

Benzodiazepines for delirium (Review)

Lonergan E, Luxenberg J, Areosa Sastre A, Wyller TB



**THE COCHRANE
COLLABORATION®**

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2009, Issue 1

<http://www.thecochranelibrary.com>



TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
BACKGROUND	3
OBJECTIVES	3
METHODS	3
RESULTS	6
DISCUSSION	7
AUTHORS' CONCLUSIONS	7
ACKNOWLEDGEMENTS	7
REFERENCES	8
CHARACTERISTICS OF STUDIES	9
DATA AND ANALYSES	11
HISTORY	11
CONTRIBUTIONS OF AUTHORS	11
DECLARATIONS OF INTEREST	11
SOURCES OF SUPPORT	11

[Intervention Review]

Benzodiazepines for delirium

Edmund Loneragan¹, Jay Luxenberg², Almudena Areosa Sastre³, Torgeir Bruun Wyller⁴

¹Emeryville, USA. ²San Francisco, USA. ³Madrid, Spain. ⁴Department of Geriatric Medicine, Ullevål University Hospital, N-0407 Oslo, Norway

Contact address: Edmund Loneragan, 4 Captain Drive, Apt 215, Emeryville, CA, 94608, USA. TEDLNRGN@aol.com. (Editorial group: Cochrane Dementia and Cognitive Improvement Group.)

Cochrane Database of Systematic Reviews, Issue 1, 2009 (Status in this issue: *New*)

Copyright © 2009 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

DOI: 10.1002/14651858.CD006379.pub2

This version first published online: 21 January 2009 in Issue 1, 2009.

Last assessed as up-to-date: 3 June 2008. (Help document - [Dates and Statuses](#) explained)

This record should be cited as: Loneragan E, Luxenberg J, Areosa Sastre A, Wyller TB. Benzodiazepines for delirium. *Cochrane Database of Systematic Reviews* 2009, Issue 1. Art. No.: CD006379. DOI: 10.1002/14651858.CD006379.pub2.

ABSTRACT

Background

Delirium occurs in 30% of hospitalised patients and is associated with prolonged hospital stay and increased morbidity and mortality. The results of uncontrolled studies have been unclear, with some suggesting that benzodiazepines may be useful in controlling non-alcohol related delirium.

Objectives

To determine the effectiveness and incidence of adverse effects of benzodiazepines in the treatment of non-alcohol withdrawal related delirium.

Search strategy

The trials were identified from a search of the Specialized Register of the Cochrane Dementia and Cognitive Improvement Group on 26 February 2008 using the search terms: (deliri* or confusion) and (benzo* or lorazepam,“ or ”alprazolam“ or ”ativan“ or diazepam or valium or chlordiazepam).

The CDCIG Specialized Register contains records from major health databases (including MEDLINE, EMBASE, CINAHL, PsycINFO, CENTRAL, LILACS) as well as many ongoing trial databases and grey literature sources.

Selection criteria

Trials had to be unconfounded, randomized and with concealed allocation of subjects. Additionally, selected trials had to have assessed patients pre- and post-treatment. Where crossover design was present, only data from the first part of the trial were to be examined.

Data collection and analysis

Two reviewers extracted data from included trials. Data were pooled where possible, and were to be analysed using appropriate statistical methods. Odd ratios or average differences were to be calculated. Only ”intention to treat“ data were to be included.

Main results

Only one trial satisfying the selection criteria could be identified. In this trial, comparing the effect of the benzodiazepine, lorazepam, with dexmedetomidine, a selective alpha-2-adrenergic receptor agonist, on delirium among mechanically ventilated intensive care unit patients, dexmedetomidine treatment was associated with an increased number of delirium- and coma-free days compared with

lorazepam treated patients (dexmedetomidine patients, average seven days; lorazepam patients, average three days; $P = 0.01$). One partially controlled study showed no advantage of a benzodiazepine (alprazolam) compared with neuroleptics in treating agitation associated with delirium, and another partially controlled study showed decreased effectiveness of a benzodiazepine (lorazepam), and increased adverse effects, compared with neuroleptics (haloperidol, chlorpromazine) for the treatment of acute confusion.

Authors' conclusions

No adequately controlled trials could be found to support the use of benzodiazepines in the treatment of non-alcohol withdrawal related delirium among hospitalised patients, and at this time benzodiazepines cannot be recommended for the control of this condition. Because of the scarcity of trials with randomization of patients, placebo control, and adequate concealment of allocation of subjects, it is clear that further research is required to determine the role of benzodiazepines in the treatment of non-alcohol withdrawal related delirium.

PLAIN LANGUAGE SUMMARY

At this time, benzodiazepines cannot be recommended for the treatment of non-alcohol related delirium

A systematic review of benzodiazepine treatment of non-alcohol related delirium discovered very few trials (one randomized, controlled study of mechanically ventilated patients, and thus poorly reflective of delirious patients as a whole; and two partially controlled studies), the results of which indicate that at this time there is no evidence to support the use of benzodiazepines in the treatment of non-alcohol withdrawal related delirium among hospitalised patients.

BACKGROUND

There are few more daunting challenges to clinicians and medical investigators than the management of delirium. Delirium, an acute confusional state described as "a transient global disorder of cognition and attention" (Luxenberg 1996), occurs in up to 30% of hospitalised patients (Johnson 1990; Sumner 1994) and has been associated with prolongation of hospital stay (McCusker 2004), subsequent deterioration in cognition (McCusker 2001), and increased morbidity and mortality (McCusker 2002). Although disorders drawn from the entire spectrum of non-trivial medical illnesses have contributed to delirium, those most often linked to this condition included infection, previous cognitive impairment, advanced age (i.e., 75 and older), surgery, and adverse drug effects, especially those of anticholinergics, and centrally acting medications. Evaluation of drug therapy of delirium has been difficult because of variations in the kinds of patients experiencing delirium (e.g. age, sex, medical conditions) and the heterogeneity of methods of evaluation and treatment (e.g. selection of drugs, dosages, duration of treatment). A major obstacle to the use of placebo controlled trials has been the imperative to provide care for severely agitated patients who are at danger to themselves and those around them. Further, as stated among the secondary objectives, it was important in the current study to identify drug-related adverse effects (e.g. benzodiazepine induced somnolence, agitation) that might obscure patient response to the drugs used to control delirium. The neurophysiological mechanisms of delirium are yet to be identified; evidence suggests pre-existing deficiencies in cholinergic neurotransmission as a common underlying factor (Tune 2002). The presence of an apolipoprotein E4 allele has been associated with prolonged duration of delirium (Ely 2007). Benzodiazepines have been effective in treating delirium due to alcohol withdrawal (Mayo-Smith 1997), and may be useful because of the absence of adverse effects shared by alternative agents (e.g., parkinsonism with haloperidol or risperidone) for this condition, but the literature is unclear about their usefulness in delirium associated with other medical problems (Adams 1984; Breitbart 1996; Salzman 1986), with some reports stating that benzodiazepines may contribute to the development of delirium in patients admitted to the intensive care unit (Dubois 2001; Marcantonio 1994; Pandharipande 2006). A literature review of delirium treatment in AIDS patients, and limited to a MEDLINE search from 1966 to 1988 (Conn 2001), found only one randomized controlled trial (Breitbart 1996) comparing a benzodiazepine (lorazepam) with neuroleptics (haloperidol, chlorpromazine) in delirium and in this study the development of unacceptable adverse effects (severe sedation, ataxia, increased confusion) among all of the lorazepam treated patients required premature discontinuance of the benzodiazepine arm of the trial. Conn et al. concluded that neuroleptics are superior to benzodiazepines in the treatment of most cases of acute confusion. To date there has not been an inclusive systematic review of controlled studies examining the effect of benzodi-

azepines in the treatment of non-alcohol related delirium in hospitalised patients.

OBJECTIVES

Primary objective

To determine the effect of benzodiazepines on hospitalised adults with delirium.

Secondary objectives

- To examine the incidence and types of adverse effects of benzodiazepines
- To examine the number of withdrawals among benzodiazepine treated and control patients
- To examine the number of patients withdrawing from treatment because of adverse effects of benzodiazepines
- To examine adverse drug effects of benzodiazepines as they confound the evaluation of the response of delirium to treatment
- To examine the effect of benzodiazepines of different classes (e.g. short-acting, intermediate acting, long acting) on the course of delirium.

To determine if response to benzodiazepines is influenced by:

- The cause of delirium: surgery, infection, stroke, drugs
- The character of delirium: hypoactive, hyperactive
- The presence of previous cognitive impairment
- Dose of drug
- Duration of treatment
- Age of the patient.

METHODS

Criteria for considering studies for this review

Types of studies

Types of studies included controlled, unconfounded, randomized, placebo-controlled trials with concealed allocation of subjects. Trials had to have included pre- and post-treatment assessment of delirium. Where crossover studies were reported, only data from the first part of the study were examined. Interrupted time series were excluded. Length of trial and number of measurements did not influence the selection of trials for study. Where indicated, individual patient data were requested for further examination.

Types of participants

These included only hospitalised adults who had delirium due to causes other than benzodiazepine toxicity or withdrawal from alcohol. Potentially correctable causes of delirium had to have been ruled out (e.g., drug-induced, pain, hypoxia) and the diagnosis of delirium had to have been made using DSM IV or DSM III criteria, or other accepted standards for diagnosing delirium. Where delirium occurred, or persisted, despite the control of an alleged cause, this was included in the present review.

Types of interventions

Intervention included treatment with benzodiazepines, of any dosage, compared with placebo or another drug. Patients who received more than one psychopharmacologic agent on a long-term basis were excluded from the study. Because delirium may have responded quickly to therapy, no minimal period of treatment was mandated but due to the fluctuating nature of delirium the response to treatment must have persisted for at least three days for the study to be included. It is acknowledged that the figure of three days was arbitrary, but the literature has been silent on the subject of spontaneous remissions and relapses of delirium, and this criterion was based on clinical experience.

Types of outcome measures

Outcomes of response to treatment of delirium with benzodiazepines were measured using one or more of the following:

- The Delirium Rating Scale (Trzepacz 1988)
- Criteria in DSM IV or DSM III (APA 1994)
- Criteria in ICD-10 (WHO 1993)
- A standard evaluation by a psychiatrist or neurologist.

Lacking official criteria for determining adverse events (DSM IV, DSM III: APA 1994; ICD-10: WHO 1993), outcomes of adverse reactions to treatment of delirium with benzodiazepines were measured as determined by the instruments applied by the investigators.

Adverse responses to treatment with benzodiazepines were measured using one or more standardized scales or scales developed by the investigators

Search methods for identification of studies

Electronic searches

See [Cochrane Dementia and Cognitive Improvement Group](#) methods used in reviews.

The Specialized Register of the Cochrane Dementia and Cognitive Improvement Group (CDCIG) was searched on 26 February 2008 for all years up to December 2005. This register contains records from the following major healthcare databases *The Cochrane Library*, MEDLINE, EMBASE, PsycINFO, CINAHL and LILACS, and many ongoing trial databases and other grey literature sources. The following search terms were used: (deliri* or confusion) and (benzo* or lorazepam, or "alprazolam" or "ativan" or diazepam or valium or chlordiazepam).

The Cochrane Library, MEDLINE, EMBASE, PsycINFO, CINAHL and LILACS were searched separately on 26 February 2008 for records added to these databases after December 2005 to February 2008. The search terms used to identify relevant controlled trials on dementia, Alzheimer's disease and mild cognitive impairment for the Group's Specialized Register can be found in the Group's module on *The Cochrane Library*. These search terms were combined with the following search terms and adapted for each database, where appropriate: (deliri* or confusion) and (benzo* or lorazepam, or "alprazolam" or "ativan" or diazepam or valium or chlordiazepam).

On 26 February 2008, the Specialized Register consisted of records from the following databases:

Healthcare databases

- *The Cochrane Library*: (2006, Issue 1);
- MEDLINE (1966 to 2006/07, week 5);
- EMBASE (1980 to 2006/07);
- PsycINFO (1887 to 2006/08, week 1);
- CINAHL (1982 to 2006/06);
- SIGLE (Grey Literature in Europe) (1980 to 2005/03);
- LILACS: Latin American and Caribbean Health Science Literature (<http://bases.bireme.br/cgi-bin/wxislind.exe/iah/online/?IsisScript=iah/iah.xis&base=LILACS&lang=i&> (last searched 29 August 2006).

Conference proceedings

- ISTP (<http://portal.isiknowledge.com/portal.cgi>) (Index to Scientific and Technical Proceedings) (to 29 August 2006);
- INSIDE (BL database of Conference Proceedings and Journals) (to June 2000);

Theses

- Index to Theses (formerly ASLIB) (<http://www.theses.com/>) (UK and Ireland theses) (1716 to 11 August 2006);
- Australian Digital Theses Program (<http://adt.caul.edu.au/>): (last update 24 March 2006);
- Canadian Theses and Dissertations (<http://www.collectionscanada.ca/thesescanada/index-e.html>): 1989 to 28 August 2006);
- DATAD - Database of African Theses and Dissertations (<http://www.aau.org/datad/backgrd.htm>);
- Dissertation Abstract Online (USA) (<http://www.lib.umi.com/dissertations/gateway>) (1861 to 28 August 2006).

Ongoing trials

UK

- National Research Register (<http://www.update-software.com/projects/nrr/>) (last searched issue 3/2006);

- ReFeR
(<http://www.refer.nhs.uk/ViewWebPage.asp?Page=Home>)
(last searched 30 August 2006);
- Current Controlled trials: Meta Register of Controlled trials (mRCT) (<http://www.controlled-trials.com/>) (last searched 30 August 2006) :
- ISRCTN Register - trials registered with a unique identifier
- Action medical research
- Kings College London
- Laxdale Ltd
- Medical Research Council (UK)
- NHS Trusts Clinical Trials Register
- National Health Service Research and Development Health Technology Assessment Programme (HTA)
- National Health Service Research and Development Programme 'Time-Limited' National Programmes
- National Health Service Research and Development Regional Programmes
- The Wellcome Trust
- Stroke Trials Registry
(<http://www.strokecenter.org/trials/index.aspx>) (last searched 31 August 2006);

Netherlands

- Netherlands Trial Register (<http://www.trialregister.nl/trialreg/index.asp>)
(last searched 31 August 2006);

USA/International

- ClinicalTrials.gov (<http://www.ClinicalTrials.gov>) (last searched 31 August 2006) (contains all records from <http://clinicalstudies.info.nih.gov/>);
- IPFMA Clinical trials Register: www.ifpma.org/clinicaltrials.html. The Ongoing Trials database within this Register searches <http://www.controlled-trials.com/isrctn>, <http://www.ClinicalTrials.gov> and <http://www.centerwatch.com/>. The ISRCTN register and [Clinicaltrials.gov](http://www.ClinicalTrials.gov) are searched separately. Centerwatch is very difficult to search for our purposes and no update searches have been done since 2003.
- The IFPMA Trial Results databases searches a wide variety of sources among which are:
- <http://www.astrazenecaclinicaltrials.com> (seroquel, statins)
- <http://www.centerwatch.com>
- <http://www.clinicalstudyresults.org>
- <http://clinicaltrials.gov>
- <http://www.controlled-trials.com>
- <http://ctr.gsk.co.uk>
- <http://www.lillytrials.com> (zyprexa)

- <http://www.rocche-trials.com> (anti-beta antibody)
- <http://www.organon.com>
- <http://www.novartisclinicaltrials.com> (rivastigmine)
- <http://www.bayerhealthcare.com>
- <http://trials.boehringer-ingenelheim.com>
- <http://www.cmrinteract.com>
- <http://www.esteve.es>
- <http://www.clinicaltrials.jp>

This part of the IPFMA database is searched and was last updated on 4 September 2006;

- Lundbeck Clinical Trial Registry
(<http://www.lundbecktrials.com>) (last searched 15 August 2006);
- Forest Clinical trial Registry
(<http://www.forestclinicaltrials.com/>) (last searched 15 August 2006).

The search strategies used to identify relevant records in MEDLINE, EMBASE, PsycINFO, CINAHL and LILACS can be found in the Group's module on *The Cochrane Library*. Trial searches included English and non-English publications.

Searching other resources

Where indicated, authors of publications and drug companies manufacturing antipsychotics were contacted for additional information. Hand searches for recent relevant articles in medical libraries were performed.

Data collection and analysis

Searching and screening of the results were performed independently by two reviewers (ETL, JL). Where the reviewers were in disagreement, the third reviewer reviewed the article or articles in dispute. Where an equal number of reviewers disagree, the decision was adjudicated by further discussion among all reviewers. The reviewers selected for relevance and against defined inclusion criteria. Trials that did not meet the criteria were excluded. Reviewers' selection of trials were compared and trials were ranked using one of the Cochrane approaches (Mulrow 1997).

- Grade A: Adequate concealment (randomization; placebo controlled; concealed allocation).
- Grade B: Uncertain.
- Grade C: Inadequate concealment; no randomization.

Only controlled studies - per above - were included in the review. Because studies satisfying criterion B (Uncertain) were eligible for inclusion in the current proposal, failure to satisfy Grade A criteria did not affect the scope of the present investigation. Trials with inadequate concealment have been shown to overestimate treatment effect (Chalmers 1983; Schulz 1994) and were excluded.

Data extraction

- 'Intention to treat analysis' was applied to data obtained on every randomized patient, without exception. In the absence of ITT data, data for 'on-treatment analysis' was extracted and indicated as such. In studies where the number of patients leaving the study was too small to affect the results, the absence of ITT did not eliminate the study from inclusion in the present review.
- Where patients were not randomised nor was treatment allocation concealed when titration periods were used, data from these titration periods were not extracted to assess safety or efficacy of haloperidol. For the same reason, data from follow-up periods were not extracted.
- Data on adverse effects and dropouts were recorded.
- For some binary and ordinal outcomes (i.e., improved versus not improved) the end point itself was of clinical relevance, because all patients, by definition, had the same initial score.
- Where present numerical scores were used to assess response to treatment; in some instances, because of variation in the way response to treatment was measured, it was necessary to operationalise outcomes as 'improved' versus 'not improved', regardless of the scale used by the authors.

Analysis of data

- The null hypothesis to be tested was that for the outcomes examined, benzodiazepines have no effect compared with placebo, or compared with another drug.
- For continuous or ordinal variables (e.g. psychometric test scores, clinical global impression scales), if analyses indicated that parametric tests were appropriate, outcome measures were treated as continuous data; the data were treated as continuous if ordinal scale data appeared to approximate a normal distribution.
- Not excluding the above approach, data were to be combined into the two categories that best represented the contrasting states of interest, and the variable were treated as binary.
- For binary outcomes the Peto method of typical odds ratio was to be used.
- A test for heterogeneity of the treatment effect between the trials was to be done using a standard chi-square statistic. Where no heterogeneity was found, a fixed effect parametric approach was to be taken.
- Where the included studies used the same outcome measures the method of weighted mean difference was to be used for meta-analysis. When different scales were used in the studies the method of standardised mean difference was to be used.
- For continuous or ordinal variables, such as psychometric test scores and clinical global impression scales, if the ordinal scale data appeared to approximate a normal dis-

tribution, or if analysis indicated that parametric tests were appropriate, outcome measures were to be treated as continuous data. A second approach, not excluding the first, where indicated, was to dichotomize the data (e.g., improved vs not improved) and treat the variable as binary. For binary outcomes the Peto method of the typical odds ratio was to be used.

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

Only one study was identified ([Pandharipande 2007](#)) that satisfied the selection criteria. This study compared the effectiveness of the short acting benzodiazepine, lorazepam, with that of the selective alpha-2 adrenergic agonist, dexmedetomidine, on duration of coma-free days, duration of delirium-free days, and duration of coma- and delirium-free days while providing adequate sedation in mechanically ventilated patients in the intensive care unit. The study had no placebo control group.

Patient population: 106 mechanically ventilated medial and surgical intensive care unit patients. Dexmedetomidine was used in 52 patients; lorazepam in 51. The average age in the dexmedetomidine group was 60 (49 to 65) and in the lorazepam group, 49 (45 to 57). There were 30 (58%) men in the dexmedetomidine group and 23 (45%) in the lorazepam group ($P = 0.20$).

No significant difference between the two groups could be identified in terms of (1) severity of illness measured by the Apache ii scores ($P = 0.75$); (2) duration of time on mechanical ventilation prior to enrolment ($P = 0.18$); (3) level of sedation measured by the Richmond Agitation Sedation Scale, RASS ([Ely 2003](#); [Sessler 2002](#)) ($P = 0.21$); (4) admission diagnoses: sepsis/acute respiratory distress/ syndrome ($P = 0.78$); (5) intensive care unit type, medical/surgical ($P = 0.97$); (6) or degree of sedation on admission to study ($P = 0.21$).

Delirium was identified using the Confusion Assessment Method of the Intensive Care Unit, CAM-ICU ([Ely 2001](#); [Lin 2004](#)). The assessment for delirium was positive if patients showed: acute onset of mental changes or fluctuating mental status plus inattention and either disorganized thinking or altered level of consciousness. The RASS scale measures level of consciousness based on patients' ability to respond to verbal or physical stimuli, with coma defined as a score of minus 4 (responsive only to physical stimuli) or minus 5 (unresponsive to physical stimuli).

Patients were identified as delirious if they had a positive Confusion Assessment Method score for the ICU, CAM-ICU ([Ely 2001](#); [Lin 2004](#)) and were responsive to verbal stimulation (RASS score of -3 or more positive). Coma was defined as a RASS score of -4 to -5).

All results were subjected to intention-to-treat analysis. Pearson chi square tests compared categorical variables between the two groups and Wilcoxon rank-sum tests compared continuous variables, including delirium-free and coma-free days. Kaplan-Meier survival curves were used to graph time to event analysis.

Two partially controlled studies (Breitbart 1996; Christensen 1998) that examined benzodiazepine treatment of non-alcohol related delirium were identified. These studies were excluded from meta-analysis because of, in one case, premature termination of the trial, and in the other, unclear separation of delirium from other clinical conditions.

Risk of bias in included studies

The study satisfied the selection criteria listed above.

Effects of interventions

The average delirium-free duration for lorazepam treated patients was seven days (5 to 10) and for dexmedetomidine was 10 days (9 to 12), $P = 0.09$. The average coma-free period for lorazepam treated patients was eight days (5 to 10) and for dexmedetomidine patients was nine days (9 to 12) ($P < 0.001$). The average duration of delirium-free plus coma-free days was three days (1 to 6) for lorazepam patients and seven days (1 to 10) for dexmedetomidine patients ($P = 0.01$). Prevalence of delirium while on treatment was 82% for lorazepam patients and 79% for dexmedetomidine patients ($P = 0.65$). Prevalence of coma was 92% for lorazepam patients and 63% for dexmedetomidine patients ($P < 0.001$). Prevalence of delirium or coma was 98% for lorazepam patients and 87% for dexmedetomidine patients ($P = 0.003$). Adequate sedation, as measured by RASS score within one point of physician goal, was achieved in 67% of dexmedetomidine patients and 55% of lorazepam patients ($P = 0.008$). The 28 day mortality (27%) of lorazepam treated patients was not significantly different from that of the dexmedetomidine patients (17%) ($P = 0.18$). Because only one study that satisfied selection criteria was found, neither meta-analysis of the results or testing of the secondary objectives of the current systematic analysis could be performed.

DISCUSSION

The results of Pandharipande 2007 supported the efficacy of dexmedetomidine in minimising delirium when used for sedation in mechanically ventilated patients compared with lorazepam. Dexmedetomidine treated patients had more coma-free or delirium-free days than lorazepam patients ($P = 0.01$), suggesting better control of acute confusion and decreased levels of sedation in contrast to lorazepam treated patients. The absence of placebo controls in this report did not permit any comment on the effect of lorazepam in the management of delirium compared with no

drug treatment at all. The use of a highly selected group of patients - those on mechanical ventilation - prevents application of the results of the study to the population of delirious patients as a whole. It should be noted that this was not a study of treatment of delirium, but rather a comparison of two agents for sedation during prolonged mechanical ventilation, a situation where the incidence of delirium is very high.

An interrupted RCT of Breitbart 1996 showed no improvement in delirium among patients briefly treated with a benzodiazepine (lorazepam) compared with improvement in delirium for patients receiving neuroleptics (haloperidol, chlorpromazine) ($P < 0.001$), based on Delirium Rating Scores. In this study the benzodiazepine arm of the trial was discontinued prematurely because of unacceptable adverse effects among the lorazepam treated patients. The greater duration of coma among lorazepam treated patients in Pandharipande 2007 corroborates the results of the interrupted trial (Breitbart 1996) in which all delirious patients treated with lorazepam developed unacceptable adverse effects, including severe sedation. A second partially controlled study (Christensen 1998) compared the effect of a benzodiazepine (alprazolam) with a neuroleptic (haloperidol) effect on behavioural manifestations due to delirium, as well as other conditions (dementia, amnesic disorders) among institutionalised patients, and found no significant difference in the outcome behavioural scales comparing benzodiazepine and neuroleptic patients. It is not enough to accept these results as simply showing no clear advantage in the use of the benzodiazepine, lorazepam, in controlling delirium, compared with other drugs. The findings of Pandharipande and of Breitbart that increased sedation and prolonged coma in lorazepam treated patients suggest that such treatment may worsen the status of delirious patients, and clinicians should be guided accordingly.

AUTHORS' CONCLUSIONS

Implications for practice

There is no evidence to support the use of benzodiazepines in the treatment of non-alcohol withdrawal related delirium among hospitalised patients.

Implications for research

Further controlled studies are necessary to establish the role of benzodiazepines in the control of non-alcohol related delirium in hospitalised patients.

ACKNOWLEDGEMENTS

The authors would like to thank the consumer editor, Caroline Marshall, for reading and commenting on this protocol.

REFERENCES

References to studies included in this review

Pandharipande 2007 *{published data only}*

Pandharipande P, Pun BT, Herr DL, et al. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients. The MRNDSS randomized controlled trial. *JAMA* 2007;**298**:2644–53.

References to studies excluded from this review

Breitbart 1996 *{published data only}*

Breitbart W, Marott R, Platt MM, et al. A double-blind trial of haloperidol, chlorpromazine and lorazepam in the treatment of delirium in hospitalized AIDS patients. *American Journal of Psychiatry* 1996;**153**:231–7.

Christensen 1998 *{published data only}*

Christensen DB, Benfield WR. Alprazolam as an alternative to low-dose haloperidol in older cognitively impaired nursing facility patients. *Journal of the American Geriatrics Society* 1998;**46**:620–5.

Additional references

Adams 1984

Adams R. Neuropsychiatric evaluation and treatment of delirium in the critically ill cancer patient. *Cancer Bulletin* 1984;**36**:156–60.

APA 1994

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. IV. American Psychiatric Publishing, Washington, DC, 1994.

Breitbart 1996

Breitbart W, Marotta R, Platt M, Weisman H, Derevenco M, Grau C, Corbera K, Raymond S, Lund S, Jacobsen P. A double-blind trial of haloperidol, chlorpromazine, and lorazepam in the treatment of delirium in hospitalized AIDS patients. *American Journal of Psychiatry* 1996;**153**:231–7.

Chalmers 1983

Chalmers TC, et al. Bias in treatment assignment in controlled trials. *New England Journal of Medicine* 1983;**309**:1358–61.

Conn 2001

Conn DK, Lief S. Diagnosing and managing delirium in the elderly. *Canadian Family Physician* 2001;**47**:101–8.

Dotson 2008

Dotson Bryan, Peeters Michael J. Sedation With Dexmedetomidine vs Lorazepam in Mechanically Ventilated Patients. *JAMA: The Journal of the American Medical Association* 2008;**299**(13):1540–.

Dubois 2001

Dubois MJ, Bergeron N, Dumont N, Dial S, Skrobik Y. Delirium in an intensive care unit: a study of risk factor. *Intensive Care Medicine* 2001;**27**:1297–304.

Ely 2001

Ely EW, Inouye SK, Bernard GR, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit. *JAMA* 2001;**286**:2703–10.

Ely 2003

Ely EW, Truman B, Shintani A, et al. Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond Agitation-Sedation Scale (RASS). *JAMA* 2003;**289**:2983–91.

Ely 2007

Ely E Wesley MD MPH, Girard Timothy D MD, Shintani Ayumi K PhD MPH, Jackson James C PsyD, Gordon Sharon M PsyD, Thomason Jason W W MD, et al. Apolipoprotein E4 polymorphism as a genetic predisposition to delirium in critically ill patients *. [Article]. *Crit Care Med* 2007;**35**(1):112–7. [MEDLINE: DOI: 10.1097/01.CCM.0000251925.18961.CA]

Johnson 1990

Johnson JC. Delirium in the elderly. *Emergency Medicine Clinics of North America* 1990;**8**:255–65.

Lin 2004

Lin SM, Liu CY, Wang CH, et al. The impact of delirium on the survival of mechanically ventilated patients. *Critical Care Medicine* 2004;**32**:2254–59.

Luxenberg 1996

Luxenberg J. Delirium in the elderly. In: Loneragan E editor(s). *Handbook of Geriatrics*. Appleton & Lange, Stamford, Connecticut, 1996.

Marcantonio 1994

Marcantonio ER, Juarez G, Goldman L, et al. The relationship of postoperative delirium with psychoactive medications. *JAMA* 1994;**272**:1518–22.

Mayo-Smith 1997

Mayo-Smith MF, for the American Society of Addiction Medicine Working Group on Pharmacological Management of Alcohol Withdrawal. Pharmacological treatment of alcohol withdrawal: a meta-analysis and evidence-based practice guidelines. *JAMA* 1997;**278**:144–51.

McCusker 2001

McCusker J, Cole M, Dendukuri N, et al. Delirium in older medical inpatients. Marker for subsequent cognitive and functional status. *Canadian Medical Association Journal* 2001;**165**:575–83.

McCusker 2002

McCusker J, Cole M, Abrahamowicz M, et al. Delirium predicts 12 month mortality. *Archives of Internal Medicine* 2002;**162**:457–63.

McCusker 2004

McCusker J, Cole MG, Dendukuri N. Does delirium increase hospital stay?. *Journal of the American Geriatrics Society* 2004;**51**:1539–46.

Mulrow 1997

Mulrow CD, Oxman AD. *Cochrane Collaboration Handbook*. Oxford Update Software, Oxford, UIK, 1997.

Pandharipande 2006

Pandharipande P, Shintani A, Peterson J, et al. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. *Anesthesiology* 2006;**104**:21–6.

Pandharipande 2008

Pandharipande Pratik P, Girard Timothy D, Ely E Wesley. Sedation With Dexmedetomidine vs Lorazepam in Mechanically Ventilated Patients—Reply. *JAMA: The Journal of the American Medical Association* 2008;**299**(13):1542–.

Salzman 1986

Salzman C, Green AI, Rodriguez-Viall F, Jaskiw GI. Benzodiazepines combined with neuroleptics for management of severe disruptive behavior. *Psychosomatics* 1996;**27**:7–22.

Schulz 1994

Schulz KF, Chalmers I, Grimes DA, Altman DG. Assessing the quality of randomization from the reports of controlled trials published in obstetrics and gynecology journals. *JAMA* 1994;**272**:125–8.

Sessler 2002

Sessler CN, Gosnell M, Grap MJ, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care patients. *American Journal of Respiratory and Critical Care Medicine* 2002;**166**:1388–44.

Sumner 1994

Sumner AD, Simons RJ. Delirium in the hospitalized elderly. *Cleveland Clinic Journal of Medicine* 1994;**61**:258–62.

Trzepacz 1988

Trzepacz PT, Baker RW, Greenhouse J. A symptom rating scale for delirium. *Psychiatry Research* 1988;**23**:89–97.

Tune 2002

Tune L. The role of antipsychotics in treating delirium. *Current Psychiatry Reports* 2002;**4**:209–12.

WHO 1993

The World Health Organization. *The ICD-10 Classification of Mental and Behavioral Disorders: Diagnostic Criteria for Research*. World Health Organization, Geneva, Switzerland, 1993.

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES**Characteristics of included studies** [ordered by study ID]**Pandharipande 2007**

Methods	Double-blind, randomized (computer-generated, permuted block randomization); intention to treat analysis
---------	--

Pandharipande 2007 (Continued)

Participants	Medial and surgical ICU patients requiring mechanical ventilation for more than 24 hours. 106 patients 54 patients (average age, 59, 23 men) in control group. 52 patients (average age 60; 30 men) received study drug. Delirium diagnosed using IC-CAM method or RASS scale
Interventions	Patients were treated for up to 120 hrs, with: control group receiving intravenous lorazepam; study group receiving intravenous dexmedetomidine). Drug infusion rate was titrated to reach a sedation level determined by the Richmond Agitation-Sedation Scale. Rescue intervention for acute agitation while on treatment included propofol infusion; for increased pain, fentanyl was given
Outcomes	Prevalence of coma was significantly higher among lorazepam patients compared with dexmedetomidine patients (92% vs 63%; $P < 0.001$). Delirium-free days were not significantly different comparing the two groups (L pts av 7 d, D pts av 9 d, $P = 0.09$); delirium-free and coma free days were significantly greater for D patients compared with L patients (Dpts av 7 d, Lpts av 3 d; $P = 0.01$)
Notes	Authors note that dexmedetomidine has analgesic properties, but that this group received more fentanyl than lorazepam patients, introducing two uncontrolled variables (pain control and sedation effect of fentanyl) that may have affected the outcomes. Authors (Prandharipande 2008) noted that the long half-life of lorazepam (8-15 hours) compared to dexmedetomidine (2 hours) could contribute to the differences in oversedation favoring the shorter acting drug.

Characteristics of excluded studies [ordered by study ID]

Breitbart 1996	Prospective randomized trial comparing the effect on delirium of lorazepam (6 patients), chlorpromazine (13 patients) and haloperidol (11 patients) in hospitalised AIDS patients. Treatment with either haloperidol or chlorpromazine improved delirium in these patients compared with no effect of lorazepam ($P < 0.01$). Because of unacceptable adverse effects (oversedation, ataxia, worsening confusion) the lorazepam arm of the study was terminated prematurely.
Christensen 1998	Randomized double-blind study comparing effect of alprazolam and low-dose haloperidol on disruptive behaviour associated with delirium, dementia, and amnesic and other cognitive disorders. 48 older, cognitively impaired nursing home patients. No significant differences in outcome scales (Clinical Global Impression; Blessed Dementia Scale; Sandoz Clinical Assessment Scale) comparing alprazolam with haloperidol treated patients. There was not adequate concealment of allocation of patients and there was no clear separation of patients with acute confusion from other conditions having cognitive impairment.

DATA AND ANALYSES

This review has no analyses.

HISTORY

Protocol first published: Issue 1, 2007

Review first published: Issue 1, 2009

CONTRIBUTIONS OF AUTHORS

ETL: drafting of review versions; all correspondence; selection of trials; extraction of data; entry of data; interpretation of data analyses; updating review

JL: drafting of review versions; selection of trials; extraction of data; interpretation of data analyses

AAS: arbiter in selection of trials; interpretation of data analyses

TW: arbiter in selection of trials; interpretation of data analyses

Contact editors: Leon Flicker and Mario Fioravanti

Consumer editor: Caroline Marshall

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Cochrane Cognitive Improvement and Dementia Group, UK.

External sources

- No sources of support supplied