the review using a funnel plot to identify small-study effects where at least 10 studies are available for meta-analysis.

Data synthesis
Meta-analyses will be conducted using the Mantel-Haenszel method for dichotomous outcomes, and the inverse variance method for continuous outcome. We will use random-effect model for all analyses. Where the statistical heterogeneity is significant (P value from Chi² test < 0.1 and I² greater than 50%), we will explore and address the source of heterogeneity as described in the Subgroup analysis and investigation of heterogeneity section.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis
Where data allow, we will conduct subgroup analysis according to:
- participant age (older than 65 years versus 65 years or younger);
- different causes of delirium (e.g. postoperative delirium, adverse events to medication or hepatic encephalopathy delirium)
- presence or absence of pre-existing dementia or neurocognitive impairment.

Investigation of heterogeneity
Where there is evidence of statistical heterogeneity (P value from Chi² < 0.1 and I² greater than 50%) of the treatment effect between trials, we will explore the source of heterogeneity. We will conduct subgroup analysis if we can identify possible sources of variation; otherwise, we will use a random-effect model to pool the data. Where statistical heterogeneity is significant in a meta-analysis, we will consider downgrading the certainty of evidence using the GRADE approach (Section 11.5; Higgins 2011).

Sensitivity analysis
Where possible, we will conduct sensitivity analysis to explore the influence of the quality of trials by excluding data from low-quality trials. We define low-quality trials as more than 50% data in one arm of the study is lost or studies with high risk of selection bias and high risk of detection bias due to non-blend outcome assessment. We will also conduct sensitivity analysis to investigate the difference between results from completers only and intention-to-treat analysis (for primary outcomes only). We will present results...
from both approaches separately and discuss the results at the full review stage.

'Summary of findings' table

For each comparison, we will use the GRADE approach to assess the quality of the body of evidence for all outcomes (Guyatt 2008; Higgins 2011). We will present the following results in 'Summary of findings' tables:

- duration of delirium;
- severity of delirium;
- adverse effects;
- persistent cognitive impairment;
- length of hospitalisation;
- mortality;
- cost of intervention.

Grading of the evidence has four possible ratings: high, moderate, low, and very low. Evidence with 'high certainty' rating indicates that we are confident in our estimate of the effect, and further research is very unlikely to change this. Whereas, a rating of 'very low' certainty implies that we are very uncertain about the estimate of the effect. Initially, the GRADE approach rates evidence from randomised controlled trials as 'high quality'. However, several factors can lead to the downgrading of the evidence, these are: study limitations (risk of bias); inconsistency; indirectness of evidence; imprecision and publication bias (Guyatt 2008; Higgins 2011).

ACKNOWLEDGEMENTS

None.

REFERENCES

Additional references

Blass 1981

Breitbart 1997

Brouquet 2010

Catic 2011

Ely 2004

Flaherty 2013

Greve 2012

Guyatt 2008

Hail 2013

Higgins 2011

Hilliard 2015

Holmes 2000

Inouye 1998
Inouye 2014

Kishi 2016

Leslie 2008

Liptzin 2005

Litvineneko 2010

Lucyk 2014

Luxenberg 1996

Maldonado 2008

Marcantonio 2011

Martinez 2012

McCusker 2003

McKhann 2002

O’Keeffe 1999

Oldenbeuving 2008

Olin 2005

Ouimet 2007

Overshott 2008

Perrr 2013

Raats 2015

Sampson 2007

Schwartz 2016

Shah 2012
Steiner 2011

Trzepacz 1988

Trzepacz 1996

Trzepacz 2001

Van Eijk 2010

Vasilevskis 2012

Yapici 2011

Young 2010

Zhang 2015

Zujalovic 2015

* Indicates the major publication for the study

APPENDICES

Appendix I. MEDLINE search strategy
1. exp Cholinesterase Inhibitors/
2. "cholinesterase inhibitor*".mp.
3. Galantamine/
4. (galantamine or galanthamine or galant?amin).mp.
5. (reminyl* or Nivalin* or Razadyne*).mp.
6. donepezil.mp.
8. rivastigmine.mp.
9. rivastigmin.mp.
11. exp Tacrine/
12. cognex.mp.
13. or/1-12
14. delir*.mp.
15. confusion.mp.
17. "acute organic psychosyndrome".mp.

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19. "metabolic encephalopathy".mp.
22. "clouding of consciousness".mp.
23. "exogenous psychosis".mp.
24. "toxic psychosis".mp.
25. "toxic confusion".mp.
26. exp Delirium/
27. or/14-26
28. 13 and 27
29. randomized controlled trial.pt.
30. controlled clinical trial.pt.
31. randomi/ed.ab.
32. placebo.ab.
33. drug therapy.fs.
34. randomly.ab.
35. trial.ab.
36. groups.ab.
37. or/29-36
38. (animals not (humans and animals)).sh.
39. 37 not 38
40. 28 and 39

CONTRIBUTIONS OF AUTHORS

ZZ: protocol development.
JX: project management, protocol development, Methodological Expectations of Cochrane Intervention Reviews (MECIR) guidance.
TD: content expert, protocol development.
SZ: protocol development.
AY: protocol development.
SW: Protocol development.
GTP: content expert, protocol development.
DY: content expert, protocol development.

DECLARATIONS OF INTEREST

All authors have no known conflict of interest.
SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

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