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

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[Intervention Review]

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

Ailan Yu[1], Shanshan Wu[1], Zongwang Zhang[1], Tom Dening[2], Sai Zhao[3], Gillian Pinner[4], Jun Xia[5], Daogui Yang[6]

[1]Anaesthesiology, Liaocheng People's Hospital, Liaocheng City, China. [2]Division of Psychiatry & Applied Psychology, The University of Nottingham, Nottingham, UK. [3]Systematic Review Solutions Ltd, The Ingenuity Centre, The University of Nottingham, Nottingham, UK. [4]Old Age Psychiatry, The University of Nottingham, Nottingham, UK. [5]Cochrane Schizophrenia Group, Institute of Mental Health, University of Nottingham, Nottingham, UK. [6]Department of Gastrointestinal Surgery, Liaocheng People's Hospital, Liaocheng, China

Contact address: Zongwang Zhang, Anaesthesiology, Liaocheng People's Hospital, No.67 Dongchang West Road, Liaocheng City, Shandong, China. zwzhang68@sina.com.

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ABSTRACT

Background

Delirium is a common clinical syndrome defined as alterations in attention with an additional disturbance in cognition or perception, which develop over a short period of time and tend to fluctuate during the course of the episode. Delirium is commonly treated in hospitals or community settings and is often associated with multiple adverse outcomes such as increased cost, morbidity, and even mortality. The first-line intervention involves a multicomponent non-pharmacological approach that includes ensuring effective communication and reorientation in addition to providing reassurance or a suitable care environment. There are currently no drugs approved specifically for the treatment of delirium. Clinically, however, various medications are employed to provide symptomatic relief, such as antipsychotic medications and cholinesterase inhibitors, among others.

Objectives

To evaluate the effectiveness and safety of cholinesterase inhibitors for treating people with established delirium in a non-intensive care unit (ICU) setting.

Search methods

We searched ALOIS, which is the Cochrane Dementia and Cognitive Improvement Group's Specialised Register, on 26 October 2017. We also cross-checked the reference lists of included studies to identify any potentially eligible trials.

Selection criteria

We included randomised controlled trials, published or unpublished, reported in English or Chinese, which compared cholinesterase inhibitors to placebo or other drugs intended to treat people with established delirium in a non-ICU setting.

Data collection and analysis

We used the standard methodological procedures expected by Cochrane. The primary outcomes were duration of delirium, severity of delirium, and adverse events. The secondary outcomes were use of rescue medications, persistent cognitive impairment, length of hospitalisation, institutionalisation, mortality, cost of intervention, leaving the study early, and quality of life. For dichotomous outcomes, we calculated the risk ratio (RR) with 95% confidence intervals (CIs); for continuous outcomes we calculated the mean difference (MD) with 95% CIs. We assessed the quality of evidence using GRADE to generate a 'Summary of findings' table.

Main results

We included one study involving 15 participants from the UK. The included participants were diagnosed with delirium based on the Confusion Assessment Method (CAM) criteria. Eight males and seven females were included, with a mean age of 82.5 years. Seven of the 15 participants had comorbid dementia at baseline. The risk of bias was low in all domains.

The study compared rivastigmine with placebo. We did not find any clear differences between the two groups in terms of duration of delirium (MD -3.6, 95% CI -15.6 to 8.4), adverse events (nausea, RR 0.30, 95% CI 0.01 to 6.29), use of rescue medications (RR 0.13, 95% CI 0.01 to 2.1), mortality (RR 0.10, 95% CI 0.01 to 1.56), and leaving the study early (RR 0.88, 95% CI 0.07 to 11.54). Evidence was not available regarding the severity of delirium, persistent cognitive impairment, length of hospitalisation, cost of intervention, or other predefined secondary outcomes.

The quality of evidence is low due to the very small sample size.

Authors' conclusions

There is insufficient evidence to support or refute the use of cholinesterase inhibitors for the treatment of delirium in non-ICU settings. No clear benefits or harms associated with cholinesterase inhibitors were observed when compared with placebo due to the lack of data. More trials are required.

PLAIN LANGUAGE SUMMARY

Cholinesterase inhibitors for people with delirium, not including those in intensive care units

Background

During a period of illness, people can develop symptoms of confusion and altered consciousness, which is known as delirium. Compared to patients with no delirium, patients with delirium spend a longer time in hospital and are less likely to survive their illness. Treatment of delirium should focus on good care of the underlying illness and strategies such as reorientation of the patient. However, medication-based treatments are still often used. Medications used for treating the symptoms of dementia (cholinesterase inhibitors) may have a role in treating delirium.

Review question

We wished to find out if treatment with a cholinesterase inhibitors reduces the severity or duration of delirium. We were also interested in side effects from cholinesterase inhibitors. Delirium is often seen in severe illnesses that require high levels of medical and nursing care, for example in the intensive care unit. In this review we focused on studies of patients who were not in a high-level care setting.

Study characteristics

We found one trial from the UK, which included 15 participants with delirium. The average age of the participants was 82.5 years; eight participants were male and seven were female. Seven participants also had a history of dementia. This trial compared rivastigmine (a type of cholinesterase inhibitor used in the treatment of dementia) with an inactive treatment (placebo).

Key results

The trial did not show any difference in effect between those participants given rivastigmine and those given placebo. The study was conducted and reported appropriately, but the small number of participants limits any conclusions that could be made about rivastigmine as a treatment for delirium.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Cholinesterase inhibitors (rivastigmine) compared to placebo for the treatment of delirium in non-ICU settings

Patient or population: people with delirium
Settings: non-ICU
Intervention: cholinesterase inhibitors (rivastigmine)*
Comparison: placebo

Outcomes	Illustrative comparative risks** (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Cholinesterase inhibitors (rivastigmine)				
Duration of delirium days Follow-up: 42 days	The mean duration was **9.9 days**	The mean duration was **3.6 days lower** (15.6 lower to 8.4 higher)	Not estimable	15 (1 study)	⊕⊕◯◯ **Low**[1]	The data were reported by Overshott 2010. The study was grossly underpowered, and the data were skewed
Severity of delirium CAM negative Follow-up: 28 days	See comment	See comment	See comment	See comment	See comment	No study reported this outcome.
Adverse events nausea Follow-up: 42 days	**143 per 1000**	**43 per 1000** (1 to 899)	**RR 0.3** (0.01 to 6.29)	15 (1 study)	⊕⊕◯◯ **Low**[1]	
Persistent cognitive impairment	See comment	See comment	See comment	See comment	See comment	No study reported this outcome.
Length of hospitalisation	See comment	See comment	See comment	See comment	See comment	No study reported this outcome.

Mortality Follow-up: 42 days	**571 per 1000**	**57 per 1000** (6 to 891)	**RR 0.1** (0.01 to 1.56)	15 (1 study)	⊕⊕◯◯ **Low**[1]	
Cost of intervention	See comment	See comment	See comment	See comment	See comment	No study reported this outcome.

*The dose of intervention: 1.5 mg once a day increasing to 1.5 mg twice a day after 7 days
The basis for the **assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CAM: Confusion Assessment Method; **CI:** confidence interval; **ICU:** intensive care unit; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1]Downgraded twice for imprecision due to very small sample size.

BACKGROUND

This review supersedes a previous Cochrane Review, 'Cholinesterase inhibitors for delirium', which was first published in Issue 1, 2008 (Other published versions of this review).

Description of the condition

Delirium is a common clinical syndrome characterised by alterations in attention and additional disturbances in cognitive function or perception, which has an acute onset and a fluctuating course (APA 2013).

Delirium is a neuropsychiatric disturbance with multiple aetiologies and can be the consequence of a medical condition, substance intoxication or withdrawal, or exposure to a toxin (APA 2013). The causes of delirium are multifactorial and include patient vulnerability factors (such as 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) (Inouye 2014; Vasilevskis 2012). The core symptoms of delirium include altered levels of attention and awareness that typically develop over a short period of time and represent a change from the patient's baseline level of attention and awareness. These alterations may fluctuate in severity throughout the course of the episode, at times worsening in the evening and overnight (APA 2013; Schwartz 2016). People with delirium experience increased mortality, postoperative complications (Raats 2015), readmissions (McKhann 2002), poorer functional outcomes (Inouye 1998), risk of dementia (Davis 2012), length of hospital stay (McCusker 2003), and higher healthcare expenditures (Leslie 2008).

Delirium can manifest as hyperactivity, hypoactivity, or mixed (when both hypoactive and hyperactive features are present) (NICE 2014). The fifth edition of the 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 standard reference diagnostic criteria (APA 2013; WHO 1993). Over the years, various diagnostic and screening instruments have been developed for making the diagnosis of delirium based on the DSM criteria, and these have been used or adapted in various research and clinical applications (Grover 2012; Oh 2017). The Confusion Assessment Method (CAM), which provides a simple diagnostic algorithm, is widely used for identification of delirium worldwide (Hshieh 2018). The 4AT, a new widely used instrument for rapid delirium screening, is also easy and brief to administer and has high sensitivity and specificity (Bellelli 2014; De 2017).

The highest incidence rates of delirium are noted in intensive care unit (ICU) settings, reaching up to 80% (Marcantonio 2017). The incidence of postoperative delirium varies depending on the type of surgical procedure. For example, rates of 12% to 50% have been reported after non-cardiac surgery (Brouquet 2010; Olin 2005; Shah 2012), up to 51% after cardiac surgery (Smulter 2013), and 12% to 61% after orthopaedic operations (Holmes 2000). The incidence of delirium in palliative care settings ranges from 3% to 45% (Perrar 2013). In general medical and geriatric medicine wards, incidence rates range from 11% to 29% (Inouye 2014). The prevalence of delirium on admission to these wards is also high (18% to 35% in general medical wards) (Inouye 2014). When combined with the incidence rates of newly occurring delirium after admission, the overall occurrence of delirium in these settings is relatively high. The epidemiology of delirium in emergency departments is not as well established (Vasilevskis 2012). Furthermore, delirium is not exclusive to hospital settings. One study found an incidence of delirium of 20% in nursing home residents who experience an acute illness (Flaherty 2013).

The ICU is an organised system that provides intensive and specialised medical and nursing care. Patients in ICU settings appear to have different characteristics when compared with patients in other settings. For example, patients in the ICU are more critically ill than patients in other settings. Treatment priorities also tend to be different. Medical treatment in the ICU focuses on multiple modalities of physiologic organ support to sustain life during a period of acute organ system insufficiency (Marshall 2017). Potential clinical heterogeneity can therefore be expected between ICU and non-ICU settings. This review complements a review on delirium in ICU settings that is being performed by the Cochrane Anaesthesia Group (Greve 2012).

Description of the intervention

The treatment of delirium aims to enhance recovery, maximise functional status, and improve clinical outcomes. In addition to general symptomatic management, a key element of management is the investigation and treatment of any reversible underlying causes (Schwartz 2016; Young 2010). According to National Institute for Health and Care Excellence (NICE) guidance, multicomponent non-pharmacological approaches are used as a first-line intervention for the treatment of delirium in adults. This strategy includes ensuring effective communication and reorientation (e.g. explaining where the person is, who they are, and what your role is), providing reassurance to people diagnosed with delirium, involving family, friends, and caregivers to help in this process, and providing a suitable care environment (NICE 2014). There are currently no drugs specifically approved by the US Food and Drug Administration (FDA) or other medicine licensing bodies to treat delirium. In practice, however, clinicians currently employ various medications for symptomatic relief (Breitbart 2012; NICE 2014). Antipsychotic medications are often used for the treatment of delirium. This is especially true for second-generation antipsychotic drugs, which, when compared with first-generation antipsychotic drugs (such as haloperidol), require a shorter time to take effect and produce fewer extrapyramidal symptoms (Kishi 2016).

According to the NICE guidelines, if a person is distressed or presents a substantial risk to themselves or others, antipsychotic drugs (olanzapine or haloperidol) are not recommended for the treatment of delirium unless non-pharmacological measures have been ineffective or inappropriate (NICE 2014). Benzodiazepines play a role in the treatment of delirium caused by withdrawal from sedatives or alcohol. However, they are not useful in the treatment of delirium from other causes because they can cause confusion and drowsiness, particularly in the elderly (Catic 2011). Some research has demonstrated that dexmedetomidine, an α2-adrenoceptor agonist, is useful in the treatment of delirium associated with cancer pain, surgery, or alcohol withdrawal (Ayeko 2015; Nguyen 2016). Though cholinesterase inhibitors such as rivastigmine, donepezil, and galantamine have been used to treat delirium, evidence regarding their effectiveness is inconsistent. One randomised controlled trial found that rivastigmine, when added to standard treatment with haloperidol, potentially increased the severity of delirium as well as mortality in people in the ICU (van Eijk 2010). However, other primary prospective studies (non-randomised) suggested that rivastigmine was useful for delirium associated with Alzheimer's disease, vascular dementia, or stroke in non-ICU settings (Litvineneko 2010; Oldenbeuving 2008). Other cholinesterase inhibitors such as donepezil have also been studied for the prevention of delirium (Liptzin 2005; Marcantonio 2011; Sampson 2007).

How the intervention might work

The mechanisms underlying the development of delirium are complex and poorly elucidated, though several theories have been proposed (Maldonado 2008). One of the leading hypotheses is that delirium results from an impairment of central cholinergic transmission, considered by some investigators to be 'a common denominator' in this disorder (Blass 1981). Acetylcholine is the main neurotransmitter that mediates learning and attention, functions that are profoundly disturbed during delirium. Impaired cholinergic function also correlates with the cognitive and behavioural changes observed in people with delirium (Trzepacz 1996). Furthermore, drugs with anticholinergic effects may induce delirium, while cholinergic drugs can improve delirium induced by lithium and anticholinergic medications (Oldenbeuving 2008). By inhibiting the activity of the enzymes that metabolise acetylcholine, cholinesterase inhibitors cause increased cholinergic activity at synapses (Masuda 2015). They have also been shown to play a role in improving cognitive function in people with dementia (Chen 2016; Li 2015; Rolinski 2012). Both delirium and dementia share cholinergic deficiency as a mechanistic hypothesis (Hshieh 2008; Wang 2009). The three cholinesterase inhibitors, rivastigmine, donepezil, and galantamine, are currently approved as first-line drugs for the treatment of dementia associated with Alzheimer's disease (Li 2015; Qaseem 2008), and are also recommended by NICE for the treatment of Lewy body diseases (i.e. dementia with Lewy bodies and Parkinson's disease dementia) (NICE 2011). By treating the presumed cholinergic deficiency in people with delirium, acetylcholinesterase inhibitors may therefore have beneficial effects.

Why it is important to do this review

This review supersedes the previous review 'Cholinesterase inhibitors for delirium', which was published in 2008 (Other published versions of this review). That review included only one trial, Liptzin 2005, which compared donepezil with placebo for the prevention and treatment of postoperative delirium in people over the age of 50 without dementia who were undergoing elective total joint replacement. More studies have since been conducted with various cholinesterase inhibitors in different settings. Compared with patients in non-ICU settings, patients in the ICU have a higher risk of delirium. In addition, different validation delirium assessment instruments and treatment strategies are employed in the management of ICU patients (Hayhurst 2016; Oh 2017). Since delirium in ICU settings as a sole scope has been examined in previous reviews (Hayhurst 2016; Trogrlić 2015), this review focused on cholinesterase inhibitors for the treatment of delirium in non-ICU settings.

OBJECTIVES

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

METHODS

Criteria for considering studies for this review

Types of studies

We planned to include randomised controlled trials, published or unpublished, which were reported in English or Chinese.

Types of participants

We planned to include participants over 16 years of age, of either sex, diagnosed with delirium by standardised diagnostic criteria (e.g. DSM-IV, DSM-V, ICD-10). If studies stated that people had delirium but did not use standardised diagnostic criteria, we planned to include these studies in the meta-analysis and conduct sensitivity analyses to test whether the inclusion criteria influenced

the results. We also planned to include participants who experienced delirium from any cause (such as medical illnesses and adverse effects from medications) with the exception of alcohol/drug withdrawal. We planned to include studies conducted in either hospital or community settings. We excluded those studies that explicitly mentioned that people were recruited in the ICU, regardless of the type of ICU (such as general ICUs and other special ICUs including coronary care units, trauma ICUs, etc.). However, if the study described the setting as a high dependency unit where patients were cared for more extensively than in a normal ward, but not to the point of intensive care, we planned to include the study.

Types of interventions

We planned to include trials assessing the effect of any of the currently marketed cholinesterase inhibitors (e.g. donepezil, rivastigmine, galantamine), administered at any dose and at any frequency, compared with placebo. We also planned to include head-to-head comparisons of a cholinesterase inhibitor with another drug intended to treat delirium (e.g. antipsychotic drugs, α2-adrenoceptor agonists, benzodiazepines, and melatonin).
We also planned to include trials involving non-pharmacological management strategies if we could extract data from the groups.

Types of outcome measures

Primary outcomes

- Response to treatment:
  - duration of delirium;
  - severity of delirium measured 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 events

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 searched ALOIS (www.medicine.ox.ac.uk/alois), the Cochrane Dementia and Cognitive Improvement Group's Specialised Register, on 26 October 2017.
ALOIS is maintained by the review group's Information Specialist and contained 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 (Cumulative Index to Nursing and Allied Health Literature), PsycINFO, and LILACS (Latin American and Caribbean Health Sciences Literature);
- monthly searches of trial registers: *meta*Register of Controlled Trials (www.isrctn.com/page/mrct); UMIN Clinical Trials Registry (www.umin.ac.jp/ctr/); World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch) (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 Core Collection.

To view a list of all sources searched for ALOIS please see About ALOIS.
We ran additional searches to ensure we had retrieved the most up-to-date results. The search strategies used for the retrieval of reports of trials from bibliographic databases and trial registries can be seen in Appendix 1.

Searching other resources

We cross-checked 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) independently assessed each abstract and title for relevance. We obtained the full texts of citations that described a potentially relevant randomised controlled trial for further assessment. Two review authors independently determined eligibility of these trials for inclusion. Any disagreements at any stage of the study selection process were resolved by discussion or by the involvement of a third review author (ZZ).

Data extraction and management

Two review authors (AY and SW) independently extracted data using prespecified data extraction forms. A pilot data extraction was performed before the formal data extraction. Any discrepancies were resolved by discussion. We collected the following information where possible.

Participant characteristics

- Age
- Sex
- Education
- Diagnostic criteria for delirium
- Severity of delirium
- Underlying aetiology of delirium
- Baseline comorbid dementia
- Setting (refers to the environment where the clinical trial was conducted, e.g. palliative care settings, general or geriatric wards, emergency departments)
- Inclusion or exclusion criteria of the original studies

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' assessment

For continuous data, we extracted the mean, standard deviation, and number of participants for each treatment group at each time point, if available. For dichotomous data, we retrieved the number in each treatment group and numbers experiencing the outcome of interest where possible. If only treatment effects and their standard errors were reported, these would be extracted.

Assessment of risk of bias in included studies

Two review authors (AY and SW) independently assessed 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 used the criteria reported in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We applied the following judgements to each domain: low risk, high risk, or unclear risk (either lack of information or uncertainty over the potential for bias). Any disagreements were resolved by consensus or by consulting a third review author (ZZ) when necessary.

Measures of treatment effect

If trials used the same rating scale to assess the outcome, we planned to calculate the mean difference (MD) with a 95% confidence interval (CI); if different rating scales were used to measure the same outcome, we planned to employ the standardised mean difference (SMD) for continuous data. The treatment effect for dichotomous outcomes was expressed as a risk ratio (RR) with a 95% CI.

Unit of analysis issues

For studies with multiple eligible treatment groups, we planned to 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 was 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 was not suitable, we planned to include all relevant experimental groups and split the shared control group.

Dealing with missing data

We planned to report missing outcome data and consider and discuss the potential impact of the missing data on the results for all outcomes. When attrition for a continuous outcome was between 0% and 50%, and only data from people who had completed the study to that point were reported, we planned to reproduce these. We anticipated that some studies would have used the method of last observation carried forward (LOCF) or other imputation methods. If less than 50% of the data had been imputed, we would present and use these data and report the imputation method used. For studies with more than 50% of imputed data, we would use the data, but would conduct a sensitivity analysis by excluding these studies to test the robustness of the result.

If standard deviations were not reported, we would first attempt to obtain the missing values from the study authors. If this was not possible, we would attempt to calculate standard deviations from the available statistics in the study report according to the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Assessment of heterogeneity

Two review authors (AY and SW) independently assessed clinical and methodology heterogeneity, and only planned on conducting meta-analyses when the study quality, participants, interventions, and outcomes were sufficiently similar. We planned on assessing statistical heterogeneity using the I^2 statistic (I^2 greater than 50% may represent substantial heterogeneity) combined with the P value from the Chi^2 test ($P < 0.1$), if a meta-analysis was to be performed (Higgins 2011).

Assessment of reporting biases

If at least 10 studies were available for meta-analysis, we planned on assessing the effect of publication bias using a funnel plot to identify small-study effects.

Data synthesis

We planned on conducting meta-analyses using the Mantel-Haenszel method for dichotomous outcomes, and the inverse variance method for continuous outcomes. We planned to use a random-effects model for all analyses. For cases in which the statistical heterogeneity was significant (P value from Chi^2 test < 0.1 and I^2 greater than 50%), we planned to 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

When data allowed, we planned to conduct a 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 delirium due to hepatic encephalopathy);
- presence or absence of pre-existing dementia or neurocognitive impairment.

Investigation of heterogeneity

Where there was evidence of statistical heterogeneity (P value from $Chi^2 < 0.1$ and I^2 greater than 50%) of the treatment effect between trials, if we could identify possible sources of variation, we planned to explore the source of the heterogeneity and conduct subgroup analyses. Otherwise, we would use a random-effects model to pool the data. Where statistical heterogeneity was significant in a meta-analysis, we would consider downgrading the quality of evidence using the GRADE approach (GRADEpro GDT 2015; Schünemann 2011a; Schünemann 2011b).

Sensitivity analysis

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

'Summary of findings' table

For each comparison, we used the GRADE approach to assess the quality of the body of evidence for all outcomes (GRADEpro GDT 2015; Schünemann 2011a; Schünemann 2011b). We presented the following results in the 'Summary of findings' tables.

- Duration of delirium
- Severity of delirium
- Adverse events
- Persistent cognitive impairment
- Length of hospitalisation
- Mortality
- Cost of intervention

Evidence was given one of four possible ratings: high, moderate, low, or very low quality. A rating of high quality indicated that we were confident in our estimate of the effect and that further research was very unlikely to change this, whereas a rating of very low quality implied that we were very uncertain about the estimate of the effect. The GRADE approach rates evidence from randomised controlled trials as high quality initially, however several factors could lead to the downgrading of the evidence, namely: study limitations (risk of bias); inconsistency; indirectness of evidence; imprecision; and publication bias (Schünemann 2011a; Schünemann 2011b).

RESULTS

Description of studies

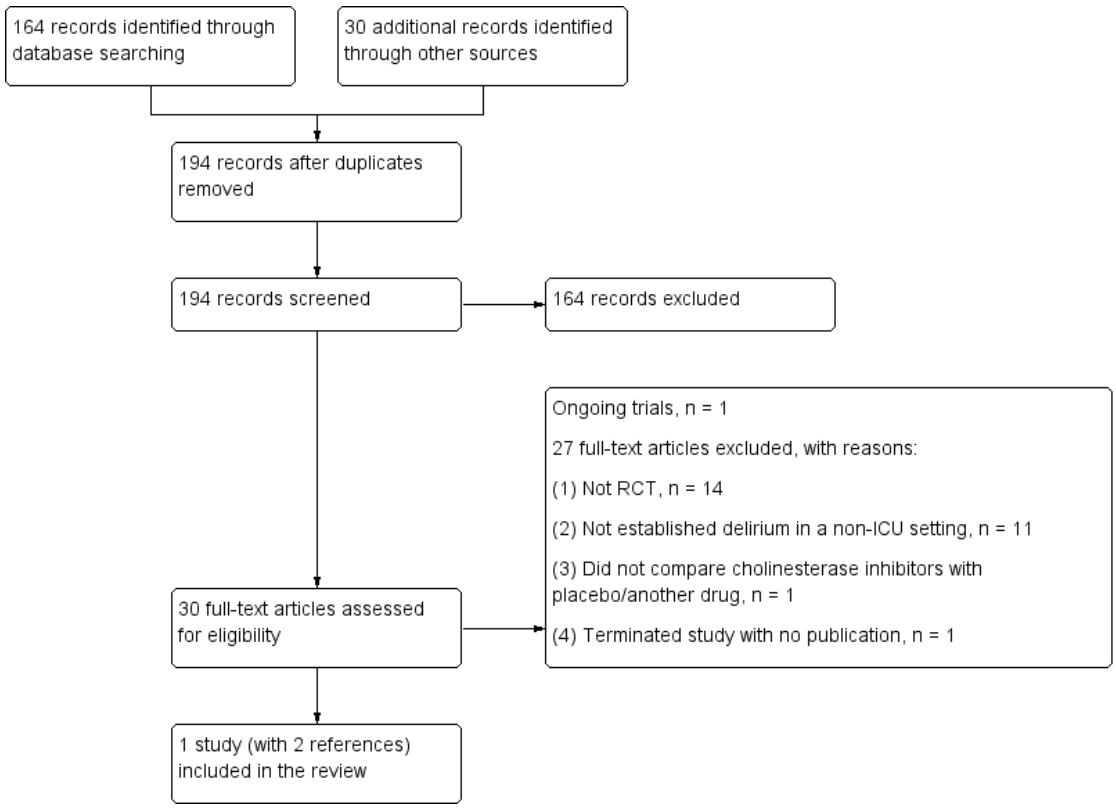
See Characteristics of included studies; Characteristics of excluded studies.

Results of the search

We identified a total of 194 records from databases (164 records) and other sources (30 records). The total number of records was

unchanged after de-duplication. We excluded 164 records based on the title and abstract. Of the remaining 30 records assessed in full, we excluded 27 records with reasons (see Excluded studies). One record is an ongoing study (NCT01487317). We eventually included only one study (Overshott 2010, with two records) in this review (see Figure 1 for more details).

Figure 1. Study flow diagram.



Included studies

Only one study with 15 participants that compared rivastigmine with placebo met the inclusion criteria for this review (see Characteristics of included studies) (Overshott 2010).

The 15 participants were recruited from the UK and were diagnosed with delirium based on the Confusion Assessment Method (CAM) criteria. Seven of the 15 participants had comorbid dementia at baseline. The mean age of the participants was 82.5 years; eight participants were male and seven were female.

The study reported the following outcomes: duration of delirium as assessed by CAM criteria, adverse events, use of rescue medications (additional psychotropic medications received), mortality, and leaving the study early. Other predefined outcomes of this review (severity of delirium, persistent cognitive impairment, length of hospitalisation, institutionalisation, cost of intervention, and quality of life) were not reported.

Excluded studies

See Characteristics of excluded studies.

We excluded a total of 27 studies from this review for the following reasons.

1. Twelve studies were not randomised controlled trials (Chapin 1977; Dautzenberg 2004; Fischer 2001; Gleason 2003; Granacher 1976; Heiser 1974; Hori 2003; Kaufer 1998; Lankarani-Fard 2006; Listed 2011; Newman 1980; Scicutella 2015; Sheldon 2010; Wengel 1999).

2. Participants of nine studies did not have a diagnosis of delirium in a non-ICU setting (EUCTR2007-000262-20-GB; Crowell 1967; Doraiswamy 2007; Liptzin 2005; Marcantonio 2011; Moretti 2004; Silver 2006; Tenovuo 2009; Van Eijk 2010; Youn 2017; Zaslavsky 2012).

3. We excluded one study due to the interventions being evaluated (Pitkala 2006). This study compared an intensified, multicomponent geriatric treatment group with a control group, and we were unable to extract data from the groups that differed only in terms of exposure to cholinesterase inhibitor versus placebo.

4. One clinical trial was terminated with no published results (NTR 537). We contacted the primary investigator, who informed us that no data had been published from this trial.

Ongoing studies

See Characteristics of ongoing studies.

We identified one ongoing study begun in France in 2011 (NCT01487317). Though recruitment was complete, no results have been reported or published. We planned to contact the primary investigator for more details but contact information was not available.

Risk of bias in included studies

The summary of risk of bias in the included study is presented in Figure 2 and Figure 3 (Overshott 2010). Please refer to the 'Risk of bias' table in Characteristics of included studies for further details.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

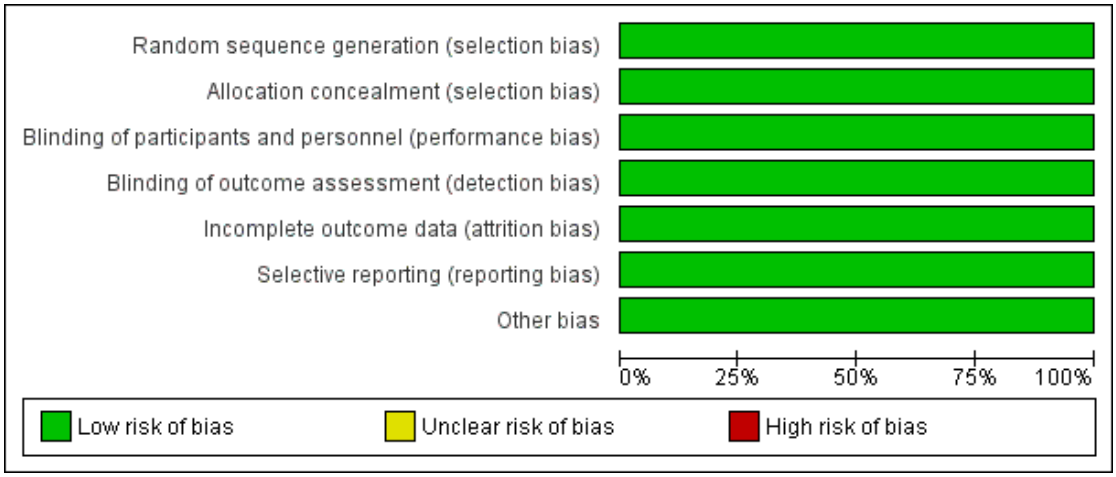
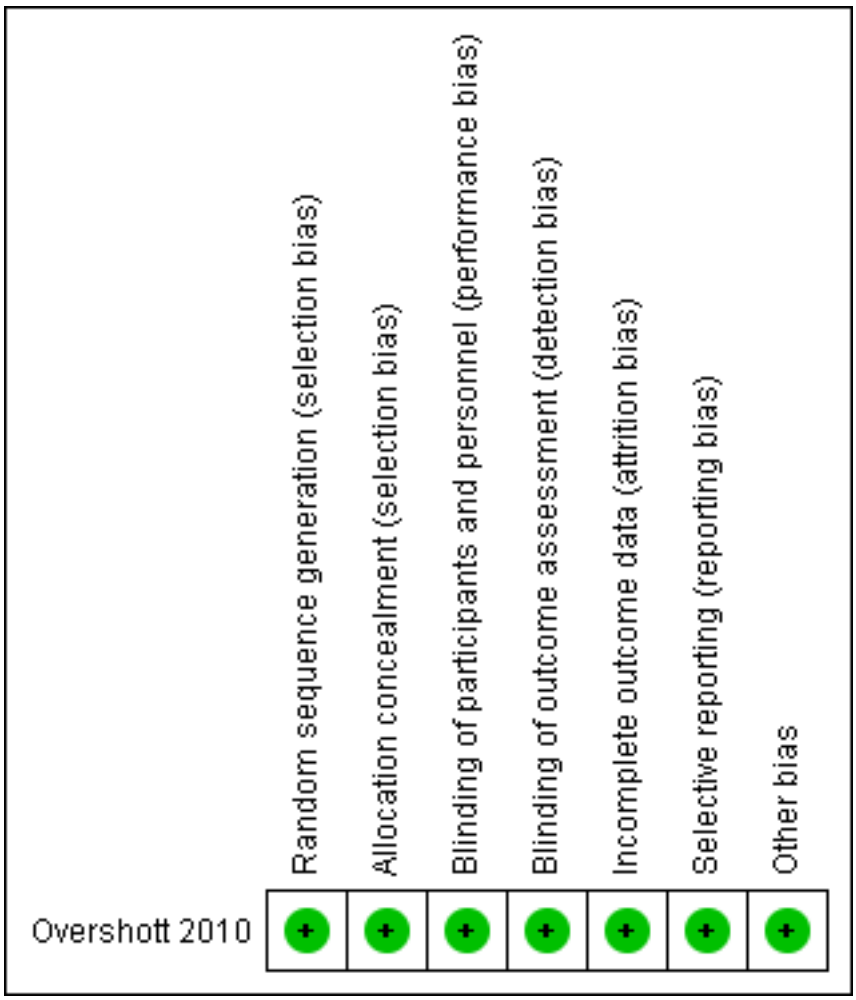


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

The included study stated that participants were randomised by numbered treatment packets developed by the special statistics department, which was independent of the research team. The random sequence was concealed before allocation. We therefore rated this study as at low risk of selection bias.

Blinding

The included study used a convincingly double-blinded design that ensured blinding of both the participants and researchers. We rated this study as at low risk of performance and detection bias.

Incomplete outcome data

Two participants left the study early due to protocol violation. One person in the rivastigmine group withdrew their consent when CAM was negative for two consecutive days. One person in the placebo group lost the trial medication after being transferred to another ward. The number of dropouts was small and balanced between the two groups. Given that the reasons for the dropouts were not related to the intervention, we rated this study as having a low risk of attrition bias.

Selective reporting

We did not obtain the protocol for this study. The study reported all outcomes that were stated in the methods section, and the

primary outcome in this review was reported as well. We rated the study as at low risk of reporting bias.

Other potential sources of bias

We found no other obvious bias in the included study and rated it as at low risk for this domain.

Effects of interventions

See: **Summary of findings for the main comparison** Cholinesterase inhibitors (rivastigmine) compared to placebo for the treatment of delirium in non-ICU settings

We included one study that involved 15 participants and compared rivastigmine with placebo (Overshott 2010). The quality of evidence for the reported outcomes was low due to the very small sample size (see Summary of findings for the main comparison).

Primary outcomes

Response to treatment: duration of delirium

The study reported that the mean (standard deviation, range) duration of delirium for participants in the rivastigmine and placebo groups was 6.3 (5.7, 1 to 19) days and 9.9 (14.6, 1 to 42) days, respectively. The mean and range of duration of delirium were shorter for the rivastigmine group compared with the placebo group, although the authors did not find a clear difference (mean difference (MD) -3.6, 95% confidence interval (CI) -15.6 to 8.4; Analysis 1.1) due to the very small sample size (lack of statistical power).

The study used unpaired t-test for this outcome to measure MD. However, we found that the data were skewed, and therefore a parameter test was not applicable. Hence, we just presented the results as other data in this review.

Response to treatment: severity of delirium

The study did not report this outcome.

Adverse events

Only one participant in the placebo group had nausea. The study found no clear difference in the incidence of nausea between the two groups (risk ratio (RR) 0.30, 95% CI 0.01 to 6.29; Analysis 1.2).

Secondary outcomes

Use of rescue medications

Three participants in the placebo group and no participants in the rivastigmine group received additional psychotropic medication due to behavioural disturbances. The study found no clear difference between the two groups (RR 0.13, 95% CI 0.01 to 2.1; Analysis 1.3).

Persistent cognitive impairment

The study did not report this outcome.

Length of hospitalisation

The study did not report this outcome.

Institutionalisation

The study did not report this outcome.

Mortality

Four participants in the placebo group and no participants in the rivastigmine group died. The study found no clear difference in mortality between the groups (RR 0.10, 95% CI 0.01 to 1.56; Analysis 1.4).

Cost of intervention

The study did not report this outcome.

Leaving the study early

One participant in the rivastigmine group and one participant in the placebo group left the study early. The study found no clear difference in withdrawals between the two groups (RR 0.88, 95% CI 0.07 to 11.54; Analysis 1.5).

Quality of life

The study did not report this outcome.

Subgroup analysis

We did not perform any subgroup analysis due to insufficient data.

Sensitivity analysis

We did not perform any sensitivity analysis due to insufficient data.

Assessment of reporting biases

We did not produce a funnel plot to assess reporting biases because no meta-analysis included at least 10 studies.

DISCUSSION

Summary of main results

We identified only one study that compared a cholinesterase inhibitor with placebo for the treatment of delirium in non-ICU patients. Based on the absolute difference, the duration of delirium was shorter in the rivastigmine group (3.6 days on average) compared with the placebo group, and no deaths occurred in the rivastigmine group. However, this study had limited data (15 participants) with low-quality evidence. Any comparative analysis would be unlikely to show an effect because the study was grossly underpowered. Hence, in actuality we did not find any clear differences in the duration of delirium, adverse events, use of rescue medications, mortality, or the number of participants leaving the study early. No evidence was available to evaluate severity of delirium or the remaining secondary outcomes.

Overall completeness and applicability of evidence

The overall completeness and applicability of the evidence in terms of the participants, interventions, and outcomes were poor and very limited in this one included study. For one, the included participants were diagnosed with delirium using CAM rather than the standardised diagnostic criteria (e.g. DSM-IV, DSM-V, ICD-10). Patient demographics were also limited in terms of country of origin (all participants were from the UK) and age distribution (the average age was over 80 years). Rivastigmine and placebo were the only interventions, and no other cholinesterase inhibitor drugs (e.g. donepezil, galantamine) were evaluated. Furthermore, there were no comparisons of a cholinesterase inhibitor with other drugs intended to treat delirium such as antipsychotic drugs, α2-adrenoceptor agonists, benzodiazepines, or melatonin. A very small amount of data was reported on outcomes such as duration of delirium, adverse events (nausea), use of rescue medications, mortality, and leaving the study early. Most predefined outcomes in this review were not reported, including the severity of delirium, persistent cognitive impairment, length of hospitalisation, institutionalisation, cost of intervention, and quality of life. The applicability of this current evidence is therefore limited.

Quality of the evidence

The included study had a low risk of bias across all domains. We downgraded the overall quality of evidence to low due to the very small sample size.

Potential biases in the review process

We minimised the potential biases in the review process by performing a thorough and complete search of the databases and other sources. Two review authors (AY and SW) independently screened and extracted the data using prespecified data extraction forms, a process that lessens the likelihood of introducing bias in the review process.

Agreements and disagreements with other studies or reviews

This review supersedes a previous Cochrane Review that was originally published in 2008 (Other published versions of this review). This latter review included one study that evaluated the possible benefit of donepezil versus placebo in the prevention and treatment of postoperative delirium in an elderly population without dementia undergoing elective total joint replacement surgery (Liptzin 2005). In this previous review, the incidence of postsurgical delirium was measured, and there was no clear difference in the duration of postsurgical delirium between the two groups. In this current updated review, we focused on the treatment of delirium. We excluded the previous study, Liptzin 2005, because 90 included participants did not have delirium at the time of randomisation, and only 15 participants developed delirium after treatment. This current review only included participants with established delirium pre-randomisation. Similar to the previous review, we found no clear difference in the duration of delirium between the rivastigmine and placebo groups in a non-ICU setting, and no clear difference between groups for other outcomes such as adverse events, use of rescue medications, mortality, and leaving the study early. However, both reviews lacked sufficient evidence to enable any firm conclusions. Though other meta-analyses have evaluated the prevention of delirium or treatment efficacy of certain interventions (Siddiqi 2016; Tampi 2016), participants did not meet the inclusion criteria of the present review (i.e. they did not have an established diagnosis of delirium).

AUTHORS' CONCLUSIONS

Implications for practice

Compared with placebo, cholinesterase inhibitors were associated with no clear benefits or harms in the treatment of delirium due to a lack of data. There is thus insufficient evidence to support or refute the use of cholinesterase inhibitors for the treatment of delirium in non-intensive care unit (ICU) settings. This conclusion is consistent with the previous review (Other published versions of this review).

Implications for research

One recent review reported that numerous studies investigated the prevention rather than the treatment of delirium (Siddiqi 2016). In this current review we also found a paucity of evidence regarding the effect of cholinesterase inhibitors in the treatment of delirium in non-ICU settings, and have identified this area as a priority for further investigation. Delirium remains a common and serious condition with no consensus about pharmacological treatment. More trials are needed with larger sample sizes (for instance 80% statistical power is warranted) that focus on the treatment of established delirium in non-ICU settings. Furthermore, important outcomes such as the severity of delirium and persistent cognitive impairment should also be evaluated.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Overshott 2010

Methods	**Study design:** parallel-group, single-centre, randomised controlled trial **Blind:** double-blind **Setting:** medical wards, the University Hospital of South Manchester NHS Trust, Manchester, UK **Follow-up:** 42 days from the beginning of treatment
Participants	**Total sample size (at randomisation):** n = 15 **Diagnostic criteria of delirium:** CAM **Age (mean/SD):** 84.3/11.2 years in intervention group; 80.6/8.5 years in control group **Sex (male/female):** 4/4 in intervention group; 4/3 in control group **Education:** not stated **Severity of delirium (assessed by MMSE, mean/SD):** 8.6/4.9 in intervention group; 7.4/7.1 in control group **Underlying aetiology of delirium (comorbid illnesses):** hypertension (5 participants), angina (5 participants), stroke (4 participants), atrial fibrillation (4 participants), diabetes (1 participants) **Baseline comorbid dementia:** 3 participants in intervention group, 4 participants in control group **Inclusion criteria:** people over the age of 65 years, identified as having delirium by the CAM **Exclusion criteria:** people were excluded if they were too ill, were taking a cholinesterase inhibitor, had blood test abnormalities (urea $\geq$ 15 mmol/L, or creatinine over 200 μmol/L, or transaminases twice the upper normal limit or a bilirubin level over 40 μmol/L), had suffered a myocardial infarction, had an unstable cardiac arrhythmia, or had severe respiratory disease
Interventions	**1. Intervention Group:** cholinesterase inhibitors, n = 8 Content: participants received rivastigmine tablets. Dosage/route/frequency: 1.5 mg once a day increasing to 1.5 mg twice a day after 7 days Treatment duration: the maximum length was 28 days. **2. Control Group:** placebo, n = 7 Content: participants received identical placebo tablets. Dosage/route/frequency: same as above Treatment duration: same as above **Any concomitant treatments:** If clinicians caring for participants of either group needed to prescribe treatment for behavioural problems, then this was in accordance with clinically derived protocol for the management of delirium with chlomethiazole and risperidone
Outcomes	1. Duration of delirium (assessed by CAM, days) 2. Adverse events (nausea) 3. Use of rescue medications (received additional psychotropic medication) 4. Mortality 5. Leaving the study early

Overshott 2010 (*Continued*)

	Unable to use (not predefined in our protocol): number of participants who assessed negative by CAM at end of study; number of participants who received antibiotics; number of discharged participants
Notes	The trial was registered with the National Research Ethics Service (reference number: 02/CM/351) and the Clinical Trials Unit at the Department of Health of England and Wales (reference number: MF 8000/12552) Conflict of interest declaration: the third author (AB) receives research funding and consultancy fees from pharmaceutical companies involved in the manufacture and marketing of drugs for Alzheimer's disease, including Janssen-Cilag, Pfizer, Novartis, Eisai, Shire, and Lundbeck

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was by numbered treatment packets by the Department of Medical Statistics in South Manchester, independent of the research team ..." (p.813) Comments: The investigators described a random component in the sequence generation process
Allocation concealment (selection bias)	Low risk	Quote: "... with the sequence concealed until outcome measures had been completed for all patients." (p.813) Comments: Allocation concealment ensured.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "... with the sequence concealed until outcome measures had been completed for all patients." (p.813). "The researchers, who were blind to allocation ..." (p.814) Comments: Blinding of participants and personnel ensured.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Each group - treatment or placebo - was assessed with the CAM daily following entry, together with a proforma for adverse events, blind to knowledge of the patients' group membership by one of two research nurses." (p.813) Comments: Blinding of outcome assessment ensured.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comments: 2 participants withdrew due to protocol violation.

Overshott 2010 (*Continued*)

Selective reporting (reporting bias)	Low risk	Comments: All outcomes stated in methods were reported in results
Other bias	Low risk	Comments: None obvious

CAM: Confusion Assessment Method
MMSE: Mini-Mental State Examination
SD: standard deviation

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Chapin 1977	Study design: not randomised controlled trial
Crowell 1967	Study design: randomised controlled trial Participants: normal male volunteers
Dautzenberg 2004	Study design: not randomised controlled trial
Doraiswamy 2007	Study design: randomised controlled trial Participants: not established delirium, people with cognitive decline on at least 1 cognitive domain
EUCTR2007-000262-20-GB	Study design: randomised controlled trial Participants: not established delirium
Fischer 2001	Study design: not randomised controlled trial
Gleason 2003	Study design: not randomised controlled trial
Granacher 1976	Study design: not randomised controlled trial
Heiser 1974	Study design: not randomised controlled trial
Hori 2003	Study design: not randomised controlled trial
Kaufer 1998	Study design: not randomised controlled trial
Lankarani-Fard 2006	Study design: not randomised controlled trial
Liptzin 2005	Study design: randomised controlled trial Participants: not established delirium

(*Continued*)

Listed 2011	Study design: not randomised controlled trial
Marcantonio 2011	Study design: randomised controlled trial Participants: not established delirium
Moretti 2004	Study design: randomised controlled trial Participants: not established delirium
Newman 1980	Study design: not randomised controlled trial
NTR 537	Terminated study with no publication
Pitkala 2006	Study design: randomised controlled trial Participants: delirium Intervention: intensified, multicomponent geriatric treatment versus usual care, cholinesterase inhibitor used in both intervention and control groups
Scicutella 2015	Study design: not randomised controlled trial
Sheldon 2010	Study design: not randomised controlled trial
Silver 2006	Study design: randomised controlled trial Participants: not established delirium, people with traumatic brain injury
Tenovuo 2009	Study design: randomised controlled trial Participants: not established delirium, people with traumatic brain injury
Van Eijk 2010	Study design: randomised controlled trial Participants: intensive care unit patients with delirium
Wengel 1999	Study design: not randomised controlled trial
Youn 2017	Study design: randomised controlled trial Participants: not established delirium, people with cognitive impairment about to undergo hip surgery
Zaslavsky 2012	Study design: randomised controlled trial Participants: not established delirium, people at risk for developing postoperative delirium

Characteristics of ongoing studies *[ordered by study ID]*

NCT01487317

Trial name or title	A randomized, double-blind, placebo-controlled study of an acetylcholinesterase inhibitor in the management of delirium in hospitalized patients aged 75 years and over
Methods	**Study design:** parallel-group, randomised controlled trial **Blind:** double-blind (participant, care provider) **Setting:** inpatients **Follow-up:** 12 months
Participants	**Total sample size:** n = 23 **Inclusion criteria:** • Patients aged 75 and over • Hospitalisation for delirium not correlated to surgery for less than 48 hours • Patients with delirium requiring the presence of features 1 (acute onset and fluctuation course), 2 (inattention), 3 (disorganised thinking), and 4 (altered level of consciousness) of the Confusion Assessment Method and DRS R-98 > 10 • Absence of any contraindications to a cholinesterase inhibitor treatment • Health insurance affiliation • Having signed an informed consent form • Caregiver/informant to provide information on patient **Exclusion criteria:** • Use of cholinesterase inhibitor or memantine medication • Contraindication to cholinesterase inhibitor medication • Frontotemporal dementia • Diseases involving short-term survival • Digestive bleeding • Ischaemic and haemorrhagic stroke related to actual onset (including haemorrhagic contusion) • Natraemia ≤ 120 mmol/L at the time of hospitalisation • Postepileptic confusion • Hepatocellular failure • Cardiorespiratory impairment at risk of transfer to intensive care unit • Major sensory deficits that could interfere with cognitive assessment (visual and auditory) • Not fluent in French • Being under guardianship • Absence of caregiver/informant to sign informed consent form
Interventions	**Intervention group:** rivastigmine transdermal patch Content: 1 transdermal patch of rivastigmine (equivalent to 4.6 mg/24 h orally) per day from randomisation to day 14. Before day 14: end of treatment, if DRS R-98 severity < 10 during 2 consecutive days. At day 14, if DRS R-98 severity ≥ 10: 1 transdermal patch of rivastigmine 9.5 mg/24 h per day from day 14 to day 30 if DRS R-98 severity < 10, the active treatment will be stopped **Control group:** placebo patch Content: 1 transdermal patch of placebo per day from randomisation to day 14. Before day 14: end of treatment if DRS R-98 severity < 10 during 2 consecutive days. At day 14 if DRS R-98 severity ≥ 10: 1 transdermal patch of placebo per day from day 14 to day 30 if DRS R-98 severity < 10, the placebo treatment will be stopped

NCT01487317 (*Continued*)

Outcomes	• Hospital length of stay from randomisation to declaration by investigator that participant can leave acute care (maximum of 12 months) • Percentage of participants with persistent delirium symptoms (DRS R-98 scale; at day 14, day 30) • Percentage of participants with persistent delirium symptoms at day 30 (CAM scale) • Percentage of participants with a dementia diagnosis at 12 months
Starting date	June 2011
Contact information	Marc Verny
Notes	The study was completed with no results reported (author contact information was not available) clinicaltrials.gov/show/NCT01487317

CAM: Confusion Assessment Method
DRS R-98: Delirium Rating Scale-Revised-98

DATA AND ANALYSES

Comparison 1. Cholinesterase inhibitors (rivastigmine) versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duration of delirium (days)			Other data	No numeric data
2 Adverse events (nausea)	1	15	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.01, 6.29]
3 Use of rescue medications	1	15	Risk Ratio (M-H, Random, 95% CI)	0.13 [0.01, 2.10]
4 Mortality	1	15	Risk Ratio (M-H, Random, 95% CI)	0.10 [0.01, 1.56]
5 Leaving the study early	1	15	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.07, 11.54]

Analysis 1.1. Comparison 1 Cholinesterase inhibitors (rivastigmine) versus placebo, Outcome 1 Duration of delirium (days).

Duration of delirium (days)

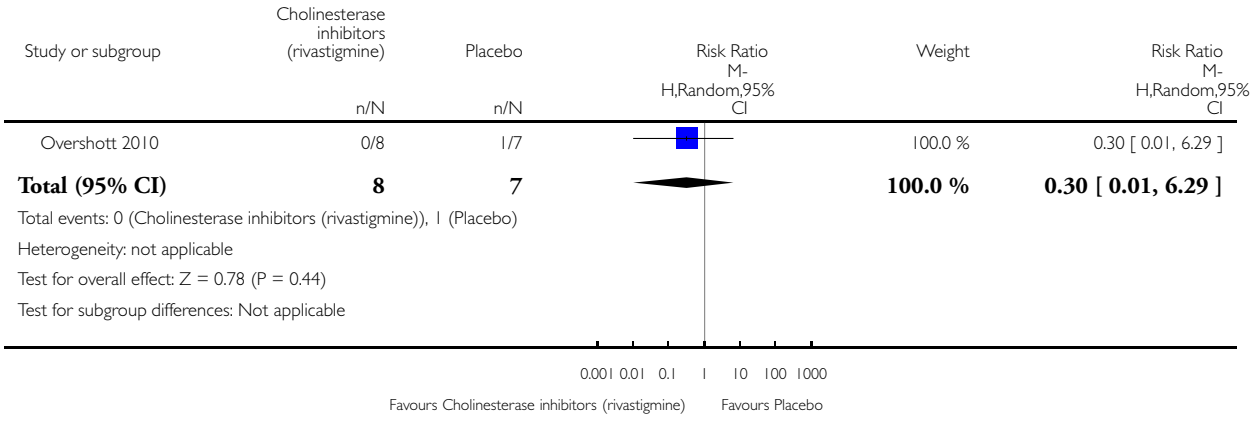
Study	Interventions	N	MD	95% CI	P value
Overshott 2010	Cholinesterase inhibitors (rivastigmine) versus placebo	15	-3.6	-15.6 to 8.4	0.5

Analysis 1.2. Comparison 1 Cholinesterase inhibitors (rivastigmine) versus placebo, Outcome 2 Adverse events (nausea).

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

Comparison: 1 Cholinesterase inhibitors (rivastigmine) versus placebo

Outcome: 2 Adverse events (nausea)

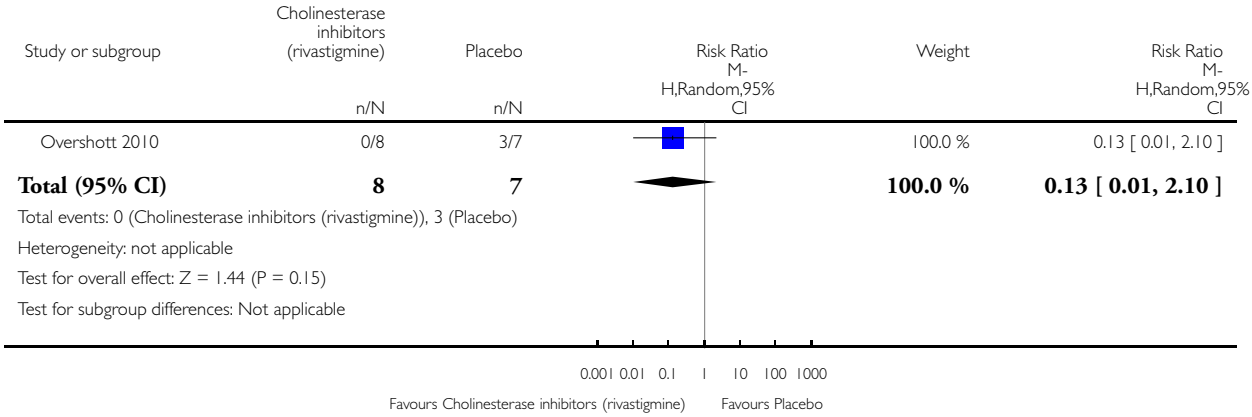


Analysis 1.3. Comparison 1 Cholinesterase inhibitors (rivastigmine) versus placebo, Outcome 3 Use of rescue medications.

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

Comparison: 1 Cholinesterase inhibitors (rivastigmine) versus placebo

Outcome: 3 Use of rescue medications

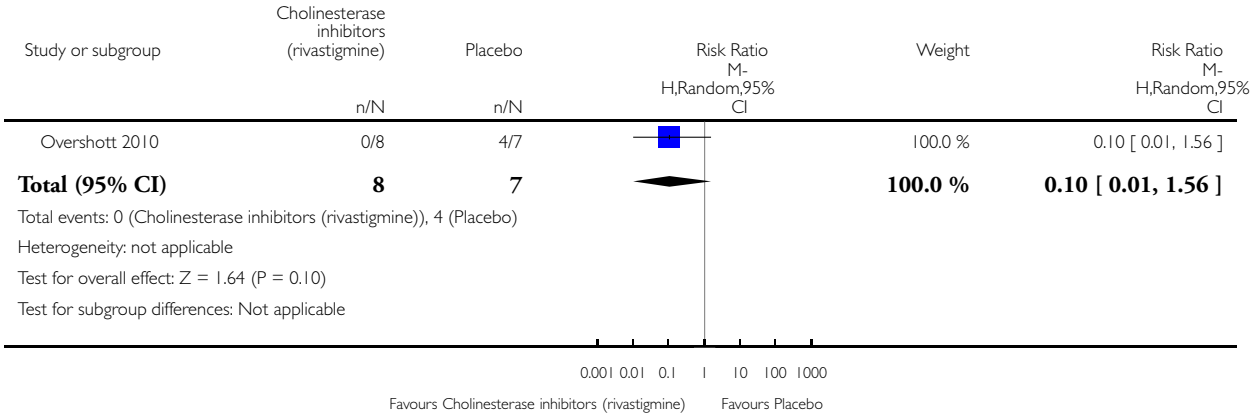


Analysis 1.4. Comparison 1 Cholinesterase inhibitors (rivastigmine) versus placebo, Outcome 4 Mortality.

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

Comparison: 1 Cholinesterase inhibitors (rivastigmine) versus placebo

Outcome: 4 Mortality

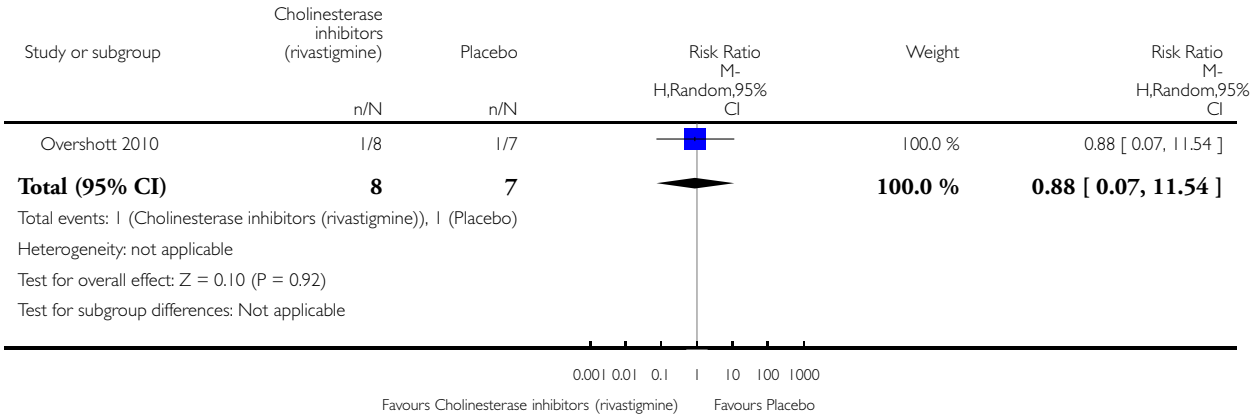


Analysis 1.5. Comparison 1 Cholinesterase inhibitors (rivastigmine) versus placebo, Outcome 5 Leaving the study early.

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

Comparison: 1 Cholinesterase inhibitors (rivastigmine) versus placebo

Outcome: 5 Leaving the study early



APPENDICES

Appendix 1. Sources searched and search strategies

Source	Search strategy	Hits retrieved
ALOIS (via CRS web) [Date of most recent search 26 October 2017]	(donepezil OR galantamine OR rivastigmine OR tacrine OR E2020 OR aricept* OR galanthamin* OR nivalin* OR razadyne* OR exelon* OR "SDZ ENA 713") AND delirium [health condition]	Dec 2016: 5 Oct 2017: 3
CENTRAL, issue 10 of 12 (The Cochrane Library) http://crso.cochrane.org/SearchSimple.php [Date of most recent search 26 October 2017]	#1 MeSH descriptor: [Delirium] this term only #2 deliri* #3 "acute confusion*" #4 "acute organic psychosyndrome" #5 "acute brain syndrome" #6 "metabolic encephalopathy" #7 "acute psycho-organic syndrome" #8 "clouded state" #9 "clouding of consciousness" #10 "exogenous psychosis" #11 "toxic psychosis" #12 "toxic confusion" #13 obnubilat* #14 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 #15 rivastigmin* #16 Exelon* #17 "SDZ ENA 713" #18 donepezil #19 rivastigmine #20 galantamine #21 tacrine #22 galanthamine #23 aricept #24 E2020 #25 Nivalin #26 Razadyne #27 Reminyl #28 exelon #29 cognex #30 #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 #31 #14 and #30 in Trials	Dec 2016: 27 Oct 2017: 6

(*Continued*)

MEDLINE In-process and other non-indexed citations and MEDLINE 1950-present (Ovid SP) [Date of most recent search 26 October 2017]	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. 7. Aricept*.mp. 8. rivastigmine.mp. 9. rivastigmin.mp. 10. Exelon*.mp. 11. exp Tacrine/ 12. cognex.mp. 13. or/1-12 14. delir*.mp. 15. confusion.mp. 16. "acute brain failure".mp. 17. "acute organic psychosyndrome".mp. 18. "acute brain syndrome".mp. 19. "metabolic encephalopathy".mp. 20. "acute psycho-organic syndrome".mp. 21. "clouded state".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	Dec 2016: 238 Oct 2017: 14
EMBASE (Ovid SP) 1974 to 2017 Oct 25 [Date of most recent search 26 October 2017]	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.	Dec 2016: 959 Oct 2017: 110

(*Continued*)

	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/ 14 obnubilat*.ti,ab. 15 or/1-14 16 exp Cholinesterase Inhibitors/ 17 “cholinesterase inhibitor*”.mp. 18 Galantamine/ 618 19 (galantamine or galanthamine or galant?amin).mp. 20 (reminyl* or Nivalin* or Razadyne*).mp. 21 donepezil.mp. 22 Aricept*.mp. 23 rivastigmine.mp. 24 rivastigmin.mp. 25 Exelon*.mp. 26 exp Tacrine/ 27 cognex.mp. 28 or/16-27 29 randomized controlled trial/ 30 controlled clinical trial/ 31 random$.ti,ab. 32 randomization/ 33 intermethod comparison/ 34 placebo.ti,ab. 35 (compare or compared or comparison).ti. 36 ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab 37 (open adj label).ti,ab. 54779 38 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab. 192050 39 double blind procedure/ 40 parallel group$1.ti,ab. 41 (crossover or cross over).ti,ab. 42 ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab 43 (assigned or allocated).ti,ab.	

(*Continued*)

	44 (controlled adj7 (study or design or trial)).ti,ab. 45 (volunteer or volunteers).ti,ab. 46 trial.ti. 47 or/29-46 48 15 and 28 and 47	
PSYCINFO (Ovid SP) 2017 week 3 [Date of most recent search 26 October 2017]	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 obnubilat*.ti,ab. 14 or/1-13 15 exp Cholinesterase Inhibitors/ 16 "cholinesterase inhibitor*".mp. 17 Galantamine/ 18 (galantamine or galanthamine or galant? amin).mp. 19 (reminyl* or Nivalin* or Razadyne*). mp. 20 donepezil.mp. 21 Aricept*.mp. 22 rivastigmine.mp. 23 rivastigmin.mp. 24 Exelon*.mp. 25 Tacrine.mp. 26 cognex.mp. 27 or/15-26 28 exp Clinical Trials/ 29 randomly.ab. 30 randomi?ed.ti,ab. 31 placebo.ti,ab. 32 groups.ab. 33 "double-blind*".ti,ab. 34 "single-blind*".ti,ab. 35 RCT.ti,ab. 36 or/28-35 37 14 and 27 and 36	Dec 2016: 23 Oct 2017: 3
CINAHL (EBSCOhost) [Date of most recent search 26 October 2017]	1 deliri* 2 "acute psycho-organic syndrome" or "clouded state" or "clouding of conscious-	Dec 2016: 17 Oct 2017: 2

(*Continued*)

	ness" or "exogenous psychosis" or "toxic psychosis" or "toxic confusion" 3 "acute brain confusion" or "acute brain failure" or "acute organic psychosyndrome" or "acute brain syndrome" or "metabolic encephalopathy" 4 "Delirium"/ 5 S1 OR S2 OR S3 OR S4 6 TX donepezil OR galantamine OR rivastigmine OR tacrine 7 TX aricept* OR E2020 8 S3 TX Galanthamin* OR nivalin* OR razadyne* OR reminyl* 9 TX exelon* OR "SDZ ENA 713" 10 S6 OR S7 OR S8 OR S9 11 MH "Clinical Trials" 12 TX trial 13 TX "single-blind*" 14 TX "double-blind*" 15 TX "treatment as usual" 16 TX randomly 17 S11 OR S12 OR S13 OR S14 OR S15 OR S16 18 S5 AND S10 AND S17	
ISI Web of Science - all databases [includes: Web of Science (1945-present); BIOSIS Previews (1926-present); MEDLINE (1950-present); Journal Citation Reports] [Date of most recent search 26 October 2017]	TOPIC: (deliri* OR "acute confusion*" OR "acute organic psychosyndrome" OR "acute brain syndrome" OR "metabolic encephalopathy" OR "acute psycho-organic syndrome" OR "clouded state" OR "clouding of consciousness" OR "exogenous psychosis" OR "toxic psychosis" OR "toxic confusion" OR obnubilat*) AND TOPIC: (donepezil OR galantamine OR rivastigmine OR tacrine OR E2020 OR aricept* OR galanthamin* OR nivalin* OR razadyne* OR exelon* OR "SDZ ENA 713") AND TOPIC:(randomised OR randomized OR randomly or placebo or "double-blind" or trial OR groups OR "controlled study" OR RCT OR "single-blind*") Timespan: All years. Search language=Auto	Dec 2016: 78 Oct 2017: 7
LILACS (BIREME) [Date of most recent search 26 October 2017]	donepezil OR donezepil OR aricept OR E2020 [Words] or rivastigmine OR nivalin OR razadyne OR reminyl OR exelon OR galanthamine OR galantamine [Words] and deliri$ OR delirio OR loucura	Dec 2016: 0 Oct 2017: 0

(*Continued*)

	[Words]	
ClinicalTrials.gov (www.clinicaltrials.gov) [Date of most recent search 26 October 2017]	delirium OR toxic psychosis OR toxic confusion | donepezil OR rivastigmine OR galantamine OR tacrine OR galanthamine OR aricept OR E2020 OR Nivalin OR Razadyne OR Reminyl OR exelon OR cognex	Dec 2016: 17 Oct 2017: 0
ICTRP (http://apps.who.int/trialsearch/) [Date of most recent search 26 October 2017]	delirium|donepezil OR rivastigmine OR galantamine OR tacrine OR galanthamine OR aricept OR E2020 OR Nivalin OR Razadyne OR Reminyl OR exelon OR cognex	Dec 2016: 38 Oct 2017: 8
TOTAL before de-duplication		1550
Total after de-duplication		1109
Total after first assessment based on titles and abstracts by CDCIG information specialist		164

CONTRIBUTIONS OF AUTHORS

SW: protocol development, selection of studies and data extraction, drafted parts of the review

ZZ: protocol development, reviewed and drafted parts of the review

TD: content expert, protocol development

SZ: protocol development, reviewed and drafted parts of the review

GP: content expert, protocol development

JX: project management, protocol development, Methodological Expectations of Cochrane Intervention Reviews (MECIR) guidance

AY: protocol development, selection of studies and data extraction, drafted parts of the review

DY: content expert, protocol development

DECLARATIONS OF INTEREST

SW: none known

ZZ: none known

TD: none known

SZ: none known

GP: none known

JX: none known

AY: none known

DY: none known

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None.

NOTES

None.