Cholinesterase inhibitors for delirium (Review)

Overshott R, Karim S, Burns A

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[Intervention Review]

Cholinesterase inhibitors for delirium

Ross Overshott[1], Salman Karim[1], Alistair Burns[2]

[1]Psychiatry Research Group, University of Manchester, Manchester, UK. [2]Psychiatric Research Group, University of Manchester, Manchester, UK

Contact address: Ross Overshott, Psychiatry Research Group, University of Manchester, 3rd Floor, University Place, Oxford Road, Manchester, M13 9PL, UK. rossovershott@hotmail.com.

A B S T R A C T

Background

Delirium is now the preferred term to describe acute confusional states. It is experienced by 10 to 30% of all hospital inpatients. Delirium is potentially reversible and is related to several adverse outcomes, including increased hospital length of stay, poor functional status, persistent cognitive impairment, need for institutional care and probably mortality. Disruption of the cholinergic system has been proposed as a key mechanism of delirium. Cholinesterase inhibitors enhance the cholinergic system and there have been reports that they might be beneficial in treating delirium.

Objectives

To assess the efficacy and safety of cholinesterase inhibitors in the treatment of delirium.

Search methods

The Cochrane Dementia and Cognitive Improvement Group's Register of Clinical Trials (which includes records from MEDLINE, EMBASE, PsycINFO, CINAHL, CENTRAL, LILACS and other databases) was searched for relevant randomised controlled trials using the terms: donepezil or aricept, galantamine or reminyl, rivastigmine OR exelon and tacrine OR cognex on 19 April 2005. As this Specialised Register only contains trials relating to dementia and cognitive impairment, in addition all years of MEDLINE, EMBASE, PsycINFO and CINAHL were searched for trials of cholinesterase inhibitors for delirium in non-demented people.

Selection criteria

Unconfounded, blinded randomised controlled trials, published or unpublished in which treatment with cholinesterase inhibitors was administered and compared with alternative interventions in patients with delirium are included.

Data collection and analysis

Two reviewers (RO, SK) independently assessed the quality of the studies according to parameters such as randomisation, blinding and how dropouts were managed. Each cholinesterase inhibitor was to be examined separately and together as a group.

The primary outcome measures of interest are length of delirium, severity of delirium and presence and severity of behavioural symptoms (e.g. agitation and hallucinations). Other outcomes of interest include: cognition, need for institutionalisation, length of hospital admission and adverse effects.

Main results

There was one included trial of donepezil compared with placebo in 15 patients. No significant difference between the treatment and placebo groups was found in the duration of delirium. The mean duration of postoperative delirium for the donepezil group was 1.0 day

(Standard Error 0.0) while for the placebo group it was 1.3 days (Standard Error 0.19). No other outcomes were measured for the patients who developed delirium.

Authors' conclusions

There is currently no evidence from controlled trials that donepezil is effective in the treatment of delirium. Further trials using cholinesterase inhibitors for the treatment of delirium are needed.

PLAIN LANGUAGE SUMMARY

No convincing evidence from one trial of the efficacy of cholinesterase inhibitors for delirium

Delirium is a confusional state that is associated with physical illness. Its characteristic features are rapid onset, altered consciousness, reduced attention and global cognitive impairment. Other symptoms are hallucinations (particularly visual hallucinations), disturbed sleep pattern and agitation. Delirium is commonly found in hospital patients and is associated with longer admissions, poor functioning level, persistent cognitive impairment and need for institutional care. Delirium is therefore an important syndrome to recognise and treat. The one included trial, of donepezil compared with placebo in 15 patients, showed no statistically significant difference in length of delirium. No other outcomes were measured.

BACKGROUND

Over the years delirium has been known under many different guises including acute brain failure, acute brain syndrome, acute dementia, organic brain syndrome and toxic confusional state. The two main international classifications of disease, the ICD-10 (WHO 1992) and DSM-IV (APA 1994), have similar diagnostic criteria for delirium: altered consciousness and attention, global disturbance of cognition and perceptual abnormalities. Delirium's other core features are rapid onset, fluctuating course, disturbance of the sleep/wake cycle and evidence of a physical cause.

The list of physical causes of delirium is inexhaustible, with infection and medication being among the most frequent. Delirium is a common, important and serious condition. It is experienced by 10 to 30% of all hospital inpatients (Lipowski 1987; Trzepacz 1996). The incidence is higher among older people with 10 to 15% of older hospital patients having a delirium on admission (Bucht 1999) and a further 10 to 40% developing delirium during their time in hospital (Fann 2000). Increased incidence rates have been reported in certain patient groups, e.g. postoperative patients, with a rate of over 60% described in patients following surgery for fractured neck of femur (Gustafson 1988). Delirium is not exclusive to hospitals and one study estimated nursing home prevalence of delirium at 58% (Sandberg 1998). Although common, delirium is poorly identified in clinical practice with nondetection rates of 33 to 66% (Inouye 1994). It is important to detect delirium as it is potentially reversible and is related to several adverse outcomes, including increased hospital length of stay, poor functional status, persistent cognitive impairment and need for institutional care (Bross 1994; Cole 1993). There is also evidence to suggest that delirium is associated with an increase in mortality (McCusker 2002; Pompei 1994; Rabins 1982) although this is not consistent (Inouye 1998).

The pathogenesis of delirium is not clearly understood and many hypotheses have been proposed. It is most likely that delirium represents a response to diffuse cerebral dysfunction, reduced metabolism and disordered neurotransmitter synthesis. The strongest evidence is for disturbance of the cholinergic neurotransmitter system (Koponen 1999). Acetylcholine is the primary neurotransmitter that facilitates learning and attention, both of which are disturbed in delirium. Impaired cholinergic neurotransmission has been correlated with cognitive and behavioural features of delirium (Itil 1966). High serum anticholinergic activity is associated with severity of delirium (Mintzer 2000; Trzepacz 1999) while anticholinergic medications are among the most implicated in iatrogenic delirium (Tune 1993). Cholinesterases are enzymes that metabolise acetylcholine and inhibiting them reduces the inactivation of acetylcholine, which increases its activity. Cholinesterase inhibitors, which act in this way, are currently only licensed for palliative treatment of Alzheimer's disease, the most common type of dementia which, like delirium, is associated with reduced cholinergic activity. The current cholinesterase inhibitors are donepezil, rivastigmine, galantamine and tacrine, and these have been shown to effect significant improvement in cognition, global functioning, behaviour and activities of daily living in Alzheimer's disease (Birks 2003; Birks 2004; Loy 2004; Qizilbash 1998).

Treatments for delirium include the identification and correction of the underlying cause, environmental and supportive interventions and pharmacological treatment. When there is severe agitation, hostility, aggressive behaviour, or the patient poses a risk to self or others, anti-psychotic medication such as haloperidol is the first choice of drug. Haloperidol is the most commonly used (Someya 2001) as it has fewer active metabolites and fewer anticholinergic, sedative and hypotensive effects than the other anti-psychotic drugs. This type of medication can, however, have severe adverse effects (Flacker 1998), especially on the extra-pyramidal system, which can cause clinical deterioration. Treatment with benzodiazepines is only recommended for delirium related to alcohol or withdrawal of benzodiazepines (Lipowski 1990) as benzodiazepines can precipitate delirium.

There is much debate regarding which medications should be used in the management of delirium. The medications most commonly used offer only symptomatic relief. Cholinesterase inhibitors, by promoting the cholinergic system may offer, in addition, actual treatment. There are several reports in the literature of cholinesterase inhibitors being of benefit in delirium (Fischer 2001; Moretti 2004; Wengel 1998). A systematic review of trials of cholinesterase inhibitors for the treatment of delirium is needed to evaluate efficacy and safety.

OBJECTIVES

The outcomes of interest include length of delirium, behavioural disturbance (including agitation, psychotic symptoms), length of stay in hospital and mortality.

METHODS

Criteria for considering studies for this review

Types of studies

Included trials have a period of treatment that exceeds one day. The management of the control group in included studies has been clearly defined as placebo or standard treatment. All included studies have utilised validated and published methods for diagnosing delirium and evaluating behavioural disturbances. Studies conducted in a hospital or community setting are included.

Types of participants

Participants included are over 16 years old, of either gender and diagnosed with delirium by a validated, operationalised, clinical criteria e.g. ICD-10 (WHO 1992); DSM IV (APA 1994); the Confusion Assessment Method (CAM 1990); Delirium Rating Scale (DRS 1988). Participants included may be suffering from any cause of delirium, including medical illnesses, drug or alcohol withdrawal and side effects from medication.

Types of interventions

Included trials have assessed the efficacy of any of the current cholinesterase inhibitors (donepezil, rivastigmine, galantamine and tacrine), orally administered in any dosage or frequency compared with placebo or standard treatment. Standard treatment includes nursing care, environmental measures and single doses of anti-psychotic or benzodiazepines for behavioural disturbances. Studies using regular anti-psychotic and/or benzodiazepine medication have been excluded.

Types of outcome measures

The primary outcomes of interest are:
1. Length of delirium

2. Severity of delirium
3. Presence and severity of behavioural symptoms (e.g. agitation and hallucinations)

The choice of rating scales selected for meta-analysis depends on which scales are used in the selected studies. Only scales which have been published and validated are included.

The secondary outcomes of interest are:
1. Cognition
2. Use of other medications (e.g. one-off doses of anti-psychotic)
3. Need for institutionalisation
4. Length of hospital admission
5. Adverse effects/side effects
6. Withdrawals
7. Reason for withdrawals
8. Activities of daily living
9. Death

Search methods for identification of studies

The trials were identified from a last updated search of the Specialized Register of the Cochrane Dementia and Cognitive Improvement Group on 19 April 2005 using the search term delir*

The Specialized Register at that time contained records from the following databases:
CENTRAL: January 2005 (issue 1);
MEDLINE: 1966 to 2005/02;
EMBASE: 1980 to 2005/01;
PsycINFO: 1887 to 2005/01;
CINAHL: 1982 to 2004/12;
SIGLE (Grey Literature in Europe): 1980 to 2004/06;
ISTP (Index to Scientific and Technical Proceedings): to May 2000;
INSIDE (BL database of Conference Proceedings and Journals): to June 2000;
Aslib Index to Theses (UK and Ireland theses): 1970 to March 2003;
Dissertation Abstract (USA): 1861 to March 2003;
ADEAR (Alzheimer's Disease Clinical Trials Database): to 25 March 2005;
National Research Register: issue 1/2005;
Current Controlled trials (last searched April 2005) which includes:
Alzheimer Society
GlaxoSmithKline
HongKong Health Services Research Fund
Medical Research Council (MRC)
NHS R&D Health Technology Assessment Programme
Schering Health Care Ltd
South Australian Network for Research on Ageing
US Dept of Veterans Affairs Cooperative Studies
National Institutes of Health (NIH)
ClinicalTrials.gov: last searched March 2005;
LILACS (Latin American and Caribbean Health Science Literature): last searched April 2003

The search strategies used to identify relevant records in MEDLINE, EMBASE, PsycINFO, CINAHL and LILACS can be found in the group's module (see About on *The Cochrane Library*)

In addition the following databases were searched:

MEDLINE 1966-2005/04 week 2 was searched with the following search strategy:

#1 "Delirium"/ all subheadings
#2 deliri*
#3 "acute confusion"
#4 "acute brain failure"
#5 "acute organic psychosyndrome"
#6 "acute brain syndrome"
#7 "metabolic encephalopathy"
#8 "acute psycho-organic syndrome"
#9 "clouded state"
#10 "clouding of consciousness"
#11 "exogenous psychosis"
#12 "toxic psychosis"
#13 "toxic confusion"
#14 #1 or #2
#15 #3 or #4 or #5 or #6
#16 #7 or #8 or #9 or #10
#17 #11 or #12 or #13
#18 #14 or #15 or #16 or #17
#19 random* or placebo* or "standard care" or "normal care" or control*
#20 "Alcohol-Withdrawal-Delirium"/ all subheadings
#21 "delirium tremens" in TI
#22 #20 or #21
#23 ((TG=animals) not (TG=humans)) and (TG =animals)
#24 #18 and #19
#25 #24 not #23
#26 #25 not #22
#27 donepezil or aricept or galantamine or reminyl or tacrine or cognex or rivastigmine or exelon
#26 and #27

EMBASE 1980-2005/02 was searched with the following search strategy:

#1 explode "delirium" tree: 1/ all subheadings
#2 deliri*
#3 "acute psycho-organic syndrome" or "clouded state" or "clouding of consciousness" or "exogenous psychosis" or "toxis psychosis" or "toxic confusion"
#4 "acute brain confusion" or "acute brain failure" or "acute organic psychosyndrome" or "acute brain syndrome" or "metabolic encephalopathy"
#5 #1 or #2 or #3 or #4
#6 "randomized-controlled-trial"/ all subheadings
#7 random* or placebo* or control* or "normal care" or "standard care"
#8 #6 or #7
#9 "delirium-tremens"/ all subheadings
#10 nonhuman* in DER
#11 (nonhuman* in DER) and (human* in DER)
#12 #10 or #11
#13 (#5 and #8) not #9
#14 #13 not #12
#15 donepezil or aricept or galantamine or reminyl or tacrine or cognex or rivastigmine or exelon
#16 #14 and #15

PsycINFO 18??- 2005/02 was searched with the following search strategy:

#1 deliri*

#2 "acute psycho-organic syndrome" or "clouded state" or "clouding of consciousness" or "exogenous psychosis" or "toxis 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-" in MJ,MN

#5 #1 or #2 or #3 or #4

#6 random* or placebo* or control* or "normal treatment" or "normal care" or "standard care" or "standard treatment"

#7 #5 and #6

#8 donepezil or aricept or tacrine or cognex or rivastigmine or exelon or galantamine or reminyl

#9 #7 and #8

Companies involved in manufacturing or marketing cholinesterase inhibitors were asked to provide information regarding ongoing trials or unpublished studies not otherwise available. Books concerning delirium and reference lists from review papers and retrieved articles were examined for additional trials.

Proceedings of relevant conferences were searched and experts in the field of delirium were contacted for further references.

Data collection and analysis

Selection of studies

The titles and abstracts of citations obtained by the search were studied by two reviewers (RO and SK). Publications deemed to be irrelevant were discarded. Articles that described a relevant randomised controlled trial were retrieved for further assessment. Retrieved trials were assessed independently (RO and SK) for inclusion in the review by the criteria above. Disagreements at any stage of study selection were resolved by discussion with AB.

Quality assessment

Randomised and blind assessment of outcome are inclusion criteria for the review. Quality of included trials were assessed according to the following criteria:

1. Adequate concealment of treatment allocation (e.g. opaque sealed numbered envelopes).
2. Method of randomisation (e.g. by computer randomisation, random number tables).
3. Adequate blinding (both of participants and outcome assessments).
4. Adequate documentation of how exclusions were handled after treatment allocation.
5. Losses to follow-up (trials should have losses of less than 25%).

The assessment of quality was performed independently by RO and SK and disagreements were resolved by discussion with AB.

Data extraction

To allow an intention-to-treat analysis, data were sought for every patient irrespective of compliance and whether or not the patient was subsequently excluded from the treatment or follow-up. Analyses of those who completed the trial on treatment (completers) were done separately. When individual patient data were not available, data were extracted from summary statistics for each study. For continuous data the mean change from baseline, the standard deviation and the number of participants for each treatment group at each assessment were obtained. In studies that do not report changes from baseline, the mean, the standard deviation and the number of participants for each treatment group at baseline and endpoint was extracted if available. For dichotomous data the number in each treatment group and the numbers experiencing the outcome of interest was retrieved. If only treatment effects and their standard errors are reported then these were extracted.

Data analysis

Statistical analysis was performed using Review Manager software. In trials that have used ordinal rating scales for measuring outcome, if the scales have a reasonably large number of categories (more than 10) the data were treated as continuous outcomes arising from a normal distribution.

Summary statistics (n, mean and standard deviation) were required for each outcome at each assessment time for each treatment group in each trial for change from baseline. When the change from baseline results are not reported, the required summary statistics were calculated from the baseline and assessment time treatment group means and standard deviations. In this case a zero correlation between the measurements at baseline and assessment time was assumed.

For trials that have used the same rating scale to assess outcome, the measure of treatment difference for the pooled trials is the weighted mean difference. Where different rating scales or tests have been used the measure of the treatment difference is the standardised mean difference, which is the absolute mean difference divided by the standard deviation. For binary outcomes, such as clinical improvement or no clinical improvement, the odds ratio is used to measure treatment effect. A weighted estimate of the typical treatment effect across trials is also calculated.

It is intended that overall estimates of the treatment difference is presented. In all cases the overall estimate from a fixed effects model is presented and a test for heterogeneity using an I^2 performed. Where there is evidence of heterogeneity of the treatment effect between trials, then either only homogenous results are pooled, or a random-effects model is used.

Sensitivity analysis was conducted, where possible, to explore the influence of high quality trials (A trials) versus moderate quality trials (B trials) versus low quality trials (C trials), as well as the effects of analysing by intention to treat, on the effect size. We intended to conduct a subgroup analysis to explore the effects of treatment in people with different causes of delirium (e.g. infection, medication) and in people of different ages (less than 65 years and more than 65 years).

R E S U L T S

Description of studies

One trial was included (Liptzin 2005) comparing donepezil with placebo in the prevention and treatment of postoperative delirium in patients over the age of 50 years without dementia undergoing elective total joint-replacement surgery. Eighty patients were randomised to receive either donepezil 5 mg once daily or a placebo tablet once daily which they commenced 14 days before the surgery and continued taking for 14 days after the surgery. The total period of randomised treatment was 28 days. The baseline demographic characteristics were similar in treatment and placebo groups. The mean age was 67 years, 36% male in the donepezil group and 49% in the placebo group. The mean Mini Mental State

Examination (MMSE) ([Folstein 1975](#)) scores were 29.15 and 28.85 for the treatment and placebo groups respectively. There were also no significant differences between the groups in race, which of the two study surgeons performed the operation, which joint, or side were operated on. At baseline, both groups were cognitively intact, with no significant differences in MMSE or Clock Drawing Test ([Sunderland 1989](#)) scores.

Participants were assessed for postoperative delirium using the Delirium Symptom Interview ([DSI 1992](#)), CAM ([CAM 1990](#)), daily medical records, nurse-observation reviews and DSM-IV Diagnostic criteria for delirium ([APA 1994](#)). Participants who were diagnosed with delirium according to DSM-IV ([APA 1994](#)) criteria were advised to double their dose, so they either received 10 mg of donepezil or two placebo capsules.

No rating scales were used to measure outcome. The duration of delirium in the treatment and placebo groups was recorded.

Risk of bias in included studies

The included study ([Liptzin 2005](#)) examines both the prevention of delirium and the treatment of delirium. It is only the treatment component that is relevant to this review. It is unclear whether the included trial meets all the quality assessment criteria of this review, as the details of the two components of the trial are not described separately. The participants, the investigators, research assistants and surgical staff were all blind to allocation. Subjects were randomised by a random numbers chart, with blocks of four in which subjects were randomised overall to 1:1 to donepezil or placebo. All comparisons in the study were made by an intention-to-treat analysis, with participants remaining in the treatment group to which they were originally assigned for analysis. The dropout rate was reported for the whole trial and not just the treated group.

Effects of interventions

There was one included trial ([Liptzin 2005](#)) which randomised 80 patients preoperatively to either receive donepezil or placebo. Fifteen patients developed delirium postoperatively: eight (20.5%) in the donepezil group and seven (17.1%) in the placebo group. Relative risk of 1.20 (95% confidence interval 0.48 to 3.00. Z = 0.39, P = 0.69). No significant difference between the treatment and placebo groups was found in the duration of delirium. It was not possible to obtain the original data from the authors of the duration of delirium for each subject. Further analysis was therefore not done. In the published paper it was reported that the mean duration of postoperative delirium for the donepezil group was 1.0 day (Standard Error 0.0) while for the placebo group it was 1.3 days (Standard Error 0.19) (difference in means -0.3%, 90% confidence interval -7.8 to 7.2, P = 0.12). It seems unlikely that the standard error for the donepezil group is 0.0 but without analysing the original data it is difficult to confirm this. No other outcomes were measured for the patients who developed delirium.

There is currently no separate data on the patients who developed a delirium in the trial for mean age, gender, baseline MMSE, type of operation and percentage who were discharged into a rehab facility. It has not been possible to obtain this data from the authors but it is hoped that it will be made available in the future.

DISCUSSION

At the beginning of this review we highlighted the frequency and associated morbidity of delirium. It is a syndrome which can have serious consequences for patients. We also outlined the reasons why cholinesterase inhibitors might be useful in treating delirium. Our search for evidence of efficacy of cholinesterase inhibitors has produced a single randomised controlled trial. This trial investigated the effectiveness of donepezil so we are unable to include data about the other cholinesterase inhibitors.

The included trial initially examined the effectiveness of donepezil in preventing delirium. Only 15 participants developed a delirium and entered the treatment part of the trial. The report of the trial paper explored only one of the outcome measures we had identified: duration of delirium. No statistical difference was found in the length of delirium between the donepezil and placebo groups. The treatment phase of the trial lacked sufficient power to show a significant difference between the groups. The study population underwent elective surgery and were therefore relatively young, physically well and cognitively intact. They were at low risk of developing delirium and those that did had a brief and relatively benign episode. As the duration of the episodes of delirium were short, it is likely that the symptoms experienced by participants were not of a severity that treatment would be expected to be beneficial.

The included study is currently the only published randomised controlled trial in this subject. There have been, however, several published case reports which describe the effective treatment of delirium with a cholinesterase inhibitor. The causes of delirium in these case reports are varied and include vascular lesions ([Kobayashi 2004](#); [Moretti 2004](#)), alcohol withdrawal ([Hori 2003](#)) and medication ([Noyan 2003](#); [Slatkin 2004](#)). Rivastigmine has also been reported to be effective in treating prolonged delirium in three patients who had not responded to antipsychotic medication ([Kalisvaart 2004](#)). Despite these positive case reports there is currently only one small published randomised controlled trial and this trial does not support the efficacy of cholinesterase inhibitors.

AUTHORS' CONCLUSIONS

Implications for practice

There is currently no evidence from controlled trials to support the efficacy of cholinesterase inhibitors in the treatment of delirium. Delirium remains a common and serious condition with no consensus on its pharmacological treatment.

Implications for research

Risk factors for developing delirium include older age, medical illness and pre-existing dementia. Researching the subject is therefore fraught with difficulties. The potential adverse outcomes of delirium, however, make it an area worthy of attention. Future trials should attempt to include subjects with severe symptoms of delirium so effectiveness for the level of behavioural disturbance that is frequently seen in clinical practice can be established. Future trials should also consider including a wide range of relevant outcomes such as length of hospital admission, functional level, cognitive abilities and institutionalisation.

ACKNOWLEDGEMENTS

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C H A R A C T E R I S T I C S   O F   S T U D I E S

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

Liptzin 2005

Methods	Allocation: Block Randomisation. Blindness: Triple - clinician, patient and assessors. Duration: 14 days.
Participants	Diagnosis: Delirium. N = 15. No demographic data available. Setting: Orthopaedic hospital ward in USA.

Liptzin 2005 *(Continued)*

	Inclusion: Clinical diagnosis of delirium following orthopaedic surgery. Over the age of 50. Exclusion: Gastroesophageal reflux disease, sick-sinus syndrome, not already taking cholinesterase inhibitors.
Interventions	Donepezil. Started at 5 mg once daily, increased to 10 mg once daily if tolerated.
Outcomes	Duration of delirium
Notes	

We were unable to include demograhic data of the patients with delirium as it was not presented in the published paper.

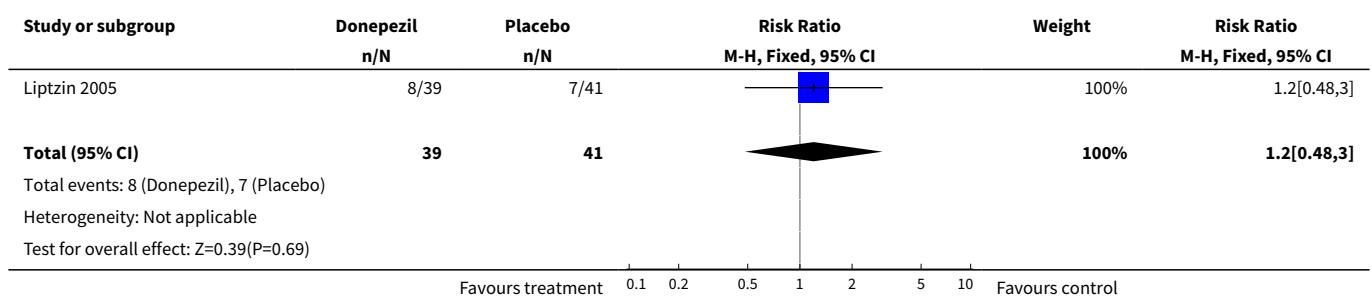### Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Hori 2003	Case report
Kalisvaart 2004	Case series
Kobayashi 2004	Case report
Moretti 2004	Open labelled study
Noyan 2003	Case report
Slatkin 2004	Case report

DATA AND ANALYSES

Comparison 1. Donepezil

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Development of delirium	1	80	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.48, 3.00]

Analysis 1.1. Comparison 1 Donepezil, Outcome 1 Development of delirium.

Study or subgroup	Donepezil n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Liptzin 2005	8/39	7/41		100%	1.2[0.48,3]
Total (95% CI)	**39**	**41**		**100%**	**1.2[0.48,3]**
Total events: 8 (Donepezil), 7 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.39(P=0.69)					

Favours treatment 0.1 0.2 0.5 1 2 5 10 Favours control

WHAT'S NEW

Date	Event	Description
23 October 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 4, 2004
Review first published: Issue 1, 2008

Date	Event	Description
7 October 2007	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Ross Overshott - all correspondance; drafting of protocol versions; selection of trials; extraction of data; entry of data; interpretation of data analyses; updating protocol

Salman Karim - drafting of protocol versions; selection of trials; extraction of data; interpretation of data analyses

Alistair Burns - arbiter in selection of trials; interpretation of data analysis

Leon Flicker - Contact Editor
Christine Sykes - Consumer Editor

DECLARATIONS OF INTEREST

Professor Burns and Dr Overshott are currently involved in a clinical trial of rivastigmine in delirium. Professor Burns has also been involved in clinical trials on cholinesterase inhibitors for Alzheimer's disease, and has received research honoraria and hospitality from Pfizer, Eisai, Novartis, Bristol Myers Squibb, Astra Zeneca, Janssen-Cilag. He holds no shares in any pharmaceutical company.

INDEX TERMS

Medical Subject Headings (MeSH)

Cholinesterase Inhibitors [*therapeutic use]; Delirium [*drug therapy]; Donepezil; Indans [*therapeutic use]; Piperidines [*therapeutic use]

MeSH check words

Humans