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[Intervention Review]

Antipsychotics for treatment of delirium in hospitalised non-ICU patients

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ABSTRACT

Background

Guidelines suggest limited and cautious use of antipsychotics for treatment of delirium where nonpharmacological interventions have failed and symptoms remain distressing or dangerous, or both. It is unclear how well these recommendations are supported by current evidence.

Objectives

Our primary objective was to assess the efficacy of antipsychotics versus nonantipsychotics or placebo on the duration of delirium in hospitalised adults. Our secondary objectives were to compare the efficacy of: 1) antipsychotics versus nonantipsychotics or placebo on delirium severity and resolution, mortality, hospital length of stay, discharge disposition, health-related quality of life, and adverse effects; and 2) atypical vs. typical antipsychotics for reducing delirium duration, severity, and resolution, hospital mortality and length of stay, discharge disposition, health-related quality of life, and adverse effects.

Search methods

We searched MEDLINE, Embase, Cochrane EBM Reviews, CINAHL, Thomson Reuters Web of Science and the Latin American and Caribbean Health Sciences Literature (LILACS) from their respective inception dates until July 2017. We also searched the Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment Database, Web of Science ISI Proceedings, and other grey literature.

Selection criteria

We included randomised and quasi-randomised trials comparing 1) antipsychotics to nonantipsychotics or placebo and 2) typical to atypical antipsychotics for the treatment of delirium in adult hospitalised (but not critically ill) patients.

Data collection and analysis

We examined titles and abstracts of identified studies to determine eligibility. We extracted data independently in duplicate. Disagreements were settled by further discussion and consensus. We used risk ratios (RR) with 95% confidence intervals (CI) as a measure of treatment effect for dichotomous outcomes, and between-group standardised mean differences (SMD) with 95% CI for continuous outcomes.

Main results

We included nine trials that recruited 727 participants. Four of the nine trials included a comparison of an antipsychotic to a nonantipsychotic drug or placebo and seven included a comparison of a typical to an atypical antipsychotic. The study populations included hospitalised medical, surgical, and palliative patients.

No trial reported on duration of delirium. Antipsychotic treatment did not reduce delirium severity compared to nonantipsychotic drugs (standard mean difference (SMD) -1.08, 95% CI -2.55 to 0.39; four studies; 494 participants; very low-quality evidence); nor was there a difference between typical and atypical antipsychotics (SMD -0.17, 95% CI -0.37 to 0.02; seven studies; 542 participants; low-quality evidence). There was no evidence antipsychotics resolved delirium symptoms compared to nonantipsychotic drug regimens (RR 0.95, 95% CI 0.30 to 2.98; three studies; 247 participants; very low-quality evidence); nor was there a difference between typical and atypical antipsychotics (RR 1.10, 95% CI 0.79 to 1.52; five studies; 349 participants; low-quality evidence). The pooled results indicated that antipsychotics did not alter mortality compared to nonantipsychotic regimens (RR 1.29, 95% CI 0.73 to 2.27; three studies; 319 participants; low-quality evidence) nor was there a difference between typical and atypical antipsychotics (RR 1.71, 95% CI 0.82 to 3.35; four studies; 342 participants; low-quality evidence).

No trial reported on hospital length of stay, hospital discharge disposition, or health-related quality of life. Adverse event reporting was limited and measured with inconsistent methods; in those reporting events, the number of events were low. No trial reported on physical restraint use, long-term cognitive outcomes, cerebrovascular events, or QTc prolongation (i.e. increased time in the heart's electrical cycle). Only one trial reported on arrhythmias and seizures, with no difference between typical or atypical antipsychotics. We found antipsychotics did not have a higher risk of extrapyramidal symptoms (EPS) compared to nonantipsychotic drugs (RR 1.70, 95% CI 0.04 to 65.57; three studies; 247 participants; very-low quality evidence); pooled results showed no increased risk of EPS with typical antipsychotics compared to atypical antipsychotics (RR 12.16, 95% CI 0.55 to 269.52; two studies; 198 participants; very low-quality evidence).

Authors' conclusions

There were no reported data to determine whether antipsychotics altered the duration of delirium, length of hospital stay, discharge disposition, or health-related quality of life as studies did not report on these outcomes. From the poor quality data available, we found antipsychotics did not reduce delirium severity, resolve symptoms, or alter mortality. Adverse effects were poorly or rarely reported in the trials. Extrapyramidal symptoms were not more frequent with antipsychotics compared to nonantipsychotic drug regimens, and no different for typical compared to atypical antipsychotics.

PLAIN LANGUAGE SUMMARY

Antipsychotics to treat delirium in hospitalised patients, not including those in intensive care units

Review question

We reviewed the evidence for the effectiveness and safety of antipsychotics for treatment of delirium in hospitalised patients, not including those in intensive care units (specialised wards for caring for very sick patients).

Background

Delirium is a public health concern as it is a new onset confused state that increases the amount of time patients spend in the hospital, as well as their chance of dying. Guidelines recommendations include reversal of any potential medical or drug triggers that may be contributing to delirium. If delirium symptoms persist and are distressing or dangerous, an antipsychotic drug may be prescribed for a short time. Antipsychotic drugs, also known as tranquillizers, are mainly used to treat psychosis (e.g. hallucinations). There are two types of antipsychotics: first generation or typical antipsychotics (e.g. haloperidol) and second generation or atypical antipsychotics (e.g. quetiapine). Both groups of antipsychotics block the brain's dopamine receptor pathways but atypical antipsychotics also act on

serotonin receptors. Atypical antipsychotics are also noted to be effective for treating both the positive symptoms (e.g. hallucinations) as well as the negative symptoms (e.g. emotional withdrawal) of psychosis. We need to understand if antipsychotics shorten the course of delirium or reduce symptoms or if they cause more harm. Therefore, we updated the existing Cochrane Review from 2007.

Study characteristics

We found nine studies with 727 participants testing antipsychotics for delirium treatment; four trials compared an antipsychotic to another drug class or placebo and seven of the nine trials compared a typical antipsychotic to an atypical antipsychotic.

Key findings

We found no evidence to support or refute the suggestion that antipsychotics shorten the course of delirium in hospitalised patients. Based on the available studies, antipsychotics do not reduce the severity of delirium or resolve symptoms compared to nonantipsychotic drugs or placebo or lower the risk of dying. We found no evidence to support or refute the suggestion that antipsychotics shorten hospital length of stay or improve health-related quality of life. Side effects were rarely reported in the studies.

Quality of the Evidence

It is important to note many clinically relevant outcomes were not reported in the studies and the overall quality of the available evidence was poor.

External funding

Canadian Frailty Network (previously Technology Evaluation in the Elderly Network [TVN]) (www.cfn-nce.ca/), Canada

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Antipsychotics for the treatment of delirium in hospitalised patients						
Patient or population: delirious patients Settings: hospital wards, not ICU Intervention: antipsychotics drugs Comparison: nonantipsychotics drugs or placebo						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Non-antipsychotics drugs or Placebo	Antipsychotics drugs				
Duration of delirium Follow-up: days						This outcome was not reported in any trial.
Delirium severity DRS, DRS-R98, MDAS ¹ Follow-up: up to 10 days	The mean DRS-R-98 score was 22.7 (3.1) at baseline and 7.4 (SD 3.3) at the end of study. ¹⁶	The standardised delirium severity score was 1.08 points lower in the intervention group (2.55 lower to 0.39 higher)		494 (4 studies)	⊕○○○ Very low-quality: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect. 2,3,4,5	SMD -1.08 (-2.55 to 0.39)
Delirium resolution DRS, DRS-R98 ¹ Follow-up: up to 10 days	Study population		RR 0.95 (0.3 to 2.98)	247 (3 studies)	⊕○○○ Very low-quality: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from	

					the estimate of effect. 6,7,8,9,10
	268 per 1000	254 per 1000 (80 to 798)			
	Moderate				
	191 per 1000	181 per 1000 (57 to 569)			
Mortality Follow-up: up to 10 days	Study population		RR 1.29 (0.73 to 2.27)	319 (3 studies)	⊕⊕○○ Low-quality: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different. ^{11,12}
	126 per 1000	163 per 1000 (92 to 286)			
	Moderate				
	143 per 1000	184 per 1000 (104 to 325)			
Hospital length of stay Follow-up: days					This outcome was not reported in any trial.
Adverse Effects - EPS Extrapyramidal Symptom Rating Scale, or not reported Follow-up: up to 10 days	Study population		RR 1.7 (0.04 to 65.57)	247 (3 studies)	⊕○○○ Very low-quality: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect. 13,14,15
	54 per 1000	91 per 1000 (2 to 1000)			
	Moderate				
	0 per 1000	0 per 1000 (0 to 0)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **DRS:** Delirium Rating Scale; **DRS-R98** = Delirium Rating Scale Revised 98; **EPS:** Extrapyramidal Symptoms; **MDAS:** Memorial Delirium Assessment Scale; **RR:** Risk ratio; **SD:** standard deviation

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ DRS = Delirium Rating Scale; DRS-R98 = Delirium Rating Scale -Revised 98; MDAS = Memorial Delirium Assessment Scale

² Only 1 of the 4 trials was considered low risk of bias across all domains. Three of the four trials had blinded delirium assessment.

³ Very high heterogeneity (97%).

⁴ Delirium severity was measured with different tools at variable time points.

⁵ Wide confidence interval that included both no effect and benefit.

⁶ All included trials had risk of bias.

⁷ Blinded delirium assessment for two of the three trials.

⁸ High degree of heterogeneity (83%)

⁹ Delirium resolution was measured with different tools at variable time points using different thresholds.

¹⁰ Wide confidence interval.

¹¹ Only 1 trial had low risk of bias across all domains.

¹² Low number of events.

¹³ All trials at risk of bias.

¹⁴ Variable tools used to assess.

¹⁵ Few events and wide confidence intervals.

¹⁶ Assumed risk taken from [Tahir 2010](#).

BACKGROUND

Description of the condition

Delirium is a dangerous and common syndrome among hospitalised patients (Inouye 2006a). It is estimated to be present in 8% to 17% of all older patients in the emergency department, and 29% to 64% of general medical and older adult inpatients (Inouye 2014). Delirium is most prevalent in frail individuals such as those with pre-existing cognitive impairments (e.g. dementia), having undergone surgery, or suffering an acute infection or critical illness (Inouye 2014; Rudolph 2011; Salluh 2010).

The *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) of the American Psychiatric Association defines delirium as a complex syndrome characterised by disturbances in attention (i.e. ability to focus, sustain or shift attention), awareness (i.e. orientation), and cognition (i.e. memory, perception) not explained by a pre-existing neurocognitive disorder (DSM-V 2013). Unlike dementia, the onset of delirium is rapid (i.e. over the course of hours or days); symptoms fluctuate and are typically reversible. The symptoms of delirium are unpredictable and irregular, contributing to its under-detection (Inouye 2001). Based on the predominance of type of psychomotor symptoms, delirium is categorized as hyperactive, hypoactive, or mixed (i.e. presenting with periods of both hyper- and hypoactivity) (Cole 2009).

The cause of delirium is thought to be multifactorial, dependent on a complex interplay of predisposing and precipitating factors (i.e. environment and iatrogenic (i.e. caused by medical examination or treatment) (Gleason 2003; Rolfson 2002), and mitigated or aggravated by a cascade of physiological events yet to be fully characterised. Predisposing risk factors are numerous and include advanced age, smoking and alcohol abuse, severe illness, and the presence of medical comorbidities such as hypertension and dementia (Gleason 2003; Inouye 1996; Inouye 2014; Rolfson 2002; Vasilevskis 2012). Patients with multiple risk factors appear to be sensitive to even minor precipitating insults, whereas those without such risk factors may develop delirium only following a major insult (e.g. sepsis). While the definitive cause of delirium is unknown, evidence suggests several biological networks may interact to cause the syndrome (Watt 2013). Postulated mechanisms include genetic factors, physiological stressors (e.g. inflammation, increased metabolism, decreased oxygenation, electrolyte imbalances), and disruptions in neurotransmitters involved in cognitive function (Cerejeira 2010; Inouye 2014). Several neurotransmitter systems have been implicated (Gaudreau 2005), but a relative acetylcholine deficiency and/or dopamine excess are most supported by current literature (Flacker 1999; Hshieh 2008; Maclulich 2013; Trzepacz 1999; Trzepacz 2000; Young 1997;).

Description of the intervention

Current professional society guidelines direct the diagnosis, prevention, and management of delirium for patients in various hospital settings (Barr 2013; British Geriatric Society 2006; NICE 2010; RCP 2006). The recommended first steps in delirium care involve identifying and reversing potential precipitating medical conditions, mitigating environmental triggers, and minimising drug exposures. Different combinations of strategies have been used and include resolving acute medical issues, managing pain, applying reorientation strategies, normalising the sleep-wake cycle, ensuring safe mobilisation, and evaluating potential drug-related causes (Fosnight 2011; Inouye 2006b; Inouye 2014; Lundstrom 2005). Numerous classes of psychoactive drugs (e.g. antipsychotics, benzodiazepines, opioids, alpha-2 agonists, and cholinesterase inhibitors) have been studied for their effect on delirium in various patient populations. However, data are inconsistent and practice remains largely governed by clinical circumstance and physician discretion. Because of the uncertainty surrounding antipsychotic effectiveness in delirium, professional societies recommend limited and cautious use, and only in cases where nonpharmacological approaches have failed and symptoms remain distressing or dangerous, or both, to the patient or healthcare staff, or both (American Psychiatric Association 1999; CEHSE 2006; NICE 2010).

Antipsychotic drug exposure is associated with notable risk that should be considered when prescribing. Studies conducted in older adult patients have shown an approximate two-fold increase in risk of cardiac or cerebrovascular incidents - similar in magnitude irrespective of antipsychotic class (i.e. typical and atypical antipsychotics) - even with short term use (Gill 2007; Mittal 2011; Ray 2009; Wang 2005). Increased mortality risk was found in one meta-analysis (Schneider 2005) of 17 placebo-controlled trials of atypical antipsychotics (or second generation antipsychotics) in dementia patients. As a consequence, the US Food and Drug Administration (FDA) issued their strictest warning label or a 'black box' warning for all antipsychotic drugs due to the association with serious hazard when used in the older adult patients. A black box warning is applied to drug labelling by the FDA when there is reasonable evidence of an association of serious and, sometimes, life-threatening adverse events. Antipsychotics have also been shown to paradoxically worsen delirium severity in some patients (Agar 2016). These are important findings, as delirious patients are often frail and have multiple comorbidities (Inouye 2014). Despite the known risks and lack of strong data showing consistent benefit, physician surveys (Carnes 2003; Meagher 2010) and observational data (Briskman 2010; Hatta 2014) show exceedingly high use of antipsychotics in hospitalised delirious patients (77% to 87%).

How the intervention might work

While relative excess of the neurotransmitter dopamine remains a leading hypothesised neurochemical substrate for delirium (Hshieh 2008; Trzepacz 1999; Trzepacz 2000; Young 1997), few

studies have examined neurotransmitter metabolism in the context of delirium trajectory (Thomas 2008; Van der Cammen 2006). The therapeutic effects of antipsychotics in delirium remain unknown, but it is postulated their effects may be mediated through a reduction of psychotic symptoms (also known as positive symptoms for patients with schizophrenia), or through sedation. There are two types of antipsychotics: first generation, also known as typical antipsychotics, (e.g. haloperidol, chlorpromazine) and second generation, also known as atypical antipsychotics, (e.g. quetiapine, olanzapine, risperidone). Both groups of antipsychotics block the brain's dopamine receptor pathways but atypical antipsychotics also act on serotonin receptors. Both are effective for managing the positive symptoms in schizophrenia (e.g. psychosis, hallucinations, agitation) but atypical antipsychotics also improve the negative symptoms such as emotional and social withdrawal.

Antipsychotics are thought to help with the psychotic symptoms of delirium but have also been shown useful in individuals who have hypoactive symptoms (Boettger 2011a; Boettger 2011b; Breitbart 2002b; Ito 2007; Platt 1994). Studies investigating changes in individual delirium symptomatology in the context of antipsychotic treatment have yielded conflicting results. It appears both cognitive and noncognitive symptoms may improve to varying extents. Specifically, where some studies demonstrate a similar trajectory for both types of symptoms (Breitbart 1996; Kim 2003; Leonard 2015; Meagher 2012; Parellada 2004; Sasaki 2003), others show a more rapid recovery of noncognitive disturbances (e.g. inattention and disorientation) (Devlin 2011; Tahir 2010).

Why it is important to do this review

Studies have shown an association between delirium and adverse outcomes such as prolonged length of hospital stay, increased hospital mortality, and higher rates of hospital readmission, institutionalisation, and functional and cognitive decline, even after adjustment for comorbidities and illness severity (Buurman 2011; Han 2010; Inouye 1998; Kakuma 2003; Leslie 2005; Levkoff 1992; McCusker 2001; McCusker 2002; Pitkala 2005; Pompei 1994; Rizzo 2001; Witlox 2010). Delirium is also known to cause distress to patients, their families, and clinical staff (Breitbart 2002a; Bruera 2009; Buss 2007; Cohen 2009; Morita 2004; Partridge 2013). The economic burden of delirium is significant: a delirious state is associated with a 20% increased risk of prolonged hospitalisation, translating to an average of more than 8 to 10 additional days in hospital (Leslie 2008; McCusker 2003; OECD 2012; WHO 2012). The annual cost of delirium has been estimated at more than USD 164 billion (Leslie 2008) in the United States, and over EUR 182 billion in 18 combined European countries (OECD 2012; WHO 2012). Delirium in hospitalised patients clearly represents a substantial public health concern.

Because of its myriad iatrogenic factors (e.g. medications, immobilisation, catheterisation, and sleep impairment) (Inouye 1999), delirium is considered a preventable adverse event (Gillick 1982;

Rothschild 2000) and is used as an indicator of quality of care in the elderly (IHI 2014; Safer Healthcare Now 2005). Notwithstanding, not all cases of delirium can be prevented and the impetus to determine safe and effective treatment strategies remains important for clinicians, patients, families, and the healthcare system.

In clinical practice, antipsychotics are often the first pharmacological treatment initiated, despite conflicting evidence supporting their efficacy and reports indicating increased risk of serious adverse events, especially in the frail elderly (Gill 2007; Mittal 2011; Ray 2009; Wang 2005). Herein, we have updated the previously published Cochrane Review (Loneragan 2007). An update was warranted, given the high prevalence of hospital delirium, its associated clinical and financial burden, and the publication of new studies in the decade since the original publication.

OBJECTIVES

Our primary objective was to assess the efficacy of antipsychotics versus nonantipsychotics or placebo on the duration of delirium in hospitalised adults (excluding critically ill populations).

Our secondary objectives were to compare the efficacy of 1) antipsychotics versus nonantipsychotics or placebo on a) delirium severity and b) delirium resolution, c) mortality, d) hospital length of stay, e) discharge disposition, f) health-related quality of life, and g) adverse effects (e.g. sudden cardiac death, QTc prolongation (i.e. increased time between the Q wave and the end of the T wave in the heart's electrical cycle), seizures, use of physical restraints); and 2) atypical versus typical antipsychotics for reducing a) delirium duration, b) delirium severity, and c) resolution, d) mortality, e) hospital length of stay, f) discharge disposition, g) health-related quality of life outcomes, and h) adverse effects (e.g. sudden cardiac death, QT prolongation, seizures, use of physical restraints).

METHODS

Criteria for considering studies for this review

Types of studies

We included all trials using a randomised or quasi-randomised design that compared an antipsychotic to a nonantipsychotic (e.g. alternative drug class such as benzodiazepines), placebo, or second antipsychotic of a different generation (secondary outcome) for the treatment of delirium. We excluded nonrandomised and cross-over interventional studies as well as observational studies.

Types of participants

We included studies of adults (> 16 years of age) diagnosed with delirium and treated in an acute care setting. We excluded trials with a primary aim of treating delirium secondary to substance/alcohol-induced withdrawal, recruiting participants solely in outpatient, psychiatric, or long-term care settings, or in an intensive care unit (a high intensity unit). A delirium diagnosis had to have been made by a trained individual (e.g. psychiatrist, geriatrician), through formal assessment using Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria (DSM-IV 1994; DSM-IV-TR 2000; DSM-V 2013), or by a validated delirium screening tool (e.g. Inouye 1990; Neelon 1996; Traube 2014). We excluded studies where antipsychotics were evaluated for delirium prevention.

Types of interventions

To answer our primary objective, we included studies comparing an antipsychotic to a nonantipsychotic drug (e.g. alternative drug class such as benzodiazepine) or placebo. We permitted inclusion of trials that had a nonantipsychotic group without a placebo group, as no drug has been consistently shown to be more effective than placebo. Therefore, a nonantipsychotic group was thought of as a placebo. We also included studies comparing a typical antipsychotic to an atypical antipsychotic to answer our secondary objectives. When antipsychotics are initiated to manage delirium symptoms in clinical practice, clinicians often select atypical antipsychotics over a typical antipsychotic. Therefore, we included trials that compared the two classes of antipsychotics, irrespective of inclusion of a placebo group in the study. We did not include trials that only examined two or more antipsychotics of the same class without an alternative drug or alternative antipsychotic class, or placebo.

A priori, we anticipated the selection of comparison treatments would be variable and that nonantipsychotic agents might include: alpha-2 agonists, antidepressants, benzodiazepines, cholinesterase inhibitors, melatonin or melatonin agonists, or opioids. No restrictions on dose, frequency, intensity, or duration of therapy were applied.

Types of outcome measures

We selected outcomes pertaining to the benefits and hazards of antipsychotic drugs that are meaningful to hospitalised patients with delirium, their families, and health care professionals.

Primary outcome

1. Total duration of delirium (days)

Secondary outcomes

1. Delirium severity, assessed by validated instruments such as Delirium Rating Scale (e.g. DRS or DRS-98-R) (Trzepacz 1988; Trzepacz 2001) and Memorial Delirium Assessment Scale (MDAS) (Breitbart 1997) (mean change from baseline to end of study period)
2. Delirium resolution (defined as reduction of DRS or DRS-98-R below a target set by the authors or complete resolution of symptoms)
3. Mortality
4. Hospital length of stay (days)
5. Hospital discharge disposition (e.g. rehabilitation, chronic care facility, home)
6. Health-related quality of life (as reported by study authors)
7. Adverse events as defined by the study authors (e.g. prolongation of the QTc interval (QT interval measures the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle), sudden cardiac death, cerebral vascular events, seizures, extrapyramidal effects, use of physical restraints, long-term cognitive impairment (e.g. change in Mini Mental Status Exam or as reported by study authors)).

Search methods for identification of studies

Electronic searches

Electronic search strategies were developed and tested through an iterative process by an experienced information scientist in consultation with our team. The concepts encompassed in the search strategy included: 1) population (i.e. patients in acute care settings diagnosed with delirium), 2) intervention (antipsychotics), and (3) comparators. Test searches were performed at various stages (i.e. before and after combining search terms) to ascertain the number of hits and verify capture of studies known to meet the inclusion criteria. We searched the following electronic databases from their respective dates of inception to July 20, 2017: MEDLINE (Ovid SP) (1946 to July 20, 2017); Embase (Ovid SP) (1947 to 2017 Week 28); Cochrane EBM Reviews - Central Register of Controlled Trials (CENTRAL) (July 20, 2017); CINAHL (EBSCOhost) (1982 to July 20, 2017); Thomson Reuters Web of Science (July 20, 2017) and Latin American and Caribbean Health Sciences Literature (LILACS) (1986 to July 20, 2017). We searched the Database of Abstracts of Reviews of Effects (DARE) and the Health Technology Assessment Database (HTA Database) to their second quarter of 2017 for published reviews on the review topic. Specific details regarding search strategies can be found in the appendices (Appendix 1; Appendix 2; Appendix 3; Appendix 4; Appendix 5; Appendix 6; Appendix 7; Appendix 8). Search strategies utilised a combination of controlled vocabulary and keywords, and vocabulary and syntax were adjusted for each database. We

limited our search to randomised controlled trials, systematic reviews, and meta-analyses. We applied a filter to limit to humans, and no language restriction was imposed.

Searching other resources

We searched conference proceedings using the Web of Science ISI Proceedings (2004 to July 2017). We searched for unpublished and ongoing trials on the following web sites: 1. www.clinicaltrials.gov/; and 2. www.who.int/trialsearch. We handsearched the reference lists of all retrieved studies for additional relevant studies. Corresponding authors of eligible trials and experts in the field were contacted to identify other potential studies. The Internet was searched using the Google search engine to find additional unpublished evidence.

Data collection and analysis

Selection of studies

Each title and abstract identified from the electronic and manual searches were independently examined by two authors (LB, LR) to identify potentially eligible trials. Selected trials were screened for relevance against defined inclusion and exclusion criteria (Appendix 9). References were organised in the reference manager Endnote (Version X6, Thomson Reuters, Carlsbad, CA, USA) ([Endnotes](#)) with reasons for exclusion documented in the notes field. The studies identified as eligible were examined independently and in full to confirm inclusion. Disagreements were resolved by discussion with an independent arbiter (NS).

Data extraction and management

We did not blind data extractors to the identity of study authors because of our familiarity with the literature on the topic. Two authors (LB, LR) revised and piloted the previous data extraction form to ensure capture of all relevant data. Once the included trials were identified and agreed upon, four authors independently extracted data. Each study was independently examined by a pair of authors (SM and MP; JL and CB). All data extraction was confirmed by a third author (LB). Any identified duplicate reports from a single study were assembled as one reference. The 'Characteristics of included studies' table ([Characteristics of included studies](#)) was created using Review Manager ([RevMan 2014](#)). As we were interested in determining if the intervention reduced the overall severity or burden of delirium, we extracted and used the highest recorded score for delirium severity for both the intervention and control arm when multiple time points were available. For example, if DRS-98-R was scored multiple times after study enrolment, then we selected only the highest of those scores for our analyses.

Assessment of risk of bias in included studies

Each data extractor independently assessed the risk of bias of each study, which was then verified by another author (NS). These assessments were done via a domain-based evaluation as recommended by The Cochrane Collaboration ([Higgins 2011](#)). The domains are:

1. Random sequence generation (i.e. selection bias);
2. Allocation concealment (i.e. selection bias);
3. Blinding of participants and personnel (i.e. performance bias);
4. Blinding of outcomes assessment (i.e. detection bias);
5. Incomplete outcome data (i.e. attrition bias);
6. Selective reporting; and
7. Other potential sources of bias.

For each domain, we assessed the risk of bias as 'low', 'high', or 'unclear'. Unclear risk was assigned if insufficient detail was reported, or if what happened in the study was known but the risk of bias was unclear or unknown. Once risk of bias assessment was agreed upon, each study was categorised as follows:

Low risk of bias: studies where all domains were considered 'low' risk of bias;

High risk of bias: studies where one or more domains were considered to be 'high' risk of bias; and

Unclear risk of bias: studies where one or more domains was scored as 'unclear' risk of bias.

We generated a 'risk of bias' graph figure and summary figure upon completion of assessment in Review Manager ([RevMan 2014](#)).

Measures of treatment effect

We used risk ratios (RRs) as measures of treatment effect for dichotomous outcomes. We used between-group mean differences (MD or SMD) and standard deviations for continuous outcomes.

Unit of analysis issues

We used data from individual participants as the unit of analysis in each trial arm. As anticipated, all included trials were parallel group design, so adjustments were not necessary for clustering.

Dealing with missing data

When necessary, we contacted the corresponding authors to clarify issues related to data reporting and/or to obtain further study details. Missing data and dropout rates were assessed for each included study and reported in the risk of bias table. For missing data (e.g. standard deviations associated with continuous outcomes) we sent the corresponding author a maximum of three emails to request the missing information. If this failed, we used established methods to impute standard deviation values. When only medians and interquartile ranges (IQR) or ranges were reported and not available from study authors we assumed the median value to be equal to the mean to permit utilisation of all of data identified. To

estimate standard deviations we used 'IQR/1.35' or 'range/4' (for studies with $n < 70$) and 'range/6' for studies with $n > 70$.

Assessment of heterogeneity

Heterogeneity can be the result of an uneven distribution of important clinical and methodological effect modifiers across studies or across comparisons. We assessed each trial for statistical and clinical heterogeneity. We evaluated statistical heterogeneity using the I^2 statistic and the X^2 test of homogeneity with $p < 0.05$ indicative of heterogeneity. We applied the categorisation values described by Higgins: low (0% to 40%), moderate (30% to 60%), substantial (50% to 90%), and considerable (75% to 100%) heterogeneity (Higgins 2003). We qualitatively assessed clinical heterogeneity by examining delirium management strategies in each trial (e.g. treatment dose, use of rescue medications or chemical restraint when primary treatment fails, non-drug treatment strategies such as noise reduction or improving the day-night cycle, medications avoided, physical restraint) as well as country of study origin, year of study publication, and single centre versus multicentre study.

Assessment of reporting biases

We planned construction and visual inspection of funnel plots to assess for possible publication bias in Review Manager 5 (RevMan 2014) for analyses where > 10 studies were available. We planned to test for funnel plot asymmetry using the test proposed by Egger (Egger 1997), but there were insufficient studies to proceed with this step.

Data synthesis

Two authors (LB, BH) entered data in Revman 5 (RevMan 2014). Three authors (LB, BH, DF) conducted the analyses and reported summary statistics for the data. We synthesised dichotomous data with risk ratios (RR) and 95% confidence intervals (CI) using the Mantel-Haenszel random-effects model (REM) to allow for adjustments that incorporated variation both within and between studies (DeMets 1987). Continuous outcomes (e.g. duration of delirium, hospital length of stay) were synthesised as pooled mean differences (MD), or standardised mean differences (SMD) (where measurement scales varied across studies) with 95% CIs using random-effects inverse variance methods. For continuous end points that involved an analysis of changes from baseline in each group, where necessary, a correlation coefficient was used to estimate the standard deviation associated with mean change in each group. We considered $P < 0.05$ (two sided) as significant.

Subgroup analysis and investigation of heterogeneity

We planned the following subgroup analyses to determine if the efficacy and safety of antipsychotics were influenced by: 1) age (< 65 versus ≥ 65 years); and 2) history of dementia.

Sensitivity analysis

We conducted sensitivity analyses to explore the effect on the pooled estimate of including only studies at low risk of bias in all but one domain and those that included a placebo group.

Data presentation - 'Summary of findings' table

We used the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) (Guyatt 2008) approach to assess the quality of the supporting evidence associated with selected outcomes. The findings are presented using a 'Summary of findings' (SoF) table summarising the amount of data identified, within-study risk of bias, directness of evidence, data heterogeneity, and precision of effect estimates. The SoF table was generated using GRADEpro software (GRADEpro GDT 2015). We selected the following outcomes a priori as being relevant for clinical practice: duration of delirium, severity of delirium, delirium resolution, mortality, hospital length of stay, and incidence of adverse effects.

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#); [Characteristics of studies awaiting classification](#); [Characteristics of ongoing studies](#)

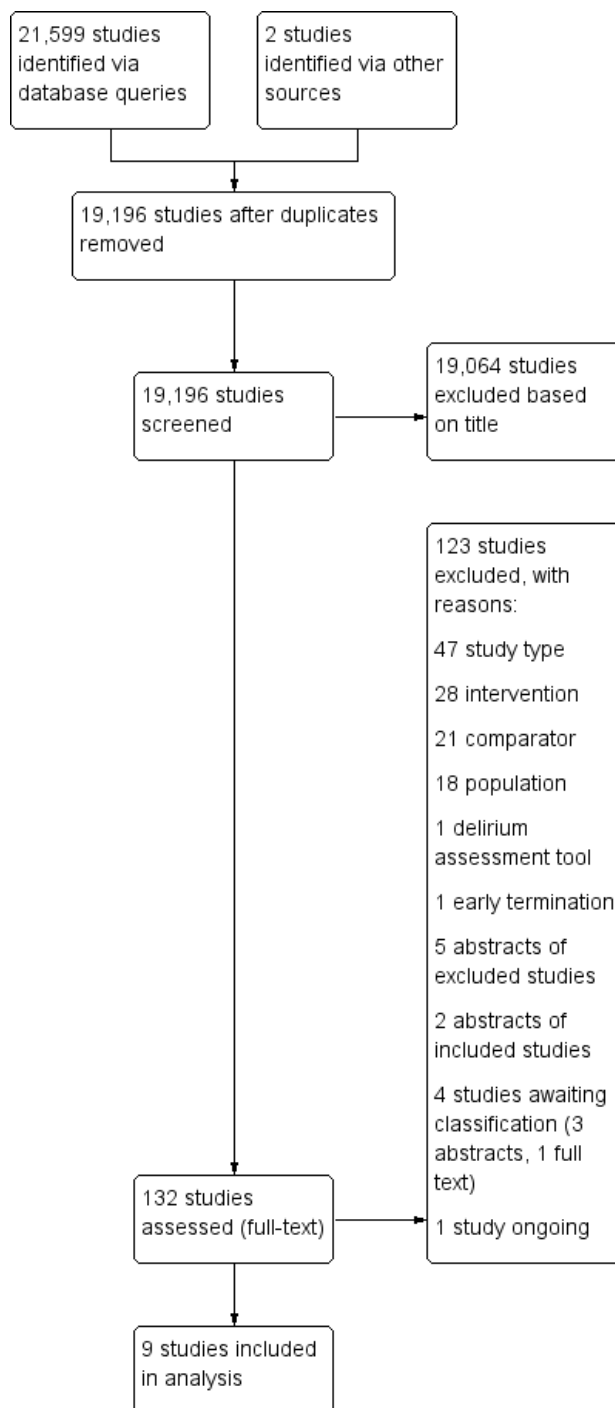
We included randomised and quasi-randomised controlled trials of adult hospitalised non-ICU patients treated for delirium. We identified eligible trials with an intervention arm including an antipsychotic drug. Delirium management for control arms included a nonantipsychotic drug (e.g. alternative drug class such as benzodiazepines), placebo, or secondary antipsychotic of alternative class (i.e. typical versus atypical).

Results of the search

We reported the results of the search outlined above in [Figure 1](#). The initial electronic database query yielded 21,599 citations. We retrieved 132 references for full-text assessment. We identified nine studies meeting inclusion criteria, and excluded the remaining 123. We classified four studies as awaiting classification ([Characteristics of studies awaiting classification](#)): one full publication (Nakamura 1997) and three conference abstracts (Djokic 2008; Jung Jin 2009; Lee 2013). We identified two trial registrations for further consideration. We classified one study as meeting inclusion criteria and ongoing (NCT02345902; [Characteristics of ongoing studies](#)), and the other as a duplicate of a study published in full and already included in the review (Hu 2004; [Characteristics of included studies](#)). When this latter study was translated into the English language, the primary author's first and last names were

reversed. We identified this upon closer inspection and classified the second trial registration as a duplicate.

Figure 1. PRISMA flow diagram of search results.



Included studies

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

We included nine randomised trials with a total of 727 participants ([Agar 2016](#); [Breitbart 1996](#); [Grover 2011](#); [Grover 2016](#); [Han 2004](#); [Hu 2004](#); [Lin 2008](#); [Maneeton 2013](#); [Tahir 2010](#)). We provide detailed descriptions of each study in the [Characteristics of included studies](#) table. Sample sizes of trials ranged from 24 ([Han 2004](#)) to 247 ([Agar 2016](#)) participants. Four of the identified trials included more than two study arms ([Agar 2016](#); [Breitbart 1996](#); [Grover 2011](#); [Hu 2004](#)). Only a single study ([Agar 2016](#)) included multiple sites; all others had a single centre design. The trials were conducted in a number of countries: Australia ([Agar 2016](#)); China ([Hu 2004](#)); India ([Grover 2011](#); [Grover 2016](#)); Korea ([Han 2004](#)); Taiwan ([Lin 2008](#)); Thailand ([Maneeton 2013](#)); United States ([Breitbart 1996](#)); and United Kingdom ([Tahir 2010](#)). All studies included hospitalised patient populations: medical only ([Breitbart 1996](#); [Hu 2004](#); [Maneeton 2013](#)), mixed medical and surgical ([Grover 2011](#); [Grover 2016](#); [Han 2004](#); [Tahir 2010](#)), and palliative ([Agar 2016](#); [Lin 2008](#)). One trial specifically evaluated participants with dementia ([Hu 2004](#)). The mean reported age of participants across trials ranged from 44 ([Grover 2011](#)) to 84 ([Tahir 2010](#)) years; 22% ([Grover 2016](#)) to 71% ([Tahir 2010](#)) of participants were female. Six studies ([Agar 2016](#); [Breitbart 1996](#); [Grover 2011](#); [Han 2004](#); [Maneeton 2013](#); [Tahir 2010](#)) provided details of funding sources; one trial received pharmaceutical industry funding ([Tahir 2010](#)).

Four trials compared one or more antipsychotic drug to a nonantipsychotic or placebo ([Agar 2016](#); [Breitbart 1996](#); [Hu 2004](#); [Tahir 2010](#)), three of these trials included a placebo group ([Agar 2016](#); [Hu 2004](#); [Tahir 2010](#)), and one compared antipsychotics (haloperidol or chlorpromazine) to the benzodiazepine lorazepam ([Breitbart 1996](#)). Seven trials compared a typical to an atypical antipsychotic drug ([Agar 2016](#); [Grover 2011](#); [Grover 2016](#); [Han 2004](#); [Hu 2004](#); [Lin 2008](#); [Maneeton 2013](#)). Of these, two ([Agar 2016](#); [Hu 2004](#)) also included a placebo group (i.e. 3-arm studies). Haloperidol was the most commonly studied antipsychotic, evaluated in all but one trial ([Tahir 2010](#)). All trials titrated study drug based on symptom response. The duration of therapy was variable and included three- ([Agar 2016](#)), six- ([Breitbart 1996](#); [Grover 2011](#); [Grover 2016](#)), seven- ([Han 2004](#); [Hu 2004](#); [Lin 2008](#); [Maneeton 2013](#)), and ten-day ([Tahir 2010](#)) administration. The use of rescue drugs such as benzodiazepines for breakthrough agitation was permitted in five trials ([Agar 2016](#); [Grover 2011](#);

[Grover 2016](#); [Lin 2008](#); [Tahir 2010](#)), prohibited in three ([Hu 2004](#); [Maneeton 2013](#); [Breitbart 1996](#)), and not reported in one ([Han 2004](#)). No trial reported on the use of physical restraints or sitters/personal attendants.

All trials used some combination of DSM criteria ([DSM-IV 1994](#); [DSM-IV-TR 2000](#); [DSM-V 2013](#)) or the Confusion Assessment Method (CAM) ([Inouye 1990](#)), or both, to detect delirium for study enrolment; subjects in all included studies were screened daily. Cointerventions for delirium management such as reorientation, family support, and environmental manipulations were used in five studies ([Agar 2016](#); [Grover 2011](#); [Grover 2016](#); [Hu 2004](#); [Maneeton 2013](#)) and not reported in the remaining four ([Breitbart 1996](#); [Han 2004](#); [Lin 2008](#); [Tahir 2010](#)).

Excluded studies

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

We excluded ten randomised trials because the population of interest was limited to critically ill individuals ([Al Qadheeb 2016](#); [Atalan 2013](#); [Bakri 2015](#); [Devlin 2010](#); [Girard 2010](#); [Hakim 2012](#); [Page 2013](#); [Reade 2009](#); [Reade 2016](#); [Skrobik 2014](#)). These trials are included in the Cochrane protocol ACE311 'Pharmacological interventions for the treatment of delirium in critically ill patients' ([Burry 2015](#)) using the operational definition of critical care/intensive care applied by this Cochrane division. We excluded five additional studies ([Jung 2009](#); [Jung 2010](#); [Kim 2010](#); [Lee 2005](#); [Sakong 2010](#)) because of lack of adequate comparator group. These five studies evaluated the effect of antipsychotic(s) on hospitalised, non-critically ill participants with delirium but did not include a nonantipsychotic arm or they compared two antipsychotics of the same class (e.g. atypical versus atypical) without a third group that included a placebo or nonantipsychotic drug.

Risk of bias in included studies

The 'Risk of bias' tables present details on the performance of the included trials for each risk of bias domain. A summary of our judgement of the methodological quality of the included studies is depicted in [Figure 2](#) and [Figure 3](#). Only one study ([Agar 2016](#)) was scored as low risk of bias across all domains. The remaining studies scored unclear risk of bias in one or more domains, or had a combination of unclear and high risk of bias across multiple domains. In particular, [Hu 2004](#) scored high risk of bias across two domains..

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

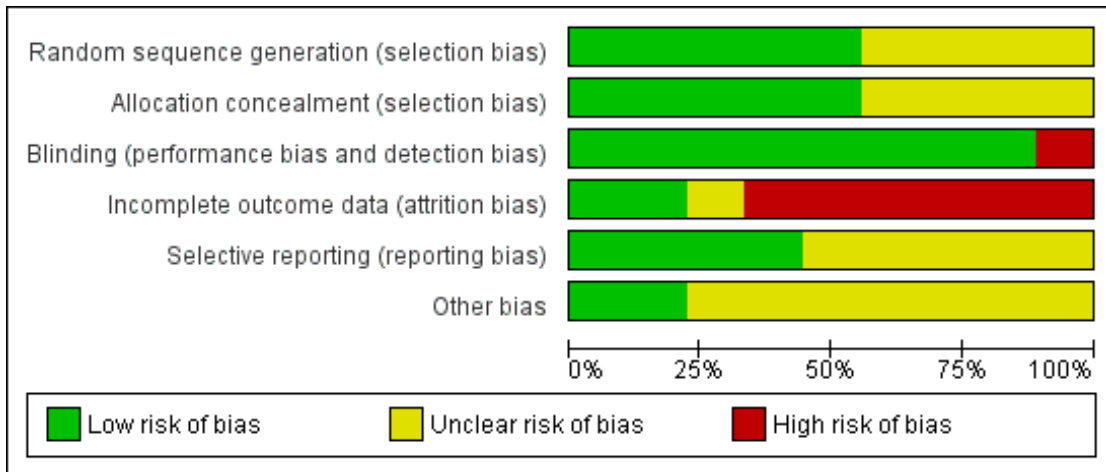


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Agar 2016	+	+	+	+	+	+
Breitbart 1996	+	+	+	?	?	?
Grover 2011	?	+	+	-	?	?
Grover 2016	+	?	+	-	?	?
Han 2004	?	?	+	-	?	+
Hu 2004	?	?	-	-	+	?
Lin 2008	?	?	+	-	?	?
Maneeton 2013	+	+	+	-	+	?
Tahir 2010	+	+	+	+	+	?

Allocation (selection bias):

Five studies (Agar 2016; Breitbart 1996; Grover 2016; Maneeton 2013; Tahir 2010) specified the use of randomisation tables. The method of sequence generation was not reported in the manuscript or available from the authors for the remaining four trials (Grover 2011; Han 2004; Hu 2004; Lin 2008), therefore, we scored these as unclear risk of bias.

We judged five studies (Agar 2016; Breitbart 1996; Grover 2011; Maneeton 2013; Tahir 2010) to have low risk of selection bias based on their allocation concealment measures. Two studies (Agar 2016; Tahir 2010) used sealed opaque envelopes and another used a pharmacist (Breitbart 1996) not otherwise involved in patient care to dispense the study drug. In Grover 2011, the randomisation and study drug dose adjustments were carried out by one investigator who did not assess outcomes. In Maneeton 2013, identical capsules were used to dispense the study drug. We judged the remaining studies (Grover 2016; Han 2004; Hu 2004; Lin 2008) to have unclear risk of selection bias due to insufficient or no detail to assess allocation concealment.

Blinding (performance bias and detection bias):

We judged all studies but one (Hu 2004) to have low risk of blinding bias. Four studies (Agar 2016; Breitbart 1996; Maneeton 2013; Tahir 2010) were double-blinded. A single-blind design was used in three studies (Grover 2011; Grover 2016; Lin 2008) that specifically reported the delirium assessment was performed by a standard blinded assessor. Although Han 2004 study was stated as double-blind, this was unlikely as the study drugs were not stated to be identical. However, one psychiatrist, blind to treatment group, performed the delirium assessments. We judged Hu 2004 study to have high risk of bias as it was not possible to blind subcutaneous haloperidol and enteral olanzapine, unless a double-dummy design was used. As no details were provided, we assumed the drug formulation was unblinded.

Incomplete outcome data (attrition bias):

We judged three studies (Agar 2016; Maneeton 2013; Tahir 2010) to have low risk of attrition bias because all used intention-to-treat analysis or had no missing data. We judged one study (Breitbart 1996) to have unclear risk of attrition bias. The lorazepam arm in Breitbart 1996 was discontinued early due to adverse events, but available data were used in the analysis. We judged five studies (Grover 2011; Grover 2016; Han 2004; Hu 2004; Lin 2008) to have high risk of attrition bias due to incomplete data or missing participants. In Grover 2011, ten participants did not complete the study; six could not be assessed at least once due to worsening clinical status, and four left hospital against medical advice.

In Grover 2016, seven participants did not complete the study; four could not be assessed because they left against medical advice, one quetiapine participant received injectable haloperidol for symptom management, and two could not be started on the study drug because of worsening clinical status. In the Han 2004 study, four participants did not complete the study, three due to medical complications and one due to spousal refusal; these participants were not included in the analysis. The Hu 2004 study made no mention of how attrition was factored into the statistical analysis despite reporting five participants not completing the study (one death, one leaving due to financial reasons, one discharge, and two withdrawals). Lastly, Lin 2008 did not report the total number of participants enrolled or lost to follow-up.

Selective reporting (reporting bias):

We found four trials were registered (Agar 2016; Hu 2004; Maneeton 2013; Tahir 2010) and, therefore, it was possible to examine reporting bias. These trials were deemed at low risk of bias. For the remaining studies, we scored them as at unclear risk of bias.

Other potential sources of bias:

Referral bias was a potential issue for four trials (Grover 2011; Grover 2016; Lin 2008; Maneeton 2013) where participants were recruited specifically from referrals to psychiatry services. Sample size calculations were not provided for five trials (Breitbart 1996; Grover 2011; Grover 2016; Han 2004; Lin 2008) so it was unclear if adequate power was attained. Two trials (Maneeton 2013; Tahir 2010) did not meet the required sample size. In one study (Maneeton 2013), 34 participants per group were needed to have adequate power to detect a meaningful difference in DRS-R-98 score; however, the final numbers were 24 and 28 participants in the quetiapine and haloperidol groups, respectively. The sample size calculation was reported in the second study (Tahir 2010), however the trial was stopped early at the request of the manufacturer due to the FDA's concern on the use of antipsychotic medication in the elderly. The study was therefore underpowered. Finally, one included study (Tahir 2010) permitted lorazepam injection for rescue, but all participants who received it were in the quetiapine group. It was unclear how lorazepam administration in only one group would influence results.

Effects of interventions

See: [Summary of findings for the main comparison Antipsychotics versus nonantipsychotics or placebo for the treatment of delirium in hospitalised patients](#); [Summary of](#)

findings 2 Typical versus atypical antipsychotics for treatment of delirium in hospitalised patients

See: [Summary of findings for the main comparison](#); [Summary of findings 2](#)

We present below our analyses for our primary outcome, duration of delirium, and our secondary outcomes of severity of delirium, delirium resolution, mortality, hospital length of stay and discharge disposition, health-related quality of life, and adverse events. For each outcome, we present first the results for the comparison of an antipsychotic versus nonantipsychotic or placebo and then the class comparison of typical versus atypical antipsychotic.

Duration of delirium

Antipsychotic versus nonantipsychotic drug or placebo

Duration of delirium was not reported for any of the four trials comparing an antipsychotic to a nonantipsychotic drug.

Typical versus atypical antipsychotic drug

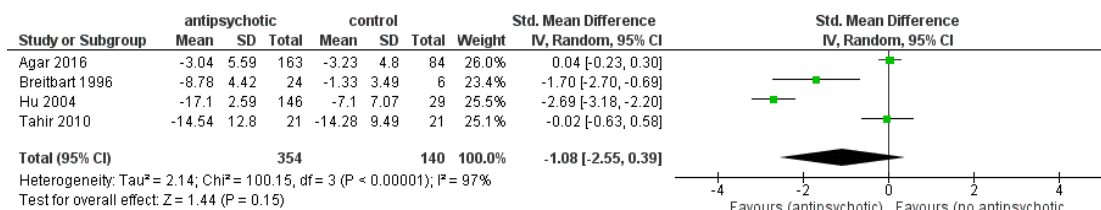
Duration of delirium was not reported for any trial comparing typical versus atypical antipsychotics drugs.

Delirium severity

Antipsychotic versus nonantipsychotic drug or placebo

Delirium severity was reported for four studies (Agar 2016; Breitbart 1996; Hu 2004; Tahir 2010). Delirium severity was scored with different tools: the DRS (Breitbart 1996; Hu 2004), DRS-98-R (Tahir 2010), and MDAS (Agar 2016), assessed at baseline and at the end of the study. Three of the studies were double-blind so delirium assessments were blinded. The pooled result indicated no difference in delirium severity (SMD -1.08, 95% CI -2.55 to 0.39; four studies; 494 participants; Analysis 1.1; Figure 4). There was substantial heterogeneity ($I^2 = 97%$). We assessed this as very low-quality evidence (downgraded due to risk of bias, inconsistency and imprecision). For sensitivity analyses, we repeated the analysis by i) removing trial(s) that did not have a placebo group (Breitbart 1996) (SMD -0.89, 95% CI -2.64 to 0.86; three studies; 464 participants; $I^2 = 98%$; Analysis 1.2) and ii) including only trials with low risk of bias (SMD 0.03, 95% CI -0.22 to 0.27; 289 participants; $I^2 = 0%$; Analysis 1.3).

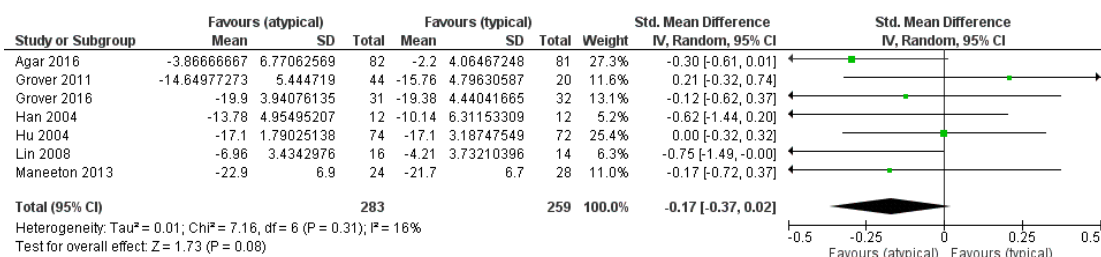
Figure 4. Forest plot of comparison: 2 severity of delirium, outcome: 2.1 antipsychotic versus no antipsychotic.



Typical versus atypical antipsychotic drug

Seven studies (Agar 2016; Grover 2011; Grover 2016; Han 2004; Hu 2004; Lin 2008; Maneeton 2013) reported this outcome. All but one trial (Han 2004) had delirium assessment by a psychiatrist or nurse blinded to the status of treatment. Delirium severity was scored with the DRS (Han 2004; Hu 2004; Lin 2008), DRS-98-R (Grover 2011; Grover 2016; Maneeton 2013) and MDAS (Agar 2016), assessed at baseline and at the end of study treatment. The pooled result showed no difference in delirium severity (SMD -0.17, 95% CI -0.37 to 0.02; 542 participants, Analysis 1.4; Figure 5). There was a low degree of heterogeneity ($I^2 = 16\%$). We assessed this as low-quality evidence (downgraded due to risk of bias, inconsistency). It was not feasible to conduct the sensitivity analysis including only trials at low risk of bias.

Figure 5. Forest plot of comparison: I severity of delirium, outcome: I.4 atypical antipsychotic versus typical antipsychotic.



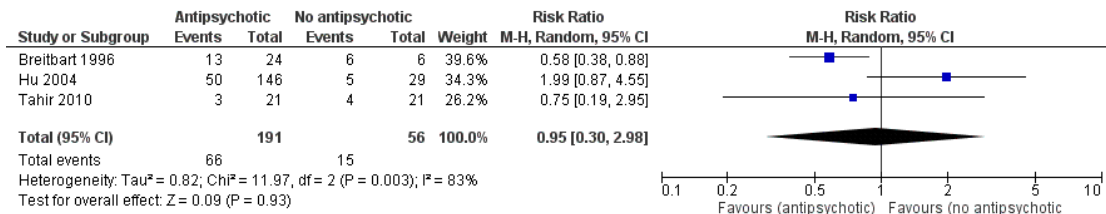
Delirium resolution

Antipsychotic versus nonantipsychotic drug or placebo

Delirium resolution was reported for three studies (Breitbart 1996; Hu 2004; Tahir 2010). The definition of resolution applied in the trials varied: complete alleviation of symptoms (Hu 2004), alleviation of symptoms to below an unspecified diagnostic threshold (Breitbart 1996), and a cutoff of DRS-R98 < 15 on day 7 (Tahir 2010). Two of the studies were double-blind so delirium assess-

ments were blinded. The pooled result indicated no significant difference in overall delirium resolution (RR 0.95, 95% CI 0.30 to 2.98; three studies, 247 participants; Analysis 2.1; Figure 6). There was a high degree of heterogeneity ($I^2 = 83\%$). We assessed this as very low-quality evidence (downgraded due to risk of bias, inconsistency, imprecision). As a sensitivity analysis, we (Analysis 2.2) included only trials with a placebo group (Hu 2004; Tahir 2010). The pooled result indicated no significant difference in overall delirium resolution (RR 1.43, 95% CI 0.58 to 3.54; two studies; 217 participants) but with less heterogeneity ($I^2 = 30\%$). It was not feasible to conduct the sensitivity analysis including only trials at low risk of bias.

Figure 6. Forest plot of comparison: 3 resolution, outcome: 3.1 antipsychotic versus no antipsychotic.

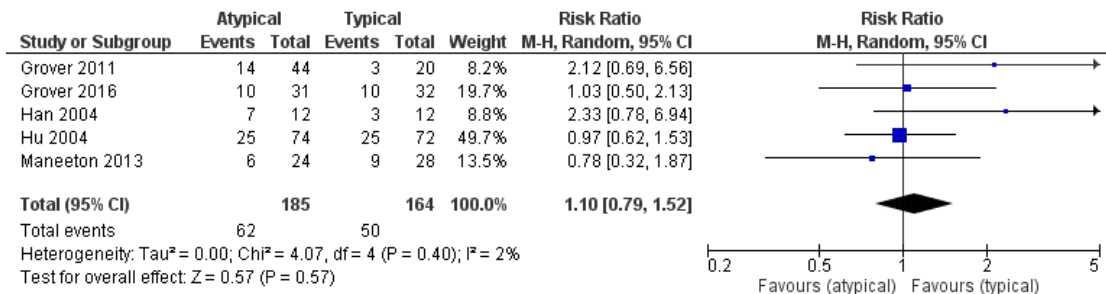


Typical versus atypical antipsychotic drug

Delirium resolution was reported for five studies (Grover 2011; Grover 2016; Han 2004; Hu 2004; Maneeton 2013). The definition of resolution varied in the trials: DRS-R98 < 10 (Grover 2011; Grover 2016), DRS-R98 < 12 (Maneeton 2013), MDAS < 13 (Han 2004), and complete alleviation of symptoms (Hu 2004). Four of the trials (Grover 2011; Grover 2016; Han 2004;

Maneeton 2013) were blinded studies and had blinded delirium assessments. The pooled result indicated no significant difference in overall delirium resolution (RR 1.10, 95% CI 0.79 to 1.52; 349 participants; Analysis 2.3; Figure 7). There was a low degree of heterogeneity (I² = 2%). We assessed this as low-quality evidence (downgraded due to risk of bias, inconsistency). It was not feasible to conduct the sensitivity analysis including only trials at low risk of bias.

Figure 7. Forest plot of comparison: 2 resolution, outcome: 2.3 atypical antipsychotic versus typical antipsychotic.



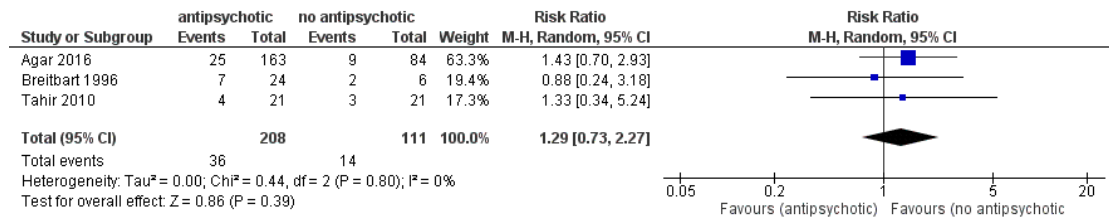
Mortality

Antipsychotic versus nonantipsychotic drug or placebo

Mortality was reported for three studies (Agar 2016; Breitbart 1996; Tahir 2010). The end point was measured at study day three (Agar 2016), within one week of study completion (Breitbart

1996), and at day 30 (Tahir 2010). The pooled result indicated no statistical difference in mortality (RR 1.29, 95% CI 0.73 to 2.27; three studies, 319 participants; Analysis 3.1; Figure 8). There was a low degree of heterogeneity (I² = 0%). We assessed this as low-quality evidence (downgraded due to risk of bias, imprecision). We conducted a sensitivity analysis with only trials that included a placebo group (Analysis 3.2). The pooled result indicated no statistical difference in mortality (RR 1.41, 95% CI 0.75 to 2.66; two studies; 289 participants; I² = 0%).

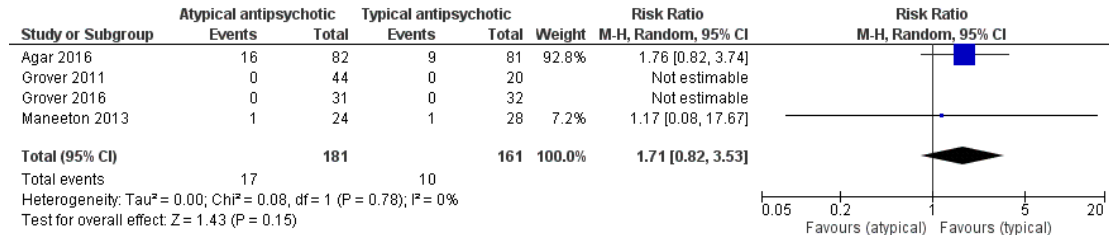
Figure 8. Forest plot of comparison: 3 mortality, outcome: 3.1 antipsychotic versus no antipsychotic.



Typical versus atypical antipsychotic drug

Mortality was reported for four studies (Agar 2016; Grover 2011; Grover 2016; Maneeton 2013). Time to end point was measured at study day three (Agar 2016) and within one week of study enrolment (Grover 2011; Grover 2016; Maneeton 2013). Mortality was very low and no deaths were reported in two studies (Grover 2011; Grover 2016). The pooled result indicated no statistical difference in overall mortality (RR 1.71, 95% CI 0.82 to 3.35; four studies; 342 participants; Analysis 3.3; Figure 9). There was a low degree of heterogeneity (I² = 0%). We assessed this as low-quality evidence (downgraded due to risk of bias, imprecision).

Figure 9. Forest plot of comparison: 3 mortality, outcome: 3.3 atypical antipsychotic versus typical antipsychotic.



Hospital length of stay (days)

Antipsychotic versus nonantipsychotic drug or placebo

No trials reported hospital length of stay, and attempts to obtain data from corresponding study authors proved unsuccessful.

Typical versus atypical antipsychotic drug

No trials reported hospital length of stay, and attempts to obtain data from corresponding study authors proved unsuccessful.

Hospital discharge disposition

Antipsychotic versus nonantipsychotic drug or placebo

No trials reported hospital discharge disposition, and attempts to obtain data from corresponding study authors proved unsuccessful.

Typical versus atypical antipsychotic drug

No trials reported hospital discharge disposition, and attempts to obtain data from corresponding study authors proved unsuccessful.

Health-related quality of life

Antipsychotic versus nonantipsychotic drug or placebo

No trials reported health-related quality of life, and attempts to obtain data from corresponding study authors proved unsuccessful.

Typical versus atypical antipsychotic drug

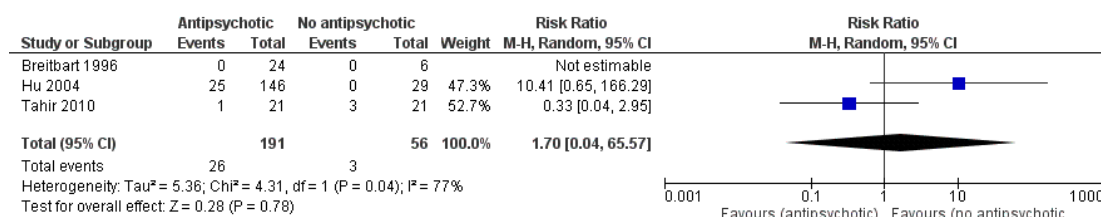
No trials reported health-related quality of life and attempts to obtain data from corresponding study authors proved unsuccessful.

Adverse events

Antipsychotic versus nonantipsychotic drug or placebo

No trials reported the use of physical restraints, long-term cognitive measures, or incidence of seizures, cerebrovascular events, sudden cardiac death or QTc abnormalities. Extrapyramidal symptoms (EPS) were reported for three studies (Breitbart 1996; Hu 2004; Tahir 2010). EPS was assessed using the Extrapyramidal Symptom Rating Scale in two trials (Breitbart 1996; Hu 2004), and the method was not reported in the other trial (Tahir 2010). The overall number of reported EPS events was low in the trials. The pooled result indicated the risk of EPS with antipsychotics was not statistically increased (RR 1.70, 95% CI 0.04 to 65.57; 247 participants; Analysis 4.1; Figure 10). There was substantial heterogeneity ($I^2 = 77\%$). We assessed the evidence as very low-quality evidence (downgraded due to risk of bias, inconsistency, imprecision). One additional study (Agar 2016) reported significantly greater mean extrapyramidal effects in risperidone versus placebo-treated participants using mixed effects modelling, without specifying the actual summary measure (0.73, 95% CI 0.09 to 1.37, $P = 0.03$) and haloperidol versus placebo-treated (0.79, 95% CI 0.17 to 1.41, $P = 0.01$) participants on each study day. Raw data were not available, thus, we were unable to pool these data with the other trials.

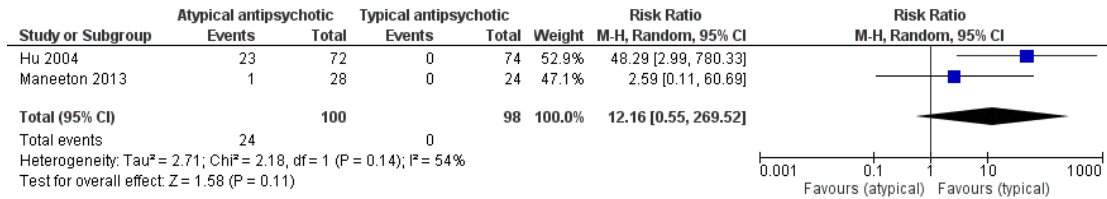
Figure 10. Forest plot of comparison: 4 adverse event, outcome: 4.1 antipsychotic versus no antipsychotic (EPS).



Typical versus atypical antipsychotic drug

No trials reported the use of physical restraints, long-term cognitive measures, cerebrovascular events, sudden cardiac death or QTc abnormalities. One trial (Maneeton 2013) reported on seizures with one seizure in the quetiapine group and no seizures in the haloperidol group. This trial also reported arrhythmias with one AV block episode in the haloperidol group and no events in the quetiapine group. Two trials (Hu 2004; Maneeton 2013) reported EPS symptoms. EPS was assessed using the Extrapyramidal Symptom Rating Scale in one trial (Hu 2004) and the other with MSAS (Maneeton 2013). The overall number of participants experiencing any EPS symptoms was low. The pooled results showed no statistical increased risk of EPS with typical antipsychotics compared to atypical antipsychotics (RR 12.16, 95% CI 0.55 to 269.52; two studies; 198 participants; Analysis 4.2; Figure 11). There was a moderate degree of heterogeneity ($I^2 = 54\%$). We assessed the evidence as very low-quality evidence (downgraded due to risk of bias, inconsistency, imprecision).

Figure 11. Forest plot of comparison: 4 adverse event, outcome: 4.2 atypical antipsychotic versus typical antipsychotic (EPS).



Subgroup analysis and investigation of heterogeneity

We intended to conduct subgroup analyses exploring the effects of controlling for age and history of dementia. However, due to the small number of included studies and lack of relevant data, these analyses could not be conducted. We found substantial heterogeneity in analysis 1.1 (Analysis 1.1), 1.2 (Analysis 1.2) and 4.1 (Analysis 4.1). When we removed the studies not at low risk of bias (Breitbart 1996 and Hu 2004; Analysis 1.3) there is no longer such variability. We believe the use of different tools to measure the outcome may potentially explain the variation identified.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Typical versus Atypical antipsychotics for treatment of delirium in hospitalised patients						
Patient or population: delirious patients Settings: hospital wards, not ICU Intervention: typical antipsychotic drug Comparison: atypical antipsychotic drug						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Atypical antipsychotic drug	Typical antipsychotic drug				
Duration of delirium Follow-up: days						This outcome was not reported in any trial.
Delirium resolution DRS, DRS-R98 ¹ Follow-up: 7 days	Study population		RR 1.1 (0.79 to 1.52)	349 (5 studies)	⊕⊕○○ Low-quality: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different. ^{2,3}	
	305 per 1000	335 per 1000 (241 to 463)				
	Moderate					
	313 per 1000	344 per 1000 (247 to 476)				
Delirium severity DRS, DRS-R98 ¹ Follow-up: 7 days	The mean DRS-R-98 score was 29.7 (SD 4.6) at the end of study. ¹⁰		The standardised delirium severity score was 0.17 points lower in the intervention group (0.37 lower to 0.02 higher)	542 (7 studies)	⊕⊕○○ Low-quality: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a	SMD -0.17 (-0.37 to 0.02)

				possibility that it is substantially different. ^{4,5}
Mortality Follow-up: 7 days	Study population	RR 1.71	342	⊕⊕○○ Low-quality: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different. ⁶
	62 per 1000 106 per 1000 (51 to 219)	(0.82 to 3.53)	(4 studies)	
	Moderate			
	18 per 1000 31 per 1000 (15 to 64)			
Hospital length of stay Follow-up: days				This outcome was not reported in any trial.
Adverse Effects - EPS Follow-up: 7 days	Study population	RR 12.16	198	⊕○○○ Very low-quality: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect. ^{7,8,9}
	0 per 1000 0 per 1000 (0 to 0)	(0.55 to 269.52)	(2 studies)	
	Moderate			
	0 per 1000 0 per 1000 (0 to 0)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **DRS:** Delirium Rating Scale; **DRS-R98** = Delirium Rating Scale Revised 98; **EPS:** Extrapyramidal Symptoms; **RR:** Risk ratio

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ DRS = Delirium Rating Scale; DRS-R98 = Delirium Rating Scale Revised 98

² All included trials had risk of bias.

- ³ Delirium resolution was measured with different tools at variable time points using different thresholds.
- ⁴ Only 1 of 7 trials was considered low risk of bias across all domains. Six of the seven trials had blinded delirium assessment.
- ⁵ Delirium severity was measured with different tools at variable time points.
- ⁶ Low number of events.
- ⁷ All trials at risk of bias.
- ⁸ Variable tools used to assess.
- ⁹ Few events and wide confidence intervals.
- ¹⁰ Assumed risk taken from [Maneeton 2013](#).

DISCUSSION

Summary of main results

We identified nine randomised trials evaluating antipsychotics for treatment of delirium in hospitalised, non-ICU patients. Four of the trials compared antipsychotics to nonantipsychotic drugs or placebo and seven compared typical to atypical antipsychotics. We found no evidence for determining the effect of antipsychotic drugs (as a class or by type) on duration of delirium. The current evidence does not support the use of an antipsychotic drug to reduce delirium severity, shorten time to resolution, or reduce mortality. We found no evidence to determine the effect of antipsychotics on length of hospital stay or health-related quality of life. Low-quality evidence showed adverse drug events were infrequently assessed but available data indicated extrapyramidal side effects were not more common with antipsychotic drugs compared to nonantipsychotic drugs or placebo and typical antipsychotics (e.g. haloperidol) were comparable to atypical antipsychotics (e.g. risperidone).

Overall completeness and applicability of evidence

The original version of this Cochrane Review included three trials (Loneragan 2007). We had anticipated finding a large number of new trials investigating antipsychotics for a number of reasons, including the known association between delirium and adverse patient outcomes, that delirium is deemed publicly important and is an indicator of quality of care in the elderly, and the fact that the 2010 NICE guidelines recommended further research. Despite the ten-year time lapse since the original version of this review, the body of evidence for treatment of delirium for hospitalised non-ICU patients with antipsychotic drugs remains limited and fraught with issues. Although we identified nine trials for inclusion, none of the trials reported on delirium duration, length of hospital stay, hospital discharge destination, health-related quality of life, and many of the adverse events we perceived were important to patients, families and clinicians. Most of the studies were single centre studies with insufficient sample size, heterogeneous study populations, and at risk of bias. Only one trial was an adequately powered trial that included a placebo group (Agar 2016) with low risk of bias across all domains. It is also important to note there were differences in how some of the outcomes were measured in the trials. For example, there were sufficient studies to pool for the outcomes, delirium severity and resolution of symptoms, but different tools were used and the time points assessed were not consistent. Our planned subgroup analyses to determine if there were differences in effect/safety in the older or dementia participant populations could not be addressed because of lack of data. We had anticipated finding more evidence in these populations as delirium is common in these subgroups.

Quality of the evidence

We scored the risk of bias for each trial and used GRADEpro software to inform the generation of evidence quality statements. Of the nine randomised controlled trials included in this review, only one trial scored low risk of bias across all domains. Although this review included only randomised controlled trials, the quality of evidence was downgraded for risk of bias, inconsistency, or imprecision. There were some notable design issues of these trials that should be factored into future trials. Guidelines suggest antipsychotics only be considered once non-drug strategies are considered ineffective or insufficient for the distressed patient. Only half of the identified trials reported that non-drug strategies were used during the study period and details of the interventions applied were not provided. Also, the use of rescue therapies for agitation, such as benzodiazepines, was not consistently reported. Physical restraint use was not reported in any trial. Use of chemical and physical restraint as rescue therapy presents an opportunity to introduce bias and thus should be standardised and reported in future trials. There was heterogeneity for some outcomes and their measurement methods. For the outcomes, severity and resolution of delirium, variable tools were used, different definitions or thresholds were applied, and the outcomes were assessed at different time points. In future trials, one must also consider the fact that delirium severity rating scales tend to focus more on hyperactive delirium, which is less common, rather than hypoactive delirium.

Potential biases in the review process

This review followed the Cochrane procedures and there were only a small number of amendments to the review process (outlined in [Differences between protocol and review](#)).

Agreement and disagreements with other studies or reviews

The original version of this Cochrane Review did not answer the specific question of the effect of antipsychotics compared to no antipsychotics on delirium outcomes in hospitalised non-ICU patients. We believe it is critical to first understand if antipsychotics as a class are effective and safe for management of delirium before comparing typical and atypical antipsychotics. We have expanded on the original review to answer this specific question before comparing typical and atypical antipsychotics. On the advice of Cochrane, we also narrowed the population by excluding the clinically unique critically ill patient population.

Our principal finding was consistent with a recent comprehensive review by Neufeld and colleagues (Neufeld 2016). Neufeld and colleagues did not find the available evidence supported antipsychotic use for prevention or treatment of delirium in any hospitalised patient population. This review included studies of any

design (prospective or historical cohort, case-control, and other observational designs) and they included both ICU and non-ICU participant populations. The generated outcomes were based on nearly all trials enrolling only critically ill participants. Kirshi and colleagues (Kishi 2016) similarly conducted a systematic review to examine antipsychotics for treatment of delirium. The review also included both ICU and non-ICU participant populations in 15 studies. Four of the studies included were unpublished or in abstract form only; these were excluded from our review as well as the Neufeld review. The primary outcomes measure for Kirshi's review was response rate at the study end point, examining many different severity and global scales. They found antipsychotics were superior to placebo or nonantipsychotic drugs in this analysis of ICU and non-ICU studies in terms of response rate (RR 0.22, 95% CI 0.15 to 0.34, $P < 0.00001$, $I^2 = 0\%$, three studies). When they performed a subgroup analysis using only ICU studies they found the pooled result was marginally superior to placebo or nonantipsychotic drugs (RR 0.25, 95% CI 0.06 to 1.02, $p = 0.05$, $N = 1$); using only non-ICU studies the result was the same as the pooled ICU and non-ICU studies with antipsychotics significantly superior to no antipsychotic (RR 0.22, 95% CI 0.15 to 0.34, $P < 0.00001$, $I^2 = 0\%$, two studies). Similarly for the analysis of delirium severity, antipsychotics were significantly superior to no antipsychotic (SMD -1.27, 95% CI -2.44 to -0.11, $P = 0.03$, $I^2 = 93\%$, two studies). For these analyses, we included two additional trials.

AUTHORS' CONCLUSIONS

Implications for practice

- Survey data indicates pharmacological interventions, such as antipsychotics, are often used to manage delirium symptoms in clinical practice. The 2010 NICE guidelines (NICE 2010) recommended clinicians should investigate and manage underlying or reversible causes of delirium. For patients that are distressed, verbal and nonverbal techniques should be used to manage symptoms; if these strategies are ineffective or insufficient, short-term (< 1 week) antipsychotic drug might be considered at the lowest effective dose.

- After updating this review, we caution clinicians to the fact that there is still insufficient evidence overall on this subject. We found no evidence to determine whether antipsychotics reduce delirium duration in hospitalised non-ICU patients (our primary objective). We found low-quality evidence that antipsychotics do not reduce delirium severity compared to nonantipsychotic drugs or placebo and low-quality evidence indicating there is no difference between typical and atypical antipsychotics. There is low-quality evidence that antipsychotics do not alter mortality or adverse event rates in delirious hospitalised patients.

Implications for research

- The 2010 NICE guidelines (NICE 2010) recommended that a large RCT should be conducted to compare typical antipsychotics and atypical antipsychotics with placebo in hospitalised patients with delirium. The NICE guidelines also recommended the study outcomes of such a trial should include recovery from delirium (defined as complete response), the duration and severity of delirium (measured with a validated tool), as well as clinically important adverse events. Such a trial has been completed for palliative care participants (Agar 2016) but not for other important hospitalised non-ICU populations.

- Our search identified a number of delirium studies published in the last decade suggesting a growing interest in this subject. However, the majority of recent studies have focused on critically ill participants, still leaving us with insufficient poor quality data for hospitalised, non-critically ill participants (e.g. general medicine, surgery). Given the limited available evidence for this review, the 2010 NICE guideline recommendations calling for new research is still justified in 2018. Well designed controlled trials are urgently needed to address this population who are frequently managed with antipsychotics despite limited evidence. In particular, we need adequately powered trials that include a placebo group and factor in nonpharmacological delirium treatment strategies that have already been shown to be helpful in this population to clarify if an antipsychotic alters delirium outcomes. These trials should clearly standardise and describe the use of rescue interventions to manage agitation (e.g. benzodiazepines and physical restraints), as such interventions are known to be associated with delirium and can introduce bias.

- Our search revealed limited data on outcomes that we deemed important for patients, their families, and the clinical team. Future studies need to examine the effect of therapy on duration of delirium or time to complete resolution, length of hospital stay, and long-term outcomes, such as cognitive impairment. In addition, to improve comparison of results among trials there is a need for standardisation of research methods and outcomes reported, specifically duration of therapy and methods of evaluating response to delirium treatment. The Del-CORs (Development of core outcome sets for effectiveness trial of interventions to prevent and/or treat delirium) group (Rose 2017) is leading the development of international consensus on outcomes for trials of interventions to prevent and/or treat delirium for critically ill, acutely hospitalised participants, palliative care, and older adults. The recommendations from this group will be essential for future well designed delirium trials.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Agar 2016

Methods	Double-blind, randomised trial comparing risperidone, haloperidol, and placebo on targeting symptoms of delirium
Participants	<p>Location: Study took place in 11 inpatient hospice or palliative care services in Australia.</p> <p>Inclusion: Participants included adult patients receiving hospice or palliative care with advanced, progressive disease that was no longer curable who required inpatient care by a specialist palliative care team. Participants were required to speak English and be able to swallow liquids. Participants needed to meet the following 3 criteria: delirium diagnosis via 1) DSM-IV-TR criteria, 2) Memorial Delirium Assessment Scale (MDAS) score of 7 or more, and 3) presence of the target symptoms of delirium associated with distress, defined as a delirium symptoms score of 1 or more (sum of the scores from items 2 (inappropriate behaviour), 3 (inappropriate communication), and 4 (illusions and hallucinations) on the Nursing Delirium Screening Scale (NuDESC) (severity range, 0 to 6)).</p> <p>Exclusion: delirium due to substance withdrawal, history of neuroleptic malignant syndrome or previous adverse reaction to an antipsychotic drug, regular use of antipsychotic drugs within 48 hours of the study, extrapyramidal disorders, prolonged QT interval, clinician-predicted survival of 7 days or fewer, cerebrovascular accident or seizure in the prior 30 days, and pregnancy or breastfeeding. Subjects included: 247 adult participants (N = 82 risperidone, mean age 74.5 ± 10.6 years, 57/82 (69%) male, N = 81 haloperidol, mean age 76.5 ± 8.2 years, 48/81 (59%) male, N = 84 placebo, mean age 73.8 ± 10.7 years, 57/84 (68%) male)</p>
Interventions	<p>Each study drug arm: 1) Participants ≤ 65 years received a 0.5 mg loading dose of study drug administered with the first dose of 0.5 mg, then 0.5 mg maintenance doses every 12 hours. Doses could be titrated by 0.25 mg on day 1 and by 0.5 mg thereafter to a maximum dose of 4 mg/d. 2) For participants > 65 years, the loading, initial, and maximum doses of the study drug were halved. The placebo solution was titrated similarly using matching volumes of solution for each dose level. Doses were increased if the sum of NuDESC scores for items 2, 3, and 4 was 1 or more at the most recent assessment. Participants were observed daily, with NuDESC scores measured every 8 hours by trained nurses. Dose reduction of the prior dose could occur for adverse effects, resolution of delirium (MDAS score of < 7 for 48 hours), or resolution of symptoms (all NuDESC item scores < 1 for 48 hours). Treatment duration was 72 hours, with the last assessment done 12 hours after the sixth dose</p> <p>Study drug was discontinued if adverse effects became unacceptable, the treating clinician deemed the treatment ineffective, or at onset of dysphagia. Maintenance of blinded study medication was optional for an additional 48 hours if a partial response occurred or to taper the dose with resolution of symptoms. All participants received individualised treatment plans, including treatment of reversible precipitants, where clinically indicated, and nonpharmacologic measures, as appropriate. Rescue drug: Subcutaneous midazolam 2.5 mg every 2 hours PRN was available when participants in any group scored 2 on the NuDESC item for inappropriate behaviour or illusions and hallucinations, and were deemed to require immediate intervention for safety or distress. Intravenous benzotropine mesylate (1 to 2 mg) could be administered for serious extrapyramidal adverse effects</p>

Outcomes	Clinical (day 3): 1) Average of last 2 delirium symptom scores on day 3, using the baseline score (average of the eligibility delirium symptom score and the score before the first dose of the study drug) as a covariate, 2) Daily MDAS score, 3) Lowest delirium symptoms score, 4) Daily use of midazolam (rescue drug), 5) Sedation, assessed by the Richmond Agitation-Sedation Scale, 6) Survival (measured at day 3 and also median survival (days)) . Adverse effects: 1) Extrapyramidal symptoms, assessed by the Extrapyramidal Symptom Rating Scale, 2) National Cancer Institute Common Terminology Criteria for Adverse Events	
Notes	Study was funded by the Australian Government's Department of Health under the National Palliative Care Strategy. Individual site funding was supplemented by grant NHMRC 480476 from the National Health and Medical Research Council, Australia. The trial was registered (ACTRN12607000562471). Baseline covariates collected included: prior cognitive impairment (all cause), Informant Questionnaire on Cognitive Decline in the Elderly score, comorbidity burden (Cumulative Illness Rating Scale score) , vision or hearing impairment, daily oral morphine and diazepam equivalents, and the Australia-modified Karnofsky Performance Status score	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Site randomisation schedules generated using random number tables at an independent and blinded central registry. Participants were randomised in blocks of 6 by site in a 1:1:1 ratio
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes were used. Site clinical trial pharmacists not otherwise involved in patient care opened treatment schedules to prepare study drug
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinded study - both participants and investigators were masked to treatment groups
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat basis. Missing scores imputed using multiple imputation, drawing 50 resamples
Selective reporting (reporting bias)	Low risk	Outcomes in methods matched those reported in results. Trial protocol was pre-registered
Other bias	Low risk	All participants were permitted pain medication, rescue benzodiazepine, and given similar nonpharmacological interventions.

Power calculations presented

Breitbart 1996

Methods	Double-blind, randomised trial comparing haloperidol, chlorpromazine, and lorazepam in the treatment of delirium
Participants	<p>Location: Study took place in a single general medicine unit of one hospital in the United States. Inclusion: Medically hospitalised adults who met the case definition for AIDS and who were undergoing treatment for AIDS-related medical problems at a single hospital were approached for participation. They recruited and consented participants prior to the episode of delirium. Participants were followed prospectively and not randomised to study drug unless they became delirious. Exclusion: AIDS-related dementia where participants could not give informed consent, patients expected to die within 24 hours, known hypersensitivity to study drugs, history of neuroleptic malignant syndrome, concurrent need for treatment with neuroleptic drugs, seizure disorder, current systemic chemotherapy for Kaposi's sarcoma, withdrawal syndrome, current/past diagnosis for schizophrenia, schizoaffective disorder, or bipolar disorder</p> <p>Subjects included 30 adult participants (N = 11 haloperidol, N = 13 chlorpromazine, N = 6 lorazepam, mean age of entire study population 39.2 ± 8.8 years, 23/30 (77%) male) hospitalised for AIDS-related medical problems and diagnosed with delirium (DSM-III criteria and Delirium Rating Scale (DRS) total score ≥ 13)</p>
Interventions	<p>The study did not include a placebo group. The authors believed withholding medication from agitated participants could pose a risk to patients and staff, hence they did not use a placebo group. They viewed lorazepam as a placebo. Study drug: Participants were randomised to one of three groups by pharmacy personnel. Groups were: haloperidol, chlorpromazine, and lorazepam. Subjects were started on the lowest dose of their respective study drug, administered either orally or intramuscularly and according to an a priori established increasing titration schedule consisting of 9 levels of dosing (table 1 in manuscript). Haloperidol was started with 0.25 mg oral/0.125 mg intramuscular, chlorpromazine at 10 mg oral/5 mg intramuscular, and lorazepam at 0.5 mg oral/0.20 mg intramuscular. Each subject was evaluated hourly using the DRS. If, after each hourly evaluation, the participant's DRS score remained ≥ 13, the next level dose of study drug was administered. After stabilisation (i.e. participant calm, asleep, not hallucinating, and DRS ≤ 12), a maintenance dose equal to one-half of the first 24-hour dose requirement was begun, given in a twice-daily regimen from day 2 of the study until a maximum of six days of treatment. Midway through the study, the participants in one group developed treatment-limiting adverse side effects as per the manuscript. All participants were in the lorazepam group. From that point forward, no further participants were randomised to the lorazepam group. Rescue drugs: No rescue drugs permitted (additional details provided by author)</p>
Outcomes	<p>Outcomes (at end of study drug, day 6):</p> <ol style="list-style-type: none"> 1. Mean drug doses administered in first 24 hours of treatment, 2. Average maintenance doses of study drug, 3. DRS score, change from baseline to day 2, and day 2 to day 6, 4. Mini-Mental State score, change from baseline to day 2, and day 2 to day 6, 5. Karnofsky Performance Status, 6. Medical Status Profile. Adverse effects: 1) Extrapyramidal symptoms, assessed by the Extrapyramidal Symptom Rating Scale, 2. Side Effects

Breitbart 1996 (Continued)

	and Symptom Checklist	
Notes	Study supported by the National Institute of Mental Health grant MH-45664	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation table (additional details provided by author)
Allocation concealment (selection bias)	Low risk	Pharmacist not involved in the study patient care indicated which study drug was to be used based on the random number table
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinded study.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Lorazepam arm discontinued early due to adverse events, but data used in analysis
Selective reporting (reporting bias)	Unclear risk	Outcomes in methods matched those reported in results. But protocol not published to confirm all outcomes were reported as planned
Other bias	Unclear risk	No rescue drugs permitted (additional details provided by author). Also, midway through the study, the participants in one group developed treatment-limiting adverse side effects as per the manuscript. All participants were in the lorazepam group. From that point forward, no further participants were randomised to the lorazepam group Note: Sample size/power calculation not reported in the manuscript

Grover 2011

Methods	Single-blind, randomised trial comparing haloperidol, risperidone, and olanzapine in the treatment of delirium
Participants	Location: Conducted in single hospital in India. Inclusion: Consecutive participants with delirium referred to the consultation-liaison psychiatry team were eligible for the study. To be included in the study, participants had to have a confirmed diagnosis

	of delirium and > 18 years of age. Exclusion: Participants with delirium secondary to alcohol or benzodiazepine withdrawal, those with dementia, those unresponsive to verbal or physical stimulus, those suffering terminal illness, and those with a comorbid psychotic/mood disorder, profound hearing or visual loss, aphasia, Parkinson's disease, history of neuroleptic malignant syndrome, prolonged QTc interval, past history of hypersensitivity to any of the study drugs. Participants included 64 adult (> 18 years) medical and surgical patients (N = 20 haloperidol, mean age 44.09 ± 16.84 years, 12/20 (60%) male, N = 21 risperidone, mean age 45.39 ± 19.18 years, 12/21 (57%) male, N = 23 olanzapine, mean age 46.5 ± 14.51 years, 21/23 (91%) males) diagnosed with delirium (CAM and DRS-R-98)
Interventions	There were three study groups: 1) Haloperidol: flexible dose ranging from 0.25 to 10 mg/day; 2) Risperidone: flexible dose ranging from 0.25 to 4 mg/day; and 3) Olanzapine: flexible dose ranging from 1.25 to 20 mg/day. Study drug was administered for 6 days and for all subjects, family members told to follow behavioural management (i. e. providing optimal level of environmental stimulation, reducing sensory impairments, making environment more familiar, providing environmental cues that facilitate orientation, and providing reassurance and information concerning delirium so as to reduce fear or demoralisation). Delirium screening occurred daily. For all participants, the etiological causes identified for delirium were treated with appropriate measures. Any medication that can cause delirium and/or was not essential for the care of the participant was discontinued. Rescue drugs: For the haloperidol and olanzapine groups, whenever rescue medication was required (e.g. severe agitation), the same drug was used in the injectable form. For the risperidone group, injectable lorazepam or haloperidol was used as rescue medication as risperidone not available in injectable form. The dose of rescue medication was titrated after daily clinical assessment; however, if the participant was agitated, titration was done more frequently
Outcomes	Outcomes (daily for 6 days by blinded investigator): 1. DRS-R-98 score, 2. Mini Mental Status Examination score. Adverse effects: 1. Simpson Angus Scale for side effects, 2. Abnormal Involuntary Movement Scale, 3. Udvalg for Kliniske Undersogelser score side effect rating scale
Notes	Study funded by Institute Research Fund. Protocol not published

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated to be randomised but no details provided. It is likely that it was done
Allocation concealment (selection bias)	Low risk	Randomisation and dose adjustments were carried out by one study investigator, however, assessments were blinded
Blinding (performance bias and detection bias) All outcomes	Low risk	Single-blinded study. However, all assessments were carried out by a single investigator (different from the one who performed

Grover 2011 (Continued)

		the randomisation and dose adjustments) who was blinded to study drug allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	Of the 74 participants consented, 64 completed the study. Six participants could not be assessed at least once during the study (due to worsened clinical status) and four left hospital against medical advice
Selective reporting (reporting bias)	Unclear risk	Outcomes in methods matched those reported in results. Trial protocol not published so unable to confirm all outcomes were reported as planned
Other bias	Unclear risk	For both groups, etiological causes of delirium were addressed and nonessential medications or medications associated with delirium were discontinued. One group (i.e. risperidone) received lorazepam or haloperidol as injectable risperidone was not available. However, haloperidol and olanzapine groups received the same drug they were assigned to for rescue. Referral bias: participants who were referred to the consultation-liaison psychiatry team were eligible for the study. It is unknown if all participants with suspected delirium are routinely referred to psychiatry in this hospital Note: Sample size/power calculation not reported.

Grover 2016

Methods	Single-blind, randomised controlled trial of quetiapine and haloperidol for the treatment of delirium
Participants	Location: Study conducted in single hospital in India. Inclusion: Consecutive patients with delirium referred to the consultation-liaison psychiatry team were eligible for the study. Only patients who fulfilled a diagnosis of delirium based on DSM-IV and > 18 years could be included in the study. Exclusion: delirium due to alcohol or benzodiazepine withdrawal, poisoning, overdoses, dementia, those unresponsive to verbal or physical stimulus, history of aphasia, profound hearing or visual loss, those with QTc prolongation, past history of hypersensitivity to the study drugs, history of neuroleptic malignant syndrome, Parkinson's disease, psychotic or mood disorders, and terminal illness. Participants included 63 adult (> 18 years) medical and surgical patients (N = 31 quetiapine, mean age 48.51 ± 19.75 years, 21/31 (68%) male, N = 32 haloperidol, mean age 44.4 ± 16.76 years, 28/32 (88%) male) diagnosed with delirium (DSM-IV criteria)

Interventions	No placebo group. The study compared: 1) Haloperidol: flexible dose ranging from 0.25 to 10 mg/day and 2) Quetiapine: flexible dose ranging from 12.5 to 75 mg/day. Study drug was adjusted daily as per the clinical judgement of treating physician who was blinded to assignment. Study drug was administered for 6 days. For all subjects, caregivers advised to provide optimal level of environmental stimulation, avoid sensory impairments of the participant, and make the environment familiar to the participant by ensuring proper environmental cues that could facilitate orientation. Delirium screening occurred daily. Rescue drugs: Benzodiazepines were not permitted. Use of other drugs to manage severe agitation not reported	
Outcomes	Outcomes (at end of study drug, day 6): 1. DRS-R-98 score, 2. Mini Mental Status Examination score, 3. Average dose of study drug, 4. Delirium response rates (DRS-R-98 < 10), 5. Delirium resolution rates (DRS-R-98 score of 0). Adverse effects: None included as an outcome or reported	
Notes	Protocol not published in advance.	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was done based on a computer-generated randomisation table, which was done prior to study start
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding (performance bias and detection bias) All outcomes	Low risk	Single-blinded study, however the investigator responsible for randomisation and drug titration was different from the one who conducted the outcome assessments (blinded clinical assessment)
Incomplete outcome data (attrition bias) All outcomes	High risk	Seven participants not included in the analysis. Two participants in each group were not available for assessment after the first 1 to 2 study days because they left against medical advice. One participant in the quetiapine group received injectable haloperidol for symptom management on study day 2, and was excluded. One participant from each group could not be started on the assigned medication due to medical deterioration
Selective reporting (reporting bias)	Unclear risk	Outcomes in methods matched those reported in results. Trial protocol not published so unable to confirm all outcomes

Grover 2016 (Continued)

		were reported as planned
Other bias	Unclear risk	<p>Manuscript source reported as 'invited manuscript.' Referral bias (same as Grover 2011): participants who were referred to the consultation-liaison psychiatry team were eligible for the study. It is unknown if all participants with suspected delirium are routinely referred to psychiatry in this hospital</p> <p>Note: Sample size/power calculation not reported.</p>

Han 2004

Methods	Double-blind, randomised trial of risperidone versus haloperidol in the treatment of delirium	
Participants	<p>Location: Study took place in a single hospital in Korea. Inclusion: All patients presenting with altered mental status who were referred to the consulting psychiatry division were evaluated. Delirium was confirmed with the Confusion Assessment Method and Delirium Rating Scale. Exclusion: any type of dementia or other psychiatric diagnosis, patients already administered an antipsychotic prior to screening for disturbing behavioural problems. Subjects included 24 adult patients (N = 12 haloperidol, mean age 66.5 ± 15.9 years, 7/12 (58%) male, N = 12 risperidone, mean age 65.6 ± 8.3 years, 6/12 (50%) male) from four medical, two intensive care, and two oncology wards, diagnosed with delirium (CAM, DRS)</p>	
Interventions	<p>No placebo group included in this study. Study groups: haloperidol: flexible dose, initial dose of 0.75 mg twice a day versus risperidone: flexible dose, initial dose of 0.5 mg twice a day. Study drug dose was increased depending on the status of delirium during the 7 days of treatment. Delirium was assessed daily. Rescue drugs: None reported</p>	
Outcomes	<p>Outcomes (One psychiatrist, blind to the status of treatment, measured the symptom changes at the same time every day for 7 days): 1. Time to response (Memorial Delirium Assessment Scale (MDAS) score < 13), 2. Response rate (MDAS < 13), 3. Mean drug dose at end of study (day 7). Adverse effects: None included as an outcome. In the results section, it was stated 'None of the 24 subjects who finished the study showed clinically significant side effects'. Method of assessment or which specific side effects examined were not reported</p>	
Notes	<p>Primary investigator supported by the Brain Korea 21 Project of the Ministry of Education and Human Resources Development, Republic of Korea</p>	
Risk of bias		
Bias	Authors' judgement	Support for judgement

Han 2004 (Continued)

Random sequence generation (selection bias)	Unclear risk	A consulting psychiatrist (not a member of the investigative team) randomly assigned participants without any knowledge of their care. Method of sequence generation not provided
Allocation concealment (selection bias)	Unclear risk	Stated as a double-blind study. However, authors stated it was not possible to obtain identical looking tablets but the 'patients and caretakers did not know the name or effects of their drug'. Likely blinded
Blinding (performance bias and detection bias) All outcomes	Low risk	Stated as a double-blind study. However, authors stated it was not possible to obtain identical looking tablets but the 'patients and caretakers did not know the name or effects of their drug'. Unlikely to have been double-blinded in design. However, a psychiatrist, blind to participant status and treatment, measured symptom change at the same time for a total of 7 days
Incomplete outcome data (attrition bias) All outcomes	High risk	Initially, N = 28 and final sample of N = 24. Two participants in the haloperidol group dropped out: one because of medical deterioration on the second study day, and one because of severe sedation on the third study day. Two participants in the risperidone group dropped out: one because of spousal refusal to participate on the second study day, and one because of a tracheotomy operation on the fourth study day. Attrition not reported in the analysis
Selective reporting (reporting bias)	Unclear risk	Trial protocol not found.
Other bias	Low risk	Sample size calculation not reported.

Hu 2004

Methods	Randomised trial comparing olanzapine, haloperidol, and placebo in the treatment of delirium
Participants	Location: Study took place in a single hospital in China. Inclusion: age > 65 years, either male or female, delirium based on DSM-IV, DRS \geq 12, total clinical global impression scale-severity of illness (CGI-SI) > 4. Exclusion: Patients with a severe mental disease, those who had taken any antipsychotic drug, patients with angle-closure glaucoma, paralytic ileus, or material abuse. Subjects

	included 175 hospitalised patients (N = 74 olanzapine, mean age 74 ± 8 years, 45/74 (60.8%) male, N = 72 haloperidol, mean age 74 ± 7 years, 48/72 (66.7%) male, N = 29 placebo, mean age 73 ± 7 years, 18/29 (62.1%) male) with a history of dementia admitted to any of the hospital's wards and diagnosed with delirium (DSM-IV, DRS score ≥ 12 and Clinical Global Impression-Severity of Illness (CGI-SI) score ≥ 4)
Interventions	Study drug: Olanzapine was started at a daily dose of 1.25 to 2.5 mg PO, and increased to a maximum daily dose of 20 mg. Haloperidol was administered in a daily dose range of 2.5 to 10 mg, intramuscularly (starting dose not provided). If CGI-SI score was reduced by ≥ 1, the dose was maintained and study drug was administered for 7 days. All subjects received 'somatic' treatment aimed at the etiological factors of delirium. Delirium was evaluated daily using the DRS and the CGI. Rescue drugs: No other centrally acting drugs were permitted, except in the instance of the development of extrapyramidal symptoms, where a maximum dose of 6 mg of benzhexol was administered
Outcomes	Outcomes (day 7): 1. DRS score, change from baseline to study completion, 2. CGI-SI (Severity) score, change from baseline to study completion, 3. CGI (Global Impression) score, change from baseline to study completion, 4. Dose and time to effect in cases where delirium was successfully treated. Adverse effects: None included as an outcome
Notes	This study was referred to as (Hua 2006) in certain reviews. The original study, cited here, was subsequently translated into English and published under the title 'Olanzapine and haloperidol for senile delirium: a randomised controlled observation'

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No mention of method of randomisation beyond stating participants were randomised in a 5:5:2 ratio to olanzapine, haloperidol, and placebo groups, respectively
Allocation concealment (selection bias)	Unclear risk	No details provided.
Blinding (performance bias and detection bias) All outcomes	High risk	Haloperidol could be given subcutaneously and olanzapine orally. No description of how treatments were concealed. No mention of blinding process. Not likely done
Incomplete outcome data (attrition bias) All outcomes	High risk	No mention of how attrition was factored into statistical analysis (not described as intention-to-treat analysis)
Selective reporting (reporting bias)	Low risk	Trial protocol identified under the first name.

Hu 2004 (Continued)

Other bias	Unclear risk	Sample size not reported. Unclear methodology regarding dosing protocol
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Lin 2008

Methods	Randomised trial of haloperidol versus olanzapine in the treatment of delirium	
Participants	Location: Study conducted in a single hospital in Taiwan. Inclusion: All participants were recruited from the hospice and palliative care center, had advanced cancer, met the DSM-IV criteria for delirium. Exclusion: past history of psychiatric disorder, coma, could not swallow oral medication, treated with neuroleptic drug within 4 weeks of the study. Subjects included 30 adult palliative and hospice care patients (N = 16 olanzapine, mean age 61.13 ± 16.5 years, 9/16 (56%) male, N = 14 haloperidol, mean age 68 ± 12.14 years, 4/14 (29%) male) diagnosed with delirium (DSM-IV criteria)	
Interventions	Study drug: Haloperidol: starting dose of 5 mg PO daily, permitted daily maximum dose 15 mg versus Olanzapine: starting dose of 5 mg PO daily, permitted daily maximum dose 15 mg. Study drug administered for 7 days. Delirium assessed via the Delirium Rating Scale (Chinese version) (DRS-c) at 24 and 48 hours, and one week into treatment. Rescue drugs: If adjunctive therapy required for acute symptoms, midazolam IM was used	
Outcomes	Outcomes (day 7): 1. DRS-c at baseline, 24 and 48 hours, and 7 days into treatment, 2. Clinical Global Impression-Severity (CGI-S) at baseline, 24 and 48 hours, and 7 days into treatment. All assessments were conducted by one assessor (research nurse) that was blinded to study assignment. Adverse effects: 1) side effects were observed and recorded on the chart by the clinical team and the assessor of the study without formal instruments	
Notes	Trial details/protocol not published in advance.	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated as a prospective randomised controlled clinical trial. Likely randomised. Methods of randomisation not stated
Allocation concealment (selection bias)	Unclear risk	Insufficient details to assess. Stated that if participant needed an antipsychotic, they were 'separated randomly to an olanzapine group or a haldol group'
Blinding (performance bias and detection bias) All outcomes	Low risk	A single individual, a nurse and counselling psychologist, performed all assessments. The assessor was blinded to subject randomisation

Lin 2008 (Continued)

Incomplete outcome data (attrition bias) All outcomes	High risk	Total number of participants enrolled and/or lost to follow-up not reported
Selective reporting (reporting bias)	Unclear risk	Outcomes in methods matched those reported in results. Trial protocol not published so unable to confirm all outcomes were reported as planned
Other bias	Unclear risk	Referral bias: A psychiatric specialist determined whether it was necessary for the participant to receive antipsychotic drug treatment based on clinical grounds. If an antipsychotic was deemed needed (criteria for use not provided), the participants were consented and randomised Note: Sample size calculation not reported.

Maneeton 2013

Methods	Randomised trial of quetiapine versus haloperidol in the treatment of delirium
Participants	Location: Study took place in a single tertiary care hospital in Thailand. Inclusion: All inpatients presumed to have delirium and needing consultation-liaison services from the psychiatric department were evaluated for inclusion, Delirium confirmed with DSM-IV. Exclusion: substance-induced delirium, known allergy or intolerance to study drugs, pregnancy or breast feeding, already receiving an antipsychotic drug, renal or hepatic failure. Subjects included 52 medically ill adult (aged 18 to 75 years) patients (N = 24 quetiapine, mean age 56.6 ± 12 years, 15/24 (62.5%) male, N = 28 haloperidol, mean age 57 ± 11.9 years, 20/28 (71%) male) diagnosed with delirium (DSM-IV-TR and CAM criteria)
Interventions	Study drugs: Quetiapine: flexible dose ranging from 25 to 100 mg/day versus haloperidol: flexible dose ranging from 0.5 to 2 mg/day. Study drug given at bedtime for 7 days, with additional doses as needed. Drug dose was adjusted based on clinical safety, sleepiness, and calmness, as measured by the Delirium Rating Scale (DRS-R-98). Subject given one dose and another every 2 to 3 hours as needed for agitation, with a daily maximum of four doses. Delirium was assessed daily via the DRS-R-98. All participants were assessed for possible causes of delirium that could be corrected using the mnemonic 'WATCHDEATH'. Environmental manipulations emphasised, such as noise control, light intensity, reassurance, and stimulus modification. Rescue drugs: Other psychotropic drugs, including benzodiazepines, were prohibited
Outcomes	Outcomes (day 7): 1. DRS-R-98 severity score, 2. DRS-R-98 noncognitive and cognitive subscale scores, 3. Delirium response rate (50% reduction of baseline DRS-R-98 score), 4. Delirium remission rate (DRS-R-98 severity score of 12 or less without relapse), 5. Total time of sleep, 6. Clinical Global Impression-Improvement (CGI-I), 7. Modified Simpson-Angus Scale (MSAS). Adverse effects: 1) Participants were assessed for possible adverse events either observed by the investigators, relatives, clinical staff, or self-report.

Maneeton 2013 (Continued)

	Formal tool not used	
Notes	Study funded by the Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand (grant number 077/52)	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation system. Subjects randomly assigned in a 1:1 manner to one of the two study groups. Randomisation codes were kept in sealed envelopes and opened after the end of the screening process
Allocation concealment (selection bias)	Low risk	Double-blinded study. Study medication, either 25 mg quetiapine or 0.5 mg haloperidol, was fully filled and concealed in identical capsules
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinded study. Participants, physicians, staff nurses, investigators, and raters were blinded to treatment assignment
Incomplete outcome data (attrition bias) All outcomes	High risk	Authors reported 32.7% study withdrawal. Stated 13/24 quetiapine- and 22/28 haloperidol-treated participants completed the study. They used intention-to-treat analysis if a participant received at least one dose of the study drug
Selective reporting (reporting bias)	Low risk	Outcomes in methods matched those reported in protocol.
Other bias	Unclear risk	Trial was registered with clinicaltrials.gov (CNT00954603). Referral bias: All inpatients presumed to have delirium and needing consultation-liaison services from the psychiatric department were evaluated for inclusion

Methods	Randomised trial comparing quetiapine versus placebo in the treatment of delirium	
Participants	Location: Study took place in a single hospital in the United Kingdom. Inclusion: DSM-IV criteria for delirium. Exclusion: major pre-existing cognitive deficits (major not defined), alcohol withdrawal, pre-existing psychosis, substance dependence, inability to comply with the constraints of the trial, on medication that interacted with quetiapine. Subjects included 42 patients (N = 21 quetiapine, mean age 84.1 ± 9.45 years, 6/21 (28.6%) male, N = 21 placebo, mean age 84.3 ± 7.16 years, 6/21 (28.6%) male) from medical, surgical, and orthopedic units diagnosed with delirium (DRS-R-98 total score ≥ 15, confirmed by DSM-IV criteria)	
Interventions	Study drugs: Participants received quetiapine or placebo, according to a flexible dosing regimen begun at 25 mg daily, with a dose titration of 25 mg/day to a maximum of 175 mg/day, in divided doses. The dose was increased only if DRS-R-98 and clinical condition showed no improvement and the drug was well tolerated, up to a maximum of 10 days. In addition to the clinical response and tolerability, information from nursing and medical staff was also considered prior to dose changes. If symptoms improved, dose was reduced in a reverse pattern from initial titration. Delirium assessment via DRS-R-98 on study days 1, 2, 3, 4, 7, and 10, with an additional follow-up on day 30. Rescue drugs: Not specified in the methods. However results reported use of lorazepam	
Outcomes	Outcomes (up to day 10): 1. DRS-R-98 score, 2. Mini-Mental Status Examination, 3. Brief Psychiatric Rating Scale, 4. Clinical Global Improvement. Adverse effects: 1. Abnormal Involuntary Movement Scale	
Notes	Investigator-initiated study sponsored by AstraZeneca UK. Funding provided for recruitment of a research assistant and trial medication. AstraZeneca UK also provided the randomisation codes. This study was stopped early	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation codes.
Allocation concealment (selection bias)	Low risk	Computer-generated randomisation codes kept in sealed envelopes in the pharmacy. Set of individual treatment codes kept for emergency out-of-hours use only
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinded study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Non-linear, mixed effects models used to estimate differences in recovery trajectories. Reasoning for the use of this statistical method described in a subsequent paper

Tahir 2010 (Continued)

		published by the authors
Selective reporting (reporting bias)	Low risk	Registered trial.
Other bias	Unclear risk	Sample size calculation reported. The trial was stopped early at the request of the manufacturer due to the FDA's concern on the use of antipsychotic medication in the elderly. The study is, therefore, underpowered. Lorazepam was administered to 4 participants in the the quetiapine group versus none in the placebo group. The quetiapine had faster resolution; unclear if this might have influenced the resolution of symptoms. Investigator-initiated study sponsored by AstraZeneca UK. Funding provided for recruitment of a research assistant and trial medication. AstraZeneca UK also provided the randomisation codes

AIDS=AcquiredImmunodeficiencySyndrome

CAM = Confusion Assessment Method

CGI = Clinical Global Impression

CGI-SI = Clinical Global Impression - Severity Scale index

DRS = Delirium Rating Scale

DRS-c = Delirium Rating Scale (Chinese version)

DRS-R-98 = Delirium Rating Scale Revised 98

DSM = Diagnostic and Statistical Manual of Mental Disorders

IM = Intramuscular injection

MDAS = Memorial Delirium Assessment Scale

NuDESC = Nursing Delirium Screening Scale

PO = *per os* or by mouth

PRN = *pro re nata* or as needed

QTc = QT interval corrected for rate

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Al Qadheeb 2016	Study population was intensive care unit patients.
Atalan 2013	Study population was intensive care unit patients.
Bakri 2015	Study population was intensive care unit patients.

(Continued)

Devlin 2010	Study population was intensive care unit patients.
Girard 2010	Study population was intensive care unit patients.
Hakim 2012	Study population was intensive care unit patients.
Jung 2009	Compared two second generation antipsychotics (risperidone and aripiprazole) with no nonantipsychotic or placebo comparator
Jung 2010	Compared two second generation antipsychotics (risperidone and quetiapine) with no nonantipsychotic or placebo comparator
Kim 2010	Compared two second generation antipsychotics (risperidone and olanzapine) with no nonantipsychotic or placebo comparator
Lee 2005	Compared two second generation antipsychotics (amisulpride and quetiapine) with no nonantipsychotic or placebo comparator
Page 2013	Study population was intensive care unit patients.
Reade 2009	Study population was intensive care unit patients.
Reade 2016	Study population was intensive care unit patients.
Sakong 2010	Compared two second generation antipsychotics (risperidone and aripiprazole) with no nonantipsychotic or placebo comparator
Skrobik 2014	Study population was intensive care unit patients.

Characteristics of studies awaiting assessment [ordered by study ID]

Djokic 2008

Methods	Randomised controlled trial to determine the efficiency of risperidone in the treatment of delirium superimposed on dementia
Participants	Study took place in a single hospital in Serbia. N = 120 subjects with mean age of 73.57 years, predominantly female (60.3%), with Alzheimer's disease (60%), dementia in Parkinson's disease (6%), vascular dementia (23%)
Interventions	Participants were randomly assigned to control group (haloperidol 1 to 4 mg/24h) or experimental group (risperidone 0.5 to 2 mg/24h) up to 28 days. Both groups were treated according to the underlying cause of delirium. All participants were assessed with The Memorial Delirium Assessment Scale (MDAS), MMSE, Brief agitation Rating Scale (BARS) and GCI scales daily
Outcomes	1. Change in MDAS scores (day 14, day 28), 2. Change in BARS scores (day 10, day 28), 3. CGI-I scores (day 28), 4. Mortality

Djokic 2008 (Continued)

Notes	Published in conference abstract form only. Unable to obtain further details from author to establish firm eligibility
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Jung Jin 2009

Methods	Randomised, open prospective study to compare intramuscular olanzapine and intramuscular haloperidol for patients with delirium
Participants	N = 62 hospitalised patients admitted to single hospital in South Korea. Patients were diagnosed as having delirium by two independent psychiatrists using DSM-IV-TR
Interventions	Intramuscular injection olanzapine and intramuscular injection of haloperidol. Details of dose and frequency not provided in the abstract
Outcomes	1. Delirium Rating Scale-revised-98 (DRS-R-98), 2. Clinical Global Impression-Severity (CGI-S), 3. Simpson-Angus Rating Scale, 4. Barnes Akathisia Rating Scale, 5. Abnormal Involuntary Movement Scale
Notes	Numeric results not reported. Published in conference abstract form only. Unable to obtain further details from author to establish firm eligibility

Lee 2013

Methods	Randomised trial comparing the efficacy and safety of aripiprazole and haloperidol in the treatment of delirium
Participants	N = 26 patients with delirium (Korean Version of Delirium Rating Scale-revised-98 (KDRS- 98)) 20 participants were analysed at the end.
Interventions	Aripiprazole or haloperidol. No information provided on the dose, titration, formulation, or duration of therapy
Outcomes	1. The Korean Version of Delirium Rating Scale-revised-98 (KDRS- 98) and Korean Version of Drug Induced Extrapyramidal Symptom Scale (DIEPSS-K) were assessed, 2. Blood samples were collected to analyse serum sodium ion concentration, plasma cortisol and prolactin level and pulse oximetry were used for measuring oxygen saturation. Time points of assessment not reported in the abstract
Notes	Numeric results not reported. Published in conference abstract form only. Unable to obtain further details from author to establish firm eligibility

Nakamura 1997

Methods	Open label randomised trial of haloperidol and mianserin in the treatment of delirium
Participants	Individuals undergoing neuropsychiatric referrals.
Interventions	Haloperidol: flexible dose of 2 to 6 mg/day per os at bed time. Mianserin: flexible dose of 10 to 60 mg/day per os at bed time

Nakamura 1997 (Continued)

Outcomes	1. Change in delirium severity, as measured by the DRS at baseline and study day 7, 2. Delirium resolution, defined as $\geq 50\%$ reduction in baseline DRS score
Notes	Published in full but unable to obtain further details from author to establish study population, exact number of individuals treated in each group, and delirium inclusion criteria

BARs=Brief Agitation Rating Scale

CGI-S = Clinical Global Impression - Severity Scale

CGI-I = Clinical Global Impression - Improvement Scale

DIEPSS-K = Korean Version of Drug Induced Extrapyramidal Symptom Scale

DRS = Delirium Rating Scale

DSM = Diagnostic and Statistical Manual of Mental Disorders

GCI =Clinical Global Impression

KDRS-98 = Korean Version of Delirium Rating Scale-revised-98

MDAS = Memorial Delirium Assessment Scale

MMSE = Mini Mental State Examination

Characteristics of ongoing studies [ordered by study ID]

NCT02345902

Trial name or title	Randomised double-blind clinical trial to compare haloperidol and nonpharmacologic treatment versus non-pharmacologic treatment and placebo, in elderly hospitalised patients with hypoactive delirium
Methods	Double-blind RCT of haloperidol versus placebo added to nonpharmacologic treatment for delirium
Participants	Study taking place in a single hospital in Mexico. Participants included hospitalised patients aged 70 years with delirium diagnosis according to the CAM or Delirium Observation Screening Scale (DOSS) and not taking any antipsychotics
Interventions	Haloperidol: 1.25 mg administered orally x 9 days. Placebo: matched placebo tablet, 1.25 mg administered orally x 9 days. Both groups will undergo nonpharmacologic delirium interventions: A. Reorientation (i.e. calendar, clocks, familiar objects), B. Glasses and hearing devices, where needed, C. Avoidance of physical restraints, D. Limitation of excessive personnel shifts or hospital room, E. A tranquil and comfortable environment, especially at night, to avoid interruptions (i.e. dim light, low levels of noise), F. Adequate schedules for medication administration and to take vital signs or medical procedures, G. Sleep hygiene (light in the room and movement during the day), H. Avoidance of dehydration, and I. Avoidance of medications use which are associated with delirium (e.g. psychoactive medications)
Outcomes	1. Change in delirium severity (via Delirium Observation Screening Scale), 2. Use of rescue haloperidol, 3. Duration of delirium, 4. Perceived stress (via Delirium Experience Questionnaire), 5. Incidence of PTSD (Mini International Neuropsychiatry Interview), 6. Cognitive impairment (via Montreal Cognitive Assessment), 7. Cerebral blood flow (via transcranial Doppler), 8. Adverse events (e.g. extrapyramidal symptoms, arrhythmias, QTc prolongation)

NCT02345902 (Continued)

Starting date	January 2016
Contact information	Dr. Maria Carmen Flores (mcflormir@gmail.com) and Dr. Sara Aguilar-Navarro (sgan30@hotmail.com)
Notes	Study sponsor: Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran. Estimated study completion: October 2018. Trial registration: https://clinicaltrials.gov/ct2/show/NCT02345902

CAM=ConfusionAssessmentMethod

DOSS = Delirium Observation Screening Scale

PTSD = Post Traumatic Stress Disorder

QTc = QT interval corrected for rate

DATA AND ANALYSES

Comparison 1. Severity of delirium

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Antipsychotic versus no antipsychotic	4	494	Std. Mean Difference (IV, Random, 95% CI)	-1.08 [-2.55, 0.39]
2 Sensitivity analysis (placebo-controlled studies only)	3	464	Std. Mean Difference (IV, Random, 95% CI)	-0.89 [-2.64, 0.86]
3 Sensitivity analysis (trials at low risk of bias)	2	289	Std. Mean Difference (IV, Random, 95% CI)	0.03 [-0.22, 0.27]
4 Typical versus atypical antipsychotic	7	542	Std. Mean Difference (IV, Random, 95% CI)	-0.17 [-0.37, 0.02]

Comparison 2. Resolution

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Antipsychotic versus no antipsychotic	3	247	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.30, 2.98]
2 Sensitivity analysis (including placebo studies)	2	217	Risk Ratio (M-H, Random, 95% CI)	1.43 [0.58, 3.54]
3 Resolution (atypical versus typical antipsychotic)	5	349	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.79, 1.52]

Comparison 3. Mortality

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality (antipsychotic versus no antipsychotic)	3	319	Risk Ratio (M-H, Random, 95% CI)	1.29 [0.73, 2.27]
2 Sensitivity analysis (including only placebo studies)	2	289	Risk Ratio (M-H, Random, 95% CI)	1.41 [0.75, 2.66]
3 Mortality (atypical versus typical antipsychotic)	4	342	Risk Ratio (M-H, Random, 95% CI)	1.71 [0.82, 3.53]

Comparison 4. Adverse Event

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Antipsychotic versus no antipsychotic (EPS)	3	247	Risk Ratio (M-H, Random, 95% CI)	1.70 [0.04, 65.57]
2 Typical versus atypical antipsychotic (EPS)	2	198	Risk Ratio (M-H, Random, 95% CI)	12.16 [0.55, 269.52]

WHAT'S NEW

Last assessed as up-to-date: 20 July 2017.

Date	Event	Description
20 July 2017	New citation required and conclusions have changed	New studies added and content extensively revised. Conclusions changed. Changes to author team and new lead author
20 July 2017	New search has been performed	Top-up searches were performed for this review in May 2011, July 2013, October 2015, November 2016 and July 20 2017. New studies were identified for inclusion in the review

HISTORY

Protocol first published: Issue 1, 2006

Review first published: Issue 2, 2007

Date	Event	Description
23 October 2008	Amended	Converted to new review format.
2 February 2007	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

LB and LR reviewed the search results.

SM, MMP, JSL, and CB extracted data for included studies.

LB, BH and DAF completed the analysis and generated the 'Summary of Findings' table and GRADE Evidence.

LB generated the first draft of the review.

NS acted as an independent arbiter for study exclusion, and verified 'risk of bias' assessments.

All authors interpreted the analysis and contributed to the write-up of the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Department of Pharmacy, Mount Sinai Hospital, Toronto, Canada.

External sources

- Canadian Frailty Network (Previously known as Technology Evaluation in the Elderly Network [TVN] (www.tvn-nce.ca)), Canada.

Funded by the Government of Canada through the Networks of Centres of Excellence (NCE), Technology Evaluation in the Elderly facilitates evidence-based research, knowledge sharing and clinical practices that improve healthcare outcomes for frail elderly Canadians, their families and caregivers.

- NIHR, UK.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- The original protocol has been modified to exclude critically ill patients as this population overlaps with the Cochrane Anaesthesia, Critical and Emergency Care Group's Protocol ACE311.

• Antipsychotics are the most commonly prescribed class of drug for the treatment of delirium in hospitalised patients. We felt it necessary to refine the original protocol's research question 'to compare the efficacy and incidence of adverse effects of haloperidol with risperidone, olanzapine, and quetiapine in the treatment of delirium' to instead explore the effects of antipsychotics versus alternative (i.e. nonantipsychotic drugs) or placebo on outcomes of hospitalised patients with delirium. We made the original primary question a secondary question.

- We included Health-related quality of life as an outcome and expanded upon the adverse events that we sought from the trials.
- The 'Summary of findings' table was generated in accordance with current Cochrane Collaboration Guidance utilising GRADE assessments.
- Authorship for this update has been changed to include new members and remove those no longer involved in the review.

INDEX TERMS

Medical Subject Headings (MeSH)

Antipsychotic Agents [adverse effects; *therapeutic use]; Benzodiazepines [adverse effects; therapeutic use]; Delirium [*drug therapy]; Haloperidol [adverse effects; therapeutic use]; Randomized Controlled Trials as Topic; Risperidone [adverse effects; therapeutic use]

MeSH check words

Adult; Female; Humans; Male