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Benzodiazepines for treatment of delirium in non-ICU settings (Protocol)

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[Intervention Protocol]

Benzodiazepines for treatment of delirium in non-ICU settings

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ABSTRACT

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

To determine the effectiveness and safety of benzodiazepines in the treatment of delirium (excluding delirium related to alcohol or benzodiazepines withdrawal) in all settings other than intensive care units (ICUs).

BACKGROUND

Description of the condition

Delirium is a clinical syndrome characterized by the rapid onset of fluctuating confusion, inattention and reduced awareness of the environment, with an underlying organic or metabolic cause. Different areas of cognition can be affected, e.g. memory, orientation, language, and perception (American Psychiatric Association 2013). There are three major types of delirium: hypoactive, hyperactive, and mixed. Hypoactive delirium is characterized by decreased responsiveness, withdrawal, and apathy, whereas hyperactive delirium is characterized by agitation, restlessness, and emotional lability (Meagher 2000). Delirium occurs across healthcare settings and populations, but is especially common in medical and surgical patients, with even higher rates in intensive care units (ICUs) and palliative care services. A systematic review by Siddiqi 2006 found delirium was present in 10% to 30% of general hospital admissions, rising to over 33% among general medical patients. Following coronary artery bypass grafting in the elderly, the incidence has been reported as 33.6% (Santos 2004), and following hip fracture the overall prevalence is 43% to 61% (Holmes 2000). The diagnosis of delirium is usually based on observation of the patient and on information obtained from the nursing staff or caregivers. The American Psychiatric Association recommends that delirium assessment in clinical practice is best achieved when medical diagnosis is supplemented with observational assessment tools (Maldonado 2008). More than 24 delirium instruments have been used in published studies (Inouye 2014). The Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria remain

the diagnostic gold standard for a diagnosis of delirium(Radtke 2008) .

Risk factors for delirium include older age, pre-existing cognitive impairment, major surgery, disruption of the circadian rhythm, malnutrition, sleep deprivation, social isolation, physical restraint, dehydration, sensory deprivation, and use of certain medications (NICE 2010). The mechanisms and risk factors for delirium differ between ICU and non-ICU patients. ICU patients have a greater number of risk factors for delirium (e.g. sedatives and analgesics to facilitate mechanical ventilation (Girard 2009; Pandharipande 2006; Pandharipande 2008). Moreover, age is a stronger predictor of delirium in non-ICU than in ICU patients (Van Rompaey 2008). Hence, the most effective prevention and treatment strategies may differ between ICU and non-ICU settings.

Delirium has been linked to poor outcomes, including increased hospital mortality and length of stay, leading to a considerable burden on caregivers or healthcare services, a higher likelihood of death, functional disability, and dementia after discharge (Buss 2007; Ely 2004; Leslie 2008; Lin 2004; Milbrandt 2004; Pisani 2009; Shankar 2014). Among non-ICU patients, hyperactive delirium has been associated with a better prognosis than hypoactive delirium (O'Keeffe 1999).

It is important to try to prevent delirium by addressing modifiable risk factors. A recent Cochrane Review of interventions to prevent delirium in non-ICU settings found evidence, based on a meta-analysis of seven randomized controlled trials (RCTs), that non-pharmacological, multicomponent interventions can reduce delirium incidence, with an overall reduction in the risk of delirium of about 30% compared with usual care (Siddiqi 2016). Once delirium is established, its management should address both the underlying causes and the symptoms. Identification and treatment of the precipitating cause is of prime importance because treatment and reversal of that cause will help in early resolution of delirium, leading to a better outcome (Meagher 2011). Current critical care guidelines recommend first and foremost the use of non-pharmacological strategies in both the prevention and treatment of delirium (Barr 2013). Non-pharmacological approaches involve addressing multiple risk factors in a systematic manner together with education and environmental manipulation. They typically involve a multidisciplinary team of nurses, therapists, trained volunteers, and geriatricians. Non-pharmacological strategies for preventing and treating delirium may include: early mobilization and re-orientation of the patient; ensuring effective communication and considering involving family, friends, and carers to help with this; engagement in social activities; normalization of the sleep-wake cycle; establishment of a good diet and hydration; and adequate oxygen delivery (Bucerius 2004; NICE 2010; O'Mahony 2011; Siddiqi 2007).

Pharmacological interventions may augment these approaches and they are currently used widely in clinical practice to manage the symptoms of delirium. However, the evidence to support this is limited and practice varies. Medications currently used in clinical practice are mainly benzodiazepines and antipsychotic drugs (AGS 2015; Young 2010), but their use is controversial because of the lack of evidence of their effectiveness and potential for harm (Schrijver 2015; Neufeld 2016; Siddiqi 2016). Current guidelines from the National Institute for Health and Care Excellence (NICE) do not support use of benzodiazepines because of an absence of evidence (NICE 2010). This was also the conclusion of an earlier Cochrane Review, which found no adequately controlled trials to support the use of benzodiazepines in the treatment of delirium not related to alcohol withdrawal in hospitalized patients (Lonergan 2009). A recent meta-analysis found that antipsychotic medications were effective for the treatment of delirium in ICU or non-ICU patients (Kishi 2016). The Clinical Practice Guideline for Postoperative Delirium in Older Adults recommends that antipsychotics are used at the lowest effective dose for the shortest possible duration to treat patients who are severely agitated or distressed, and are threatening substantial harm to self or others, or both. It also recommends that, in these circumstances, benzodiazepines should not be used as a first-line treatment, except when they are specifically indicated (including, but not limited to, treatment of alcohol or benzodiazepine withdrawal) (AGS 2015). Some reports have stated that benzodiazepines may actually contribute to the development of delirium in ICU patients (Barr 2013; Pandharipande 2006). Current guidelines also associate use of benzodiazepines with increased postoperative delirium (AGS 2015).

Description of the intervention

Benzodiazepines are a class of psychoactive drugs that enhance the effect of the neurotransmitter gamma-aminobutyric acid (GABA) at the GABA-A receptor, resulting in sedative, hypnotic (sleep-inducing), anxiolytic (anti-anxiety), anticonvulsant, and muscle relaxant effects. They are used for the treatment of anxiety disorders, sleep disorders, and seizures (Dold 2012). They are also recommended for controlling severely agitated behaviour in the hospital emergency department or in psychiatric inpatient settings, where evidence suggests that they are at least as effective as antipsychotic drugs (NICE 2005). Benzodiazepines have been effective in treating delirium due to alcohol withdrawal (Mayo-Smith 1997). One systematic review reported that benzodiazepines exercised a protective function against alcohol withdrawal symptoms, but their efficacy for non-alcohol withdrawal related delirium has not been established (Amato 2010).

Most benzodiazepines are administered orally; however, they can also be given intravenously, intramuscularly, or rectally. The benzodiazepine family is large and includes drugs with different metabolic characteristics. Benzodiazepines may be categorized as short-, intermediate-, or long-acting (e.g. short-acting with an elimination half-life of less than six hours and long-acting with an elimination half-life of more than 24 hours) (Dold 2012). Long-

acting benzodiazepines or those with long-acting active metabolites, such as diazepam and chlordiazepoxide, are often prescribed for alcohol withdrawal or for anxiety, where constant dose levels are required throughout the day. Short-acting and intermediate-acting benzodiazepines are often preferred for treatment of insomnia (Page 2002; Shorter 2005).

The adverse effects experienced most frequently are drowsiness, dizziness, and problems with concentration. 'Paradoxical effects' may occur, including irritability, impulsivity, and seizures. Respiratory depression is a rare but very severe adverse effect of benzodiazepines in short-term treatment (Dold 2012; Woods 1992). Importantly, benzodiazepines themselves can actually cause or worsen delirium. For example, benzodiazepine use may be a risk factor for the development of delirium in adult ICU patients (Barr 2013).

How the intervention might work

The mechanism of action of benzodiazepine mainly involves enhancement of the effect of the inhibiting neurotransmitter GABA, which results in sedative, anti-anxiety effects. The usefulness of benzodiazepines in the management of symptoms of delirium may be greatest in those patients who require significant sedation, are undergoing alcohol or benzodiazepine withdrawal, or where antipsychotics are contraindicated (e.g. in Parkinson's disease or neuroleptic malignant syndrome) (Inouye 2006; Kostas 2013).

Why it is important to do this review

Delirium is a very common condition associated with significant morbidity, mortality, and costs. There is uncertainty about the efficacy of pharmacological treatment strategies. Benzodiazepines have been effective in treating delirium due to alcohol withdrawal and, in practice, are prescribed for patients with delirium due to other causes. This Cochrane Review aims to find the best evidence related to the efficacy and safety of benzodiazepines for the treatment of non-alcohol withdrawal related delirium in non-ICU settings.

OBJECTIVES

To determine the effectiveness and safety of benzodiazepines in the treatment of delirium (excluding delirium related to alcohol or benzodiazepines withdrawal) in all settings other than intensive care units (ICUs).

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomized controlled trials (RCTs) and quasi-RCTs (those in which the method of allocation to treatment is known but is not strictly random, e.g. sequence generated by alternation, date of birth, or case record number), including those that use an open-label study design.

Types of participants

We will include studies that report on adult patients (aged 18 or older) with delirium due to causes other than benzodiazepine or alcohol withdrawal. The diagnosis of delirium must be made using the Diagnostic and Statistical Manual of Mental Disorders (DSM)-III (APA 1980), DSM-III-R (APA 1987), DSM-IV (APA 1994), DSM (2000)(APA 2000) , DSM (2013) (APA 2013), or the International Statistical Classification of Diseases and Related Health Problems (ICD)-10 criteria (WHO 1993), or a diagnostic tool validated against these, e.g. confusion assessment method (CAM) (Inouye 1990), or delirium rating scale (DRS) (Trzepacz 1988). Participants may be treated in any setting other than intensive care units (ICUs), including medical and surgical wards, palliative care facilities, nursing homes, and other long-term care facilities.

Types of interventions

We will include trials that assess the effect of benzodiazepines, of any dosage and any means of administration, compared with placebo.

We will also include head-to-head comparisons of benzodiazepines with another drug intended to treat delirium (e.g. anti-psychotic, cholinesterase inhibitor).

Included trials may involve non-pharmacological management strategies provided we can extract data from groups that differed only in exposure to benzodiazepines and placebo/comparator medication.

Types of outcome measures

Primary outcomes

1. The length of delirium episode, defined as the time from which it is first identified to when it is first resolved, measured in days.
2. Severity of delirium. We anticipate that this may be measured differently in different trials. If possible, we will use the highest severity recorded. If this is not available, other measures of severity may be used. Symptom severity may have been

measured using any validated scale, e.g. the Delirium Rating Scale (DRS) (Trzepacz 1988), the Memorial Delirium Assessment Scale (Breitbart 1997), or the Delirium Index (McCusker 1988).

3. Any adverse event, counted as the number of participants who experienced at least one adverse event.

Secondary outcomes

1. Length of hospital admission.
2. Mortality from all causes (e.g. 15-day, 30-day, and other based on reports by study authors).
3. Discharge to care home.
4. Readmission to hospital.
5. Use of physical restraints.
6. Individual side effects, such as falls and injuries, pressure sores, depression, disinhibition, hypotension, suppressed breathing, nausea and changes in appetite, blurred vision.

Search methods for identification of studies

To identify studies for inclusion we developed detailed search strategies for each electronic database.

Electronic searches

We will search ALOIS (www.medicine.ox.ac.uk/alois), which is the Cochrane Dementia and Cognitive Improvement Group's Specialized Register.

The Information Specialist of the Cochrane Dementia and Cognitive Improvement Group maintains ALOIS, which contains dementia and cognitive improvement studies identified from the following sources.

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

To view a list of all sources searched for ALOIS see About ALOIS on the ALOIS website.

We will run additional separate searches in many of the above sources to ensure that the most up-to-date results are retrieved. The search strategy that will be used for the retrieval of reports of trials from MEDLINE (via the Ovid SP platform) is in Appendix 1.

Searching other resources

We will check the reference lists of all included studies for further potentially eligible studies.

Data collection and analysis

Selection of studies

Two review authors (RZ and JHS) will independently screen the titles and abstracts of all citations identified by the search strategy, and will code studies as either 'retrieve' or 'do not retrieve'. We will obtain the full text of any citation that may potentially be eligible for inclusion. After we exclude duplicate articles, we will independently examine all full-text articles to identify which meet the inclusion criteria. We will independently record the reason for exclusion of articles after full-text assessment in a 'Characteristics of excluded studies' table. We will resolve disagreements by a consensus meeting between three review authors (RZ, JHS, and HCS). We will present the study selection process in a PRISMA diagram.

Data extraction and management

We will use an electronic data extraction form to extract information on source, eligibility, methods, participants, intervention, comparator, outcomes, results, and miscellaneous notes according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Additionally, we will extract details of the funding source, declarations of interest of the primary investigators, and the methods used to control possible conflicts of interests. Two review authors will pre-test the form using two studies. We will adapt it thereafter if necessary.

Two review authors (XL and NL) will independently assess each included study and extract data. We will resolve disagreements by consensus or by involving a third review author (YHJ). One review author (XL) will transfer data into Review Manager 5 (RevMan 5) (RevMan 2014). Another review author (NL) will double-check that study characteristics and outcome data are entered correctly by comparing the data presented in the systematic review with the study reports.

Assessment of risk of bias in included studies

Two review authors (YHJ and NL) will independently examine the methodological quality of the included trials using the criteria as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will resolve disagreements by discussion. We will consult a third review author (HCS) to make a final consensus decision.

We will assess the risk of bias separately for different domains, namely the following.

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessors.
5. Incomplete outcome data.
6. Selective reporting.
7. Other biases.

We will classify the risk of bias in each domain as either low, high, or unclear risk of bias and will also assign an overall risk of bias to each study.

1. Low risk: describes studies where all domains are considered to be at low risk of bias.
2. High risk: describes studies where one or more domains are considered to be at high risk of bias.
3. Unclear risk: describes studies where one or more domain(s) have unclear risk of bias.

Upon completion of the 'Risk of bias' assessments we will generate a 'Risk of bias' graph and 'Risk of bias' summary figure using RevMan 5 (RevMan 2014).

Measures of treatment effect

We will use risk ratio (RR) with 95% confidence intervals (CIs) as measures of treatment effect for dichotomous data, and use the hazard ratio (HR) for time-to-event data. We will express findings for continuous outcomes in terms of mean differences (MD) and 95% CIs, or standardized mean differences (SMD) if the study authors applied different scales to measure the same outcome.

Unit of analysis issues

Individual participants will be the unit of analysis. We will also consider solutions to specific issues in the analysis.

When studies have more than one intervention group (e.g. different doses of benzodiazepines), we will combine all relevant experimental intervention groups of the study into a single group or select one pair of interventions and exclude the others depending on specific circumstances, for example, size of difference in drug doses. We will only use the data for each group of participants once in the meta-analysis.

Dealing with missing data

As far as possible, we will try to analyse data on an intention-to-treat basis in which all randomized participants are analysed in the groups to which they were originally assigned. If necessary, we will attempt to contact the study authors for missing data or key study characteristics. If this fails we will explore the cause of the missing data, the amount and distribution across intervention groups, and the likely difference in outcome between participants with and without data. If the authors of the primary study have imputed missing data, then we will analyse the imputation method to establish if it is likely to lead to serious bias. If fewer than 50% of the data has been imputed, we will generally tend to present and use these data and report the imputation method used. Where relevant, we will consider using sensitivity analyses to compare different ways of handling missing data.

When only treatment per protocol (TPP) data is available in studies, we will usually rate it as at high risk of bias due to incomplete outcome data, unless the number of switches is too small to make any important difference to the estimated intervention effect.

Assessment of heterogeneity

We will explore the clinical heterogeneity across studies based on variability or differences in the characteristics of participants, interventions, comparators,and outcomes. In addition, we will look for diversity across studies regarding variability of study design, risk of bias, or methods and frequency of rating delirium.

We will evaluate for the presence of heterogeneity within meta-analyses using the Cochran Q test and I^2 statistic that measures the percentage of variability that cannot be attributed to random error. We will consider the I^2 statistic thresholds to represent heterogeneity that: might not be important (0% to 40%), might be moderate heterogeneity (30% to 60%), might be substantial heterogeneity (50% to 90%), and be considerable heterogeneity (75% to 100%) and we will consider also the magnitude and direction of treatment effects and strength of evidence for heterogeneity (P value from the Chi^2 test) (Higgins 2011).

In circumstances where we detect substantial heterogeneity, we will explore the possible explanations in subgroup analyses.

Assessment of reporting biases

If sufficient numbers of studies (more than 10) are eligible for inclusion, we will use a funnel plot to assess publication bias (Egger 1997). If we find asymmetry of the funnel plot upon inspection and we further confirm this by statistical tests, we will discuss possible explanations and take this into account in our interpretation of the overall estimate of treatment effects.

Data synthesis

We will conduct separate meta-analyses for the following types of comparisons.

1. Benzodiazepines versus placebo.
2. Benzodiazepines versus other drug.

We will analyse the data using RevMan 5 (RevMan 2014). According to the extent of heterogeneity between trials, we will use either a fixed-effect or random-effects model. We will only use a fixed-effect model if we consider all trials in a meta-analysis are likely to be estimating the same underlying effect.

Subgroup analysis and investigation of heterogeneity

Where there is evidence of statistical heterogeneity of the treatment effect between trials, we will explore the source of heterogeneity. We will conduct subgroup analysis if we are able to identify possible sources of variation; otherwise, we will use a random-effects model to pool the data.

We will conduct subgroup analysis to explore the effects of the following.

1. Short-acting, intermediate-acting, and long-acting benzodiazepines.
2. Treatment in people with and without pre-existing dementia.
3. Treatment in people with different reasons for hospitalization.

Sensitivity analysis

We will perform sensitivity analyses to test the robustness of our conclusions throughout the review process by performing the following.

1. Excluding trials at high risk of bias.
2. Contrasting the pooled effects between studies that used validated scales.

'Summary of findings' table

We will use the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach to assess the quality of the supporting evidence behind each estimate of treatment effect (Schünemann 2011). Quality is defined as the degree of confidence that can be placed in the estimates of treatment benefits and harms. There are four possible ratings: high, moderate, low, and very low. Rating evidence as high quality implies that we are confident in our estimate of the effect, and further research is very unlikely to change this. A rating of very low quality implies that we are very uncertain about the obtained summary estimate of the effect. The GRADE approach rates evidence from RCTs that do not have serious limitations as high quality. However, several factors can lead to the downgrading of the evidence to moderate, low, or very low. The degree of downgrading is determined by the seriousness of these factors: study limitations (risk of bias); inconsistency; indirectness of evidence; imprecision; and publication bias (Guyatt 2008; Higgins 2011). We will present all outcomes of the review, including a summary of the amount of data, the magnitude of the effect size, and the overall quality of the evidence, in 'Summary of findings' tables, which we will create using GRADEproGDT software (GRADEpro GDT 2014). We have preselected the following outcomes: the length of delirium episode, severity of delirium, length of hospital admission, mortality from all causes, falls, and any adverse effects.

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REFERENCES

Additional references

AGS 2015
American Geriatrics Society Expert Panel on Postoperative Delirium in Older Adults. American Geriatrics Society abstracted clinical practice guideline for postoperative delirium in older adults. *Journal of the American Geriatrics Society* 2015;**63**(1):142–50.

Amato 2010
Amato L, Minozzi S, Vecchi S, Davoli M. Benzodiazepines for alcohol withdrawal. *Cochrane Database of Systematic Reviews* 2010, Issue 3. [DOI: 10.1002/14651858.CD005063.pub3]

APA 1980
American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-3)*. 3rd Edition. Washington, DC: American Psychiatric Publishing, 1980.

APA 1987
American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-3R)*. 3rd Edition. Washington, DC: American Psychiatric Publishing, 1987.

APA 1994
American Psychiatric Association. *Diagnostic and StatisticalManual of Mental Disorders (DSM-4)*. 4th Edition. Washington, DC: American Psychiatric Publishing, 1994.

APA 2000
American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th ed, text revised (DSM-IV-TR). *Washington DC: American Psychiatric Association* 2000.

APA 2013
American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*. 5th Edition. Arlington: American Psychiatric Publishing, 2013.

Barr 2013
Barr J, Fraser GL, Puntillo K, Ely EW, Gélinas C, Dasta JF, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Critical Care Medicine* 2013;**41**(1):263-306.

Breitbart 1997
Breitbart W, Rosenfeld B, Roth A, Smith MJ, Cohen K, Passik S. The Memorial Delirium Assessment Scale. *Journal of Pain and Symptom Management* 1997;**13**(3):128–37.

Bucerius 2004
Bucerius J, Gummert JF, Borger MA, Walther T, Doll N, Falk V, et al. Predictors of delirium after cardiac surgery delirium: effect of beating-heart (off-pump) surgery. *Journal of Thoracic and Cardiovascular Surgery* 2004;**127**(1):57-64.

Buss 2007
Buss MK, Vanderwerker LC, Inouye SK, Zhang B, Block SD, Prigerson HG. Associations between caregiver-perceived delirium in patients with cancer and generalized anxiety in their caregivers. *Journal of Palliative Medicine* 2007;**10**(5):1083–92.

Dold 2012
Dold M, Li C, Tardy M, Khorsand V, Gillies D, Leucht S. Benzodiazepines for schizophrenia. *Cochrane Database of Systematic Reviews* 2012, Issue 11. [DOI: 10.1002/14651858.CD006391.pub2]

Egger 1997
Egger M, Davey Smith G, Schneider M, Minder C. Biasin meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**(7109):629-34.

Ely 2004
Ely EW, Shintani A, Truman B, Speroff T, Gordon SM, Harrell FE Jr, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. *Journal of the American Medical Association* 2004;**291**(14):1753-62.

Girard 2009
Girard TD, Pandharipande PP, Ely EW. Delirium in the intensive care unit. *International Review of Psychiatry* 2009;**21**(1):43–58.

GRADEpro GDT 2014 [Computer program]
GRADE Working Group, McMaster University. GRADEpro GDT. Version accessed 08 March 2017. Hamilton (ON): GRADE Working Group, McMaster University, 2014.

Guyatt 2008
Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;**336**(7650):924-6.

Higgins 2011
Higgins JPT, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org. The Cochrane Collaboration,2011. Available from www.cochrane–handbook.org.

Holmes 2000
Holmes JD, House AO. Psychiatric illness in hip fracture. *Age and Ageing* 2000;**29**(6):537-46.

Inouye 2006
Inouye SK. Delirium in older persons. *New England Journal of Medicine* 2006;**354**(11):1157-65.

Inouye 2014
Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. *Lancet* 2014;**383**(9920):911-22.

Kishi 2016
Kishi T, Hirota T, Matsunaga S, Iwata N. Antipsychotic medications for the treatment of delirium: a systematic review and meta-analysis of randomised controlled trials. *Journal of Neurology, Neurosurgery, and Psychiatry* 2016;**87**(7):764–74.

Kostas 2013
Kostas TR, Zimmerman KM, Rudolph JL. Improving delirium care: prevention, monitoring, and assessment. *Neurohospitalist* 2013;**3**(4):194–202.

Leslie 2008
Leslie DL, Marcantonio ER, Zhang Y, Leo-Summers L, Inouye SK. One year health-care costs associated with delirium in the elderly population. *Archives of Internal Medicine* 2008;**168**(1):27–32.

Lin 2004
Lin SM, Liu CY, Wang CH, Lin HC, Huang CD, Huang PY, et al. The impact of delirium on the survival of mechanically ventilated patients. *Critical Care Medicine* 2004;**32**(11):2254–9.

Lonergan 2009
Lonergan E. Benzodiazepines for delirium. *International Journal of Evidence-based Healthcare* 2009;**8**(2):103–4.

Maldonado 2008
Maldonado JR. Delirium in the acute care setting: characteristics, diagnosis and treatment. *Critical Care Clinics* 2008;**24**(4):657–722.

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. *Journal of the American Medical Association* 1997;**278**(2):144-51.

McCusker 1988
McCusker J, Cole M, Bellavance F, Primeau F. Reliability and validity of a new measure of severity of delirium. *International Psychogeriatrics* 1988;**10**(4):421–33.

Meagher 2000
Meagher DJ, Trzepacz PT. Motoric subtypes of delirium. *Seminars in Clinical Neuropsychiatry* 2000;**5**(2):75–85.

Meagher 2011
Meagher DJ, Leonard M, Donnelly S, Conroy M, Adamis D, Trzepacz PT. A longitudinal study of motor subtypes in delirium: relationship with other phenomenology, etiology, medication exposure and prognosis. *Journal of Psychosomatic Research* 2011;**71**(6):395–403.

Milbrandt 2004
Milbrandt EB, Deppen S, Harrison PL, Shintani AK, Speroff T, Stiles RA, et al. Costs associated with delirium in mechanically ventilated patients. *Critical Care Medicine* 2004;**32**(4):955–62.

Neufeld 2016
Neufeld K J, Yue J, Robinson T N, et al. Antipsychotic Medication for Prevention and Treatment of Delirium in Hospitalized Adults: A Systematic Review and Meta-Analysis. *Journal of the American Geriatrics Society* 2016;**64**(4):705.

NICE 2005
National Institute for Health and Care Excellence. Violence: the short-term management of disturbed/violent behaviour in psychiatric in-patient settings and emergency departments. Clinical guideline [CG25]. Published February 2005. www.nice.org.uk/guidance/cg25 (accessed 12 January 2016).

NICE 2010
National Institute for Health and Care Excellence. Delirium: Diagnosis, prevention and management. Clinical guideline [CG103]. Published July 2010. www.nice.org.uk/guidance/cg103 (accessed 12 January 2016).

O'Mahony 2011
O'Mahony R, Murthy L, Akunne A, Young J, Guideline Development Group. Synopsis of the National Institute for Health and Clinical Excellence guideline for prevention of delirium. *Annals of Internal Medicine* 2011;**154**(11):746–51.

O'Keeffe 1999
O'Keeffe ST, Lavan JN. Clinical significance of delirium subtypes in older people. *Age and Ageing* 1999;**28**(2):115–9.

Page 2002
Page C, Curtis M, Sutter MC, Walker M, Hoffman B. *Integrated Pharmacology*. 2nd Edition. St Louis, Missouri: Mosby CV, 2002.

Pandharipande 2006
Pandharipande P, Shintani A, Peterson J, Pun BT, Wilkinson GR, Dittus RS, et al. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. *Anesthesiology* 2006;**104**(1):21–6.

Pandharipande 2008
Pandharipande P, Cotton BA, Shintani A, Thompson J, Pun BT, Morris JA Jr, et al. Prevalence and risk factors for development of delirium in surgical and trauma intensive care unit patients. *Journal of Trauma* 2008;**65**(1):34–41.

Pisani 2009
Pisani MA, Kong SY, Kasl SV, Murphy TE, Araujo KL, Van Ness PH. Days of delirium are associated with 1-year mortality in an older intensive care unit population. *American Journal of Respiratory and Critical Care Medicine* 2009;**180**(11):1092–7.

Radtke 2008
Radtke F, Franck M M, Luetz A, et al. Comparison of three scores to screen for delirium in the recovery room. *Bja British Journal of Anaesthesia* 2008;**101**(3):338–343.

RevMan 2014 [Computer program]
Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Santos 2004
Santos FS, Velasco IT, Fráguas R Jr. Risk factors for delirium in the elderly after coronary artery bypass graft surgery. *International Psychogeriatrics* 2004;**16**(2):175-93.

Schrijver 2015
Schrijver E J, De G K, de Vries O J, et al. Efficacy and safety of haloperidol for in-hospital delirium prevention and treatment: A systematic review of current evidence. *European Journal of Internal Medicine* 2015;**27**:14–23.

Schünemann 2011
Schünemann HJ, Oxman AD, Higgins JPT, Vist GE, Glasziou P, Guyatt GH. Chapter 11: Presenting results and 'Summary of findings' tables. In: Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org. The Cochrane Collaboration, 2011. Available from www.cochrane–handbook.org.

Shankar 2014
Shankar KN, Hirschman KB, Hanlon AL, Naylor MD. Burden in caregivers of cognitively impaired elderly adults at time of hospitalization: a cross-sectional analysis. *Journal of the American Geriatric Society* 2014;**62**(2):276–84.

Shorter 2005
Shorter E. *"Benzodiazepines". A Historical Dictionary of Psychiatry*. Oxford: Oxford University Press, 2005.

Siddiqi 2006
Siddiqi N, House AO, Holmes JD. Occurrence and outcome of delirium in medical in-patients: a systematic literature review. *Age and Ageing* 2006;**35**(4):350–64.

Siddiqi 2007
Siddiqi N, Stockdale R, Britton AM, Holmes J. Interventions for preventing delirium in hospitalised patients. *Cochrane Database of Systematic Reviews* 2007, Issue CD005563. [DOI: 10.1002/14651858.CD005563.pub2]

Siddiqi 2016
Siddiqi N, Harrison JK, Clegg A, Teale EA, Young J, Taylor J, et al. Interventions for preventing delirium in hospitalised non-ICU patients. *Cochrane Database of Systematic Reviews* 2016, Issue 3. [DOI: 10.1002/14651858.CD005563.pub3]

Trzepacz 1988
Trzepacz PT, Baker RW, Greenhouse J. A symptom rating scale for delirium. *Psychiatry Research* 1988;**23**(1):89-97.

Van Rompaey 2008
Van Rompaey B, Schuurmans MJ, Shortridge-Baggett LM, Truijen S, Bossaert L. Risk factors for intensive care delirium: a systematic review. *Intensive Critical Care Nursing* 2008;**24**(2):98-107.

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

Woods 1992
Woods JH, Katz JL, Winger G. Benzodiazepines: use, abuse, and consequences. *Pharmacological Reviews* 1992;**44**(2):151–347.

Young 2010
Young J, Murthy L, Westby M, Akunne A, O'Mahony R, Guideline Development Group. Diagnosis, prevention, and management of delirium: summary of NICE guidance. *BMJ* 2010;**341**:c3704.

* *Indicates the major publication for the study*

APPENDICES

Appendix 1. MEDLINE search strategy

1. exp Benzodiazepines/
2. (Adinazolam or alprazolam or Bentazepam or benzodiazepine* or bromazepan or Brotizolam or camazepam or Chlordiazepoxide or Clobazam or Clotiazepam or Cloxazolam or Diazepam or Etizolam or flunitrazepam or flurazepam or Flutoprazepam or halazepam or Ketazolam or Loflazepate or loprazolam or Lormetazepam or Metaclazepam or midazolam or nitrazepam or oxzepam or prazepam or Propazepam or Ripazepam or Serazepine or temazepan or Tofisopam or triazolam).tw.
3. exp Anti-Anxiety Agents/
4. or/1-3
5. exp Delirium/
6. (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*).tw.
7. 5 or 6
8. (randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.
9. 4 and 7 and 8
10. exp animals/ not humans.sh.
11. 9 not 10

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