



Comparative Effectiveness Review
Number 219

Antipsychotics for the Prevention and Treatment of Delirium



Antipsychotics for the Prevention and Treatment of Delirium

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Key Messages

Purpose of Review

To assess the benefits and harms of antipsychotics for the prevention and treatment of delirium among adult patients.

Key Messages

- Haloperidol or second-generation antipsychotics used to prevent or treat delirium did not decrease length of stay in hospital.
- There was little or no evidence to determine the effect of antipsychotics on cognitive function, delirium severity, or caregiver burden, or for sedation when used for prevention.
- Second-generation antipsychotics may lower the occurrence of delirium in postoperative patients.
- Haloperidol or second-generation antipsychotics used to prevent or treat delirium may lead to little or no difference in sedation or extrapyramidal side effects (problems with muscles such as spasms or restlessness). Heart-related side effects tended to occur more frequently with the use of antipsychotics, in particular QT interval prolongation (a type of heart rhythm problem) in second-generation antipsychotics.
- Future studies are needed to assess the effects of using antipsychotics on patient agitation and distress, subsequent memories of delirium, caregiver burden and distress, inappropriate continuation of antipsychotic therapy, and long-term cognitive and functional outcomes.

This report is based on research conducted by the Johns Hopkins University Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-2015-00006-I-2). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

Two investigators were members of the guideline panel for a 2018 Society for Clinical Care Medicine guideline for the management of pain, sedation, delirium, rehabilitation, and sleep for critically ill patients. Two investigators co-authored the American Geriatric Society guidelines for post-operative delirium in older adults. None of the other investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

The information in this report is intended to help healthcare decision makers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of healthcare services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of healthcare in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new healthcare technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the healthcare system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the website (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input.

If you have comments on this systematic review, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

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Key Informants

In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than \$5,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

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In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

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Peer Reviewers must disclose any financial conflicts of interest greater than \$5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential nonfinancial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

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Antipsychotics for the Prevention and Treatment of Delirium

Structured Abstract

Objectives. To assess benefits and harms of antipsychotics for the prevention and treatment of delirium in adult patient populations.

Data sources. We searched PubMed[®], Embase[®], the Cochrane Central Register of Controlled Trials (CENTRAL), Cumulative Index to Nursing and Allied Health Literature (CINAHL[®]), and PsycINFO[®] through March 2019. We also hand-searched the reference lists of included articles, relevant reviews, and delirium-specific bibliographic repositories.

Review methods. We included randomized controlled trials (RCTs) of antipsychotics that evaluated benefits or harms, and also observational studies that reported harms. Two reviewers independently screened search results for eligibility, serially abstracted data, and independently assessed the risk of bias of the studies and graded the strength of evidence (SOE) for prespecified critical outcomes: delirium severity, cognitive functioning, length of stay in hospital, inappropriate continuation of antipsychotic drugs, falls, sedation, and caregiver burden/strain.

Results. We identified 14 RCTs and 1 observational study evaluating the use of antipsychotics in prevention of delirium. For the treatment of delirium, we identified 19 RCTs and 25 observational studies. Two RCTs were classified as both a prevention and treatment trial. In trials of the prevention of delirium across all populations, there was no difference in delirium incidence for haloperidol versus placebo (relative risk [RR], 0.94; 95% confidence interval [CI], 0.77 to 1.16). Second-generation antipsychotics, compared with placebo, may decrease delirium incidence in postoperative patients at risk for delirium (RR, 0.36; 95% CI, 0.26 to 0.50). Antipsychotics (both haloperidol and second-generation), compared to placebo, demonstrated no differences for length of stay in hospital (low SOE for second-generation antipsychotics and high SOE for haloperidol). We were unable to draw conclusions regarding the effect of antipsychotics on sedation, falls, and delirium severity (insufficient SOE). We found no studies evaluating cognitive functioning, inappropriate continuation of antipsychotic drugs, or caregiver burden/strain. For treatment of delirium, there was little to no difference in effect of haloperidol and second-generation antipsychotics compared with placebo for length of stay in hospital (moderate SOE) and sedation (low and moderate SOE, respectively) with insufficient or no evidence for cognitive functioning or delirium severity. Also, effects of second-generation antipsychotics were not significantly different compared with haloperidol for delirium severity (moderate SOE), cognitive functioning (low SOE), length of stay in hospital (moderate SOE), and sedation (moderate SOE). We found no studies reporting inappropriate continuation of antipsychotic drugs, falls, or caregiver burden/strain. We did not find statistically significant differences for haloperidol or second-generation antipsychotics in neurological harms, including extrapyramidal side effects and neuroleptic malignant syndrome. However, cardiac harms tended to occur more frequently with antipsychotics, specifically prolongation of QT interval with second-generation antipsychotics.

Conclusions. Haloperidol or second-generation antipsychotics, compared to placebo, used for the prevention or treatment of delirium did not improve length of stay in hospital. We found little or no evidence to determine the effect of antipsychotics on cognitive function, delirium severity, or caregiver burden. Second-generation antipsychotics may decrease delirium incidence in postoperative patients, but this evidence is limited and requires more study. We did not detect neurological harms associated with haloperidol or second-generation antipsychotics used for the prevention or treatment of delirium. However, cardiac effects tended to occur more frequently in those receiving antipsychotics. Future studies should include standardized, clinically meaningful measures of patient distress, subsequent memories of delirium, caregiver burden and distress, inappropriate continuation of antipsychotic therapy, and long-term cognitive and functional outcomes.

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Evidence Summary

Introduction

Background

Delirium is a syndrome characterized by an abrupt impairment in cognition, with a specific deficit in attention, that is associated with an underlying medical cause or causes.¹ Delirium is a common and important condition in all healthcare settings, but is particularly prevalent in older adults and patients with critical illness. Delirium is strongly associated with increased mortality and longer hospital stay, with an estimated cost of \$38 to \$152 billion annually for patients aged 70 years or older.² Additionally, delirium experienced during a hospitalization is strongly associated with new or worsening long-term cognitive impairment.³

Preventive and therapeutic interventions are needed to reduce the burden of delirium and associated long-term cognitive impairments. Currently, there are no medications approved by the U.S. Food and Drug Administration for the prevention and treatment of delirium. Antipsychotics, medications approved for use in psychotic conditions such as schizophrenia, are frequently used in patients with delirium or at risk of delirium despite the lack of clear evidence to support their use.⁴ Previous reviews of antipsychotics for delirium were inconclusive about benefit or harm owing to few studies, particularly in older adults and other susceptible patient populations, and heterogeneity of interventions.^{5,6} Chronic use of antipsychotics in management of conditions other than delirium has been shown to increase the risk of stroke and sudden death in older adults, and particularly those with dementia.⁷⁻⁹ Recently, increasing numbers of randomized controlled trials (RCTs) of antipsychotic medications have been conducted for the treatment or prevention of delirium. We conducted a systematic review of the benefits and harms of antipsychotics for the prevention and treatment of delirium.

Key Questions

We sought to address two Key Questions:

1. What are the benefits and harms of antipsychotics compared with each other, placebo, or non-drug approaches to **prevent** delirium?
2. What are the benefits and harms of antipsychotics compared with each other, placebo, or non-drug approaches to **treat** delirium?

For each Key Question, we first considered evidence about the overall population and then considered the following populations or settings:

- Persons aged 65 years or older
- Persons with dementia
- Patients in an intensive care unit
- Patients in a post-acute care facility
- Patients in palliative or hospice care
- Patients in postoperative care

Methods

We followed the methods outlined in the Agency for Healthcare Research and Quality's (AHRQ's) Methods Guide for Effectiveness and Comparative Effectiveness Reviews.¹⁰ Our protocol is posted on the AHRQ Effective Health Care Program's website (www.effectivehealthcare.ahrq.gov) and registered on PROSPERO (CRD42018109552). The searches were conducted in March 2019. Details of the methodology can be found in the full report.

Results

After screening abstracts and full-text, we included 57 studies (published in 62 articles). Of the eligible studies, 15 studies, including 14 RCTs and 1 observational study, addressed the prevention of delirium. Forty-four studies, including 19 RCTs and 25 observational studies or non-randomized trials, addressed the treatment of delirium. Two trials enrolled patients with and without delirium; we classified these as both a prevention and treatment trial for the purposes of this report.^{11, 12} The trials for prevention of delirium evaluated delirium incidence, length of hospital stay, sedation and severity, with most of the studies focused on postoperative or intensive care unit-based populations. The treatment trials primarily evaluated hospital length of stay and sedation effects, with most of the studies focused on inpatients, particularly those with critical illness. Evidence tables with details about the included studies are in the appendixes of the full report.

Antipsychotics for the Prevention of Delirium

Table A summarizes the evidence for the use of antipsychotics for the prevention of delirium. The critical outcomes for the prevention of delirium in adults at risk for delirium included: cognitive functioning, delirium severity, length of stay in the hospital, inappropriate continuation of antipsychotic medication once initiated, and sedation. Critical outcomes varied by patient group and are listed in Table A.

In the prevention of delirium across all populations, haloperidol made little to no difference on delirium incidence compared with placebo (relative risk [RR], 0.94; 95% confidence interval [CI], 0.77 to 1.16) or length of hospital stay (high strength of evidence); there was insufficient evidence to determine the effect of haloperidol versus placebo on delirium severity, sedation, or cognitive outcomes. Second-generation antipsychotics decreased the incidence of delirium compared with placebo in patients at risk of delirium (RR, 0.36; 95% CI, 0.26 to 0.50); the studies included in this meta-analysis included postoperative patients only. However there was no effect on the length of hospital stay (low strength of evidence) and insufficient evidence to determine the impact on the severity of delirium for second-generation antipsychotics versus placebo. We were unable to draw conclusions for any type of drug-drug comparisons between second-generation antipsychotics or comparisons to any other types of therapies (i.e., other than antipsychotics) due to the absence or insufficiency of evidence.

We also examined different populations at risk of delirium. There was insufficient evidence to determine the impact of haloperidol or second-generation antipsychotics on delirium severity, sedation, or falls in patients 65 years of age and older. Haloperidol used in patients at risk for delirium in the intensive care unit had little to no effect on length of stay in hospital (high strength of evidence). We found insufficient or no evidence for haloperidol or second-generation antipsychotics on cognitive functioning, delirium severity, inappropriate continuation, or

sedation for patients at risk of delirium in the intensive care unit. Haloperidol or second-generation antipsychotics for the prevention of delirium in postoperative patients had little to no effect on the hospital length of stay for second-generation agents (low strength of evidence) and insufficient or no evidence for the other critical outcomes. We found no evidence for antipsychotics in patients at risk for delirium with dementia, those in a post-acute care facility, and among patients in palliative or hospice care.

Antipsychotics for the Treatment of Delirium

Table B summarizes the effects of antipsychotics used for the treatment of delirium. The critical outcomes for the treatment of delirium in adults with delirium included: cognitive functioning, delirium severity, length of stay in the hospital, inappropriate continuation of antipsychotic medication once initiated, and sedation. Critical outcomes by patient group are listed in Table B.

Haloperidol or second-generation antipsychotics for the treatment of delirium had little or similar effect on hospital length of stay (moderate strength of evidence) or sedation (low strength of evidence for haloperidol and moderate strength of evidence for second-generation antipsychotics; RR, 1.10; 95% CI, 0.78 to 1.53) compared with placebo. In comparing haloperidol with second-generation antipsychotics, there were no clinically meaningful differences for cognitive functioning (low strength of evidence), and delirium severity (e.g., mean between-group difference in Delirium Rating Scale-R-98 scores, -0.03; 95% CI, -2.04 to 1.98), length of stay in hospital, and sedation (all moderate strength of evidence; RR, 1.26; 95% CI, 0.92 to 1.72). We were unable to draw conclusions for any type of drug-drug comparisons between second-generation antipsychotics or comparisons with any other types of therapies (i.e., other than antipsychotics) due to the absence of studies or insufficient evidence.

Antipsychotics compared with placebo or head-to-head trials in patients in intensive care unit settings showed no or similar effect on length of stay in hospital (moderate strength of evidence) or sedation (moderate strength of evidence). Patients being treated with haloperidol or second-generation antipsychotics compared with those who received placebo in palliative care or hospice settings may have slightly less improvement in delirium severity over time (low strength of evidence). We found no or insufficient evidence for the effects of antipsychotics to treat delirium among patients aged 65 years or older, those with dementia, among patients in a post-acute care facility, and among patients in postoperative care.

Table A. Summary of the strength of evidence and conclusion for the effects of antipsychotics used for the prevention of delirium on critical outcomes among adults at risk for delirium

Critical Outcome	Populations Assessed*	Haloperidol Versus Placebo	Second-Generation Antipsychotics Versus Placebo	Haloperidol Versus Second-Generation Antipsychotics	Second-Generation Antipsychotics Versus Second-Generation Antipsychotics	Haloperidol Versus Other Therapies	Second-Generation Antipsychotics Versus Other Therapies
Cognitive functioning	Overall						
	Aged ≥ 65 yrs						
	Critically ill						
	Postoperative						
Delirium severity	Overall	Insufficient	Insufficient				
	Aged ≥ 65 yrs	Insufficient	Insufficient				
	Critically ill	Insufficient					
	Postoperative	Insufficient	Insufficient				
Falls	Aged ≥ 65 yrs	Insufficient					
Length of stay in hospital	Overall	High; =	Low; =	Insufficient		Insufficient	
	Critically ill	High; =	Insufficient	Insufficient		Insufficient	
	Postoperative	Insufficient	Low; =				
Inappropriate continuation of antipsychotic medication	Overall						
	Aged ≥ 65 yrs						
	Critically ill						
	Postoperative						
Sedation	Overall	Insufficient					
	Aged ≥ 65 yrs	Insufficient					
	Critically ill	Insufficient					

Blank cells indicate no evidence.

Conclusion: = we concluded that there was little to no difference between interventions; + favors the intervention over control; - favors the control over the intervention

Strength of evidence: Insufficient = the body of evidence has unacceptable deficiencies, precluding a conclusion; Low = low confidence that the evidence reflects the true effect and further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate; Moderate = indicating moderate confidence that the evidence reflects the true effect but further research could change our confidence in the estimate of the effect and may change the estimate; High = high confidence that the evidence reflects the true effect and further research is very unlikely to change our confidence in the estimate of the effect

* We did not find any evidence for the critical outcomes among the following populations at risk for delirium: persons with dementia, patients in a postacute care facility, and patients in palliative or hospice care.

Table B. Summary of the strength of evidence and conclusion for the effects of antipsychotics used for the treatment of delirium on critical outcomes among adults with delirium

Critical Outcome	Populations Assessed*	Haloperidol Versus Placebo	Second-Generation Antipsychotics Versus Placebo	Haloperidol Versus Second-Generation Antipsychotics	Second-Generation Antipsychotics Versus Second-Generation Antipsychotics	Haloperidol Versus Other Therapies	Second-Generation Antipsychotics Versus Other Therapies
Cognitive functioning	Overall		Insufficient	Low; =	Insufficient	Insufficient	
	Critically ill						
Delirium severity	Overall	Insufficient	Insufficient	Moderate; =	Insufficient	Insufficient	
	Critically ill						
	Palliative	Low; -	Low; -	Insufficient			
Caregiver burden/strain	Palliative						
Length of stay in hospital	Overall	Moderate; =	Moderate; =	Moderate; =		Insufficient	
	Critically ill	Moderate; =	Moderate; =	Moderate; =			
Inappropriate continuation of antipsychotic medication	Overall						
	Critically ill						
Sedation	Overall	Low; =	Moderate; =	Moderate; =	Insufficient		
	Critically ill	Moderate; =	Moderate; =	Moderate; =			
	Palliative						

Blank cells indicate no evidence.

Conclusion: = we concluded that there was little to no difference between interventions; + favors the intervention over control; - favors the control over the intervention
 Strength of evidence: Insufficient = the body of evidence has unacceptable deficiencies, precluding a conclusion; Low = low confidence that the evidence reflects the true effect and further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate; Moderate = indicating moderate confidence that the evidence reflects the true effect but further research could change our confidence in the estimate of the effect and may change the estimate; High = high confidence that the evidence reflects the true effect and further research is very unlikely to change our confidence in the estimate of the effect

* We did not find any evidence for the critical outcomes among the following populations with delirium: persons aged 65 years and older, persons with dementia, patients in a post-acute care facility, patients in palliative or hospice care, and patients in post-operative care.

Adverse Effects

We evaluated cardiac and neurological harms. Most or all of the studies assessing cardiac effects included critically ill patients who may be at a higher risk of cardiac events compared to other patient populations. In all RCTs and observational studies evaluating haloperidol versus placebo, second-generation antipsychotics versus placebo, haloperidol versus second-generation antipsychotics, and second-generation antipsychotics versus second-generation antipsychotics, there were no statistically significant differences in the occurrence of any of types of cardiac effects reported. However, potentially important cardiac effects cannot be excluded since these tended to occur more frequently with antipsychotics.

Studies that reported neurological harms included critically ill patients who may be at a higher risk of neurological events compared to other patient populations. Extrapyramidal symptoms were the most commonly monitored neurological adverse effect. Apart from a single RCT in patients receiving palliative care which reported a statistically significant increase in extrapyramidal symptoms for both haloperidol compared with placebo and for second-generation antipsychotics compared with placebo, the larger body of evidence in all other patient populations, found no statistically significant increase in any neurological effect for any first- or second-generation antipsychotic compared with placebo or in other head-to-head trials.

Discussion

Second-generation antipsychotics may lower the incidence of delirium in postoperative patients at risk of delirium, but the evidence is limited and requires further study. For those being treated for delirium in palliative care or hospice settings, haloperidol or second-generation antipsychotics may have slightly less improvement in delirium severity than those treated with placebo. However, for all other antipsychotics and outcomes, we found little to no effect or there was not enough evidence to determine the effect.

The greatest challenge to the applicability of this body of evidence is related to the populations and outcomes studied. Trials were often conducted in medical and surgical critically ill patients. The overall results of this report may not be directly applicable to other populations, including postoperative patients, older inpatients, and patients with dementia. Critically ill patients may have differing pathophysiological etiologies of delirium compared with other populations, as well as more severe physiological and metabolic derangements. Any benefit and risk of antipsychotics for prevention or treatment of delirium within the context of critical illness may not be generalizable to other populations, such as those with dementia, in postacute care, or in palliative care.

For the vast majority of outcomes predetermined to be of critical importance by our panel of experts and key informants, studies did not exist or were inadequate in design or number to answer the key questions. There was insufficient or no evidence for many comparisons and outcomes due to the paucity of studies. For instance, there was insufficient evidence comparing haloperidol with second-generation antipsychotics and for drug-drug comparisons within the class of second-generation antipsychotics. Poor reporting meant that the risk of bias was frequently unclear, especially regarding sequence generation and allocation concealment for the RCTs.

Moreover, there was also frequent unclear risk of bias related to missing outcome data and selective outcome reporting. There was inconsistency in measurement instruments used and approaches to statistical analysis and reporting, even in evaluating the same outcome domain,

such as delirium severity. Many studies were underpowered, with insufficient duration to adequately assess longer-term clinical outcomes, particularly related to cognitive impairment - a well-known sequela of delirium. Finally, study designs were fairly heterogeneous, using different dosing routes, and a range of doses and frequencies of different antipsychotic agents. Combining heterogeneous treatment and prevention approaches may bias the findings toward the null hypothesis. So too, combining a range of dosing exposures may obscure adverse outcomes, associated with higher doses of medications.

Future studies evaluating pharmacologic prevention and treatment strategies should examine patient groups that are anticipated to have similarity with respect to their delirium risk factor(s) and associated pathophysiology given that these factors may affect response to therapy. Research focused on more homogeneous patient groups is needed. This applies to postoperative patient populations where larger well-controlled trials of second-generation antipsychotics in the prevention of delirium are needed to clarify whether there is any beneficial role for the perioperative setting.

Heterogeneity of outcome domains and measurement instruments emphasize the need for greater standardization. Such standardization would assist with comparison, synthesis and meta-analysis of studies and reduce omission of critical outcomes in future trials in an effort to reduce research waste. In particular, careful identification of the outcomes of greatest importance to clinicians, patients/caregivers and researchers will advance future research. The field would benefit from the development of standardized, clinically meaningful measures of the following outcomes: patient agitation and distress, subsequent memories of delirium, caregiver burden and distress, inappropriate continuation of antipsychotic therapy, and long-term cognitive and functional outcomes.

A striking finding resulting from this review was the lack of investigation of many important patient and care-giver centered outcomes in the study of delirium prevention and treatment. Much more research is needed to study questions such as the comparison between the pharmacologic and non-pharmacologic approaches, quality of life outcomes and best treatment approaches in populations of patients such as those with pre-existing dementia. Studies answering these questions will have important implications for policy and treatment recommendations for patients within our healthcare system.

Conclusions

Haloperidol or second-generation antipsychotics, compared with placebo, used for the prevention or treatment of delirium did not improve clinically important outcomes. In postoperative patients, second-generation antipsychotics may decrease delirium incidence. We did not detect neurological harms associated with haloperidol or second-generation antipsychotics used for the prevention or treatment of delirium, but cardiac effects tended to occur more frequently in antipsychotics compared with placebo. Future studies should include standardized, clinically meaningful measures of patient agitation and distress, subsequent memories of delirium, caregiver burden and distress, inappropriate continuation of antipsychotic therapy, and long-term cognitive and functional outcomes.

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Introduction

Background

Delirium is a syndrome characterized by an abrupt impairment in cognition, with a specific deficit in attention, that is associated with an underlying medical cause or causes.¹ Delirium is a common condition in all healthcare settings, but it is particularly prevalent in older adults and in patients with critical illness. Advanced age is an independent risk factor for delirium,² with a prevalence of over 70 percent in critically ill patients aged 60 years and older.^{3,4} Delirium is strongly associated with increased mortality and longer hospital stays, with an estimated cost of \$38 to \$152 billion U.S. dollars annually for patients aged 70 years and older.⁵

Delirium experienced during a hospitalization is associated with new or worsening long-term cognitive impairment. A large, multi-site prospective study of critically ill patients in the United States found that, among 12-month survivors, about 25 percent had cognitive test scores similar to patients with mild Alzheimer's disease.⁶ A 2018 systematic review reported that delirium duration is the modifiable factor most strongly associated with long-term cognitive impairment after critical illness.⁷ These findings are consistent with community-based epidemiological studies of older adults, demonstrating that delirium is significantly associated with incident dementia (odds ratio [OR], 8.7) in those without pre-existing cognitive impairment,⁸ with accelerated cognitive decline⁹ in those with pre-existing dementia, and with worsening dementia severity (OR, 3.1) and global function (OR, 2.8).

Preventive and therapeutic interventions are needed to reduce the burden of delirium and associated long-term cognitive impairments. Currently, there are no medications approved by the U.S. Food and Drug Administration for the prevention and treatment of delirium. Antipsychotics, medications approved for use in patients with psychotic disorders such as schizophrenia, are frequently used in patients with delirium or those at risk for delirium despite the lack of clear evidence to support their use.¹⁰ First-generation antipsychotic medications, including haloperidol, were developed as early as the 1950s and are associated with more neurologic (also referred to as extrapyramidal) symptoms. Second-generation antipsychotics developed in the 1980s are thought to have fewer neurologic symptoms because of novel mechanisms of actions in the brain.¹¹ Table 1 lists the antipsychotic agents by drug class. Previous reviews of antipsychotics for delirium were inconclusive about benefit or harm owing to few studies, particularly in older adults and other susceptible patient populations, and heterogeneity of interventions.^{12,13} Chronic use of antipsychotics in management of conditions other than delirium is associated with increased risk of stroke and sudden death in older adults - particularly those with dementia.¹⁴⁻¹⁶ Recently completed randomized controlled trials of antipsychotic medications for the treatment and prevention of delirium are not included in these previous reviews.

Table 1. Antipsychotic agents

Class	Antipsychotic
First-generation antipsychotic	<ul style="list-style-type: none">• Chlorpromazine• Droperidol• Fluphenazine• Haloperidol• Loxapine• Molindone• Perphenazine• Pimozide• Prochlorperazine• Thiothixene• Thioridazine• Trifluoperazine
Second-generation antipsychotic	<ul style="list-style-type: none">• Aripiprazole• Asenapine• Brexpiprazole• Cariprazine• Clozapine• Iloperidone• Lurasidone• Olanzapine• Paliperidone• Quetiapine• Risperidone• Ziprasidone

We conducted a systematic review of the benefits and harms of antipsychotics for the prevention and treatment of delirium.

Scope and Key Questions

Key Questions

Key Question 1. What are the benefits and harms of antipsychotics compared with each other, placebo, or non-drug approaches to **prevent** delirium?

- a. What are the benefits and harms of antipsychotics compared with each other, placebo, or non-drug approaches to **prevent** delirium in **persons aged 65 years and older**?
- b. What are the benefits and harms of antipsychotics compared with each other, placebo, or non-drug approaches to **prevent** delirium in **persons with dementia**?
- c. What are the benefits and harms of antipsychotics compared with each other, placebo, or non-drug approaches to **prevent** delirium in **patients in an intensive care unit**?

- d. What are the benefits and harms of antipsychotics compared with each other, placebo, or non-drug approaches to **prevent** delirium in **patients in a post-acute care facility**?
- e. What are the benefits and harms of antipsychotics compared with each other, placebo, or non-drug approaches to **prevent** delirium in **patients in palliative or hospice care**?
- f. What are the benefits and harms of antipsychotics compared with each other, placebo, or non-drug approaches to **prevent** delirium in **patients in postoperative care**?

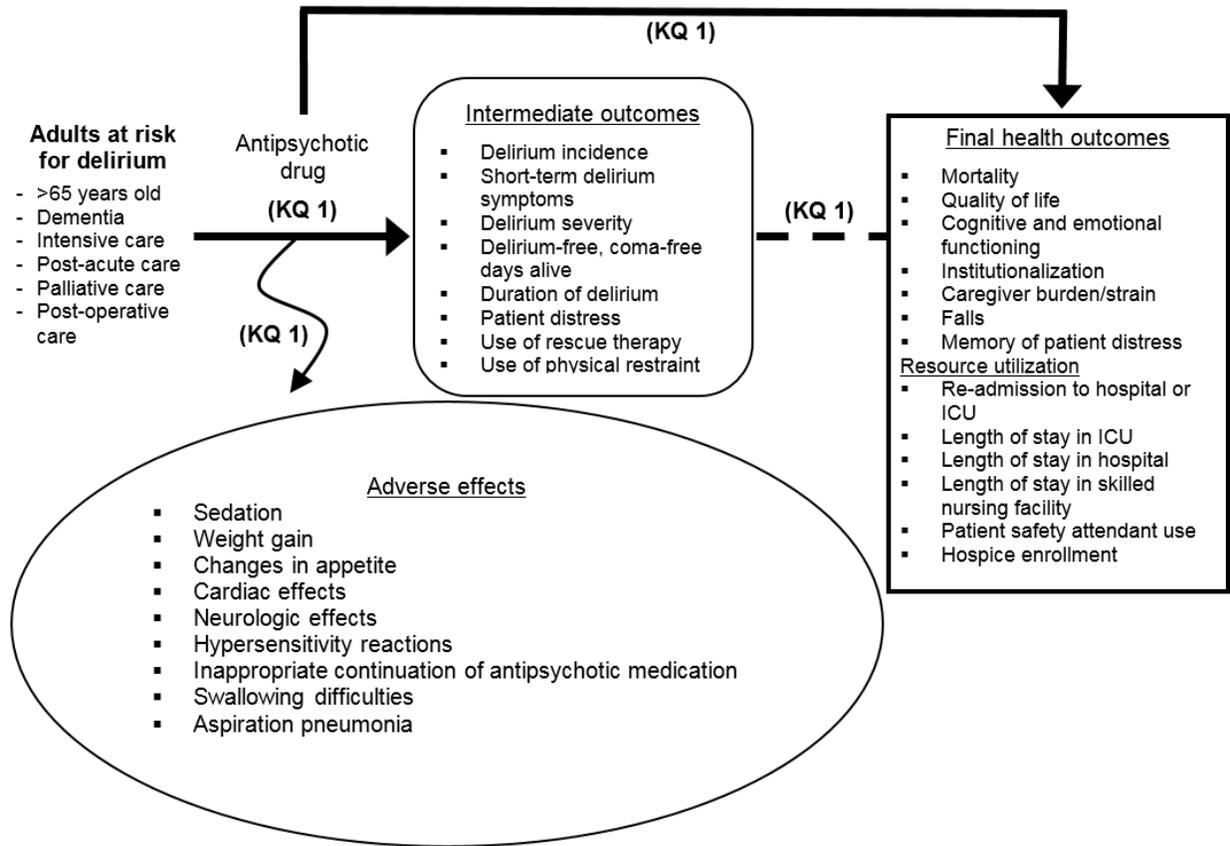
Key Question 2. What are the benefits and harms of antipsychotics compared with each other, placebo, or non-drug approaches to **treat** delirium?

- a. What are the benefits and harms of antipsychotics compared with each other, placebo, or non-drug approaches to **treat** delirium in **persons aged 65 years and older**?
- b. What are the benefits and harms of antipsychotics compared with each other, placebo, or non-drug approaches to **treat** delirium in **persons with dementia**?
- c. What are the benefits and harms of antipsychotics compared with each other, placebo, or non-drug approaches to **treat** delirium in **patients in an intensive care unit**?
- d. What are the benefits and harms of antipsychotics compared with each other, placebo, or non-drug approaches to **treat** delirium in **patients in a post-acute care facility**?
- e. What are the benefits and harms of antipsychotics compared with each other, placebo, or non-drug approaches to **treat** delirium in **patients in palliative or hospice care**?
- f. What are the benefits and harms of antipsychotics compared with each other, placebo, or non-drug approaches to **treat** delirium in **patients in postoperative care**?

Analytic Framework

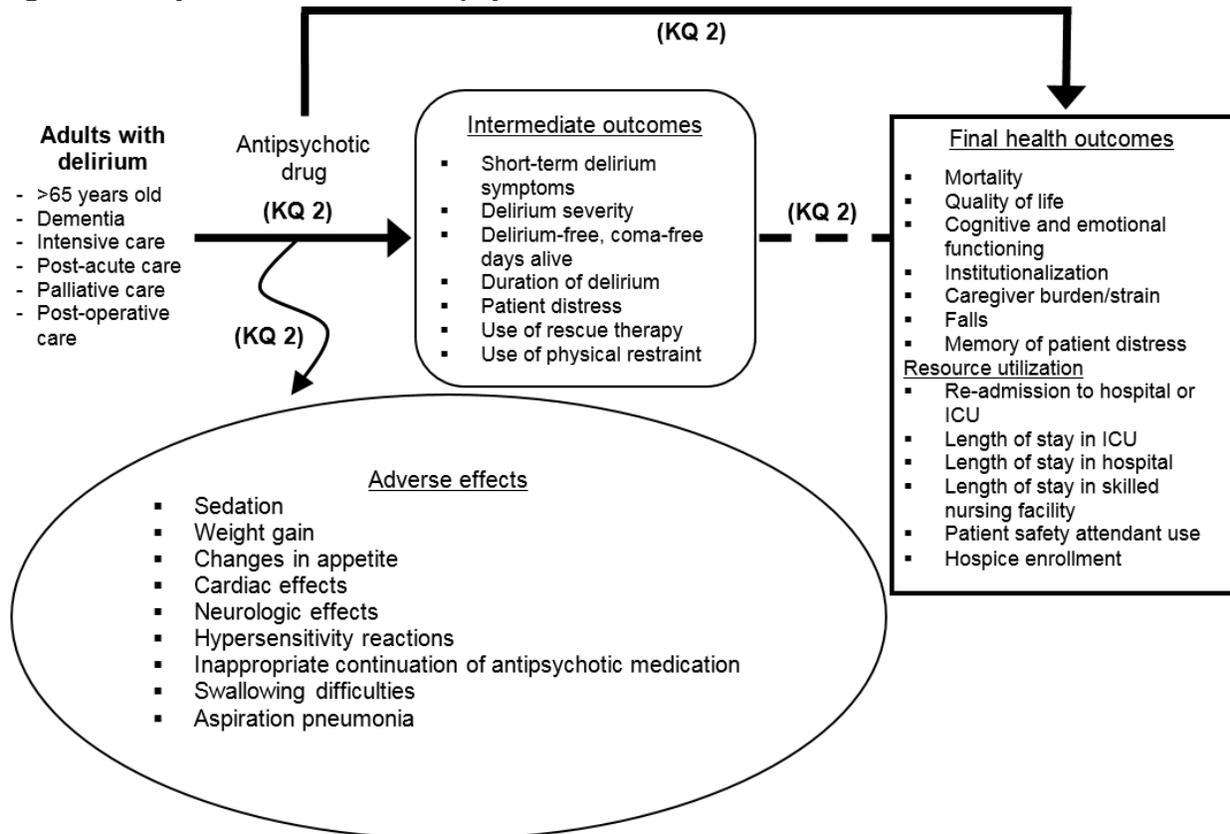
Figures 1 and 2 graphically display the Key Questions.

Figure 1. Analytic framework for antipsychotics for delirium prevention



ICU = intensive care unit; KQ = Key Question

Figure 2. Analytic framework for antipsychotics for delirium treatment



ICU = intensive care unit; KQ = Key Question

Methods

We followed the methods outlined in the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews.¹⁷

Topic Refinement and Protocol Development

A professional society nominated the topic for the review and the scope was initially developed by the Scientific Resource Center for AHRQ's Effective Health Care Program. Preliminary Key Questions were posted on AHRQ's website for public comment.

We further refined the Key Questions with input from Key Informants, representatives from AHRQ, representatives from the nominating partner, and from public comments. Key Informants included patient advocates; representatives from rehabilitation, nursing, geriatrics and palliative care, critical care, pharmacy; and representatives from government agencies.

We recruited a Technical Expert Panel (TEP) to review a draft of the protocol. The TEP included representatives from critical care, geriatrics and palliative care, internal medicine, pharmacy, psychology, and nursing. With the feedback from the TEP and the AHRQ and professional society representatives, we finalized the protocol and posted it on the AHRQ Effective Health Care Program's website (www.effectivehealthcare.ahrq.gov). We also registered the protocol on PROSPERO (CRD42018109552).

Literature Search Strategy

Search Strategy

We searched the following databases for primary studies through March 2019: PubMed[®], Embase[®], the Cochrane Central Register of Controlled Trials (CENTRAL), Cumulative Index to Nursing and Allied Health Literature (CINAHL[®]), and PsycINFO[®]. We developed a search strategy for PubMed based on an analysis of medical subject headings (MeSH[®]) and text words from eligible primary studies identified a priori (Appendix A). Our search was peer reviewed by a medical librarian with experience in developing literature searches in the field of delirium. We handsearched the reference lists of included articles and relevant reviews. We also handsearched the references included in several delirium-specific bibliographic repositories.¹⁸⁻²⁰ We will update the search during the peer review process.

We conducted grey literature searches of ClinicalTrials.gov to identify data and studies not reported in the published literature, to assess for publication and reporting bias, and to inform future research needs. Studies identified through grey literature searches were considered for inclusion in the review under two conditions: 1) they were a source of a unique study that met inclusion criteria and provided enough methodologic detail to assess risk of bias, or 2) they were matched to an original publication that had been included in the review when the abstract or presentation reported data on an outcome that was not reported in the original publication. The team searched ClinicalTrials.gov to identify any relevant registered trials. We will update the ClinicalTrials.gov literature search during the peer review process. We reviewed any material that was submitted through the Supplemental Evidence and Data for Systematic Reviews (SEADS) portal and the Federal Register.

Inclusion and Exclusion Criteria

Table 2 lists our inclusion and exclusion criteria using the PICOTS (Population, Intervention, Comparison, Outcomes, Timing, Setting and Study) design framework.

Table 2. Inclusion and exclusion criteria

PICOTS	Inclusion Criteria	Exclusion Criteria
Population	<ul style="list-style-type: none"> • KQ 1: adults who are at risk of delirium • KQ 2: adults with delirium 	<ul style="list-style-type: none"> • KQ 2: studies that did not use a validated instrument to diagnose delirium²¹ • Studies of children
Intervention	<ul style="list-style-type: none"> • Studies that evaluated an antipsychotic drug, including: <ul style="list-style-type: none"> ○ Any first-generation agent (chlorpromazine, droperidol, fluphenazine, haloperidol, loxapine, molindone, perphenazine, pimozide, prochlorperazine, thiothixene, thioridazine, trifluoperazine) ○ Any second-generation agent (aripiprazole, asenapine, brexpiprazole, cariprazine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone) 	<ul style="list-style-type: none"> • Studies in which the effects of the antipsychotic drugs cannot be isolated
Comparison	<ul style="list-style-type: none"> • KQ 1: non-drug approaches to preventing delirium, including placebo, active control, and usual care • KQ 2: non-drug approaches to treating delirium, including placebo, active control, and usual care 	<ul style="list-style-type: none"> • Studies that do not have a comparison group for outcomes other than adverse events
Outcomes	<ul style="list-style-type: none"> • Studies addressing the following outcomes: <ul style="list-style-type: none"> • Intermediate outcomes (delirium incidence, short-term delirium symptoms*; delirium severity; delirium-free, coma-free days alive; duration of delirium; patient distress; use of rescue therapy; use of physical restraint) • Final health or patient-centered outcomes (mortality; quality of life; cognitive and emotional functioning; long-term cognitive impairment; institutionalization; caregiver burden/strain; falls; memory of patient distress) • Resource utilization (readmission to the hospital or ICU; length of stay in ICU; length of stay in hospital; length of stay in skilled nursing facility; patient safety attendant use; hospice enrollment) • Adverse effects (sedation; weight gain; changes in appetite; cardiac effects; neurologic effects; paradoxical reactions; hypersensitivity reactions; inappropriate continuation of antipsychotics; swallowing difficulties; aspiration pneumonia) 	
Timing and setting	<ul style="list-style-type: none"> • Studies of any length of followup 	
Type of study	<ul style="list-style-type: none"> • RCTs for all outcomes except adverse events • RCTs, non-RCTs, and prospective cohort studies with and without a comparison group for adverse events • Studies in any language 	<ul style="list-style-type: none"> • Studies with no original data • Meeting abstracts

ICU = intensive care unit; KQ = Key Question; PICOTS = population, intervention, comparison, outcomes, timing and setting, and type of study; RCT = randomized controlled trial

* For short-term delirium symptoms, we considered agitation and/or increased psychomotor activity, sleep-wake cycle disturbances, and delusions.

Process for Study Selection

Two reviewers independently screened each abstract. Both reviewers needed to agree that an article met at least one of the exclusion criteria to be excluded (see Table 2 for inclusion/exclusion criteria). We tracked and resolved differences between reviewers through consensus adjudication. Articles promoted on the basis of the abstract screen underwent another screen using the same process.

Data Extraction and Data Management

We created and pilot tested standardized forms for data extraction (Appendix B). Each article underwent double review by the study investigators for data abstraction. The second reviewer confirmed the first reviewer's abstracted data for completeness and accuracy. Reviewer pairs were formed to include personnel with both clinical and methodological expertise.

For all articles, the reviewers extracted information on general study characteristics (e.g., study design, study period, and followup); study participants (e.g., population, age, sex, presence of dementia, setting, presence of substance use, presence of hypertension); interventions (e.g., dose, administration, frequency of use, and duration of use); comparisons; the method of ascertainment of outcomes; and the outcome results, including measures of variability. Non-drug interventions were categorized following the scheme developed by Oh and colleagues.²² We contacted the authors of the included studies for additional data, if necessary.

All information from the article review process was entered into a DistillerSR database (Evidence Partners Inc., Ottawa, Canada) by the first reviewer. We used the DistillerSR database to maintain the data and to create detailed evidence tables and summary tables.

Risk of Bias Assessment

Two reviewers independently assessed risk of bias for each study. For randomized controlled trials (RCTs), we used the Cochrane Risk of Bias Tool.²³ For observational studies, we used the Cochrane Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) tool.²⁴ We resolved differences between reviewers through consensus. We judged the overall risk of bias for each study based on the adjudicated ratings for the individual risk of bias items. RCTs had three overall ratings for risk of bias (low, high, and unclear) and observational studies had five overall ratings (low, moderate, serious, critical, and no information).

Data Synthesis

We organized the report by Key Question and, then, by outcome. We conducted qualitative synthesis for each Key Question. We created detailed evidence tables containing all information extracted from eligible studies. We conducted meta-analyses when there were sufficient data (i.e., at least three studies) and studies were sufficiently homogenous with respect to key variables (e.g., population characteristics, study duration, treatment, and outcome definition). We decided as a team what could be pooled in a meta-analysis. For the subquestion regarding persons aged 65 years and older, we included any study in which at least 50 percent of the population was aged 65 years and older.

Although the drugs may have different mechanisms of action, we anticipated that most drugs within a class would have similar clinical effects. Therefore, we combined studies of unique medications within classes when reporting outcomes. If we saw substantial statistical heterogeneity ($I^2 > 50\%$) in pooled estimates for any outcome, we explored whether this

was a result of pooling studies of unique medications. We then stratified studies by medication and repeated the pooled analyses and measures of heterogeneity. We also conducted sensitivity analyses by omitting one study at a time to assess the influence of any single study on the pooled estimates.

For continuous outcomes, we calculated a mean difference by using a random-effects model with the DerSimonian and Laird formula in settings of low heterogeneity²⁵ or with appropriate analyses when there is higher heterogeneity.²⁶ Because methods to transform medians where there are skewed data can under- and over-estimate the true effect in a meta-analysis, we decided not to conduct meta-analysis in these circumstances (e.g., for length of stay in hospital).²⁷ For dichotomous outcomes, we calculated a pooled effect estimate of the relative risk between the trial arms of RCTs, with each study weighted by the inverse variance, by using a random-effects model with the DerSimonian and Laird formula for calculating between-study variance in settings of low heterogeneity²⁵ or with appropriate analyses when there is higher heterogeneity.²⁶

For the outcome of delirium severity, we used a crosswalk^{28, 29} to convert the scores for the Memorial Delirium Assessment Scale (MDAS) or the Confusion Assessment Method-Severity (CAM-S) to the Delirium Rating Scale-Revised-98 (DRS-R-98).

We planned to examine publication bias using Begg's test and Egger's test, including evaluation of the asymmetry of funnel plots for each comparison of interest for the outcomes for which meta-analyses were conducted and there were at least 10 studies.^{30, 31} Publication bias was also qualitatively considered as part of the strength of evidence determination.

We used STATA statistical software (Intercooled, version 12.1, StataCorp, College Station, TX) for all meta-analyses.

We qualitatively summarized studies that were not amenable to pooling.

Grading the Body of Evidence for Each Key Question

We graded the strength of evidence using the grading scheme recommended by the Guide for Conducting Comparative Effectiveness Reviews.³² We applied evidence grades to the bodies of evidence about each comparison for each critical outcome.

Critical outcomes were determined a priori and separately for each subpopulation. We asked the Key Informants and the Technical Experts to select the five most important outcomes for each of the patient subpopulations, with at least one outcome being a potential adverse effect. We defined importance as those outcomes that have the greatest relevance to decision-making about the use of antipsychotics for the prevention or treatment of delirium in the specific patient group. Table 3 lists the outcomes that were considered critical for each subpopulation.

We assessed the study limitations, consistency, directness, precision, and reporting bias. When scoring study limitations, we considered how well the study design and the study methods (using risk of bias assessments) protected against bias. We classified evidence into four categories: (1) "high" grade (indicating high confidence that the evidence reflects the true effect and further research is very unlikely to change our confidence in the estimate of the effect); (2) "moderate" grade (indicating moderate confidence that the evidence reflects the true effect but further research could change our confidence in the estimate of the effect and may change the estimate); (3) "low" grade (indicating low confidence that the evidence reflects the true effect and further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate); and (4) "insufficient" grade (indicating evidence is unavailable or the body of evidence has unacceptable deficiencies, precluding a conclusion).

Table 3. Critical outcomes for each subpopulation

Subpopulation	Critical Outcomes
Overall	<ul style="list-style-type: none"> • Cognitive functioning • Delirium severity • Length of stay in hospital • Inappropriate continuation of antipsychotics • Sedation
Persons aged 65 years and older	<ul style="list-style-type: none"> • Cognitive functioning • Delirium severity • Falls • Inappropriate continuation of antipsychotics • Sedation
Persons with dementia	<ul style="list-style-type: none"> • Cognitive functioning • Caregiver burden/strain • Length of stay in hospital • Inappropriate continuation of antipsychotics
Patients in an intensive care unit	<ul style="list-style-type: none"> • Cognitive functioning • Delirium severity • Length of stay in hospital • Inappropriate continuation of antipsychotics • Sedation
Patients in a post-acute care facility	<ul style="list-style-type: none"> • Cognitive functioning • Falls • Length of stay in hospital • Sedation
Patients in palliative or hospice care	<ul style="list-style-type: none"> • Caregiver burden/strain • Delirium severity • Sedation
Patients in post-operative care	<ul style="list-style-type: none"> • Cognitive functioning • Delirium severity • Length of stay in hospital • Inappropriate continuation of antipsychotics

Peer Review and Public Commentary

Experts in the fields of critical care, geriatrics, hospital medicine, nursing, palliative care, pharmacy, psychology, and surgery and individuals representing stakeholder and user communities were invited to provide external peer review of this systematic review; AHRQ and an associate editor also provided comments. The draft report was posted on the AHRQ website for 4 weeks to elicit public comment. We addressed all reviewer comments, revising the text as appropriate, and documented everything in a disposition of comments report that will be made available 3 months after the Agency posts the final systematic review on the Effective Health Care website.

Results

Search Results

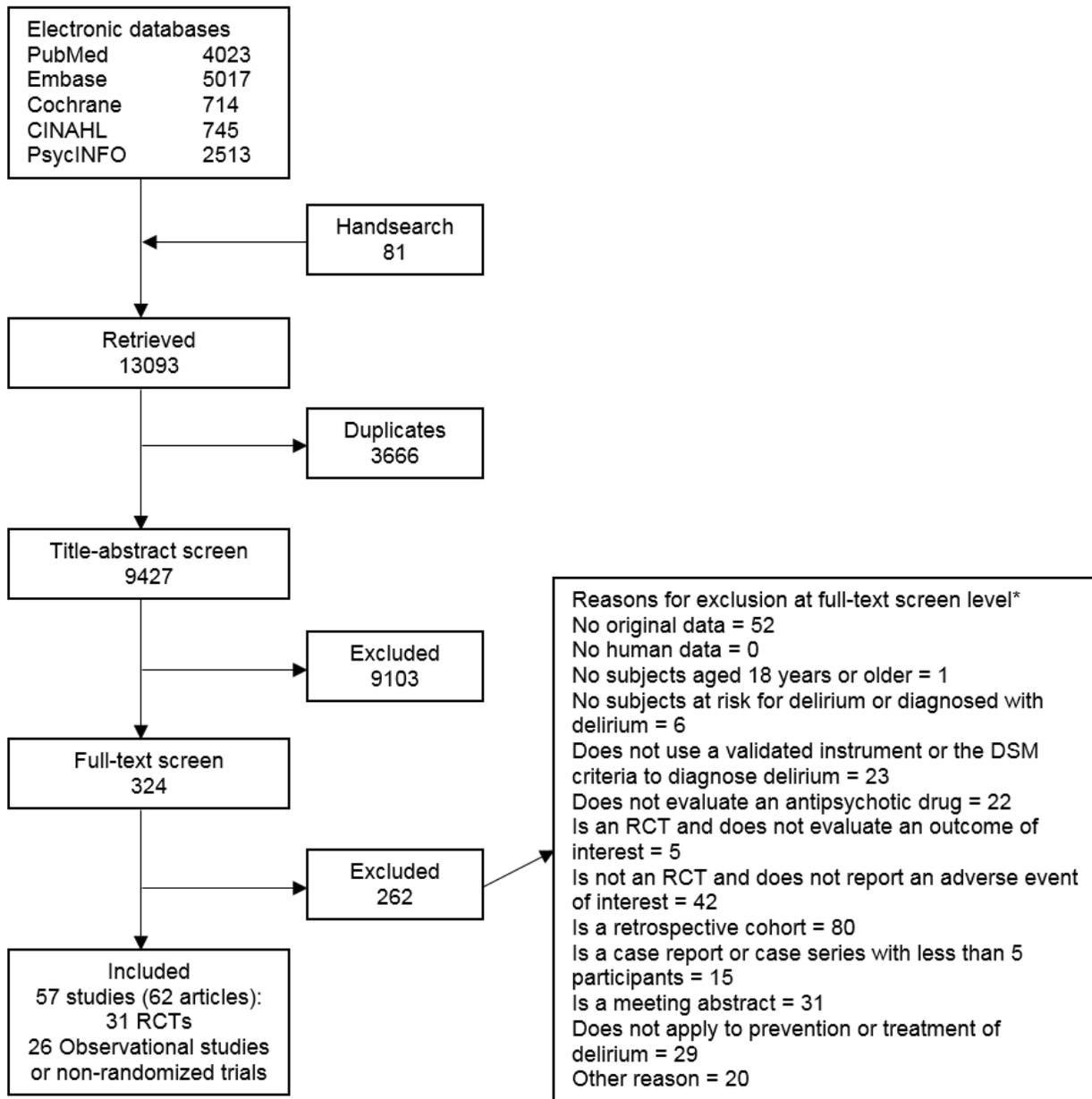
We retrieved 9,427 unique citations (Figure 3). After screening abstracts and full-text, we included 57 studies (published in 62 articles). Appendix C provides a list of the included articles and the articles excluded at full-text screen.

Of the eligible studies, 15 studies, including 14 randomized controlled trials (RCTs)³³⁻⁴⁶ and 1 observational study,⁴⁷ addressed the prevention of delirium. Forty-four studies, including 19 RCTs^{44, 45, 48-64} and 25 observational studies or non-randomized trials,⁶⁵⁻⁸⁹ addressed the treatment of delirium. Two trials enrolled patients with and without delirium; we classified these as both a prevention and treatment trial for the purposes of this report.^{44, 45}

Tables 4 and 5 list the included studies by population by comparison. We found one study that compared haloperidol with another first-generation antipsychotic.⁵¹ We decided not to discuss this comparison further because of the infrequent use of chlorpromazine in current clinical practice.

Details of the included studies are provided in the Evidence Tables in Appendix D.

Figure 3. Summary of the literature search



Abbreviations: CINAHL = Cumulative Index to Nursing and Allied Health Literature; DSM = Diagnostic and Statistical Manual; RCT = randomized controlled trial

Table 4. Number of studies evaluating antipsychotics for the prevention of delirium for overall and subpopulations

	Overall Patient Population	Patients, Aged 65 Years Or Older	Patients With Dementia	Patients In Intensive Care Unit	Patients In Post-Acute Care Facility	Patients In Palliative Or Hospice Care	Patients In Post-Operative Care
Haloperidol vs. placebo	11 ^{33-35, 37, 38, 41-46}	4 ^{35, 37, 41, 43}	0	7 ^{33, 34, 42-46}	0	0	5 ^{35, 37, 38, 43, 46}
Second-generation antipsychotic vs. placebo	3 ^{36, 39, 40}	2 ^{36, 39}	0	0	0	0	3 ^{36, 39, 40}
Haloperidol vs. second-generation antipsychotic	1 ⁴⁴	0	0	1 ⁴⁴	0	0	0
Second-generation antipsychotic vs. second-generation antipsychotic	0	0	0	0	0	0	0
Haloperidol vs. other treatment	1 ³³	0	0	1 ³³	0	0	0
Second-generation antipsychotic vs. other treatment	0	0	0	0	0	0	0
No comparison	1 ⁴⁷	0	0	1 ⁴⁷	0	0	0

Table 5. Number of studies evaluating antipsychotics for the treatment of delirium for overall and subpopulations

	Overall Patient Population	Patients, Aged 65 Years Or Older	Patients With Dementia	Patients In Intensive Care Unit	Patients In Post-Acute Care Facility	Patients In Palliative Or Hospice Care	Patients In Post-Operative Care
Haloperidol vs. placebo	5 ^{44, 45, 48, 57, 79}	1 ⁵⁷	0	3 ^{44, 45, 79}	0	1 ⁴⁸	0
Second-generation vs. placebo	6 ^{44, 48, 52, 57, 63, 79}	1 ⁵⁷	0	3 ^{44, 52, 79}	0	1 ⁴⁸	0
Haloperidol vs. second-generation antipsychotic	20 ^{44, 48, 53-58, 61, 62, 64-66, 68, 70, 75, 79, 84, 85, 89}	1 ⁵⁷	0	4 ^{44, 53, 79, 85}	0	2 ^{48, 61}	0
Second-generation antipsychotic vs. second-generation antipsychotic	7 ^{54, 59, 60, 66, 68, 69, 89}	0	0	1 ⁵⁴	0	0	0
Haloperidol vs. other treatment	3 ⁴⁹⁻⁵¹	0	0	0	0	0	1 ⁴⁹
Second-generation antipsychotic vs. other treatment	0	0	0	0	0	0	0
No comparison	15 ^{67, 71-74, 76-78, 80-83, 86-88}						

Key Question 1. Benefits and Harms of Antipsychotics To Prevent Delirium

Key Points – Overall

Delirium Severity

- We were unable to draw a conclusion regarding the effects of antipsychotics on delirium severity in patients at risk for delirium for the following comparisons:
 - Haloperidol versus placebo (insufficient evidence)
 - Second-generation antipsychotics versus placebo (insufficient evidence)
 - Haloperidol versus second-generation antipsychotics (no trials)
 - Second-generation antipsychotics versus second-generation antipsychotics (no trials)
 - Haloperidol versus other therapies (no trials)
 - Second-generation antipsychotics versus other therapies (no trials)

Cognitive Functioning

- We found no trials evaluating cognitive functioning in patients at risk for delirium that compared an antipsychotic with a placebo, another antipsychotic, or another treatment.

Length of Stay in Hospital

- We concluded that there was little to no difference in length of stay in hospital for patients at risk of delirium for the following comparisons:
 - Haloperidol versus placebo (Strength of evidence [SOE]: High)
 - Second-generation antipsychotics versus placebo (SOE: Low)
- We are unable to draw a conclusion regarding the effects of antipsychotics on length of stay in hospital for patients at risk for delirium for the following comparisons:
 - Haloperidol versus second-generation antipsychotics (insufficient evidence)
 - Second-generation antipsychotics versus second-generation antipsychotics (no trials)
 - Haloperidol versus other therapies (insufficient evidence)
 - Second-generation antipsychotics versus other therapies (no trials)

Inappropriate Continuation of Antipsychotics

- We found no studies evaluating inappropriate continuation of antipsychotics in patients at risk for delirium that compared an antipsychotic with a placebo, another antipsychotic, or another treatment.

Sedation

- We were unable to draw a conclusion regarding the effects of antipsychotics on sedation in patients at risk for delirium for the following comparisons:
 - Haloperidol versus placebo (insufficient evidence)
 - Second-generation antipsychotics versus placebo (no studies)
 - Haloperidol versus second-generation antipsychotics (no studies)
 - Second-generation antipsychotics versus second-generation antipsychotics (no studies)
 - Haloperidol versus other therapies (no studies)

- Second-generation antipsychotics versus other therapies (no studies)

Intermediate Outcomes

Delirium Incidence – Overall

Haloperidol Versus Placebo

Nine randomized controlled trials (RCTs) directly compared delirium incidence between haloperidol and placebo groups. These RCTs enrolled 3,408 patients in both surgical and medical intensive care and non-intensive care unit settings and used a variety of validated delirium detection instruments. Five of the trials were low risk of bias,^{34, 37, 41, 42, 46} three had unclear risk of bias,^{33, 38, 43} and one had high risk of bias owing to lack of blinding and allocation concealment.³⁵ Intravenous haloperidol was administered in all except two trials; in those two exceptions, oral doses were given.^{37, 41} These nine trials were pooled, as they each identified new onset of delirium (incidence) within the week after exposure to prophylactic haloperidol or placebo. We found no clinically meaningful difference in the relative risk of delirium in the comparison of haloperidol with placebo (relative risk [RR], 0.94; 95% confidence interval [CI], 0.77 to 1.16, I-squared, 44%; Figure 4). Exclusion of any one trial did not change the inference of the meta-analysis. We considered the results to be consistent and precise, but this is limited due to some trials with high or unclear risk of bias.

Second-Generation Antipsychotics Versus Placebo

Three RCTs, two with low risk of bias^{36, 39} and one with high risk of bias due to lack of blinding,⁴⁰ enrolled 627 patients without delirium prior to surgery and compared delirium occurrence in the postoperative setting following randomization with postoperative risperidone or placebo^{36, 40} or peri-operative olanzapine or placebo.³⁹ Two of these trials included patients aged 65 years and older prior to either on-pump cardiac or joint-replacement surgery. We found a statistically significant and clinically meaningful difference in the relative risk of delirium favoring second-generation antipsychotics compared with placebo for the prevention of delirium (RR, 0.36; 95% CI, 0.26 to 0.50, I-squared, 0%) (Figure 4). Exclusion of any one trial did not change the inference of the meta-analysis. Although the results were consistent and precise, all of the studies were conducted in the postoperative setting and these results may not apply to all adult patients at risk for delirium.

Haloperidol Versus Other Therapies

We found one three-arm RCT, with unclear risk of bias that evaluated delirium incidence and, in addition to a placebo arm, compared intravenous haloperidol with intravenous dexmedetomidine, administered for treatment of agitation.³³ This RCT enrolled patients with severe systemic illness in the intensive care unit. The results of this trial favored the use of dexmedetomidine over haloperidol for the prevention of delirium.

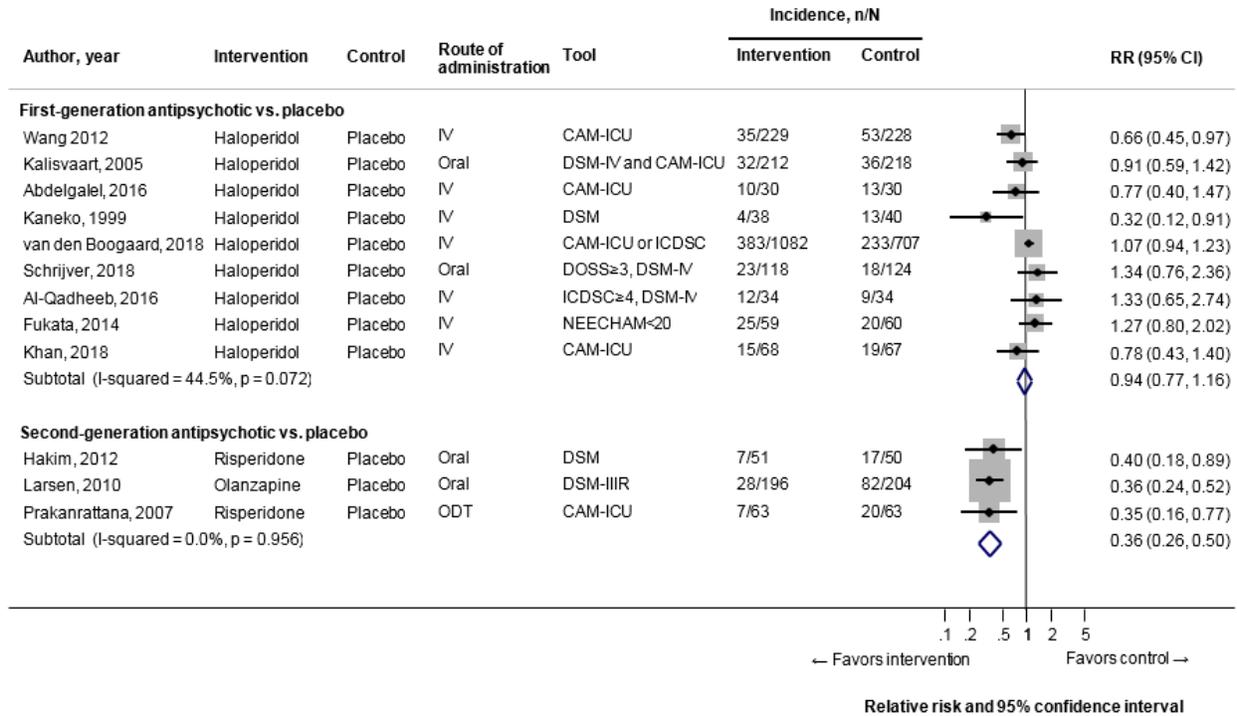
Other Comparisons

We found no delirium prevention trials evaluating delirium incidence for the following comparisons:

- Haloperidol versus second-generation antipsychotics
- Second-generation antipsychotics versus second-generation antipsychotics

- Second-generation antipsychotics versus other therapies.

Figure 4. Meta-analysis of delirium incidence in trials comparing either haloperidol or second-generation antipsychotics with placebo among patients at risk for delirium



CAM-ICU = Confusion Assessment Method for the ICU; CI = confidence interval; DOSS = Delirium Observation Screening Scale; DSM = Diagnostic and Statistical Manual of Mental Disorders; DSM-III-R = Diagnostic and Statistical Manual of Mental Disorders, 3rd ed. Revision; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, 4th ed.; ICDSC = Intensive Care Delirium Screening Checklist; IV = intravenous; n = incidence within arm; N = total arm population; NEECHAM = Neelon-Champagne Confusion Scale; p = p-value; RR = relative risk

Short-Term Delirium Symptoms – Overall

Haloperidol Versus Placebo

We found two RCTs, one with low risk of bias and one with unclear risk of bias, enrolling critically ill mechanically ventilated patients or patients undergoing elective gastrointestinal surgery.^{38, 45} These trials compared the effect of haloperidol and placebo on two different delirium symptoms: agitation and sleep duration. Haloperidol compared to placebo did not change sleep duration.³⁸ Haloperidol compared to placebo was statistically significantly associated with decreased agitation.⁴⁵ We concluded that these single studies provided insufficient evidence to make a determination about the impact of haloperidol on short-term delirium symptoms when used to prevent delirium.

Other Comparisons

We found no delirium prevention trials evaluating delirium symptoms for the following comparisons:

- Second-generation antipsychotics versus placebo
- Haloperidol versus second-generation antipsychotics
- Second-generation antipsychotics versus second-generation antipsychotics

- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies.

Delirium Severity – Overall

Haloperidol Versus Placebo

Three RCTs, with low risk of bias, compared haloperidol with placebo and assessed delirium severity using the same instrument, the Delirium Rating Scale-Revised-98, in different populations with inconsistent results.^{37, 41, 46} We conducted a meta-analysis, but there was substantial statistical heterogeneity (I-squared, 82%). When we conducted a profile likelihood analysis, the results would change the inference and remained limited by substantial heterogeneity (I-squared, 70%). Also, one trial was missing the Delirium Rating Scale-Revised-98 results for over half of the patients (54%).⁴¹ We were unable to draw conclusions based on the inconsistency and methodological limitations. (SOE: Insufficient)

Second-Generation Antipsychotics Versus Placebo

Two RCTs, with low risk of bias, compared second-generation antipsychotics with placebo and assessed delirium severity using two instruments, the Delirium Rating Scale-Revised-98 and the Intensive Care Delirium Screening Checklist, in surgical populations with inconsistent results.^{36, 39} We were unable to draw conclusions based on the inconsistent results and nonrepresentativeness in these two trials. (SOE: Insufficient)

Other Comparisons

We found no delirium prevention trials evaluating delirium severity for the following comparisons:

- Haloperidol versus second-generation antipsychotics
- Second-generation antipsychotics versus second-generation antipsychotics
- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies.

Strength of Evidence

Table 6 summarizes the strength of evidence findings for antipsychotics for the prevention of delirium in terms of delirium severity.

Table 6. Strength of evidence domains for trials evaluating antipsychotics for the prevention of delirium in terms of delirium severity

Comparison	Number Of Trials (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength Of Evidence	Summary
Haloperidol vs. placebo	3 ^{37, 41, 46} (807)	Moderate*	Indirect [†]	Inconsistent	Precise	Undetected	Insufficient	We are unable to draw a conclusion.
Second-generation antipsychotics vs. placebo	2 ^{36, 39} (501)	Low	Indirect [‡]	Inconsistent	Precise	Undetected	Insufficient	We are unable to draw a conclusion.
Haloperidol vs. second-generation antipsychotics	No trials							
Second-generation antipsychotics vs. second-generation antipsychotics	No trials							
Haloperidol vs. other therapies	No trials							
Second-generation antipsychotics vs. other therapies	No trials							

* Moderate rating for study limitations is primarily due to missing Delirium Rating Scale-Revised-98 scores in 53.7% of the patients in one trial⁴¹

[†] Indirect rating due to a limited patient population (medical and/or surgical, but not including critical illness); results may not be generalizable to other patients with delirium.

[‡] Indirect rating due to a single patient population; results may not be generalizable to other patients with delirium.

Delirium-Free, Coma-Free Days Alive – Overall

Haloperidol Versus Placebo

We identified four RCTs, comparing haloperidol with placebo that assessed delirium- and coma-free days alive at different followup time points in populations of medical and surgical patients in intensive care units.⁴²⁻⁴⁵ Three trials, with low risk of bias, reported no statistically significant effect on delirium- and coma-free days alive for haloperidol compared with placebo.^{42, 44, 45} However, one trial, with unclear risk of bias, reported a statistically greater number of delirium- and coma-free days for haloperidol compared with placebo.⁴³ Based on our calculations of the same data we found no statistically or clinically significant difference in this study. We concluded that haloperidol had no effect on delirium-free or coma-free days alive; we considered the evidence from these trials to be consistent and precise, although limited to patients in intensive care units.

Second-Generation Antipsychotics Versus Placebo

We identified one RCT, with low risk of bias and enrolling patients receiving mechanical ventilation, that compared second-generation antipsychotics with placebo for delirium- and coma-free days.⁴⁴ This trial, with 21-day followup, reported no statistically significant effect on delirium- and coma-free days alive for ziprasidone compared with placebo.

Haloperidol Versus Second-Generation Antipsychotics

We identified one RCT, with low risk of bias and enrolling patients receiving mechanical ventilation, that compared haloperidol with second-generation antipsychotics for delirium- and coma-free days.⁴⁴ This trial, with 21-day followup, reported no statistically significant effect on delirium- and coma-free days alive for ziprasidone compared with haloperidol.

Other Comparisons

We found no delirium prevention trials evaluating delirium- and coma-free days alive that compared for the following comparisons:

- Second-generation antipsychotics versus second-generation antipsychotics
- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies.

Duration of Delirium – Overall

Haloperidol Versus Placebo

Seven RCTs, comparing haloperidol with placebo for the prevention of delirium in patients admitted to medical or surgical intensive care units or acute inpatient medical or surgical wards, reported the duration of delirium. Six of these RCTs had low risk of bias,^{34, 37, 41, 44-46} and one had high risk of bias owing to lack of blinding and allocation concealment.³⁵ Six of the seven trials reported no statistically significant difference in delirium duration between haloperidol and placebo.^{34, 35, 41, 44-46} One perioperative study found a significant difference favoring haloperidol.³⁷ We did not conduct a meta-analysis because these trials generally provided results as median values only. The skewed nature of length of stay data precluded conversion or transformation of the data. Based on the consistent findings in six of seven trials we concluded

that haloperidol has no effect on delirium duration when used as a preventive agent in all populations at risk of delirium.

Second-Generation Antipsychotics Versus Placebo

Three RCTs, with low risk of bias, compared a second-generation antipsychotic with placebo for the prevention of delirium and assessed delirium duration in medical and surgical patients in intensive care units and post-surgical acute inpatient wards.^{36, 39, 44} Two of the trials demonstrated no statistically significant effect on delirium duration.^{36, 44} A third study demonstrated a statistically significant shorter duration of delirium in the placebo group in a postoperative population.³⁹ We did not conduct a meta-analysis because two trials provided results as median values. The skewed nature of length of stay data precluded conversion or transformation of the data. These studies highlight the heterogeneity of patient populations and design of interventions. There is insufficient evidence regarding the impact of perioperative use of second-generation antipsychotics versus placebo on delirium duration.

Haloperidol Versus Second-Generation Antipsychotics

One three-arm RCT, with low risk of bias, enrolled patients receiving mechanical ventilation in mixed medical and surgical intensive care units.⁴⁴ This RCT reported no statistically significant effect on delirium duration for patients randomized to treatment with a median daily dose of 15 mg oral haloperidol compared with patients randomized to a median daily dose of 113 mg of oral ziprasidone.

Other Comparisons

We found no delirium prevention trials evaluating delirium duration for the following comparisons:

- Second-generation antipsychotics versus second-generation antipsychotics
- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies.

Patient Distress – Overall

We found no trials evaluating patient distress in patients at risk for delirium that compared an antipsychotic with a placebo, another antipsychotic, or another treatment.

Use of Rescue Therapy – Overall

Haloperidol Versus Placebo

Four RCTs, three with low risk of bias^{41, 44, 45} and one with uncertain risk of bias,⁴³ compared haloperidol with placebo for the prevention of delirium in 941 patients and reported on the use of rescue therapy, defined as the use of any open-label antipsychotic. Three of the RCTs, of which one was a three-arm trial,⁴⁴ enrolled medical and/or surgical patients in the intensive care unit setting; one RCT enrolled patients on acute inpatient wards.⁴¹ We found no statistically significant between-group difference in the use of rescue therapy when comparing haloperidol with placebo (pooled RR, 0.63; 95% CI, 0.34 to 1.15; I-squared, 62%; Figure 5). This is a possibly relevant decrease in use of open-label antipsychotic but the potential impact is difficult to assess. Exclusion of any one study did not change the inference from the meta-analysis.

Second-Generation Antipsychotics Versus Placebo

One three-arm RCT, with low risk of bias, enrolled medical and surgical patients requiring mechanical ventilation in the intensive care unit and included the comparison of ziprasidone with placebo for the prevention of delirium. There was no between-group difference in the use of rescue therapy, defined as the use of any open-label antipsychotic.⁴⁴

Haloperidol Versus Second-Generation Antipsychotics

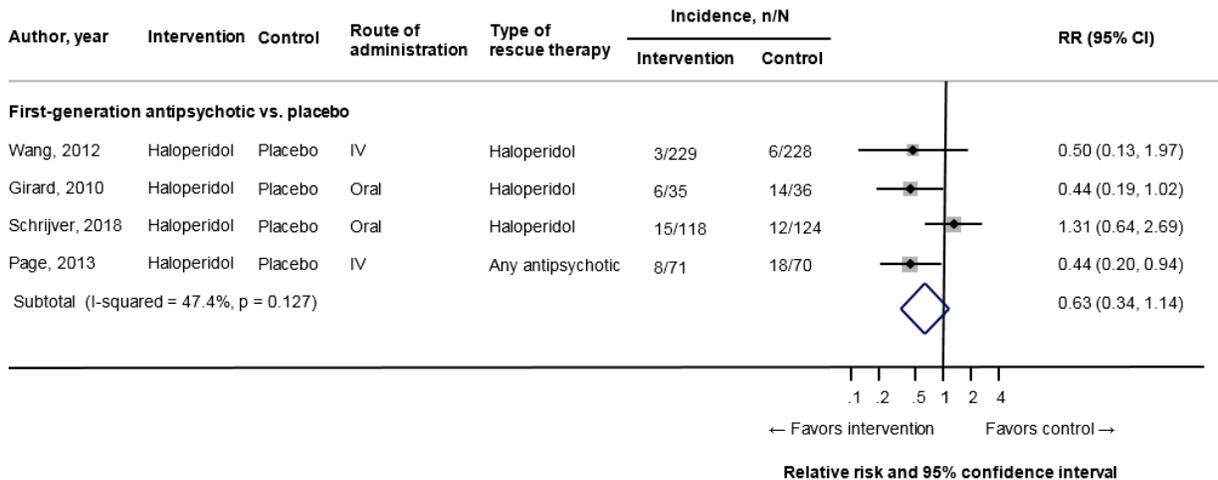
One three-arm RCT, with low risk of bias, enrolled medical and surgical patients requiring mechanical ventilation in the intensive care unit and included the comparison of ziprasidone with haloperidol for the prevention of delirium. We found no between-group difference in the use of rescue therapy, defined as the use of any open-label antipsychotic.⁴⁴

Other Comparisons

We found no delirium prevention trials evaluating the use of rescue therapy for the following comparisons:

- Second-generation antipsychotics versus second-generation antipsychotics
- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies.

Figure 5. Meta-analysis of use of rescue therapy in trials comparing haloperidol with placebo in patients at risk for delirium



CI = confidence interval; IV = intravenous; n = incidence within arm; N = total arm population; p = p-value; RR = relative risk.

Use of Physical Restraint – Overall

Haloperidol Versus Placebo

One three-arm RCT with low risk of bias, enrolled critically ill patients without delirium admitted to surgical and medical intensive care units and compared restraint use between placebo and two haloperidol arms (1 mg or 2 mg, 3 times per day).⁴² This trial reported a small statistically non-significant difference in the number of patients requiring restraint, favoring placebo. Another two-arm RCT, enrolling patients undergoing major non-cardiac thoracic surgery compared haloperidol (0.5 mg, 3 times per day for 4 days) with placebo, reported no

difference in use of physical restraint.⁴⁶ There is inconsistent evidence on the use of physical restraint.

Second-Generation Antipsychotics Versus Placebo

One RCT, with low risk of bias, enrolled patients undergoing joint replacement surgery. This RCT randomized patients to prophylactic use of 5 mg olanzapine or placebo before and after surgery and reported restraint use.³⁹ This trial reported no statistical difference in restraint use in patients randomized to olanzapine versus placebo. There were few events, so the results were imprecise.

Other Comparisons

We found no delirium prevention trials evaluating restraint use for the following comparisons:

- Haloperidol versus second-generation antipsychotics
- Second-generation antipsychotics versus second-generation antipsychotics
- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies.

Final Health or Patient-Centered Outcomes

Mortality – Overall

Haloperidol Versus Placebo

We conducted a meta-analysis of eight RCTs^{33, 34, 41-46} that compared haloperidol with placebo; one of these studies was excluded from the analysis because there were no deaths.⁴⁶ Six of these RCTs had low risk of bias,^{34, 41, 42, 44-46} and two RCTs had unclear risk of bias.^{33, 43} Our analysis showed no between-group differences in short-term mortality, defined as mortality while in hospital or up to 30 days after randomization, for haloperidol compared with placebo (pooled RR, 0.98; 95% CI, 0.82 to 1.17) (Figure 6). We tested the effect of each individual trial on the combined point estimate. No single trial influenced the pooled results. No substantial statistical heterogeneity was identified. All but one⁴¹ of the RCTs enrolled critically ill patients.

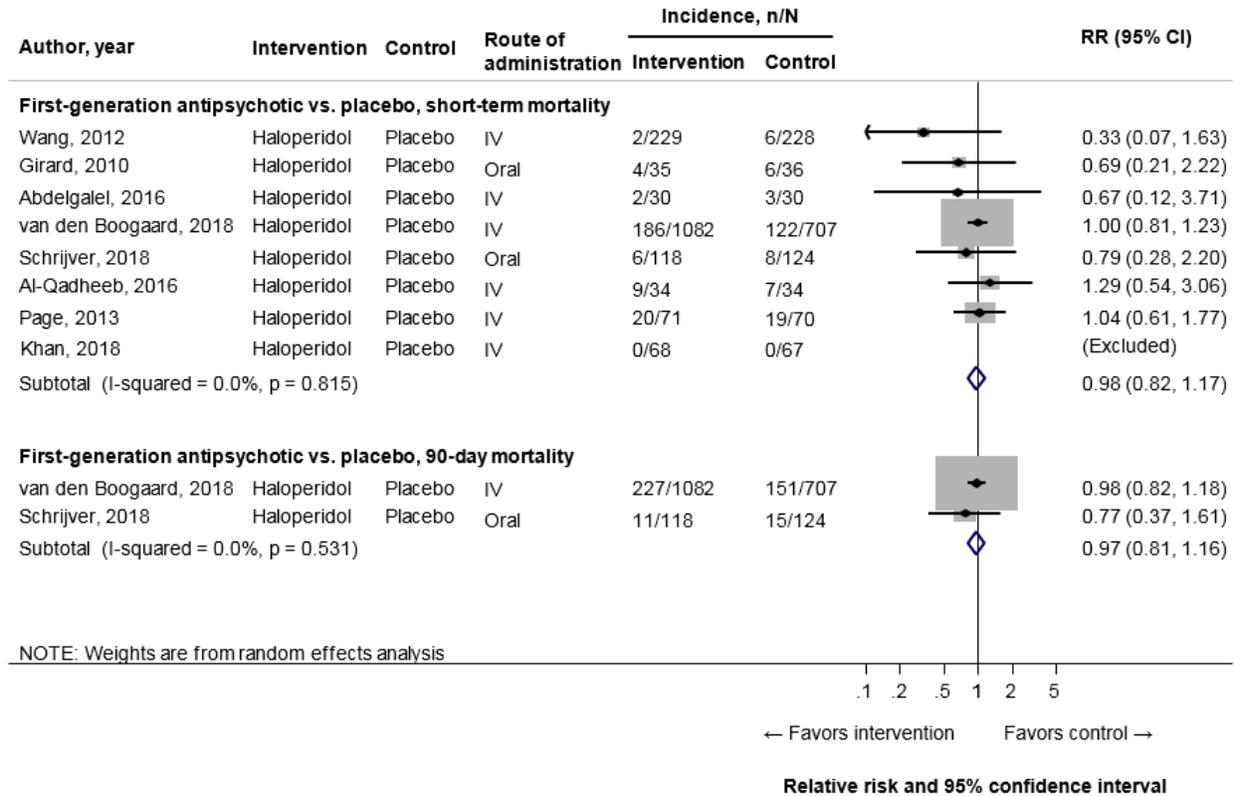
Of these eight RCTs, two trials, with low risk of bias,^{41, 42} also examined 90-day mortality, including the largest trial with 1,789 critically ill patients.⁴² The results of a meta-analysis of these trials were similar to the results for short-term mortality, with no between-group differences when comparing haloperidol with placebo (pooled RR, 0.97; 95% CI, 0.81 to 1.16; Figure 6). One RCT also examined 180-day mortality, with no between-group differences when comparing haloperidol with placebo (RR, 0.95; 95% CI, 0.53 to 1.70).⁴¹

One RCT, with low risk of bias and enrolling 1,789 critically ill patients, reported no statistically significant effect on survival at 28 days for haloperidol (median, 28 days; interquartile range [IQR], 28 to 28 days) compared with placebo (median, 28 days; IQR, 28 to 28 days) (differences in median, 0 days; 95% CI, 0 to 0 days).⁴² This trial reported a similar effect on survival at 90 days for haloperidol (median, 90 days; IQR, 90 to 90 days) compared with placebo (median, 90 days; IQR, 90 to 90 days) (differences in median, 0 days; 95% CI, 0 to 0 days).

Second-Generation Antipsychotics Versus Placebo

Two RCTs, with low risk of bias, compared second-generation antipsychotics (risperidone and ziprasidone) with placebo and reported no between-group differences in short-term mortality, defined as mortality while in hospital or up to 30 days after randomization.^{36, 44}

Figure 6. Meta-analysis of mortality in trials comparing haloperidol with placebo in patients at risk for delirium



CI = confidence interval; IV = intravenous; n = incidence within arm; N = total arm population; p = p-value; RR = relative risk.

Haloperidol Versus Second-Generation Antipsychotics

One RCT, with low risk of bias, compared the second-generation antipsychotic, ziprasidone, with haloperidol and reported no between-group differences in short-term mortality, defined as mortality while in hospital or up to 30 days after randomization.⁴⁴

Haloperidol Versus Other Therapies

One RCT, with unclear risk of bias, compared haloperidol with dexmedetomidine and reported no between-group differences in short-term mortality, defined as mortality while in hospital or up to 30 days after randomization.³³

Other Comparisons

We found no delirium prevention trials evaluating mortality for the following comparisons:

- Second-generation antipsychotics versus second-generation antipsychotics
- Second-generation antipsychotics versus other therapies.

Institutionalization – Overall

Haloperidol Versus Placebo

One RCT, with low risk of bias, compared oral haloperidol with placebo for the prevention of delirium and reported on new institutionalization. The RCT enrolled patients aged 70 years and older admitted to medical or surgical acute inpatient wards.⁴¹ This trial reported no statistically significant between-group difference in new institutionalization at the time of discharge, at 3 months followup, or 6 months followup.

Second-Generation Antipsychotics Versus Placebo

One RCT, with low risk of bias and enrolling orthopedic surgery patients aged 65 years and older and treated with oral olanzapine or placebo, reported a statistically significant between-group difference in institutionalization (defined as discharge to a rehabilitation or skilled nursing facility) favoring the second-generation antipsychotic.³⁹

Other Comparisons

We found no delirium prevention trials evaluating institutionalization for the following comparisons:

- Haloperidol versus second-generation antipsychotics
- Second-generation antipsychotics versus second-generation antipsychotics
- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies.

Falls – Overall

Haloperidol Versus Placebo

One RCT, with high risk of bias owing to lack of blinding and allocation concealment, compared haloperidol with no intervention for the prevention of delirium in patients undergoing abdominal or orthopedic surgery and reported on falls as an adverse outcome.³⁵ A single fall occurred in one patient on day seven of the trial, four days after the last dose of haloperidol was administered and was determined by the authors as unlikely to be related to the study intervention.

Other Comparisons

We found no delirium prevention trials evaluating falls for the following comparisons:

- Second-generation antipsychotics versus placebo
- Haloperidol versus second-generation antipsychotics
- Second-generation antipsychotics versus second-generation antipsychotics
- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies.

Other Final Health or Patient-Centered Outcomes – Overall

We found no trials in patients at risk for delirium that compared an antipsychotic with a placebo, another antipsychotic, or another treatment and evaluated the following final health or patient-centered outcomes:

- Quality of life
- Cognitive functioning
- Caregiver burden/strain
- Memory of patient distress

Resource Utilization Outcomes

Readmission to Hospital – Overall

Haloperidol Versus Placebo

One RCT, with low risk of bias, compared haloperidol with placebo for the prevention of delirium in hospitalized medical and surgical patients aged 65 years and older.⁴¹ This trial demonstrated no statistically significant between-group differences on readmission to the acute care hospital of treatment group at 3 months followup or 6 months followup.

Other Comparisons

We found no delirium prevention trials evaluating readmission to the acute care hospital for the following comparisons:

- Second-generation antipsychotics versus placebo
- Haloperidol versus second-generation antipsychotics
- Second-generation antipsychotics versus second-generation antipsychotics
- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies.

Readmission to Intensive Care Unit – Overall

Haloperidol Versus Placebo

Two RCTs, with low risk of bias, compared haloperidol with placebo in critically ill medical and surgical patients.^{42, 45} Both RCTs demonstrated no effect on readmission to the intensive care unit, but these results were imprecise.

Other Comparisons

We found no delirium prevention trials evaluating readmission to the intensive care unit for the following comparisons:

- Second-generation antipsychotics versus placebo
- Haloperidol versus second-generation antipsychotics
- Second-generation antipsychotics versus second-generation antipsychotics
- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies.

Length of Stay in Hospital – Overall

Haloperidol Versus Placebo

Eight RCTs comparing haloperidol with placebo assessed length of stay in hospital in medical and surgical patients in both intensive and non-intensive care units.^{33, 37, 41-46} Six RCTs

had low risk of bias,^{37, 41, 42, 44-46} and two RCTs had unclear risk of bias.^{33, 43} We did not conduct a meta-analysis because these trials generally provided results as median values and the length of stay in hospital data are skewed, precluding conversion or transformation of the data.

Seven of the eight RCTs reported no statistically significant difference in length of stay in hospital for the overall trial population when comparing haloperidol versus placebo.^{37, 41-46} One of the eight RCTs reported a statistically significant difference in length of stay in hospital, with fewer days in hospital for patients receiving haloperidol compared with patients receiving placebo.³³ Considering the consistent findings in seven of eight trials, we concluded that there was no effect of haloperidol compared with placebo on the length of stay in hospital. (SOE: High)

Second-Generation Antipsychotics Versus Placebo

Three RCTs comparing second-generation antipsychotics with placebo assessed length of stay in hospital.^{36, 40, 44} Two RCTs had low risk of bias,^{36, 44} and one RCT had high risk of bias, owing to lack of blinding of participants and unclear risk of bias in selective outcome reporting.⁴⁰ We did not conduct a meta-analysis because these trials generally provided results as median values and the length of stay in hospital data are skewed, precluding conversion or transformation of the data. Across all these trials, second-generation antipsychotics compared with placebo had no effect on length of stay in hospital. (SOE: Low)

Haloperidol Versus Second-Generation Antipsychotics

One RCT, with low risk of bias, compared haloperidol with ziprasidone and assessed length of stay in hospital in medical and surgical patients in intensive care units.⁴⁴ This three-arm trial, enrolling patients receiving mechanical ventilation, reported no statistically significant effect on length of stay in hospital for ziprasidone compared with haloperidol. We were unable to draw a conclusion on the effect of haloperidol compared with second-generation antipsychotics due to lack of evidence. (SOE: Insufficient)

Haloperidol Versus Other Therapies

One RCT, with unclear risk of bias and enrolling critically ill patients, compared haloperidol with dexmedetomidine and reported significantly shorter length of stay in hospital in the dexmedetomidine group compared with haloperidol.³³ We are unable to draw a conclusion. (SOE: Insufficient)

Other Comparisons

We found no delirium prevention trials evaluating length of stay in hospital for the following comparisons:

- Second-generation antipsychotics versus second-generation antipsychotics
- Second-generation antipsychotics versus other therapies.

Strength of Evidence

Table 7 summarizes the SOE of evidence findings for antipsychotics for the prevention of delirium in terms of length of stay in hospital.

Table 7. Strength of evidence domains for trials evaluating antipsychotics for the prevention of delirium in terms of length of stay in hospital

Comparison	Number Of Trials (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength Of Evidence	Summary
Haloperidol vs. placebo	8 ^{33, 37, 41-46} (3385)	Low	Direct	Consistent	Precise	Undetected	High	All RCTs were conducted in medical and surgical patients in both intensive and non-intensive care units. Most trials (n=7) reported no statistically significant difference when comparing haloperidol to placebo.
Second-generation antipsychotics vs. placebo	3 ^{36, 40, 44} (328)	Medium	Indirect*	Consistent	Imprecise	Undetected	Low	All RCTs reported no statistically significant difference.
Haloperidol vs. second-generation antipsychotics	1 ⁴⁴ (101)	Low	Indirect†	Consistency unknown, (single study)	Imprecise	Undetected	Insufficient	We were unable to draw a conclusion.
Second-generation antipsychotics vs. second-generation antipsychotics	No trials							
Haloperidol vs. other therapies	1 ³³ (90)	Medium	Indirect†	Consistency unknown, (single study)	Imprecise	Undetected	Insufficient	We were unable to draw a conclusion.
Second-generation antipsychotics vs. other therapies	No trials							

RCT = randomized controlled trial

* Indirect rating due to a limited patient population (critical care and postoperative); results may not be generalizable to other patients with delirium.

† Indirect rating due to a single patient population in one RCT; results may not be generalizable to other patients with delirium.

Length of Stay in Intensive Care Unit – Overall

Haloperidol Versus Placebo

Seven RCTs, five with low risk of bias^{34, 42, 44-46} and two with uncertain risk of bias,^{33, 43} comparing haloperidol with placebo for the prevention of delirium in patients admitted to medical or surgical intensive care units, reported length of stay in the intensive care unit. We did not conduct a meta-analysis because these trials generally provided results as median values. The skewed nature of length of stay data precluded conversion or transformation of the data. Because all of the studies reported either no statistical difference, or no meaningful clinical difference we concluded that there is no effect on length of stay in the intensive care unit for all patients at risk of delirium for haloperidol compared with placebo.

Second-Generation Antipsychotics Versus Placebo

Three RCTs, two with low risk of bias^{36, 44} and one with high risk of bias owing to a lack of blinding,⁴⁰ compared oral second-generation antipsychotics with placebo for the prevention of delirium in critically ill and post-surgical patients and evaluated the length of stay in the intensive care unit. We did not conduct a meta-analysis because these trials generally provided results as median values. The skewed nature of length of stay data precluded conversion or transformation of the data. All three RCTs consistently reported no statistically significant effect on length of stay in the intensive care unit.

Haloperidol Versus Second-Generation Antipsychotics

One RCT, with low risk of bias, enrolled patients with and without delirium who were receiving mechanical ventilation.⁴⁴ This three-arm trial reported no statistically significant effect on length of stay in the intensive care unit for those patients randomized to receive a median daily dose of 40 mg of oral ziprasidone compared with placebo.

Haloperidol Versus Other Therapies

One three-arm RCT, with unclear risk of bias, included adult patients with severe systemic illness in an intensive care unit and demonstrated a statistically significant difference in length of stay in the intensive care unit in 30 patients randomized to receive a 2.5 loading dose of haloperidol followed by 0.5 to 2.0 mg per hour, based on sedation level versus 30 patients randomized to receive dexmedetomidine.³³

Other Comparisons

We found no delirium prevention trials evaluating length of stay in the intensive care unit for the following comparisons:

- Second-generation antipsychotics versus second-generation antipsychotics
- Second-generation antipsychotics versus other therapies.

Patient Safety Attendant Use – Overall

Second-Generation Antipsychotics Versus Placebo

One RCT, with low risk of bias and enrolling 400 orthopedic surgery patients aged 65 years and older and treated with 10 mg of oral olanzapine in the perioperative setting or placebo,

reported no statistically significant between-group difference in patient safety attendant use (RR, 2.34; 95% CI, 0.73 to 7.48).³⁹

Other Comparisons

We found no delirium prevention trials evaluating patient safety attendant use for the following comparisons:

- Haloperidol versus placebo
- Haloperidol versus second-generation antipsychotics
- Second-generation antipsychotics versus second-generation antipsychotics
- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies.

Other Resource Utilization Outcomes – Overall

We found no trials in patients at risk for delirium that compared an antipsychotic with a placebo, another antipsychotic, or another treatment and evaluated the following resource utilization outcomes:

- Length of stay in skilled nursing facility
- Hospice enrollment

Adverse Effects

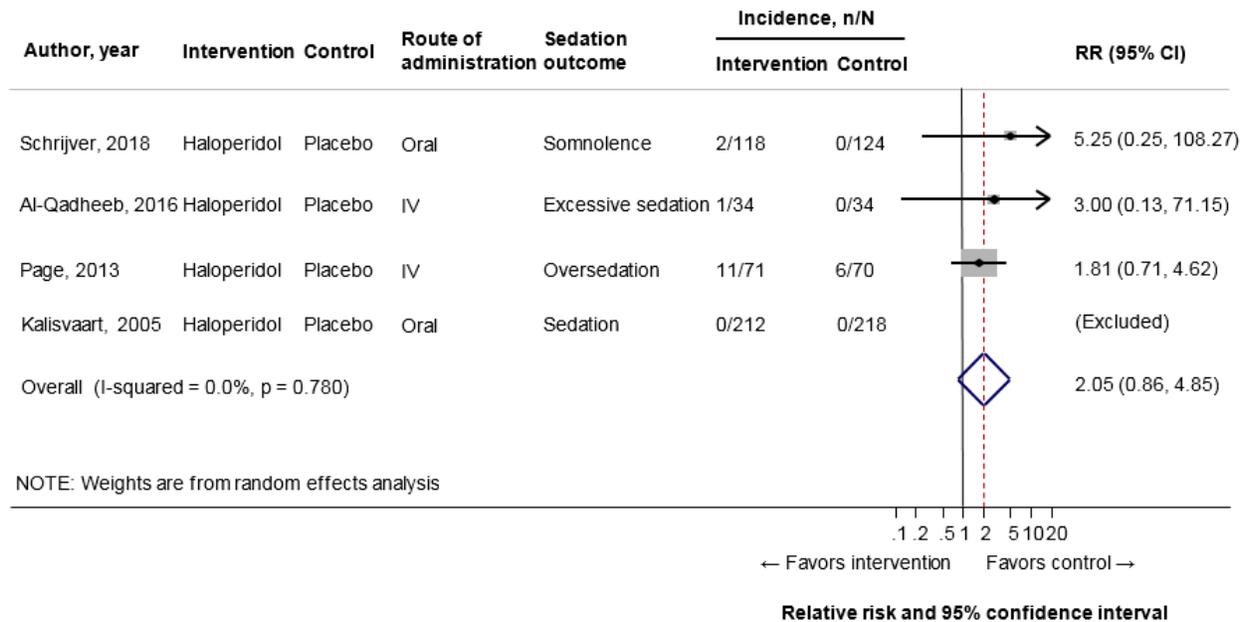
Sedation – Overall

Haloperidol Versus Placebo

Four RCTs, all with low risk of bias and enrolling a total of 881 patients, compared haloperidol with placebo for the prevention of delirium and reported on sedation (described as excessive or oversedation, or daytime somnolence).^{34, 37, 41, 45} Two RCTs, enrolled medical and surgical patients in the intensive care unit and administered multiple doses of intravenous haloperidol or placebo for treatment and/or prevention of delirium (maximum daily dose range: 4 to 7.5 mg).^{34, 45} Two RCTs enrolled medical and surgical patients admitted to the acute inpatient wards and administered multiple doses of oral haloperidol for the prevention of delirium (maximum daily dose range: 1.5 to 2 mg).^{37, 41} One trial found no sedation in either arm and was not included in the meta-analysis.³⁷ The remaining trials were combined and although we found no statistically significant between-group difference in sedation (pooled RR, 2.05; 95% CI, 0.86 to 4.85; I-squared, 0%) (Figure 7), given the few events in these trials, we were unable to draw a conclusion about the effects of haloperidol on sedation. Exclusion of any one trial did not change the inference from the meta-analysis. (SOE: Insufficient)

We did not find any observational studies addressing this outcome for this comparison in patients at risk for delirium.

Figure 7. Meta-analysis of sedation in trials comparing haloperidol with placebo in patients at risk for delirium



NOTE: Weights are from random effects analysis

CI = confidence interval; IV = intravenous; n = incidence within arm; N = total arm population; p = p-value; RR = relative risk.

Other Comparisons

We found no studies of delirium prevention evaluating sedation for the following comparisons:

- Second-generation antipsychotics versus placebo
- Haloperidol versus second-generation antipsychotics
- Second-generation antipsychotics versus second-generation antipsychotics
- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies.

Strength of Evidence

Table 8 summarizes the strength of evidence findings for antipsychotics used for the prevention of delirium in terms of sedation.

Table 8. Strength of evidence domains for studies reporting sedation in the evaluation of antipsychotics for delirium prevention

Comparison	Number Of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength Of Evidence	Summary
Haloperidol vs. placebo	4 ^{34, 37, 41, 45} (881)	Low	Direct	Consistent	Imprecise*	Undetected	Insufficient	We are unable to draw a conclusion.
Second-generation antipsychotics vs. placebo	No studies							
Haloperidol vs. second-generation antipsychotics	No studies							
Second-generation antipsychotics vs. second-generation antipsychotics	No studies							
Haloperidol vs. other therapies	No studies							
Second-generation antipsychotics vs. other therapies	No studies							

* Numbers of events were few.

Cardiac Effects – Overall

Haloperidol Versus Placebo

Seven RCTs, five with low risk of bias^{34, 42, 44-46} and two with uncertain risk of bias,^{33, 43} compared haloperidol with placebo for the prevention of delirium in patients admitted to medical or surgical intensive care units and reported a range of cardiac effects. All seven trials administered haloperidol intravenously (maximum fixed daily dose range: 1.5 to 7.5 mg) except one that administered oral doses (maximum fixed daily dose: 20 mg).⁴⁴ Two of the RCTs were three-arm trials.^{33, 44} We found no statistical difference in the occurrence of each of three types of cardiac effects across all six RCTs. There were few cardiac events in these trials, so the results are imprecise.

Six RCTs reported arrhythmias (including atrial fibrillation, supraventricular tachycardia, and monomorphic ventricular tachycardia) in 2,713 patients in intervention and placebo arms.^{33, 42-46} One trial reported no ventricular arrhythmias in either group and was not included in the meta-analysis.⁴⁴ Although we found no statistically significant between-group difference in arrhythmias (pooled RR, 1.27; 95% CI, 0.72 to 2.21; I-squared, 0%) more arrhythmias were reported in the intervention arms (Figure 8).

Seven RCTs reported corrected QT interval prolongation in 2,781 patients randomized to intervention and placebo arms.^{33, 34, 42-46} We found no statistically significant between-group difference in corrected QT interval prolongation (pooled RR, 1.11; 95% CI, 0.80 to 1.55; I-squared, 0%) (Figure 8).

Three RCTs reported hypotension^{33, 34, 45} in 299 critically ill patients in both the intervention and placebo arms. We found no statistically significant between-group difference in hypotension (pooled RR, 1.15; 95% CI, 0.40 to 3.32; I-squared, 0%) (Figure 8).

In addition to the trials included in the meta-analysis above, one RCT with low risk of bias, randomized 242 patients aged 70 years and older, at risk of delirium, and admitted from the Emergency Department to surgical or medical units. This trial reported no statistically significant difference in acute coronary syndrome in those patients randomized to 2 mg per day of oral haloperidol versus placebo (RR, 1.05; 95% CI, 0.15 to 7.34).⁴¹

We did not find any observational studies addressing this outcome for this comparison in patients at risk for delirium.

Second-Generation Antipsychotics Versus Placebo

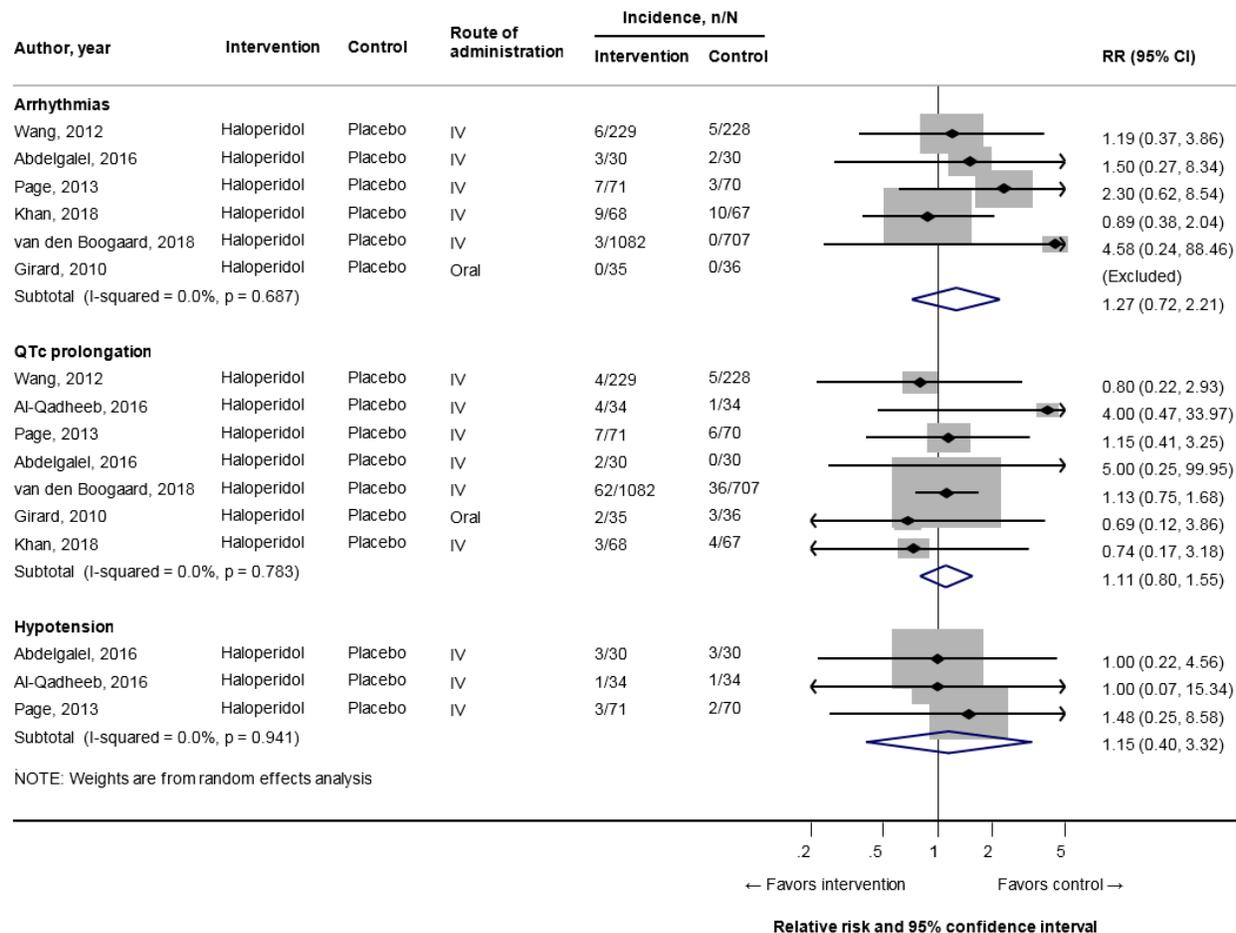
Four RCTs, three with low risk of bias^{36, 39, 44} and one with high risk of bias owing to a lack of blinding,⁴⁰ compared oral second-generation antipsychotics with placebo for the prevention of delirium in critically ill and post-surgical patients and evaluated a variety of cardiac effects. There were no statistically significant between-group differences in the occurrence of cardiac effects across all four RCTs. The results were consistent, but imprecise.

Three RCTs reported no statistically significant between-group differences in the occurrence of arrhythmias.

Two RCTs reported corrected QT interval prolongation. One three-arm trial, of mechanically ventilated, critically ill patients, compared oral ziprasidone with placebo and reported no statistically significant between group differences in corrected QT interval prolongation.⁴⁴ The other RCT included cardiac surgery patients receiving oral risperidone versus placebo and reported no occurrences of corrected QT interval prolongation.³⁶

We did not find any observational studies addressing cardiac effects for second-generation anti-psychotics compared with placebo in patients at risk for delirium.

Figure 8. Meta-analysis of cardiac effects in trials comparing haloperidol with placebo in patients at risk for delirium



CI = confidence interval; IV = intravenous; n = incidence within arm; monomorphic MT = monomorphic ventricular tachycardia; N = total arm population; p = p-value; QTc = QT interval; RR = relative risk.

Haloperidol Versus Second-Generation Antipsychotics

One RCT, with low risk of bias and enrolling patients with and without delirium, evaluated cardiac effects.⁴⁴ This three-arm trial included mechanically ventilated, critically ill patients treated with oral haloperidol or ziprasidone and reported no statistically significant between-group differences in the prolongation of the corrected QT interval; no ventricular arrhythmias occurred in either group.⁴⁴

We did not find any observational studies addressing cardiac effects for haloperidol compared with second-generation antipsychotics in patients at risk for delirium.

Haloperidol Versus Other Therapies

One three-arm RCT, with unclear risk of bias, compared haloperidol with dexmedetomidine in the prevention of delirium in critically ill adults and reported no statistically significant between-group differences for the following cardiac outcomes: arrhythmias, prolongation of the corrected QT interval, hypotension, or bradycardia.³³

We did not find any observational studies addressing cardiac effects for haloperidol compared with other therapies in patients at risk for delirium.

Other Comparisons

We found no studies of delirium prevention evaluating cardiac effects for the following comparisons:

- Second-generation antipsychotics versus second-generation antipsychotics
- Second-generation antipsychotics versus other therapies.

Studies With No Comparison Group

In one observational study with 177 critically ill patients at high risk of delirium who received haloperidol prophylaxis, nine patients (5%) had to stop the use of haloperidol because of QTc prolongation.⁴⁷

Neurologic Effects – Overall

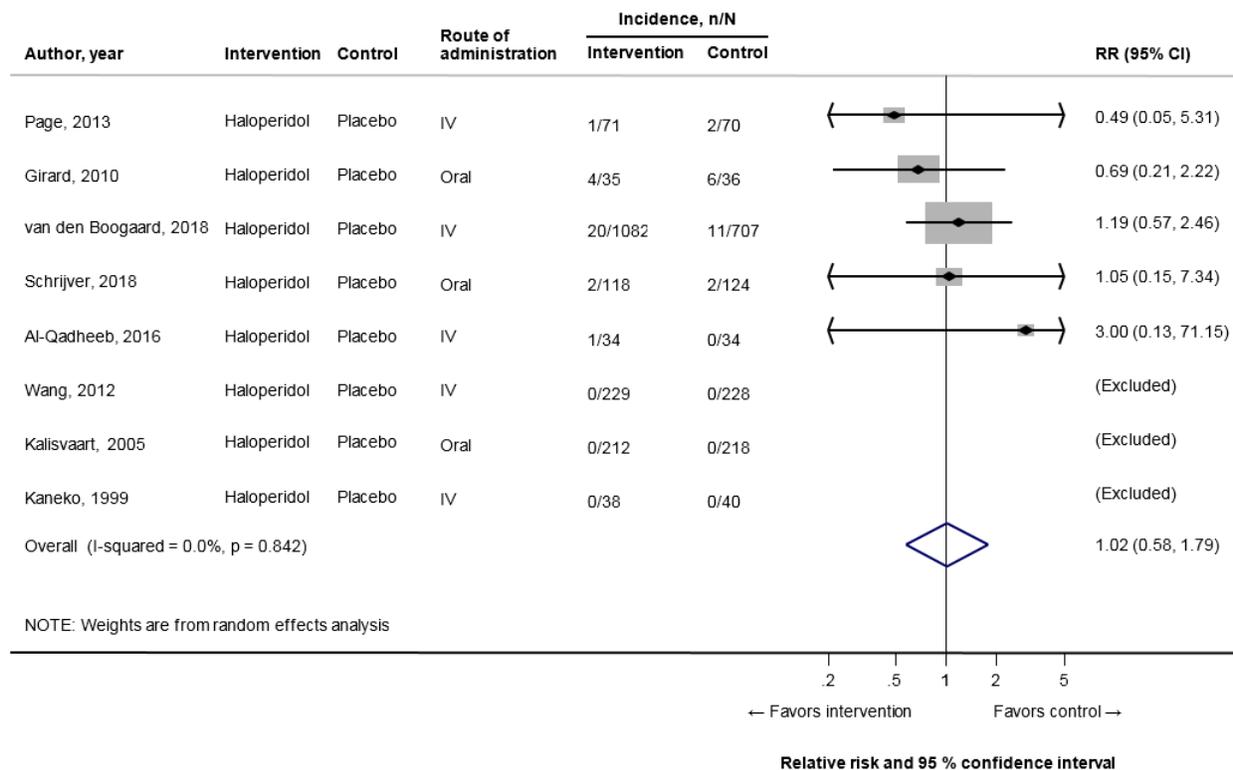
Haloperidol Versus Placebo

Six RCTs,^{34, 41, 42, 44-46} with low risk of bias, compared haloperidol with placebo for the prevention of delirium in 2,480 patients admitted to medical or surgical intensive care units or acute inpatient wards and reported a range of neurologic effects. Four trials administered haloperidol intravenously (maximum fixed daily dose range: 1.5 to 7.5 mg)^{34, 42, 45, 46} and two administered oral doses of haloperidol (maximum fixed daily dose range: 2 to 20 mg).^{41, 44} One RCT was a three-arm study.⁴⁴ We found no statistically significant difference in between-group occurrence of extrapyramidal side effects (including akathisia, muscle stiffness, and dystonic movements such as torticollis) in a meta-analysis of five trials (pooled RR, 1.02; 95% CI, 0.58 to 1.79; I-squared, 0%) (Figure 9). Exclusion of any one trial did not change the inference from the meta-analysis. We excluded one study from the analysis because they reported individual symptoms of extrapyramidal side effects.⁴⁶ This trial reported no statistically significant differences in elbow rigidity, wrist rigidity, or resting tremor and no events of dystonia, tardive dyskinesia, or pseudoparkinsonism.

The three RCTs described above monitored the occurrence of neuroleptic malignant syndrome. One RCT reported no statistically significant between-group difference in patients randomized to intervention and placebo for 3 mg and 6 mg daily intravenous dosage arms, respectively, finding that 2 cases of suspected neuroleptic malignant syndrome occurred in patients randomized to placebo while no cases were detected in the haloperidol group.⁴² The other two RCTs reported no occurrence of neuroleptic malignant syndrome in either the haloperidol or placebo arms in critically ill, mechanically ventilated patients or thoracic surgery patients.^{44, 46}

We did not find any observational studies addressing neurologic effects that compared haloperidol with placebo in patients at risk for delirium.

Figure 9. Meta-analysis of extrapyramidal side effects in trials comparing haloperidol with placebo in patients at risk for delirium



CI = confidence interval; EPS = extrapyramidal symptoms; IV = intravenous; n = incidence within arm; N = total arm population; p = p-value; RR = relative risk.

Second-Generation Antipsychotics Versus Placebo

Two RCTs, with low risk of bias, compared oral second-generation antipsychotics with placebo for the prevention of delirium in critically ill and post-surgical patients and reported neurologic effects.^{36, 44} This three-arm trial, enrolling mechanically ventilated, critically ill patients, compared oral ziprasidone versus placebo and reported no statistically significant between-group differences in akathisia or extrapyramidal symptoms not including akathisia. Neuroleptic malignant syndrome did not occur in either group in this study. The other RCT included cardiac surgery patients receiving oral risperidone versus placebo and reported no statistically significant between-group differences in extrapyramidal side effects.³⁶ There were few events in both trials, so the results are imprecise.

We did not find any observational studies addressing neurologic effects that compared second-generation antipsychotics with placebo in patients at risk for delirium.

Haloperidol Versus Second-Generation Antipsychotics

One three-arm RCT, with low risk of bias, enrolling mechanically ventilated, critically ill patients, compared oral haloperidol with ziprasidone for the treatment and prevention of delirium and reported no statistically significant between-group differences in akathisia or extrapyramidal symptoms not including akathisia, and reported no instances of neuroleptic malignant syndrome.⁴⁴

We did not find any observational studies addressing neurologic effects that compared haloperidol with second-generation antipsychotics in patients at risk for delirium.

Other Comparisons

We found no studies of delirium prevention evaluating neurologic effects for the following comparisons:

- Second-generation antipsychotics versus second-generation antipsychotics
- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies.

Studies With No Comparison Group

In one observational study with 177 critically ill patients at high risk of delirium who received intravenous haloperidol prophylaxis, one patient (1%) had to stop haloperidol because of an extrapyramidal side effect described as “signs of Parkinsonism,” and one patient (1%) had to stop haloperidol because of suspected neuroleptic malignant syndrome.⁴⁷

Other Adverse Effects – Overall

We found no studies in patients at risk for delirium that compared an antipsychotic with a placebo, another antipsychotic, or another treatment and evaluated the following adverse events:

- Weight gain
- Changes in appetite
- Hypersensitivity reactions
- Inappropriate continuation of antipsychotics
- Swallowing difficulties
- Aspiration pneumonia

Key Question 1a. Benefits and Harms of Antipsychotics To Prevent Delirium in Persons Aged 65 Years and Older

Key Points – Aged 65 Years and Older

Delirium Severity

- We were unable to draw a conclusion regarding the effects of antipsychotics on delirium severity in patients aged 65 years and older at risk for delirium for the following comparisons:
 - Haloperidol versus placebo (insufficient evidence)
 - Second-generation antipsychotics versus placebo (insufficient evidence)
 - Haloperidol versus second-generation antipsychotics (no trials)
 - Second-generation antipsychotics versus second-generation antipsychotics (no trials)
 - Haloperidol versus other therapies (no trials)
 - Second-generation antipsychotics versus other therapies (no trials)

Falls

- We were unable to draw a conclusion regarding the effects of antipsychotics on falls in patients aged 65 years and older at risk for delirium for the following comparisons:
 - Haloperidol versus placebo (insufficient evidence)
 - Second-generation antipsychotics versus placebo (no trials)
 - Haloperidol versus second-generation antipsychotics (no trials)

- Second-generation antipsychotics versus second-generation antipsychotics (no trials)
- Haloperidol versus other therapies (no trials)
- Second-generation antipsychotics versus other therapies (no trials)

Sedation

- We were unable to draw a conclusion regarding the effects of antipsychotics on sedation for the following comparisons:
 - Haloperidol versus placebo (insufficient evidence)
 - Second-generation antipsychotics versus placebo (no studies)
 - Haloperidol versus second-generation antipsychotics (no studies)
 - Second-generation antipsychotics versus second-generation antipsychotics (no studies)
 - Haloperidol versus other therapies (no studies)
 - Second-generation antipsychotics versus other therapies (no studies)

Cognitive Functioning, Inappropriate Continuation of Antipsychotics

- We found no studies evaluating cognitive functioning or inappropriate continuation of antipsychotics in patients aged 65 years and older with delirium that compared an antipsychotic with a placebo, another antipsychotic, or another treatment.

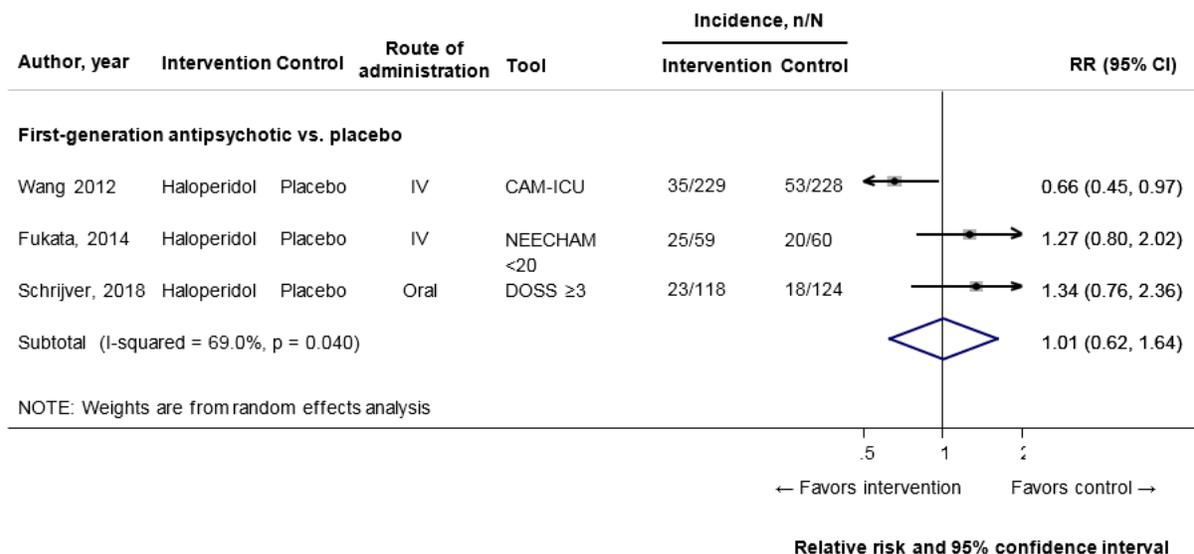
Intermediate Outcomes

Delirium Incidence – Aged 65 Years and Older

Haloperidol Versus Placebo

Three RCTs, one at low risk of bias,⁴¹ one at unclear risk of bias,⁴³ and one at high risk of bias owing to lack of blinding and allocation concealment,³⁵ enrolled 820 patients, aged 65 years and older, in surgical intensive care and non-intensive medical and surgical acute hospital ward settings. Three different validated delirium detection instruments were used to directly compare delirium occurrence between haloperidol and placebo groups. Intravenous haloperidol was administered in the surgical intensive care unit setting,⁴³ and oral doses were administered to patients on inpatient ward settings.^{37, 41} These trials were pooled and included in a meta-analysis because they identified new onset of delirium (incidence) over time after exposure to prophylactic haloperidol or placebo. There was little to no difference in the relative risk of delirium for haloperidol compared with placebo (pooled RR, 1.01; 95% CI, 0.62 to 1.64, I-squared, 69%) (Figure 10). Exclusion of any one study did not change the inference of the meta-analysis. These results were inconsistent and imprecise.

Figure 10. Meta-analysis of delirium incidence in trials comparing haloperidol with placebo in patients aged 65 years and older at risk for delirium



CAM-ICU = Confusion Assessment Method for the Intensive Care Unit; CI = confidence interval; DOSS = Delirium Observation Screening Scale; IV = intravenous; MMSE = Mini-mental state examination; n = incidence within arm; N = total arm population; p = p-value; RR = relative risk.

Second-Generation Antipsychotics Versus Placebo

Two RCTs, with low risk of bias, enrolled patients aged 65 years and older without delirium prior to surgery and compared delirium occurrence in the postoperative setting and both reported a decreased incidence of delirium in the intervention group.^{36, 37} These results were consistent, but imprecise.

Other Comparisons

We found no delirium prevention trials evaluating delirium incidence for the following comparisons:

- Haloperidol versus second-generation antipsychotics
- Second-generation antipsychotics versus second-generation antipsychotics
- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies.

Delirium Severity – Aged 65 Years and Older

Haloperidol Versus Placebo

One RCT, with low risk of bias, enrolled patients aged 70 years and older in medical or surgical specialty and reported no statistically significant effect in terms of the Delirium Rating Scale-Revised-98 scores for haloperidol compared with placebo.⁴¹ However, Delirium Rating Scale-Revised-98 scores were missing in 53.7 percent of the subjects and, therefore, the results should be interpreted with caution. We were unable to draw conclusions. (SOE in persons aged 65 years and older: Insufficient)

Second-Generation Antipsychotics Versus Placebo

The findings presented in the “Delirium Severity - Overall” results section are wholly represented by this subgroup. Please refer to the “Delirium Severity - Overall” results section. (SOE in persons aged 65 years and older: Insufficient)

Other Comparisons

We found no delirium prevention trials evaluating delirium severity in persons aged 65 years and older for the following comparisons:

- Haloperidol versus second-generation antipsychotics
- Second-generation antipsychotics versus second-generation antipsychotics
- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies.

Strength of Evidence

Table 9 summarizes the strength of evidence findings for the effects of antipsychotics on delirium severity in persons aged 65 years and older at risk for delirium.

Table 9. Strength of evidence domains for trials evaluating antipsychotics for the prevention of delirium in terms of delirium severity in patients aged 65 years and older

Comparison	Number Of Trials (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength Of Evidence	Summary
Haloperidol vs. placebo	1 ⁴¹ (242)	Low	Direct	Consistency unknown, (single study)	Imprecise	Undetected	Insufficient	We were unable to draw a conclusion.
Second-generation antipsychotics vs. placebo	2 ^{36, 39} (501)	Low	Direct	Inconsistent	Precise	Undetected	Insufficient	We were unable to draw a conclusion.
Haloperidol vs. second-generation antipsychotics	No trials							
Second-generation antipsychotics vs. second-generation antipsychotics	No trials							
Haloperidol vs. other therapies	No trials							
Second-generation antipsychotics vs. other therapies	No trials							

Delirium-Free, Coma-Free Days Alive – Aged 65 Years and Older

Haloperidol Versus Placebo

One RCT, with unclear risk of bias, enrolled patients aged 65 years and older admitted to the intensive care unit after noncardiac surgery and reported longer delirium-free and coma-free days for haloperidol (mean, 6.8 days; standard deviation [SD], 0.7) compared with placebo (mean, 6.7 days; SD, 0.9) ($P = 0.03$) for the overall study population.⁴³ Our own calculation shows a non-statistically significant difference between the two means for the overall study population with a mean difference of 0.1 (95% CI, -0.05 to 0.25). This difference in delirium-free, coma-free days alive was not considered to be a clinically significant difference.

Other Comparisons

We found no delirium prevention trials evaluating delirium- and coma-free days in persons aged 65 years and older for the following comparisons:

- Second-generation antipsychotics versus placebo
- Haloperidol versus second-generation antipsychotics
- Second-generation antipsychotics versus second-generation antipsychotics
- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies.

Duration of Delirium – Aged 65 Years and Older

Haloperidol Versus Placebo

Two RCTs that compared haloperidol with placebo or no medication for the prevention of delirium in patients aged 65 years and older did not demonstrate a statistically significant difference in delirium duration.^{35, 41}

Second-Generation Antipsychotics Versus Placebo

Two RCTs, with low risk of bias, compared a second-generation antipsychotic with placebo for the prevention of delirium and reported inconsistent results.

Haloperidol Versus Second-Generation Antipsychotics

One RCT, with low risk of bias, enrolled patients with and without delirium who received mechanical ventilation.⁴⁴ This three-arm trial reported no statistically significant effect on delirium duration for a median daily dose of 20 mg oral ziprasidone compared with a median daily dose of 15 mg oral haloperidol.

Other Comparisons

We found no delirium prevention trials evaluating delirium duration in patients aged 65 years and older for the following comparisons:

- Second-generation antipsychotics versus second-generation antipsychotics
- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies.

Use of Rescue Therapy – Aged 65 Years and Older

Haloperidol Versus Placebo

Two RCTs compared haloperidol with placebo for the prevention of delirium in patients aged 65 years and older and reported on the use of rescue therapy, defined as the use of any open-label antipsychotic.^{41, 43} One RCT, with low risk of bias, randomized patients aged 70 years and older and at risk of delirium and admitted from the Emergency Department to surgical or medical units.⁴¹ The other RCT, with unclear risk of bias, included adult patients aged 65 years and older undergoing non-cardiac surgery and recovery in an intensive care unit.⁴³ Both trials reported no statistically significant difference in the use of rescue medications in those patients randomized to haloperidol compared with placebo. However, these results were inconsistent and imprecise.

Other Comparisons

We found no delirium prevention trials evaluating the use of rescue therapy in patients aged 65 years and older for the following comparisons:

- Haloperidol versus second-generation antipsychotics
- Second-generation antipsychotics versus second-generation antipsychotics
- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies.

Use of Physical Restraint – Aged 65 Years and Older

Second-Generation Antipsychotics Versus Placebo

The findings presented in the “Use of Physical Restraint - Overall” results section are wholly represented by this subgroup. Please refer to the “Use of Physical Restraint - Overall” results section.

Other Comparisons

We found no delirium prevention trials evaluating the use of physical restraint for patients aged 65 years and older for the following comparisons:

- Haloperidol versus placebo
- Haloperidol versus second-generation antipsychotics
- Second-generation antipsychotics versus second-generation antipsychotics
- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies.

Other Intermediate Outcomes – Aged 65 Years and Older

We found no trials enrolling patients aged 65 years and older at risk for delirium that compared an antipsychotic with a placebo, another antipsychotic, or another treatment and evaluated the following intermediate outcomes:

- Short-term delirium symptoms
- Patient distress

Final Health or Patient-Centered Outcomes

Mortality – Aged 65 Years and Older

Haloperidol Versus Placebo

Two RCTs compared haloperidol with placebo and reported no between-group differences in short-term mortality, defined as mortality while in hospital or up to 30 days after randomization.^{41, 43} One RCT, with unclear risk of bias, enrolled patients aged 65 years and older in an intensive care unit. The other RCT, with low risk of bias, enrolled medical and surgical patients aged 70 years and older.⁴¹ Both trials reported no statistically significant difference in short-term mortality when comparing haloperidol with placebo. One of the trials also examined 90-day and 180-day mortality.⁴¹ The results were similar to the short-term mortality, with no between-group differences when comparing haloperidol with placebo at 90 days^a and at 180 days.^a There were few events in both trials, so the results are imprecise.

Second-Generation Antipsychotics Versus Placebo

One RCT, with low risk of bias, enrolled patients aged 65 years and older and compared risperidone with placebo. This trial reported no between-group differences in short-term mortality, defined as mortality while in hospital or up to 30 days after randomization.³⁶

Other Comparisons

We found no delirium prevention trials evaluating mortality in patients aged 65 years and older for the following comparisons:

- Haloperidol versus second-generation antipsychotics
- Second-generation antipsychotics versus second-generation antipsychotics
- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies.

Institutionalization – Aged 65 Years and Older

Haloperidol Versus Placebo

The findings presented in the “Institutionalization - Overall” results section are wholly represented by this subgroup. Please refer to the “Institutionalization - Overall” results section.

Second-Generation Antipsychotics Versus Placebo

The findings presented in the “Institutionalization - Overall” results section are wholly represented by this subgroup. Please refer to the “Institutionalization - Overall” results section.

Other Comparisons

We found no delirium prevention trials evaluating institutionalization in patients aged 65 years and older for the following comparisons:

- Haloperidol versus second-generation antipsychotics

^a Schrijver et al. reported mortality outcomes as odds ratios: i) 30-day mortality (OR, 0.78; 95% CI, 0.26 to 2.33; $P = 0.65$); ii) 90-day mortality (OR, 0.77; 95% CI, 0.34 to 1.75; $P = 0.53$); iii) 180-day mortality (OR, 0.98; 95% CI, 0.49 to 2.00; $P = 0.96$)

- Second-generation antipsychotics versus second-generation antipsychotics
- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies.

Falls – Aged 65 Years and Older

Haloperidol Versus Placebo

One RCT, with high risk of bias owing to a lack of blinding and allocation concealment, compared haloperidol with no intervention for the prevention of delirium and reported on falls as an adverse outcome.³⁵ The trial enrolled patients aged 75 years and older undergoing abdominal or orthopedic surgery. A single fall occurred in one patient on day seven of the trial, four days after the last dose of haloperidol was administered. The study authors determined that the fall was unlikely to be related to the study intervention. We were unable to draw a conclusion. (SOE: Insufficient)

Other Comparisons

We found no delirium prevention trials evaluating falls in patients aged 65 years and older for the following comparisons:

- Second-generation antipsychotics versus placebo
- Haloperidol versus second-generation antipsychotics
- Second-generation antipsychotics versus second-generation antipsychotics
- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies.

Strength of Evidence

Table 10 summarizes the strength of evidence findings for the effects of antipsychotics in terms of falls in patients aged 65 years and older.

Table 10. Strength of evidence domains for trials reporting falls in the evaluation of antipsychotics for the prevention of delirium in patients 65 years of age and older

Comparison	Number Of Trials (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength Of Evidence	Summary
Haloperidol vs. placebo	1 ³⁵ (119)	High*	Direct	Unknown	Imprecise [†]	Undetected	Insufficient	We were unable to draw a conclusion.
Second-generation antipsychotics vs. placebo	No trials							
Haloperidol vs. second-generation antipsychotics	No trials							
Second-generation antipsychotics vs. second-generation antipsychotics	No trials							
Haloperidol vs. other therapies	No trials							
Second-generation antipsychotics vs. other therapies	No trials							

* RCT was open-label and lacking in allocation concealment.

† Only one fall was reported during the study.

Other Final Health or Patient-Centered Outcomes – Aged 65 Years and Older

We found no trials in patients aged 65 years and older at risk for delirium that compared an antipsychotic with a placebo, another antipsychotic, or another treatment and evaluated the following final health or patient-centered outcomes:

- Quality of life
- Cognitive functioning
- Caregiver burden/strain
- Memory of patient distress

Resource Utilization Outcomes

Readmission to Hospital – Aged 65 Years and Older

Haloperidol Versus Placebo

One RCT, with low risk of bias, compared haloperidol with placebo for the prevention of delirium in hospitalized medical and surgical patients aged 65 years of age and older.⁴¹ This RCT reported no statistically significant effect on readmission to the acute care hospital by treatment group at 3 months or 6 months followup.

Other Comparisons

We found no delirium prevention trials evaluating readmission to the acute care hospital in patients aged 65 years and older for the following comparisons:

- Second-generation antipsychotics versus placebo
- Haloperidol versus second-generation antipsychotics
- Second-generation antipsychotics versus second-generation antipsychotics
- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies.

Length of Stay in Hospital – Aged 65 Years and Older

Haloperidol Versus Placebo

Two RCTs compared haloperidol with placebo and assessed length of stay in hospital for patients aged 65 or older.^{41, 43} One RCT, with low risk of bias, enrolled patients aged 70 years and older in medical or surgical specialty.⁴¹ The other RCT, with unclear risk of bias, enrolled patients aged 65 years and older admitted to the intensive care unit after noncardiac surgery.⁴³ Both trials consistently reported no statistically significant effect on length of stay in hospital for haloperidol compared with placebo for the overall study population. One of the trials also reported no statistically significant effect on length of stay in hospital for haloperidol compared with placebo in patients who had developed postoperative delirium.⁴³

Second-Generation Antipsychotics Versus Placebo

One RCT, with low risk of bias, enrolled patients aged 65 years and older who experienced subsyndromal delirium after on-pump cardiac surgery examined the effect of risperidone

compared with placebo on length of stay in hospital.³⁶ This trial reported no statistically significant effect for risperidone compared with placebo.

Other Comparisons

We found no delirium prevention trials evaluating length of stay in hospital for patients aged 65 years and older for the following comparisons:

- Haloperidol versus second-generation antipsychotics
- Second-generation antipsychotics versus second-generation antipsychotics
- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies.

Length of Stay in Intensive Care Unit – Aged 65 Years and Older

Haloperidol Versus Placebo

One RCT, with unclear risk of bias, enrolled patients aged 65 years and older undergoing non-cardiac surgery and recovery in an intensive care unit.⁴³ This trial reported a statistically significant difference for length of stay in the intensive care unit for patients randomized to a 0.5 mg loading dose of haloperidol followed by 0.1 mg per hour infusion compared with placebo. However, this difference of less than 2 hours in the intensive care unit is not clinically important.

Second-Generation Antipsychotics Versus Placebo

One RCT, with low risk of bias, enrolled cardiac surgery patients aged 65 years and older with subsyndromal delirium in the postoperative setting and reported no statistically significant difference in length of stay in the intensive care unit for those randomized to receive 1 mg per day of oral risperidone compared with placebo.³⁶

Other Comparisons

We found no delirium prevention trials evaluating length of stay in the intensive care unit among patients aged 65 years and older for the following comparisons:

- Haloperidol versus second-generation antipsychotics
- Second-generation antipsychotics versus second-generation antipsychotics
- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies.

Patient Safety Attendant Use – Aged 65 Years and Older

Second-Generation Antipsychotics Versus Placebo

One RCT, with low risk of bias and enrolling orthopedic surgery patients aged 65 years and older, compared treatment with 10 mg of oral olanzapine in the perioperative setting with placebo and reported no statistically significant between-group difference in patient safety attendant.³⁹

Other Comparisons

We found no delirium prevention trials evaluating patient safety attendant use for patients aged 65 years and older for the following comparisons:

- Haloperidol versus placebo

- Haloperidol versus second-generation antipsychotics
- Second-generation antipsychotics versus second-generation antipsychotics
- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies.

Other Resource Utilization Outcomes – Aged 65 years and older

We found no trials in patients aged 65 years and older at risk for delirium that compared an antipsychotic with a placebo, another antipsychotic, or another treatment and evaluated the following resource utilization outcomes:

- Readmission to intensive care unit
- Length of stay in skilled nursing facility
- Hospice enrollment.

Adverse Effects

Sedation – Aged 65 Years and Older

Haloperidol Versus Placebo

One RCT, with low risk of bias, enrolled patients aged 70 years and older admitted to medical or surgical acute inpatient wards from the Emergency Department and reported on sedation (described as somnolence) in patients randomized to oral haloperidol (maximum fixed daily dose: 2mg) compared with placebo for the prevention of delirium.⁴¹ There was no statistically significant between-group difference in the relative risk of developing somnolence. However, there were too few events in this trial to draw a conclusion about the effects of haloperidol on sedation. (SOE: Insufficient)

We did not find any observational studies addressing sedation that compared haloperidol with placebo in patients aged 65 years and older at risk for delirium.

Other Comparisons

We found no studies of delirium prevention evaluating sedation in patients aged 65 years and older for the following comparisons:

- Second-generation antipsychotics versus placebo
- Haloperidol versus second-generation antipsychotics
- Second-generation antipsychotics versus second-generation antipsychotics
- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies.

Strength of Evidence

Table 11 summarizes the strength of evidence findings for the effects of antipsychotics in terms of sedation in patients aged 65 years and older.

Table 11. Strength of evidence domains for studies reporting sedation in the evaluation of antipsychotics for delirium prevention

Comparison	Number Of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength Of Evidence	Summary
Haloperidol vs. placebo	1 ⁴¹ (242)	Low	Direct	Unknown (single study)	Imprecise*	Undetected	Insufficient	We are unable to draw a conclusion.
Second-generation antipsychotics vs. placebo	No studies							
Haloperidol vs. second-generation antipsychotics	No studies							
Second-generation antipsychotics vs. second-generation antipsychotics	No studies							
Haloperidol vs. other therapies	No studies							
Second-generation antipsychotics vs. other therapies	No studies							

* Numbers of events were few.

Cardiac Effects – Aged 65 Years and Older

Haloperidol Versus Placebo

Two RCTs compared haloperidol with placebo for the prevention of delirium in patients aged 65 years and older and reported no statistically significant between-group difference in cardiac effects.^{41, 43} There were few events in the trials, so the results are imprecise.

One RCT, with low risk of bias and enrolling patients aged 70 years and older admitted from the Emergency Department to medical or surgical acute inpatient wards, compared oral haloperidol (maximum fixed daily dose: 2 mg) with placebo for the prevention of delirium and reported on adverse cardiac events.⁴¹ This trial reported no statistically significant between-group difference in acute coronary syndrome.

Another RCT, with unclear risk of bias, enrolled patients aged 65 years and older undergoing non-cardiac surgery and recovery in an intensive care unit.⁴³ Patients randomized to a 0.5 mg loading dose of haloperidol, followed by 0.1 mg per hour infusion did not have any statistically significant between-group differences when compared with placebo in corrected QT interval prolongation or the development of arrhythmia during study drug infusion.

We did not find any observational studies addressing cardiac effects that compared haloperidol with placebo in patients aged 65 years and older at risk for delirium.

Second-Generation Antipsychotics Versus Placebo

Two RCTs compared olanzapine with placebo and reported on cardiac effects.^{36, 39} One RCT, with low risk of bias and enrolling orthopedic surgery patients aged 65 years and older treated with 10 mg of oral olanzapine versus placebo in the perioperative period, reported no statistically significant between-group differences in arrhythmias or atrial fibrillation.³⁹ Another RCT, with low risk of bias, enrolled cardiac surgery patients aged 65 years and older with subsyndromal delirium in the postoperative period and reported no prolongation of the corrected QT interval patients randomized to 1 mg per day of risperidone compared with placebo.³⁶

We did not find any observational studies addressing cardiac effects that compared second-generation antipsychotics with placebo in patients aged 65 years and older at risk for delirium.

Other Comparisons

We found no studies of delirium prevention evaluating cardiac effects in patients aged 65 years and older for the following comparisons:

- Haloperidol versus second-generation antipsychotics
- Second-generation antipsychotics versus second-generation antipsychotics
- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies.

Neurologic Effects – Aged 65 Years and Older

Haloperidol Versus Placebo

Three RCTs compared haloperidol with placebo or no medication for the prevention of delirium in patients aged 65 years and older and reported no statistically significant between-group difference in neurologic symptoms.^{35, 41, 43} There were few events in the trials, so the results are imprecise.

One RCT, with low risk of bias, randomized patients aged 70 years and older at risk of delirium and admitted from the Emergency Department to surgical or medical units.⁴¹ There was no statistically significant between-group difference in neurologic symptoms in those patients randomized to 2 mg per day of oral haloperidol compared with placebo for occurrence of extrapyramidal side effects or reports of adverse events including transient ischemic attacks.

One RCT, with high risk of bias owing to a lack of blinding and allocation concealment, enrolled patients aged 75 years and older undergoing elective digestive or orthopedic surgeries in an open-label study.³⁵ This trial reported no between-group differences in adverse events including confusions and loss of consciousness in patients randomized to 2.5 mg per day of oral haloperidol compared with those patients randomized to no drug.

One RCT, with unclear risk of bias, enrolled patients aged 65 years and older undergoing non-cardiac surgery and recovery in an intensive care unit.⁴³ This trial reported the absence of the occurrence of neuroleptic malignant syndrome in patients in either arm.

We did not find any observational studies addressing neurologic effects that compared haloperidol with placebo in patients aged 65 years and older at risk for delirium.

Second-Generation Antipsychotics Versus Placebo

One RCT, with low risk of bias, compared oral second-generation antipsychotics with placebo for the prevention of delirium in post-surgical patients and reported neurologic effects.³⁶ This trial enrolled 101 cardiac surgery patients receiving oral risperidone versus placebo and reported no statistically significant between-group differences in extrapyramidal side effects.³⁶

We did not find any observational studies addressing neurologic effects that compared second-generation antipsychotics with placebo in patients aged 65 years and older at risk for delirium.

Haloperidol Versus Second-Generation Antipsychotics

One RCT, with low risk of bias, enrolled cardiac surgery patients aged 65 years and older with subsyndromal delirium in the postoperative setting and reported no statistically significant between-group difference in neurologic effects, including extrapyramidal symptoms for those randomized to receive 1 mg per day of oral risperidone compared with.³⁶

We did not find any observational studies addressing neurologic effects that compared haloperidol with second-generation antipsychotics in patients aged 65 years and older at risk for delirium.

Other Comparisons

We found no studies of delirium prevention that evaluated neurologic effects in patients aged 65 years and older for the following comparisons:

- Second-generation antipsychotics versus second-generation antipsychotics
- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies.

Other Adverse Effects – Aged 65 Years and Older

We found no studies in patients aged 65 years and older at risk for delirium that compared an antipsychotic with a placebo, another antipsychotic, or another treatment and evaluated the following adverse events:

- Weight gain

- Changes in appetite
- Hypersensitivity reactions
- Inappropriate continuation of antipsychotics
- Swallowing difficulties
- Aspiration pneumonia

Key Question 1b. Benefits and Harms of Antipsychotics To Prevent Delirium in Persons with Dementia

We found no trials evaluating antipsychotics for the prevention of delirium in persons with dementia.

Key Question 1c. Benefits and Harms of Antipsychotics To Prevent Delirium in Patients in an Intensive Care Unit

Key Points – Intensive Care Unit

Delirium Severity

- We were unable to draw a conclusion regarding the effects of antipsychotics on delirium severity for the following comparisons:
 - Haloperidol versus placebo (insufficient evidence)
 - Second-generation antipsychotics versus placebo (no trials)
 - Haloperidol versus second-generation antipsychotics (no trials)
 - Second-generation antipsychotics versus second-generation antipsychotics (no trials)
 - Haloperidol versus other therapies (no trials)
 - Second-generation antipsychotics versus other therapies (no trials)

Length of Stay in Hospital

- In critically ill medical and surgical patients, there was little to no difference in length of stay in hospital for haloperidol compared with placebo. (SOE: High)
- We were unable to draw a conclusion regarding the effects of antipsychotics on length of stay in hospital for the following comparisons:
 - Second-generation antipsychotics versus placebo (insufficient evidence)
 - Haloperidol versus second-generation antipsychotics (insufficient evidence)
 - Second-generation antipsychotics versus second-generation antipsychotics (no trials)
 - Haloperidol versus other therapies (insufficient evidence)
 - Second-generation antipsychotics versus other therapies (no trials)

Cognitive Functioning, Inappropriate Continuation of Antipsychotics

- We found no studies evaluating cognitive functioning or inappropriate continuation of antipsychotics in patients in an intensive care unit at risk for delirium that compared an antipsychotic with a placebo, another antipsychotic, or another treatment.

Sedation

- We were unable to draw a conclusion regarding the effects of antipsychotics on sedation for the following comparisons:
 - Haloperidol versus placebo (insufficient evidence)
 - Second-generation antipsychotics versus placebo (no studies)
 - Haloperidol versus second-generation antipsychotics (no studies)
 - Second-generation antipsychotics versus second-generation antipsychotics (no studies)
 - Haloperidol versus other therapies (no studies)
 - Second-generation antipsychotics versus other therapies (no studies)

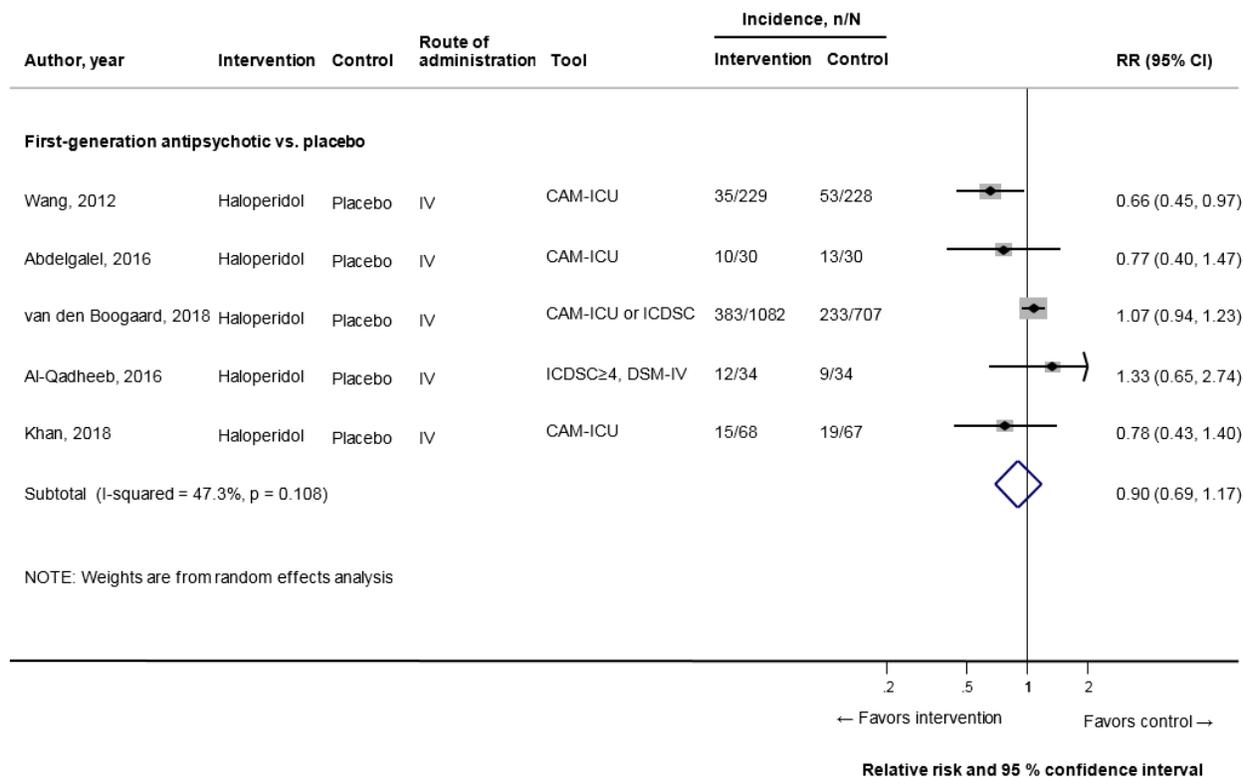
Intermediate Outcomes

Delirium Incidence – Intensive Care Unit

Haloperidol Versus Placebo

Five RCTs, three with low risk of bias^{34, 42, 46} and two with unclear risk of bias,^{33, 43} directly compared delirium occurrence in patients randomized to haloperidol and placebo groups. The five RCTs enrolled 2,557 patients in both surgical and medical intensive care unit settings and used a variety of validated delirium detection instruments. Intravenous haloperidol was administered in all trials. We conducted a meta-analysis of these trials because they identified new onset of delirium (incidence) after exposure to prophylactic haloperidol or placebo in surgical and medical intensive care unit patients. We found no difference in the relative risk of delirium in the pooled analysis (RR, 0.90; 95% CI, 0.69 to 1.17, I-squared, 47%) (Figure 11). Exclusion of any one study did not change the inference of the meta-analysis. We considered these results to be consistent, but imprecise.

Figure 11. Meta-analysis of delirium incidence in trials comparing haloperidol with placebo in critically ill patients at risk for delirium



CAM-ICU = Confusion Assessment Method for the Intensive Care Unit; CI = confidence interval; DOSS = Delirium Observation Screening Scale; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, 4th ed.; ICDSC = Intensive Care Delirium Screening Checklist; IV = intravenous; n = incidence within arm; N = total arm population; p = p-value; RR = relative risk.

Second-Generation Antipsychotics Versus Placebo

One RCT,³⁶ with low risk of bias, and one RCT, with high risk of bias owing to a lack of blinding,⁴⁰ compared delirium occurrence in the postoperative setting following randomization to risperidone or placebo. These two RCTs enrolled patients without delirium prior to cardiac surgery and recovery in the intensive care unit. Both of these trials demonstrated statistically significant between-group differences in the incidence of delirium.

Haloperidol Versus Other Therapies

The findings presented in the “Delirium Incidence - Overall” results section are wholly represented by this subgroup. Please refer to the “Delirium Incidence - Overall” results section.

Other Comparisons

We found no delirium prevention trials evaluating delirium incidence among critically ill patients for the following comparisons:

- Haloperidol versus second-generation antipsychotics
- Second-generation antipsychotics versus second-generation antipsychotics
- Second-generation antipsychotics versus other therapies.

Short-Term Delirium Symptoms – Intensive Care Unit

Haloperidol Versus Placebo

One RCT, with low risk of bias, included patients receiving mechanical ventilation enrolled within 72 hours of intensive care unit admission.⁴⁵ This study showed a statistically significant effect of haloperidol on the proportion of patients with a Richmond Agitation-Sedation Scale (RASS) score of +2 or more compared with the placebo.

Other Comparisons

We found no delirium prevention trials evaluating short-term delirium symptoms in critically ill patients for the following comparisons:

- Second-generation antipsychotics versus placebo
- Haloperidol versus second-generation antipsychotics
- Second-generation antipsychotics versus second-generation antipsychotics
- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies.

Delirium Severity – Intensive Care Unit

Haloperidol Versus Placebo

One low risk of bias RCT evaluated delirium severity in 135 patients at risk of delirium undergoing major non-cardiac thoracic surgery randomized to intravenous haloperidol or placebo.⁴⁶ No statistically significant between-group differences were found in delirium severity between haloperidol and placebo among patients who developed delirium (results provided by author). Because the results were imprecise, we are unable to draw any conclusions about the effects of haloperidol versus placebo on delirium severity among patients in the intensive care unit at risk for delirium. (SOE: Insufficient)

Other Comparisons

We found no delirium prevention trials evaluating delirium severity for critically ill patients for the following comparisons:

- Second-generation antipsychotics versus placebo
- Haloperidol versus second-generation antipsychotics
- Second-generation antipsychotics versus second-generation antipsychotics
- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies.

Strength of Evidence

Table 12 summarizes the strength of evidence findings for antipsychotics for the prevention of delirium in terms of delirium severity for critically ill patients.

Table 12. Strength of evidence domains for trials evaluating antipsychotics for the prevention of delirium in terms of delirium severity for patients in an intensive care unit

Comparison	Number Of Trials (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength Of Evidence	Summary
Haloperidol vs. placebo	1 ⁴⁶ (135)	Low	Direct	Consistency unknown, (single study)	Imprecise	Undetected	Insufficient	We are unable to draw any conclusions.
Second-generation antipsychotics vs. placebo	No trials							
Haloperidol vs. second-generation antipsychotics	No trials							
Second-generation antipsychotics vs. second-generation antipsychotics	No trials							
Haloperidol vs. other therapies	No trials							
Second-generation antipsychotics vs. other therapies	No trials							

Delirium-Free, Coma-Free Days Alive – Intensive Care Unit

Haloperidol Versus Placebo

The findings presented in the “Delirium-Free, Coma-Free Days Alive - Overall” results section are wholly represented by this subgroup. Please refer to the “Delirium-Free, Coma-Free Days Alive - Overall” results section.

Second-Generation Antipsychotics Versus Placebo

The findings presented in the “Delirium-Free, Coma-Free Days Alive - Overall” results section are wholly represented by this subgroup. Please refer to the “Delirium-Free, Coma-Free Days Alive - Overall” results section.

Haloperidol Versus Second-Generation Antipsychotics

The findings presented in the “Delirium-Free, Coma-Free Days Alive - Overall” results section are wholly represented by this subgroup. Please refer to the “Delirium-Free, Coma-Free Days Alive - Overall” results section.

Other Comparisons

We found no delirium prevention trials evaluating delirium- and coma-free days in critically ill patients for the following comparisons:

- Second-generation antipsychotics versus second-generation antipsychotics
- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies.

Duration of Delirium – Intensive Care Unit

Haloperidol Versus Placebo

Four RCTs,^{34, 44-46} with low risk of bias, compared haloperidol with placebo for the prevention of delirium in patients admitted to medical or surgical intensive care units and requiring mechanical ventilation. All four of the trials consistently reported no statistically significant difference in delirium duration in haloperidol compared with placebo. We did not conduct a meta-analysis because these trials generally provided results as median values. The skewed nature of length of stay data precluded conversion or transformation of the data.

Second-Generation Antipsychotics Versus Placebo

One RCT, with low risk of bias, enrolled patients with and without delirium who received mechanical ventilation in mixed medical and surgical intensive care units.⁴⁴ This three-arm trial reported no statistically significant effect on delirium duration for 30 patients randomized to a median dose of 113 mg per day of oral ziprasidone compared with 36 patients randomized to placebo.

Haloperidol Versus Second-Generation Antipsychotics

The findings presented in the “Duration of Delirium - Overall” results section are wholly represented by this subgroup. Please refer to the “Duration of Delirium - Overall” results section.

Other Comparisons

We found no delirium prevention trials evaluating delirium duration in critically ill patients for the following comparisons:

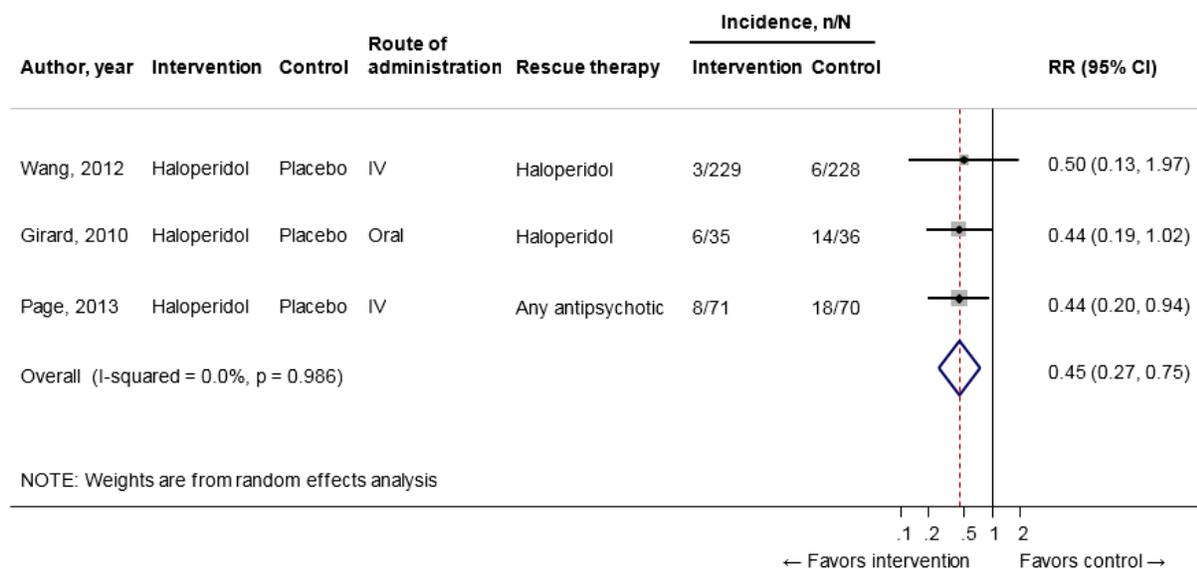
- Second-generation antipsychotics versus second-generation antipsychotics
- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies.

Use of Rescue Therapy – Intensive Care Unit

Haloperidol Versus Placebo

Three RCTs, two with low risk of bias^{44, 45} and one with uncertain risk of bias,⁴³ compared haloperidol with placebo for the prevention of delirium and reported on the use of rescue therapy, defined as the use of any open-label antipsychotic. All three RCTs, of which one was a three-arm trial,⁴⁴ enrolled medical and/or surgical patients in the intensive care unit setting. We found a statistically significant between-group difference in the use of rescue therapy favoring the haloperidol group (pooled RR, 0.45; 95% CI, 0.27 to 0.75; I-squared, 0%) (Figure 12). This is a possibly relevant decrease but the potential impact is difficult to assess. Exclusion of any one study did not change the inference from the meta-analysis.

Figure 12. Meta-analysis of the use of rescue therapy in trials comparing haloperidol with placebo in critically ill patients at risk for delirium



Relative risk and 95% confidence interval

CI = confidence interval; IV = intravenous; n = incidence within arm; N = total arm population; p = p-value; RR = relative risk.

Second-Generation Antipsychotics Versus Placebo

The findings presented in the “Use of Rescue Therapy - Overall” results section are wholly represented by this subgroup. Please refer to the “Use of Rescue Therapy - Overall” results section.

Haloperidol Versus Second-Generation Antipsychotics

The findings presented in the “Use of Rescue Therapy - Overall” results section are wholly represented by this subgroup. Please refer to the “Use of Rescue Therapy - Overall” results section.

Other Comparisons

We found no delirium prevention trials evaluating the use of rescue therapy in critically ill patients for the following comparisons:

- Second-generation antipsychotics versus second-generation antipsychotics
- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies.

Use of Physical Restraint – Intensive Care Unit

Haloperidol Versus Placebo

The findings presented in the “Use of Physical Restraint - Overall” results section are wholly represented by this subgroup. Please refer to the “Use of Physical Restraint - Overall” results section.

Other Comparisons

We found no delirium prevention trials evaluating the use of physical restraint for critically ill patients for the following comparisons:

- Second-generation antipsychotics versus placebo
- Haloperidol versus second-generation antipsychotics
- Second-generation antipsychotics versus second-generation antipsychotics
- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies.

Other Intermediate Outcomes – Intensive Care Unit

We found no trials in patients in an intensive care unit at risk for delirium that compared an antipsychotic with a placebo, another antipsychotic, or another treatment and evaluated the following intermediate outcomes:

- Patient distress

Final Health or Patient-Centered Outcomes

Mortality – Intensive Care Unit

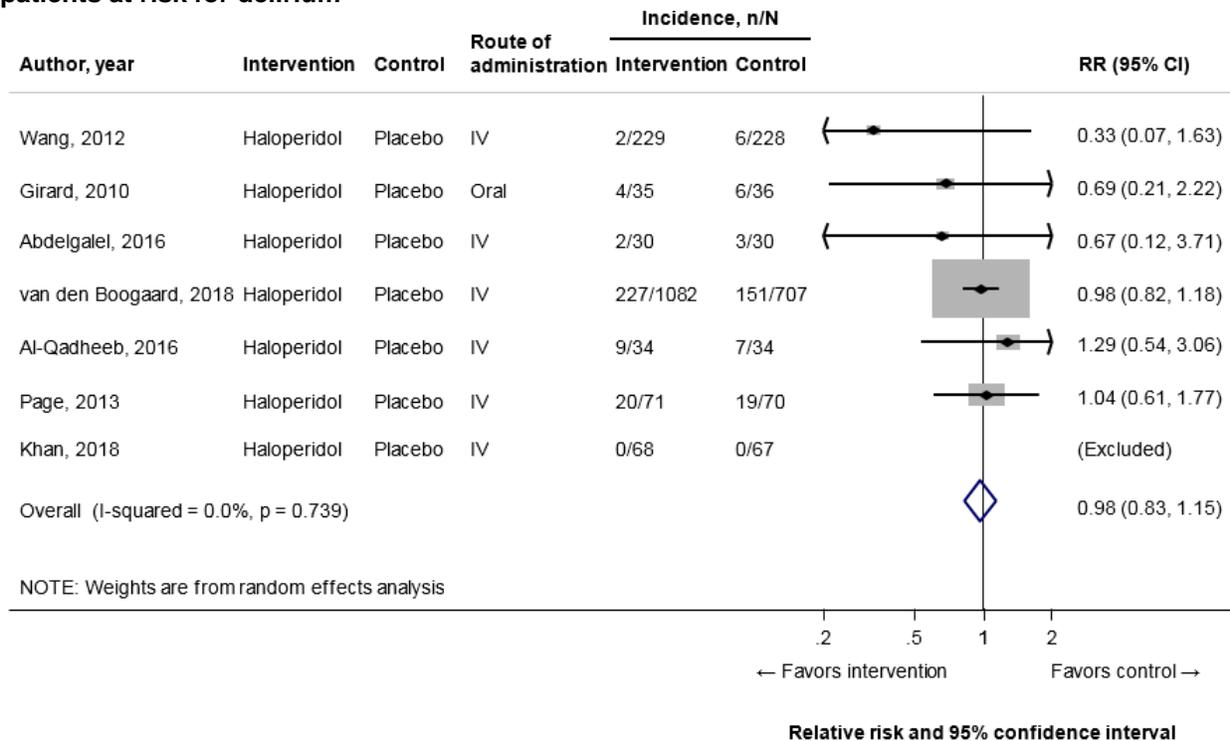
Haloperidol Versus Placebo

We conducted a meta-analysis of seven RCTs that compared haloperidol with placebo in patients in intensive care units; one study was excluded from the analysis because there were no events. We found no between-group differences in short-term mortality, defined as mortality while in hospital or up to 30 days after randomization (pooled RR, 0.98; 95% CI, 0.83 to 1.15; $P = 0.74$; Figure 13).^{33, 34, 42-46} Five of the RCTs were low risk of bias^{34, 42, 44-46} and two of the RCTs had unclear risk of bias.^{33, 43} The evidence was consistent and precise. We tested the effect

of each individual trial on the combined point estimate. No single trial influenced the pooled results. No substantial statistical heterogeneity was identified.

The largest trial, with low risk of bias enrolling a total of 1,789 critically ill patients, also examined 90-day mortality.⁴² The result was similar to the short-term mortality, with no between-group differences in comparing 3 mg or 6 mg haloperidol with placebo (RR, 0.99; 95% CI, 0.77 to 1.27).

Figure 13. Meta-analysis of mortality in trials comparing haloperidol with placebo in critically ill patients at risk for delirium



CI = confidence interval; IV = intravenous; n = incidence within arm; N = total arm population; p = p-value; RR = relative risk.

Second-Generation Antipsychotics Versus Placebo

One RCT, with low risk of bias, compared ziprasidone with placebo and reported no between-group differences in short-term mortality, defined as mortality while in hospital or up to 30 days after randomization.⁴⁴

Haloperidol Versus Second-Generation Antipsychotics

The findings presented in the “Mortality - Overall” results section are wholly represented by this subgroup. Please refer to the “Mortality - Overall” results section.

Haloperidol Versus Other Therapies

The findings presented in the “Mortality - Overall” results section are wholly represented by this subgroup. Please refer to the “Mortality - Overall” results section.

Other Comparisons

We found no delirium prevention trials evaluating mortality in critically ill patients for the following comparisons:

- Second-generation antipsychotics versus second-generation antipsychotics
- Second-generation antipsychotics versus other therapies.

Other Final Health or Patient-Centered Outcomes – Intensive Care Unit

We found no trials in patients in an intensive care unit at risk for delirium that compared an antipsychotic with a placebo, another antipsychotic, or another treatment and evaluated the following final health or patient-centered outcomes:

- Quality of life
- Cognitive functioning
- Institutionalization
- Caregiver burden/strain
- Falls
- Memory of patient distress

Resource Utilization Outcomes

Readmission to Intensive Care Unit – Intensive Care Unit

Haloperidol Versus Placebo

The findings presented in the “Readmission to Intensive Care Unit - Overall” results section are wholly represented by this subgroup. Please refer to the “Readmission to Intensive Care Unit - Overall” results section.

Other Comparisons

We found no delirium prevention trials evaluating readmission to intensive care unit in critically ill patients for the following comparisons:

- Second-generation antipsychotics versus placebo
- Haloperidol versus second-generation antipsychotics
- Second-generation antipsychotics versus second-generation antipsychotics
- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies.

Length of Stay in Hospital – Intensive Care Unit

Haloperidol Versus Placebo

Six RCTs compared haloperidol with placebo and assessed length of stay in hospital for medical and surgical patients in intensive care units.^{33, 42-46} Four of the RCTs had low risk of bias,^{42, 44-46} and two of the RCTs had unclear risk of bias.^{33, 43} We did not conduct a meta-analysis because these trials generally provided results as median values and the length of stay data are skewed, precluding conversion or transformation of the data. Five of the RCTs reported no statistically significant difference in length of stay in hospital when comparing haloperidol with placebo.⁴²⁻⁴⁶ However, one three-arm RCT reported significantly shorter length of stay in hospital in the haloperidol group compared with placebo.³³

In summary, we concluded that haloperidol compared to placebo did not affect the length of stay in hospital when used to prevent delirium. (SOE for patients in the intensive care unit: High)

Second-Generation Antipsychotics Versus Placebo

One RCT, with low risk of bias and enrolling patients receiving mechanical ventilation, reported no statistically significant effect on length of stay in hospital for ziprasidone compared with placebo.⁴⁴ We were unable to draw conclusions based upon this one study. (SOE for patients in the intensive care unit: Insufficient)

Haloperidol Versus Second-Generation Antipsychotics

The findings presented in the “Length of Stay in Hospital - Overall” results section are wholly represented by this subgroup. Please refer to the “Length of Stay in Hospital - Overall” results section. We were unable to draw a conclusion. (SOE for patients in the intensive care unit: Insufficient)

Haloperidol Versus Other Therapies

The findings presented in the “Length of Stay in Hospital - Overall” results section are wholly represented by this subgroup. Please refer to the “Length of Stay in Hospital - Overall” results section. We were unable to draw a conclusion. (SOE for patients in the intensive care unit: Insufficient)

Other Comparisons

We found no delirium prevention trials evaluating length of stay in hospital for critically ill patients for the following comparisons:

- Second-generation antipsychotics versus second-generation antipsychotics
- Second-generation antipsychotics versus other therapies.

Strength of Evidence

Table 13 summarizes the strength of evidence findings for antipsychotics for the prevention of delirium in terms of length of stay in hospital for critically ill patients.

Table 13. Strength of evidence domains for trials evaluating antipsychotics for the prevention of delirium in terms of length of stay in hospital for patients in an intensive care unit

Comparison	Number Of Trials (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength Of Evidence	Summary
Haloperidol vs. placebo	6 ^{33, 42-46} (2,623)	Low	Direct	Consistent	Precise	Undetected	High	All RCTs were conducted in medical and surgical patients in intensive care units. There was no statistically significant difference in length of stay in hospital comparing haloperidol to placebo.
Second-generation antipsychotics vs. placebo	1 ⁴⁴ (101)	Low	Direct	Consistency unknown, (single study)	Imprecise	Undetected	Insufficient	We were unable to draw a conclusion.
Haloperidol vs. second-generation antipsychotics	1 ⁴⁴ (101)	Low	Direct	Consistency unknown, (single study)	Imprecise	Undetected	Insufficient	We were unable to draw a conclusion.
Second-generation antipsychotics vs. second-generation antipsychotics	No trials							
Haloperidol vs. other therapies	1 ³³ (90)	Medium	Direct	Consistency unknown, (single study)	Imprecise	Undetected	Insufficient	We were unable to draw a conclusion.
Second-generation antipsychotics vs. other therapies	No trials							

RCT = randomized controlled trial.

Length of Stay in Intensive Care Unit – Intensive Care Unit

Haloperidol Versus Placebo

The findings presented in the “Length of Stay in Intensive Care Unit - Overall” results section are wholly represented by this subgroup. Please refer to the “Length of Stay in Intensive Care Unit - Overall” results section.

Second-Generation Antipsychotics Versus Placebo

One RCT, with low risk of bias, enrolled patients with and without delirium who were receiving mechanical ventilation in mixed medical and surgical intensive care units.⁴⁴ This three-arm RCT reported no statistically significant effect on length of stay in the intensive care unit for patients randomized to receive a median dose of 113 mg per day of oral ziprasidone compared with patients receiving placebo.

Haloperidol Versus Second-Generation Antipsychotics

One RCT, with low risk of bias, enrolled patients with and without delirium who were receiving mechanical ventilation in mixed medical and surgical intensive care units.⁴⁴ This three-arm RCT reported no statistically significant effect on length of stay in the intensive care unit for patients randomized to receive a median dose of 15 mg per day of oral haloperidol compared with a median dose of 113 mg per day of oral ziprasidone.⁴⁴

Haloperidol Versus Other Therapies

One three-arm RCT, with unclear risk of bias, enrolled adult patients with severe systemic illness in an intensive care unit and demonstrated a statistically significant difference in length of stay in the intensive care unit for 30 patients randomized to receive a 2.5 mg loading dose of haloperidol followed by 0.5 to 2.0 mg per hour, based on sedation level compared with 30 patients randomized to receive 1.0 mcg/kg loading dose of dexmedetomidine followed by 0.2 to 0.7 mcg/kg per hour.³³

Other Comparisons

We found no delirium prevention trials evaluating length of stay in the intensive care unit for the following comparisons:

- Second-generation antipsychotics versus second-generation antipsychotics
- Second-generation antipsychotics versus other therapies.

Other Resource Utilization Outcomes – Intensive Care Unit

We found no trials in critically ill patients at risk for delirium that compared an antipsychotic with a placebo, another antipsychotic, or another treatment and evaluated the following resource utilization outcomes:

- Readmission to hospital
- Length of stay in skilled nursing facility
- Patient safety attendant use
- Hospice enrollment

Adverse Effects

Sedation – Intensive Care Unit

Haloperidol Versus Placebo

Two RCTs, both with low risk of bias, compared haloperidol with placebo in patients requiring mechanical ventilation in a medical or surgical intensive care unit and reported on sedation (described as excessive or oversedation).^{34, 45} There were too few events in these trials to draw a conclusion about the effects of haloperidol on sedation. (SOE: Insufficient)

We did not find any observational studies addressing sedation that compared haloperidol with placebo in critically ill patients at risk for delirium.

Other Comparisons

We found no studies of delirium prevention evaluating sedation in critically ill patients for the following comparisons:

- Second-generation antipsychotics versus placebo
- Haloperidol versus second-generation antipsychotics
- Second-generation antipsychotics versus second-generation antipsychotics
- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies.

Strength of Evidence

Table 14 summarizes the strength of evidence findings for antipsychotics for the prevention of delirium in terms of sedation in critically ill patients.

Table 14. Strength of evidence domains for studies reporting sedation in the evaluation of antipsychotics for delirium prevention in patients in an intensive care unit

Comparison	Number Of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength Of Evidence	Summary
Haloperidol vs. placebo	2 ^{34, 45} (209)	Low	Direct	Consistent	Imprecise*	Undetected	Insufficient	We are unable to draw a conclusion.
Second-generation antipsychotics vs. placebo	No studies							
Haloperidol vs. second-generation antipsychotics	No studies							
Second-generation antipsychotics vs. second-generation antipsychotics	No studies							
Haloperidol vs. other therapies	No studies							
Second-generation antipsychotics vs. other therapies	No studies							

* Numbers of events were few and confidence intervals wide with only two single center studies contributing data.

Cardiac Effects – Intensive Care Unit

Haloperidol Versus Placebo

The findings presented in the “Cardiac Effects - Overall” results section are wholly represented by this subgroup. Please refer to the “Cardiac Effects - Overall” results section.

Second-Generation Antipsychotics Versus Placebo

One RCT, with low risk of bias, compared ziprasidone with placebo and reported on cardiac effects.⁴⁴ This three-arm trial included patients included 66 mechanically ventilated, critically ill patients treated with oral ziprasidone versus placebo, and reported no statistically significant between-group differences in corrected QT interval; no ventricular arrhythmias occurred in either arm.

We did not find any observational studies addressing cardiac effects that compared second-generation antipsychotics with placebo in critically ill patients at risk for delirium.

Haloperidol Versus Second-Generation Antipsychotics

The findings presented in the “Cardiac Effects - Overall” results section are wholly represented by this subgroup. Please refer to the “Cardiac Effects - Overall” results section.

Haloperidol Versus Other Therapies

The findings presented in the “Cardiac Effects - Overall” results section are wholly represented by this subgroup. Please refer to the “Cardiac Effects - Overall” results section.

Other Comparisons

We found no studies of delirium prevention evaluating cardiac effects in critically ill patients for the following comparisons:

- Second-generation antipsychotics versus second-generation antipsychotics
- Second-generation antipsychotics versus other therapies.

Studies With No Comparison Group

The findings presented in the “Cardiac Effects - Overall” results section are wholly represented by this subgroup. Please refer to the “Cardiac Effects - Overall” results section.

Neurologic Effects – Intensive Care Unit

Haloperidol Versus Placebo

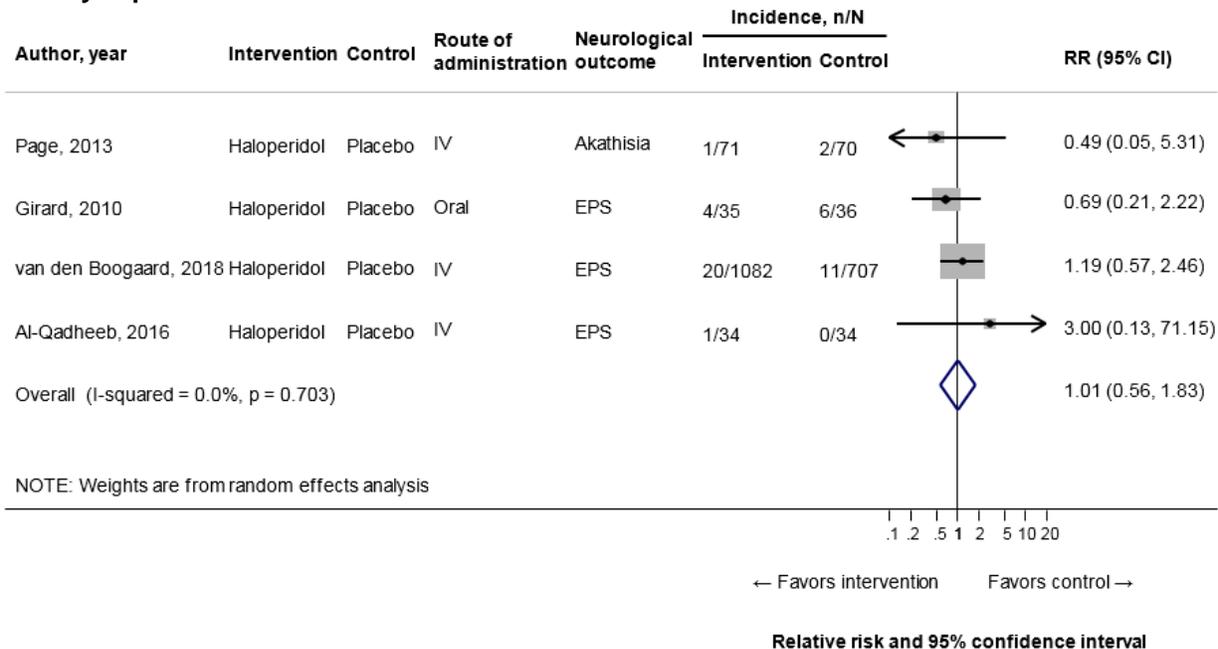
Five RCTs,^{34, 42, 44-46} with low risk of bias, compared haloperidol with placebo for the prevention of delirium in 2,235 patients admitted to medical or surgical intensive care units and reported a range of neurologic effects. Four of the trials administered haloperidol intravenously (maximum daily dose range, 1.5 to 7.5 mg),^{34, 42, 45, 46} and one of the trials administered oral doses (maximum daily dose, 20 mg).⁴⁴ One of the RCTs was a three-arm study.⁴⁴ There was no difference in between-group occurrence of extrapyramidal side effects (including akathisia, muscle stiffness, and dystonic movements such as torticollis) (pooled RR, 1.01; 95% CI, 0.56 to 1.83; I-squared, 0%) (Figure 14). Exclusion of any one trial did not change the inference from the meta-analysis. We excluded one study from the analysis because they reported individual

symptoms of extrapyramidal side effects.⁴⁶ This trial reported no statistically significant differences in elbow rigidity, wrist rigidity, or resting tremor and no events of dystonia, tardive dyskinesia, or pseudoparkinsonism.

Three RCTs reported the occurrence of neuroleptic malignant syndrome.^{42, 44, 46} One RCT reported no statistically significant between-group difference in patients randomized to intervention and placebo for 3 mg and 6 mg daily intravenous dosage arms.⁴² The other two RCTs reported no occurrence of neuroleptic malignant syndrome in either the haloperidol or the placebo arms in 206 critically ill, mechanically ventilated patients.^{44, 46}

We did not find any observational studies addressing neurologic effects that compared haloperidol with placebo in critically ill patients at risk for delirium.

Figure 14. Meta-analysis of neurologic effects in trials comparing haloperidol with placebo in critically ill patients at risk for delirium



CI = confidence interval; EPS = extrapyramidal symptoms; IV = intravenous; n = incidence within arm; N = total arm population; p = p-value; RR = relative risk.

Second-Generation Antipsychotics Versus Placebo

One RCT, with low risk of bias, compared oral second-generation antipsychotics with placebo for the prevention of delirium in critically ill and post-surgical patients and evaluated neurologic effects.⁴⁴ This three-arm study included a total of 101 mechanically ventilated, critically ill patients treated with oral ziprasidone versus placebo and reported no statistically significant between-group differences in akathisia or extrapyramidal symptoms not including akathisia. Neuroleptic malignant syndrome did not occur in either group in this study.

We did not find any observational studies addressing neurologic effects that compared second-generation antipsychotics with placebo in critically ill patients at risk for delirium.

Haloperidol Versus Second-Generation Antipsychotics

One three-arm RCT, with low risk of bias, compared oral haloperidol with ziprasidone in mechanically ventilated, critically ill patients and reported no statistically significant between-

group differences in akathisia or extrapyramidal symptoms not including akathisia. This trial also reported no instances of neuroleptic malignant syndrome.⁴⁴

We did not find any observational studies addressing neurologic effects that compared haloperidol with second-generation antipsychotics in critically ill patients at risk for delirium.

Other Comparisons

We found no studies of delirium prevention evaluating neurologic effects in critically ill patients for the following comparisons:

- Second-generation antipsychotics versus second-generation antipsychotics
- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies.

Studies With No Comparison Group

In one observational study with 177 critically ill patients at high risk of delirium who received intravenous haloperidol prophylaxis, one patient (1%) had to stop haloperidol because of an extrapyramidal side effect described as “signs of Parkinsonism,” and one patient (1%) had to stop haloperidol because of suspected neuroleptic malignant syndrome.⁴⁷

Other Adverse Effects – Intensive Care Unit

We found no studies in critically ill patients at risk for delirium that compared an antipsychotic with a placebo, another antipsychotic, or another treatment and evaluated the following adverse events:

- Weight gain
- Changes in appetite
- Hypersensitivity reactions
- Inappropriate continuation of antipsychotics
- Swallowing difficulties
- Aspiration pneumonia

Key Question 1d. Benefits and Harms of Antipsychotics To Prevent Delirium in Patients in a Post-Acute Care Facility

We found no trials evaluating antipsychotics for the prevention of delirium in patients in a post-acute care facility.

Key Question 1e. Benefits and Harms of Antipsychotics To Prevent Delirium in Patients in Palliative or Hospice Care

We found no trials evaluating antipsychotics for the prevention of delirium in patients in palliative or hospice care.

Key Question 1f. Benefits and Harms of Antipsychotics To Prevent Delirium in Patients in Postoperative Care

Key Points – Postoperative Care

Delirium Severity

- We were unable to draw a conclusion regarding the effects of antipsychotics on delirium severity in patients in postoperative care for the following comparisons:
 - Haloperidol versus placebo (insufficient evidence)
 - Second-generation antipsychotics versus placebo (insufficient evidence)
 - Haloperidol versus second-generation antipsychotics (no trials)
 - Second-generation antipsychotics versus second-generation antipsychotics (no trials)
 - Haloperidol versus other therapies (no trials)
 - Second-generation antipsychotics versus other therapies (no trials)

Length of Stay in Hospital

- We concluded that there was little to no difference in length of stay in hospital for postoperative patients treated with second-generation antipsychotics versus those treated with placebo. (SOE: Low)
- We were unable to draw a conclusion regarding the effects of antipsychotics on length of stay in hospital for patients in postoperative care for the following comparisons:
 - Haloperidol versus placebo (insufficient evidence)
 - Haloperidol versus second-generation antipsychotics (no trials)
 - Second-generation antipsychotics versus second-generation antipsychotics (no trials)
 - Haloperidol versus other therapies (no trials)
 - Second-generation antipsychotics versus other therapies (no trials)

Cognitive Functioning and Inappropriate Continuation of Antipsychotics

- We found no studies evaluating cognitive functioning or inappropriate continuation of antipsychotics in postoperative patients at risk for delirium that compared an antipsychotic with a placebo, another antipsychotic, or another treatment.

Intermediate Outcomes

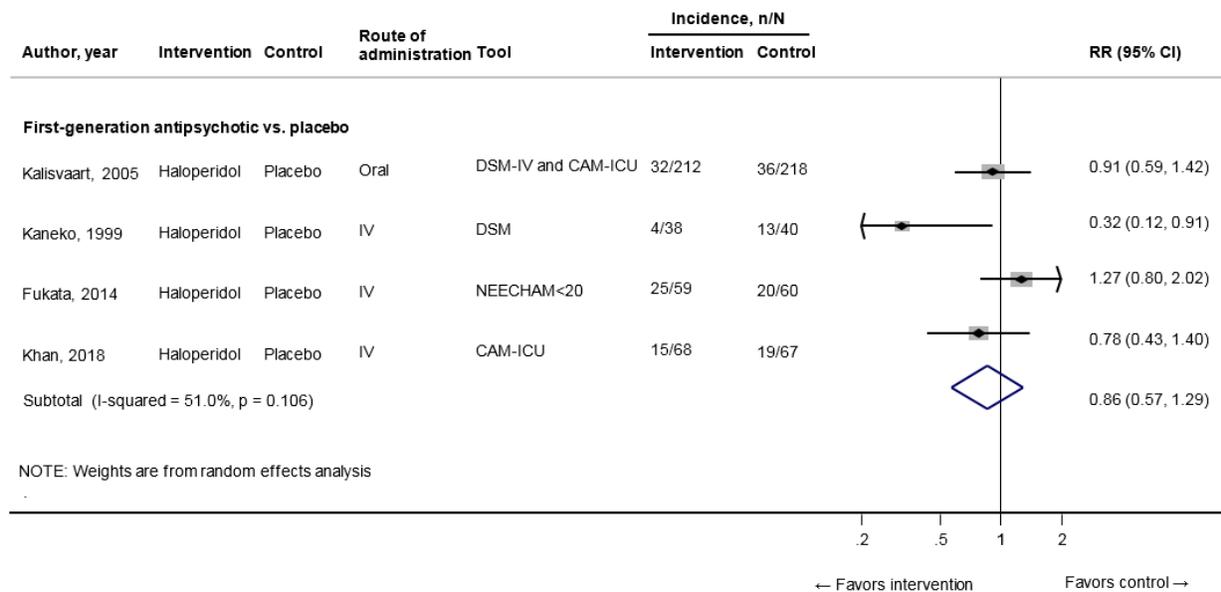
Delirium Incidence – Postoperative Care

Haloperidol Versus Placebo

Four RCTs, two with low risk of bias,^{37, 46} one with unclear risk of bias,³⁸ and one with high risk of bias owing to a lack of blinding and allocation concealment,³⁵ enrolling postoperative patients and employing different validated delirium detection instruments, directly compared delirium incidence between haloperidol and placebo groups. Three trials administered intravenous haloperidol,^{35, 38, 46} and one trial³⁷ administered oral doses. We included these trials in a meta-analysis because they identified new onset of delirium (incidence) in postoperative patients after exposure to prophylactic haloperidol or placebo. We found no difference in the

relative risk of delirium in the meta-analysis (RR, 0.86; 95% CI, 0.57 to 1.29; I-squared, 51%) (Figure 15). Exclusion of any one trial did not change the inference of the meta-analysis. Owing to the substantial statistical heterogeneity, we also conducted a profile likelihood method of meta-analysis, and found a similar non-statistically significant effect on delirium incidence comparing haloperidol with placebo (pooled RR, 0.92 95% CI, 0.52 to 1.26; I-squared, 0%).

Figure 15. Meta-analysis of delirium incidence in trials comparing haloperidol with placebo in postoperative patients at risk for delirium



CAM-ICU = Confusion Assessment Method for the Intensive Care Unit; CI = confidence interval; IV = intravenous; DSM = Diagnostic and Statistical Manual of Mental Disorders; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, 4th ed.; n = incidence within arm; N = total arm population; NEECHAM = Neelon-Champagne Confusion Scale; p = p-value; RR = relative risk.

Second-Generation Antipsychotics Versus Placebo

The findings presented in the “Delirium Incidence - Overall” results section are wholly represented by this subgroup. Please refer to the “Delirium Incidence - Overall” results section.

Other Comparisons

We found no delirium prevention trials evaluating delirium incidence in postoperative patients for the following comparisons:

- Haloperidol versus second-generation antipsychotics
- Second-generation antipsychotics versus second-generation antipsychotics
- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies.

Short-Term Delirium Symptoms – Postoperative Care

Haloperidol Versus Placebo

One RCT, with unclear risk of bias, compared haloperidol with placebo and assessed the delirium symptom of sleep duration during day and night.³⁸ This trial, enrolling patients

undergoing elective gastrointestinal surgery, reported no statistically significant difference between the haloperidol group and the placebo group in the average and total time of sleep.

Other Comparisons

We found no delirium prevention trials evaluating postoperative short-term delirium symptoms for the following comparisons:

- Second-generation antipsychotics versus placebo
- Haloperidol versus second-generation antipsychotics
- Second-generation antipsychotics versus second-generation antipsychotics
- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies.

Delirium Severity – Postoperative Care

Haloperidol Versus Placebo

Two RCTs, with low risk of bias, enrolled acute or elective hip surgery patients or patients undergoing non-cardiac thoracic surgery and assessed delirium severity by the highest value of the Delirium Rating Scale-Revised-98.^{37, 46} One RCT reported significantly lower delirium severity during the first three days after the onset of delirium in the haloperidol group compared with the placebo³⁷ and the second reported no statistical difference in severity among those who developed delirium (results provided by author).⁴⁶ We were unable to draw conclusions. (SOE in patients in postoperative care: Insufficient)

Second-Generation Antipsychotics Versus Placebo

The findings presented in the “Delirium Severity - Overall” results section are wholly represented by this subgroup. Please refer to the “Delirium Severity - Overall” results section.

Other Comparisons

We found no delirium prevention trials evaluating postoperative delirium severity for the following comparisons:

- Haloperidol versus second-generation antipsychotics
- Second-generation antipsychotics versus second-generation antipsychotics
- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies.

Strength of Evidence

Table 15 summarizes the strength of evidence findings for antipsychotics for the prevention of delirium in terms of delirium severity in postoperative patients.

Table 15. Strength of evidence domains for trials evaluating antipsychotics for the prevention of delirium in terms of delirium severity in postoperative patients

Comparison	Number Of Trials (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength Of Evidence	Summary
Haloperidol vs. placebo	2 ^{37, 46} (565)	Low	Direct	Inconsistent	Precise	Undetected	Insufficient	We were unable to draw a conclusion.
Second-generation antipsychotics vs. placebo	2 ^{36, 39} (501)	Low	Direct	Inconsistent	Precise	Undetected	Insufficient	We were unable to draw a conclusion
Haloperidol vs. second-generation antipsychotics	No trials							
Second-generation antipsychotics vs. second-generation antipsychotics	No trials							
Haloperidol vs. other therapies	No trials							
Second-generation antipsychotics vs. other therapies	No trials							

Duration of Delirium – Postoperative Care

Haloperidol Versus Placebo

Three RCTs, two with low risk of bias^{37, 46} and one at high risk of bias owing to lack of blinding and allocation concealment,³⁵ compared haloperidol with placebo for the prevention of delirium in postoperative patients and reported different findings.

Second-Generation Antipsychotics Versus Placebo

Two RCTs, with low risk of bias, compared a second-generation antipsychotic with placebo for the prevention of delirium and assessed delirium duration in postoperative patients.^{36, 39} One trial demonstrated no statistically significant within group difference for delirium duration,³⁶ and the other trial demonstrated a statistically significant shorter duration of delirium favoring the placebo group.³⁹

Other Comparisons

We found no delirium prevention trials evaluating delirium duration among patients in postoperative care for the following comparisons:

- Haloperidol versus second-generation antipsychotics
- Second-generation antipsychotics versus second-generation antipsychotics
- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies.

Use of Rescue Therapy – Postoperative Care

Haloperidol Versus Placebo

One RCT, with unclear risk of bias, enrolled patients aged 65 years and older undergoing non-cardiac surgery and recovery in an intensive care unit.⁴³ There was no statistically significant difference in the use of rescue medications (defined as the use of any open-label antipsychotic agent) in those patients randomized to a 0.5 mg loading dose of haloperidol followed by 0.1 mg per hour infusion compared with placebo.

Other Comparisons

We found no delirium prevention trials evaluating the use of rescue therapy among patients in postoperative care for the following comparisons:

- Second-generation antipsychotics versus placebo
- Haloperidol versus second-generation antipsychotics
- Second-generation antipsychotics versus second-generation antipsychotics
- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies.

Use of Physical Restraint – Postoperative Care

Haloperidol Versus Placebo

One RCT with low risk of bias enrolled patients undergoing major thoracic non-cardiac surgery in an intensive care unit.⁴⁶ This trial reported no difference in restraint use between the patients randomized to intravenous haloperidol compared with placebo.

Second-Generation Antipsychotics Versus Placebo

The findings presented in the “Use of Physical Restraint - Overall” results section are wholly represented by this subgroup. Please refer to the “Use of Physical Restraint - Overall” results section.

Other Comparisons

We found no delirium prevention trials evaluating the use of physical restraint in patients in postoperative care for the following comparisons:

- Haloperidol versus second-generation antipsychotics
- Second-generation antipsychotics versus second-generation antipsychotics
- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies

Other Intermediate Outcomes – Postoperative Care

We found no trials in patients in postoperative care with delirium that compared an antipsychotic with a placebo, another antipsychotic, or another treatment and evaluated the following intermediate outcomes:

- Delirium- and coma-free days alive
- Patient distress

Final Health or Patient-Centered Outcomes

Mortality – Postoperative Care

Haloperidol Versus Placebo

One RCT, with low risk of bias and enrolling patients after non-cardiac thoracic surgery, compared intravenous haloperidol with placebo and reported no in-hospital mortality.⁴⁶

Second-Generation Antipsychotics Versus Placebo

One RCT, with low risk of bias and enrolling patients after cardiac surgery, compared risperidone with placebo and reported no between-group differences in short-term mortality, defined as mortality while in hospital or up to 30 days after randomization.³⁶

Other Comparisons

We found no delirium prevention trials evaluating mortality in postoperative settings for the following comparisons:

- Haloperidol versus second-generation antipsychotics
- Second-generation antipsychotics versus second-generation antipsychotics

- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies.

Institutionalization – Postoperative Care

Second-Generation Antipsychotics Versus Placebo

The findings presented in the “Institutionalization - Overall” results section are wholly represented by this subgroup. Please refer to the “Institutionalization - Overall” results section.

Other Comparisons

We found no delirium prevention trials evaluating institutionalization in postoperative settings for the following comparisons:

- Haloperidol versus placebo
- Haloperidol versus second-generation antipsychotics
- Second-generation antipsychotics versus second-generation antipsychotics
- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies.

Other Final Health or Patient-Centered Outcomes – Postoperative Care

We found no trials in postoperative patients at risk for delirium that compared an antipsychotic with a placebo, another antipsychotic, or another treatment and evaluated the following final health or patient-centered outcomes:

- Quality of life
- Cognitive functioning
- Caregiver burden/strain
- Falls
- Memory of patient distress

Resource Utilization Outcomes

Length of Stay in Hospital – Postoperative Care

Haloperidol Versus Placebo

Two RCTs, both with low risk of bias, enrolled acute or elective hip surgery patients or patients undergoing non-cardiac thoracic surgery and reported different findings.^{37, 46} One trial reported significantly shorter length of stay in hospital in the haloperidol group compared with placebo,³⁷ and the other reported no statistically significant difference.⁴⁶ We were unable to draw conclusions. (SOE in patients in postoperative care: Insufficient)

Second-Generation Antipsychotics Versus Placebo

Two RCTs comparing second-generation antipsychotics with placebo assessed length of stay in hospital.^{36, 40} One trial had low risk of bias,³⁶ and the other trial had high risk of bias primarily owing to a lack of blinding and unclear potential for selective outcome reporting.⁴⁰ Both trials

reported no effect on length of stay in hospital when comparing second-generation antipsychotics with placebo in postoperative settings. (SOE in patients in postoperative care: Low)

Other Comparisons

We found no delirium prevention trials evaluating length of stay in hospital in postoperative settings for the following comparisons:

- Haloperidol versus second-generation antipsychotics
- Second-generation antipsychotics versus second-generation antipsychotics
- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies.

Strength of Evidence

Table 16 summarizes the strength of evidence findings for antipsychotics for the prevention of delirium in terms of length of stay in hospital in postoperative patients.

Table 16. Strength of evidence domains for trials evaluating antipsychotics for the prevention of delirium in terms of length of stay in hospital in postoperative patients

Comparison	Number Of Trials (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength Of Evidence	Summary
Haloperidol vs. placebo	2 ^{37, 46} (565)	Low	Direct	Inconsistent	Precise	Undetected	Insufficient	We were unable to draw a conclusion.
Second-generation antipsychotics vs. placebo	2 ^{36, 40} (227)	Medium	Direct	Consistent	Imprecise	Undetected	Low	All RCTs reported no statistically significant difference.
Haloperidol vs. second-generation antipsychotics	No trials							
Second-generation antipsychotics vs. second-generation antipsychotics	No trials							
Haloperidol vs. other therapies	No trials							
Second-generation antipsychotics vs. other therapies	No trials							

RCT = randomized controlled trial.

Length of Stay in Intensive Care Unit – Postoperative Care

Haloperidol Versus Placebo

Two RCTs, one with low risk of bias⁴⁶ and a second with unclear risk of bias,⁴³ enrolled patients undergoing major thoracic non-cardiac surgery and recovery in an intensive care unit. One trial reported no difference in intensive care length of stay⁴⁶ and the second reported a statistically significant difference for length of stay in the intensive care unit for patients randomized to intravenous haloperidol compared with placebo.⁴³ However, this difference of less than 2 hours in the intensive care unit is not considered clinically important.

Second-Generation Antipsychotics Versus Placebo

Two trials each compared risperidone with placebo and reported no statistically significant difference in length of stay in the intensive care unit. One RCT, with low risk of bias, enrolled cardiac surgery patients with postoperative subsyndromal delirium.³⁶ The other RCT, with high risk of bias owing to a lack of blinding, enrolled cardiac surgery patients randomized to treatment with a single dose of 1 mg sublingual risperidone versus placebo.⁴⁰ There were no statistically significant between-group differences in length of stay in the intensive care unit in either trial.

Other Comparisons

We found no delirium prevention trials evaluating length of stay in the intensive care unit among postoperative patients for the following comparisons:

- Haloperidol versus second-generation antipsychotics
- Second-generation antipsychotics versus second-generation antipsychotics
- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies.

Patient Safety Attendant Use – Postoperative Care

Second-Generation Antipsychotics Versus Placebo

The findings presented in the “Patient Safety Attendant Use - Overall” results section are wholly represented by this subgroup. Please refer to the “Patient Safety Attendant Use - Overall” results section.

Other Comparisons

We found no delirium prevention trials evaluating patient safety attendant use in postoperative settings for the following comparisons:

- Haloperidol versus placebo
- Haloperidol versus second-generation antipsychotics
- Second-generation antipsychotics versus second-generation antipsychotics
- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies.

Other Resource Utilization Outcomes – Postoperative Care

We found no trials in postoperative patients at risk of delirium that compared an antipsychotic with a placebo, another antipsychotic, or another treatment and evaluated the following resource utilization outcomes:

- Readmission to hospital
- Readmission to intensive care unit
- Length of stay in skilled nursing facility
- Hospice enrollment

Adverse Effects

Sedation – Postoperative Care

Haloperidol Versus Placebo

One RCT, with low risk of bias and enrolling patients undergoing elective and emergent hip surgeries at risk of delirium, reported no evidence of sedation in those randomized to 1.5 mg per day of oral perioperative haloperidol or placebo.³⁷

We did not find any observational studies addressing sedation that compared haloperidol with placebo in postoperative patients at risk for delirium.

Other Comparisons

We found no studies of delirium prevention evaluating sedation in postoperative patients for the following comparisons:

- Second-generation antipsychotics versus placebo
- Haloperidol versus second-generation antipsychotics
- Second-generation antipsychotics versus second-generation antipsychotics
- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies.

Cardiac Effects – Postoperative Care

Haloperidol Versus Placebo

One RCT, with low risk of bias and enrolling patients undergoing major thoracic non-cardiac surgery at risk of delirium, reported no evidence of cardiac side effects including arrhythmias or corrected QT interval prolongation in those randomized to intravenous haloperidol versus placebo.⁴⁶

Second-Generation Antipsychotics Versus Placebo

We identified three trials assessing different cardiac effects.^{36, 39, 40} One RCT, with low risk of bias, enrolled cardiac surgery patients with postoperative subsyndromal delirium, randomized to receive 1 mg per day oral risperidone versus placebo, and reported no corrected QT interval prolongation in either arm.³⁶ Two of the RCTs reported no statistically significant between-group differences in the occurrence of arrhythmias. One RCT, with low risk of bias and enrolling orthopedic surgery patients treated with 10 mg oral perioperative olanzapine versus placebo, reported no statistically significant difference in arrhythmias or atrial fibrillation.³⁹ One RCT,

with high risk of bias, owing to a lack of blinding, and enrolling 126 cardiac surgery patients treated with a 1 mg sublingual dose risperidone versus placebo, reported no statistically significant between-group differences in arrhythmias.⁴⁰

We did not find any observational studies addressing cardiac effects that compared second-generation antipsychotics with placebo in postoperative patients at risk for delirium.

Other Comparisons

We found no studies of delirium prevention evaluating cardiac effects in a postoperative setting for the following comparisons:

- Haloperidol versus second-generation antipsychotics
- Second-generation antipsychotics versus second-generation antipsychotics
- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies.

Neurologic Effects – Postoperative Care

Haloperidol Versus Placebo

Four RCTs compared haloperidol with placebo for the prevention of delirium in postoperative patients and reported neurologic outcomes.^{35, 37, 38, 46} Two RCTs, with low risk of bias and enrolling patients undergoing elective and emergent hip surgeries and major non-cardiac thoracic surgery at risk of delirium, reported no statistically significant differences in extrapyramidal effects in patients randomized to haloperidol versus placebo.^{37, 46}

One RCT, with unclear risk of bias, randomized patients undergoing gastrointestinal surgery to an intervention arm receiving 5 mg per day of intravenous haloperidol or a placebo group. This trial reported no evidence of extrapyramidal symptoms in patients in either arm of the study.³⁸

One RCT, with high risk of bias owing to a lack of blinding and allocation concealment, enrolling patients aged 75 years and older undergoing elective digestive or orthopedic surgeries in an open-label study, randomized patients to 2.5 mg per day of oral haloperidol or no drug.³⁵ This study reported no significant between-group difference in the occurrence of convulsions.

We did not find any observational studies addressing neurologic effects that compared haloperidol with placebo in postoperative patients at risk for delirium.

Second-Generation Antipsychotics Versus Placebo

One RCT, with low risk of bias, enrolled cardiac surgery patients with postoperative subsyndromal delirium and randomized to receive 1 mg per day of oral risperidone or placebo. This trial reported no statistically significant between-group differences in extrapyramidal side effects.³⁶

We did not find any observational studies addressing neurologic effects that compared second-generation antipsychotics with placebo in postoperative patients at risk for delirium.

Other Comparisons

We found no studies of delirium prevention evaluating neurologic effects in a postoperative setting for the following comparisons:

- Haloperidol versus second-generation antipsychotics
- Second-generation antipsychotics versus second-generation antipsychotics

- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies.

Other Adverse Effects – Postoperative Care

We found no studies in postoperative patients at risk for delirium that compared an antipsychotic with a placebo, another antipsychotic, or another treatment and evaluated the following adverse events:

- Weight gain
- Changes in appetite
- Hypersensitivity reactions
- Inappropriate continuation of antipsychotics
- Swallowing difficulties
- Aspiration pneumonia

Key Question 2. Benefits and Harms of Antipsychotics To Treat Delirium

Key Points – Overall

Delirium Severity

- There was little to no effect for haloperidol versus second-generation antipsychotics on delirium severity as evaluated by the Delirium Severity Rating Scale-Revised-98 (pooled mean between-group differences, 0.0; 95% CI, -2.0 to 2.0). (SOE: Moderate)
- We were unable to draw a conclusion regarding the effects of antipsychotics on delirium severity for the following comparisons:
 - Haloperidol versus placebo (insufficient evidence)
 - Second-generation antipsychotics versus placebo (insufficient evidence)
 - Second-generation antipsychotics versus second-generation antipsychotics (insufficient evidence)
 - Haloperidol versus other therapies (insufficient evidence)
 - Second-generation antipsychotics versus other therapies (no trials)

Cognitive Functioning

- There was no clinically important or statistically significant difference in Mini-Mental State Exam scores comparing haloperidol with second-generation antipsychotics (range in mean differences, 0.14 to 0.15). (SOE: Low)
- We were unable to draw a conclusion regarding the effects of antipsychotics on cognitive functioning for the following comparisons:
 - Haloperidol versus placebo (no trials)
 - Second-generation antipsychotics versus placebo (insufficient evidence)
 - Second-generation antipsychotics versus second-generation antipsychotics (insufficient evidence)
 - Haloperidol versus other therapies (insufficient evidence)
 - Second-generation antipsychotics versus other therapies (no trials)

Length of Stay in Hospital

- RCTs, conducted exclusively in critically ill patients, reported length of stay in hospital:
 - Little to no difference comparing haloperidol versus placebo, with the largest trial reporting no clinically important difference (SOE: Moderate)
 - Similar effects for second-generation antipsychotics versus placebo, with the largest trial reporting no clinically important difference (SOE: Moderate)
 - No clinically important or statistically significant difference for haloperidol versus second-generation antipsychotics (SOE: Moderate)
- We were unable to draw a conclusion regarding the effects of antipsychotics on length of stay in hospital for the following comparisons:
 - Second-generation antipsychotics versus second-generation antipsychotics (no trials)
 - Haloperidol versus other therapies (insufficient evidence)
 - Second-generation antipsychotics versus other therapies (no trials)

Sedation

- In critically ill patients, there was no clinically important or statistically significant difference in rates of sedation when comparing haloperidol with placebo. (SOE: Low)
- In trials that mostly enrolled patients with critical illness, there was no clinically important or statistically significant difference in rates of sedation for the following comparisons:
 - Second-generation antipsychotics versus placebo (pooled RR, 1.10; 95% CI, 0.78 to 1.53) (SOE: Moderate)
 - Haloperidol versus second-generation antipsychotics (pooled RR, 1.26; 95% CI, 0.92 to 1.72) (SOE: Moderate)
- We were unable to draw a conclusion regarding the effects of antipsychotics on sedation for the following comparisons:
 - Second-generation antipsychotics versus second-generation antipsychotics (insufficient evidence)
 - Haloperidol versus other therapies (no studies)
 - Second-generation antipsychotics versus other therapies (no studies)

Inappropriate Continuation of Antipsychotics

- We found no trials evaluating inappropriate continuation of antipsychotics in patients with delirium that compared an antipsychotic with a placebo, another antipsychotic, or another treatment.

Intermediate Outcomes

Delirium Incidence – Overall

Second-Generation Antipsychotics Versus Placebo

One RCT, with low risk of bias and enrolling patients admitted to a medical or surgical intensive care unit, compared quetiapine with placebo. This trial reported no statistically significant effect on delirium incidence within 14 days.⁵²

Other Comparisons

We found no delirium treatment trials evaluating delirium incidence for the following comparisons:

- Haloperidol versus placebo
- Haloperidol versus second-generation antipsychotics
- Second-generation antipsychotics versus second-generation antipsychotics
- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies

Short-Term Delirium Symptoms – Overall

Haloperidol Versus Placebo

One RCT, with low risk of bias, compared haloperidol with placebo in critically ill patients receiving mechanical ventilation and enrolled within 72 hours of intensive care unit admission.⁴⁵ The trial evaluated short-term delirium symptom of agitation, defined as a Richmond Agitation-Sedation Scale score of greater than or equal to +2, and reported no statistically significant effect on agitation.

Second-Generation Antipsychotics Versus Placebo

Two RCTs,^{52, 63} with small sample sizes and low risk of bias, compared quetiapine with placebo and provided imprecise and inconsistent evidence. Each trial used different measures of short-term delirium symptoms. One of these trials enrolled critically ill patients and reported a potentially clinically important fewer hours of Sedation-Agitation Scale score of equal to or greater than five for the quetiapine group,⁵² the other trial enrolled non-critically ill patients⁶³ and reported no statistically significant difference using the Brief Psychiatric Rating Scale.

Haloperidol Versus Second-Generation Antipsychotics

Two RCTs compared second-generation antipsychotics with haloperidol using different measures of sleep duration.^{54, 62} One trial, with low risk of bias, enrolled inpatients with hyperactive delirium.⁶² The other trial, a three-arm RCT with unclear risk of bias, compared olanzapine, risperidone, and haloperidol in non-critically ill inpatients.⁵⁴ These two trials, each with a small sample size, provided consistent but imprecise evidence of no significant difference in sleep duration for second-generation antipsychotics compared with haloperidol.

Second-Generation Antipsychotics Versus Second-Generation Antipsychotics

One three-arm RCT, with unclear risk of bias, compared olanzapine with risperidone in non-critically ill inpatients.⁵⁴ This trial evaluated the short-term delirium symptom of increased duration of sleep and reported no statistically significant effect on this outcome for risperidone compared with olanzapine.

Other Comparisons

We found no delirium treatment trials evaluating short-term delirium symptoms in patients with delirium for the following comparisons:

- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies

Delirium Severity – Overall

Haloperidol Versus Placebo

Two three-arm RCTs comparing haloperidol with placebo assessed delirium severity using different instruments in different patient populations with inconsistent results.^{48, 57} (SOE: Insufficient)

Second-Generation Antipsychotics Versus Placebo

Three RCTs compared three different second-generation antipsychotics with placebo, assessing delirium severity using different instruments in different patient populations, with inconsistent results.^{48, 57, 63} (SOE: Insufficient)

Haloperidol Versus Second-Generation Antipsychotics

Eight RCTs comparing haloperidol with three different second-generation antipsychotics (olanzapine, risperidone, and quetiapine) assessed delirium severity using different instruments in different patient populations.^{54-58, 61, 62, 64} Six of the eight RCTs enrolled medical and surgical inpatients with and without critical illness,^{54-58, 64} one enrolled patients receiving palliative care,⁶¹ and one enrolled inpatients with hyperactive delirium.⁶² Two of the eight RCTs had high risk of bias, primarily owing to a lack of blinding and missing outcome data,^{58, 61} and three had low risk of bias.^{55, 62, 64} The three remaining RCTs had unclear risk of bias.^{54, 56, 57} Across these trials comparing haloperidol with second-generation antipsychotics, there was no clinically important or statistically significant difference of delirium severity comparing second-generation antipsychotics with haloperidol. (SOE: Moderate)

We conducted a meta-analysis of the five trials that evaluated delirium severity using Delirium Rating Scale-Revised-98 or the Memorial Delirium Assessment Scale that we converted to a Delirium Rating Scale-Revised-98 score (range, 0 to 48).^{54-56, 62, 64} One of the four RCTs was a three-arm trial with unclear risk of bias that compared both olanzapine and risperidone with haloperidol in a total of 64 inpatients without critical illness; we used the olanzapine with haloperidol comparison in our meta-analysis.⁵⁴ The meta-analysis showed no statistically significant difference in delirium severity (pooled mean between-group difference, 0.0; 95% CI, -2.0 to 2.0; I-squared, 25%) (Figure 16). We tested the effect of each individual trial on the combined point estimate; no single trial influenced the pooled results. No substantial statistical heterogeneity was identified. We repeated the meta-analysis using the data for a comparison of risperidone with haloperidol for the one three-arm RCT,⁵⁴ and the results were similar to the comparison of olanzapine with haloperidol, with a very small non-statistically significant between-group difference in the reduction of delirium severity (pooled mean between-group difference, -0.3; 95% CI, -2.4 to 1.7; I-squared, 11%) (Figure 16).

Three RCTs with a total of 257 patients evaluated change in delirium severity using the Clinical Global Impression scale (range, 1 to 7).^{53, 57, 58} We could not conduct a meta-analysis because these trials did not use the same measure from the Clinical Global Impression scale. Across the three RCTs, there was no clinically important or statistically significant difference in delirium severity or improvement.

We were unable to combine the following two RCTs owing to the use of heterogeneous delirium severity rating scales. The Delirium Rating Scale is a different instrument than the revised version (Delirium Rating Scale-Revised-98) and there is no crosswalk to convert the scores. Two RCTs evaluating delirium severity using the Delirium Rating Scale compared

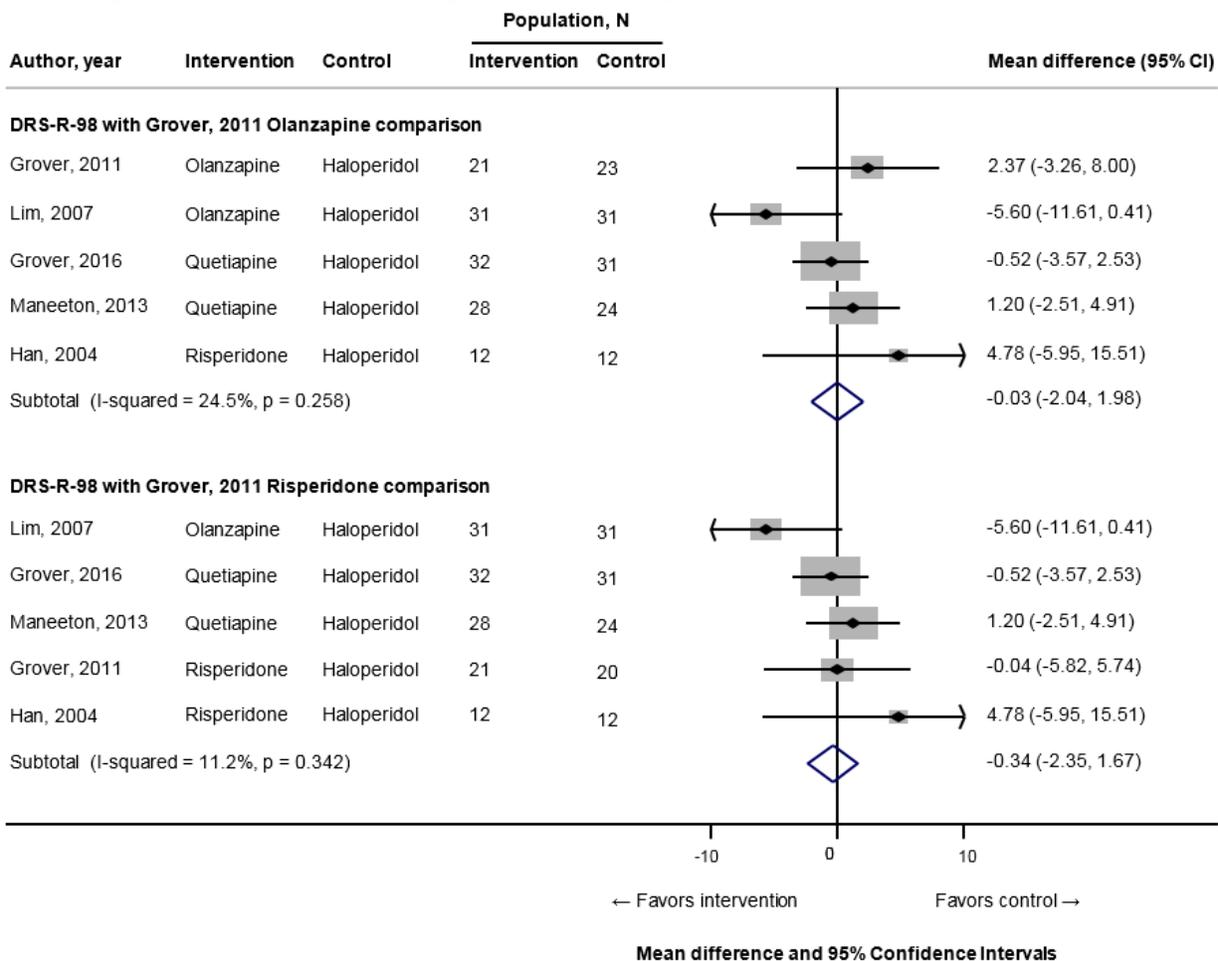
olanzapine with haloperidol and reported no statistically significant difference in delirium severity reduction from baseline.^{57, 61}

One RCT, with high risk of bias, evaluated delirium severity using the Memorial Delirium Assessment Scale.⁵⁸ We were unable to include this trial in the meta-analysis because it did not report sufficiently detailed information. This RCT compared olanzapine with haloperidol in inpatients and reported similar delirium severity at the end of the study for olanzapine compared with haloperidol. Using the same scale, the RCT also reported a reduction in delirium severity for patients receiving olanzapine compared with those receiving haloperidol over the study period.

Three RCTs evaluated the percentage of patients with Delirium Rating Scale-Revised-98 scores of less than a threshold of either 10 or 12 (indicating lower delirium symptoms), comparing a second-generation antipsychotic (e.g., quetiapine, olanzapine, and risperidone) with haloperidol.^{54, 55, 62} These RCTs demonstrated no statistically significant difference in percentage of patients with Delirium Rating Scale-Revised-98 scores of less than this threshold (pooled RR, 0.96; 95% CI, 0.80 to 1.16; I-squared, 0.0%) (Figure 17). We tested the effect of each individual study on the combined point estimate. No single study influenced the pooled results. No substantial statistical heterogeneity was identified.

One three-arm RCT, with unclear risk of bias, compared olanzapine and haloperidol in a total of 175 inpatients aged 65 years and older and reported no statistically significant difference in the percentage of patients with “significant improvement” or “complete alleviation” on the Clinical Global Impression scale for olanzapine (82%) compared with haloperidol (88%) (RR, 0.94; 95% CI, 0.82 to 1.08).⁵⁷

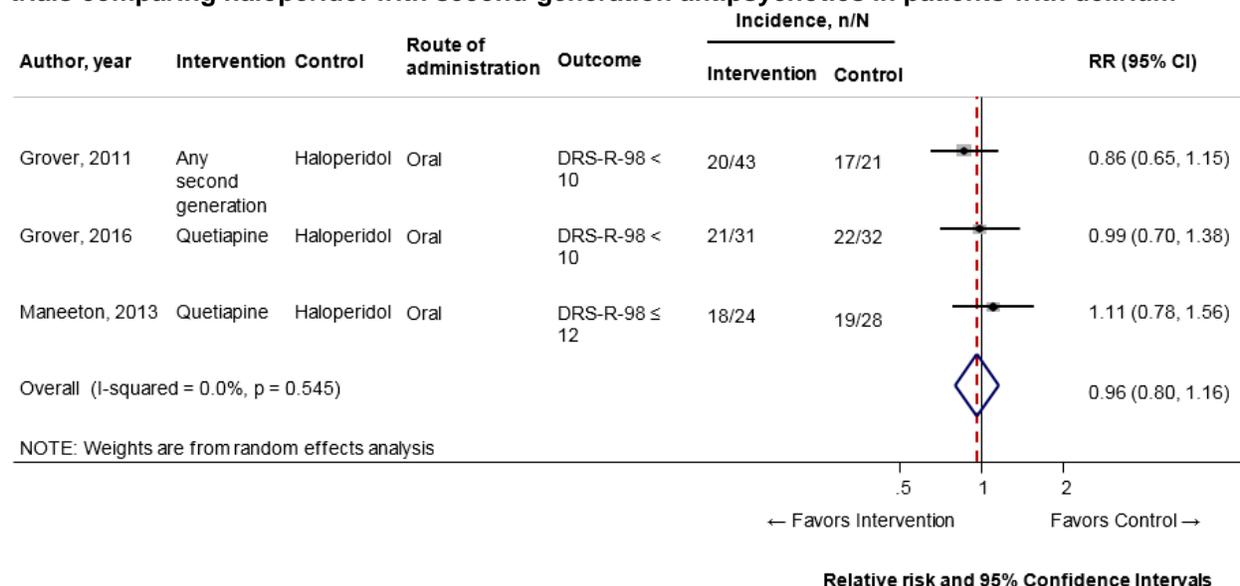
Figure 16. Meta-analysis of delirium severity scores as measured by the DRS-R-98* in trials comparing haloperidol with second-generation antipsychotics in patients with delirium



* Han, 2004 assessed delirium severity with the Memorial Delirium Assessment Scale. We converted these scores to the DRS-R-98.

CI = confidence interval; DRS-R-98 = Delirium Rating Scale-Revised-98; N = sample size; p = p-value.

Figure 17. Meta-analysis of patients with delirium severity scores below identified threshold in trials comparing haloperidol with second-generation antipsychotics in patients with delirium



CI = confidence interval; DRS-R-98 = Delirium Rating Scale-Revised-98; N = total arm population; n = incidence within arm; p = p-value, RR = relative risk.

Second-Generation Antipsychotics Versus Second-Generation Antipsychotics

Three RCTs compared different second-generation antipsychotics and evaluated delirium severity using the Delirium Rating Scale-Revised-98.^{54, 59, 60} We were unable to conduct a meta-analysis because one of the trials did not report sufficient data. Across all three RCTs, with a total of 127 patients, there was no statistically significant difference in second-generation antipsychotics compared with other second-generation antipsychotics. However, the first RCT had unclear risk of bias,⁵⁴ and the other two RCTs, with a total of 72 inpatients, had high risk of bias owing to a lack of blinding or missing outcome data;^{59, 60} we were unable to draw a conclusion. (SOE: Insufficient)

Haloperidol Versus Other Therapies

Two RCTs, with a total of 126 patients, each evaluating a different patient population and using a different delirium severity instrument, compared haloperidol with three different therapies.^{50, 51} We were unable to draw a conclusion owing to the small sample size and consequent lack of precision, comparisons with different types of therapies, and the use of different delirium severity measurement instruments. (SOE: Insufficient)

Second-Generation Antipsychotics Versus Other Therapies

We found no trials evaluating delirium severity in patients with delirium that compared second-generation antipsychotics with other therapies.

Strength of Evidence

Table 17 summarizes the strength of evidence for antipsychotics for the treatment of delirium in terms of delirium severity.

Table 17. Strength of evidence domains for trials evaluating antipsychotics for the treatment of delirium in terms of delirium severity

Comparison	Number Of Trials (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength Of Evidence	Summary
Haloperidol vs. placebo	2 ^{48, 57} (424)	Medium	Indirect	Inconsistent	Imprecise	Undetected	Insufficient	We were unable to draw a conclusion.
Second-generation antipsychotics vs. placebo	3 ^{48, 57, 63} (466)	Medium	Direct	Inconsistent	Imprecise	Undetected	Insufficient	We were unable to draw a conclusion.
Haloperidol vs. second-generation antipsychotics	8 ^{54-58, 61, 62, 64} (570)	Medium	Direct	Consistent	Precise	Undetected	Moderate	Haloperidol vs. second-generation antipsychotics had no clinically important or statistically significant differences (pooled mean between-group differences for DRS-R-98 (5 trials): 0.0; 95% CI, -2.0 to 2.0).
Second-generation antipsychotics vs. second-generation antipsychotics	3 ^{54, 59, 60} (127)	High	Direct	Consistent	Imprecise	Undetected	Insufficient	We were unable to draw a conclusion.
Haloperidol vs. other therapies	2 ^{50, 51} (126)	Medium	Indirect	Unknown*	Imprecise	Undetected	Insufficient	We were unable to draw a conclusion.
Second-generation antipsychotics vs. other therapies	No trials							

* Consistency is unknown since each “other” therapy comparator group (i.e., lorazepam, ondansetron, and dexmedetomidine) was not replicated in a second RCT. Abbreviations: CGI = Clinical Global Impression; CI = confidence interval; DRS-R-98 = Delirium Rating Scale-Revised-98; RCT = randomized controlled trial.

Delirium- and Coma-Free Days Alive – Overall

Haloperidol Versus Placebo

Three RCTs, with low risk of bias, compared haloperidol with placebo and assessed delirium- and coma-free days alive at different followup times among populations of medical and surgical patients in intensive care units.^{44, 45, 53} All three trials provided consistent evidence of no difference in delirium- and coma-free days alive comparing haloperidol with placebo. We did not conduct a meta-analysis because these trials generally provided results as median values, and the data for delirium- and coma-free days alive may be skewed, precluding transformation of the data.

Second-Generation Antipsychotics Versus Placebo

Two RCTs, with low risk of bias, compared ziprasidone with placebo at different followup times among populations of medical and surgical patients in intensive care units. Both well-designed RCTs demonstrated consistent evidence of no statistically significant effect of ziprasidone on delirium- and coma-free days alive.^{44, 53}

Haloperidol Versus Second-Generation Antipsychotics

Two RCTs, with low risk of bias, compared ziprasidone with haloperidol at different followup times among populations of medical and surgical patients in intensive care units.^{44, 53} There was consistent and precise evidence of no difference in delirium- and coma-free days alive.

Other Comparisons

We found no delirium treatment trials evaluating delirium- and coma-free days alive for the following comparisons:

- Second-generation antipsychotics versus second-generation antipsychotics
- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies

Duration of Delirium – Overall

Haloperidol Versus Placebo

Three RCTs, with low risk of bias, compared haloperidol with placebo and assessed delirium duration in medical and surgical patients in intensive care units.^{44, 45, 53} There was consistent and precise evidence of no statistically significant effect on delirium duration for haloperidol compared with placebo. We did not conduct a meta-analysis because these trials generally provided results as median values and delirium duration data may be skewed, precluding conversion or transformation of the data.

Second-Generation Antipsychotics Versus Placebo

Three RCTs, with low risk of bias, compared a second-generation antipsychotic with placebo and assessed delirium duration in medical and surgical patients in intensive care units.^{44, 52, 53} There was consistent and precise evidence of no statistically significant effect of second-generation antipsychotics on delirium duration. We did not conduct a meta-analysis because

these trials generally provided results as median values and delirium duration data may be skewed, precluding conversion or transformation of the data.

Haloperidol Versus Second-Generation Antipsychotics

Six RCTs, with various risk of bias, assessed the effect of haloperidol on duration of delirium compared with quetiapine, ziprasidone, risperidone, or olanzapine in medical and surgical inpatients both with and without critical illness.^{44, 53, 56, 58, 62, 64} Two of the RCTs, with low risk of bias and enrolling critically ill patients (N=566 and N=101), reported no statistically significant effect on delirium duration;^{44, 53} these trials were not included in our meta-analysis because results were provided only as median values and delirium duration data may be skewed, precluding conversion or transformation. However, our meta-analysis of the four RCTs reporting mean values^{56, 58, 62, 64} showed a non-clinically important increase in number of days with delirium for second-generation antipsychotics compared with haloperidol (pooled mean between-group difference, 0.2; 95% CI, 0.0 to 0.4; I-squared, 38%) (Figure 18). There was consistent and precise evidence of little to no difference in delirium duration for haloperidol compared with second-generation antipsychotics.

Second-Generation Antipsychotics Versus Second-Generation Antipsychotics

One RCT, with high risk of bias primarily owing to a lack of blinding, compared amisulpride with quetiapine and assessed delirium duration in 31 inpatients. This RCT reported no statistically significant effect for amisulpride compared with quetiapine.⁶⁰

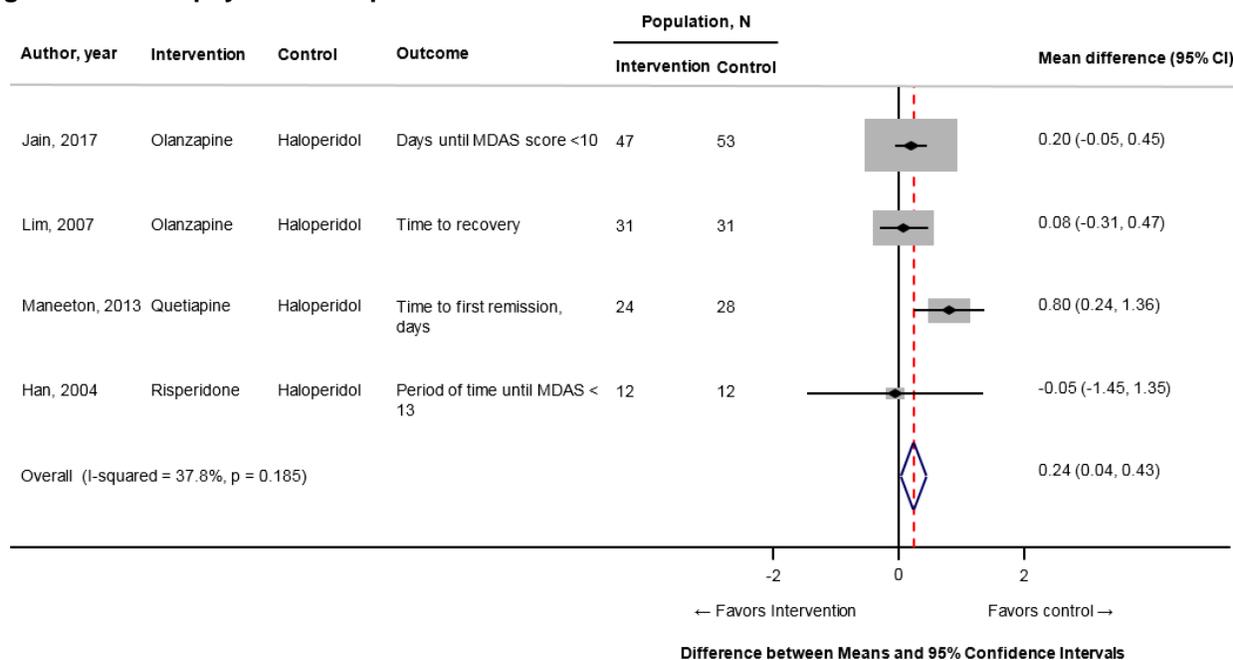
Haloperidol Versus Other Therapies

One RCT, with unclear risk of bias, compared haloperidol with morphine and assessed delirium duration in post-cardiac surgery patients with hyperactive delirium and reported no statistically significant effect for haloperidol compared with morphine.⁴⁹

Second-Generation Antipsychotics Versus Other Therapies

We found no trials evaluating delirium duration that compared second-generation antipsychotics with other therapies.

Figure 18. Meta-analysis of duration of delirium in trials comparing haloperidol with second-generation antipsychotics in patients with delirium



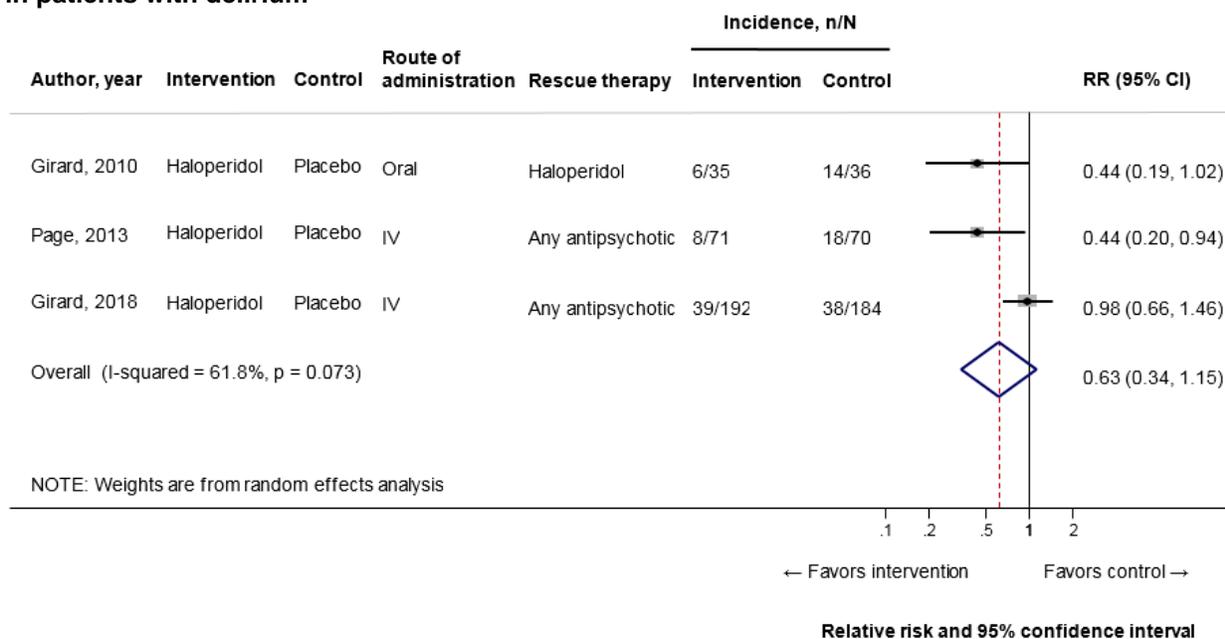
CI=confidence interval; MDAS=Memorial Delirium Assessment Scale; N=sample size; p=p-value

Use of Rescue Therapy – Overall

Haloperidol Versus Placebo

Three RCTs, with low risk of bias, compared haloperidol with placebo and reported on rescue therapy, defined as the use of any open-label antipsychotic.^{44, 45, 53} All three RCTs, two of which were three-arm trials,^{44, 53} enrolled medical and surgical critically ill patients. We found a non-statistically significant decrease in the use of rescue therapy in the haloperidol group (pooled RR, 0.63; 95% CI, 0.34 to 1.15; I-squared, 62%) (Figure 19). This is a possibly relevant decrease but the potential impact is difficult to assess. Excluding the largest RCT⁵³ changed the inference of the meta-analysis, suggesting a statistically significant decrease in the use of rescue therapy in patients treated with haloperidol (pooled RR with this RCT removed, 0.44; 95% CI, 0.25 to 0.77). This trial was not qualitatively different from the other two smaller RCTs, so we retained it in the overall meta-analysis. Owing to the substantial statistical heterogeneity, we also conducted a profile likelihood method of meta-analysis and found a similar non-statistically significant decrease in the use of rescue therapy in the haloperidol group (pooled RR, 0.66 95% CI, 0.30 to 1.19; I-squared, 42%). There was consistent but imprecise evidence of little decrease in the use of rescue therapy for haloperidol.

Figure 19. Meta-analysis of the use of rescue therapy in trials comparing haloperidol with placebo in patients with delirium



CI = confidence interval; IV = intravenous; N = total arm population; n = incidence within arm; p = p-value, RR = relative risk

Second-Generation Antipsychotics Versus Placebo

Two three-arm RCTs, with low risk of bias, compared ziprasidone with placebo and reported on rescue therapy, defined as the use of any open-label antipsychotic.^{44, 53} Both RCTs, enrolling medical and surgical critically ill patients, reported no effect of ziprasidone on the use of rescue therapy. The evidence from these trials was consistent but imprecise.

Haloperidol and Second-Generation Antipsychotics Versus Placebo

One three-arm RCT, with low risk of bias, compared haloperidol and risperidone with placebo and reported on rescue therapy, defined as per-protocol use of midazolam.⁴⁸ This trial, enrolling patients receiving palliative care, reported a statistically significant decrease in the use of rescue therapy in the placebo group compared with the combined haloperidol and risperidone groups on all three study days.⁴⁸ Because data was only reported for the combination of risperidone and haloperidol, we were unable to determine if results would be similar if data were collected for each of these two antipsychotic medications separately. However, for the use of rescue therapy, findings from this one RCT appear to favor avoidance of antipsychotics in patients receiving palliative care.

Haloperidol Versus Second-Generation Antipsychotics

Three RCTs, enrolling critically ill patients and patients receiving palliative care, compared haloperidol with two second-generation antipsychotics (ziprasidone and olanzapine). Two^{44, 53} of the RCTs had low risk of bias and one had potential for a high risk of bias.⁶¹ Across all three RCTs, there was no evidence of statistically significant differences between haloperidol and second-generation antipsychotics in the use of rescue therapies.^{44, 53, 61} There was consistent but imprecise evidence of no statistically significant difference in the use of rescue therapy for haloperidol compared with second-generation antipsychotics.

Second-Generation Antipsychotics Versus Second-Generation Antipsychotics

One RCT, with high risk of bias, compared risperidone with olanzapine in inpatients and reported non-statistically significant increases in the use of two separate rescue therapies (haloperidol and any benzodiazepine) for risperidone compared with olanzapine.⁵⁹

Haloperidol Versus Other Therapies

One three-arm RCT, with low risk of bias, compared haloperidol with ondansetron and dexmedetomidine in trauma patients in an intensive care unit and reported on rescue therapy, defined as the use of open-label haloperidol.⁵⁰ When comparing haloperidol with ondansetron, the RCT reported a statistically significant decrease in the use of rescue therapy. When comparing haloperidol with dexmedetomidine, the RCT reported a non-statistically significant decrease in the use of rescue therapy.

Second-Generation Antipsychotics Versus Other Therapies

We found no trials evaluating the use of rescue therapy in patients with delirium that compared second-generation antipsychotics with other therapies.

Other Intermediate Outcomes – Overall

We found no trials enrolling patients with delirium that compared an antipsychotic with a placebo, another antipsychotic, or another treatment and evaluated the following intermediate outcomes:

- Patient distress
- Use of physical restraint

Final Health or Patient-Centered Outcomes

Mortality – Overall

Haloperidol Versus Placebo

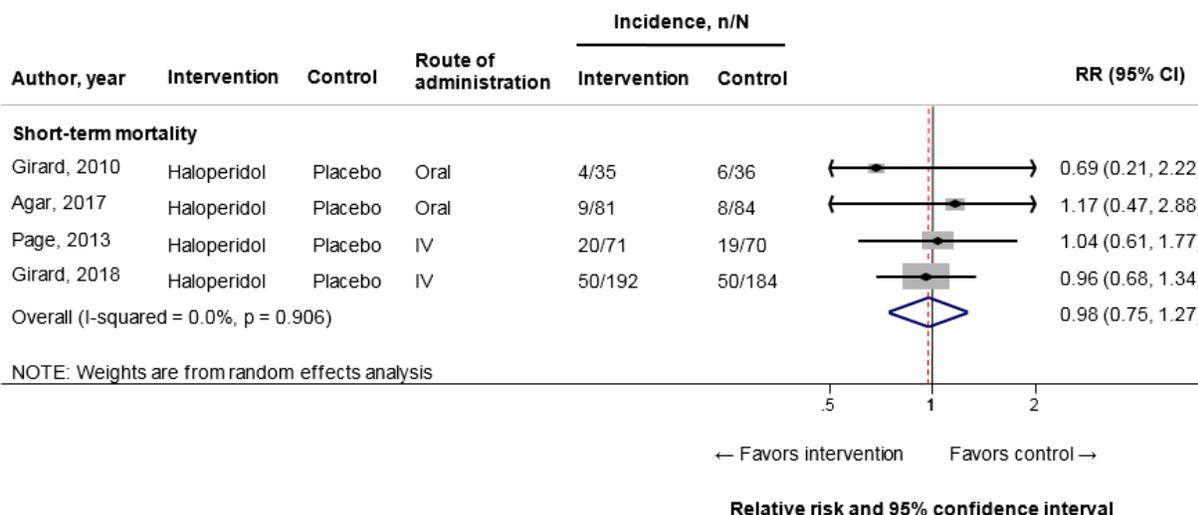
Four RCTs, with low risk of bias, compared haloperidol with placebo and showed no between-group difference in short-term mortality, defined as mortality while in hospital or up to 30 days after randomization (pooled RR, 0.98; 95% CI, 0.75 to 1.27; I-squared, 0%) (Figure 20).^{44, 45, 48, 53} We tested the effect of each individual trial on the combined point estimate. No single trial influenced the pooled results. No substantial statistical heterogeneity was identified. Three of the four RCTs enrolled critically ill patients,^{44, 45, 53} and the fourth RCT enrolled a total of 249 patients receiving palliative care.⁴⁸ Excluding the RCT enrolling patients receiving palliative care did not result in any material change to the pooled results. There was consistent but imprecise evidence of no statistically significant difference in short-term mortality for haloperidol compared with placebo.

Notably, the one RCT with low risk of bias and enrolling patients receiving palliative care was a three-arm trial and performed a time-to-event analysis that included comparison of haloperidol versus placebo. This comparison showed a decreased survival rate for the haloperidol group (median survival time, 16 vs. 26 days; hazard ratio [HR], 1.73; 95% CI, 1.20 to 2.50; $P = 0.003$).⁴⁸ However, in an analysis of short-term mortality associated with the 72-hour treatment duration, there was no statistically significant effect when comparing haloperidol

with placebo (RR, 1.17; 95% CI, 0.47 to 2.88). Thus, it is unclear how much of the longer-term mortality risk is attributable to haloperidol use during the trial period.

Of these four RCTs, the largest trial was a three-arm trial with low risk of bias that also evaluated 90-day mortality in a total of 566 critically ill patients.⁵³ The results of this evaluation were consistent with our meta-analysis results for short-term mortality with no between-group difference in comparing haloperidol with placebo.

Figure 20. Meta-analysis of mortality in trials comparing haloperidol with placebo in patients with delirium



CI = confidence interval; IV = intravenous; N = total arm population; n = incidence within arm; p = p-value, RR = relative risk.

Second-Generation Antipsychotics Versus Placebo

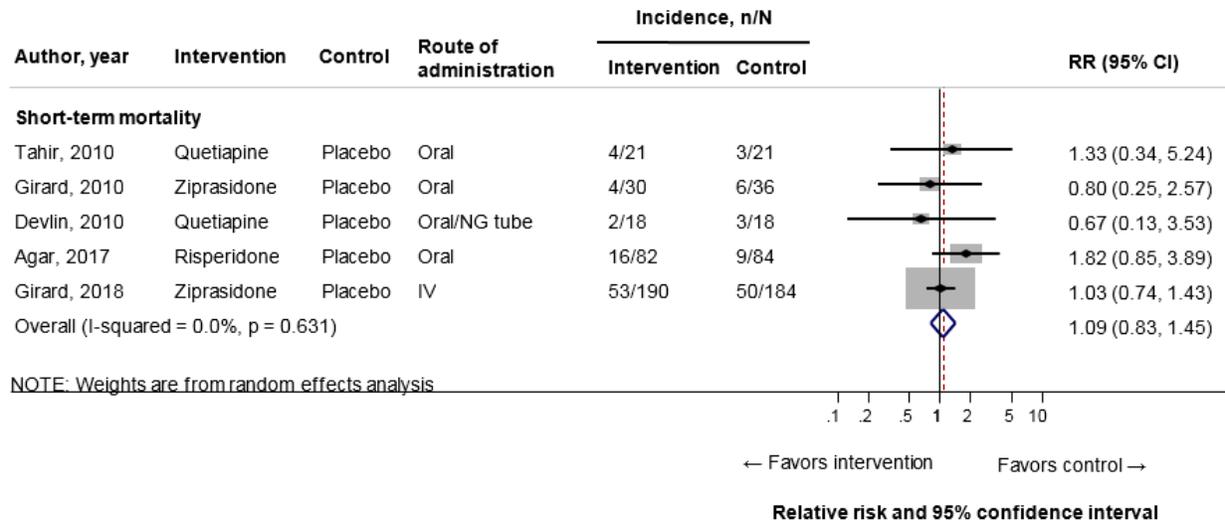
Our meta-analysis of five RCTs, with low risk of bias, found no between-group difference in short-term mortality, defined as mortality while in hospital or up to 30 days after randomization, for a second-generation antipsychotic compared with placebo (pooled RR, 1.09; 95% CI, 0.83 to 1.45; I-squared, 0%) (Figure 21).^{44, 48, 52, 53, 63} Two of the RCTs evaluated quetiapine and ziprasidone; three of the RCTs evaluated risperidone. We tested the effect of each individual trial on the combined point estimate. No single trial influenced the pooled results. No substantial statistical heterogeneity was identified. Three of the five RCTs enrolled medical and surgical critically ill patients;^{44, 52, 53} the others enrolled medical and surgical inpatients without critical illness⁶³ and patients receiving palliative care.⁴⁸ Excluding the RCT that enrolled patients receiving palliative care⁴⁸ did not result in any material change to the pooled results. There was consistent but imprecise evidence of no statistically significant difference in short-term mortality for second-generation antipsychotics compared with placebo.

The one RCT that enrolled patients receiving palliative care performed a time-to-event analysis comparing risperidone with placebo. This three-arm RCT reported a non-statistically significant decrease in survival for the risperidone group (median survival time, 17 vs. 26 days; HR, 1.29; 95% CI, 0.91 to 1.84; *P* = 0.14).⁴⁸ In an analysis of short-term mortality associated with the 72-hour treatment duration there also was no statistically significant effect when comparing risperidone with placebo (RR, 1.82; 95% CI, 0.85 to 3.89).

Of these five RCTs, the largest was a three-arm, low risk of bias trial that also evaluated 90-day mortality in a total of 566 critically ill patients.⁵³ The results of this evaluation were

consistent with the meta-analysis results for short-term mortality, with no between-group difference reported when comparing risperidone with placebo.

Figure 21. Meta-analysis of mortality in trials comparing second-generation antipsychotics with placebo in patients with delirium



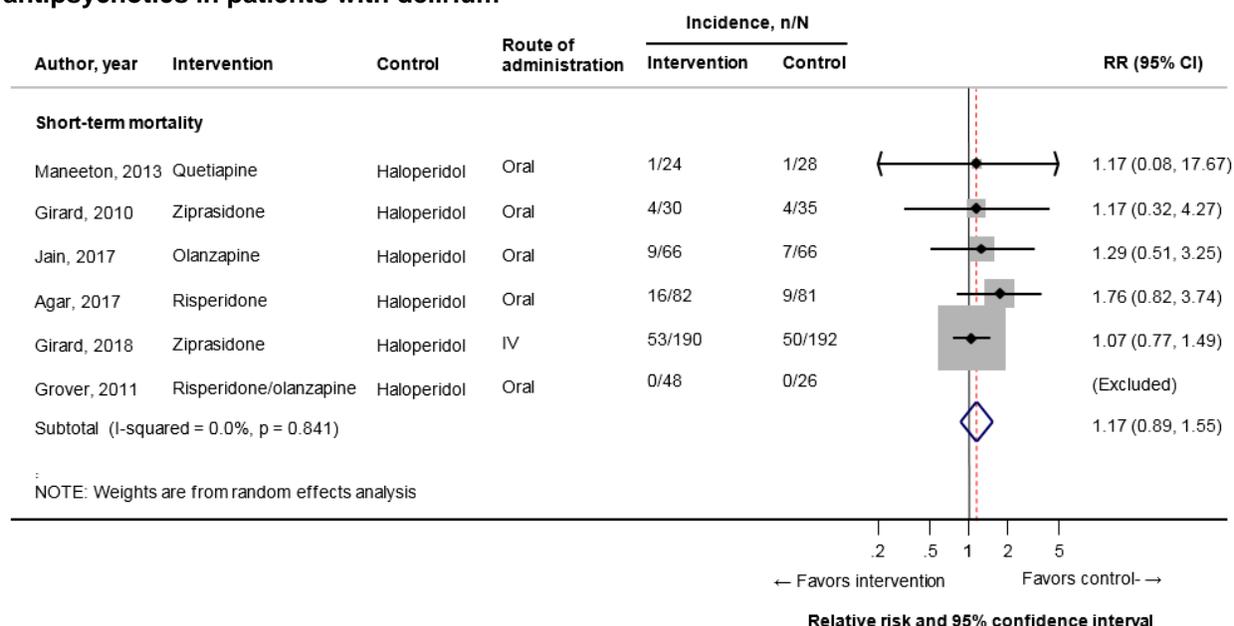
CI = confidence interval; IV = intravenous; N = total arm population; n = incidence within arm; NG = nasogastric tube; p = p-value, RR = relative risk.

Haloperidol Versus Second-Generation Antipsychotics

Our meta-analysis of six RCTs, with seven comparisons of haloperidol with a second-generation antipsychotic, showed no between-group difference in short-term mortality, defined as mortality while in hospital or up to 30 days after randomization (pooled RR, 1.17; 95% CI, 0.89 to 1.55; I-squared, 0%) (Figure 22).^{44, 48, 53, 54, 58, 62} One of these seven comparisons evaluated quetiapine and each of the following second-generation antipsychotics were evaluated twice: risperidone, olanzapine, and ziprasidone. Four of the six RCTs were low risk of bias;^{44, 48, 53, 62} one RCT had unclear risk of bias;⁵⁴ and one RCT was high risk of bias, primarily owing to a lack of blinding and missing outcome data.⁵⁸ We tested the effect of each individual trial on the combined point estimate. No single trial influenced the pooled results. No substantial statistical heterogeneity was identified. Five of the six RCTs enrolled medical and surgical inpatients,^{44, 53, 54, 58, 62} with two of these five RCTs specifically focused on critically ill patients.^{44, 53} The remaining RCT enrolled patients receiving palliative care.⁴⁸ Excluding the RCT that enrolled patients receiving palliative care did not result in any material change to the pooled results. There was consistent but imprecise evidence of no statistically significant difference in short-term mortality for second-generation antipsychotics compared with haloperidol.

Of these six RCTs, the largest was a three-arm, low risk of bias trial that also evaluated 90-day mortality. This RCT compared haloperidol with ziprasidone in a total of 566 critically ill patients. The results of this RCT were consistent with the results of our meta-analysis, reporting no between-group difference for short-term mortality.⁵³

Figure 22. Meta-analysis of mortality in trials comparing haloperidol with second-generation antipsychotics in patients with delirium



NOTE: Weights are from random effects analysis

CI = confidence interval; IV = intravenous; N = total arm population; n = incidence within arm; p = p-value, RR = relative risk.

Second-Generation Antipsychotics Versus Second-Generation Antipsychotics

One three-arm RCT, with unclear risk of bias, compared risperidone with olanzapine in non-critically ill inpatients and reported no deaths in either treatment group.⁵⁴

Haloperidol Versus Other Therapies

Two RCTs, with unclear risk of bias, compared haloperidol with another therapy, and both reported no statistically significant differences.^{49, 51}

Second-Generation Antipsychotics Versus Other Therapies

We found no trials evaluating mortality in patients with delirium that compared second-generation antipsychotics with other therapies.

Cognitive Functioning – Overall

Second-Generation Antipsychotics Versus Placebo

One RCT, with low risk of bias, compared quetiapine with placebo in medical and surgical inpatients without critical illness.⁶³ This RCT reported no clinically important or statistically significant effect on the Mini-Mental State Exam score for quetiapine compared with placebo at day 10. We were unable to draw a conclusion based upon on this small single study. (SOE: Insufficient)

Haloperidol Versus Second-Generation Antipsychotics

Two small RCTs compared haloperidol with three different second-generation antipsychotics. Overall, there were no clinically important or statistically significant differences in cognitive function, measured with the Mini-Mental State Exam score (mean differences of

0.14 and 0.15),^{54,55} when comparing haloperidol with second-generation antipsychotics. (SOE: Low)

Second-Generation Antipsychotics Versus Second-Generation Antipsychotics

One three-arm RCT, with unclear risk of bias and enrolling non-critically ill inpatients, compared risperidone with olanzapine.⁵⁴ This RCT reported no statistically significant effect on the Mini-Mental State Exam score for risperidone compared with olanzapine.⁵⁴ We were unable to draw a conclusion based upon this single small study. (SOE: Insufficient)

Haloperidol Versus Other Therapies

One three-arm RCT, with unclear risk of bias and enrolling medical inpatients with acquired immunodeficiency syndrome, compared lorazepam with haloperidol.⁵¹ This RCT reported no statistically significant effect on the Mini-Mental State Exam score for lorazepam compared with haloperidol. We were unable to draw a conclusion based upon this single small study. (SOE: Insufficient)

Other Comparisons

We found no delirium treatment trials evaluating cognitive functioning in patients with delirium for the following comparisons:

- Haloperidol versus placebo
- Second-generation antipsychotics versus other therapies

Strength of Evidence

Table 18 summarizes the strength of evidence of the effects of antipsychotics on cognitive functioning in patients with delirium.

Table 18. Strength of evidence domains for trials evaluating antipsychotics for the treatment of delirium in terms of cognitive functioning

Comparison	Number Of Trials (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength Of Evidence	Summary
Haloperidol vs. placebo	No trials							
Second-generation antipsychotics vs. placebo	1 ⁶³ (42)	Low	Indirect	Consistency unknown (single study)	Imprecise	Undetected	Insufficient	We were unable to draw a conclusion.
Haloperidol vs. second-generation antipsychotics	2 ^{54, 55} (127)	Medium	Indirect	Consistent	Imprecise	Undetected	Low	RCTs of inpatients reported no clinically important or statistically significant difference in MMSE scores (mean differences 0.14 and 0.15).
Second-generation antipsychotics vs. second-generation antipsychotics	1 ⁵⁴ (64)	Medium	Indirect	Consistency unknown (single study)	Imprecise	Undetected	Insufficient	We were unable to draw a conclusion.
Haloperidol vs. other therapies	1 ⁵¹ (30)	Medium	Indirect	Consistency unknown (single study)	Imprecise	Undetected	Insufficient	We were unable to draw a conclusion.
Second-generation antipsychotics vs. other therapies	No trials							

MMSE = Mini-Mental State Exam; RCT = randomized controlled trials.

Other Final Health or Patient-Centered Outcomes - Overall

We found no trials enrolling patients with delirium that compared an antipsychotic with a placebo, another antipsychotic, or another treatment and evaluated the following final health or patient-centered outcomes:

- Quality of life
- Institutionalization
- Caregiver burden/strain
- Falls
- Memory of patient distress

Resource Utilization Outcomes

Readmission to Intensive Care Unit – Overall

Haloperidol Versus Placebo

Two RCTs, with low risk of bias, compared haloperidol with placebo in critically ill medical and surgical patients.^{45, 53} Both RCTs reported no effect on readmission to the intensive care unit. The evidence was consistent but imprecise.

Second-Generation Antipsychotics Versus Placebo

One three-arm RCT, with low risk of bias, compared ziprasidone with placebo in critically ill medical and surgical patients.⁵³ This RCT reported no statistically significant effect on readmission to the intensive care unit (RR, 0.76; 95% CI, 0.42 to 1.36).

Haloperidol Versus Second-Generation Antipsychotics

One three-arm RCT, with low risk of bias, included a comparison of ziprasidone with haloperidol in critically ill medical and surgical patients.⁵³ This RCT reported no statistically significant effect on readmission to the intensive care unit.

Haloperidol Versus Other Therapies

One RCT, with an unclear risk of bias, compared haloperidol with morphine in post-cardiac surgery patients with hyperactive delirium and reported no statistically significant effect on readmission to the intensive care unit.⁴⁹

Other Comparisons

We found no delirium treatment trials evaluating readmission to the intensive care unit in patients with delirium for the following comparisons:

- Second-generation antipsychotics versus second-generation antipsychotics
- Second-generation antipsychotics versus other therapies

Length of Stay in Hospital – Overall

Haloperidol Versus Placebo

Three RCTs, with low risk of bias, compared haloperidol with placebo and assessed length of stay in hospital in medical and surgical patients in intensive care units.^{44, 45, 53} We did not conduct a meta-analysis because these trials generally provided results as median values and the data for length of stay are skewed, precluding conversion or transformation of the data. While the two smaller RCTs (N=101 and N=141) each reported clinically important effects, the largest trial (N=566) found no clinically important effect, and all three RCTs reported no statistically significant effect on length of stay in hospital. Haloperidol did not shorten or lengthen the length of stay in hospital in patients in intensive care units. (SOE: Moderate)

Second-Generation Antipsychotics Versus Placebo

Three RCTs, with low risk of bias, compared a second-generation antipsychotic with placebo and assessed length of stay in hospital in medical and surgical patients in the intensive care units.^{44, 52, 53} We did not conduct a meta-analysis because these trials generally provided results as median values and the data for length of stay are skewed, precluding conversion or transformation of the data. While the two smaller RCTs (N=101 and N=36) each reported potentially clinically important effects (about a 2-day difference), the largest trial (N=566) found no clinically important effect, and all three RCTs reported no statistically significant effect on length of stay in hospital. Second-generation antipsychotics did not shorten or lengthen length of stay in hospital in medical and surgical patients in intensive care units. (SOE: Moderate)

Haloperidol Versus Second-Generation Antipsychotics

Two RCTs, with low risk of bias, compared ziprasidone with haloperidol and assessed length of stay in hospital in medical and surgical patients in intensive care units.^{44, 53} We did not conduct a meta-analysis because these trials generally provided results as median values and the data for length of stay are skewed, precluding conversion or transformation of the data. There was no clinically important or statistically significant effect on length of stay in hospital for haloperidol compared with second-generation antipsychotics. (SOE: Moderate)

Haloperidol Versus Other Therapies

One RCT, with an unclear risk of bias, compared haloperidol with morphine and assessed length of stay in hospital in post-cardiac surgery patients with hyperactive delirium. This RCT reported no statistically significant effect for haloperidol compared with morphine.⁴⁹ We were unable to draw conclusions on the effect of haloperidol compared with other therapies on length of stay based on this single small study. (SOE: Insufficient)

Other Comparisons

We found no delirium treatment trials evaluating length of stay in hospital in patients with delirium for the following comparisons:

- Second-generation antipsychotics versus second-generation antipsychotics
- Second-generation antipsychotics versus other therapies

Strength of Evidence

Table 19 summarizes the strength of evidence of the effects of antipsychotics on length of stay in hospital in patients with delirium.

Table 19. Strength of evidence domains for trials evaluating antipsychotics for the treatment of delirium in terms of length of stay in hospital

Comparison	Number Of Trials (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength Of Evidence	Summary
Haloperidol vs. placebo	3 ^{44, 45, 53} (808)	Low	Indirect*	Consistent	Precise	Undetected	Moderate	RCTs, conducted exclusively in critically ill patients, reported no statistically significant difference, with the largest RCT reporting no clinically important difference.
Second-generation antipsychotics vs. placebo	3 ^{44, 52, 53} (703)	Low	Indirect*	Consistent	Precise	Undetected	Moderate	RCTs, conducted exclusively in critically ill patients, reported no statistically significant difference, with the largest RCT reporting no clinically important difference.
Haloperidol vs. second-generation antipsychotics	2 ^{44, 53} (667)	Low	Indirect*	Consistent	Precise	Undetected	Moderate	RCTs, conducted exclusively in critically ill patients, reported no clinically important or statistically significant difference.
Second-generation antipsychotics vs. second-generation antipsychotics	No trials							
Haloperidol vs. other therapies	1 ⁴⁹ (53)	High	Indirect	Consistency unknown (single study)	Imprecise	Undetected	Insufficient	We were unable to draw a conclusion.
Second-generation antipsychotics vs. other therapies	No trials							

* Indirect rating owing to a single patient population in all RCTs and results may not be generalizable to other patients with delirium.

RCT = randomized controlled trial.

Length of Stay in Intensive Care Unit - Overall

Haloperidol Versus Placebo

Three RCTs, with low risk of bias, compared haloperidol with placebo and assessed length of stay in intensive care unit in medical and surgical critically ill patients.^{44, 45, 53} We did not conduct a meta-analysis because these RCTs generally provided results as median values and the data for length of stay are skewed, precluding conversion or transformation of the data. There was inconsistent and imprecise evidence of little or no effect on length of stay in the intensive care unit for haloperidol compared with placebo.

Second-Generation Antipsychotics Versus Placebo

Three RCTs, with low risk of bias, compared a second-generation antipsychotic with placebo and assessed length of stay in the intensive care unit in critically ill medical and surgical patients.^{44, 52, 53} We did not conduct a meta-analysis because these trials generally provided results as median values and the data for length of stay are skewed, precluding conversion or transformation of the data. There was inconsistent and imprecise evidence of little or no effect on length of stay in the intensive care unit for a second-generation antipsychotic compared with placebo.

Haloperidol Versus Second-Generation Antipsychotics

Two RCTs, with low risk of bias, compared haloperidol with ziprasidone and assessed length of stay in the intensive care unit in critically ill medical and surgical patients.^{44, 53} We did not conduct a meta-analysis because these trials generally provided results as median values and the data for length of stay are skewed, precluding conversion or transformation of the data. There was inconsistent evidence of no statistically significant difference on length of stay in the intensive care unit for haloperidol compared with ziprasidone.

Haloperidol Versus Other Therapies

One RCT, with unclear risk of bias, compared haloperidol with morphine and assessed length of stay in the intensive care unit in post-cardiac surgery patients with hyperactive delirium.⁴⁹ This RCT reported no statistically significant effect for haloperidol compared with morphine.

Other Comparisons

We found no delirium treatment trials evaluating length of stay in the intensive care unit in patients with delirium for the following comparisons:

- Second-generation antipsychotics versus second-generation antipsychotics
- Second-generation antipsychotics versus other therapies

Other Resource Utilization Outcomes – Overall

We found no trials enrolling patients with delirium that compared an antipsychotic with a placebo, another antipsychotic, or another treatment and evaluated the following resource utilization outcomes:

- Readmission to hospital
- Length of stay in skilled nursing facility
- Patient safety attendant use

- Hospice enrollment

Adverse Effects

Sedation – Overall

Haloperidol Versus Placebo

Two RCTs, with low risk of bias, compared haloperidol with placebo in critically ill medical and surgical patients.^{45, 53} The smaller trial (N=141) reported a potentially clinically important but not statistically significant effect on oversedation for haloperidol compared with placebo. However, the larger trial (N=566) reported no clinically important or statistically significant difference. Overall, there was no clinically important or statistically significant effect of haloperidol compared with placebo on sedation. (SOE: Low)

We did not find any observational studies or non-randomized trials that compared haloperidol with placebo and reported on sedation.

Second-Generation Antipsychotics Versus Placebo

Three RCTs, with low risk of bias, compared second-generation antipsychotics with placebo in medical and surgical inpatients with and without critical illness.^{52, 53, 63} Our meta-analysis demonstrated no clinically important or statistically significant between-group difference in the onset of sedation (pooled RR, 1.10; 95% CI, 0.78 to 1.53; I-squared, 0.0%) (Figure 23). (SOE: Moderate) We tested the effect of each individual trial on the combined point estimate. No single trial influenced the pooled results. No substantial heterogeneity was identified.

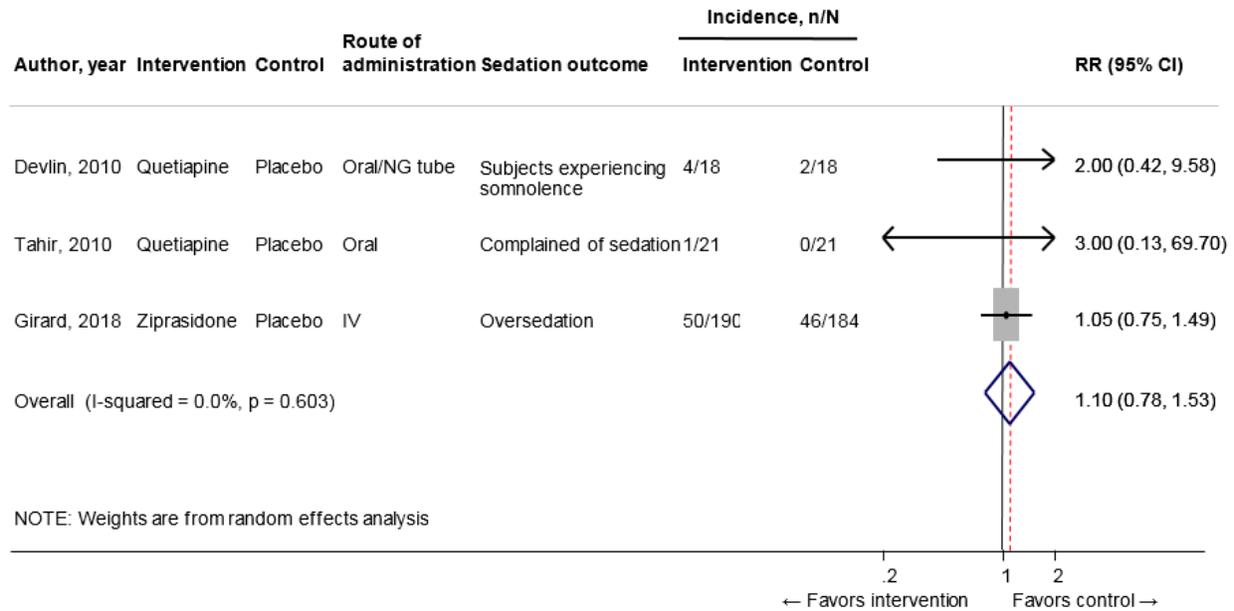
We did not find any observational studies or non-randomized trials that compared a second-generation antipsychotic with placebo and reported on sedation.

Haloperidol Versus Second-Generation Antipsychotics

Six RCTs,^{53, 54, 56, 58, 62, 64} with varying risk of bias, plus five observational studies with comparison groups^{66, 68, 75, 84, 89} enrolled medical and surgical inpatients with and without critical illness. These studies reported no clinically important or statistically significant differences in sedation-related effects in haloperidol compared with second-generation antipsychotics. (SOE: Moderate)

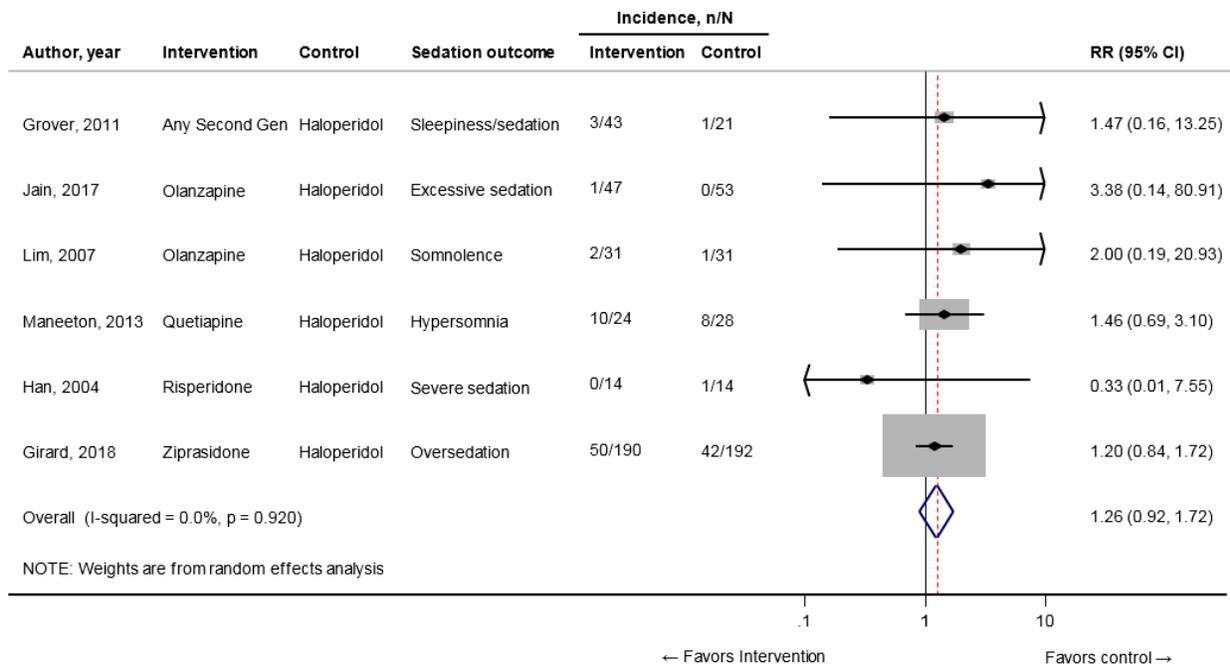
The six RCTs compared four different second-generation antipsychotics (ziprasidone, olanzapine, quetiapine, and risperidone) with haloperidol in medical and surgical inpatients with and without critical illness on sedation-related effects. Four of the six RCTs had low risk of bias;^{53, 54, 62, 64} one RCT had unclear risk of bias;⁵⁶ and one RCT had high risk of bias, primarily owing to a lack of blinding and missing outcome data.⁵⁸ A meta-analysis of the six RCTs found no statistically significant between-group difference in the onset of sedation (pooled RR, 1.26; 95% CI, 0.92 to 1.72; I-squared, 0.0%) (Figure 24).^{53, 54, 56, 58, 62, 64} We tested the effect of each individual trial on the combined point estimate. No single trial influenced the pooled results. No substantial heterogeneity was identified.

Figure 23. Meta-analysis of sedation in trials comparing second-generation antipsychotics with placebo in patients with delirium



CI = confidence interval; IV = intravenous; N = total arm population; n = incidence within arm; NG = nasogastric tube; p = p-value, RR = relative risk.

Figure 24. Meta-analysis of sedation outcomes in trials comparing second-generation antipsychotics with haloperidol



CI = confidence interval; IV = intravenous; N = total arm population; n = incidence within arm; p = p-value; RR = relative risk.

We also identified five observational studies evaluating inpatients without critical illness (sample size range, 22 to 84) for sedation-related effects. One study had a moderate risk of bias,⁶⁸ and the others all had potential for serious risk of bias.^{66, 75, 84, 89} Four different second-generation antipsychotics (quetiapine, risperidone, olanzapine, and aripiprazole) were compared with haloperidol, with no study reporting a statistically significant difference in sedation-related effects.

Second-Generation Antipsychotics Versus Second-Generation Antipsychotics

Three RCTs^{54, 59, 60} and four observational studies^{66, 68, 69, 89} evaluated sedation-related effects in inpatients without critical illness for second-generation antipsychotics compared with second-generation antipsychotics. The trials were small and, owing to unclear and high risk of bias and imprecise findings, we were unable to draw conclusions. (SOE: Insufficient)

These three RCTs included one trial with unclear risk of bias⁵⁴ and two trials with high risk of bias,^{59, 60} with sample sizes ranging from 31 to 64 inpatients without critical illness. Two RCTs compared risperidone with olanzapine,^{54, 59} and one RCT compared amisulpride with quetiapine.⁶⁰ All three RCTs reported no statistically significant differences in the comparisons. One RCT reported no oversedation events in either group,⁶⁰ and the other RCTs reported imprecise effects (RR, 8.00; 95% CI, 0.44 to 146)⁵⁴ and (RR, 0.88; 95% CI, 0.32 to 2.46).⁵⁹

The four observational studies with comparison groups had moderate^{68, 69} or serious^{66, 89} risk of bias. These four studies evaluated inpatients (sample size range, 40 to 84) with and without critical illness. Comparisons were made between five different second-generation antipsychotics (risperidone, olanzapine, quetiapine, aripiprazole, and lurasidone); no study reported a statistically significant difference in sedation-related outcomes.

Other Comparisons

We found no studies of delirium treatment evaluating sedation in patients with delirium for the following comparisons:

- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies

Studies With No Comparison Group

Thirteen observational studies without a comparison group evaluated sedation-related side effects of second-generation antipsychotics in a total of 331 patients who were predominantly medical and surgical inpatients without critical illness. Twelve of the studies reported a range of 0 percent to 30 percent of patients experiencing a sedation-related effect.^{67, 71-74, 76, 78, 80-83, 87} One study of 17 inpatients⁷⁷ reported, without any explanation for the finding, that 76 percent of patients had daytime sleepiness.

Strength of Evidence

Table 20 summarizes the strength of evidence findings for the effects of antipsychotics on sedation in patients with delirium.

Table 20. Strength of evidence domains for trials evaluating antipsychotics for the treatment of delirium in terms of sedation

Comparison	Number Of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength Of Evidence	Summary
Haloperidol vs. placebo	2 ^{45, 53} (707)	Low	Indirect*	Consistent	Imprecise	Undetected	Low	In patients with critical illness, there was no clinically important or statistically significant difference in sedation.
Second-generation antipsychotics vs. placebo	3 ^{52, 53, 63} (644)	Low	Indirect*	Consistent	Precise	Undetected	Moderate	In patients with critical illness, there was no clinically important or statistically significant difference in sedation (pooled RR, 1.10; 95% CI, 0.78 to 1.53).
Haloperidol vs. second-generation antipsychotics	6 RCTs ^{53, 54, 56, 58, 62, 64} (872) [and 5 observational studies with comparison group ^{66, 68, 75, 84, 89} (444)]	Low	Indirect*	Consistent	Precise	Undetected	Moderate	In patients with critical illness, there was no clinically important statistically significant difference in sedation (pooled RR, 1.26; 95% CI, 0.92 to 1.72).
Second-generation antipsychotics vs. second-generation antipsychotics	3 RCTs ^{54, 59, 60} (127) [and 4 observational studies with comparison group ^{66, 68, 69, 89} (318)]	High	Indirect	Inconsistent	Imprecise	Undetected	Insufficient	We were unable to draw a conclusion.
Haloperidol vs. other therapies	No studies							
Second-generation antipsychotics vs. other therapies	No studies							

* Indirect rating owing to data entirely or predominantly coming from a single patient population across the RCTs such that the results may not be generalizable to other patients with delirium.

CI = confidence interval; RCT = randomized controlled trial; RR = relative risk.

Cardiac Effects – Overall

Haloperidol Versus Placebo

Three RCTs,^{44, 45, 53} with low risk of bias, and one observational study,⁷⁹ with potential for serious risk of bias, compared haloperidol with placebo for a variety of cardiac effects. All of the studies evaluated critically ill patients. In each of these studies, there was no statistically significant difference in a variety of cardiac effects for haloperidol compared with placebo. However, different cardiac effects tended to occur more frequently in the haloperidol group which can be potentially clinically important.

For the specific cardiac effect of prolongation of the corrected QT interval, all the studies reported data.^{44, 45, 53, 79} We conducted a meta-analysis of the three RCTs and found no statistically significant between-group difference for haloperidol compared with placebo (pooled RR, 1.13; 95% CI, 0.62 to 2.05; I-squared, 0%) (Figure 25). We tested the effect of each individual trial on the combined point estimate. No single trial influenced the pooled results. No substantial heterogeneity was identified. The observational study, enrolling 925 patients with and without delirium in the coronary care unit, reported on prolongation of the corrected QT interval at multiple time points.⁷⁹ This observational study reported no clinically important or statistically significant difference for haloperidol compared with placebo in patients with delirium. Additional cardiac effects evaluated in the three RCTs are reported below.

For the specific cardiac effect of hypotension, one RCT compared haloperidol with placebo in 141 critically ill patients receiving mechanical ventilation enrolled within 72 hours of intensive care unit admission.⁴⁵ This RCT reported no statistically significant difference in hypotension for haloperidol (4%) compared with placebo (3%).

For the specific cardiac effect of arrhythmia, all three RCTs reported data. One three-arm RCT, enrolling patients receiving mechanical ventilation, reported no instances of ventricular arrhythmia events in any study group.⁴⁴ Another RCT, enrolling critically ill patients, reported no instances of permanent discontinuation of the study drug owing to suspected torsades de pointes.⁵³ Another RCT, enrolling critically ill patients receiving mechanical ventilation within 72 hours of intensive care unit admission, reported no statistically significant difference in the incidence of atrial fibrillation, bradycardia, and supraventricular tachycardia for haloperidol compared with placebo.⁴⁵

Second-Generation Antipsychotics Versus Placebo

Three RCTs,^{44, 52, 53} with low risk of bias, and one observational study,⁷⁹ with potential for serious risk of bias, compared second-generation antipsychotics with placebo for a variety of cardiac effects. All four studies evaluated critically ill patients. Across all of these studies and the variety of cardiac effects, there was no statistically significant difference in second-generation antipsychotics compared with placebo. However, there was a potential increase in QT interval prolongation for second-generation antipsychotics compared with placebo.

For the specific cardiac effect of prolongation of the corrected QT interval, all four of these studies reported data.^{44, 52, 53, 79} We conducted a meta-analysis of the three RCTs, two of which compared ziprasidone with placebo,^{44, 53} and one that compared quetiapine with placebo.⁵² Our meta-analysis demonstrated a potentially clinically important, but not statistically significant, between-group difference for second-generation antipsychotics compared with placebo (pooled RR, 1.57; 95% CI, 0.90 to 2.76; I-squared, 0%) (Figure 25). Exclusion of one of the three trials⁵²

haloperidol. However, there was a potentially clinically important increase in episodes of QT interval prolongation for ziprasidone.

For the specific cardiac effect of prolongation of the corrected QT interval, three RCTs,^{44, 53, 64} with low risk of bias, and one observational study,⁷⁹ with potential for serious risk of bias, reported data. One RCT reported no statistically significant difference in the incidence of prolongation of the corrected QT interval to more than 500 milliseconds for ziprasidone (17%) compared with haloperidol (6%). Another RCT, a three-arm trial enrolling critically ill patients, reported no statistically significant difference in the incidence of temporary discontinuation of the study drug owing to prolongation of the corrected QT interval for ziprasidone (11%) compared with haloperidol (7%).⁵³ This RCT also reported no incidence of permanent discontinuation of the study drug owing to suspected torsades de pointes in either of the randomization groups. One RCT of inpatients reported no incidence of QT interval prolongation in either group.⁶⁴ One observational study, with potential for serious risk of bias, enrolled patients with and without delirium in the coronary care unit.⁷⁹ This observational study compared quetiapine with haloperidol and reported on prolongation of the corrected QT interval at multiple time points. This study reported no clinically important or statistically significant difference for quetiapine compared with haloperidol in patients with delirium.

For the specific cardiac effect of hypotension, two observational studies with comparison groups reported data.^{68, 70} One study, with moderate risk of bias, reported no statistically significant difference in the incidence of orthostatic hypotension for quetiapine (3%) compared with haloperidol (0%). This study also reported no orthostatic hypotension in the risperidone group.⁶⁸ Another observational study, with potential for serious risk of bias, compared four different second-generation antipsychotics (aripiprazole, olanzapine, quetiapine, and risperidone) with haloperidol in inpatients. This study reported no statistically significant difference in the incidence of rapid decline in systolic blood pressure for quetiapine (0.1%) or risperidone (0.1%) compared with haloperidol (0%).⁷⁰ This study also reported no hypotension in the quetiapine and aripiprazole groups.

For the specific cardiac effect of arrhythmia, three RCTs,^{44, 62, 64} with low risk of bias, and one observational study,⁶⁸ with moderate risk of bias, reported data. Two of the three RCTs reported no incidence of ventricular arrhythmia in either group.^{44, 64} One RCT, enrolling inpatients with hyperactive delirium, reported no statistically significant difference in the incidence of study drug withdrawal owing to atrioventricular block for quetiapine (0%) compared with haloperidol (3.6%).⁶² One three-arm observational study,⁶⁸ with moderate risk of bias and enrolling a total of 56 inpatients, reported no statistically significant difference in the incidence of arrhythmias for quetiapine (0%) or risperidone (7%) compared with haloperidol (9%).

Second-Generation Antipsychotics Versus Second-Generation Antipsychotics

Three observational studies, enrolling inpatients with and without critical illness, compared second-generation antipsychotics with second-generation antipsychotics.⁶⁸⁻⁷⁰ These studies reported no statistically significant differences in the incidence of different types of cardiac effects.

One observational study, with moderate risk of bias and enrolling critically ill patients, reported no difference in the incidence of a corrected QT interval increase of more than 60 milliseconds from baseline for quetiapine (10%) compared with lurasidone (10%).⁶⁹ This study also reported no statistically significant difference in discontinuation of the study medication

owing to prolonged QT interval for quetiapine (5%) compared with lurasidone (0%). The evidence was consistent but imprecise, due to a very low number of events.

For the specific cardiac effect of hypotension, two observational studies reported data.^{68,70} One three-arm study, with moderate risk of bias, compared risperidone with quetiapine and reported no statistically significant difference in the instances of orthostatic hypotension.⁶⁸ A five-arm study, with potential for high risk of bias, compared four different second-generation antipsychotics (aripiprazole, olanzapine, quetiapine, and risperidone) with haloperidol in a total of 2,453 inpatients.⁷⁰ This study reported no statistically significant difference in the incidence of rapid decline in systolic blood pressure for quetiapine (0.1%) compared with aripiprazole (0%), or olanzapine (0%), and for risperidone (0.1%) compared with aripiprazole (0%), olanzapine (0%), or quetiapine (0.1%).

For the specific cardiac effect of arrhythmia, two observational studies, with moderate risk of bias, reported data. One three-arm observational study, with moderate risk of bias and enrolling a total of 56 patients, reported no statistically significant difference in the incidence of arrhythmia for risperidone (7%) compared with quetiapine (0%).⁶⁸ Another study, enrolling 40 critically ill patients, compared quetiapine with lurasidone and reported no instances of life-threatening arrhythmia or torsades de pointes in either group.⁶⁹

Haloperidol Versus Other Therapies

One three-arm RCT, with low risk of bias, compared haloperidol with ondansetron and dexmedetomidine in trauma patients in an intensive care unit.⁵⁰ This trial reported no incidence of hypotension, bradycardia, or prolongation of corrected QT interval in any of the study groups.

We did not find any observational studies or non-randomized trials that compared haloperidol with other therapies and reported on cardiac outcomes.

Second-Generation Antipsychotics Versus Other Therapies

We found no studies evaluating cardiac effects in patients with delirium that compared second-generation antipsychotics with other therapies.

Studies With No Comparison Group

Five observational studies, without comparison groups and with variable risk of biases, evaluated various cardiac effects of three different second-generation antipsychotics (aripiprazole, quetiapine, and risperidone) in a total of 77 inpatients with and without critical illness.^{74,77,78,80,86} The results varied across these studies.

Two studies reported the specific cardiac effect of prolongation of the corrected QT interval.^{78,86} One observational study, with potential for serious risk of bias and enrolling 14 inpatients receiving aripiprazole, reported three (21%) instances of corrected QT interval prolongation.⁸⁶ Another observational study, with moderate risk of bias and enrolling 10 inpatients receiving risperidone, reported no change in the corrected QT interval.⁷⁸ Three studies reported data about the specific cardiac effect of hypotension.^{77,78,80} Two of these studies, with potential for high risk of bias and enrolling a total of 41 inpatients receiving quetiapine, reported data. One study reported two instances (12%) of hypotension,⁷⁷ the other study reported no hypotension.⁸⁰ One observational study, with moderate risk of bias, and enrolling 10 inpatients receiving risperidone, reported one instance (10%) of discontinuation of the study drug owing to hypotension.⁷⁸

Two studies reported the specific cardiac effects of arrhythmia or myocardial infarction.^{74, 86} One observational study, with moderate risk of bias and enrolling 12 critically ill patients receiving quetiapine, reported one (8%) fatal acute myocardial infarction.⁷⁴ Another observational study, with potential for serious risk of bias and enrolling 14 inpatients receiving aripiprazole, reported one (7%) cardiac arrest and no instance of ventricular arrhythmia.⁸⁶

Neurologic Effects – Overall

Haloperidol Versus Placebo

Four RCTs, with low risk of bias, compared haloperidol with placebo for a number of neurologic effects.^{44, 45, 48, 53} Three of the four trials evaluated critically ill patients,^{44, 45, 53} and the fourth evaluated patients receiving palliative care.⁴⁸ Overall, across a variety of neurologic effects, including extrapyramidal symptoms and neuroleptic malignant syndrome, only the single RCT enrolling patients receiving palliative care reported a statistically significant increase in extrapyramidal symptoms for haloperidol compared with placebo.

For the neurologic effect of extrapyramidal symptoms, we conducted a meta-analysis with three of the RCTs, all of which evaluated critically ill patients. This meta-analysis demonstrated no between-group difference in extrapyramidal symptoms comparing haloperidol with placebo (pooled RR, 0.77; 95% CI, 0.29 to 2.02; I-squared, 0%) (Figure 26).^{44, 45, 53} We tested the effect of each individual trial on the combined point estimate. No single trial influenced the pooled results. No substantial statistical heterogeneity was identified. One of the three RCTs, a three-arm trial enrolling a total of 566 critically ill patients, also reported no instances of temporarily holding the study drug owing to extrapyramidal symptoms.⁵³ In addition, the fourth RCT, a three-arm trial comparing haloperidol with placebo in a total of 249 patients receiving palliative care, reported increased extrapyramidal symptoms (evaluated using the Extra Pyramidal Symptom Rating Scale score) in the haloperidol group (mean difference, 0.8; 95% CI, 0.2 to 1.4; $P = 0.01$).⁴⁸

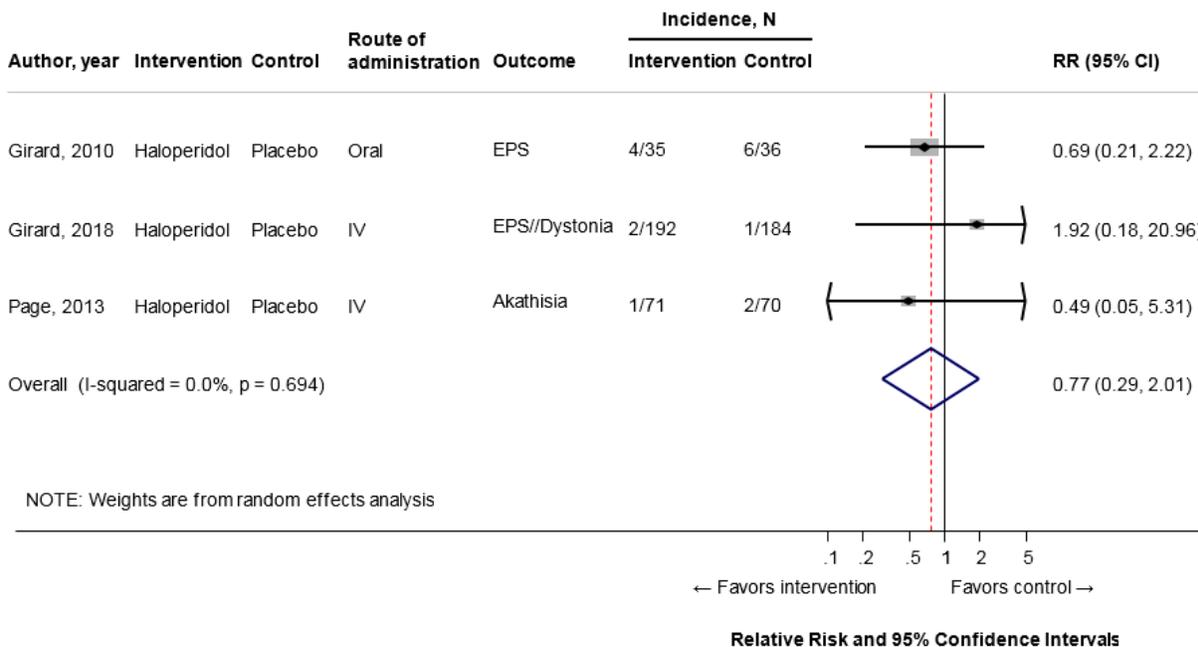
For the specific neurologic effect of akathisia, one three-arm RCT enrolling patients receiving mechanical ventilation, reported a non-statistically significant increase in the incidence of akathisia for haloperidol (29%) compared with placebo (19%).⁴⁴

For the specific neurologic effects of muscle stiffness, torticollis, and dystonia, two RCTs reported data. One RCT evaluated patients receiving mechanical ventilation and enrolled within 72 hours of intensive care unit admission. This trial reported no statistically significant effect on muscle stiffness for haloperidol (1.4%) compared with placebo (1.4%) and on torticollis for haloperidol (0%) compared with placebo (1.4%).⁴⁵ Another RCT, a three-arm trial enrolling critically ill patients, reported no instances of temporarily holding the study drug owing to dystonia.⁵³

Two three-arm RCTs reported data on the neurologic effect of neuroleptic malignant syndrome. One RCT, enrolling patients receiving mechanical ventilation, reported no incidence of neuroleptic malignant syndrome in the haloperidol or placebo groups.⁴⁴ Another RCT, a three-arm trial enrolling critically ill patients, reported no incidence of permanent discontinuation of the study drug owing to suspected neuroleptic malignant syndrome.⁵³

We did not find any observational studies or non-randomized trials that compared haloperidol with placebo and reported on neurologic effects.

Figure 26. Meta-analysis of neurological outcomes in trials comparing haloperidol with placebo in patients with delirium



CI = confidence interval; EPS = extrapyramidal symptoms; IV = intravenous; N = total arm population; n = incidence within arm; p = p-value; RR = relative risk

Second-Generation Antipsychotics Versus Placebo

Five RCTs, with low risk of bias, compared second-generation antipsychotics with placebo for a number of different neurologic effects.^{44, 48, 52, 53, 63} Three of the five trials evaluated critically ill patients, one evaluated inpatients without critical illness, and one evaluated patients receiving palliative care. Overall, across a variety of neurologic effects, including extrapyramidal symptoms and neuroleptic malignant syndrome, only the single RCT that enrolled patients receiving palliative care reported a statistically significant increase in extrapyramidal symptoms for risperidone compared with placebo.

For the neurologic effect of extrapyramidal symptoms, we conducted a meta-analysis with three RCTs that enrolled inpatients with and without critical illness.^{44, 53, 63} This meta-analysis demonstrated no increase in extrapyramidal symptoms comparing second-generation antipsychotics with placebo (pooled RR, 0.44; 95% CI, 0.14 to 1.38; I-squared, 0%) (Figure 27). We tested the effect of each individual trial on the combined point estimate. No single trial influenced the pooled results. No substantial statistical heterogeneity was identified. One of the three RCTs, a three-arm trial enrolling a total of 566 critically ill patients, also reported no instances of temporarily holding the study drug owing to extrapyramidal symptoms.⁵³ Another RCT, evaluating quetiapine compared with placebo in 36 medical and surgical critically ill patients, reported no incidence of extra pyramidal symptoms in either randomization group.⁵² In addition, a three-arm RCT, comparing risperidone and placebo in a total of 249 patients receiving palliative care, reported increased symptoms (evaluated using the Extra Pyramidal Symptom Rating Scale score) in the risperidone group (mean difference, 0.7; 95% CI, 0.1 to 1.4; $P = 0.03$).⁴⁸

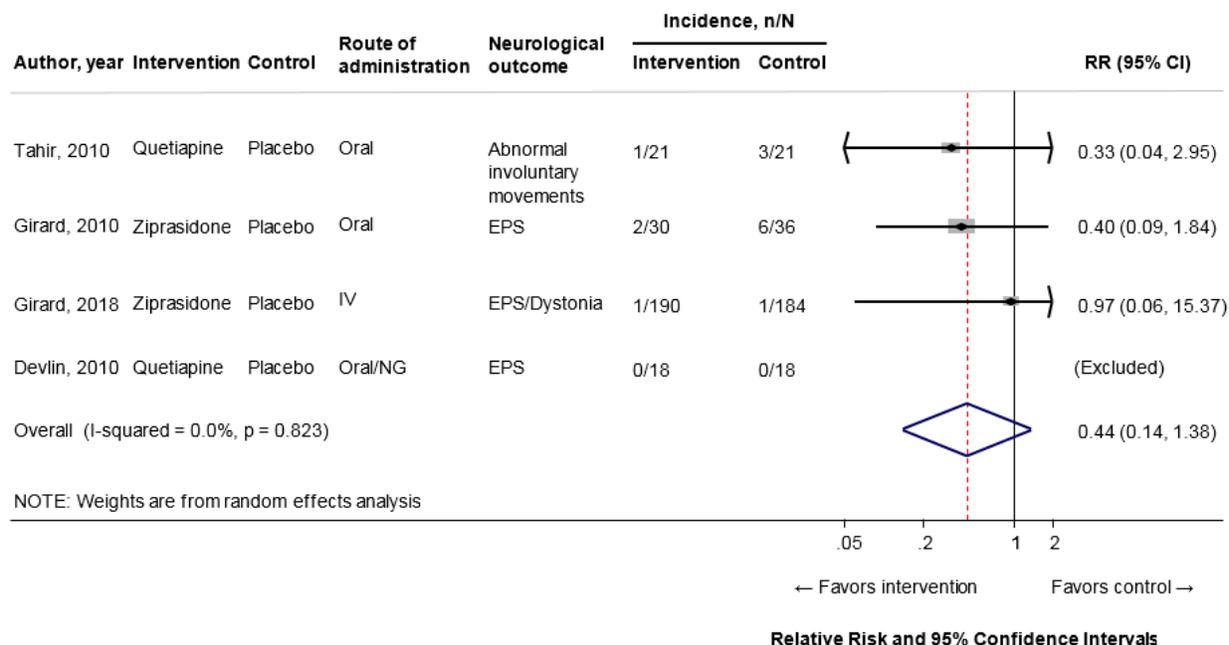
For the specific neurological effect of akathisia, one three-arm RCT, enrolling patients receiving mechanical ventilation, reported no statistically significant effect in incidence of akathisia for ziprasidone (20%) compared with placebo (19%).⁴⁴

For the specific neurological effects of dystonia, one three-arm RCT, enrolling critically ill patients, reported no instances of temporarily holding the study drug owing to dystonia.⁵³

For the neurological effect of neuroleptic malignant syndrome, two three-arm RCTs reported data. One RCT, enrolling patients receiving mechanical ventilation, reported no incidence of neuroleptic malignant syndrome in the ziprasidone or placebo groups.⁴⁴ Another three-arm RCT, enrolling critically ill patients, reported no incidence of permanent discontinuation of the study drug owing to suspected neuroleptic malignant syndrome.⁵³

We did not find any observational studies or non-randomized trials that compared a second-generation antipsychotic with placebo and reported on neurologic effects.

Figure 27. Meta-analysis of neurologic outcomes in trials comparing second-generation antipsychotics with placebo



CI = confidence interval; EPS = extrapyramidal symptoms; IV = intravenous; N = total arm population; n = incidence within arm; p = p-value; RR = relative risk

Haloperidol Versus Second-Generation Antipsychotics

Eight RCTs^{44, 53, 54, 56, 58, 61, 62, 64} and eight observational studies with a comparison group^{65, 66, 68, 70, 75, 84, 85, 89} compared second-generation antipsychotics with haloperidol for a number of different neurological effects. One RCT evaluated patients receiving palliative care,⁶¹ four RCTs and seven observational studies evaluated inpatients without critical illness,^{54, 58, 62, 64-66, 68, 70, 75, 84, 89} two RCTs^{44, 53} and one observational study evaluated critically ill patients,⁸⁵ and one RCT evaluated inpatients with and without critical illness.⁵⁶ Overall, across a variety of neurologic effects, including extrapyramidal symptoms and neuroleptic malignant syndrome, no RCT or observational study reported a statistically significant difference when comparing second-generation antipsychotics with haloperidol.

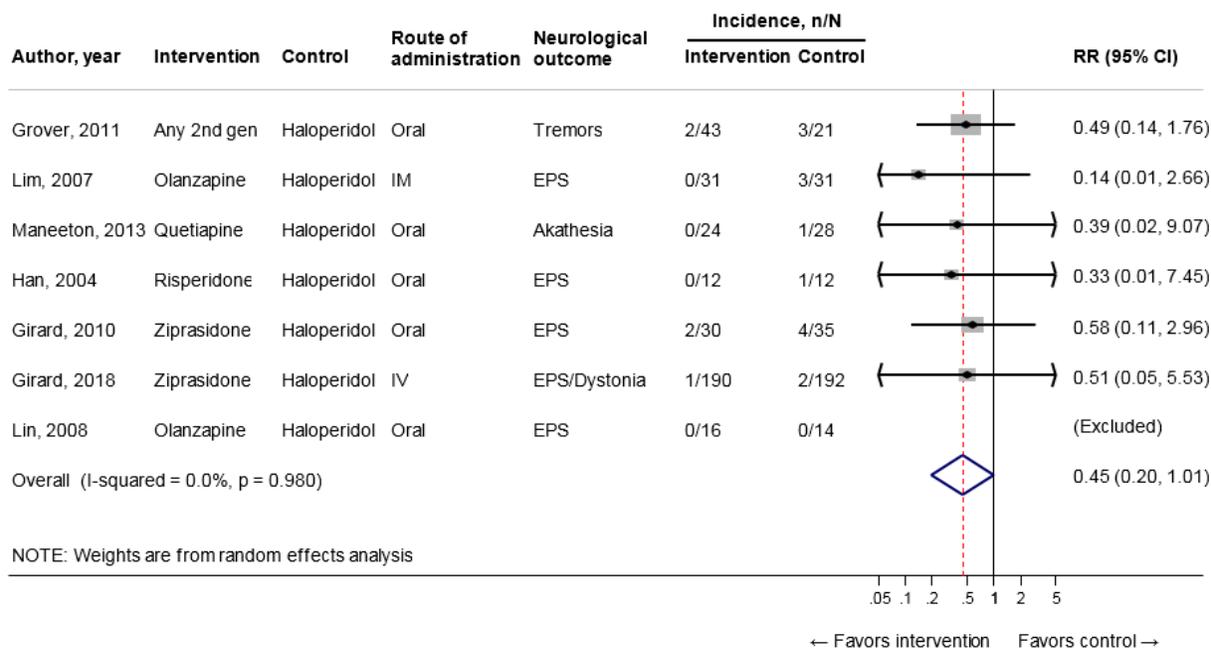
For the neurologic effect of extrapyramidal symptoms, we conducted a meta-analysis of the six RCTs that evaluated inpatients with and without critical illness.^{44, 53, 54, 56, 62, 64} For the purpose of this meta-analysis, we combined the olanzapine and risperidone groups to compare them with the haloperidol group in one study.⁵⁴ Four of the six RCTs had low risk of bias,^{44, 53, 62, 64} and two RCTs had unclear risk of bias.^{54, 56} The meta-analysis showed a potentially clinically important but not statistically significant between-group difference in the incidence of extrapyramidal symptoms in second-generation antipsychotics compared with haloperidol (pooled RR, 0.45; 95% CI, 0.20 to 1.01; I-squared, 0%) (Figure 28). We tested the effect of each individual trial on the combined point estimate. No single trial influenced the pooled results. No substantial statistical heterogeneity was identified. One of the five RCTs, enrolling inpatients with hyperactive delirium, also evaluated extrapyramidal symptoms using the Modified Simpson Angus Scale.⁶² This RCT reported no statistically significant effect for quetiapine compared with haloperidol.

Seven RCTs^{44, 53, 54, 58, 61, 62, 64} and eight observational studies with a comparison group^{65, 66, 68, 70, 75, 84, 85, 89} evaluated various neurologic effects related to extrapyramidal symptoms: akathisia; bradykinesia; drug-induced parkinsonism; dystonia; rigidity; tremors; tics; abnormal movements of jaw, tongue, lips, and perioral region; and withdrawal of study drug owing to extrapyramidal symptoms. Of the seven RCTs, two had potential for high risk of bias, primarily owing to a lack of blinding and missing outcome data;^{58, 61} four were low risk of bias;^{44, 53, 62, 64} and one had unclear risk of bias.⁵⁴ Of the eight observational studies, one had a low risk of bias,⁸⁵ one had a moderate risk of bias,⁶⁸ and the rest had potential for serious risk of bias.^{65, 66, 70, 75, 84, 89} Sample sizes for these observational studies with a comparison group ranged from 22 to 2,453. Five different second-generation antipsychotics (aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone) were compared with haloperidol, and no trial or observational study with a comparison group reported statistically significant differences in various neurologic effects related to extrapyramidal symptoms.

For the neurologic effect of neuroleptic malignant syndrome, two three-arm RCTs, with low risk of bias, reported data.^{44, 53} One RCT, enrolling patients receiving mechanical ventilation, reported no incidence of neuroleptic malignant syndrome in the second-generation antipsychotics or haloperidol groups.⁴⁴ One three-arm trial, enrolling critically ill patients, reported no incidence of permanent discontinuation of the study drug owing to suspected neuroleptic malignant syndrome.⁵³

One RCT, with low risk of bias and enrolling inpatients with hyperactive delirium, reported no statistically significant difference in withdrawal of drug owing to seizures for quetiapine (4%) compared to haloperidol (0%).⁶²

Figure 28. Meta-analysis of neurologic outcomes in trials comparing haloperidol with second-generation antipsychotics in patients with delirium



NOTE: Weights are from random effects analysis

Relative Risk and 95% Confidence Intervals

CI = confidence interval; EPS = extrapyramidal symptoms; IM = intramuscular; IV = intravenous; N = total arm population; n = incidence within arm; p = p-value; RR = relative risk

Haloperidol Versus Other Therapies

One three-arm RCT, with an unclear risk of bias, compared haloperidol with lorazepam in medical inpatients with acquired immunodeficiency syndrome and reported no statistically significant between-group difference in the Extra Pyramidal Symptom Rating Scale.⁵¹

We did not find any observational studies or non-randomized trials that compared haloperidol with other therapies and reported on neurologic effects.

Second-Generation Antipsychotics Versus Second-Generation Antipsychotics

Three RCTs^{54, 59, 60} and four observational studies with a comparison group^{66, 68, 70, 89} compared second-generation antipsychotics with second-generation antipsychotics for a number of different neurologic effects in inpatients without critical illness. Of the three RCTs, two had high risk of bias^{59, 60} and one had unclear risk of bias.⁵⁴ Of the four observational studies, one study had moderate risk of bias⁶⁸ and three studies had potential for serious risk of bias.^{66, 70, 89} Five different second-generation antipsychotics were compared with each other (aripiprazole, olanzapine, quetiapine, risperidone, and amisulpride) for various neurological effects related to extrapyramidal symptoms: akathisia; bradykinesia; drug-induced parkinsonism; dystonia; dyskinesia; rigidity; tremors; and abnormal movements of jaw, tongue, lips, and perioral region. No RCT or observational study with a comparison group reported statistically significant differences in extrapyramidal symptoms. The evidence was consistent but imprecise.

Studies With No Comparison Group

Twelve observational studies without a comparison group, with a total of 251 patients who were predominantly medical and surgical inpatients without critical illness, evaluated various

neurologic effects of four different second-generation antipsychotics (aripiprazole, quetiapine, risperidone, and paliperidone).^{71, 72, 74, 76-78, 80-83, 86, 88} The results varied across these studies.

For the neurologic effect of extrapyramidal symptoms, four studies reported no incidence,^{74, 76, 80, 81} and two studies reported no statistically significant increase comparing baseline and final assessments of extrapyramidal symptoms scores.^{78, 83} In contrast, four studies reported a range from 5 percent to 13 percent of patients experiencing extrapyramidal symptoms.^{71, 72, 77, 88}

For the neurologic effect of cerebrovascular accidents, two studies reported no incidence of such events.^{82, 86}

Aspiration Pneumonia – Overall

Haloperidol Versus Second-Generation Antipsychotics

One cohort study, with potential for high risk of bias, compared aripiprazole, olanzapine, quetiapine, and risperidone with haloperidol in inpatients.⁷⁰ This study demonstrated no statistically significant effect on the incidence of aspiration pneumonia for aripiprazole compared with haloperidol, olanzapine compared with haloperidol, quetiapine compared with haloperidol, and risperidone compared with haloperidol.

Second-Generation Antipsychotics Versus Second-Generation Antipsychotics

One cohort study, with potential for high risk of bias and enrolling inpatients, compared aripiprazole, olanzapine, quetiapine, and risperidone.⁷⁰ This study reported no statistically significant effect on the incidence of aspiration pneumonia for olanzapine compared with aripiprazole, quetiapine compared with aripiprazole, risperidone compared with aripiprazole, risperidone compared with quetiapine, quetiapine compared with olanzapine, and risperidone compared with olanzapine.

Other Comparisons

We found no studies of delirium treatment evaluating aspiration pneumonia in patients with delirium for the following comparisons:

- Haloperidol versus placebo
- Second-generation antipsychotics versus placebo
- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies

Studies With No Comparison Group

One single-arm cohort study, enrolling 14 medically ill patients with delirium treated with aripiprazole, reported aspiration pneumonia in one patient (7%).⁸⁶

Adverse Effects – Overall

We found no studies in patients with delirium that compared an antipsychotic with a placebo, another antipsychotic, or another treatment and evaluated the following adverse events:

- Weight gain
- Changes in appetite
- Hypersensitivity reactions
- Inappropriate continuation of antipsychotics
- Swallowing difficulties

Key Question 2a. Benefits and Harms of Antipsychotics To Treat Delirium in Persons Aged 65 Years and Older

Key Points – Aged 65 Years and Older

Delirium Severity

- We were unable to draw a conclusion regarding the effects of antipsychotics on cognitive functioning for the following comparisons:
 - Haloperidol versus placebo (insufficient evidence)
 - Second-generation antipsychotics versus placebo (insufficient evidence)
 - Second-generation antipsychotics versus second-generation antipsychotics (insufficient evidence)
 - Haloperidol versus other therapies (insufficient evidence)
 - Second-generation antipsychotics versus other therapies (no trials)

Cognitive Functioning, Falls, Inappropriate Continuation of Antipsychotics, or Sedation

- We found no studies evaluating cognitive functioning, falls, inappropriate continuation of antipsychotics, or sedation in patients aged 65 years and older with delirium that compared an antipsychotic with a placebo, another antipsychotic, or another treatment.

Intermediate Outcomes

Delirium Severity – Aged 65 Years and Older

Haloperidol Versus Placebo

One three-arm RCT, with unclear risk of bias and enrolling inpatients aged 65 years and older, compared haloperidol with placebo.⁵⁷ This RCT evaluated delirium severity at day seven, using the Delirium Rating Scale, with a lower score for haloperidol compared with placebo. Those patients randomized to haloperidol had a greater reduction in delirium severity score than patients randomized to placebo.

This RCT also reported lower delirium severity at day seven, evaluated using the Clinical Global Impression scale, for haloperidol compared with placebo. Using the Clinical Global Impression scale and 7-day followup, the RCT reported a statistically significant reduction in delirium severity for haloperidol compared with placebo. This trial also reported a statistically significant increase in the number of patients with a “significant improvement” or “complete alleviation” for haloperidol (88%) compared with placebo (31%).⁵⁷ We were unable to draw conclusions about the effect of haloperidol compared with placebo on delirium severity based upon this single study. (SOE: Insufficient)

Second-Generation Antipsychotics Versus Placebo

One three-arm RCT, with unclear risk of bias and enrolling inpatients aged 65 years and older, compared olanzapine with placebo.⁵⁷ This RCT evaluated delirium severity at day seven, using the Delirium Rating Scale, with a lower score for olanzapine compared with placebo.

This RCT also reported lower delirium severity at day seven, evaluated using the Clinical Global Impression scale, for olanzapine compared with placebo. Using the Clinical Global Impression scale and 7-day followup, the RCT reported a statistically significant reduction in delirium severity for olanzapine compared with placebo. This trial also reported a statistically significant increase in the number of patients with a “significant improvement” or “complete alleviation” for olanzapine (82%) compared with placebo (31%).⁵⁷ We were unable to draw conclusions based upon this single trial. (SOE: Insufficient)

Haloperidol Versus Second-Generation Antipsychotics

One three-arm RCT, with unclear risk of bias and enrolling inpatients aged 65 years and older, compared haloperidol with olanzapine.⁵⁷ This RCT evaluated delirium severity at day seven, using the Delirium Rating Scale, with a lower score for olanzapine compared with haloperidol. There was no statistically significant difference in reduction from baseline between treatment groups.

This RCT also reported higher delirium severity at day seven, evaluated using the Clinical Global Impression scale, for olanzapine compared with haloperidol. Using the Clinical Global Impression scale and 7-day followup, the RCT reported no statistically significant difference in reduction in delirium severity for olanzapine compared with haloperidol and a non-statistically significant difference in the number of patients with a “significant improvement” or “complete alleviation” for olanzapine (82%) compared with haloperidol (88%).⁵⁷ We were unable to draw conclusions based upon this single trial. (SOE: Insufficient)

Other Comparisons

We found no delirium treatment trials evaluating delirium severity in patients aged 65 years and older with delirium for the following comparisons:

- Second-generation antipsychotics versus second-generation antipsychotics
- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies

Strength of Evidence

Table 21 summarizes the strength of evidence findings for the effects of antipsychotics on delirium severity in patients aged 65 years and older with delirium.

Table 21. Strength of evidence domains for trials evaluating antipsychotics for the treatment of delirium in terms of delirium severity in patients aged 65 years and older

Comparison	Number Of Trials (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength Of Evidence	Summary
Haloperidol vs. placebo	1 ⁵⁷ (175)	High	Direct	Consistency unknown (single study)	Imprecise	Undetected	Insufficient	We were unable to draw a conclusion.
Second-generation antipsychotics vs. placebo	1 ⁵⁷ (175)	High	Direct	Consistency unknown (single study)	Imprecise	Undetected	Insufficient	We were unable to draw a conclusion.
Haloperidol vs. second-generation antipsychotics	1 ⁵⁷ (175)	High	Direct	Consistency unknown (single study)	Imprecise	Undetected	Insufficient	We were unable to draw a conclusion.
Second-generation antipsychotics vs. second-generation antipsychotics	No trials							
Haloperidol vs. other therapies	No trials							
Second-generation antipsychotics vs. other therapies	No trials							

Other Intermediate Outcomes – Aged 65 Years and Older

We found no trials enrolling patients aged 65 years and older with delirium that compared an antipsychotic with a placebo, another antipsychotic, or another treatment and evaluated the following intermediate outcomes:

- Delirium incidence
- Short-term delirium symptoms
- Delirium- and coma-free days alive
- Duration of delirium
- Patient distress
- Use of rescue therapy
- Use of physical restraint

Final Health or Patient-Centered Outcomes – Aged 65 Years and Older

We found no trials enrolling patients aged 65 years and older with delirium that compared an antipsychotic with a placebo, another antipsychotic, or another treatment and evaluated the following final health or patient-centered outcomes:

- Mortality
- Quality of life
- Cognitive functioning
- Institutionalization
- Caregiver burden/strain
- Falls
- Memory of patient distress

Resource Utilization Outcomes – Aged 65 Years and Older

We found no trials enrolling patients aged 65 years and older with delirium that compared an antipsychotic with a placebo, another antipsychotic, or another treatment and evaluated the following resource utilization outcomes:

- Readmission to hospital
- Readmission to intensive care unit
- Length of stay in hospital
- Length of stay in intensive care unit
- Length of stay in skilled nursing facility
- Patient safety attendant use
- Hospice enrollment

Adverse Effects – Aged 65 Years and Older

We found no studies enrolling patients aged 65 years and older with delirium that compared an antipsychotic with a placebo, another antipsychotic, or another treatment and evaluated the following adverse events:

- Sedation

- Weight gain
- Changes in appetite
- Cardiac effects
- Neurologic effects
- Hypersensitivity reactions
- Inappropriate continuation of antipsychotics
- Swallowing difficulties
- Aspiration pneumonia

Key Question 2b. Benefits and Harms of Antipsychotics To Treat Delirium in Persons With Dementia

We found no studies evaluating antipsychotics for the treatment of delirium in persons with dementia.

Key Question 2c. Benefits and Harms of Antipsychotics To Treat Delirium in Patients in an Intensive Care Unit

Key Points – Intensive Care Unit

Length of Stay in Hospital

- All RCTs reported no statistically significant difference in length of stay in hospital for critically ill patients for the following comparisons:
 - Haloperidol with placebo (SOE: Moderate)
 - Second-generation antipsychotics with placebo (SOE: Moderate)
 - Haloperidol with second-generation antipsychotics (SOE: Moderate)

Sedation

- There was no clinically important or statistically significant difference in sedation for critically ill patients for the following comparisons:
 - Haloperidol with placebo (SOE: Moderate)
 - Second-generation antipsychotics with placebo (SOE: Moderate)
 - Haloperidol with second-generation antipsychotics (SOE: Moderate)
- We are unable to draw a conclusion regarding the effects of antipsychotics on sedation in critically ill patients for the following comparisons:
 - Second-generation antipsychotics with second-generation antipsychotics (insufficient evidence)
 - Haloperidol with other therapies (no studies)
 - Second-generation antipsychotics versus other therapies (no studies)

Delirium Severity, Cognitive Functioning, and Inappropriate Continuation of Antipsychotics

- We found no trials evaluating delirium severity, cognitive functioning, or inappropriate continuation of antipsychotics in critically ill patients with delirium that compared an antipsychotic with a placebo, another antipsychotic, or another treatment.

Intermediate Outcomes

Delirium Incidence – Intensive Care Unit

Second-Generation Antipsychotics Versus Placebo

The findings presented in the “Delirium Incidence - Overall” results section are wholly represented by this subgroup. Please refer to the “Delirium Incidence - Overall” results section.

Other Comparisons

We found no delirium treatment trials evaluating delirium incidence in critically ill patients with delirium for the following comparisons:

- Haloperidol versus placebo
- Haloperidol versus second-generation antipsychotics
- Second-generation antipsychotics versus second-generation antipsychotics
- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies.

Short-Term Delirium Symptoms – Intensive Care Unit

Haloperidol Versus Placebo

The findings presented in the “Short-Term Delirium Symptoms - Overall” results section are wholly represented by this subgroup. Please refer to the “Short-Term Delirium Symptoms - Overall” results section.

Second-Generation Antipsychotics Versus Placebo

One RCT, with low risk of bias, compared quetiapine with placebo in medical and surgical critically ill patients.⁵² This RCT reported on agitation, defined as the number of hours with a Sedation-Agitation Scale score of equal to or greater than 5, and reported fewer hours of agitation for patients receiving quetiapine compared with placebo.

Other Comparisons

We found no delirium treatment trials evaluating short-term delirium symptoms in critically ill patients with delirium for the following comparisons:

- Haloperidol versus second-generation antipsychotics
- Second-generation antipsychotics versus second-generation antipsychotics
- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies

Delirium- and Coma-Free Days Alive – Intensive Care Unit

Haloperidol Versus Placebo

The findings presented in the “Delirium- and Coma-Free Days Alive - Overall” results section are wholly represented by this subgroup. Please refer to the “Delirium- and Coma-Free Days Alive - Overall” results section.

Second-Generation Antipsychotics Versus Placebo

The findings presented in the “Delirium- and Coma-Free Days Alive - Overall” results section are wholly represented by this subgroup. Please refer to the “Delirium- and Coma-Free Days Alive - Overall” results section.

Haloperidol Versus Second-Generation Antipsychotics

The findings presented in the “Delirium- and Coma-Free Days Alive - Overall” results section are wholly represented by this subgroup. Please refer to the “Delirium- and Coma-Free Days Alive - Overall” results section.

Other Comparisons

We found no delirium treatment trials evaluating delirium- and coma-free days alive in critically ill patients with delirium for the following comparisons:

- Second-generation antipsychotics versus second-generation antipsychotics
- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies

Duration of Delirium – Intensive Care Unit

Haloperidol Versus Placebo

The findings presented in the “Duration of Delirium - Overall” results section are wholly represented by this subgroup. Please refer to the “Duration of Delirium - Overall” results section.

Second-Generation Antipsychotics Versus Placebo

The findings presented in the “Duration of Delirium - Overall” results section are wholly represented by this subgroup. Please refer to the “Duration of Delirium - Overall” results section.

Haloperidol Versus Second-Generation Antipsychotics

Two RCTs, with low risk of bias, compared ziprasidone with haloperidol and assessed delirium duration in medical and surgical patients in intensive care units.^{44, 53} There was consistent and precise evidence from these well-conducted trials of no difference in delirium duration for second-generation antipsychotics compared with haloperidol. We did not conduct a meta-analysis because these trials provided results as median values and delirium duration data may be skewed, precluding conversion or transformation of the data.

Other Comparisons

We found no delirium treatment trials evaluating delirium duration in critically ill patients with delirium for the following comparisons:

- Second-generation antipsychotics versus second-generation antipsychotics
- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies

Use of Rescue Therapy – Intensive Care Unit

Haloperidol Versus Placebo

The findings presented in the “Use of Rescue Therapy - Overall” results section are wholly represented by this subgroup. Please refer to the “Use of Rescue Therapy - Overall” results section.

Second-Generation Antipsychotics Versus Placebo

The findings presented in the “Use of Rescue Therapy - Overall” results section are wholly represented by this subgroup. Please refer to the “Use of Rescue Therapy - Overall” results section.

Haloperidol Versus Second-Generation Antipsychotics

Two RCTs, with low risk of bias, compared ziprasidone with haloperidol and assessed the use of rescue therapy, defined as the use of any open-label antipsychotic.^{44, 53} Both of these trials, enrolling medical and surgical patients in intensive care units, reported no statistically significant effect on the use of rescue therapy. The evidence was consistent but imprecise.

Other Comparisons

We found no delirium treatment trials evaluating the use of rescue therapy in critically ill patients with delirium for the following comparisons:

- Second-generation antipsychotics versus second-generation antipsychotics
- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies

Other Intermediate Outcomes – Intensive Care Unit

We found no trials enrolling critically ill patients with delirium that compared an antipsychotic with a placebo, another antipsychotic, or another treatment and evaluated the following intermediate outcomes:

- Delirium severity
- Patient distress
- Use of physical restraint

Final Health or Patient-Centered Outcomes

Mortality – Intensive Care Unit

Haloperidol Versus Placebo

Three RCTs, with low risk of bias and enrolling medical and surgical critically ill patients, compared haloperidol with placebo. All three RCTs reported no between-group difference in short-term mortality, defined as mortality while in hospital or up to 30 days after randomization (pooled RR, 1.08; 95% CI, 0.85 to 1.36; I-squared, 0%) (Figure 29).^{44, 45, 53} We tested the effect of each individual trial on the combined point estimate. No single trial influenced the pooled results. No substantial statistical heterogeneity was identified. There was consistent but imprecise evidence of no difference for short-term mortality.

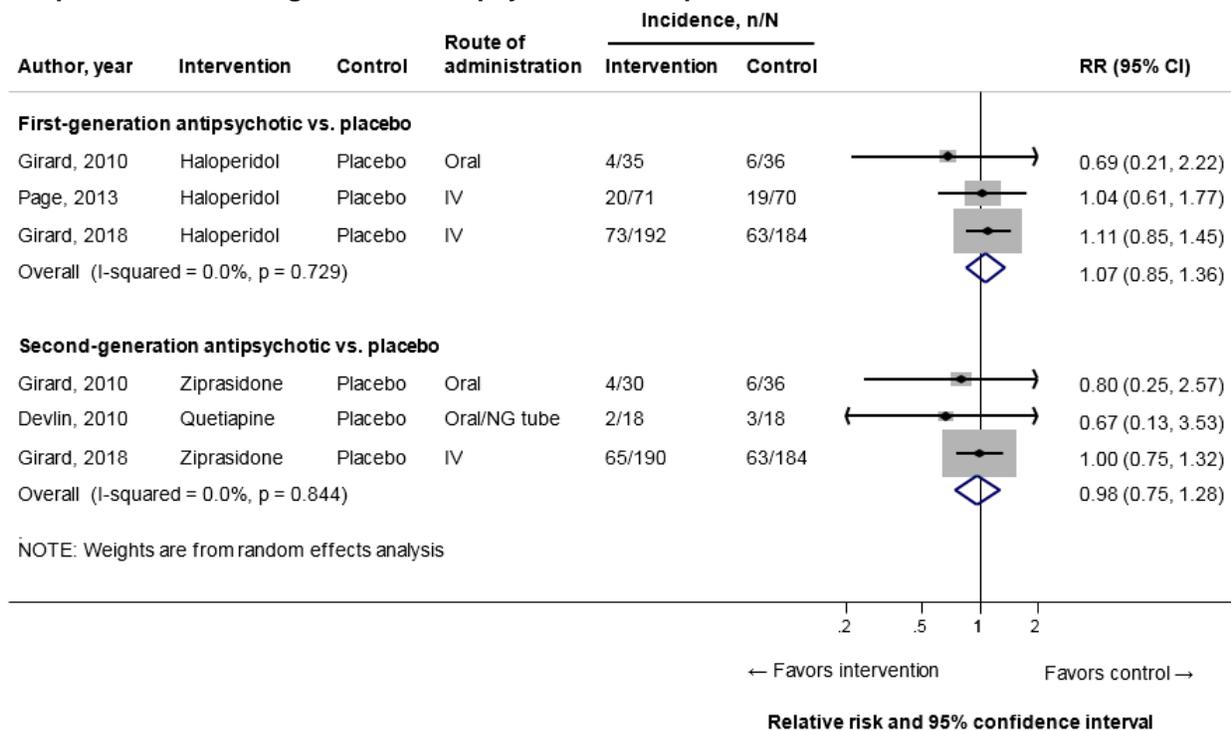
Of these three RCTs, the largest trial was a three-arm RCT, with low risk of bias, that also evaluated 90-day mortality in a total of 566 critically ill patients. The results of this evaluation were consistent with the results of our meta-analysis, with no between-group difference in short-term mortality when comparing haloperidol with placebo.⁵³

Second-Generation Antipsychotics Versus Placebo

Three RCTs, with low risk of bias and enrolling medical and surgical critically ill patients, compared a second-generation antipsychotic with placebo. All three RCTs reported no between-group difference in short-term mortality, defined as mortality while in hospital or up to 30 days after randomization (pooled RR, 0.98; 95% CI, 0.75 to 1.28; I-squared, 0.0%) (Figure 29).^{44, 52, 53} Two of the RCTs evaluated ziprasidone, and one RCT evaluated quetiapine. We tested the effect of each individual trial on the combined point estimate. No single trial influenced the pooled results. No substantial statistical heterogeneity was identified. The evidence was consistent but imprecise.

Of these three RCTs, the largest trial was a three-arm RCT, with low risk of bias, that also evaluated 90-day mortality in a total of 566 critically ill patients. The results of this evaluation were consistent with the results of our meta-analysis, with no between-group difference reported for short-term mortality comparing risperidone with placebo.⁵³

Figure 29. Meta-analysis of mortality in trials with an intensive care unit population comparing haloperidol or second-generation antipsychotics with placebo



CI = confidence interval; IV = intravenous; N = total arm population; n = incidence within arm; NG = nasogastric tube; p = p-value; RR = relative risk

Haloperidol Versus Second-Generation Antipsychotics

Two RCTs, with low risk of bias and enrolling medical and surgical critically ill patients, compared haloperidol with ziprasidone.^{44, 53} These RCTs assessed short-term mortality, defined

as mortality while in hospital or up to 30 days after randomization. There was consistent but imprecise evidence of no effect on short-term mortality.

Other Comparisons

We found no delirium treatment trials evaluating mortality in critically ill patients with delirium for the following comparisons:

- Second-generation antipsychotics versus second-generation antipsychotics
- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies

Other Final Health or Patient-Centered Outcomes – Intensive Care Unit

We found no trials enrolling critically ill patients with delirium that compared an antipsychotic with a placebo, another antipsychotic, or another treatment and evaluated the following final health or patient-centered outcomes:

- Quality of life
- Cognitive functioning
- Institutionalization
- Caregiver burden/strain
- Falls
- Memory of patient distress

Resource Utilization Outcomes

Readmission to Intensive Care Unit – Intensive Care Unit

Haloperidol Versus Placebo

The findings presented in the “Readmission to Intensive Care Unit - Overall” results section are wholly represented by this subgroup. Please refer to the “Readmission to Intensive Care Unit - Overall” results section.

Second-Generation Antipsychotics Versus Placebo

The findings presented in the “Readmission to Intensive Care Unit - Overall” results section are wholly represented by this subgroup. Please refer to the “Readmission to Intensive Care Unit - Overall” results section.

Haloperidol Versus Second-Generation Antipsychotics

The findings presented in the “Readmission to Intensive Care Unit - Overall” results section are wholly represented by this subgroup. Please refer to the “Readmission to Intensive Care Unit - Overall” results section.

Other Comparisons

We found no delirium treatment trials evaluating readmission to the intensive care unit in critically ill patients with delirium for the following comparisons:

- Second-generation antipsychotics versus second-generation antipsychotics

- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies

Length of Stay in Hospital – Intensive Care Unit

Haloperidol Versus Placebo

The findings presented in the “Length of Stay in Hospital - Overall” results section are wholly represented by this subgroup. Please refer to the “Length of Stay in Hospital - Overall” results section. (SOE for patients in the intensive care unit: Moderate)

Second-Generation Antipsychotics Versus Placebo

The findings presented in the “Length of Stay in Hospital - Overall” results section are wholly represented by this subgroup. Please refer to the “Length of Stay in Hospital - Overall” results section. (SOE for patients in the intensive care unit: Moderate)

Haloperidol Versus Second-Generation Antipsychotics

The findings presented in the “Length of Stay in Hospital - Overall” results section are wholly represented by this subgroup. Please refer to the “Length of Stay in Hospital - Overall” results section. (SOE for patients in the intensive care unit: Moderate)

Other Comparisons

We found no delirium treatment trials evaluating length of stay in hospital for critically ill patients with delirium for the following comparisons:

- Second-generation antipsychotics versus second-generation antipsychotics
- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies

Strength of Evidence

Table 22 summarizes the strength of evidence findings for length of stay in hospital for critically ill patients with delirium.

Table 22. Strength of evidence domains for trials evaluating antipsychotics for the treatment of delirium in terms of length of stay in hospital for patients in an intensive care unit

Comparison	Number Of Trials (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength Of Evidence	Summary
Haloperidol vs. placebo	3 ^{44, 45, 53} (808)	Low	Direct	Consistent	Precise	Undetected	Moderate	All RCTs reported no statistically significant difference.
Second-generation antipsychotics vs. placebo	3 ^{44, 52, 53} (703)	Low	Direct	Consistent	Precise	Undetected	Moderate	All RCTs reported no statistically significant difference.
Haloperidol vs. second-generation antipsychotics	2 ^{44, 53} (667)	Low	Direct	Consistent	Precise	Undetected	Moderate	All RCTs reported no statistically significant difference.
Second-generation antipsychotics vs. second-generation antipsychotics	No trials							
Haloperidol vs. other therapies	No trials							
Second-generation antipsychotics vs. other therapies	No trials							

Abbreviations: RCT = randomized controlled trial.

Length of Stay in Intensive Care Unit – Intensive Care Unit

Haloperidol Versus Placebo

The findings presented in the “Length of Stay in Intensive Care Unit - Overall” results section are wholly represented by this subgroup. Please refer to the “Length of Stay in Intensive Care Unit - Overall” results section.

Second-Generation Antipsychotics Versus Placebo

The findings presented in the “Length of Stay in Intensive Care Unit - Overall” results section are wholly represented by this subgroup. Please refer to the “Length of Stay in Intensive Care Unit - Overall” results section.

Haloperidol Versus Second-Generation Antipsychotics

The findings presented in the “Length of Stay in Intensive Care Unit - Overall” results section are wholly represented by this subgroup. Please refer to the “Length of Stay in Intensive Care Unit - Overall” results section.

Other Comparisons

We found no delirium treatment trials evaluating length of stay in the intensive care unit for critically ill patients with delirium for the following comparisons:

- Second-generation antipsychotics versus second-generation antipsychotics
- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies

Other Resource Utilization Outcomes – Intensive Care Unit

We found no trials enrolling critically ill patients with delirium that compared an antipsychotic with a placebo, another antipsychotic, or another treatment and evaluated the following resource utilization outcomes:

- Readmission to hospital
- Length of stay in skilled nursing facility
- Patient safety attendant use
- Hospice enrollment

Adverse Effects

Sedation – Intensive Care Unit

Haloperidol Versus Placebo

The findings presented in the “Sedation - Overall” results section are wholly represented by this subgroup. Please refer to the “Sedation - Overall” results section. (SOE for patients in the intensive care unit: Moderate)

Second-Generation Antipsychotics Versus Placebo

Two RCTs, with low risk of bias, compared second-generation antipsychotics with placebo in inpatients with critical illness.^{52, 53} The smaller trial (N=36) reported a potentially clinically important but not statistically significant effect on sedation-related effects for quetiapine compared with placebo. However, the larger trial (N=566) reported no clinically important or statistically significant difference for ziprasidone compared with placebo. Overall, there was no clinically important or statistically significant effect of haloperidol compared with placebo on sedation. (SOE for patients in the intensive care unit: Moderate)

Haloperidol Versus Second-Generation Antipsychotics

One three-arm RCT, with low risk of bias, compared ziprasidone with haloperidol in critically ill patients and reported on the instances of temporarily holding the study drug owing to oversedation. This RCT reported no clinically important or statistically significant difference in the ziprasidone group compared with the haloperidol group.⁵³ (SOE for patients in the intensive care unit: Moderate)

Second-Generation Antipsychotics Versus Second-Generation Antipsychotics

One observational study that compared quetiapine with lurasidone in critically ill patients reported on the instances of discontinuation of the study drug owing to increased sedation. This observational study, with moderate risk of bias, reported no statistically significant difference for the quetiapine group (20%) compared with the lurasidone group (10%).⁶⁹ This study also reported no statistically significant difference in the percentage of time patients were oversedated, defined as a Richmond Agitation-Sedation Scale lower than or equal to -3, in the quetiapine group compared with the lurasidone group. We were unable to draw conclusions regarding sedation when comparing second-generation antipsychotics in patients in the intensive care unit. (SOE for patients in the intensive care unit: Insufficient)

Other Comparisons

We found no studies of delirium treatment evaluating sedation in critically ill patients with delirium for the following comparisons:

- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies

Strength of Evidence

Table 23 summarizes the strength of evidence findings for antipsychotics in terms of sedation in critically ill patients.

Table 23. Strength of evidence domains for studies evaluating antipsychotics for the treatment of delirium in terms of sedation in patients in the intensive care unit

Comparison	Number Of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength Of Evidence	Summary
Haloperidol vs. placebo	2 ^{45, 53} (707)	Low	Direct	Consistent	Imprecise	Undetected	Moderate	In critically ill patients, there was no clinically important or statistically significant difference in sedation.
Second-generation antipsychotics vs. placebo	2 ^{52, 53} (602)	Low	Direct	Consistent	Precise	Undetected	Moderate	There was no clinically important or statistically significant difference.
Haloperidol vs. second-generation antipsychotics	1 ⁵³ (566)	Low	Direct	Consistency unknown (single study)	Precise	Undetected	Moderate	There was no clinically important or statistically significant difference.
Second-generation antipsychotics vs. second-generation antipsychotics	1 observational study with comparison group ⁶⁹ (40)	Medium	Direct	Consistency unknown (single study)	Imprecise	Undetected	Insufficient	We were unable to draw a conclusion.
Haloperidol vs. other therapies	No studies							
Second-generation antipsychotics vs. other therapies	No studies							

Abbreviations: CI = confidence interval; RR = relative risk

Cardiac Effects – Intensive Care Unit

Haloperidol Versus Placebo

The findings presented in the “Cardiac Effects - Overall” results section are wholly represented by this subgroup. Please refer to the “Cardiac Effects - Overall” results section.

Second-Generation Antipsychotics Versus Placebo

The findings presented in the “Cardiac Effects - Overall” results section are wholly represented by this subgroup. Please refer to the “Cardiac Effects - Overall” results section.

Haloperidol Versus Second-Generation Antipsychotics

Two RCTs, with low risk of bias, and one observational study, with a comparison group and potential for serious risk of bias, evaluated different cardiac events in patients receiving haloperidol compared with second-generation antipsychotics.^{44, 53, 79} All three studies enrolled critically ill patients. Across all three studies and types of cardiac events, there were no statistically significant differences in haloperidol compared with second-generation antipsychotics. The evidence was consistent but imprecise.

One three-arm RCT, enrolling patients receiving mechanical ventilation with and without delirium, reported no statistically significant difference in the incidence of prolongation of the corrected QT interval to more than 500 milliseconds for ziprasidone (17%) compared with haloperidol (6%).⁴⁴ This RCT also reported no incidence of ventricular arrhythmia in either randomization group.

Another three-arm RCT, enrolling critically ill patients, reported no statistically significant difference in the incidence of temporary discontinuation of the study drug owing to prolongation of the corrected QT interval for ziprasidone (11%) compared with haloperidol (7%).⁵³ This RCT also reported no incidence of permanent discontinuation of the study drug owing to suspected torsades de pointes in either randomization group.

One observational study, with comparison groups and potential for serious risk of bias, enrolled a total of 925 patients with and without delirium in the coronary care unit. This observational study compared haloperidol with quetiapine on prolongation of the corrected QT interval at multiple time points. This study reported no clinically important or statistically significant difference for haloperidol compared with quetiapine in patients with delirium.⁷⁹

Second-Generation Antipsychotics Versus Second-Generation Antipsychotics

One observational study, with moderate risk of bias, enrolled medical and cardiac critically ill patients.⁶⁹ This study reported no statistically significant difference in a corrected QT interval increase of more than 60 milliseconds from baseline for quetiapine (10%) compared with lurasidone (10%). This observational study also reported no statistically significant difference in discontinuation of study medication owing to prolonged QT interval for quetiapine (5%) compared with lurasidone (0%).

Other Comparisons

We found no studies of delirium treatment evaluating cardiac effects in critically ill patients with delirium for the following comparisons:

- Haloperidol versus other therapies

- Second-generation antipsychotics versus other therapies

Neurologic Effects – Intensive Care Unit

Haloperidol Versus Placebo

Three RCTs, with low risk of bias, compared haloperidol with placebo for a number of different neurologic effects in critically ill patients.^{44, 45, 53} Overall, across a variety of neurologic effects, including extrapyramidal symptoms and neuroleptic malignant syndrome, no RCT demonstrated a statistically significant difference for haloperidol compared with placebo. The evidence was consistent but imprecise.

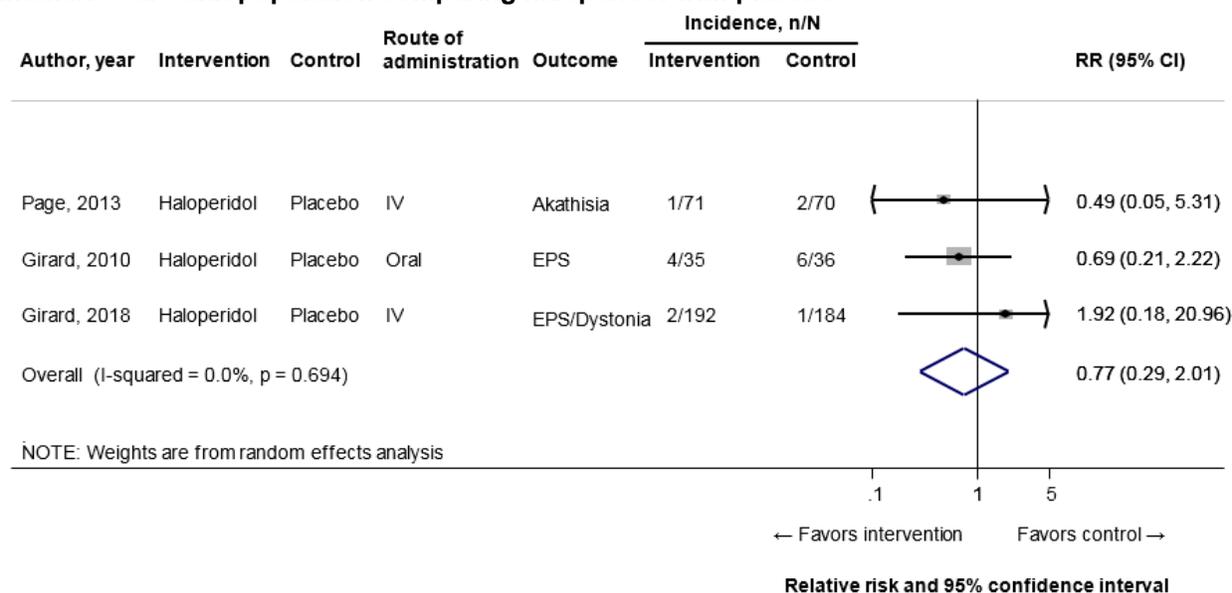
For the neurologic effect of extrapyramidal symptoms, we conducted a meta-analysis of the three RCTs^{44, 45, 53} which demonstrated no between-group difference in extrapyramidal symptoms comparing haloperidol with placebo (pooled RR, 0.77; 95% CI, 0.29 to 2.02; I-squared, 0%) (Figure 30). We tested the effect of each individual trial on the combined point estimate. No single trial influenced the pooled results. No substantial statistical heterogeneity was identified. One of the three RCTs, a three-arm trial enrolling critically ill patients, also reported no instances of temporarily holding the study drug owing to extrapyramidal symptoms.⁵³

For the specific neurologic effect of akathisia, one three-arm RCT, enrolling patients receiving mechanical ventilation, reported a non-statistically significant increase in the incidence of akathisia for haloperidol (29%) compared with placebo (19%).⁴⁴

For the specific neurologic effects of muscle stiffness, torticollis, and dystonia, two RCTs reported data. One RCT evaluated patients receiving mechanical ventilation enrolled within 72 hours of intensive care unit admission. This trial reported no statistically significant effect on muscle stiffness for haloperidol (1%) compared with placebo (1.4%) and no statistically significant effect on torticollis for haloperidol (0%) compared with placebo (1.4%).⁴⁵ Another RCT, a three-arm trial enrolling critically ill patients, reported no instances of temporarily holding the study drug owing to dystonia.⁵³

For the neurologic effect of neuroleptic malignant syndrome, two three-arm RCTs reported data. One RCT, enrolling patients receiving mechanical ventilation, reported no incidence of neuroleptic malignant syndrome in the haloperidol or placebo groups.⁴⁴ Another RCT, a three-arm trial enrolling critically ill patients, reported no incidence of permanent discontinuation of the study drug owing to suspected neuroleptic malignant syndrome.⁵³

Figure 30. Meta-analysis of neurological extrapyramidal symptoms outcomes in trials with an intensive care unit population comparing haloperidol with placebo



CI = confidence interval; EPS = extrapyramidal symptoms; IV = intravenous; N = total arm population; n = incidence within arm; p = p-value; RR = relative risk

Second-Generation Antipsychotics Versus Placebo

Three RCTs, with low risk of bias, compared two second-generation antipsychotics (ziprasidone and quetiapine) with placebo for a number of different neurologic effects in critically ill patients.^{44, 52, 53} Overall, across a variety of neurologic effects, including extrapyramidal symptoms and neuroleptic malignant syndrome, no RCT demonstrated a statistically significant difference in second-generation antipsychotics compared with placebo.^{44, 52, 53}

Haloperidol Versus Second-Generation Antipsychotics

Two RCTs^{44, 53}, with low risk of bias, and one observational study with a comparison group⁸⁵ compared second-generation antipsychotics (ziprasidone and olanzapine) with haloperidol for a number of different neurologic effects in critically ill patients. Overall, across a variety of neurologic effects, including extrapyramidal symptoms and neuroleptic malignant syndrome, neither of the two trials^{44, 53} nor the observational study⁸⁵ demonstrated a statistically significant difference in second-generation antipsychotics compared with haloperidol. The evidence was consistent but imprecise.

Other Comparisons

We found no studies of delirium treatment evaluating neurologic effects in critically ill patients with delirium for the following comparisons:

- Second-generation antipsychotics versus second-generation antipsychotics
- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies

Other Adverse Effects – Intensive Care Unit

We found no studies enrolling critically ill patients with delirium that compared an antipsychotic with a placebo, another antipsychotic, or another treatment and evaluated the following adverse events:

- Weight gain
- Changes in appetite
- Hypersensitivity reactions
- Inappropriate continuation of antipsychotics
- Swallowing difficulties
- Aspiration pneumonia

Key Question 2d. Benefits and Harms of Antipsychotics To Treat Delirium in Patients in a Post-Acute Care Facility

We found no studies evaluating antipsychotics for the treatment of delirium in patients in a post-acute care facility.

Key Question 2e. Benefits and Harms of Antipsychotics To Treat Delirium in Patients in Palliative or Hospice Care

Key Points – Palliative or Hospice Care

Delirium Severity

- In patients in palliative or hospice care, there was less improvement with haloperidol than placebo in delirium severity by day three using two severity measures (mean between-group difference for the delirium symptom score, 0.2; 95% CI, 0.1 to 0.4, and for the Memorial Delirium Assessment Scale, 0.8; 95% CI, -0.03 to 1.5), but the magnitude of this difference may not be clinically important. (SOE: Low)
- In patients in palliative or hospice care, there was less improvement with risperidone than placebo in delirium severity by day three using two severity measures (mean between-group difference for the delirium symptom score, 0.5; 95% CI, 0.1 to 0.9, and for the Memorial Delirium Assessment Scale, 1.0; 95% CI, 0.2 to 1.8), but the magnitude of this difference may not be clinically important. (SOE: Low)
- We were unable to draw a conclusion regarding the effects of antipsychotics on delirium severity in patients in palliative or hospice care for the following comparisons:
 - Haloperidol versus second-generation antipsychotics (insufficient evidence)
 - Second-generation antipsychotics versus second-generation antipsychotics (no studies)
 - Haloperidol versus other therapies (no studies)
 - Second-generation antipsychotics versus other therapies (no studies)

Caregiver Burden/Strain and Sedation

- We found no studies evaluating caregiver burden/strain or sedation in patients in palliative or hospice care with delirium that compared an antipsychotic with a placebo, another antipsychotic, or another treatment.

Intermediate Outcomes

Delirium Severity – Palliative or Hospice Care

Haloperidol Versus Placebo

One three-arm RCT, with low risk of bias, enrolled patients receiving palliative care.⁴⁸ This RCT reported less improvement in delirium severity by day three for haloperidol compared with placebo when evaluated using a delirium symptom score. However, this difference is of uncertain clinical importance. When severity was evaluated using the Memorial Delirium Assessment Scale, this RCT reported no statistically significant difference in improvement in delirium severity by day three. We concluded that haloperidol compared to placebo has no clinically important effect on delirium severity in palliative care patients. (SOE in patients in palliative or hospice care: Low)

Second-Generation Antipsychotics Versus Placebo

One three-arm RCT, with low risk of bias, enrolled patients receiving palliative care.⁴⁸ This RCT reported less improvement in delirium severity by day three for risperidone compared with placebo when evaluated using both a delirium symptom score and the Memorial Delirium Assessment Scale.⁴⁸ (SOE in patients in palliative or hospice care: Low)

Haloperidol Versus Second-Generation Antipsychotics

One RCT, with high risk of bias primarily owing to a lack of blinding and missing outcome data, compared olanzapine with haloperidol in patients receiving palliative care.⁶¹ This RCT reported a lower delirium severity score at day seven, as evaluated using the Delirium Rating Scale, for olanzapine compared with haloperidol but the between-group difference in reduction of delirium severity from baseline during the 7 day followup was not statistically significant.. This RCT also reported no difference in delirium severity score at day seven or in reduction of delirium severity from baseline during the 7 day followup, as evaluated using the Clinical Global Impression scale for olanzapine compared with haloperidol.⁶¹ We were unable to draw conclusions from this single study. (SOE in patients in palliative or hospice care: Insufficient)

Other Comparisons

We found no delirium treatment trials evaluating delirium severity in patients in palliative or hospice care with delirium for the following comparisons:

- Second-generation antipsychotics versus second-generation antipsychotics
- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies

Strength of Evidence

Table 24 summarizes the strength of evidence findings for antipsychotics in terms of delirium severity in patients in palliative or hospice care.

Table 24. Strength of evidence domains for trials evaluating antipsychotics for the treatment of delirium in terms of delirium severity in patients in palliative or hospice care

Comparison	Number Of Trials (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength Of Evidence	Summary
Haloperidol vs. placebo	1 ⁴⁸ (249)	Low	Direct	Consistency unknown (single study)	Imprecise	Undetected	Low*	Haloperidol had less improvement in delirium severity by day 3 using two severity measures (mean between group difference for delirium symptom score: 0.2; 95% CI, 0.1 to 0.4, and for Memorial Delirium Assessment Scale: 0.8; 95% CI, -0.03 to 1.5), but the magnitude of this difference may not be clinically important.
Second-generation antipsychotics vs. placebo	1 ⁴⁸ (249)	Low	Direct	Consistency unknown (single study)	Imprecise	Undetected	Low*	Risperidone had less improvement in delirium severity by day 3 using two severity measures (mean between group difference for delirium symptom score: 0.5; 95% CI, 0.1 to 0.9, and for Memorial Delirium Assessment Scale: 1.0; 95% CI, 0.2 to 1.8), but the magnitude of this difference may not be clinically important.
Haloperidol vs. second-generation antipsychotics	1 ⁶¹ (30)	High	Direct	Consistency unknown (single study)	Imprecise	Undetected	Insufficient	We were unable to draw a conclusion.
Second-generation antipsychotics vs. second-generation antipsychotics	No trials							
Haloperidol vs. other therapies	No trials							
Second-generation antipsychotics vs. other therapies	No trials							

* Rating based on a single multi-site study in Australia with imprecise results; additional trials are needed to determine if results are stable and generalizable.

CI = confidence interval

Use of Rescue Therapy – Palliative or Hospice Care

Haloperidol and Second-Generation Antipsychotics Versus Placebo

The findings presented in the “Use of Rescue Therapy - Overall” results section are wholly represented by this subgroup. Please refer to the “Use of Rescue Therapy - Overall” results section.

Haloperidol Versus Second-Generation Antipsychotics

One RCT, with high risk of bias primarily owing to a lack of blinding and missing outcome data, compared olanzapine with haloperidol in patients receiving palliative care.⁶¹ This RCT reported no statistically significant difference in the use of rescue therapy, defined as the use of as needed midazolam.

Other Comparisons

We found no delirium treatment trials evaluating the use of rescue therapy in patients in palliative or hospice care with delirium for the following comparisons:

- Haloperidol versus placebo
- Second-generation antipsychotics versus placebo
- Second-generation antipsychotics versus second-generation antipsychotics
- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies

Other Intermediate Outcomes – Palliative or Hospice Care

We found no trials in patients in palliative or hospice care with delirium that compared an antipsychotic with a placebo, another antipsychotic, or another treatment and evaluated the following intermediate outcomes:

- Delirium incidence
- Short-term delirium symptoms
- Delirium- and coma-free days alive
- Duration of delirium
- Patient distress
- Use of physical restraint

Final Health or Patient-Centered Outcomes

Mortality – Palliative or Hospice Care

Haloperidol Versus Placebo

One three-arm RCT, with low risk of bias and enrolling patients receiving palliative care, compared haloperidol with placebo.⁴⁸ In an analysis of mortality associated with the 72-hour treatment duration, this RCT reported no statistically significant effect when comparing haloperidol with placebo. However, the RCT also performed a time-to-event analysis showing decreased survival for the haloperidol group compared with the placebo group. It is unclear how

much of the longer-term mortality risk is attributable to haloperidol use during the relatively brief 72-hour study period.

Second-Generation Antipsychotics Versus Placebo

One three-arm RCT, with low risk of bias and enrolling patients receiving palliative care, compared risperidone with placebo.⁴⁸ In an analysis of mortality associated with the 72-hour treatment duration, the RCT reported no statistically significant effect when comparing risperidone with placebo. The RCT performed a time-to-event analysis that demonstrated a non-statistically significant decrease in survival for the risperidone group compared with the placebo group.

Haloperidol Versus Second-Generation Antipsychotics

One three-arm RCT, with low risk of bias and enrolling patients receiving palliative care, compared haloperidol with second-generation antipsychotics.⁴⁸ In an analysis of mortality associated with the 72-hour treatment duration, the RCT reported no statistically significant effect when comparing risperidone with haloperidol.

Other Comparisons

We found no delirium treatment trials evaluating mortality in patients in palliative or hospice care with delirium for the following comparisons:

- Second-generation antipsychotics versus second-generation antipsychotics
- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies

Other Final Health or Patient-Centered Outcomes – Palliative or Hospice Care

We found no trials enrolling patients in palliative or hospice care with delirium that compared an antipsychotic with a placebo, another antipsychotic, or another treatment and evaluated the following final health or patient-centered outcomes:

- Quality of life
- Cognitive functioning
- Institutionalization
- Caregiver burden/strain
- Falls
- Memory of patient distress

Resource Utilization Outcomes – Palliative or Hospice Care

We found no trials enrolling patients in palliative or hospice care with delirium that compared an antipsychotic with a placebo, another antipsychotic, or another treatment and evaluated the following resource utilization outcomes:

- Readmission to hospital
- Readmission to intensive care unit
- Length of stay in hospital
- Length of stay in intensive care unit
- Length of stay in skilled nursing facility

- Patient safety attendant use
- Hospice enrollment

Adverse Effects

Neurologic Effects – Palliative or Hospice Care

Haloperidol Versus Placebo

One three-arm RCT, with low risk of bias and enrolling patients receiving palliative care, compared haloperidol with placebo.⁴⁸ This RCT reported a statistically significant difference of more extrapyramidal symptoms, evaluated using the Extra Pyramidal Symptom Rating Scale, for haloperidol compared with placebo.

We did not find any observational studies or non-randomized trials that compared haloperidol with placebo and reported on neurologic effects.

Second-Generation Antipsychotics Versus Placebo

One three-arm RCT, with low risk of bias and enrolling patients receiving palliative care, compared risperidone with placebo.⁴⁸ This RCT reported a statistically significant difference of more extrapyramidal symptoms, evaluated using the Extra Pyramidal Symptom Rating Scale, for risperidone compared with placebo.

We did not find any observational studies or non-randomized trials that compared a second-generation antipsychotic with placebo and reported on neurologic effects.

Haloperidol Versus Second-Generation Antipsychotics

One RCT, with high risk of bias, primarily owing to a lack of blinding and missing outcome data, and enrolling patients receiving palliative care, compared olanzapine with haloperidol.⁶¹ This RCT reported no extrapyramidal symptoms in either group.

We did not find any observational studies or non-randomized trials that compared haloperidol with a second-generation antipsychotic and reported on neurologic effects.

Other Comparisons

We found no studies of delirium treatment evaluating neurologic effects in patients receiving palliative care with delirium for the following comparisons:

- Second-generation antipsychotics versus second-generation antipsychotics
- Haloperidol versus other therapies
- Second-generation antipsychotics versus other therapies

Other Adverse Effects – Palliative or Hospice Care

We found no studies enrolling patients in palliative or hospice care with delirium that compared an antipsychotic with a placebo, another antipsychotic, or another treatment and evaluated the following adverse events:

- Sedation
- Weight gain
- Changes in appetite
- Cardiac effects

- Hypersensitivity reactions
- Inappropriate continuation of antipsychotics
- Swallowing difficulties
- Aspiration pneumonia

Key Question 2f. Benefits and Harms of Antipsychotics To Treat Delirium in Patients in Postoperative Care

Key Points – Postoperative Care

Length of Stay in Hospital

- We were unable to draw a conclusion regarding the effects of antipsychotics on length of stay in hospital for patients in postoperative care for the following comparisons:
 - Haloperidol versus placebo (no trials)
 - Second-generation antipsychotics versus placebo (no trials)
 - Haloperidol versus second-generation antipsychotics (no trials)
 - Second-generation antipsychotics versus second-generation antipsychotics (no trials)
 - Haloperidol versus other therapies (insufficient evidence)
 - Second-generation antipsychotics versus other therapies (no trials)

Delirium Severity, Cognitive Functioning, Inappropriate Continuation of Antipsychotics

- We found no trials evaluating delirium severity, cognitive functioning, or inappropriate continuation of antipsychotics in postoperative patients with delirium that compared an antipsychotic with a placebo, another antipsychotic, or another treatment.

Intermediate Outcomes

Duration of Delirium – Postoperative

Haloperidol Versus Other Therapies

The findings presented in the “Duration of Delirium - Overall” results section are wholly represented by this subgroup. Please refer to the “Duration of Delirium - Overall” results section.

Other Comparisons

We found no delirium treatment trials evaluating delirium duration in postoperative patients with delirium for the following comparisons:

- Haloperidol versus placebo
- Second-generation antipsychotics versus placebo
- Haloperidol versus second-generation antipsychotics
- Second-generation antipsychotics versus second-generation antipsychotics
- Second-generation antipsychotics versus other therapies

Other Intermediate Outcomes – Postoperative

We found no trials enrolling postoperative patients with delirium that compared an antipsychotic with a placebo, another antipsychotic, or another treatment and evaluated the following intermediate outcomes:

- Delirium incidence
- Short-term delirium symptoms
- Delirium severity
- Delirium- and coma-free days alive
- Patient distress
- Use of rescue therapy
- Use of physical restraint

Final Health or Patient-Centered Outcomes

Mortality – Postoperative

Haloperidol Versus Other Therapies

One RCT, with unclear risk of bias and enrolling 53 post-cardiac surgery patients with hyperactive delirium, compared haloperidol with morphine. This trial reported no statistically significant between-group difference (RR, 2.08; 95% CI, 0.20 to 21.55).⁴⁹

Other Comparisons

We found no delirium treatment trials evaluating mortality in postoperative patients with delirium for the following comparisons:

- Haloperidol versus placebo
- Second-generation antipsychotics versus placebo
- Haloperidol versus second-generation antipsychotics
- Second-generation antipsychotics versus second-generation antipsychotics
- Second-generation antipsychotics versus other therapies.

Resource Utilization Outcomes

Readmission to Intensive Care Unit – Postoperative

Haloperidol Versus Other Therapies

The findings presented in the “Readmission to the Intensive Care Unit - Overall” results section are wholly represented by this subgroup. Please refer to the “Readmission to the Intensive Care Unit - Overall” results section.

Other Comparisons

We found no delirium treatment trials evaluating readmission to intensive care unit in postoperative patients with delirium for the following comparisons:

- Haloperidol versus placebo
- Second-generation antipsychotics versus placebo
- Haloperidol versus second-generation antipsychotics

- Second-generation antipsychotics versus second-generation antipsychotics
- Second-generation antipsychotics versus other therapies

Length of Stay in Hospital – Postoperative

Haloperidol Versus Other Therapies

The findings presented in the “Length of Stay in Hospital - Overall” results section are wholly represented by this subgroup. Please refer to the “Length of Stay in Hospital - Overall” results section. (SOE in patients in postoperative care: Insufficient)

Other Comparisons

We found no delirium treatment trials evaluating length of stay in hospital in postoperative patients with delirium for the following comparisons:

- Haloperidol versus placebo
- Second-generation antipsychotics versus placebo
- Haloperidol versus second-generation antipsychotics
- Second-generation antipsychotics versus second-generation antipsychotics
- Second-generation antipsychotics versus other therapies

Strength of Evidence

Table 25 summarizes the strength of evidence findings for length of stay in hospital in patients in postoperative care.

Table 25. Strength of evidence domains for trials evaluating antipsychotics for the treatment of delirium in terms of length of stay in hospital for postoperative patients

Comparison	Number Of Trials (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength Of Evidence	Summary
Haloperidol vs. placebo	No trials							
Second-generation antipsychotics vs. placebo	No trials							
Haloperidol vs. second-generation antipsychotics	No trials							
Second-generation antipsychotics vs. second-generation antipsychotics	No trials							
Haloperidol vs. other therapies	1 ⁴⁹ (53)	High	Indirect	Consistency unknown (single study)	Imprecise	Undetected	Insufficient	We were unable to draw a conclusion.
Second-generation antipsychotics vs. other therapies	No trials							

Length of Stay in Intensive Care Unit – Postoperative

Haloperidol Versus Other Therapies

The findings presented in the “Length of Stay in Intensive Care Unit - Overall” results section are wholly represented by this subgroup. Please refer to the “Length of Stay in Intensive Care Unit - Overall” results section.

Other Comparisons

We found no delirium treatment trials evaluating length of stay in the intensive care unit in postoperative patients with delirium for the following comparisons:

- Haloperidol versus placebo
- Second-generation antipsychotics versus placebo
- Haloperidol versus second-generation antipsychotics
- Second-generation antipsychotics versus second-generation antipsychotics
- Second-generation antipsychotics versus other therapies

Other Resource Utilization Outcomes – Postoperative

We found no trials enrolling postoperative patients with delirium that compared an antipsychotic with a placebo, another antipsychotic, or another treatment and evaluated the following resource utilization outcomes:

- Readmission to hospital
- Length of stay in skilled nursing facility
- Patient safety attendant use
- Hospice enrollment

Other Final Health or Patient-Centered Outcomes – Postoperative

We found no trials enrolling postoperative patients with delirium that compared an antipsychotic with a placebo, another antipsychotic, or another treatment and evaluated the following final health or patient-centered outcomes:

- Quality of life
- Cognitive functioning
- Institutionalization
- Caregiver burden/strain
- Falls
- Memory of patient distress

Adverse Effects – Postoperative

We found no studies enrolling postoperative patients with delirium that compared an antipsychotic with a placebo, another antipsychotic, or another treatment and evaluated the following adverse events:

- Sedation
- Weight gain
- Changes in appetite
- Cardiac effects

- Neurologic effects
- Hypersensitivity reactions
- Inappropriate continuation of antipsychotics
- Swallowing difficulties
- Aspiration pneumonia

Discussion

Key Findings and Strength of Evidence

We identified 57 studies evaluating the effectiveness and harms of antipsychotics for the prevention (15 studies) and treatment (44 studies) (2 studies were classified as both prevention and treatment) of delirium. The trials for the prevention of delirium evaluated delirium incidence, length of stay in hospital, sedation, and severity, with most of the studies focused on postoperative and/or intensive care unit-based populations. The treatment trials primarily evaluated length of stay in hospital and sedation effects, with most of the studies focused on inpatients, particularly those with critical illness.

In the prevention of delirium across all populations, trials of haloperidol versus placebo demonstrated no effect on delirium incidence or length of stay in hospital (high strength of evidence); there was insufficient evidence to determine the effect of haloperidol versus placebo on delirium severity or sedation. Our meta-analysis found a statistically significant difference in the relative risk of delirium favoring second-generation antipsychotics versus placebo for the prevention of delirium. However, there was no effect on the length of stay in hospital (low strength of evidence) and insufficient evidence to determine the impact on the severity of delirium for second-generation antipsychotics compared with placebo. We were unable to draw conclusions for any type of drug-to-drug comparisons between second-generation antipsychotics or comparisons with any other types of therapies (i.e., other than antipsychotics) owing to the absence of studies or insufficient evidence.

In the treatment of delirium, trials using haloperidol or second-generation antipsychotics demonstrated no effect on length of stay in hospital (moderate strength of evidence) or sedation (low strength of evidence for haloperidol and moderate strength of evidence for second-generation antipsychotics) compared with placebo. The comparison of haloperidol with second-generation antipsychotics demonstrated no statistically significant differences for cognitive functioning (low strength of evidence), delirium severity, length of stay in hospital, and sedation (all moderate strength of evidence). We were unable to draw conclusions for any type of drug-to-drug comparisons between second-generation antipsychotics or comparisons with any other types of therapies (i.e., other than antipsychotics) owing to the absence of studies or insufficient evidence.

We specifically evaluated cardiac and neurological harms. Most or all of the studies assessing cardiac effects included critically ill patients who may be at a higher risk of cardiac events compared with other patient populations. In all randomized controlled trials (RCTs) and observational studies evaluating haloperidol versus placebo, second-generation antipsychotics versus placebo, haloperidol versus second-generation antipsychotics, and second-generation antipsychotics versus second-generation antipsychotics, there were no statistically significant differences in the occurrence of any of type of cardiac effects reported; however, we cannot exclude a potentially important increase in cardiac events for antipsychotics compared to placebo, particularly for QT interval prolongation for second-generation antipsychotics compared to haloperidol or placebo.

Studies that reported neurological harms included critically ill patients who may be at a higher risk of neurological events compared with other patient populations. Monitoring for neuroleptic malignant syndrome and various manifestations of extrapyramidal symptoms were the most commonly reported neurological effects. Symptom reporting within the extrapyramidal designation was heterogeneous and likely represented a wide variety of measurement methods.

Furthermore, studies included a variety of doses, frequencies and routes of antipsychotics, potentially obscuring the true frequencies of adverse neurologic side effects at the higher antipsychotic exposures. A single RCT evaluating patients receiving palliative care demonstrated a statistically significant increase in extrapyramidal symptoms for both haloperidol compared with placebo and for second-generation antipsychotics compared with placebo. Otherwise, across the larger body of evidence in all other patient populations, no study reported a statistically significant increase in any neurological effect for haloperidol compared with placebo, or second-generation antipsychotics compared with placebo, haloperidol compared with second-generation antipsychotics and second-generation antipsychotics compared with second-generation antipsychotics.

Findings in Relationship to What Is Already Known

Several systematic reviews have examined the risks and benefits of antipsychotic treatments for delirium but none of these existing reviews had the same scope as ours. For instance, we considered prevention and treatment studies separately and examined the evidence for specific subpopulations, in addition to looking at the data overall.

Kishi et al., reviewed antipsychotics for the treatment, but not prevention, of delirium in adult patients, with no subgroup analysis in older adults.¹³ A major conclusion of this review was that antipsychotics are superior to placebo/usual care. That finding contradicts our findings and those of other more recent systematic reviews and guidelines that have concluded that there is no evidence that antipsychotics improve the outcomes among hospitalized adults with delirium.^{12, 90} Although we included all of the published studies reviewed by Kishi et al., recently completed trials were also added to our synthesis and contributed to our conclusions.

Neufeld et al., conducted a systematic review of antipsychotics as part of an American Geriatrics Society clinical practice guideline.¹² This systematic review focused on antipsychotics for delirium prevention or treatment in adult surgical and medical inpatients, including the critically ill. The review combined populations and did not examine the results for subpopulations.¹² The review concluded “current evidence does not support the use of antipsychotics for prevention or treatment of delirium.” The search for this systematic review ended in 2013; consequently, it excluded important, newer studies included in this report.

The Society for Critical Care Medicine recently published clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the intensive care unit.⁹¹ Notably, this guideline focused on critically ill patients only. Also a systematic review was not conducted to support the guideline, in that there was no duplicate, independent process for the screening and data abstraction. This guideline suggested not using haloperidol or a second-generation antipsychotic to prevent or treat delirium in critically ill adults (conditional recommendation, very low to low quality of evidence).

A recently published Cochrane systematic review included RCTs evaluating pharmacological or non-pharmacological interventions for preventing delirium in critically ill patients.⁹² In terms of antipsychotics, this review reported on only two RCTs comparing haloperidol with placebo, with no reporting on any trials of second-generation antipsychotics.^{42, 45} Both of these RCTs are included in our review. With respect to the comparison of haloperidol with placebo, the conclusions from this Cochrane review (“There is probably little or no difference between haloperidol and placebo for preventing ICU delirium”) are consistent with the findings in our review.

Another Cochrane review evaluating pharmacologic and non-pharmacologic interventions in non-intensive care unit hospitalized adults concluded, from a pre-planned subgroup analysis of surgical patients, that there was no evidence for the effectiveness of first-generation antipsychotics, such as haloperidol.⁹⁰ However, delirium incidence was reported to be lower for postoperative patients treated with a second-generation antipsychotic (olanzapine) compared with placebo and adjudicated to be derived from moderate-quality evidence. Our review came to the same conclusion; however we also concluded that there were no between-group differences for second-generation antipsychotics versus placebo in length of stay in hospital (low strength of evidence) and insufficient evidence to understand the impact on severity of delirium symptoms for both the postoperative subgroup and across all populations.

Applicability

The greatest challenge to the applicability of this body of evidence is related to the populations and outcomes studied. In terms of study population, existing trials were often conducted in medical and surgical critically ill patients. Hence, the overall results of this report may not be directly applicable to other populations, including postoperative patients, older inpatients, and patients with dementia.

Critically ill patients may have differing pathophysiological etiologies of delirium compared with other populations, as well as more severe physiological and metabolic derangements. They also routinely receive relatively high doses of deliriogenic medications, such as sedatives (e.g., benzodiazepines and propofol). For similar reasons, critically ill patients may be more susceptible to the potentially harmful effects of antipsychotics. Hence, any benefit and risk of antipsychotics for prevention or treatment of delirium within the context of critical illness may not be generalizable to other populations.

Implications for Clinical and Policy Decisionmaking

There is no Food and Drug Administration-approved medication for the prevention or treatment of delirium. Our findings do not support the use of antipsychotics for the routine treatment of delirium. While the use of second-generation antipsychotic medications may be associated with decreased incidence of postoperative delirium, this review did not identify improved outcomes associated with the use of these agents.

Notably, across a range of cardiac and neurological effects evaluated, there was little evidence of increased serious harms related to antipsychotics compared with placebo or with other antipsychotics (i.e., drug-to-drug comparisons), even in critically ill patients who may be at greater risk of harmful side effects. However, across different types of cardiac events, the absolute number tended to be greater for antipsychotics compared to placebo, which may be clinically relevant. Moreover, inappropriate continuation of antipsychotics and associated long-term harms from inadvertent prolonged use were not evaluated in any studies that met our inclusion criteria. Given that observational studies of routine clinical practice demonstrate frequent inappropriate continuation of antipsychotics, this is an important issue.⁹³⁻⁹⁵

Given the lack of effectiveness of antipsychotics for the treatment of delirium, particularly in critically ill adults, and the lack of improved outcomes associated with the use of second-generation antipsychotics in preventing postoperative delirium, the use of other non-pharmacological therapies with low cost, burden, and harms warrants consideration for clinical practice as recommended by existing clinical practice guidelines.^{91, 96}

Limitations of the Systematic Review Process

The systematic review process, despite its rigor, had some limitations: our review may have missed studies that are currently in progress as well as studies not in the peer-reviewed literature. Owing to heterogeneity in the populations, interventions, and outcome measures, we were unable to conduct a network meta-analysis. Such an analysis could potentially provide important drug-to-drug comparison information that the current trials do not provide.

Limitations of the Evidence Base

There was insufficient or no evidence for many comparisons and outcomes owing to the paucity of studies. The body of evidence with the most studies and the highest strength of evidence (i.e., moderate) was generally from studies of critically ill adults. There was insufficient evidence comparing haloperidol with second-generation antipsychotics and for drug-to-drug comparisons within the class of second-generation antipsychotics. Inadequate reporting meant that the risk of bias assessment of RCTs was frequently unclear, especially regarding sequence generation and allocation concealment.

Moreover, there was frequent unclear risk of bias related to missing outcome data and selective outcome reporting. There was inconsistency in the use of measurement instruments and approaches to statistical analysis and reporting, even in evaluating the same outcome domain, such as delirium severity.

Many studies were underpowered, with short duration. Many studies were of insufficient duration to adequately assess longer-term clinical outcomes, particularly related to cognitive impairment—a well-known sequela of delirium.

Finally, study designs were fairly heterogeneous, using different dosing routes, and a range of doses and frequencies of different antipsychotics. Combining heterogeneous treatment and prevention approaches may bias the findings toward the null hypothesis. So, too, combining a range of dosing exposures may obscure adverse outcomes associated with higher doses of medications.

Research Recommendations

Studies evaluating pharmacologic prevention and treatment strategies should evaluate patient groups that are anticipated to have similar delirium risk factor(s) and associated pathophysiology, including anticholinergic agents and other medications taken before delirium occurs, given that these factors may affect response to therapy. With the exception of critically ill patients, there were either no RCTs or insufficient evidence from existing studies that evaluated the effect of antipsychotics on treatment outcomes in all patient subpopulations. Research that is focused on more homogeneous patient groups within each subpopulation is needed. This also applies to postoperative patient populations, where larger, well-controlled trials of second-generation antipsychotics in the prevention of delirium are needed to clarify whether there is any beneficial role for the perioperative setting.

The outcomes of currently published RCTs on the use of antipsychotics on the treatment and prevention of delirium focus predominantly on the length of stay in hospital and sedation. Other critical outcomes, including delirium severity, were reported in a minority of the studies and, often, the measures used were heterogeneous, making it difficult to synthesize results and conduct meta-analyses. For example, median lengths of stay data were reported in many studies. Since such data are often skewed, length of stay measures could not be pooled. Important

outcomes such as impact on cognitive functioning, caregiver burden, and inappropriate continuation of medications were absent in the current literature.

Heterogeneity of outcome domains and measurement instruments emphasize the need for greater standardization. Such standardization would assist with comparison, synthesis, and meta-analysis of studies and would reduce omission of critical outcomes in future trials (which would also reduce research waste). In particular, careful identification of the outcomes of greatest importance to clinicians, patients/caregivers, and researchers would advance future research. The field would benefit from the development of standardized, clinically meaningful measures of the following outcomes: patient agitation and distress, subsequent memories of delirium, caregiver burden and distress, inappropriate continuation of antipsychotics, and long-term cognitive and functional outcomes. Research currently underway to define core outcomes for delirium, core measurement instruments, and crosswalks to directly compare different delirium severity measures are important advances for the field.⁹⁷ The National Institute on Aging-funded delirium research network, known as the Network for Investigation of Delirium: Unifying Scientists (NIDUS; <https://deliriumnetwork.org/>), aims to help facilitate some of these research recommendations.⁹⁸

Delirium assessment methods for use in both prevention and treatment trials require ongoing refinement and scrutiny. A recent multinational interdisciplinary perspective calls for the development and validation of objective tools to screen for delirium and diagnose the condition in critically ill patients by including the electroencephalogram, or computer-based applications. The delirium field would benefit from better phenotyping of delirium subtypes, through adoption and development of more detailed standardized measurement tools. The NIDUS group is currently developing web-based resources for delirium measurement instruments and is building infrastructure related to delirium measurement methods.

[\(https://deliriumnetwork.org/measurement/\)](https://deliriumnetwork.org/measurement/)

Given the lack of evidence to support antipsychotics for treatment of delirium, and weak evidence for limited benefits of the prevention of postoperative delirium, both pharmacological and non-pharmacological therapies should continue to be evaluated in RCTs with well-powered designs that include the study of more homogenous populations of patients. A striking finding resulting from this review was the lack of investigation of many important patient and care-giver centered outcomes in the study of delirium prevention and treatment. Much more research is needed to study questions such as the comparison between the pharmacologic and non-pharmacologic approaches, quality of life outcomes and best treatment approaches in populations of patients such as those with pre-existing dementia. Studies answering these questions will have important implications for policy and treatment recommendations for patients within our healthcare system.

Conclusions

Haloperidol or second-generation antipsychotics, compared to placebo, used for the prevention or treatment of delirium did not improve clinically important outcomes. In a subgroup of postoperative patients, second-generation antipsychotics may decrease delirium incidence but this evidence is limited and requires more study. We did not detect neurological harms associated with haloperidol or second-generation antipsychotics used for the prevention or treatment of delirium, but cardiac effects tended to occur more frequently in antipsychotics compared with placebo.

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Abbreviations and Acronyms

AGS	American Geriatric Society
AHRQ	Agency for Healthcare Research and Quality
AIDS	acquired immunodeficiency syndrome
APACHE II	Acute Physiology and Chronic Health Evaluation 2
ASA	American Society of Anesthesiologists
bid	twice daily
BMT	bone marrow transplant
BPRS	Brief Psychiatric Rating Scale
BUN	blood urea nitrogen ratio
CAM-ICU	Confusion Assessment Method for the ICU
CAM-S	Confusion Assessment Method-Severity
CCU	coronary care unit
CENTRAL	Cochrane Central Register of Controlled Trials
CGI	Clinical Global Impressions Scale
CGI-GI	Clinical Global Impressions Scale-Global Impression
CI	confidence interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
d	days
DRS	Delirium Rating Scale
DRS-R-98	Delirium Rating Scale Revised-98
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th ed.
EPC	Evidence-based Practice Center
EPS	extrapyramidal symptoms
ESRS	Extrapyramidal Symptom Rating Scale
g	gram
HR	Hazard ratio
ICDSC	Intensive Care Delirium Screening Checklist
ICU	intensive care unit
IQR	interquartile range
IV	intravenous
JHU	Johns Hopkins University
MDAS	Memorial Delirium Assessment Scale
MeSH	medical subject headings
mg	milligram
mg/day	milligram per day
mg/hr	milligram per hour

min	minutes
ml	millimeter
ml/hr	millimeter per hour
MMSE	Mini-Mental State Examination
MV	mechanical ventilation
N	sample size
NaCl	sodium chloride
NCGG	National Center for Geriatrics and Gerontology
NEECHAM	Neelon and Champagne Confusion Scale
NG	nadogastric tube
NuDESC	Nursing Delirium Screening Scale
OR	odds ratio
p	p-value
qd	once daily
qid	four times a day
QT	Q and T wave interval
QTc	corrected QT interval
RASS	Richmond Agitation and Sedation Scale
RCT	randomized controlled trial
ROBINS-I	Risk of Bias in Non-Randomized Studies of Interventions
RR	risk ratio
SAS	Sedation Agitated Scale
SCID	severe combined immunodeficiency
SD	standard deviation
SE	standard error
SEADS	Supplemental Evidence and Data for Systematic Reviews
SNF	skilled nursing facility
T3	time point three
TEP	Technical Expert Panel
tid	three times daily
ug/kg	microgram per kilogram
UKU	Udvalg for Kliniske Undersøgelser Scale
US	United States

Appendix A. Detailed Search Strategy

PubMed Search String, run on June 4, 2018

#	String	Hits
1	Confusion[mh] OR delirium*[tiab] OR delerium*[tiab] OR deliria*[tiab] OR delirious[tiab] OR delerious[tiab] OR confusion*[tiab] OR "agitated emergence"[tiab] OR "altered consciousness"[tiab] OR "dis orientation"[tiab] OR "dis oriented"[tiab] OR "dis orientations"[tiab] OR "emergence agitation"[tiab] OR "emergence excitement"[tiab] OR "postanaesthetic excitement"[tiab] OR "postanesthetic excitement"[tiab] OR disorient*[tiab] OR hallucinat*[tiab] OR illusion*[tiab] OR illusor*[tiab]	72,336
2	Antipsychotic agents[mh] OR antipsychotic*[tiab] OR neuroleptic*[tiab]	72,597
3	Chlorpromazine[mh] OR chlorpromazine*[tiab] OR Droperidol[mh] OR droperidol*[tiab] OR Fluphenazine[mh] OR fluphenazine*[tiab] OR Haloperidol[mh] OR haloperidol*[tiab] OR Loxapine[mh] OR loxapine*[tiab] OR Molindone[mh] OR molindone*[tiab] OR Perphenazine[mh] OR perphenazine*[tiab] OR Pimozide[mh] OR pimozide*[tiab] OR Prochlorperazine[mh] OR prochlorperazine*[tiab] OR Thiothixene[mh] OR thiothixene*[tiab] OR tiotixene*[tiab] OR Thioridazine[mh] OR thioridazine*[tiab] OR Trifluoperazine[mh] OR trifluoperazine*[tiab]	55,379
4	Aripiprazole[mh] OR aripiprazole*[tiab] OR Asenapine[nm] OR asenapine*[tiab] OR Brexpiprazole[nm] OR brexpiprazole*[tiab] OR Cariprazine[nm] OR cariprazine*[tiab] OR Clozapine[mh] OR clozapine*[tiab] OR Iloperidone[nm] OR iloperidone*[tiab] OR Lurasidone hydrochloride[mh] OR lurasidone*[tiab] OR Olanzapine[nm] OR olanzapine*[tiab] OR Paliperidone palmitate[mh] OR paliperidone*[tiab] OR Quetiapine fumarate[mh] OR quetiapine*[tiab] OR Risperidone[mh] OR risperidone*[tiab] OR Ziprasidone[nm] OR ziprasidone*[tiab]	28,785
5	#1 AND (#2 OR #3 OR #4)	3881
6	Animals[mh] NOT humans[mh]	4,460,022
7	#5 NOT #6	3837
8	Addresses[ptyp] OR News[ptyp] OR Patient Education Handout[ptyp] OR Bibliography[ptyp] OR Dictionary[ptyp] OR Directory[ptyp] OR Legal Cases[ptyp] OR Legislation[ptyp] OR Newspaper Article[ptyp] OR Periodical Index[ptyp]	257,594
9	#7 NOT #8	3834

Embase Search String, run on June 6, 2018

#	String	Hits
1	'delirium'/exp OR delirium:ti,ab OR delerium*:ti,ab OR deliria*:ti,ab OR delirious:ti,ab OR delirious:ti,ab OR confusion*:ti,ab OR "agitated emergence":ti,ab OR "altered consciousness":ti,ab OR "dis orientation":ti,ab OR "dis oriented":ti,ab OR "dis orientations":ti,ab OR "emergence agitation":ti,ab OR "emergence excitement":ti,ab OR "postanaesthetic excitement":ti,ab OR "postanesthetic excitement":ti,ab OR disorient*:ti,ab OR hallucinate*:ti,ab OR illusion*:ti,ab OR illusor*:ti,ab	94,891
2	'Neuroleptic agent'/exp OR antipsychotic*:ti,ab OR neuroleptic*:ti,ab	287,109
3	chlorpromazine*:ti,ab OR droperidol*:ti,ab OR fluphenazine*:ti,ab OR haloperidol*:ti,ab OR loxapine*:ti,ab OR molindone*:ti,ab OR perphenazine*:ti,ab OR pimozide*:ti,ab OR prochlorperazine*:ti,ab OR thiothixene*:ti,ab OR tiotixene*:ti,ab OR thioridazine*:ti,ab OR trifluoperazine*:ti,ab	53,228
4	aripiprazole*:ti,ab OR asenapine*:ti,ab OR brexpiprazole*:ti,ab OR cariprazine*:ti,ab OR clozapine*:ti,ab OR iloperidone*:ti,ab OR lurasidone*:ti,ab OR olanzapine*:ti,ab OR paliperidone*:ti,ab OR quetiapine*:ti,ab OR risperidone*:ti,ab OR ziprasidone*:ti,ab	39,504
5	#1 AND (#2 OR #3 OR #4)	8274
6	Animals/exp NOT humans/exp	5,290,387
7	#5 NOT #6	8,219
8	[conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim OR 'case report'/exp	8,222,104
9	#7 not #8	4,853

Cochrane Search String, run on June 8, 2018

#	String	Hits
1	[mh Confusion] OR delirium*:ti,ab,kw OR delerium*:ti,ab,kw OR deliria*:ti,ab,kw OR delirious:ti,ab,kw OR delerious:ti,ab,kw OR confusion*:ti,ab,kw OR "agitated emergence":ti,ab,kw OR "altered consciousness":ti,ab,kw OR "dis orientation":ti,ab,kw OR "dis oriented":ti,ab,kw OR "dis orientations":ti,ab,kw OR "emergence agitation":ti,ab,kw OR "emergence excitement":ti,ab,kw OR "postanaesthetic excitement":ti,ab,kw OR "postanesthetic excitement":ti,ab,kw OR disorient*:ti,ab,kw OR hallucinat*:ti,ab,kw OR illusion*:ti,ab,kw OR illusor*:ti,ab,kw	6055
2	antipsychotic*:ti,ab,kw OR neuroleptic*:ti,ab,kw	9669
3	[mh Chlorpromazine] OR chlorpromazine*:ti,ab,kw OR [mh Droperidol] OR droperidol*:ti,ab,kw OR [mh Fluphenazine] OR fluphenazine*:ti,ab,kw OR [mh Haloperidol] OR haloperidol*:ti,ab,kw OR [mh Loxapine] OR loxapine*:ti,ab,kw OR [mh Molindone] OR molindone*:ti,ab,kw OR [mh Perphenazine] OR perphenazine*:ti,ab,kw OR [mh Pimozide] OR pimozide*:ti,ab,kw OR [mh Prochlorperazine] OR prochlorperazine*:ti,ab,kw OR [mh Thiothixene] OR thiothixene*:ti,ab,kw OR tiotixene*:ti,ab,kw OR [mh Thioridazine] OR thioridazine*:ti,ab,kw OR [mh Trifluoperazine] OR trifluoperazine*:ti,ab,kw	6631
4	[mh Aripiprazole] OR aripiprazole*:ti,ab,kw OR asenapine*:ti,ab,kw OR brexpiprazole*:ti,ab,kw OR cariprazine*:ti,ab,kw OR [mh Clozapine] OR clozapine*:ti,ab,kw OR iloperidone*:ti,ab,kw OR lurasidone*:ti,ab,kw OR olanzapine*:ti,ab,kw OR paliperidone*:ti,ab,kw OR quetiapine*:ti,ab,kw OR [mh Risperidone] OR risperidone*:ti,ab,kw OR ziprasidone*:ti,ab,kw	8273
5	#1 AND (#2 OR #3 OR #4) Limit to Trials	793 710

CINAHL Search String, run on June 8, 2018

#	String	Hits
1	(MM "Delirium") OR (MM "ICU Psychosis") OR TI (delirium* OR delerium* OR deliria* OR delirious OR delerious OR confusion* OR "agitated emergence" OR "altered consciousness" OR "dis orientation" OR "dis oriented" OR "dis orientations" OR "emergence agitation" OR "emergence excitement" OR "postanaesthetic excitement" OR "postanesthetic excitement" OR disorient* OR hallucinat* OR illusion* OR illusor*) OR AB (delirium* OR delerium* OR deliria* OR delirious OR delerious OR confusion* OR "agitated emergence" OR "altered consciousness" OR "dis orientation" OR "dis oriented" OR "dis orientations" OR "emergence agitation" OR "emergence excitement" OR "postanaesthetic excitement" OR "postanesthetic excitement" OR disorient* OR hallucinat* OR illusion* OR illusor*)	12,245
2	(MM "Antipsychotic Agents+") OR TI (antipsychotic* OR neuroleptic*) OR AB (antipsychotic* OR neuroleptic*)	9447
3	TI (chlorpromazine* OR droperidol* OR fluphenazine* OR haloperidol* OR loxapine* OR molindone* OR perphenazine* OR pimozide* OR prochlorperazine* OR thiothixene* OR tiotixene* OR thioridazine* OR trifluoperazine*) OR AB (chlorpromazine* OR droperidol* OR fluphenazine* OR haloperidol* OR loxapine* OR molindone* OR perphenazine* OR pimozide* OR prochlorperazine* OR thiothixene* OR tiotixene* OR thioridazine* OR trifluoperazine*)	1317
4	TI (aripiprazole* OR asenapine* OR brexpiprazole* OR cariprazine* OR clozapine* OR iloperidone* OR lurasidone* OR olanzapine* OR paliperidone* OR quetiapine* OR risperidone* OR ziprasidone*) OR AB (aripiprazole* OR asenapine* OR brexpiprazole* OR cariprazine* OR clozapine* OR iloperidone* OR lurasidone* OR olanzapine* OR paliperidone* OR quetiapine* OR risperidone* OR ziprasidone*)	3399
5	S1 AND (S2 OR S3 OR S4)	475

PsycINFO Search String, run on June 8, 2018

#	String	Hits
1	(MM "Delirium") OR (MM "ICU Psychosis") OR TI (delirium* OR delerium* OR deliria* OR delirious OR delerious OR confusion* OR "agitated emergence" OR "altered consciousness" OR "dis orientation" OR "dis oriented" OR "dis orientations" OR "emergence agitation" OR "emergence excitement" OR "postanaesthetic excitement" OR "postanesthetic excitement" OR disorient* OR hallucinat* OR illusion* OR illuser*) OR AB (delirum* OR delerium* OR deliria* OR delirious OR delerious OR confusion* OR "agitated emergence" OR "altered consciousness" OR "dis orientation" OR "dis oriented" OR "dis orientations" OR "emergence agitation" OR "emergence excitement" OR "postanaesthetic excitement" OR "postanesthetic excitement" OR disorient* OR hallucinat* OR illusion* OR illuser*)	52,283
2	(MM "Antipsychotic Agents+") OR TI (antipsychotic* OR neuroleptic*) OR AB (antipsychotic* OR neuroleptic*)	36,343
3	TI (chlorpromazine* OR droperidol* OR fluphenazine* OR haloperidol* OR loxapine* OR molindone* OR perphenazine* OR pimozide* OR prochlorperazine* OR thiothixene* OR tiotixene* OR thioridazine* OR trifluoperazine*) OR AB (chlorpromazine* OR droperidol* OR fluphenazine* OR haloperidol* OR loxapine* OR molindone* OR perphenazine* OR pimozide* OR prochlorperazine* OR thiothixene* OR tiotixene* OR thioridazine* OR trifluoperazine*)	13,995
4	TI (aripiprazole* OR asenapine* OR brexpiprazole* OR cariprazine* OR clozapine* OR iloperidone* OR lurasidone* OR olanzapine* OR paliperidone* OR quetiapine* OR risperidone* OR ziprasidone*) OR AB (aripiprazole* OR asenapine* OR brexpiprazole* OR cariprazine* OR clozapine* OR iloperidone* OR lurasidone* OR olanzapine* OR paliperidone* OR quetiapine* OR risperidone* OR ziprasidone*)	18770
5	S1 AND (S2 OR S3 OR S4) Limits: Academic journals	2583 2471

Appendix B. Screening and Data Abstraction Forms

Figure B-1. Abstract screening form

Refid: 1, There and Back Again: A Review of Residency and Return Migrations in Sharks, with Implications for Population Structure and Management.
Chapman DD, Feldheim KA, Papastamatiou Y, Hueter RE

[Submit Form](#) and go to or [Skip to Next](#)  

1. Exclude article because:

- No original data (e.g., review article, commentary, or editorial)
- No human data reported (e.g., evaluated outcomes in animals only)
- No subjects ≥ 18 years of age
- No subjects either at risk for delirium or diagnosed with delirium
- Does not evaluate an antipsychotic drug (see list below)
- Is a case report(s) or case series with <5 participants
- Is a meeting abstract
- Does not apply to prevention or treatment of delirium
- Other (specify)

[Clear Response](#)

2. Include or unclear

- Include or unclear

[Clear Response](#)

Figure B-2. Article screening form

Refid: 1, There and Back Again: A Review of Residency and Return Migrations in Sharks, with Implications for Population Structure and Management.
Chapman DD, Feldheim KA, Papastamatiou Y, Hueter RE

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1. Does this article apply:

No (answer reasons for exclusion)

Exclude article from review

- No original data (e.g., review article, commentary, or editorial)
- No human data reported (e.g., evaluated outcomes in animals only)
- Less than 50% of participants are ≥ 18 years of age
- No subjects either at risk for delirium or diagnosed with delirium
- Does not use a validated instrument or the DSM criteria to measure delirium (see below)
- Does not evaluate an antipsychotic drug (see below) or the effects of the antipsychotic drug cannot be isolated
- Is an RCT and does not evaluate an outcome of interest (see below)
- Is not an RCT and does not report one of our adverse events (see below)
- Is a retrospective cohort
- Is a case report(s) or case series with < 5 participants
- Is a meeting abstract
- Does not apply to prevention or treatment of delirium
- Other please specify

[Clear Response](#)

Yes

Figure B-3. Study design

Refid: 1, There and Back Again: A Review of Residency and Return Migrations in Sharks, with Implications for Population Structure and Management. Chapman DD, Feldheim KA, Papastamatiou Y, Hueter RE

Submit Form

and go to

or Skip to Next



EPC Antipsychotics for the Prevention and Treatment of Delirium Study Design Form

1. Study design

Select an Answer

2. Does the study evaluate the prevention or treatment of delirium?

Select an Answer

3. Does the study apply to one of our subgroups of interest? (Check all that apply)

- Persons aged 65 or older
- Persons with dementia
- Patients in an intensive care unit
- Patients in a post-acute care facility
- Patients in palliative or hospice care
- Patients in post-operative care
- None of the above

4. Specify the patient population (provide a simple summary (e.g., cardiac surgery patients))

5. Country (check all that apply and then fill in specific countries)

United States

North America (not US)

South America

Europe

Asia

Africa

Australia

Not reported

6. Study start year (enter 4-digit number)

Start year

Not reported

[Clear Response](#)

7. Funding (check all that apply)

Industry

Government

Nonprofit

Other

None

Not reported

8. Tool used to diagnose delirium (check all that apply; use the text box to identify the threshold used to diagnose, if specified)

- a. 3-Minute Diagnostic Confusion Assessment Method (3D-CAM)
 - b. 4AT Rapid Clinical Test for Delirium (4AT)
 - c. Brief Confusion Assessment Method (bCAM)
 - d. Confusion Assessment Method (CAM)
 - e. Confusion Assessment Method – Severity Scale (CAM-S)
 - f. Confusion Assessment Method for the Intensive Care Unit (CAM-ICU)
 - g. Communication Capacity Scale and Agitation Distress Scale (CCS & ADS)
 - h. Confusional State Evaluation (CSE)
 - i. Cognitive Test for Delirium (CTD)
 - j. Delirium Index (DI, DIDX)
 - k. Delirium-O-Meter (DOM)
 - l. Delirium Observation Screening Scale (DOSS)
 - m. Delirium Rating Scale – Revised-98 (DRS-R-98)
 - n. Delirium Symptom Interview (DSI)
 - o. Diagnostic and Statistical Manual of Mental Disorders (DSM)
 - p. Family Confusion Assessment Method (FAM-CAM)
 - q. Intensive Care Delirium Screening Checklist (ICDSC)
 - r. Memorial Delirium Assessment Scale (MDAS)
 - s. The Neelon and Champagne Confusion Scale (NEECHAM)
 - t. Nursing Delirium Screening Checklist (Nu-DESC)
 - u. Recognizing Acute Delirium as Part of Your Routine (RADAR)
 - v. Recoverable Cognitive Dysfunction Scale épérage Actif du Delirium Adapté à la Routine] (RCDS)
 - w. Single Question in Delirium (SQiD)
 - x. Other (in addition to one of the tools marked above)
-

Inclusion and exclusion criteria

Age < <input type="radio"/> Inclusion <input type="text"/> <input type="radio"/> Exclusion <input type="text"/> Clear Response
Age > <input type="radio"/> Inclusion <input type="text"/> <input type="radio"/> Exclusion <input type="text"/> Clear Response
Geographic location (e.g. ICU) <input type="radio"/> Inclusion <input type="text"/> <input type="radio"/> Exclusion <input type="text"/> Clear Response
Any psychiatric comorbidity <input type="radio"/> Inclusion <input type="radio"/> Exclusion Clear Response
History of dementia <input type="radio"/> Inclusion <input type="radio"/> Exclusion Clear Response
History of any substance or alcohol use disorder <input type="radio"/> Inclusion <input type="radio"/> Exclusion Clear Response
Recent antipsychotic use <input type="radio"/> Inclusion <input type="radio"/> Exclusion Clear Response
History of sedative use <input type="radio"/> Inclusion <input type="radio"/> Exclusion Clear Response

17. Has the study been registered in a clinical trials registry?

Select an Answer ▼

18. Comments (limit 250 characters)

Figure B-4. Intervention form

1. Identify the group being reported on this form (Mandatory question)

Select an Answer ▼

Complete this table for pharmacologic interventions.

<p>2. Pharmacologic intervention</p> <p>Select an Answer ▼</p>	<p>3. Route of administration</p> <p>Select an Answer ▼</p>	<p>4. Dose</p> <p><input type="checkbox"/> Planned dose (specify dose) <input type="text"/></p> <p><input type="checkbox"/> Titrated dose</p> <p><input type="checkbox"/> Not reported</p> <p>5. If titrated dose, specify:</p> <p><input type="checkbox"/> Mean dose <input type="text"/></p> <p><input type="checkbox"/> Median dose <input type="text"/></p> <p><input type="checkbox"/> Range <input type="text"/></p> <p><input type="checkbox"/> Maximum dose <input type="text"/></p> <p><input type="checkbox"/> Not reported</p> <p><input type="checkbox"/> Not applicable</p> <p>6. Specify unit</p> <p>Select an Answer ▼</p>	<p>7. Frequency</p> <p>Select an Answer ▼</p>	<p>8. Duration</p> <p><input type="checkbox"/> Mean <input type="text"/></p> <p><input type="checkbox"/> Median <input type="text"/></p> <p><input type="checkbox"/> Planned <input type="text"/></p> <p><input type="checkbox"/> Until discharge <input type="text"/></p> <p><input type="checkbox"/> Not reported</p> <p><input type="checkbox"/> Not applicable</p>
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Complete this table for non-pharmacologic interventions.

<p>9. Non-pharmacologic intervention (check all that apply. Definitions are on the right)</p> <p><input type="checkbox"/> Orientation and therapeutic activities</p> <p><input type="checkbox"/> Fluid repletion</p> <p><input type="checkbox"/> Early mobilization</p> <p><input type="checkbox"/> Feeding assistance</p> <p><input type="checkbox"/> Vision and hearing</p> <p><input type="checkbox"/> Sleep enhancement</p> <p><input type="checkbox"/> Infection prevention</p> <p><input type="checkbox"/> Pain management</p> <p><input type="checkbox"/> Hypoxia protocol</p> <p><input type="checkbox"/> Psychoactive medication protocol</p> <p><input type="checkbox"/> None</p>	<p>Orientation and therapeutic activities</p> <ul style="list-style-type: none"> ▪ Provide lighting, signs, calendars, clocks ▪ Reorient the patient to time, place, person, your role ▪ Introduce cognitively stimulating activities (eg, reminiscing) ▪ Facilitate regular visits from family, friends <p>Fluid repletion</p> <ul style="list-style-type: none"> ▪ Encourage patients to drink; consider parenteral fluids if necessary ▪ Seek advice regarding fluid balance in patients with comorbidities (heart failure, renal disease) <p>Early mobilization</p> <ul style="list-style-type: none"> ▪ Encourage early postoperative mobilization, regular ambulation ▪ Keep walking aids (canes, walkers) nearby at all times ▪ Encourage all patients to engage in active, range-of-motion exercises <p>Feeding assistance</p> <ul style="list-style-type: none"> ▪ Follow general nutrition guidelines and seek advice from dietician as needed ▪ Ensure proper fit of dentures <p>Vision and hearing</p> <ul style="list-style-type: none"> ▪ Resolve reversible cause of the impairment ▪ Ensure working hearing and visual aids are available and used by patients who need them <p>Sleep enhancement</p> <ul style="list-style-type: none"> ▪ Avoid medical or nursing procedures during sleep if possible ▪ Schedule medications to avoid disturbing sleep ▪ Reduce noise at night <p>Infection prevention</p> <ul style="list-style-type: none"> ▪ Look for and treat infections ▪ Avoid unnecessary catheterization ▪ Implement infection-control procedures <p>Pain management</p> <ul style="list-style-type: none"> ▪ Assess for pain, especially in patients with communication difficulties ▪ Begin and monitor pain management in patients with known or suspected pain <p>Hypoxia protocol</p> <ul style="list-style-type: none"> ▪ Assess for hypoxia and oxygen saturation <p>Psychoactive medication protocol</p> <ul style="list-style-type: none"> ▪ Review medication list for both types and number of medications
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Figure B-5. Population characteristics form

EPC Antipsychotics for the Prevention and Treatment of Delirium
Population Form

	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
N for baseline characteristics <input type="radio"/> Not reported Clear Response	N1 <input type="text"/>	N2 <input type="text"/>	N3 <input type="text"/>	N4 <input type="text"/>	N5 <input type="text"/>	N6 <input type="text"/>
Age <input type="radio"/> Not reported Clear Response	Age1 <input type="checkbox"/> Mean <input type="text"/> <input type="checkbox"/> Median <input type="text"/> <input type="checkbox"/> % \geq 65 years <input type="text"/> <input type="checkbox"/> Range <input type="text"/>	Age2 <input type="checkbox"/> Mean <input type="text"/> <input type="checkbox"/> Median <input type="text"/> <input type="checkbox"/> % \geq 65 years <input type="text"/> <input type="checkbox"/> Range <input type="text"/>	Age3 <input type="checkbox"/> Mean <input type="text"/> <input type="checkbox"/> Median <input type="text"/> <input type="checkbox"/> % \geq 65 years <input type="text"/> <input type="checkbox"/> Range <input type="text"/>	Age4 <input type="checkbox"/> Mean <input type="text"/> <input type="checkbox"/> Median <input type="text"/> <input type="checkbox"/> % \geq 65 years <input type="text"/> <input type="checkbox"/> Range <input type="text"/>	Age5 <input type="checkbox"/> Mean <input type="text"/> <input type="checkbox"/> Median <input type="text"/> <input type="checkbox"/> % \geq 65 years <input type="text"/> <input type="checkbox"/> Range <input type="text"/>	Age6 <input type="checkbox"/> Mean <input type="text"/> <input type="checkbox"/> Median <input type="text"/> <input type="checkbox"/> % \geq 65 years <input type="text"/> <input type="checkbox"/> Range <input type="text"/>
Sex <input type="radio"/> Not reported Clear Response	Sex1 <input type="checkbox"/> N male <input type="text"/> <input type="checkbox"/> % male <input type="text"/>	Sex2 <input type="checkbox"/> N male <input type="text"/> <input type="checkbox"/> % male <input type="text"/>	Sex3 <input type="checkbox"/> N male <input type="text"/> <input type="checkbox"/> % male <input type="text"/>	Sex4 <input type="checkbox"/> N male <input type="text"/> <input type="checkbox"/> % male <input type="text"/>	Sex5 <input type="checkbox"/> N male <input type="text"/> <input type="checkbox"/> % male <input type="text"/>	Sex6 <input type="checkbox"/> N male <input type="text"/> <input type="checkbox"/> % male <input type="text"/>
Comorbid dementia <input type="radio"/> Not reported Clear Response	Dementia1 <input type="checkbox"/> N <input type="text"/> <input type="checkbox"/> % <input type="text"/>	Dementia2 <input type="checkbox"/> N <input type="text"/> <input type="checkbox"/> % <input type="text"/>	Dementia3 <input type="checkbox"/> N <input type="text"/> <input type="checkbox"/> % <input type="text"/>	Dementia4 <input type="checkbox"/> N <input type="text"/> <input type="checkbox"/> % <input type="text"/>	Dementia5 <input type="checkbox"/> N <input type="text"/> <input type="checkbox"/> % <input type="text"/>	Dementia6 <input type="checkbox"/> N <input type="text"/> <input type="checkbox"/> % <input type="text"/>
Any substance use disorder (excluding tobacco) <input type="radio"/> Specify how defined <input type="text"/> <input type="radio"/> Not reported Clear Response	Substance use1 <input type="checkbox"/> N <input type="text"/> <input type="checkbox"/> % <input type="text"/>	Substance use2 <input type="checkbox"/> N <input type="text"/> <input type="checkbox"/> % <input type="text"/>	Substance use3 <input type="checkbox"/> N <input type="text"/> <input type="checkbox"/> % <input type="text"/>	Substance use4 <input type="checkbox"/> N <input type="text"/> <input type="checkbox"/> % <input type="text"/>	Substance use5 <input type="checkbox"/> N <input type="text"/> <input type="checkbox"/> % <input type="text"/>	Substance use6 <input type="checkbox"/> N <input type="text"/> <input type="checkbox"/> % <input type="text"/>
Hypertension <input type="radio"/> Not reported Clear Response	Hypertension1 <input type="checkbox"/> N <input type="text"/> <input type="checkbox"/> % <input type="text"/>	Hypertension2 <input type="checkbox"/> N <input type="text"/> <input type="checkbox"/> % <input type="text"/>	Hypertension3 <input type="checkbox"/> N <input type="text"/> <input type="checkbox"/> % <input type="text"/>	Hypertension4 <input type="checkbox"/> N <input type="text"/> <input type="checkbox"/> % <input type="text"/>	Hypertension5 <input type="checkbox"/> N <input type="text"/> <input type="checkbox"/> % <input type="text"/>	Hypertension6 <input type="checkbox"/> N <input type="text"/> <input type="checkbox"/> % <input type="text"/>

43. Comments (limit 250 characters)

Figure B-7. Outcomes definition form (rescue therapy specific)

Please fill out one form for each outcome. Indicate the outcome being reported on this form.

Outcome (data must be from an RCT)	Definition	Timing
<p>Outcome</p> <ul style="list-style-type: none"> <input type="radio"/> Short-term delirium symptoms (agitation and/or increased psychomotor activity) <input type="radio"/> Short-term delirium symptoms (sleep-wake cycle disturbances) <input type="radio"/> Short-term delirium symptoms [delusions (e.g., psychotic symptoms, illusions, perceptual disturbances, hallucinations)] <input type="radio"/> Delirium severity <input type="radio"/> Delirium-free, coma-free days <input type="radio"/> Duration of delirium <input type="radio"/> Patient distress <input checked="" type="radio"/> Use of rescue therapy <input type="radio"/> Use of physical restraint <input type="radio"/> Mortality <input type="radio"/> Survival (time to death) <input type="radio"/> Quality of life <input type="radio"/> Cognitive functioning <input type="radio"/> Institutionalization <input type="radio"/> Caregiver burden <input type="radio"/> Falls <input type="radio"/> Memory of patient distress <input type="radio"/> Re-admissions to hospital <input type="radio"/> Re-admissions to intensive care unit <input type="radio"/> Length of stay in the hospital <input type="radio"/> Length of stay in the intensive care unit <input type="radio"/> Length of stay in a skilled nursing facility/rehab facility <input type="radio"/> Sitter use <input type="radio"/> Hospice enrollment <input type="radio"/> Delirium incidence <p>Clear Response</p>	<p>4. Specify drug and dose of rescue therapy</p> <p><input type="checkbox"/> Drug <input type="text"/></p> <p><input type="checkbox"/> Dose <input type="text"/></p>	<p>8. Specify the time of assessment</p> <p><input type="text" value="-"/></p>

Figure B-8. Outcomes definition form (quality of life specific)

Please fill out one form for each outcome. Indicate the outcome being reported on this form.

Outcome (data must be from an RCT)	Definition	Timing
<p>Outcome</p> <ul style="list-style-type: none"> <input type="radio"/> Short-term delirium symptoms (agitation and/or increased psychomotor activity) <input type="radio"/> Short-term delirium symptoms (sleep-wake cycle disturbances) <input type="radio"/> Short-term delirium symptoms (delusions (e.g., psychotic symptoms, illusions, perceptual disturbances, hallucinations)) <input type="radio"/> Delirium severity <input type="radio"/> Delirium-free, coma-free days <input type="radio"/> Duration of delirium <input type="radio"/> Patient distress <input type="radio"/> Use of rescue therapy <input type="radio"/> Use of physical restraint <input type="radio"/> Mortality <input type="radio"/> Survival (time to death) <input checked="" type="radio"/> Quality of life <input type="radio"/> Cognitive functioning <input type="radio"/> Institutionalization <input type="radio"/> Caregiver burden <input type="radio"/> Falls <input type="radio"/> Memory of patient distress <input type="radio"/> Re-admissions to hospital <input type="radio"/> Re-admissions to intensive care unit <input type="radio"/> Length of stay in the hospital <input type="radio"/> Length of stay in the intensive care unit <input type="radio"/> Length of stay in a skilled nursing facility/rehab facility <input type="radio"/> Sitter use <input type="radio"/> Hospice enrollment <input type="radio"/> Delirium incidence <p>Clear Response</p>	<p>5. Specify how quality of life is defined</p> <ul style="list-style-type: none"> <input type="radio"/> SF-36 <input type="text"/> <input type="radio"/> EQ-5D <input type="text"/> <input type="radio"/> Other <input type="text"/> <p>Clear Response</p>	<p>8. Specify the time of assessment</p> <p><input type="text"/></p>

Figure B-9. Outcomes definition form (cognitive function specific)

Please fill out one form for each outcome. Indicate the outcome being reported on this form.

Outcome (data must be from an RCT)	Definition	Timing
<p>Outcome</p> <ul style="list-style-type: none"> <input type="radio"/> Short-term delirium symptoms (agitation and/or increased psychomotor activity) <input type="radio"/> Short-term delirium symptoms (sleep-wake cycle disturbances) <input type="radio"/> Short-term delirium symptoms (delusions (e.g., psychotic symptoms, illusions, perceptual disturbances, hallucinations)) <input type="radio"/> Delirium severity <input type="radio"/> Delirium-free, coma-free days <input type="radio"/> Duration of delirium <input type="radio"/> Patient distress <input type="radio"/> Use of rescue therapy <input type="radio"/> Use of physical restraint <input type="radio"/> Mortality <input type="radio"/> Survival (time to death) <input type="radio"/> Quality of life <input checked="" type="radio"/> Cognitive functioning <input type="radio"/> Institutionalization <input type="radio"/> Caregiver burden <input type="radio"/> Falls <input type="radio"/> Memory of patient distress <input type="radio"/> Re-admissions to hospital <input type="radio"/> Re-admissions to intensive care unit <input type="radio"/> Length of stay in the hospital <input type="radio"/> Length of stay in the intensive care unit <input type="radio"/> Length of stay in a skilled nursing facility/rehab facility <input type="radio"/> Sitter use <input type="radio"/> Hospice enrollment <input type="radio"/> Delirium incidence <p>Clear Response</p>	<p>6. Specify how cognitive functioning is defined</p> <ul style="list-style-type: none"> <input checked="" type="radio"/> Mini Mental Status: <input type="text"/> <input type="radio"/> Montreal Cognitive Assessment <input type="text"/> <input type="radio"/> Other: <input type="text"/> <p>Clear Response</p>	<p>8. Specify the time of assessment</p> <p>- <input type="text"/></p>

Figure B-10. Outcomes definition form (delirium severity specific)

Please fill out one form for each outcome. Indicate the outcome being reported on this form.

Outcome (data must be from an RCT)	Definition	Timing
<p>Outcome</p> <ul style="list-style-type: none"> <input type="radio"/> Short-term delirium symptoms (agitation and/or increased psychomotor activity) <input type="radio"/> Short-term delirium symptoms (sleep-wake cycle disturbances) <input type="radio"/> Short-term delirium symptoms [delusions (e.g. psychotic symptoms, illusions, perceptual disturbances, hallucinations)] <input checked="" type="radio"/> Delirium severity <input type="radio"/> Delirium-free, coma-free days <input type="radio"/> Duration of delirium <input type="radio"/> Patient distress <input type="radio"/> Use of rescue therapy <input type="radio"/> Use of physical restraint <input type="radio"/> Mortality <input type="radio"/> Survival (time to death) <input type="radio"/> Quality of life <input type="radio"/> Cognitive functioning <input type="radio"/> Institutionalization <input type="radio"/> Caregiver burden <input type="radio"/> Falls <input type="radio"/> Memory of patient distress <input type="radio"/> Re-admissions to hospital <input type="radio"/> Re-admissions to intensive care unit <input type="radio"/> Length of stay in the hospital <input type="radio"/> Length of stay in the intensive care unit <input type="radio"/> Length of stay in a skilled nursing facility/rehab facility <input type="radio"/> Sitter use <input type="radio"/> Hospice enrollment <input type="radio"/> Delirium incidence <p>Clear Response</p>	<p>3. Specify how delirium severity is defined</p> <ul style="list-style-type: none"> <input type="radio"/> DRS-R-98 <input type="radio"/> Visual analog scale <input type="radio"/> Other <input style="width: 50px;" type="text"/> <p>Clear Response</p>	<p>8. Specify the time of assessment</p> <p><input style="width: 100px;" type="text"/></p>

Figure B-11. Outcomes definition form (general)

Please fill out one form for each outcome. Indicate the outcome being reported on this form.

Outcome (data must be from an RCT)	Definition	Timing
<p>Outcome</p> <ul style="list-style-type: none"> <input type="radio"/> Short-term delirium symptoms (agitation and/or increased psychomotor activity) <input type="radio"/> Short-term delirium symptoms (sleep-wake cycle disturbances) <input type="radio"/> Short-term delirium symptoms (delusions (e.g., psychotic symptoms, illusions, perceptual disturbances, hallucinations)) <input type="radio"/> Delirium severity <input type="radio"/> Delirium-free, coma-free days <input checked="" type="radio"/> Duration of delirium <input type="radio"/> Patient distress <input type="radio"/> Use of rescue therapy <input type="radio"/> Use of physical restraint <input type="radio"/> Mortality <input type="radio"/> Survival (time to death) <input type="radio"/> Quality of life <input type="radio"/> Cognitive functioning <input type="radio"/> Institutionalization <input type="radio"/> Caregiver burden <input type="radio"/> Falls <input type="radio"/> Memory of patient distress <input type="radio"/> Re-admissions to hospital <input type="radio"/> Re-admissions to intensive care unit <input type="radio"/> Length of stay in the hospital <input type="radio"/> Length of stay in the intensive care unit <input type="radio"/> Length of stay in a skilled nursing facility/rehab facility <input type="radio"/> Sitter use <input type="radio"/> Hospice enrollment <input type="radio"/> Delirium incidence <p>Clear Response</p>	<div style="border: 1px solid black; padding: 5px;"> <p>7. Specify definition</p> <p><input type="radio"/> Define <input style="width: 50px;" type="text"/></p> <p><input type="radio"/> Not applicable</p> <p>Clear Response</p> </div>	<p>8. Specify the time of assessment</p> <div style="border: 1px solid black; width: 100%; height: 20px; margin-top: 5px;"></div>

Figure B-12. Outcomes definition form (adverse events: appetite change specific)

Adverse event table (data can be from an RCT, controlled clinical trial, or prospective cohort with or without a comparison)	Definition	Timing of outcome
<p>9. Adverse event</p> <ul style="list-style-type: none"> <input type="radio"/> Sedation <input type="radio"/> Weight <input checked="" type="radio"/> Change in appetite <input type="radio"/> Cardiac effects <input type="radio"/> Neurologic effects <input type="radio"/> Hypersensitivity reactions <input type="radio"/> Inappropriate continuation of antipsychotic medication <input type="radio"/> Swallowing difficulties <input type="radio"/> Aspiration pneumonia <p>Clear Response</p>	<p>11. Specify change in appetite outcome</p> <ul style="list-style-type: none"> <input type="radio"/> Increase in appetite <input type="radio"/> Decrease in appetite <p>Clear Response</p>	<p>15. Specify the time of assessment</p> <p>— <input style="width: 100px;" type="text"/></p>

Figure B-13. Outcomes definition form (adverse events: cardiac effects specific)

Adverse event table (data can be from an RCT, controlled clinical trial, or prospective cohort with or without a comparison)	Definition	Timing of outcome
<p>9. Adverse event</p> <ul style="list-style-type: none"> <input type="radio"/> Sedation <input type="radio"/> Weight <input type="radio"/> Change in appetite <input checked="" type="radio"/> Cardiac effects <input type="radio"/> Neurologic effects <input type="radio"/> Hypersensitivity reactions <input type="radio"/> Inappropriate continuation of antipsychotic medication <input type="radio"/> Swallowing difficulties <input type="radio"/> Aspiration pneumonia <p>Clear Response</p>	<p>12. Specify cardiac outcome</p> <ul style="list-style-type: none"> <input type="radio"/> Prolongation in the QTc interval <input style="width: 50px;" type="text"/> <input type="radio"/> Prolongation in the QT interval <input style="width: 50px;" type="text"/> <input type="radio"/> Other <input style="width: 50px;" type="text"/> <p>Clear Response</p>	<p>15. Specify the time of assessment</p> <p>— <input style="width: 100px;" type="text"/></p>

Figure B-14. Outcomes definition form (adverse events: neurologic effects specific)

Adverse event table (data can be from an RCT, controlled clinical trial, or prospective cohort with or without a comparison)	Definition	Timing of outcome
<p>9. Adverse event</p> <ul style="list-style-type: none"> <input type="radio"/> Sedation <input type="radio"/> Weight <input type="radio"/> Change in appetite <input type="radio"/> Cardiac effects <input checked="" type="radio"/> Neurologic effects <input type="radio"/> Hypersensitivity reactions <input type="radio"/> Inappropriate continuation of antipsychotic medication <input type="radio"/> Swallowing difficulties <input type="radio"/> Aspiration pneumonia <p>Clear Response</p>	<p>13. Specify neurologic outcome</p> <ul style="list-style-type: none"> <input type="radio"/> Extrapyramidal symptoms <input style="width: 50px;" type="text"/> <input type="radio"/> Other <input style="width: 50px;" type="text"/> <p>Clear Response</p>	<p>15. Specify the time of assessment</p> <p>— <input style="width: 100px;" type="text"/></p>

Figure B-15. Outcomes definition form (adverse events: weight specific)

Adverse event table (data can be from an RCT, controlled clinical trial, or prospective cohort with or without a comparison)	Definition	Timing of outcome
<p>9. Adverse event</p> <ul style="list-style-type: none"> <input type="radio"/> Sedation <input checked="" type="radio"/> Weight <input type="radio"/> Change in appetite <input type="radio"/> Cardiac effects <input type="radio"/> Neurologic effects <input type="radio"/> Hypersensitivity reactions <input type="radio"/> Inappropriate continuation of antipsychotic medication <input type="radio"/> Swallowing difficulties <input type="radio"/> Aspiration pneumonia <p>Clear Response</p>	<p>10. Specify weight outcome</p> <ul style="list-style-type: none"> <input checked="" type="radio"/> Weight gain <input type="text"/> <input type="radio"/> Weight loss <input type="text"/> <p>Clear Response</p>	<p>15. Specify the time of assessment</p> <p><input type="text"/></p>

Figure B-16. Outcomes definition form (general adverse events)

Adverse event table (data can be from an RCT, controlled clinical trial, or prospective cohort with or without a comparison)	Definition	Timing of outcome
<p>9. Adverse event</p> <ul style="list-style-type: none"> <input checked="" type="radio"/> Sedation <input type="radio"/> Weight <input type="radio"/> Change in appetite <input type="radio"/> Cardiac effects <input type="radio"/> Neurologic effects <input type="radio"/> Hypersensitivity reactions <input type="radio"/> Inappropriate continuation of antipsychotic medication <input type="radio"/> Swallowing difficulties <input type="radio"/> Aspiration pneumonia <p>Clear Response</p>	<p>14. Specify outcome definition</p> <ul style="list-style-type: none"> <input checked="" type="radio"/> Define <input type="text"/> <input type="radio"/> Not applicable <p>Clear Response</p>	<p>15. Specify the time of assessment</p> <p><input type="text"/></p>

Figure B-17. Outcomes data extraction form

Continuous outcomes

Table I. Mean difference from other intervention group measures of outcome (between-group difference). When filling out this table, please note that the point estimate should reflect this formula: (Final - Baseline for the intervention group) - (Final - Baseline for the reference group). You do not need to calculate this.

Intervention group (Please be consistent with the labeling in the intervention form)	N for analysis	Point estimate (please specify negative/positive sign)	Measure of variability	95% CI or IQR	p-value (Record exact p-value)	Indicate reference group
	<input type="radio"/> N for analysis: <input type="text"/> <input type="radio"/> Baseline N: <input type="text"/> Clear Response	<input type="radio"/> Mean <input type="radio"/> Median <input type="radio"/> Other (specify): <input type="text"/> <input type="radio"/> Not reported Clear Response	<input type="radio"/> SE <input type="radio"/> SD <input type="radio"/> Other (specify): <input type="text"/> <input type="radio"/> Not reported Clear Response	<input type="radio"/> 95% CI <input type="radio"/> IQR <input type="radio"/> Not reported Clear Response	<input type="radio"/> Not reported Clear Response	
Group 1	<input type="radio"/> N for analysis: <input type="text"/> <input type="radio"/> Baseline N: <input type="text"/> Clear Response	<input type="text"/>	<input type="text"/>	<input type="checkbox"/> Lower limit: <input type="text"/> <input type="checkbox"/> Upper limit: <input type="text"/>	<input type="text"/>	Select an Answer ▼
Group 2	<input type="radio"/> N for analysis: <input type="text"/> <input type="radio"/> Baseline N: <input type="text"/> Clear Response	<input type="text"/>	<input type="text"/>	<input type="checkbox"/> Lower limit: <input type="text"/> <input type="checkbox"/> Upper limit: <input type="text"/>	<input type="text"/>	Select an Answer ▼
Group 3	<input type="radio"/> N for analysis: <input type="text"/> <input type="radio"/> Baseline N: <input type="text"/> Clear Response	<input type="text"/>	<input type="text"/>	<input type="checkbox"/> Lower limit: <input type="text"/> <input type="checkbox"/> Upper limit: <input type="text"/>	<input type="text"/>	Select an Answer ▼
Group 4	<input type="radio"/> N for analysis: <input type="text"/> <input type="radio"/> Baseline N: <input type="text"/> Clear Response	<input type="text"/>	<input type="text"/>	<input type="checkbox"/> Lower limit: <input type="text"/> <input type="checkbox"/> Upper limit: <input type="text"/>	<input type="text"/>	Select an Answer ▼
Group 5	<input type="radio"/> N for analysis: <input type="text"/> <input type="radio"/> Baseline N: <input type="text"/> Clear Response	<input type="text"/>	<input type="text"/>	<input type="checkbox"/> Lower limit: <input type="text"/> <input type="checkbox"/> Upper limit: <input type="text"/>	<input type="text"/>	Select an Answer ▼
Group 6	<input type="radio"/> N for analysis: <input type="text"/> <input type="radio"/> Baseline N: <input type="text"/> Clear Response	<input type="text"/>	<input type="text"/>	<input type="checkbox"/> Lower limit: <input type="text"/> <input type="checkbox"/> Upper limit: <input type="text"/>	<input type="text"/>	Select an Answer ▼

Table II. Mean difference from baseline to final measures of outcome (within-group difference)
 (This should be Final - Baseline. If values decrease, be sure to indicate with a negative sign (-)).

Intervention group (Please be consistent with the labeling in the intervention form)	N for analysis	Point estimate (please specify negative/positive sign) <input type="radio"/> Mean <input type="radio"/> Median <input type="radio"/> Other (specify): <input type="text"/> <input type="radio"/> Not reported Clear Response	Measure of variability <input type="radio"/> SE <input type="radio"/> SD <input type="radio"/> Other (specify): <input type="text"/> <input type="radio"/> Not reported Clear Response	95% CI or IQR <input type="radio"/> 95% CI <input type="radio"/> IQR <input type="radio"/> Not reported Clear Response	p-value (Record exact p-value) <input type="radio"/> Not reported Clear Response
Group 1	<input type="radio"/> N for analysis: <input type="text"/> <input type="radio"/> Baseline N: <input type="text"/> Clear Response	- <input type="text"/>	- <input type="text"/>	<input type="checkbox"/> Lower limit: <input type="text"/> <input type="checkbox"/> Upper limit: <input type="text"/>	- <input type="text"/>
Group 2	<input type="radio"/> N for analysis: <input type="text"/> <input type="radio"/> Baseline N: <input type="text"/> Clear Response	- <input type="text"/>	- <input type="text"/>	<input type="checkbox"/> Lower limit: <input type="text"/> <input type="checkbox"/> Upper limit: <input type="text"/>	- <input type="text"/>
Group 3	<input type="radio"/> N for analysis: <input type="text"/> <input type="radio"/> Baseline N: <input type="text"/> Clear Response	- <input type="text"/>	- <input type="text"/>	<input type="checkbox"/> Lower limit: <input type="text"/> <input type="checkbox"/> Upper limit: <input type="text"/>	- <input type="text"/>
Group 4	<input type="radio"/> N for analysis: <input type="text"/> <input type="radio"/> Baseline N: <input type="text"/> Clear Response	- <input type="text"/>	- <input type="text"/>	<input type="checkbox"/> Lower limit: <input type="text"/> <input type="checkbox"/> Upper limit: <input type="text"/>	- <input type="text"/>
Group 5	<input type="radio"/> N for analysis: <input type="text"/> <input type="radio"/> Baseline N: <input type="text"/> Clear Response	- <input type="text"/>	- <input type="text"/>	<input type="checkbox"/> Lower limit: <input type="text"/> <input type="checkbox"/> Upper limit: <input type="text"/>	- <input type="text"/>
Group 6	<input type="radio"/> N for analysis: <input type="text"/> <input type="radio"/> Baseline N: <input type="text"/> Clear Response	- <input type="text"/>	- <input type="text"/>	<input type="checkbox"/> Lower limit: <input type="text"/> <input type="checkbox"/> Upper limit: <input type="text"/>	- <input type="text"/>

Table III. Baseline measures of cohort

Intervention group (Please be consistent with the labeling in the intervention form)	N for analysis	Point estimate (please specify negative/positive sign)	Measure of variability	95% CI or IQR	p-value (Record exact p-value)	Indicate reference group
Group 1	<input type="radio"/> N for analysis: <input type="text"/> <input type="radio"/> Baseline N: <input type="text"/> Clear Response	<input type="radio"/> Mean: <input type="text"/> <input type="radio"/> Median: <input type="text"/> <input type="radio"/> Other (specify): <input type="text"/> <input type="radio"/> Not reported Clear Response	<input type="radio"/> SE: <input type="text"/> <input type="radio"/> SD: <input type="text"/> <input type="radio"/> Other (specify): <input type="text"/> <input type="radio"/> Not reported Clear Response	<input type="radio"/> 95% CI: <input type="text"/> <input type="radio"/> IQR: <input type="text"/> <input type="radio"/> Not reported Clear Response	<input type="radio"/> Not reported Clear Response	<input type="text" value="Select an Answer"/>
Group 2	<input type="radio"/> N for analysis: <input type="text"/> <input type="radio"/> Baseline N: <input type="text"/> Clear Response	<input type="radio"/> Mean: <input type="text"/> <input type="radio"/> Median: <input type="text"/> <input type="radio"/> Other (specify): <input type="text"/> <input type="radio"/> Not reported Clear Response	<input type="radio"/> SE: <input type="text"/> <input type="radio"/> SD: <input type="text"/> <input type="radio"/> Other (specify): <input type="text"/> <input type="radio"/> Not reported Clear Response	<input type="checkbox"/> Lower limit: <input type="text"/> <input type="checkbox"/> Upper limit: <input type="text"/>	<input type="radio"/> Not reported Clear Response	<input type="text" value="Select an Answer"/>
Group 3	<input type="radio"/> N for analysis: <input type="text"/> <input type="radio"/> Baseline N: <input type="text"/> Clear Response	<input type="radio"/> Mean: <input type="text"/> <input type="radio"/> Median: <input type="text"/> <input type="radio"/> Other (specify): <input type="text"/> <input type="radio"/> Not reported Clear Response	<input type="radio"/> SE: <input type="text"/> <input type="radio"/> SD: <input type="text"/> <input type="radio"/> Other (specify): <input type="text"/> <input type="radio"/> Not reported Clear Response	<input type="checkbox"/> Lower limit: <input type="text"/> <input type="checkbox"/> Upper limit: <input type="text"/>	<input type="radio"/> Not reported Clear Response	<input type="text" value="Select an Answer"/>
Group 4	<input type="radio"/> N for analysis: <input type="text"/> <input type="radio"/> Baseline N: <input type="text"/> Clear Response	<input type="radio"/> Mean: <input type="text"/> <input type="radio"/> Median: <input type="text"/> <input type="radio"/> Other (specify): <input type="text"/> <input type="radio"/> Not reported Clear Response	<input type="radio"/> SE: <input type="text"/> <input type="radio"/> SD: <input type="text"/> <input type="radio"/> Other (specify): <input type="text"/> <input type="radio"/> Not reported Clear Response	<input type="checkbox"/> Lower limit: <input type="text"/> <input type="checkbox"/> Upper limit: <input type="text"/>	<input type="radio"/> Not reported Clear Response	<input type="text" value="Select an Answer"/>
Group 5	<input type="radio"/> N for analysis: <input type="text"/> <input type="radio"/> Baseline N: <input type="text"/> Clear Response	<input type="radio"/> Mean: <input type="text"/> <input type="radio"/> Median: <input type="text"/> <input type="radio"/> Other (specify): <input type="text"/> <input type="radio"/> Not reported Clear Response	<input type="radio"/> SE: <input type="text"/> <input type="radio"/> SD: <input type="text"/> <input type="radio"/> Other (specify): <input type="text"/> <input type="radio"/> Not reported Clear Response	<input type="checkbox"/> Lower limit: <input type="text"/> <input type="checkbox"/> Upper limit: <input type="text"/>	<input type="radio"/> Not reported Clear Response	<input type="text" value="Select an Answer"/>
Group 6	<input type="radio"/> N for analysis: <input type="text"/> <input type="radio"/> Baseline N: <input type="text"/> Clear Response	<input type="radio"/> Mean: <input type="text"/> <input type="radio"/> Median: <input type="text"/> <input type="radio"/> Other (specify): <input type="text"/> <input type="radio"/> Not reported Clear Response	<input type="radio"/> SE: <input type="text"/> <input type="radio"/> SD: <input type="text"/> <input type="radio"/> Other (specify): <input type="text"/> <input type="radio"/> Not reported Clear Response	<input type="checkbox"/> Lower limit: <input type="text"/> <input type="checkbox"/> Upper limit: <input type="text"/>	<input type="radio"/> Not reported Clear Response	<input type="text" value="Select an Answer"/>

Table IV. Final measures of outcome

Intervention group (Please be consistent with the labeling in the intervention form)	N for analysis	Point estimate (please specify negative/positive sign)	Measure of variability	95% CI or IQR	p-value (Record exact p-value)	Indicate reference group
Group 1	<input type="radio"/> N for analysis <input type="text"/> <input type="radio"/> Baseline N <input type="text"/> Clear Response	<input type="text"/> - Clear Response	<input type="radio"/> SE <input type="text"/> <input type="radio"/> SD <input type="text"/> <input type="radio"/> Other (specify): <input type="text"/> <input type="radio"/> Not reported Clear Response	<input type="checkbox"/> 95% CI <input type="text"/> <input type="checkbox"/> IQR <input type="text"/> <input type="checkbox"/> Not reported Clear Response	<input type="radio"/> Not reported Clear Response	<input type="text"/> Select an Answer ▼
Group 2	<input type="radio"/> N for analysis <input type="text"/> <input type="radio"/> Baseline N <input type="text"/> Clear Response	<input type="text"/> - Clear Response	<input type="radio"/> SE <input type="text"/> <input type="radio"/> SD <input type="text"/> <input type="radio"/> Other (specify): <input type="text"/> <input type="radio"/> Not reported Clear Response	<input type="checkbox"/> Lower limit <input type="text"/> <input type="checkbox"/> Upper limit <input type="text"/> 	<input type="text"/> - 	<input type="text"/> Select an Answer ▼
Group 3	<input type="radio"/> N for analysis <input type="text"/> <input type="radio"/> Baseline N <input type="text"/> Clear Response	<input type="text"/> - Clear Response	<input type="radio"/> SE <input type="text"/> <input type="radio"/> SD <input type="text"/> <input type="radio"/> Other (specify): <input type="text"/> <input type="radio"/> Not reported Clear Response	<input type="checkbox"/> Lower limit <input type="text"/> <input type="checkbox"/> Upper limit <input type="text"/> 	<input type="text"/> - 	<input type="text"/> Select an Answer ▼
Group 4	<input type="radio"/> N for analysis <input type="text"/> <input type="radio"/> Baseline N <input type="text"/> Clear Response	<input type="text"/> - Clear Response	<input type="radio"/> SE <input type="text"/> <input type="radio"/> SD <input type="text"/> <input type="radio"/> Other (specify): <input type="text"/> <input type="radio"/> Not reported Clear Response	<input type="checkbox"/> Lower limit <input type="text"/> <input type="checkbox"/> Upper limit <input type="text"/> 	<input type="text"/> - 	<input type="text"/> Select an Answer ▼
Group 5	<input type="radio"/> N for analysis <input type="text"/> <input type="radio"/> Baseline N <input type="text"/> Clear Response	<input type="text"/> - Clear Response	<input type="radio"/> SE <input type="text"/> <input type="radio"/> SD <input type="text"/> <input type="radio"/> Other (specify): <input type="text"/> <input type="radio"/> Not reported Clear Response	<input type="checkbox"/> Lower limit <input type="text"/> <input type="checkbox"/> Upper limit <input type="text"/> 	<input type="text"/> - 	<input type="text"/> Select an Answer ▼
Group 6	<input type="radio"/> N for analysis <input type="text"/> <input type="radio"/> Baseline N <input type="text"/> Clear Response	<input type="text"/> - Clear Response	<input type="radio"/> SE <input type="text"/> <input type="radio"/> SD <input type="text"/> <input type="radio"/> Other (specify): <input type="text"/> <input type="radio"/> Not reported Clear Response	<input type="checkbox"/> Lower limit <input type="text"/> <input type="checkbox"/> Upper limit <input type="text"/> 	<input type="text"/> - 	<input type="text"/> Select an Answer ▼

Dichotomous Outcomes

Table V. Incidence of the outcome by intervention group

Intervention group (Please be consistent with the labeling in the intervention form)	N for analysis	Outcome measure/numerator	Denominator	p-value (Record exact p-value)	Indicate reference group
		<input type="radio"/> Not reported Clear Response	<input type="text" value="Select an Answer"/>	<input type="radio"/> Not reported Clear Response	
Group 1	<input checked="" type="radio"/> N for analysis: <input type="text"/> <input type="radio"/> Baseline N: <input type="text"/> Clear Response	<input type="checkbox"/> # of patients with one or more events: <input type="text"/> <input type="checkbox"/> % of patients with one or more events: <input type="text"/> <input type="checkbox"/> # of events: <input type="text"/>	<input type="text" value="-"/>	<input type="text" value="-"/>	<input type="text" value="Select an Answer"/>
Group 2	<input checked="" type="radio"/> N for analysis: <input type="text"/> <input type="radio"/> Baseline N: <input type="text"/> Clear Response	<input type="checkbox"/> # of patients with one or more events: <input type="text"/> <input type="checkbox"/> % of patients with one or more events: <input type="text"/> <input type="checkbox"/> # of events: <input type="text"/>	<input type="text" value="-"/>	<input type="text" value="-"/>	<input type="text" value="Select an Answer"/>
Group 3	<input checked="" type="radio"/> N for analysis: <input type="text"/> <input type="radio"/> Baseline N: <input type="text"/> Clear Response	<input type="checkbox"/> # of patients with one or more events: <input type="text"/> <input type="checkbox"/> % of patients with one or more events: <input type="text"/> <input type="checkbox"/> # of events: <input type="text"/>	<input type="text" value="-"/>	<input type="text" value="-"/>	<input type="text" value="Select an Answer"/>
Group 4	<input checked="" type="radio"/> N for analysis: <input type="text"/> <input type="radio"/> Baseline N: <input type="text"/> Clear Response	<input type="checkbox"/> # of patients with one or more events: <input type="text"/> <input type="checkbox"/> % of patients with one or more events: <input type="text"/> <input type="checkbox"/> # of events: <input type="text"/>	<input type="text" value="-"/>	<input type="text" value="-"/>	<input type="text" value="Select an Answer"/>
Group 5	<input checked="" type="radio"/> N for analysis: <input type="text"/> <input type="radio"/> Baseline N: <input type="text"/> Clear Response	<input type="checkbox"/> # of patients with one or more events: <input type="text"/> <input type="checkbox"/> % of patients with one or more events: <input type="text"/> <input type="checkbox"/> # of events: <input type="text"/>	<input type="text" value="-"/>	<input type="text" value="-"/>	<input type="text" value="Select an Answer"/>
Group 6	<input checked="" type="radio"/> N for analysis: <input type="text"/> <input type="radio"/> Baseline N: <input type="text"/> Clear Response	<input type="checkbox"/> # of patients with one or more events: <input type="text"/> <input type="checkbox"/> % of patients with one or more events: <input type="text"/> <input type="checkbox"/> # of events: <input type="text"/>	<input type="text" value="-"/>	<input type="text" value="-"/>	<input type="text" value="Select an Answer"/>

Table VI. Measure of association for comparison of outcomes between intervention groups

Table VI. Measures of association for comparison of outcome between intervention groups

Intervention group (Please be consistent with the labeling in the intervention form)	N for analysis	Point estimate <input type="radio"/> Relative risk <input type="radio"/> Relative hazard <input type="radio"/> Odds ratio <input type="radio"/> Risk difference <input type="radio"/> Other: <input type="text"/> <input type="radio"/> Not reported Clear Response	Measure of variability <input type="radio"/> SE <input type="radio"/> SD <input type="radio"/> Not reported Clear Response	95% Confidence Interval <input type="radio"/> Not reported Clear Response	p-value (Record exact p-value) <input type="radio"/> Not reported Clear Response	Indicate reference group
Group 1	<input type="radio"/> N for analysis: <input type="text"/> <input type="radio"/> Baseline N: <input type="text"/> Clear Response	<input type="text"/>	<input type="text"/>	<input type="checkbox"/> Lower limit: <input type="text"/> <input type="checkbox"/> Upper limit: <input type="text"/>	<input type="text"/>	Select an Answer ▼
Group 2	<input type="radio"/> N for analysis: <input type="text"/> <input type="radio"/> Baseline N: <input type="text"/> Clear Response	<input type="text"/>	<input type="text"/>	<input type="checkbox"/> Lower limit: <input type="text"/> <input type="checkbox"/> Upper limit: <input type="text"/>	<input type="text"/>	Select an Answer ▼
Group 3	<input type="radio"/> N for analysis: <input type="text"/> <input type="radio"/> Baseline N: <input type="text"/> Clear Response	<input type="text"/>	<input type="text"/>	<input type="checkbox"/> Lower limit: <input type="text"/> <input type="checkbox"/> Upper limit: <input type="text"/>	<input type="text"/>	Select an Answer ▼
Group 4	<input type="radio"/> N for analysis: <input type="text"/> <input type="radio"/> Baseline N: <input type="text"/> Clear Response	<input type="text"/>	<input type="text"/>	<input type="checkbox"/> Lower limit: <input type="text"/> <input type="checkbox"/> Upper limit: <input type="text"/>	<input type="text"/>	Select an Answer ▼
Group 5	<input type="radio"/> N for analysis: <input type="text"/> <input type="radio"/> Baseline N: <input type="text"/> Clear Response	<input type="text"/>	<input type="text"/>	<input type="checkbox"/> Lower limit: <input type="text"/> <input type="checkbox"/> Upper limit: <input type="text"/>	<input type="text"/>	Select an Answer ▼
Group 6	<input type="radio"/> N for analysis: <input type="text"/> <input type="radio"/> Baseline N: <input type="text"/> Clear Response	<input type="text"/>	<input type="text"/>	<input type="checkbox"/> Lower limit: <input type="text"/> <input type="checkbox"/> Upper limit: <input type="text"/>	<input type="text"/>	Select an Answer ▼

Figure B-18. Risk of bias for randomized controlled trials

RefId: 1, There and Back Again: A Review of Residency and Return Migrations in Sharks, with Implications for Population Structure and Management.
Chapman DD, Feldheim KA, Papastamatiou Y, Hueter RE

[Submit Form](#) and go to or [Skip to Next](#)  

Cochrane Risk of Bias Assessment Tool

Sequence Generation

Look for a description of the method used to generate the allocation sequence to assign participants to treatment arms. This should provide enough detail to allow assessment of whether it should produce comparable groups.

Was the allocation sequence adequately generated? Select the response that fits best:

The investigators describe a random component in the sequence generation process such as:

- Referring to a random number table
- Using a computer random number generator
- Coin tossing
- Shuffling cards or envelopes
- Throwing dice
- Drawing of lots
- Minimization (Minimization may be implemented without a random element, and this is considered to be equivalent to being random.)

[Clear Response](#)

Text fragment from manuscript to support above decision

Risk of Bias in Sequence Generation is:

Low High Unclear [Clear Response](#)

Allocation Concealment

Look for a description of the method used to conceal the allocation sequence prior to group assignment. It should provide enough detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrollment.

Was allocation adequately concealed? (Select the single category mostly closely describing the method used)

Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation:

- Central allocation (including telephone, web-based, and pharmacy-controlled, randomization)
- Sequentially numbered drug containers of identical appearance
- Sequentially numbered, opaque, sealed envelopes

[Clear Response](#)

Text fragment from manuscript to support above decision

Risk of Bias in Allocation Concealment is:

Low High Unclear [Clear Response](#)

Blinding of participants, personnel and outcome assessors

Look for a description of all measures used, if any, to blind study participants, personnel and outcome assessors from knowledge of which intervention a participant received. Note any information on whether the intended blinding was successful.

Blinding for outcomes for each population group:

- Overall: Long-term cognitive impairment, delirium severity, length of stay in hospital, inappropriate continuation of antipsychotic medication, or sedation
- Patients over age 65 years: Long-term cognitive impairment, delirium severity, falls, inappropriate continuation of antipsychotic medication, or sedation
- Patients with dementia: Length of stay in hospital, caregiver burden/strain, long-term cognitive impairment, inappropriate continuation of antipsychotic medication
- Patients in the intensive care unit: Delirium severity, length of stay in hospital, long-term cognitive impairment, inappropriate continuation of antipsychotic medication, or sedation
- Patients in post-acute care: Long-term cognitive impairment, falls, length of stay in hospital, sedation
- Patients in palliative care: Caregiver burden/strain, delirium severity, sedation
- Patients in post-operative care: Length of stay in hospital, long-term cognitive impairment, delirium severity, inappropriate continuation of antipsychotic medication

Was knowledge of the allocated intervention adequately prevented during this study? Select the option most closely describing the status of blinding:

Any one of the following is considered adequate blinding:

- No blinding, but the review authors judge that the outcome and the outcome measurement are not likely to be influenced by lack of blinding.
- Blinding of participants and key study personnel ensured, and it is unlikely that the blinding could have been broken.
- Either participants or some key study personnel were not blinded, but outcome assessment was blinded and the non-blinding of others is unlikely to introduce bias.

[Clear Response](#)

Text fragment from manuscript to support above decision

Risk of Bias in binding of participants, personnel and outcomes assessors is:

Low High Unclear [Clear Response](#)

Incomplete Outcome Data

Primary Outcome: Describe the completeness of outcome data for the primary outcome, including attrition and exclusions from the analysis.

Were attrition and exclusions reported?

[Clear Response](#)

Were incomplete outcome data adequately addressed? Select the statement below that best characterizes the status of incomplete outcome data.

No missing outcome data

Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias) because:

- Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups;
- For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate;
- For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size;
- Missing data have been imputed using appropriate methods.

[Clear Response](#)

Provide text fragments from the manuscript or other evidence to support your decision:

23. Risk of bias from missing outcome data

Low High Unclear [Clear Response](#)

(Instructions to review coordinator: repeat these questions for any additional main outcome or class of outcomes.)

Selective Outcome Reporting

Are reports of the study free of suggestion of selective outcome reporting? Select the statement below that best characterizes the completeness of outcome reporting.

- The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way.
- The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified. (Note to refer: convincing text of this nature may be uncommon.)

[Clear Response](#)

Provide text fragments from the manuscript or other evidence to support your decision:

Risk of Biases from Selective Outcome Reporting

Low High Unclear [Clear Response](#)

(Instructions to review coordinator: repeat these questions for any additional main outcome or class of outcomes.)

Other Sources of Bias

State any important concerns about bias not addressed in the other domains in the tool. Was the study apparently free of other problems that could put it at a high risk of bias?

Select the responses that apply:

The study appears to be free of other sources of bias.

[Clear Response](#)

Provide text fragments from the manuscript or other evidence to support your decision:

and go to

Figure B-19. Risk of bias for observational studies

RefId: 1. There and Back Again: A Review of Residency and Return Migrations in Sharks, with Implications for Population Structure and Management.
Chapman DD, Feldheim KA, Papastamatiou Y, Hueter RE

Submit Form and go to or Skip to Next  

Risk of bias assessment

1. BIAS DUE TO CONFOUNDING

Signalling question	Description	Location in text or source <small>reference, pg. & #/fig/table/other</small>
<p>1.1 Is there potential for confounding of the effect of intervention in this study?</p> <p>If N/PN to 1.1: the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered</p> <p><input type="radio"/> Yes <input type="radio"/> Probably yes <input type="radio"/> Probably no <input type="radio"/> No Clear Response</p>	<input type="text"/>	<input type="text"/>
<p>If Y/PY to 1.1: determine whether there is a need to assess time-varying confounding:</p> <p>1.2. Was the analysis based on splitting participants' follow up time according to intervention received?</p> <p>If N/PN, answer questions relating to baseline confounding (1.4 to 1.6) If Y/PY, proceed to question 1.3.</p> <p><input type="radio"/> Yes <input type="radio"/> Probably yes <input type="radio"/> Probably no <input type="radio"/> No <input type="radio"/> No information Clear Response</p>	<input type="text"/>	<input type="text"/>
<p>1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?</p> <p>If N/PN, answer questions relating to baseline confounding (1.4 to 1.6) If Y/PY, answer questions relating to both baseline and time-varying confounding (1.7 and 1.8)</p> <p><input type="radio"/> Yes <input type="radio"/> Probably yes <input type="radio"/> Probably no <input type="radio"/> No <input type="radio"/> No information Clear Response</p>	<input type="text"/>	<input type="text"/>

<i>Questions relating to baseline confounding only</i>		
<p>14. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?</p> <p><input type="radio"/> Yes <input type="radio"/> Probably yes <input type="radio"/> Probably no <input type="radio"/> No <input type="radio"/> No information Clear Response</p>	<input type="text"/>	<input type="text"/>
If Y/PY to 14		
<p>15. Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?</p> <p><input type="radio"/> Yes <input type="radio"/> Probably yes <input type="radio"/> Probably no <input type="radio"/> No <input type="radio"/> No information Clear Response</p>	<input type="text"/>	<input type="text"/>
<p>16. Did the authors control for any post-intervention variables that could have been affected by the intervention?</p> <p><input type="radio"/> Yes <input type="radio"/> Probably yes <input type="radio"/> Probably no <input type="radio"/> No <input type="radio"/> No information Clear Response</p>	<input type="text"/>	<input type="text"/>
<i>Questions relating to baseline and time-varying confounding</i>		
<p>17. Did the authors use an appropriate analysis method that adjusted for all the important confounding domains and for timevarying confounding?</p> <p><input type="radio"/> Yes <input type="radio"/> Probably yes <input type="radio"/> Probably no <input type="radio"/> No <input type="radio"/> No information Clear Response</p>	<input type="text"/>	<input type="text"/>
If Y/PY to 17		
<p>18. Were confounding domains that were adjusted for measured validly and reliably by the variables available in this study?</p> <p><input type="radio"/> Yes <input type="radio"/> Probably yes <input type="radio"/> Probably no <input type="radio"/> No <input type="radio"/> No information Clear Response</p>	<input type="text"/>	<input type="text"/>

<p>DOMAIN 1: RISK OF BIAS JUDGEMENT</p> <p> <input type="radio"/> Low <input type="radio"/> Moderate <input type="radio"/> Serious <input type="radio"/> Critical <input type="radio"/> No information </p> <p>Clear Response</p>	<p>Support for judgement</p> <input type="text"/>	<p>Optional:</p> <p>What is the predicted direction of bias due to confounding?</p> <p> <input type="radio"/> Favours experimental <input type="radio"/> Favours comparator <input type="radio"/> Unpredictable </p> <p>Clear Response</p> <p>Rationale</p> <input type="text"/>
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2. BIAS IN SELECTION OF PARTICIPANTS INTO THE STUDY

Signalling question	Description <small>Plus location in text or source (reference, pg & ¶/fig/table/other)</small>	Location in text or source <small>(reference, pg & ¶/fig/table/other)</small>
<p>2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?</p> <p>If N/PN to 2.1: go to 2.4</p> <p> <input type="radio"/> Yes <input type="radio"/> Probably yes <input type="radio"/> Probably no <input type="radio"/> No <input type="radio"/> No information Clear Response </p>	<input type="text"/>	<input type="text"/>
<p>If Y/PY to 2.1</p> <p>2.2. Were the postintervention variables that influenced selection likely to be associated with intervention?</p> <p> <input type="radio"/> Yes <input type="radio"/> Probably yes <input type="radio"/> Probably no <input type="radio"/> No <input type="radio"/> No information Clear Response </p>	<input type="text"/>	<input type="text"/>

<p>If Y/PY to 2.2</p> <p>2.3 Were the postintervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?</p> <p><input type="radio"/> Yes <input type="radio"/> Probably yes <input type="radio"/> Probably no <input type="radio"/> No <input type="radio"/> No information Clear Response</p>	<input type="text"/>	<input type="text"/>
<p>2.4. Do start of follow-up and start of intervention coincide for most participants?</p> <p><input type="radio"/> Yes <input type="radio"/> Probably yes <input type="radio"/> Probably no <input type="radio"/> No <input type="radio"/> No information Clear Response</p>	<input type="text"/>	<input type="text"/>
<p>If Y/PY to 2.2 and 2.3, or N/PN to 2.4:</p> <p>2.5. Were adjustment techniques used that are likely to correct for the presence of selection biases?</p> <p><input type="radio"/> Yes <input type="radio"/> Probably yes <input type="radio"/> Probably no <input type="radio"/> No <input type="radio"/> No information Clear Response</p>	<input type="text"/>	<input type="text"/>
<p>DOMAIN 2: RISK OF BIAS JUDGEMENT</p> <p><input type="radio"/> Low <input type="radio"/> Moderate <input type="radio"/> Serious <input type="radio"/> Critical <input type="radio"/> No information</p> <p>Clear Response</p>	<p>Support for judgement</p> <input type="text"/>	<p>Optional:</p> <p>What is the predicted direction of bias due to selection of participants into the study?</p> <p><input type="radio"/> Favours experimental <input type="radio"/> Favours comparator <input type="radio"/> Towards null <input type="radio"/> Away from null <input type="radio"/> Unpredictable</p> <p>Clear Response</p> <p>Rationale</p> <input type="text"/>

3. BIAS IN CLASSIFICATION OF INTERVENTIONS

Signalling question	Description Plus location in text or source (reference, pg & ¶/fig/table/other)	Location in text or source <small>(reference, pg & ¶/fig/table/other)</small>
<p>3.1 Were intervention groups clearly defined?</p> <p> <input type="radio"/> Yes <input type="radio"/> Probably yes <input type="radio"/> Probably no <input type="radio"/> No <input type="radio"/> No information Clear Response </p>	<input type="text"/>	<input type="text"/>
<p>3.2 Was the information used to define intervention groups recorded at the start of the intervention?</p> <p> <input type="radio"/> Yes <input type="radio"/> Probably yes <input type="radio"/> Probably no <input type="radio"/> No <input type="radio"/> No information Clear Response </p>	<input type="text"/>	<input type="text"/>
<p>3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?</p> <p> <input type="radio"/> Yes <input type="radio"/> Probably yes <input type="radio"/> Probably no <input type="radio"/> No <input type="radio"/> No information Clear Response </p>	<input type="text"/>	<input type="text"/>
<p>DOMAIN 3: RISK OF BIAS JUDGEMENT</p> <p> <input type="radio"/> Low <input type="radio"/> Moderate <input type="radio"/> Serious <input type="radio"/> Critical <input type="radio"/> No information </p> <p>Clear Response</p>	<p>Support for judgement</p> <input type="text"/>	<p>Optional:</p> <p>What is the predicted direction of bias due to measurement of outcomes or interventions?</p> <p> <input type="radio"/> Favours experimental <input type="radio"/> Favours comparator <input type="radio"/> Towards null <input type="radio"/> Away from null <input type="radio"/> Unpredictable </p> <p>Clear Response</p> <p>Rationale</p> <input type="text"/>

4. BIAS DUE TO DEVIATIONS FROM INTENDED INTERVENTIONS

Signalling question	Description	Location in text or source <small>(reference, pg. #/fig/table/other)</small>
<p>4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?</p> <p><input type="radio"/> Yes <input type="radio"/> Probably yes <input type="radio"/> Probably no <input type="radio"/> No Clear Response</p>	<input type="text"/>	<input type="text"/>
<p>If Y/PY to 4.1</p> <p>4.2. Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?</p> <p>If your aim for this study is to assess the effect of starting and adhering to intervention, answer questions 4.3 to 4.6</p> <p><input type="radio"/> Yes <input type="radio"/> Probably yes <input type="radio"/> Probably no <input type="radio"/> No <input type="radio"/> No information Clear Response</p>	<input type="text"/>	<input type="text"/>
<p>4.3. Were important co-interventions balanced across intervention groups?</p> <p><input type="radio"/> Yes <input type="radio"/> Probably yes <input type="radio"/> Probably no <input type="radio"/> No <input type="radio"/> No information Clear Response</p>	<input type="text"/>	<input type="text"/>
<p>4.4. Was the intervention implemented successfully for most participants?</p> <p><input type="radio"/> Yes <input type="radio"/> Probably yes <input type="radio"/> Probably no <input type="radio"/> No <input type="radio"/> No information Clear Response</p>	<input type="text"/>	<input type="text"/>
<p>4.5. Did study participants adhere to the assigned intervention regimen?</p> <p><input type="radio"/> Yes <input type="radio"/> Probably yes <input type="radio"/> Probably no <input type="radio"/> No <input type="radio"/> No information Clear Response</p>	<input type="text"/>	<input type="text"/>
<p>If N/PN to 4.3, 4.4 or 4.5</p> <p>4.6. Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?</p> <p><input type="radio"/> Yes <input type="radio"/> Probably yes <input type="radio"/> Probably no <input type="radio"/> No <input type="radio"/> No information Clear Response</p>	<input type="text"/>	<input type="text"/>

<p>DOMAIN 4: RISK OF BIAS JUDGEMENT</p> <p> <input type="radio"/> Low <input type="radio"/> Moderate <input type="radio"/> Serious <input type="radio"/> Critical <input type="radio"/> No information </p> <p>Clear Response</p>	<p>Support for judgement</p> <div style="border: 1px solid #ccc; height: 40px; width: 100%;"></div> <p>Optional:</p> <p>What is the predicted direction of bias due to deviations from the intended interventions?</p> <p> <input type="radio"/> Favours experimental <input type="radio"/> Favours comparator <input type="radio"/> Towards null <input type="radio"/> Away from null <input type="radio"/> Unpredictable </p> <p>Clear Response</p> <p>Rationale</p> <div style="border: 1px solid #ccc; height: 20px; width: 100%;"></div>
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5. BIAS DUE TO MISSING DATA

Signalling question	Description	Location in text or source
<p>5.1 Were outcome data available for all, or nearly all, participants?</p> <p> <input type="radio"/> Yes <input type="radio"/> Probably yes <input type="radio"/> Probably no <input type="radio"/> No Clear Response </p>	<div style="border: 1px solid #ccc; height: 20px; width: 100%;"></div>	<div style="border: 1px solid #ccc; height: 20px; width: 100%;"></div>
<p>5.2 Were participants excluded due to missing data on intervention status?</p> <p> <input type="radio"/> Yes <input type="radio"/> Probably yes <input type="radio"/> Probably no <input type="radio"/> No <input type="radio"/> No information Clear Response </p>	<div style="border: 1px solid #ccc; height: 20px; width: 100%;"></div>	<div style="border: 1px solid #ccc; height: 20px; width: 100%;"></div>
<p>5.3 Were participants excluded due to missing data on other variables needed for the analysis?</p> <p> <input type="radio"/> Yes <input type="radio"/> Probably yes <input type="radio"/> Probably no <input type="radio"/> No <input type="radio"/> No information Clear Response </p>	<div style="border: 1px solid #ccc; height: 20px; width: 100%;"></div>	<div style="border: 1px solid #ccc; height: 20px; width: 100%;"></div>

<p>If PN/N to 5.1, or Y/PY to 5.2 or 5.3</p> <p>5.4 Are the proportion of participants and reasons for missing data similar across interventions?</p> <p><input type="radio"/> Yes <input type="radio"/> Probably yes <input type="radio"/> Probably no <input type="radio"/> No <input type="radio"/> No information Clear Response</p>	<input type="text"/>	<input type="text"/>
<p>If PN/N to 5.1, or Y/PY to 5.2 or 5.3</p> <p>5.5 Is there evidence that results were robust to the presence of missing data?</p> <p><input type="radio"/> Yes <input type="radio"/> Probably yes <input type="radio"/> Probably no <input type="radio"/> No <input type="radio"/> No information Clear Response</p>	<input type="text"/>	<input type="text"/>
<p>DOMAIN 5: RISK OF BIAS JUDGEMENT</p> <p><input type="radio"/> Low</p> <p><input type="radio"/> Moderate</p> <p><input type="radio"/> Serious</p> <p><input type="radio"/> Critical</p> <p><input type="radio"/> No Information</p> <p>Clear Response</p>	<p>Support for judgement</p> <input type="text"/>	<p>Optional:</p> <p>What is the predicted direction of bias due to missing data?</p> <p><input type="radio"/> Favours experimental</p> <p><input type="radio"/> Favours comparator</p> <p><input type="radio"/> Towards null</p> <p><input type="radio"/> Away from null</p> <p><input type="radio"/> Unpredictable</p> <p>Clear Response</p> <p>Rationale</p> <input type="text"/>

6. BIAS IN MEASUREMENT OF OUTCOMES

Signalling question	Description	Location in text or source <small>(reference, pg. C, RT/fig/table/other)</small>
<p>6.1 Could the outcome measure have been influenced by knowledge of the intervention received?</p> <p><input type="radio"/> Yes <input type="radio"/> Probably yes <input type="radio"/> Probably no <input type="radio"/> No Clear Response</p>	<input type="text"/>	<input type="text"/>
<p>6.2 Were outcome assessors aware of the intervention received by study participants?</p> <p><input type="radio"/> Yes <input type="radio"/> Probably yes <input type="radio"/> Probably no <input type="radio"/> No <input type="radio"/> No information Clear Response</p>	<input type="text"/>	<input type="text"/>
<p>6.3 Were the methods of outcome assessment comparable across intervention groups?</p> <p><input type="radio"/> Yes <input type="radio"/> Probably yes <input type="radio"/> Probably no <input type="radio"/> No <input type="radio"/> No information Clear Response</p>	<input type="text"/>	<input type="text"/>

<p>6.4 Were any systematic errors in measurement of the outcome related to intervention received?</p> <p> <input type="radio"/> Yes <input type="radio"/> Probably yes <input type="radio"/> Probably no <input type="radio"/> No <input type="radio"/> No information Clear Response </p>	<input type="text"/>	<input type="text"/>
<p>DOMAIN 6: RISK OF BIAS JUDGEMENT</p> <p> <input type="radio"/> Low <input type="radio"/> Moderate <input type="radio"/> Serious <input type="radio"/> Critical <input type="radio"/> No information </p> <p>Clear Response</p>	<p>Support for judgement</p> <input type="text"/>	<p>Optional</p> <p>What is the predicted direction of bias due to measurement of outcomes?</p> <p> <input type="radio"/> Favours experimental <input type="radio"/> Favours comparator <input type="radio"/> Towards null <input type="radio"/> Away from null <input type="radio"/> Unpredictable </p> <p>Clear Response</p> <p>Rationale</p> <input type="text"/>

7. BIAS IN SELECTION OF REPORTED RESULT

Signalling question	Description <small>Plus location in text or source (reference, pg & #/fig/table/other)</small>	Location in text or source <small>(reference, pg & #/fig/table/other)</small>
<p>Is the reported effect estimate likely to be selected, on the basis of the results, from_</p> <p>7.1 _ multiple outcome measurements within the outcome domain?</p> <p> <input type="radio"/> Yes <input type="radio"/> Probably yes <input type="radio"/> Probably no <input type="radio"/> No <input type="radio"/> No information Clear Response </p>	<input type="text"/>	<input type="text"/>
<p>7.2 _ multiple analyses of the intervention-outcome relationship?</p> <p> <input type="radio"/> Yes <input type="radio"/> Probably yes <input type="radio"/> Probably no <input type="radio"/> No <input type="radio"/> No information Clear Response </p>	<input type="text"/>	<input type="text"/>
<p>7.3 _ different <i>subgroups</i>?</p> <p> <input type="radio"/> Yes <input type="radio"/> Probably yes <input type="radio"/> Probably no <input type="radio"/> No <input type="radio"/> No information Clear Response </p>	<input type="text"/>	<input type="text"/>

DOMAIN 7: RISK OF BIAS JUDGEMENT

- Low
- Moderate
- Serious
- Critical
- No Information

[Clear Response](#)

Support for judgement

Optional:

What is the predicted direction of bias due to measurement of outcomes or intervention?

- Favours experimental
- Favours comparator
- Towards null
- Away from null
- Unpredictable

[Clear Response](#)

Rationale:

OVERALL BIAS

RISK OF BIAS JUDGEMENT

- Low
- Moderate
- Serious
- Critical
- No Information

[Clear Response](#)

Support for judgement

Optional:

What is the predicted direction of bias due to measurement of outcomes or intervention?

- Favours experimental
- Favours comparator
- Towards null
- Away from null
- Unpredictable

[Clear Response](#)

Rationale:

Appendix C. Included and Excluded Articles

Included Articles

1. Abdelgalel EF. Dexmedetomidine versus haloperidol for prevention of delirium during non-invasive mechanical ventilation. *Egyptian Journal of Anaesthesia*. 2016;32(4):473-81. doi: 10.1016/j.egja.2016.05.008.
2. Agar MR, Lawlor PG, Quinn S, et al. Efficacy of Oral Risperidone, Haloperidol, or Placebo for Symptoms of Delirium Among Patients in Palliative Care: A Randomized Clinical Trial. *JAMA Intern Med*. 2017 Jan 1;177(1):34-42. doi: 10.1001/jamainternmed.2016.7491. PMID: 27918778.
3. Al-Qadheeb NS, Skrobik Y, Schumaker G, et al. Preventing ICU Subsyndromal Delirium Conversion to Delirium With Low-Dose IV Haloperidol: A Double-Blind, Placebo-Controlled Pilot Study. *Crit Care Med*. 2016 Mar;44(3):583-91. doi: 10.1097/ccm.0000000000001411. PMID: 26540397.
4. Atalan N, Efe Sevim M, Akgun S, et al. Morphine is a reasonable alternative to haloperidol in the treatment of postoperative hyperactive-type delirium after cardiac surgery. *J Cardiothorac Vasc Anesth*. 2013 Oct;27(5):933-8. doi: 10.1053/j.jvca.2013.01.017. PMID: 23791495.
5. Bakri MH, Ismail EA, Ibrahim A. Comparison of dexmedetomidine or ondansetron with haloperidol for treatment of postoperative delirium in trauma patients admitted to intensive care unit: Randomized controlled trial. *Anaesthesia, Pain and Intensive Care*. 2015;19(2):118-23.
6. Boettger S, Breitbart W, Passik S. Haloperidol and risperidone in the treatment of delirium and its subtypes. *European Journal of Psychiatry*. 2011;25(2):59-67.
7. Boettger S, Jenewein J, Breitbart W. Haloperidol, risperidone, olanzapine and aripiprazole in the management of delirium: A comparison of efficacy, safety, and side effects. *Palliative & supportive care*. 2015;13(4):1079-85. doi: 10.1017/s1478951514001059.
8. Breitbart W, Marotta R, Platt MM, et al. A double-blind trial of haloperidol, chlorpromazine, and lorazepam in the treatment of delirium in hospitalized AIDS patients. *Am J Psychiatry*. 1996 Feb;153(2):231-7. doi: 10.1176/ajp.153.2.231. PMID: 8561204.
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11. Charoenporn V. Efficacy and safety of antipsychotic medications in the treatment of delirium. *Journal of the Medical Association of Thailand*. 2018;101(3):361-6.
12. Devlin JW, Roberts RJ, Fong JJ, et al. Efficacy and safety of quetiapine in critically ill patients with delirium: a prospective, multicenter, randomized, double-blind, placebo-controlled pilot study. *Crit Care Med*. 2010 Feb;38(2):419-27. doi: 10.1097/CCM.0b013e3181b9e302. PMID: 19915454.
13. Drinkwater B, Billyard T. Effect of intravenous haloperidol on the duration of delirium and coma in critically ill patients (hope-ICU). *Journal of the Intensive Care Society*. 2014;15(2):167-8. doi: 10.1177/175114371401500218.
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Excluded Articles

1. Anon. Antipsychotics in the treatment of delirium in the palliative phase? *Geneesmiddelenbulletin*. 2017;51(2):23-4. -**No original data**
2. Anon. Effect of haloperidol on survival among critically ill adults with a high risk of delirium: The REDUCE randomised controlled trial. *J Intensive Care Soc*. 2019 Feb;20(1):74-6. doi: 10.1177/1751143718799920. PMID: 30792766. -**No original data**
3. Anon. Haloperidol or Placebo? Similar Outcomes for Treating Delirium. *AACN Bold Voices*. 2014;6(1):13-. PMID: 104135047. Language: English. Entry Date: 20140110. Revision Date: 20150710. Publication Type: Journal Article. -**No original data**
4. Anon. In patients receiving palliative care, risperidone or haloperidol increased delirium symptoms vs placebo. *Annals of internal medicine*. 2017;166(6):JC32. doi: 10.7326/acpjc-2017-166-6-032. PMID: CN-01616421. -**Meeting abstract**
5. Anon. Quetiapine + haloperidol = faster resolution of ICU delirium. *Journal of the National Medical Association*. 2010;102(7):662. -**Meeting abstract**
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Appendix D. Evidence Tables

Evidence Table D-1. Study design characteristics for studies comparing interventions to prevent development of delirium

Author, year	Study design	Location	Subgroup	Patient population	Start year	Funding
Abdelgalel, 2016 ¹	RCT	Africa: Egypt	ICU	Adult intensive care patients of ASA physical status III and IV aged between 26 and 70 years	2014	Not reported
Al-Qadheeb, 2016 ²	RCT	United States	ICU	MV patients with subsyndromal delirium	Not reported	Government
Fukata, 2014 ³	RCT	Asia: Japan	Aged 65+, post-operative	Delirium after abdominal or orthopedic surgery in elderly patients	2007	Government, Other: National Center for Geriatrics and Gerontology (NCGG),
Girard, 2010 ⁴	RCT	United States	ICU, post-operative	> 18 years MV medical and surgical ICU patients	2005	Industry, Government, Nonprofit, Other: The Hartford Geriatrics Health Outcomes Research Scholars Award Program
Hakim, 2012 ⁵	RCT	Africa: Egypt	Aged 65+, post-operative	Patients 65 years or older experiencing subsyndromal delirium after on-pump cardiac surgery	2007	Not reported
Kalisvaart, 2005 ⁶	RCT	Europe: Netherlands	Post-operative	Acute or elective hip surgery patients ≥ 70 years is at risk of delirium: MMSE between less than or equal to 24; dehydration=BUN/creatinine greater than or equal to 18, low visual acuity and/or increased severity of illness on APACHE II of 16 or greater.	2000	Other: Medical Center Alkmaar
Kaneko, 1999 ⁷	RCT	Asia: Japan	ICU, post-operative	Scheduled for elective gastrointestinal surgery and admitted to ICU	1995	Not reported
Khan, 2018 ⁸	RCT	United States	ICU, post-operative	English speaking individuals undergoing thoracic surgery	2013	Government
Larsen, 2010 ⁹	RCT	United States	Aged 65+, post-operative	Post-operative elderly joint replacement surgery patients	2005	Nonprofit
Page, 2013 ¹⁰	RCT	Europe: UK	ICU	ICU patients needing MV within 72 hours of admission were enrolled	2010	Government

Author, year	Study design	Location	Subgroup	Patient population	Start year	Funding
Prakanrattana, 2007 ¹¹	RCT	Asia: Thailand	Post-operative	Elective Cardiac Surgery with cardiopulmonary bypass	Not reported	Other: Sriraj Grant for Research Development
Schrijver, 2018 ¹²	RCT	Europe: Netherlands	Aged 65+	Medical and surgical patients	2012	Other: Dutch Hospital Patient Safety Program
Schrijver, 2018 ¹³	RCT	Europe: Netherlands	Aged 65+	Medical and surgical patients age 70 and above, with at least three ECGs	2012	Other: Dutch Hospital Patient Safety Program
van den Boogaard, 2013 ¹⁴	Prospective cohort with a comparison group, analyzed as a single group	Europe: the Netherlands	ICU	Patients in the ICU who are at a high risk of delirium	2010	Not reported
van den Boogaard, 2018 ¹⁵	RCT	Europe: Netherlands	ICU	ICU patients at high risk of delirium	2013	Nonprofit
Wang, 2012 ¹⁶	RCT	Asia: China	Aged 65+, ICU	Patients 65 or older admitted to the ICU after noncardiac surgery	2009	Not reported

APACHE II= Acute Physiology and Chronic Health Evaluation 2; ASA=American Society of Anesthesiologists; BUN=blood urea nitrogen ratio; ICU=intensive care unit; MMSE=Mini-Mental State Examination; MV=mechanical ventilation; NCGG=National Center for Geriatrics and Gerontology; RCT=randomized controlled trial

Evidence Table D-2. Study design characteristics for studies comparing interventions to treat delirium

Author, year	Study design	Location	Subgroup	Patient population	Start year	Funding
Agar, 2017 ¹⁷	RCT	Australia: Australia	Palliative	Patients in Hospice and palliative care with delirium	2008	Government
Atalan, 2013 ¹⁸	RCT	Asia: Turkey	Post-operative	Post cardiac surgery patients with hyperactive type delirium	2010	Not reported
Bakri, 2015 ¹⁹	RCT	Asia: Saudi Arabia	ICU	ICU trauma patients without severe injury, comatose, or moribund patients were excluded	Not reported	None
Boettger, 2011 ²⁰	Cohort w/ comparison group	United States	None	Cancer patients	2004	None
Boettger, 2015 ²¹	Cohort w/ comparison group	United States	None	Cancer patients	2000	None
Breitbart, 1996 ²²	RCT	United States	None	Medically hospitalized adult patients with AIDS and a DRS score of 13 or greater (delirium)	Not reported	Government
Breitbart, 2002 ²³	Cohort w/o comparison group	United States	None	Cancer patients	2000	Not reported
Carrasco, 2016 ²⁴	Cohort w/ comparison group	Europe: Spain	Aged 65+, ICU	Non-intubated ICU patients refractory to haloperidol	2013	Other: no external funding
Charoenporn, 2018 ²⁵	Cohort w/ comparison group	Asia: Thailand	None	Physically ill patients	2015	None
Devlin, 2010 ²⁶	RCT	North America (not US): United States, Canada	ICU	Patients admitted to Medical & Surgical ICU with delirium.	2006	Industry, Nonprofit
Drinkwater, 2014 ²⁷	RCT	Europe: UK	ICU	Adult patients requiring mechanical ventilation within 72 hours of ICU admission	Not reported	Not reported
Fox, 2018 ²⁸	Cohort w/ comparison group	United States	ICU	Critically ill patients in the medical and cardiovascular ICU	2014	None
Girard, 2010 ⁴	RCT	United States	ICU, post-operative	> 18 years MV medical and surgical ICU patients	2005	Industry, Government, Nonprofit, Other: The Hartford Geriatrics Health Outcomes Research Scholars Award Program
Girard, 2018 ²⁹	RCT	United States	ICU	Patients over 18 years of age in the medical or surgical ICU, with delirium	2011	Government
Grover, 2011 ³⁰	RCT	Asia: India	None	Consecutive patients >-18 yo referred to psychiatry and diagnosed with delirium	Not reported	Government
Grover, 2016 ³¹	RCT	Asia: India	None	Patients >18 years old referred to Psychiatry who met DSM-IV criteria for delirium	Not reported	Not reported
Han, 2004 ³²	RCT	Asia: South Korea	None	All patients presenting with altered mental status (from both ICU and non-ICU units) who were referred to the consulting psychiatry division were evaluated.	Not reported	Government
Hatta, 2014 ³³	Cohort w/ comparison group	Asia: Japan	None	Patients in a general hospital who developed delirium and were managed by a psychiatrist	2011	Nonprofit

Author, year	Study design	Location	Subgroup	Patient population	Start year	Funding
Horikawa, 2003 ³⁴	Cohort w/o comparison group	Asia: Japan	None	Medical and surgical inpatients	2001	Not reported
Hu, 2006 ³⁵	RCT	Asia: China	Aged 65+	Inpatients with senile delirium aged 65-99	2001	Not reported
Hui, 2017 ³⁶	Randomized controlled trial, analyzed as cohort	United States	Palliative	Advanced cancer patients with hyperactive or mixed delirium in the acute palliative care unit	2014	Government, Nonprofit
Ikezawa, 2008 ³⁷	Open-label trial	Asia: Japan	None	Elderly patients with hyperactive-hypervallent delirium	1998	Not reported
Jain, 2017 ³⁸	RCT	Asia: India	None	Medical and surgical inpatients	2011	None
Kim, 2001 ³⁹	Open label study	Asia: South Korea	None	Medico-surgical patients from Neurology, Neurosurgery and BMT unit	Not reported	Not reported
Kim, 2003 ⁴⁰	Cohort w/o comparison group	United States	None	Patients in the acute medical units	Not reported	Industry
Kim, 2005 ⁴¹	Cohort w/ comparison group	Asia: South Korea	None	Hospital patients referred to the psychiatry division	Not reported	Not reported
Kim, 2010 ⁴²	RCT	Asia: Korea	None	General hospital inpatients who met DSM-IV diagnostic criteria for delirium	Not reported	Nonprofit
Kishi, 2012 ⁴³	Cohort w/o comparison group	Asia: Japan	None	Delirious cancer patients	Not reported	Not reported
Konkayev, 2015 ⁴⁴	Cohort w/ comparison group	Asia: Kazakhstan	Aged 65+, ICU, post-operative	Patients who needed surgery for a traumatology or orthopedic condition and had to stay in the ICU	2012	Not reported
Lee, 2005 ⁴⁵	RCT	Asia: South Korea	None	Patients referred to the Psychiatric Consultation that met DSM-IV criteria for delirium	Not reported	Not reported
Lim, 2007 ⁴⁶	RCT	Asia: Korea	None	Patients from internal medicine, PMR, neurology, neurosurgery, orthopedic surgery, or general surgery that were referred to the psychiatric department	2006	Not reported
Lin, 2008 ⁴⁷	RCT	Asia: Taiwan	Palliative	Patients receiving hospice or palliative care with advanced cancer and met DSM-IV criteria for delirium	2003	Not reported
Maneeton, 2007 ⁴⁸	Open-label study	Asia: Thailand	None	All physically ill in-patients whose pcp consulted psychiatrists	2005	None
Maneeton, 2013 ⁴⁹	RCT	Asia: Thailand	None	General adult population (age 18-75) with hyperactive delirium, referred to psychiatry consult liaison service at tertiary care hospital in Thailand	2009	Nonprofit
Mittal, 2004 ⁵⁰	Cohort w/o comparison group	United States	None	Hospitalized patients	2000	Industry
Naksuk, 2017 ⁵¹	Case control analyzed as cohort with comparison group	United States	ICU	Patients admitted to the coronary care unit	2004	None
Omura, 2003 ⁵²	Cohort w/o comparison group	Asia: Japan	Aged 65+	Hospitalized patients	2001	Not reported
Pae, 2004 ⁵³	Cohort w/o comparison group	Asia: S. Korea	None	Delirious patients recruited from the departments of neurosurgery, orthopedic surgery, and oncology	Not reported	Industry
Page, 2013 ¹⁰	RCT	Europe: UK	ICU	ICU patients needing MV within 72 hours of admission were enrolled	2010	Government
Parellada, 2004 ⁵⁴	Cohort w/o comparison group	Europe: Spain	None	General hospital patients	2000	Industry

Author, year	Study design	Location	Subgroup	Patient population	Start year	Funding
Sasaki, 2003 ⁵⁵	Cohort w/o comparison group	Asia: Japan	None	Inpatients and outpatients	2001	Not reported
Sipahimalani, 1998 ⁵⁶	Cohort w/ comparison group	United States	None	Hospital patients	Not reported	Not reported
Skrobik, 2004 ⁵⁷	Cohort w/ comparison group	North America (not US): Canada	ICU	Medical-surgical ICU	2000	Industry
Straker, 2006 ⁵⁸	Cohort w/o comparison group	Not reported	None	Medically ill delirium patients	2004	Not reported
Tahir, 2010 ⁵⁹	RCT	Europe: Wales	None	Patients in medical, surgical and orthopedic wards, who met the DSM-IV criteria for delirium on the same day if they had a DRS-R-98 total score of 15 or more	2003	Industry
Toda, 2005 ⁶⁰	Cohort w/o comparison group	Asia: Japan	None	Hospital patients with delirium	Not reported	Not reported
Yoon, 2011 ⁶¹	Open-label pilot trial	Asia: Korea	None	Patients who were referred to psychiatrists at Korea University Ansan Hospital	2009	Not reported
Yoon, 2013 ⁶²	Cohort w/ comparison group	Asia: Korea	None	Referred to consultation-liaison psychiatric service for a mental status change	Not reported	Not reported

DRS-R-98=Delirium Rating Scale Revised-98; DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th ed.; ICU=intensive care unit; MV=mechanical ventilation; RCT=randomized clinical trial; US=United States

Evidence Table D-3. Patient characteristics for studies comparing interventions to prevent development of delirium

Author, year	Arm	N	Age, mean	Male, n (%)	Dementia, n (%)	Substance use disorder, n (%)	Hypertension, n (%)	Comments
Abdelgalel, 2016 ¹	1	30	49.1	21 (70)	0 (0)	Not reported	Not reported	
	2	30	51	22 (73)	0 (0)	Not reported	Not reported	
	3	30	51.1	24 (80)	0 (0)	Not reported	Not reported	
Al-Qadheeb, 2016 ²	1	34	59.3	20 (58.8)	0 (0)	Alcohol use - moderate: 16 (47.1)	Not reported	
	2	34	61.7	18 (52.9)	0 (0)	Alcohol use - moderate: 14 (41.1)	Not reported	
Fukata, 2014 ³	1	62	80.2	32 (52)	Not reported	Not reported	Not reported	Considered high risk for postoperative delirium groups as preoperative MMSE < 25 and preoperative NEECHAM < 27
	2	59	80.5	32 (54)	Not reported	Not reported	Not reported	Considered high risk for postoperative delirium groups as preoperative MMSE < 25 and preoperative NEECHAM < 27
Girard, 2010 ⁴	1	36	Median: 56	22 (61)	Not reported	Not reported	Not reported	
	2	35	Median: 51	20 (57)	Not reported	Not reported	Not reported	
	3	30	Median: 54	21 (70)	Not reported	Not reported	Not reported	
Hakim, 2012 ⁵	1	50	Percent over age 65: 100	36 (72)	0 (0)	Not reported	Not reported	
	2	51	Percent over age 65: 100	33 (65)	0 (0)	Not reported	Not reported	
Kalisvaart, 2005 ⁶	1	218	79.57	47 (21.6)	Not reported	Not reported	Not reported	
	2	212	78.71	40 (18.9)	Not reported	Not reported	Not reported	
Kaneko, 1999 ⁷	1	40	73.1	26 (65)	Not reported	Not reported	12 (30)	
	2	40	72.4	24 (60)	Not reported	Not reported	13 (34.2)	
Khan, 2018 ⁸	1	67	Median: 62.3 (IQR 52.6 to 69.2)	54 (80.6)	Not reported	Not reported	Not reported	
	2	68	Median: 60 (IQR to 51.8-68)	46 (67.6)	Not reported	Not reported	Not reported	
Larsen, 2010 ⁹	1	204	74	81 (39.7)	0 (0)	Not reported	Not reported	123 in placebo group and 94 in Olanzapine group are females
	2	196	73.4	102 (52)	0 (0)	Not reported	Not reported	123 in placebo group and 94 in Olanzapine group are females
Page, 2013 ¹⁰	1	70	68.7	45 (64)	0 (0)	Not reported	Not reported	
	2	71	67.9	37 (52)	0 (0)	Not reported	Not reported	
Prakanrattana, 2007 ¹¹	1	63	60.7	38 (60)	Not reported	Not reported	26 (41)	
	2	63	61.3	36 (57)	Not reported	Not reported	27 (43)	
Schrijver, 2018 ¹²	1	124	83.4	51 (41)	Not reported	Not reported	Not reported	
	2	118	83.5	57 (48)	Not reported	Not reported	Not reported	
Schrijver, 2018 ¹³	1	34	93.7	13 (38.2)	Not reported	Not reported	20 (58.8)	
	2	38	81.6	20 (52.6)	Not reported	Not reported	22 (57.9)	
van den Boogaard, 2013 ¹⁴	1	177	63	115 (65)	2 (1)	Alcohol abuse: 20 (11)	Not reported	

Author, year	Arm	N	Age, mean	Male, n (%)	Dementia, n (%)	Substance use disorder, n (%)	Hypertension, n (%)	Comments
van den Boogaard, 2018 ¹⁵	1	707	67	434 (61)	0 (0)	Not reported	Not reported	
	2	350	66.1	206 (59)	0 (0)	Not reported	Not reported	
	3	732	66.7	459 (63)	0 (0)	Not reported	Not reported	
Wang, 2012 ¹⁶	1	228	74.4	143 (62.7)	Not reported	Alcoholism: 19 (8.3)	125 (54.8)	
	2	229	74	145 (63.3)	Not reported	Alcoholism: 14 (6.1)	128 (55.9)	

MMSE=Mini-Mental State Examination; MV=mechanical ventilation; N=sample size; NEECHAM=Neelon and Champagne Confusion Scale

Evidence Table D-4. Patient characteristics for studies comparing interventions to treat delirium

Author, year	Arm	N	Age, mean	Male, n (%)	Dementia, n (%)	Substance use disorder, n (%)	Hypertension, n (%)	Comments
Agar, 2017 ¹⁷	1	84	73.8 (Percent over age 65: 80)	57 (68)	Not reported	Not reported	Not reported	
	2	81	76.5 (Percent over age 65: 90)	48 (59)	Not reported	Not reported	Not reported	
	3	82	74.5 (Percent over age 65: 78)	57 (70)	Not reported	Not reported	Not reported	
Atalan, 2013 ¹⁸	1				Not reported	Not reported	16 (61.5)	
	2	26	66	21 (80.2)	0 (0)	Not reported	Not reported	
Bakri, 2015 ¹⁹	1	32	31	29 (91)	Not reported	Not reported	Not reported	
	2	32	30	28 (88)	Not reported	Not reported	Not reported	
	3	32	32	30 (94)	Not reported	Not reported	Not reported	
Boettger, 2011 ²⁰	1	32	61.97	20 (62.5)	Not reported	Not reported	Not reported	
	2	32	67.5	20 (62.5)	Not reported	Not reported	Not reported	
Boettger, 2015 ²¹	1	21	69.6 (Range: 36 to 85)	(47.6)	(28.6)	Not reported	Not reported	
	2	21	64 (Range: 36 to 79)	(38.1)	(23.8)	Not reported	Not reported	
	3	21	65.6 (Range: 51 to 84)	(38.1)	(28.6)	Not reported	Not reported	
	4	21	67.2 (Range: 29 to 84)	(47.6)	(23.8)	Not reported	Not reported	
Breitbart, 1996 ²²	1	13	Not reported	Not reported	Not reported	Not reported	Not reported	Demographic data given as overall sample: Age: 39.2 (Range 23-56); N=23 (77%) men; dementia, substance use disorder, and hypertension data not reported.
	2	11	Not reported	Not reported	Not reported	Not reported	Not reported	Demographic data given as overall sample: Age: 39.2 (Range 23-56); N=23 (77%) men; dementia, substance use disorder, and hypertension data not reported.
	3	6	Not reported	Not reported	Not reported	Not reported	Not reported	Demographic data given as overall sample: Age: 39.2 (Range 23-56); N=23 (77%) men; dementia, substance use disorder, and hypertension data not reported.

Author, year	Arm	N	Age, mean	Male, n (%)	Dementia, n (%)	Substance use disorder, n (%)	Hypertension, n (%)	Comments
Breitbart, 2002 ²³	1	79	60.6 (Range: 19 to 89)	40 (51)	14 (17)	Not reported	Not reported	
Carrasco, 2016 ²⁴	1	86	71.3	77 (90)	Not reported	Not reported	Not reported	
Charoenporn, 2018 ²⁵	1	11	70.5	8 (72.7)	2 (18.2)	Not reported	Not reported	
	2	31	76.4	13 (41.9)	10 (32.3)	Not reported	Not reported	
	3	14	69.4	6 (42.9)	1 (7.1)	Not reported	Not reported	
Devlin, 2010 ²⁶	1	18	63.6	(56)	0 (0)	Not reported	Not reported	
	2	18	62.4	(56)	0 (0)	Not reported	Not reported	
Drinkwater, 2014 ²⁷	1	71	Not reported	Not reported	Not reported	Not reported	Not reported	
	2	71	Not reported	Not reported	Not reported	Not reported	Not reported	
Fox, 2018 ²⁸	1	20	67.2	10 (50)	Not reported	Not reported	Not reported	
	2	20	66	11 (55)	Not reported	Not reported	Not reported	
Girard, 2010 ⁴	1	36	Median: 56	22 (61)	Not reported	Not reported	Not reported	
	2	35	Median: 51	20 (57)	Not reported	Not reported	Not reported	
	3	30	Median: 54	21 (70)	Not reported	Not reported	Not reported	
Girard, 2018 ²⁹	1	184	59	107 (58)	Not reported	Not reported	Not reported	Severe dementia excluded
	2	192	61	108 (56)	Not reported	Not reported	Not reported	Severe dementia excluded
	3	190	61	108 (57)	Not reported	Not reported	Not reported	Severe dementia excluded
Grover, 2011 ³⁰	1	21	44.09 (Percent over age 65: 14) (Range: 20 to 72)	13 (62)	0 (0)	Not reported	Not reported	
	2	23	45.39 (Percent over age 65: 26) (Range: 19 to 78)	14 (61)	0 (0)	Not reported	Not reported	
	3	20	46.5 (Percent over age 65: 10) (Range: 27 to 78)	18 (90)	0 (0)	Not reported	Not reported	
Grover, 2016 ³¹	1	32	44.4 (Range: 18 to 76)	28 (87.5)	0 (0)	Not reported	Not reported	
	2	31	48.51 (Range: 18 to 85)	21 (67.74)	0 (0)	Not reported	Not reported	

Author, year	Arm	N	Age, mean	Male, n (%)	Dementia, n (%)	Substance use disorder, n (%)	Hypertension, n (%)	Comments
Han, 2004 ³²	1	12	66.5	7 (58)	0 (0)	Not reported	Not reported	Patients with any type of dementia or other psychiatric diagnosis determined with the SCID were excluded.
	2	12	65.6	6 (50)	0 (0)	Not reported	Not reported	Patients with any type of dementia or other psychiatric diagnosis determined with the SCID were excluded.
Hatta, 2014 ³³	1	61	70.2	29 (48)	15 (25)	Not reported	Not reported	Age, gender, and presence of comorbid dementia were not balanced across groups.
	2	480	71.9	322 (67)	95 (20)	Not reported	Not reported	Age, gender, and presence of comorbid dementia were not balanced across groups.
	3	87	66.6	53 (61)	17 (20)	Not reported	Not reported	Age, gender, and presence of comorbid dementia were not balanced across groups.
	4	779	74.4	475 (61)	261 (34)	Not reported	Not reported	Age, gender, and presence of comorbid dementia were not balanced across groups.
	5	835	73.5	544 (65)	259 (31)	Not reported	Not reported	Age, gender, and presence of comorbid dementia were not balanced across groups.
Horikawa, 2003 ³⁴	1	10	56.8 (Range: 22 to 81)	6 (60)	Not reported	history of substance abuse: 0 (0)	Not reported	
Hu, 2006 ³⁵	1	29	73	18 (62.1)	Not reported	Not reported	Not reported	
	2	72	74	48 (66.7)	Not reported	Not reported	Not reported	
	3	74	74	45 (60.8)	Not reported	Not reported	Not reported	
Hui, 2017 ³⁶	1	29	64 (Range: 30 to 88)	13 (44.8)	0 (0)	Not reported	Not reported	
Ikezawa, 2008 ³⁷	1	22	73.6 (Range: 60 to 86)	8 (36.4)	Not reported	Not reported	Not reported	Substance use already excluded
Jain, 2017 ³⁸	1	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	
	2	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	
Kim, 2001 ³⁹	1	20	45.8 (Range: 19 to 74)	15 (75)	1 (5)	Not reported	Not reported	
Kim, 2003 ⁴⁰	1	12	74	12 (100)	2 (17)	Not reported	Not reported	

Author, year	Arm	N	Age, mean	Male, n (%)	Dementia, n (%)	Substance use disorder, n (%)	Hypertension, n (%)	Comments
Kim, 2005 ⁴¹	1	24	Not reported	Not reported	0 (0)	Not reported	Not reported	Mean age overall: 71.26 years; 25 were male
	2	18	Not reported	Not reported	0 (0)	Not reported	Not reported	Mean age overall: 71.26 years; 25 were male
Kim, 2010 ⁴²	1	15	68.3	9 (60)	0 (0)	Not reported	Not reported	Reported female gender
	2	17	66.7	9 (53)	0 (0)	Not reported	Not reported	Reported female gender
Kishi, 2012 ⁴³	1	29	68.9	20 (69)	(0)	Not reported	Not reported	
Konkayev, 2015 ⁴⁴	1	30	82.7 (Percent over age 65: 100)	(33.3)	0 (0)	0 (0)	22 (73)	
	2	43	80.3 (Percent over age 65: 100)	(25.5)	0 (0)	0 (0)	26 (60.5)	
Lee, 2005 ⁴⁵	1	15	63.1	8 (53.3)	Not reported	Not reported	Not reported	
	2	16	60.8	12 (75)	Not reported	Not reported	Not reported	
Lim, 2007 ⁴⁶	1	31	67.3	15 (48.4)	Not reported	Not reported	Not reported	
	2	31	66.2	17 (55.8)	Not reported	Not reported	Not reported	
Lin, 2008 ⁴⁷	1	14	68 (Range: 39 to 87)	4 (29)	Not reported	Not reported	Not reported	
	2	16	61.13 (Range: 23 to 80)	9 (56)	Not reported	Not reported	Not reported	
Maneeton, 2007 ⁴⁸	1	17	55.6	10 (58.8)	Not reported	Not reported	Not reported	Mean (SD) age 55.6 (18.6); none of patients had a history of psychiatric illness
Maneeton, 2013 ⁴⁹	1	28	57	20 (71.4)	Not reported	Not reported	Not reported	
	2	24	56.6	15 (62.5)	Not reported	Not reported	Not reported	
Mittal, 2004 ⁵⁰	1	10	64.7	8 (80)	0 (0)	Not reported	Not reported	
Naksuk, 2017 ⁵¹	1	681	Not reported	Not reported	Not reported	Not reported	Not reported	Population characteristics were reported for patients with delirium who received vs. did not receive antipsychotics.
	2	124	Not reported	Not reported	Not reported	Not reported	Not reported	Population characteristics were reported for patients with delirium who received vs. did not receive antipsychotics.
	3	59	Not reported	Not reported	Not reported	Not reported	Not reported	Population characteristics were reported for patients with delirium who received vs. did not receive antipsychotics.
Omura, 2003 ⁵²	1	24	76.5	10 (42)	12 (50)	Not reported	Not reported	
Pae, 2004 ⁵³	1	22	69.1 (Range: 48 to 85)	13 (59)	7 (32)	Not reported	Not reported	
Page, 2013 ¹⁰	1	70	68.7	45 (64)	0 (0)	Not reported	Not reported	
	2	71	67.9	37 (52)	0 (0)	Not reported	Not reported	
Parellada, 2004 ⁵⁴	1	64	67.3	40 (62.5)	Not reported	Not reported	Not reported	

Author, year	Arm	N	Age, mean	Male, n (%)	Dementia, n (%)	Substance use disorder, n (%)	Hypertension, n (%)	Comments
Sasaki, 2003 ⁵⁵	1	12	67.3	10 (83)	Not reported	Not reported	Not reported	
Sipahimalani, 1998 ⁵⁶	1	11	64.5	10 (91)	3 (27)	alcohol dependence: 0 (0)	1 (9)	
	2	11	63.5	6 (55)	3 (27)	alcohol dependence: 2 (18)	1 (9)	
Skrobik, 2004 ⁵⁷	1	45	63.26	31 (69)	Not reported	Not reported	Not reported	
	2	28	67.5	22 (79)	Not reported	Not reported	Not reported	
Straker, 2006 ⁵⁸	1	14	70.9	6 (43)	2 (14)	Not reported	10 (71)	Hypertension data obtained from Table 1.
Tahir, 2010 ⁵⁹	1	21	84.3 (Range: 71 to 98)	6 (28.6)	0 (0)	0 (0)	Not reported	
	2	21	84.1 (Range: 58 to 95)	6 (28.6)	0 (0)	0 (0)	Not reported	
Toda, 2005 ⁶⁰	1	10	61.1	5 (50)	1 (10)	Not reported	Not reported	
Yoon, 2011 ⁶¹	1	15	66.09	8 (53.3)	0 (0)	0 (0)	Not reported	Age : 66.09 (SD 20.69); dementia and substance were excluded
Yoon, 2013 ⁶²	1	23	74	12 (52.2)	0 (0)	Not reported	Not reported	
	2	18	69.5	8 (44.4)	0 (0)	Not reported	Not reported	
	3	18	73.3	8 (44.4)	0 (0)	Not reported	Not reported	
	4	21	70.1	8 (38.1)	0 (0)	Not reported	Not reported	

N=sample size; SCID=severe combined immunodeficiency; SD=standard deviation

Evidence Table D-5. Intervention characteristics for studies comparing interventions to prevent development of delirium

Author, year	Arm	Drug	Route of Administration	Dose	Frequency	Duration	Non-pharmaceutical intervention	Comments
Abdelgalel, 2016 ¹	1	Placebo	Intravenous	Planned dose: 2-8ml, loading dose 10ml over 10 min if needed (if RASS > 2+)	Per hour per day	Not reported	None	
	2	Haloperidol	Intravenous	Planned dose: 0.5– 2 mg/h preceded by a loading dose of 2.5 mg intravenously over 10 min if needed (if RASS > 2+)	Per hour	Not reported	None	
	3	Dexmedetomidine	Intravenous	Planned dose: 0.2–0.7 mcg/kg/h preceded by a loading dose of 1.0 ug/kg intravenously over 10 min if needed (if RASS > 2+)	Per hour	Not reported	None	
Al-Qadheeb, 2016 ²	1	Placebo	Intravenous	Planned dose: 5% dextrose	Four times a day (qid)	Planned duration: 10 days or until discharge	Early mobilization, Pain management	An early mobilization protocol was implemented in one of the three study ICUs part-way through the study
	2	Haloperidol	Intravenous	Planned dose: 1mg	Four times a day (qid)	Planned duration: 10 days or until discharge	Early mobilization, Pain management	1 mg every 6 hours until delirium or therapy ≥ 10 days or ICU discharged occurred; An early mobilization protocol was implemented in one of the three study ICUs part-way through the study;
Fukata, 2014 ³	1	Placebo	Not reported	Not reported	Not reported	Not reported	None	The non-intervention group did not receive preventive treatment, and delirium was evaluated in the same way as in the intervention group
	2	Haloperidol	Intravenous	Planned dose: 2.5mg	Once a day (qd)	Planned duration: 3 days	None	
Girard, 2010 ⁴	1	Placebo	Oral	Planned dose: 5ml	Twice a day (bid)	Median: 5 (IQR 3 to 7) days	None	
	2	Haloperidol	Oral	Planned dose: 5mg Median: 15mg (Range 10.8 to 17mg)	Per Day	Median: 7 (4 to 10)	None	
	3	Ziprasidone	Oral	Planned dose: 40mg Median: 113mg (Range 81 to 140mg)	Per Day	Median: 4 (3 to 10)	None	

Author, year	Arm	Drug	Route of Administration	Dose	Frequency	Duration	Non-pharmaceutical intervention	Comments
Hakim, 2012 ⁵	1	Placebo	Oral	Planned dose: given every 12 hours	Twice a day (bid)	Not reported	Pain management	
	2	Risperidone	Oral	Planned dose: 0.5mg	Twice a day (bid)	Not reported	Pain management	
Kalisvaart, 2005 ⁶	1	Placebo	Oral	Not reported: Not applicable	Three times a day (tid)	Planned duration: Trial medication was started on admission and continued until 3 days after surgery. A maximum delay for surgery of 72 hours was permitted.	Orientation and therapeutic activities, Fluid repletion, Sleep enhancement, Pain management	Enhancement of orientation and cognition; sensory and mobility-improving advice; attention to pain and sleeping problems; extra attention to fluid and food intake
	2	Haloperidol	Oral	Planned dose: 0.5mg	Three times a day (tid)	Planned duration: Trial medication was started on admission and continued until 3 days after surgery. A maximum delay for surgery of 72 hours was permitted.	Orientation and therapeutic activities, Fluid repletion, Sleep enhancement, Pain management	Enhancement of orientation and cognition; sensory and mobility-improving advice; attention to pain and sleeping problems; extra attention to fluid and food intake
Kaneko, 1999 ⁷	1	Placebo	Intravenous	Planned dose: 1 ml (0.9% normal saline)	Once a day (qd)	Planned duration: 5 days post surgery	None	
	2	Haloperidol	Intravenous	Planned dose: 5mg	Once a day (qd)	Planned duration: 5 days post surgery	None	
Khan, 2018 ⁸	1	Placebo	Intravenous	Planned dose: 5mg	3 times daily	Planned duration: 4 days (11 doses total)	None	groups received non-pharma as part of the rescue
	2	Haloperidol	Intravenous	Planned dose: 5mg	3 times daily	Planned duration: 4 days (11 doses total)	None	groups received non-pharma as part of the rescue
Larsen, 2010 ⁹	1	Placebo	Oral	Planned dose: 5mg	Once before and once after surgery	Planned duration: Once before and once after surgery	Pain management	
	2	Olanzapine	Oral	Planned dose: 5mg	Once before and once after surgery	Planned duration: Once before and once after surgery	Pain management	

Author, year	Arm	Drug	Route of Administration	Dose	Frequency	Duration	Non-pharmaceutical intervention	Comments
Page, 2013 ¹⁰	1	Placebo	Intravenous	Planned dose: 0.5ml	Three times a day (tid)	Planned duration: 14 days or 2 consecutive days of delirium free coma free days or until discharge	Early mobilization, Pain management	Study drug was discontinued in all patients on ICU discharge, when the patient was delirium-free for two consecutive days, or after a maximum of 14 days treatment, whichever came first.; The same volumes administered IV: 0.5 ml of study drug (2.5 mg dissolved) and placebo;
	2	Haloperidol	Intravenous	Planned dose: 2.5mg	Three times a day (tid)	Planned duration: 14 days or 2 consecutive days of delirium free coma free days or until discharge	Early mobilization, Pain management	Study drug was discontinued in all patients on ICU discharge, when the patient was delirium-free for two consecutive days, or after a maximum of 14 days treatment, whichever came first.; The same volumes administered IV: 0.5 ml of study drug (2.5 mg dissolved) and placebo;
Prakanrattana, 2007 ¹¹	1	Placebo	Sublingual	Planned dose: Not applicable	Once a day (qd)	Planned duration: 1 day	Pain management	Only one dose of risperidone or placebo after the patient wakes up in the ICU post-operatively; Note that the placebo was a listerine strip.
	2	Risperidone	Orally disintegrating tablet	Planned dose: 1mg	Once a day (qd)	Planned duration: 1 day	Pain management	
Schrijver, 2018 ¹²	1	Placebo	Oral	Not reported	Twice a day (bid)	Mean: 7 days	None	
	2	Haloperidol	Oral	Planned dose: 1mg	Twice a day (bid)	Mean: 7 days	None	
Schrijver, 2018 ¹³	1	Placebo	Oral	Not reported	Twice a day (bid)	Mean: 7 days	None	
	2	Haloperidol	Oral	Planned dose: 1mg	Twice a day (bid)	Mean: 7 days	None	
van den Boogaard, 2013 ¹⁴	1	Haloperidol	Intravenous	Planned dose: 1mg Median: 2mg	Three times a day (tid)	Mean: 5	None	Or a lower dose of 0.5 mg/8h when then were 80 years or older, had a body weight < 50 kg, had a serum creatinine level > 150 umol/L or had a serum bilirubin level > 50 umol/L.

Author, year	Arm	Drug	Route of Administration	Dose	Frequency	Duration	Non-pharmaceutical intervention	Comments
van den Boogaard, 2018 ¹⁵	1	Placebo	Intravenous	Planned dose: 0.9% NaCl	Three times a day (tid)	Planned duration: 28 days	Early mobilization, Vision and hearing, Sleep enhancement	Nonpharmacological delirium interventions are the part of daily ICU care in this study and prophylactic pharmacological study was conducted in addition to this.; Other nonpharmacological interventions reported are reduction of sedation and benzodiazepines, awakening trials.;
	2	Haloperidol	Intravenous	Planned dose: 1mg	Three times a day (tid)	Planned duration: 28 days	Early mobilization, Vision and hearing, Sleep enhancement	Dose of study medication was reduced by 50% of the patients are 80 years or older, had body weight of 50kg or less or had liver failure at the time of inclusion
	3	Haloperidol	Intravenous	Planned dose: 2mg	Three times a day (tid)	Planned duration: 28 days	Early mobilization, Vision and hearing, Sleep enhancement	Lower dose is given for patients aged 80 years or older, had a body weight of 50 kg or less or had liver failure
Wang, 2012 ¹⁶	1	Placebo	Intravenous	Planned dose: Normal saline	Three times a day (tid)	Not applicable	Pain management	Normal saline was used as placebo
	2	Haloperidol	Intravenous	Planned dose: 0.5 mg followed by continuous infusion at a rate of 1 mL/hr (0.1 mg/hr haloperidol)	1 hour after enrollment and continued for 12 hours	Planned duration: 12 hours	Pain management	

bid=twice daily; ICU=intensive care unit; mg/h=milligram per hour; mg=milligram; min=minutes; ml/hr=millimeter per hour; ml=millimeter; NaCl=sodium chloride; qd=once daily; qid=four times a day; RASS=Richmond Agitation and Sedation Scale; tid=three times daily

Evidence Table D-6. Intervention characteristics for studies comparing interventions to treat delirium

Author, year	Arm	Drug	Route of Administration	Dose	Frequency	Duration	Non-pharmaceutical intervention	Comments
Agar, 2017 ¹⁷	1	Placebo	Oral	Titrated dose: Maximum 4 mg/d	Twice a day (bid)	Planned duration: 3 days	Orientation and therapeutic activities, Fluid repletion, Vision and hearing	A 0.5 mg loading dose 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; for those patients over the age of 65 the loading, initial and max doses were one half that listed for the remainder of the population.
	2	Haloperidol	Oral	Titrated dose: Maximum 4 mg/d	Twice a day (bid)	Planned duration: 3 days	Orientation and therapeutic activities, Fluid repletion, Vision and hearing	A 0.5 mg loading dose 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; for those patients over the age of 65 the loading, initial and max doses were one half that listed for the remainder of the population.
	3	Risperidone	Oral	Titrated dose: Maximum 4 mg/d	Twice a day (bid)	Planned duration: 3 days	Orientation and therapeutic activities, Fluid repletion, Vision and hearing	A 0.5 mg loading dose 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; for those patients over the age of 65 the loading, initial and max doses were one half that listed for the remainder of the population.
Atalan, 2013 ¹⁸	1	Haloperidol	Intramuscular	Titrated dose: Maximum 20mg	Per day	Planned duration: Until discharge	Pain management	Postoperative analgesia was achieved by providing 1 g of paracetamol intravenously every 8 hours and 50 mg of dexketoprofen intravenously twice a day. Postoperative pain was recorded once a day using the verbal version of the visual analog scale.
	2	morphine sulfate	Intramuscular	Titrated dose: Maximum 20mg	Per day	Planned duration: Until discharge	Pain management	Postoperative analgesia was achieved by providing 1 g of paracetamol intravenously every 8 hours and 50 mg of dexketoprofen intravenously twice a day. Postoperative pain was recorded once a day using the verbal version of the visual analog scale.

Author, year	Arm	Drug	Route of Administration	Dose	Frequency	Duration	Non-pharmaceutical intervention	Comments
Bakri, 2015 ¹⁹	1	Dexmedetomidine	Intravenous	Planned dose: 1 ug/kg	Twice a day (bid)	Planned duration: 3 days	None	
	2	Haloperidol	Intravenous	Planned dose: 5 mg	Twice a day (bid)	Planned duration: 3 days	None	
	3	Ondansetron	Intravenous	Planned dose: 8 mg	Twice a day (bid)	Planned duration: 3 days	None	
Boettger, 2011 ²⁰	1	Haloperidol	Not reported	Titrated dose: Mean 4.6mg (Range: 1 to 10mg)	Not reported	Not reported	None	Mean dose was 4.6 mg (range 1 to 10 mg) at baseline, 4.9 mg (range 1 to 10 mg) at T2 (days 2 to 3), and 4.8 mg (range 1 to 16 mg) at T3 (4 to 7 days)
	2	Risperidone	Not reported	Titrated dose: Mean 1.0 (Range: 0.25 to 2)	Not reported	Not reported	None	Mean dose was 1.0 mg (0.25 to 2 mg) at baseline, 1.2 mg (range 0.25 to 3 mg) at T2 (days 2 to 3), and 1.3 mg (0.25 to 3 mg) at T3 (days 4 to 7).
Boettger, 2015 ²¹	1	Aripiprazole	Not reported	Titrated dose: Mean 15.2mg (Range: 5 to 30mg)	Not reported	Not reported	None	Mean dose was 15.2 mg (range 5 to 30 mg) at baseline, 16.0 mg (range 10 to 30 mg) at T2 (2 to 3 days), and 18.3 mg (range 10 to 30 mg) at T3 (4 to 7 days).
	2	Haloperidol	Not reported	Titrated dose: Mean 4.9mg (Range: 1.5 to 16mg)	Not reported	Not reported	None	Mean dose was 4.9 mg (range 1, 5 to 16mg) at baseline, 5.5 mg (range 1.5 to 16mg) at T2 (2 to 3 days), and 5.5 mg (range 1.5 to 16mg) at T3 (4 to 7 days).
	3	Olanzapine	Not reported	Titrated dose: Mean 3.5mg (Range: 2.5 to 10mg)	Not reported	Not reported	None	Mean dose was 3.5 mg (range 2.5 to 10 mg) at baseline, 5.2 mg (range 2.5 to 15 mg) at T2 (2 to 3 days), and 7.1 mg (range 2.5 to 20 mg) at T3 (4 to 7 days).
	4	Risperidone	Not reported	Titrated dose: Mean 0.9mg (Range: 0.5 to 2mg)	Not reported	Not reported	None	Mean dose was 0.9 mg (range 0.5 to 2 mg) at baseline, 1.1 mg (range 0.5 to 3 mg) at T2 (2 to 3 days), and 1.3 mg (range 0.5 to 3 mg) at T3 (4 to 7 days).

Author, year	Arm	Drug	Route of Administration	Dose	Frequency	Duration	Non-pharmaceutical intervention	Comments
Breitbart, 1996 ²²	1	Chlorpromazine	Oral or intramuscular	Titration dose: Oral: 10 to 200mg, Intramuscular: 5 to 100mg	Per day	Planned duration: 6 days	None	"The maintenance dose was equal to one to half of the first 24 hour dose requirement, given twice a day regimen."
	2	Haloperidol	Oral or intramuscular	Titration dose: oral: 0.25 to 5.0mg, Intramuscular: 0.125 to 3.0mg	Per day	Planned duration: 6 days	None	"The maintenance dose was equal to one to half of the first 24 hour dose requirement, given twice a day regimen."
	3	Lorazepam	Oral or intramuscular	Titration dose: Oral: 0.50 to 4.0mg, Intramuscular: 0.2 to 2.0mg	Per day	Planned duration: 6 days	None	"The maintenance dose was equal to one to half of the first 24 hour dose requirement, given twice a day regimen."
Breitbart, 2002 ²³	1	Olanzapine	Oral	Titration dose: Mean 3.0mg (Range: 2.5 to 10mg)	either once or twice a day	Not reported	None	Mean dose was 3.0 mg (range 2.5 to 10mg) at baseline, 4.6 mg (range 2.5 to 15 mg) at T2 (days 2 to 3), and 6.3 mg (range 2.5 to 20mg) at T3 (days 4 to 7).
Carrasco, 2016 ²⁴	1	Haloperidol	Intravenous	Titration dose: (Range: 0.5 to 1mg/hr)	Not reported	Not reported	None	
Charoenporn, 2018 ²⁵	1	Haloperidol	Oral	Titration dose: Mean 0.9mg; Median 0.5mg	Not reported	Planned duration: 7 days	None	
	2	Quetiapine	Oral	Titration dose: Mean 26.7; Median 25	Not reported	Planned duration: 7 days	None	
	3	Risperidone	Oral	Titration dose: Mean 0.6mg; Median 0.5mg	Not reported	Planned duration: 7 days	None	

Author, year	Arm	Drug	Route of Administration	Dose	Frequency	Duration	Non-pharmaceutical intervention	Comments
Devlin, 2010 ²⁶	1	Placebo	either orally or via NG tube	Titrated dose: Mean 50; Median 210mg (IQR 116 to 293); Maximum 200mg	Twice a day (bid)	Median: 186 (IQR 108 to 228) hours; Planned dose: 10 days or earlier if shows no signs of delirium or if ICU discharge prior to 10 days of therapy	None	
	2	Quetiapine	Either orally or NG tube	Titrated dose: Mean 50; Median 110mg (IQR 88 to 191); Maximum 200mg	Twice a day (bid)	Median: 102 (IQR 84 to 168) hours; Planned dose: 10 days or earlier if shows no signs of delirium or if ICU discharge prior to 10 days of therapy	None	
Drinkwater, 2014 ²⁷	1	Placebo	Intravenous	Planned dose: 5ml (0.9% saline)ml	8 hourly	Planned duration: until patient delirium free for 48 hours (CAM to ICU)until discharged or after 14 days	None	For non to resolving agitation, open to label haloperidol could be administered in 2.5 to 5mg doses up to 10 mg in a 24 to hour period
	2	Haloperidol	Intravenous	Planned dose: 2.5mg	8 hourly	Planned duration: delirium free for 48 hours (CAM to ICU) or until 14 days or until discharged	None	
Fox, 2018 ²⁸	1	Lurasidone	Not reported	Titrated dose: Mean 42.6mg	Not reported	Not reported	None	Overall duration of atypical antipsychotic treatment during the hospital stay was similar (6.0 [5.0 to 11.5] vs 11.0 [7.0 to 16.0] days, P = 0.28).
	2	Quetiapine	Not reported	Titrated dose: Mean 153.8mg	Twice a day (bid)	Not reported	None	Overall duration of atypical antipsychotic treatment during the hospital stay was similar (6.0 [5.0 to 11.5] vs 11.0 [7.0 to 16.0] days, P = 0.28).

Author, year	Arm	Drug	Route of Administration	Dose	Frequency	Duration	Non-pharmaceutical intervention	Comments
Girard, 2010 ⁴	1	Placebo	Oral	Planned dose: 5ml	Twice a day (bid)	Median: 5 (IQR 3 to 7) days	None	
	2	Haloperidol	Oral	Planned dose: 5mg; Median: 15mg (10.8 to 17)	Per day	Median: 7 (4 to 10)	None	After enrollment 5 mg haloperidol as a solution, if no temporary gastric access IM (no more than 8 total doses). Second dose to 12 hour, then subsequent doses every 6 hours. Frequency reduced to every 8 hour when CAM to ICU negative on 2 consecutive assessments; reduced to every 12 hours when patients were delirium/coma to free on three consecutive assessments, and discontinued when patients were delirium/coma to free on four consecutive assessments. Frequency was reduced in a similar manner when patients were over sedated (RASS \geq 2 levels deeper than target RASS). Dosing frequency was increased when over sedation resolved. All study drug was discontinued on study day 14.
	3	Ziprasidone	Oral	Planned dose: 40mg; Median: 113mg (81 to 140)	Per day	Median: 4 (3 to 10)	None	
Girard, 2018 ²⁹	1	Placebo	Intravenous	Titration dose: Not reported	Twice a day (bid)	Median: 4; Planned dose: 14 days or until discharge	None	First dose for <70: 0.5ml placebo. First dose for \geq 70: 0.25ml. Placebo administered every 12 hours
	2	Haloperidol	Intravenous	Titration dose: Mean 11; Median; Maximum 10mg	Twice a day (bid)	Median: 4; Planned dose: 14 days or until discharge	None	First dose for <70: 2.5mg per 0.5ml haloperidol. First dose for \geq 70: 1.25mg per 0.25ml haloperidol. Administered every 12 hours
	3	Ziprasidone	Intravenous	Titration dose: Mean 20; Median; Maximum 20mg	Twice a day (bid)	Median: 4; Planned dose: 14 days or until discharge	None	First dose for <70: 5mg per 0.5ml ziprasidone. First dose for \geq 70: 2.5mg per 0.25ml ziprasidone. Administered every 12 hours

Author, year	Arm	Drug	Route of Administration	Dose	Frequency	Duration	Non-pharmaceutical intervention	Comments
Grover, 2011 ³⁰	1	Haloperidol	Oral	Titration dose: Mean 0.88mg (Range: 0.25 to 5mg per day)	Per day	Planned duration: 6 days	Orientation and therapeutic activities, Vision and hearing, Psychoactive medication protocol	
	2	Olanzapine	Oral	Titration dose: Mean 3.05mg (Range: 1.25 to 10 mg per day)	Per day	Planned duration: 6 days	Orientation and therapeutic activities, Vision and hearing, Psychoactive medication protocol	
	3	Risperidone	Oral	Titration dose: Mean 0.95mg (Range: 0.5 to 2.0mg per day)	per day	Planned duration: 6 days	Orientation and therapeutic activities, Vision and hearing, Psychoactive medication protocol	
Grover, 2016 ³¹	1	Haloperidol	Oral	Titration dose: Mean 0.67 ± 0.35mg (Range: 0.25 to 1.25mg)	per day	Planned duration: 6 days	Orientation and therapeutic activities, Vision and hearing, Psychoactive medication protocol	
	2	Quetiapine	Oral	Titration dose: Mean 31.83 ± 4.10mg (Range: 12.5 to 75mg)	Per day	Planned duration: 6 days	Orientation and therapeutic activities, Vision and hearing, Psychoactive medication protocol	Note that mean/SD for seroquel differs between text (results on page 368) and Table 1 26.63 +/- 15.61, but the range is same

Author, year	Arm	Drug	Route of Administration	Dose	Frequency	Duration	Non-pharmaceutical intervention	Comments
Han, 2004 ³²	1	Haloperidol	Oral	Titration dose: Mean 1.7mg (Range: 1.0 to 3.0mg)	Twice a day (bid)	Planned duration: 7 days	None	At the end of the study (the seventh day), the mean dose of the haloperidol group was 1.71 mg (SD0.84, range1.0–3.0); The initial starting dose of each drug was 0.75 mg (haloperidol) or 0.5 mg (risperidone) twice a day. The dosage was increased depending on the status of delirium during the 7 days.
	2	Risperidone	Oral	Titration dose: Mean 1.02mg (Range: 0.5 to 2.0mg)	Twice a day (bid)	Planned duration: 7 days	None	The initial starting dose of each drug was 0.75 mg (haloperidol) or 0.5 mg (risperidone) twice a day. The dosage was increased depending on the status of delirium during the 7 days. At the end of the study (the seventh day), the mean dose of the haloperidol group was 1.71 mg (SD0.84, range1.0–3.0), and the mean dose of the risperidone group was 1.02 mg (SD0.41, range0.5–2.0).
Hatta, 2014 ³³	1	Aripiprazole	Not reported	Titration dose: Maximum 7.23mg	Not reported	Not reported	None	43% of patients took this drug for 1 week or less; 25% for 2 weeks or less, and 33% for over 2 weeks; There was a priority for non-pharmacological management for delirium, which included minimize drug side effects, fluid repletion, orientation and therapeutic activities, limit sensory underload or overload, and early mobilization.
	2	Haloperidol	Intravenous	Titration dose: Maximum 6.40mg	Not reported	Not reported	None	52% of patients took this drug for 1 week or less; 19% for 2 weeks or less, and 29% for over 2 weeks; There was a priority for non-pharmacological management for delirium, which included minimize drug side effects, fluid repletion, orientation and therapeutic activities, limit sensory underload or overload, and early mobilization.

Author, year	Arm	Drug	Route of Administration	Dose	Frequency	Duration	Non-pharmaceutical intervention	Comments
Hatta, 2014 ³³ (continued)	3	Olanzapine	Not reported	Titrated dose: Maximum 10.2mg	Not reported	Not reported	None	67% of patients took this drug for 1 week or less; 17% for 2 weeks or less, and 18% for over 2 weeks; There was a priority for non to pharmacological management for delirium, which included minimize drug side effects, fluid repletion, orientation and therapeutic activities, limit sensory underload or overload, and early mobilization.
	4	Quetiapine	Not applicable	Titrated dose: Maximum 71.8mg	Not reported	Not reported	None	60% of patients took this drug for 1 week or less; 19% for 2 weeks or less, and 21% for over 2 weeks; There was a priority for non to pharmacological management for delirium, which included minimize drug side effects, fluid repletion, orientation and therapeutic activities, limit sensory underload or overload, and early mobilization.
	5	Risperidone	Not applicable	Titrated dose: Maximum 1.35mg	Not reported	Not reported	None	49% of patients took this drug for 1 week or less; 25% for 2 weeks or less, and 26% for over 2 weeks; There was a priority for non to pharmacological management for delirium, which included minimize drug side effects, fluid repletion, orientation and therapeutic activities, limit sensory underload or overload, and early mobilization.
Horikawa, 2003 ³⁴	1	Risperidone	Oral	Titrated dose: 0.5mg	Once a day (qd)	Mean: 19.4 days	None	Haloperidol at a dose of 0.75 to 5.0 mg/day had been used in all patients, but not continuously, without any effect.
Hu, 2006 ³⁵	1	None	Not applicable	Not reported	Not reported	Planned duration: 1 week	None	Given somatic treatment aiming at delirium, not any drug for central nervous system was used
	2	Haloperidol	Intramuscular	Titrated dose: (Range: 2.5 to 10mg)	Once a day (qd)	Planned duration: 1 week	None	
	3	Olanzapine	Oral or sublingually	Titrated dose: (Range: 1.25 to 20mg)	Once a day (qd)	Planned duration: 1 week	None	

Author, year	Arm	Drug	Route of Administration	Dose	Frequency	Duration	Non-pharmaceutical intervention	Comments
Hui, 2017 ³⁶	1	Haloperidol	Intravenous	Titrated dose: Not reported	2 mg every 4 hours, and another 2 mg every hour as needed for agitation	Planned duration: Until discharge	None	
Ikezawa, 2008 ³⁷	1	Risperidone	Oral	Titrated dose: Mean 1.5 (0.7) (Range: 0.5 to 3mg)	Once or twice	Mean: 11.7 (3.5)	None	
Jain, 2017 ³⁸	1	Haloperidol	Oral	Titrated dose: Mean 2.10mg	Once a day (qd)	Mean: 3.37 days	None	
	2	Olanzapine	Oral	Titrated dose: Mean 5.49mg	Once a day (qd)	Mean: 3.57 days	None	
Kim, 2001 ³⁹	1	Olanzapine	Oral	Titrated dose: Mean 5.9 (1.5); Median ; Maximum 8.8 (2.2)	Not reported	Mean: 6.6 (1.7)	None	
Kim, 2003 ⁴⁰	1	Quetiapine	Not reported	Titrated dose: 25mg	Twice a day (bid)	Planned duration: 3 months	None	Mean dose is the mean dose when patients were maximally stabilized.
Kim, 2005 ⁴¹	1	Haloperidol	Not reported	Titrated dose: Not reported	Not reported	Mean: 8.5 days	None	Mean starting dose: 2.67 mg (range 0.75 to 10.0 mg/day); Mean ending dose 1.67 mg (range 0.50 to 2.50 mg/day).
	2	Risperidone	Not reported	Titrated dose: Not reported	Not reported	Mean: 4.8 days	None	Mean starting dose 0.97 mg (range 0.5 to 5.0 mg/day); mean ending dose 1.19 (range 0.5 to 5.0 mg/day)
Kim, 2010 ⁴²	1	Olanzapine	Not reported	Titrated dose: Mean 2.4± 1.7mg (Range: 1.25 to 7.5mg)	Per day	Planned duration: 7 days	None	The mean doses at last observation 2.4 ± 1.7 for olanzapine group
	2	Risperidone	Not reported	Titrated dose: Mean 0.9 ± 0.6mg (Range: 0.25 to 2mg)	Per day	Planned duration: 7 days	None	The mean doses of last observation were 0.9 ± 0.6 mg/day
Kishi, 2012 ⁴³	1	Risperidone	Oral	Titrated dose: Mean 1.4mg	Once a day (qd)	Planned duration: 7 days	None	

Author, year	Arm	Drug	Route of Administration	Dose	Frequency	Duration	Non-pharmaceutical intervention	Comments
Konkayev, 2015 ⁴⁴	1	Dexmedetomidine	Infusion	Titrated dose: Median 0.93mg/kg/hour (Range: 0.2 to 1.4mg/kg/hour)	Continuous	Not reported	Pain management	Fentanyl and propofol were also used to manage symptoms, if necessary; Less people in the dexmedetomidine group (10%) were on propofol than in the haloperidol (42%). More people in the haloperidol group (72%) were on fentanyl than in the dexmedetomidine group (43%).
	2	Haloperidol	Intravenous infusion	Titrated dose: Median 0.12mg/kg/h (Range: 0.10 to 0.15mg/kg/h)	Continuous	Not reported	Pain management	
Lee, 2005 ⁴⁵	1	Quetiapine	Not reported	Titrated dose: Mean 113 ± 85.5mg (Range: 50 to 300mg)	Per day	Planned duration: or into remission	None	
	2	Amisulpride	Not reported	Titrated dose: Mean 156.4±97.5mg (Range: 50 to 800mg)	Per day	Planned duration: or remission	None	
Lim, 2007 ⁴⁶	1	Haloperidol	Intramuscular	Titrated (5 to 20 mg)	Other: More than 2 hours apart	Not reported	None	
	2	Olanzapine	Intramuscular	Titrated (5 to 20 mg)	Other: More than 2 hours apart	Not reported	None	
Lin, 2008 ⁴⁷	1	Haloperidol	Oral	Titrated dose: start dose 5mg	Once a day (qd)	Planned duration: 7 days	None	
	2	Olanzapine	Oral	Titrated dose: start dose 5mg	Once a day (qd)	Planned duration: 7 days	None	
Maneeton, 2007 ⁴⁸	1	Quetiapine	Oral	Titrated dose: Mean 45.7 (28.7); Maximum 100mg (Range: 25 to 100mg)	Once or twice per day	Planned duration: 7 days	None	Dose between 25 to 100 mg/day; Mean start dose (SD) is 36.8 (24.8); During the present study, lorazepam at the maximum dose of 2 mg/day was an additional medication that could be used if needed but never used for any of patients Mean (SD)
Maneeton, 2013 ⁴⁹	1	Haloperidol	Oral	Titrated dose: Mean 0.8 (SD 0.3) (Range: 0.5 to 2.0mg)	Per day	Planned duration: 7 days	Orientation and therapeutic activities	
	2	Quetiapine	Oral	Titrated dose: Mean 67.6 (SD 9.7) (Range: 25 to 100mg)	per day	Planned duration: 7 days	Orientation and therapeutic activities	

Author, year	Arm	Drug	Route of Administration	Dose	Frequency	Duration	Non-pharmaceutical intervention	Comments
Mittal, 2004 ⁵⁰	1	Risperidone	Not reported	Titrated dose: Mean 0.75mg	Twice a day (bid)	Planned duration: 5 days	None	Mean dosage on day 1 was 1.35 mg/day (range 1.0 to 2.0 mg/day). Mean maintenance dosage was 0.75 mg/day (range 0.5 to 1.50 mg/day).
Naksuk, 2017 ⁵¹	1	None		Not reported		Not reported	None	This group developed delirium, but did not receive antipsychotics.
	2	Haloperidol	Not reported	Titrated dose: Median 5.0mg (Range: 1.0 to 57.5mg)	Not reported	Median: 1.0	None	Duration obtained from Table 2. Range in duration as 1 to 10 days; Dose is average dose per day, obtained from Table 2.
	3	Quetiapine	Not reported	Titrated dose: Median 25.0mg (Range: 4.2 to 150.0mg)	Not reported	Median: 2.0	None	Median duration obtained from Table 2. Range in duration was 1.0 to 8.0 days; Dose is average dose per day, obtained from Table 2.
Omura, 2003 ⁵²	1	Quetiapine	Not reported	Titrated dose: Mean 54.7mg (Range: 25 to 125mg)	once a day (13 patients), twice a day (5 patients), 3 times per day (6 patients)	Not reported	None	
Pae, 2004 ⁵³	1	Quetiapine	Oral	Titrated dose: Mean 127.1mg	Not reported	Mean: 8.5 days	None	
Page, 2013 ¹⁰	1	Placebo	Intravenous	Planned dose: 0.5ml	Three times a day (tid)	Planned duration: 14 days or 2 consecutive days of delirium free coma free days or until discharge	Early mobilization, Pain management	Study drug was discontinued in all patients on ICU discharge, when the patient was delirium to free for two consecutive days, or after a maximum of 14 days treatment, whichever came first.; The same volumes administered IV: 0.5 ml of study drug (2.5 mg dissolved) and placebo
	2	Haloperidol	Intravenous	Planned dose: 2.5mg	Three times a day (tid)	Planned duration: 14 days or 2 consecutive days of delirium free coma free days or until discharge	Early mobilization, Pain management	Study drug was discontinued in all patients on ICU discharge, when the patient was delirium to free for two consecutive days, or after a maximum of 14 days treatment, whichever came first; The same volumes administered IV: 0.5 ml of study drug (2.5 mg dissolved) and placebo
Parellada, 2004 ⁵⁴	1	Risperidone	Oral	Titrated dose: Mean day 1, 2.6; day 3, 2.6; day 7, 1.5mg	Twice a day (bid)	Planned duration: 7 days	None	

Author, year	Arm	Drug	Route of Administration	Dose	Frequency	Duration	Non-pharmaceutical intervention	Comments
Sasaki, 2003 ⁵⁵	1	Quetiapine	Oral	Titrated dose: Mean 44.9; Median ; Maximum 63.5mg	Once a day (qd)	Mean: 4.8 days	None	
Sipahimalani, 1998 ⁵⁶	1	Haloperidol	Orally, except one patient received haloperidol intravenously	Titrated dose: (Range: 1.5 to 10mg)	Not reported	Mean: 14.6 days	None	
	2	Olanzapine	Not reported	Titrated dose: Mean 8.2; Median ; Maximum 15mg	Once a day (qd)	Mean: 23.6 days	None	
Skrobik, 2004 ⁵⁷	1	Haloperidol	Oral	Titrated dose: Mean 6.5mg (Range: 1 to 28mg)	per day	Not reported	None	Duration of therapy is not mentioned, but the study data is collected for 5 days, so can we assume the duration of therapy as 5 days.
	2	Olanzapine	Oral	Titrated dose: Mean 4.54mg (Range: 2.5 to 13.5mg)	per day	Not reported	None	
Straker, 2006 ⁵⁸	1	Aripiprazole	Not reported	Titrated dose: Mean 8.9mg (Range: 5 to 15mg)	Not reported	Planned duration: 7 days	None	Only two patients received a dose higher than 10 mg; Four patients also received as to needed haloperidol in the first few days of treatment.
Tahir, 2010 ⁵⁹	1	Placebo	Oral	Titrated dose: Mean 25; Maximum 175mg	Once a day (qd)	Planned duration: 10 days	None	
	2	Quetiapine	Oral	Titrated dose: Mean 40mg (Range: 25 to 175mg)	Once a day (qd)	Planned duration: 10 days	None	

Author, year	Arm	Drug	Route of Administration	Dose	Frequency	Duration	Non-pharmaceutical intervention	Comments
Toda, 2005 ⁶⁰	1	Risperidone	Oral	Titration dose: Mean 0.92; Median ; Maximum 1.38	Once a day (qd)	Planned duration: until remission, which ranged from 1 to 48 days	None	
Yoon, 2011 ⁶¹	1	Paliperidone	Oral	Titration dose: Mean 3.75 (1.06); Maximum 9mg	Once a day (qd)	Planned duration: 7 days	None	Start dose was 3 mg/d
Yoon, 2013 ⁶²	1	Haloperidol	Not reported	Titration dose: Mean 1.2mg (Range: 0.5 to 10mg)	Not reported	Mean duration: 4.7 days; Planned duration: 6 days	None	The initial starting dose was determined on the basis of age, degree of severity of delirium, and the general medical or postsurgical condition of the individual subject. Dose was adjusted according to clinical judgment based on daily overall impression of delirium over 6 days primarily, and on clinical assessments of the degree of improvement in delirium symptoms and the +/- to of adverse events.
	2	Olanzapine	Not reported	Titration dose: Mean 2.9mg (Range: 1 to 20mg)	Not reported	Mean duration: 5.3; Planned duration: 6 days	None	
	3	Quetiapine	Not reported	Titration dose: Mean 47.9mg (Range: 25 to 200mg)	Not reported	Mean duration: 4.8 days; Planned duration: 6 days	None	
	4	Risperidone	Not reported	Titration dose: Mean 1.1mg (Range: 0.25 to 4mg)	Not reported	Mean duration: 5.1 days; Planned duration: 6 days	None	

bid=twice daily; bid=twice daily; g=gram; IQR=interquartile range; mg/d=milligram per day; mg/hr=milligram per hour; mg=milligram; ml=millimeter; NG=nadogastric tube; qd=once daily; SD=standard deviation; T3=time point three; ug/kg=microgram per kilogram

Evidence Table D-7. Short-term continuous delirium symptom outcomes for studies comparing interventions to prevent development of delirium

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	Mean (SD) sleep time, intervention group	Mean (SD) sleep time, control group	Mean difference (95% CI) in sleep time
First-generation antipsychotic vs. placebo								
Kaneko, 1999 ⁷	Scheduled for elective gastrointestinal surgery and admitted to ICU	Haloperidol (Planned dose: 5mg), 38	Placebo (Planned dose: 1 ml (0.9% normal saline)ml), 40	Intravenous	Night time sleeping (min)	500 (55.38)	418.46 (112.3)	81.54 (42.24 to 120.84)
Kaneko, 1999 ⁷	Scheduled for elective gastrointestinal surgery and admitted to ICU	Haloperidol (Planned dose: 5mg), 38	Placebo (Planned dose: 1 ml (0.9% normal saline)ml), 40	Intravenous	Daytime sleeping (min)	260 (73.85)	289.2 (76.95)	-29.2 (-62.67 to 4.27)

CI=confidence interval; ICU=intensive care unit; mg=milligram; min=minutes; ml=millimeter; N=sample size; SD=standard deviation

Evidence Table D-8. Short-term binary delirium symptom outcomes for studies comparing interventions to prevent development of delirium

Author, year	Population	Intervention group	Control group	Route of administration	Outcome definition	Time of assessment	n / N (%), control group	n / N (%), intervention group	Relative risk (95% CI)
First-generation antipsychotic vs. placebo									
Page, 2013 ¹⁰	ICU patients needing MV within 72 hours of admission were enrolled	Haloperidol (Planned dose: 2.5mg)	Placebo (Planned dose: 0.5ml)	Intravenous	RASS +2	14 days	20/70 (28.6)	13/71 (18.3)	Not reported, p=0.0075

CI=confidence interval; ICU=intensive care unit; mg=milligram; min=minutes; ml=millimeter; MV=mechanical ventilation; N=sample size; p=p-value; RASS=Richmond Agitation and Sedation Scale; SD=standard deviation

Evidence Table D-9. Continuous delirium severity outcomes for studies comparing interventions to prevent development of delirium

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	Mean (SD) delirium severity score, intervention group	Mean (SD) delirium severity score, control group	Mean between-group difference (95% CI) in delirium severity score
First-generation antipsychotic vs. placebo								
Kalisvaart, 2005 ⁶	Acute or elective hip surgery patients, ≥ 70 years, at risk of delirium: MMSE between less than or equal to 24; dehydration=BUN/creatinine > or = to 18, low visual acuity and/or increased severity of illness on APACHE II of 16 or greater.	Haloperidol (Planned dose: 0.5mg), 36	Placebo (Not applicable), 32	Oral	DRS-R-98	14.4 (3.4)	18.41 (4.4)	-4.01 (-5.88 to -2.14)
Khan, 2018 ⁸	English speaking individuals undergoing thoracic surgery	Haloperidol (Planned dose: 0.5mg, Planned duration: 4 days (11 doses total)), 68	Placebo (Planned dose: NR, Planned duration: 4 days (11 doses total)), 67	Intravenous	DRS-R-98, total population	Baseline: Mean 1.81 (SD 2.11) Final: Mean 1.19 (SD 1.52)	Baseline: Mean 2.9 (SD 4) Final: Mean 1.5 (SD 2.18)	-0.31 (-0.94 to 0.32)
Khan, 2018 ⁸	English speaking individuals undergoing thoracic surgery	Haloperidol (Planned dose: 0.5mg, Planned duration: 4 days (11 doses total)), 7	Placebo (Planned dose: NR, Planned duration: 4 days (11 doses total)), 17	Intravenous	DRS-R-98, only patients with delirium	Baseline: Mean 4.1 (SD 3.4) Final: Mean 3 (SD 2.4)	Baseline: Mean 6.5 (SD 6.2) Final: Mean 2.6 (SD 2.8)	0.4 (-1.69 to 2.49)
Schrijver, 2018 ¹²	Medical and surgical patients	Haloperidol (Planned dose: 1mg), 23	Placebo, 18	Oral	Maximum DRS-R-98 score	15.1 (7.6)	12.67 (13.5)	2.43 (-4.27 to 9.14)

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	Mean (SD) delirium severity score, intervention group	Mean (SD) delirium severity score, control group	Mean between-group difference (95% CI) in delirium severity score
Second-generation antipsychotic vs. placebo								
Hakim, 2012 ⁵	Patients 65 years or older experiencing subsyndromal delirium after on-pump cardiac surgery	Risperidone (Planned dose: 0.5mg), 7	Placebo (Planned dose: given every 12 hours), 17	Oral	Highest score on the ICDSC	Median: 6 (IQR 5 to 7)	Median: 5 (IQR 4 to 5)	p=0.234
Larsen, 2010 ⁹	Post-operative elderly joint replacement surgery patients	Olanzapine (Planned dose: 5mg), 28	Placebo (Planned dose: 5mg), 82	Oral	DRS-R-98	16.4 (3.7)	14.5 (2.7)	1.9 (0.69 to 3.11)

CI=confidence interval; DRS-R-98= Delirium Rating Scale Revised-98; ICDSC=Intensive Care Delirium Screening Checklist; IQR=interquartile range; mg=milligram; MMSE= Mini-Mental State Examination; p=p-value; SD=standard deviation

Evidence Table D-10. Delirium free days outcomes for studies comparing interventions to prevent development of delirium

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	Median (IQR) days, intervention group	Median (IQR), days, control group	Measure of association (95% CI)
First-generation antipsychotic vs. placebo								
Girard, 2010 ⁴	> 18 years MV medical and surgical ICU patients	Haloperidol (Planned dose: 5, Median dose: 15mg (0.8-17mg)), 35	Placebo (Planned dose: 5ml), 36	Oral	Delirium/coma-free days during the 21-day study period.	14 (6 to 18)	12.5 (1.2 to 17.2)	P = 0.66 across the three groups
Page, 2013 ¹⁰	ICU patients needing MV within 72 hours of admission were enrolled	Haloperidol (Planned dose: 2.5mg), 71	Placebo (Planned dose: 0.5ml), 70	Intravenous	Alive, delirium free, and coma free days in first 14 days, median (IQR)	5 (0 to 10)	6 (0 to 11)	Mean difference - 0.48 (95% CI: - 2.08 to 1.21), p=0.53
Page, 2013 ¹⁰	ICU patients needing MV within 72 hours of admission were enrolled	Haloperidol (Planned dose: 2.5mg), 71	Placebo (Planned dose: 0.5ml), 70	Intravenous	Alive, delirium free, and coma free days in first 28 days	19 (0 to 24)	19.5 (0 to 25)	Mean difference - 0.26 (95% CI: - 3.72 to 3.46), p=0.57
van den Boogaard, 2018 ¹⁵	ICU patients at high risk of delirium	Haloperidol (Planned dose: 2mg), 608	Placebo (Planned dose: 0.9% NaCl), 599	Intravenous	Number of delirium- and coma-free, median (IQR), db	26 (17 to 28)	26 (19 to 28)	Mean difference 0 (95% CI: 0 to 0)
van den Boogaard, 2018 ¹⁵	ICU patients at high risk of delirium	Haloperidol (Planned dose: 1mg), 299	Placebo (Planned dose: 0.9% NaCl), 599	Intravenous	Number of delirium- and coma-free, median (IQR), db	26 (17 to 28)	26 (19 to 28)	Not reported
Wang, 2012 ¹⁶	Patients 65 or older admitted to the ICU after non-cardiac surgery	Haloperidol (Planned dose: 0.5 mg followed by continuous infusion at a rate of 1 mL/hr (0.1 mg/hr haloperidol), 35	Placebo (Planned dose: Normal), 53	Intravenous	Number of delirium free days, in patients who developed post-operative delirium	Mean 5.7 (SD 0.7)	Mean 5.6 (SD 1)	Mean difference 0.1 (95% CI: -0.26 to 0.46)

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	Median (IQR) days, intervention group	Median (IQR), days, control group	Measure of association (95% CI)
Wang, 2012 ¹⁶	Patients 65 or older admitted to the ICU after non-cardiac surgery	Haloperidol (Planned dose: 0.5 mg followed by continuous infusion at a rate of 1 mL/hr (0.1 mg/hr haloperidol), 229	Placebo (Planned dose: Normal saline), 228	Intravenous	Coma and delirium free days for all the patients in the group	Mean 6.8 (SD 0.7)	Mean 6.7 (SD 0.9)	Mean difference 0.1 (95% CI: -0.05 to 0.25)
Second-generation antipsychotic vs. placebo								
Girard, 2010 ⁴	> 18 years MV medical and surgical ICU patients	Ziprasidone (Planned dose: 40 Median dose: 113mg (81 to 140mg)), 30	Placebo (Planned dose: 5ml), 36	Oral	Delirium/coma-free days during the 21-day study period.	15 (9.1 to 18)	12.5 (1.2 to 17.2)	P = 0.66 across the three groups
First-generation antipsychotic vs. second-generation antipsychotic								
Girard, 2010 ⁴	> 18 years MV medical and surgical ICU patients	Ziprasidone (Planned dose: 40 Median dose: 113mg (81 to 140mg)), 30	Haloperidol (Planned dose: 5mg, Median dose: 15mg (10.8-17), 35	Oral	Delirium/coma-free days during the 21-day study period.	15 (9.1 to 18)	14 (6 to 18)	P = 0.66 across the three groups

CI=confidence interval; ICU=intensive care unit; IQR=interquartile range; Mg/hr=milligram per hour; ml/hr=millimeter per hour; ml=millimeter; MV=mechanical ventilation; N=sample size; NaCl=sodium chloride; p=p-value; SD=standard deviation

Evidence Table D-11. Duration of delirium outcomes for studies comparing interventions to prevent development of delirium

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	Mean (SD) days, intervention group	Mean (SD) days, control group	Mean between-group difference (95% CI)
First-generation antipsychotic vs. placebo								
Al-Qadheeb, 2016 ²	MV patients with subsyndromal delirium	Haloperidol (Planned dose: 1mg), 34	Placebo (Planned dose: 5% dextrose), 34	Intravenous	Duration of first episode of delirium (d)	1.67 (0.8)	3 (1.6)	-1.33 (-1.93 to -0.73)
Fukata, 2014 ³	Delirium after abdominal or orthopedic surgery in elderly patients	Haloperidol (Planned dose: 2.5mg), 59	Placebo, 60	Intravenous	Persistence of delirium	1.38 (0.9)	1.1 (0.8)	0.28 (-0.03 to 0.59)
Girard, 2010 ⁴	> 18 years MV medical and surgical ICU patients	Haloperidol (Planned dose: 5 Median dose: 15 (10.8-17), 35	Placebo (Planned dose: 5ml), 36	Oral	Delirium days	4.33 (3.9)	4 (3.2)	0.33 (-1.33 to 1.99)
Kalisvaart, 2005 ⁶	Acute or elective hip surgery patients ≥ 70 years, at risk of delirium: MMSE between less than or equal to 24; dehydration=BUN/creatinine> or = to 18, low visual acuity and/or increased severity of illness on APACHE II of 16 or greater.	Haloperidol (Planned dose: 0.5mg), 32	Placebo (Not applicable), 36	Oral	Delirium duration, days	5.4 (4.9)	11.8 (7.5)	-6.4 (-9.41 to -3.39)

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	Mean (SD) days, intervention group	Mean (SD) days, control group	Mean between-group difference (95% CI)
Khan, 2018 ⁸	English speaking individuals undergoing thoracic surgery	Haloperidol (Planned dose: 0.5mg, Planned duration: 4 days (11 doses total)), 68	Placebo (Planned dose: NR, Planned duration: 4 days (11 doses total)), 67	Intravenous	Delirium days	Median: 1 (IQR 1 to 2)	Median: 1 (IQR 1 to 2)	p=0.71
Page, 2013 ¹⁰	ICU patients needing MV within 72 hours of admission were enrolled	Haloperidol (Planned dose: 2.5mg), 71	Placebo (Planned dose: 0.5ml), 70	Intravenous	Days in delirium	5 (4.7)	4.67 (5.6)	0.33 (-1.38 to 2.04)
Page, 2013 ¹⁰	ICU patients needing MV within 72 hours of admission were enrolled	Haloperidol (Planned dose: 2.5mg), 71	Placebo (Planned dose: 0.5ml), 70	Intravenous	Days in delirium	5.67 (6.3)	5 (6.3)	0.67 (-1.41 to 2.75)
Schrijver, 2018 ¹²	Medical and surgical patients	Haloperidol (Planned dose: 1mg), 23	Placebo, 18	Oral	Days	3.67 (2.4)	3.33 (4)	0.34 (-1.68 to 2.36)

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	Mean (SD) days, intervention group	Mean (SD) days, control group	Mean between-group difference (95% CI)
Second-generation antipsychotic vs. placebo								
Girard, 2010 ⁴	> 18 years MV medical and surgical ICU patients	Ziprasidone (Planned dose: 40 Median dose: 113mg (81-140mg)), 30	Placebo (Planned dose: 5ml), 36	Oral	Delirium days	4.67 (4.7)	4 (3.2)	0.67 (-1.27 to 2.61)
Hakim, 2012 ⁵	Patients 65 years or older experiencing subsyndromal delirium after on-pump cardiac surgery	Risperidone (Planned dose: 0.5mg),	Placebo (Planned dose: given every 12 hours),	Oral	Failure to treat subsyndromal delirium with risperidone			Subhazard ratio: 3.83 (SE 1.67) (95% CI: 1.63 to 8.98), p=0.002
Hakim, 2012 ⁵	Patients 65 years or older experiencing subsyndromal delirium after on-pump cardiac surgery	Risperidone (Planned dose: 0.5mg), 7	Placebo (Planned dose: given every 12 hours), 17	Oral	Duration of clinical delirium, for affected patients, days	3 (1.6)	3.33 (0.8)	-0.33 (-1.34 to 0.68)
Larsen, 2010 ⁹	Post-operative elderly joint replacement surgery patients	Olanzapine (Planned dose: 5mg), 28	Placebo (Planned dose: 5mg), 82	Oral	Duration of delirium	2.2 (1.3)	1.6 (0.7)	0.6 (0.21 to 0.99)
First-generation antipsychotic vs. second-generation antipsychotic								
Girard, 2010 ⁴	> 18 years MV medical and surgical ICU patients	Ziprasidone (Planned dose: 40 Median dose: 113mg (81-140mg)), 30	Haloperidol (Planned dose: 5 Median dose: 15mg (10.8-17mg)), 35	Oral	Delirium days	4.67 (4.7)	4.33 (4)	0.34 (-1.78 to 2.46)

CI=confidence interval; d=days; ICU=intensive care unit; mg=milligram; ml=millimeter; MV=mechanical ventilation; N=sample size; SD=standard deviation; SE=standard error

Evidence Table D-12. Use of rescue therapy outcomes in studies comparing interventions to prevent development of delirium

Author, year	Population	Intervention group	Control group	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
First-generation antipsychotic vs. placebo								
Abdelgalel, 2016 ¹	Adult intensive care patients of ASA physical status III and IV aged between 26 and 70 years	Haloperidol (Planned dose: 0.5– 2 mg/h preceded by a loading dose of 2.5 mg intravenously over 10 min if needed (if RASS > 2+)	Placebo (Planned dose: 2-8ml, loading dose 10ml over 10 min if needed (if RASS > 2+)	Intravenous	Midazolam Mean total dose ranged from 5.5 to 30 mg)	8 / 30 (26.7%)	11 / 30 (36.7%)	0.73 (0.34 to 1.55)
Abdelgalel, 2016 ¹	Adult intensive care patients of ASA physical status III and IV aged between 26 and 70 years	Haloperidol (Planned dose: 0.5– 2 mg/h preceded by a loading dose of 2.5 mg intravenously over 10 min if needed (if RASS > 2+)	Placebo (Planned dose: 2-8ml, loading dose 10ml over 10 min if needed (if RASS > 2+)	Intravenous	Fentanyl Range in mean total dose, 100.5 to 480.1 mg	8 / 30 (26.7%)	10 / 30 (33.3%)	0.80 (0.37 to 1.74)
Abdelgalel, 2016 ¹	Adult intensive care patients of ASA physical status III and IV aged between 26 and 70 years	Haloperidol (Planned dose: 0.5– 2 mg/h preceded by a loading dose of 2.5 mg intravenously over 10 min if needed (if RASS > 2+)	Placebo (Planned dose: 2-8ml, loading dose 10ml over 10 min if needed (if RASS > 2+)	Intravenous	Propofol range in total mean dose, 320.2 to 1151.4 mg	10 / 30 (33.3%)	13 / 30 (43.3%)	0.77 (0.40 to 1.47)
Girard, 2010 ⁴	> 18 years MV medical and surgical ICU patients	Haloperidol (Planned dose: 5mg; Median dose: 15mg (10.8-17)	Placebo (Planned dose: 5ml),	Oral	Haloperidol varies for each group	6 / 35 (17%)	14 / 36 (39%)	0.44 (0.19 to 1.02)
Page, 2013 ¹⁰	ICU patients needing MV within 72 hours of admission were enrolled	Haloperidol (Planned dose: 2.5mg)	Placebo (Planned dose: 0.5ml)	Intravenous	Any anti-psychotic	8 / 71 (11%)	18 / 70 (26%)	0.44 (0.20 to 0.94)

Author, year	Population	Intervention group	Control group	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
Page, 2013 ¹⁰	ICU patients needing MV within 72 hours of admission were enrolled	Haloperidol (Planned dose: 2.5mg)	Placebo (Planned dose: 0.5ml)	Intravenous	Open Label Haloperidol	6 / 71 (8%)	15 / 70 (21%)	0.39 (0.16 to 0.96)
Schrijver, 2018 ¹²	Medical and surgical patients	Haloperidol (Planned dose: 1mg)	Placebo	Oral	Haloperidol mean daily dose ranged from 1.3 to 1.4 mg in the haloperidol and placebo groups.	15 / 118 (12.7%)	12 / 124 (9.7%)	1.31 (0.64 to 2.69)
Wang, 2012 ¹⁶	Patients 65 or older admitted to the ICU after noncardiac surgery	Haloperidol (Planned dose: 0.5 mg followed by continuous infusion at a rate of 1 mL/hr (0.1 mg/hr haloperidol)	Placebo (Planned dose: Normal saline)	Intravenous	Haloperidol	3 / 229 (1.3%)	6 / 228 (2.6%)	0.50 (0.13 to 1.97)
Second-generation antipsychotic vs. placebo								
Girard, 2010 ⁴	> 18 years MV medical and surgical ICU patients	Ziprasidone (Planned dose: 40 Median dose: 113 (81-140)	Placebo (Planned dose: 5ml)	Oral	Haloperidol varies for each group	9 / 30 (30%)	14 / 36 (39%)	0.77 (0.39 to 1.53)
First-generation antipsychotic vs. second-generation antipsychotic								
Girard, 2010 ⁴	> 18 years MV medical and surgical ICU patients	Ziprasidone (Planned dose: 40 Median dose: 113 (81-140)	Haloperidol (Planned dose: 5 Median dose: 15 (10.8-17)	Oral	Haloperidol varies for each group	9 / 30 (30%)	6 / 35 (17%)	1.75 (0.70 to 4.35)

Author, year	Population	Intervention group	Control group	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
First-generation antipsychotic vs. other								
Abdelgalel, 2016 ¹	Adult intensive care patients of ASA physical status III and IV aged between 26 and 70 years	Haloperidol (Planned dose: 0.5– 2 mg/h preceded by a loading dose of 2.5 mg intravenously over 10 min if needed (if RASS > 2+))	Dexmedetomidine (Planned dose: 0.2–0.7 mcg/kg/h preceded by a loading dose of 1.0 ug/kg intravenously over 10 min if needed (if RASS > 2+))	Intravenous	Midazolam Mean total dose ranged from 5.5 to 30 mg)	8 / 30 (26.7%)	2 / 30 (6.7%)	4.00 (0.92 to 17.30)
Abdelgalel, 2016 ¹	Adult intensive care patients of ASA physical status III and IV aged between 26 and 70 years	Haloperidol (Planned dose: 0.5– 2 mg/h preceded by a loading dose of 2.5 mg intravenously over 10 min if needed (if RASS > 2+))	Dexmedetomidine (Planned dose: 0.2–0.7 mcg/kg/h preceded by a loading dose of 1.0 ug/kg intravenously over 10 min if needed (if RASS > 2+))	Intravenous	Fentanyl Range in mean total dose, 100.5 to 480.1 mg	8 / 30 (26.7%)	2 / 30 (6.7%)	4.00 (0.92 to 17.30)
Abdelgalel, 2016 ¹	Adult intensive care patients of ASA physical status III and IV aged between 26 and 70 years	Haloperidol (Planned dose: 0.5– 2 mg/h preceded by a loading dose of 2.5 mg intravenously over 10 min if needed (if RASS > 2+))	Dexmedetomidine (Planned dose: 0.2–0.7 mcg/kg/h preceded by a loading dose of 1.0 ug/kg intravenously over 10 min if needed (if RASS > 2+))	Intravenous	Propofol Range in total mean dose, 320.2 to 1151.4 mg	10 / 30 (33.3%)	3 / 30 (10%)	3.33 (1.02 to 10.92)

ASA=American Society of Anesthesiologists; CI=confidence interval; ICU=intensive care unit; IV=intravenous; Mg/hr=milligram per hour; mg=milligram; MV=mechanical ventilation; N=sample size; RASS=Richmond Agitation and Sedation Scale

Evidence Table D-13. Use of physical restraint outcomes in studies comparing interventions to prevent development of delirium

Author, year	Population	Intervention group	Control group	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
First-generation antipsychotic vs. placebo								
van den Boogaard, 2018 ¹⁵	ICU patients at high risk of delirium	Haloperidol (Planned dose: 1mg)	Placebo (Planned dose: 0.9% NaCl)	Intravenous	Incidence, No. (%)	102 / 350 (30%)	169 / 707 (24.8%)	1.22 (0.98 to 1.50)
van den Boogaard, 2018 ¹⁵	ICU patients at high risk of delirium	Haloperidol (Planned dose: 2mg)	Placebo (Planned dose: 0.9% NaCl)	Intravenous	Incidence, No. (%)	191 / 732 (27%)	169 / 707 (24.8%)	1.09 (0.91 to 1.31)
Khan, 2018 ⁸	English speaking individuals undergoing thoracic surgery	Haloperidol (Planned dose: 0.5mg, Planned duration: 4 days (11 doses total)),	Placebo (Planned dose: NR, Planned duration: 4 days (11 doses total)),	Intravenous	Physically restrained	24 / 68 (35.3%)	25 / 67 (37.3%)	RR 0.95 (95% CI: 0.60 to 1.48), p=0.513
Second-generation antipsychotic vs. placebo								
Larsen, 2010 ⁹	Post-operative elderly joint replacement surgery patients	Olanzapine (Planned dose: 5mg)	Placebo (Planned dose: 5mg)	Oral		5 / 196 (2.6%)	0 / 204 (%)	11.45 (0.64 to 205.64)

CI=confidence interval; N=sample size; NaCl=sodium chloride

Evidence Table D-14. Mortality outcomes in studies comparing interventions to prevent development of delirium

Author, year	Population	Intervention group	Control group	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
First-generation antipsychotic vs. placebo								
Abdelgalel, 2016 ¹	Adult intensive care patients of ASA physical status III and IV aged between 26 and 70 years	Haloperidol (Planned dose: 0.5– 2 mg/h preceded by a loading dose of 2.5 mg intravenously over 10 min if needed (if RASS > 2+))	Placebo (Planned dose: 2-8ml, loading dose 10ml over 10 min if needed (if RASS > 2+))	Intravenous	Mortality	2 / 30 (6.7%)	3 / 30 (10%)	0.67 (0.12 to 3.71)
Al-Qadheeb, 2016 ²	MV patients with subsyndromal delirium	Haloperidol (Planned dose: 1mg)	Placebo (Planned dose: 5% dextrose)	Intravenous	Died in ICU	9 / 34 (26.5%)	7 / 34 (20.6%)	1.29 (0.54 to 3.06)
Al-Qadheeb, 2016 ²	MV patients with subsyndromal delirium	Haloperidol (Planned dose: 1mg),	Placebo (Planned dose: 5% dextrose)	Intravenous	Died in hospital	9 / 34 (26.5%)	7 / 34 (20.6%)	1.29 (0.54 to 3.06)
Girard, 2010 ⁴	> 18 years MV medical and surgical ICU patients	Haloperidol (Planned dose: 5 Median dose: 15 (10.8-17)	Placebo (Planned dose: 5ml)	Oral	21-day mortality, n (%)	4 / 35 (11%)	6 / 36 (17%)	0.69 (0.21 to 2.22)
Khan, 2018 ⁸	English speaking individuals undergoing thoracic surgery	Haloperidol (Planned dose: 0.5mg, Planned duration: 4 days (11 doses total)), 68	Placebo (Planned dose: NR, Planned duration: 4 days (11 doses total)), 67	Intravenous	In-hospital mortality	0 / 68 (0%)	0 / 67 (0%)	
Page, 2013 ¹⁰	ICU patients needing MV within 72 hours of admission were enrolled	Haloperidol (Planned dose: 2.5mg),	Placebo (Planned dose: 0.5ml)	Intravenous		20 / 71 (28.2%)	19 / 70 (27.1%)	1.04 (0.61 to 1.77)
Schrijver, 2018 ¹²	Medical and surgical patients	Haloperidol (Planned dose: 1mg)	Placebo	Oral	Not applicable	6 / 118 (5.1%)	8 / 124 (6.5%)	0.79 (0.28 to 2.20)

Author, year	Population	Intervention group	Control group	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
Schrijver, 2018 ¹²	Medical and surgical patients	Haloperidol (Planned dose: 1mg)	Placebo	Oral	In-hospital mortality	4 / 118 (3.5%)	3 / 124 (2.5%)	1.40 (0.32 to 6.13)
Schrijver, 2018 ¹²	Medical and surgical patients	Haloperidol (Planned dose: 1mg)	Placebo	Oral	Not applicable	11 / 118 (9.9%)	15 / 124 (12.5%)	0.77 (0.37 to 1.61)
Schrijver, 2018 ¹²	Medical and surgical patients	Haloperidol (Planned dose: 1mg)	Placebo	Oral	Not applicable	18 / 118 (17.3%)	20 / 124 (17.5%)	0.95 (0.53 to 1.70)
van den Boogaard, 2018 ¹⁵	ICU patients at high risk of delirium	Haloperidol (Planned dose: 2mg)	Placebo (Planned dose: 0.9% NaCl)	Intravenous	Number of patients died by the time of assessment at 90 days	153 / 732 (20.9%)	151 / 707 (21.4%)	0.98 (0.80 to 1.20)
van den Boogaard, 2018 ¹⁵	ICU patients at high risk of delirium	Haloperidol (Planned dose: 1mg)	Placebo (Planned dose: 0.9% NaCl)	Intravenous	Number of patients died by the time of assessment at 90 days	74 / 350 (21.1%)	151 / 707 (21.4%)	0.99 (0.77 to 1.27)
van den Boogaard, 2018 ¹⁵	ICU patients at high risk of delirium	Haloperidol (Planned dose: 2mg)	Placebo (Planned dose: 0.9% NaCl)	Intravenous	Number of patients died at 28 days assessment	122 / 732 (16.7%)	122 / 707 (17.3%)	0.97 (0.77 to 1.21)

Author, year	Population	Intervention group	Control group	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
van den Boogaard, 2018 ¹⁵	ICU patients at high risk of delirium	Haloperidol (Planned dose: 1mg)	Placebo (Planned dose: 0.9% NaCl)	Intravenous	Number of patients died at 28 days assessment	64 / 350 (18.3%)	122 / 707 (17.3%)	1.06 (0.81 to 1.39)
Wang, 2012 ¹⁶	Patients 65 or older admitted to the ICU after noncardiac surgery	Haloperidol (Planned dose: 0.5 mg followed by continuous infusion at a rate of 1 mL/hr (0.1 mg/hr haloperidol))	Placebo (Planned dose: Normal saline)	Intravenous	All-cause mortality for all the patients in the groups	2 / 229 (0.9%)	6 / 228 (2.6%)	0.33 (0.07 to 1.63)
Wang, 2012 ¹⁶	Patients 65 or older admitted to the ICU after noncardiac surgery	Haloperidol (Planned dose: 0.5 mg followed by continuous infusion at a rate of 1 mL/hr (0.1 mg/hr haloperidol))	Placebo (Planned dose: Normal saline)	Intravenous	All-cause mortality, in patients who developed post-operative delirium	0 / 35 (0%)	4 / 53 (7.5%)	0.17 (0.01 to 3.00)
Second-generation antipsychotic vs. placebo								
Girard, 2010 ⁴	> 18 years MV medical and surgical ICU patients	Ziprasidone (Planned dose: 40 Median dose: 113 (81-140))	Placebo (Planned dose: 5ml)	Oral	21-day mortality, n (%)	4 / 30 (13%)	6 / 36 (17%)	0.80 (0.25 to 2.57)
Hakim, 2012 ⁵	Patients 65 years or older experiencing subsyndromal delirium after on-pump cardiac surgery	Risperidone (Planned dose: 0.5mg),	Placebo (Planned dose: given every 12 hours)	Oral	Died of cardiogenic shock	2 / 51 (3.9%)	1 / 50 (2%)	1.96 (0.18 to 20.95)

Author, year	Population	Intervention group	Control group	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
First-generation antipsychotic vs. second-generation antipsychotic								
Girard, 2010 ⁴	> 18 years MV medical and surgical ICU patients	Ziprasidone (Planned dose: 40 Median dose: 113 (81-140))	Haloperidol (Planned dose: 5 Median dose: 15 (10.8-17))	Oral	21-day mortality, n (%)	4 / 30 (13%)	4 / 35 (11%)	1.17 (0.32 to 4.27)
First-generation antipsychotic vs. other								
Abdelgalel, 2016 ¹	Adult intensive care patients of ASA physical status III and IV aged between 26 and 70 years	Haloperidol (Planned dose: 0.5– 2 mg/h preceded by a loading dose of 2.5 mg intravenously over 10 min if needed (if RASS > 2+))	Dexmedetomidine (Planned dose: 0.2–0.7 mcg/kg/h preceded by a loading dose of 1.0 ug/kg intravenously over 10 min if needed (if RASS > 2+))	Intravenous	Mortality	2 / 30 (6.7%)	2 / 30 (6.7%)	1.00 (0.15 to 6.64)

ASA=American Society of Anesthesiologists; CI=confidence interval; ICU=intensive care unit; Mg/hr=milligram per hour; mg=milligram; MV=mechanical ventilation; n=sample size; NaCl=sodium chloride; RASS=Richmond Agitation and Sedation Scale

Evidence Table D-15. Survival outcomes in studies comparing interventions to prevent development of delirium

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	Median (IQR) days, intervention group	Median (IQR), days, control group	Difference in Medians (95% CI)
First-generation antipsychotic vs. placebo								
van den Boogaard, 2018 ¹⁵	ICU patients at high risk of delirium	Haloperidol (Planned dose: 1mg), 350	Placebo (Planned dose: 0.9% NaCl), 707	Intravenous	Median number of days patients survived at the time of 28 days assessment	28 (28 to 28)	28 (28 to 28)	0 (0 to 0)
van den Boogaard, 2018 ¹⁵	ICU patients at high risk of delirium	Haloperidol (Planned dose: 2mg), 732	Placebo (Planned dose: 0.9% NaCl), 707	Intravenous	Median number of days patients survived at the time of 28 days assessment	28 (28 to 28)	28 (28 to 28)	0 (0 to 0)
van den Boogaard, 2018 ¹⁵	ICU patients at high risk of delirium	Haloperidol (Planned dose: 1mg), 350	Placebo (Planned dose: 0.9% NaCl), 707	Intravenous	Median number of days patients survived at the time of 90 days assessment	90 (90 to 90)	90 (90 to 90)	0 (0 to 0)
van den Boogaard, 2018 ¹⁵	ICU patients at high risk of delirium	Haloperidol (Planned dose: 2mg), 732	Placebo (Planned dose: 0.9% NaCl), 707	Intravenous	Median number of days patients survived at the time of 90 days assessment	90 (90 to 90)	90 (90 to 90)	0 (0 to 0)

CI=confidence interval; ICU=intensive care unit; IQR=interquartile range; Mg/hr=milligram per hour; mg=milligram; MV=mechanical ventilation; n=sample size; NaCl=sodium chloride

Evidence Table D-16. Institutionalization outcomes in studies comparing interventions to prevent development of delirium

Author, year	Population	Intervention group	Control group	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
First-generation antipsychotic vs. placebo								
Schrijver, 2018 ¹²	Medical and surgical patients	Haloperidol (Planned dose: 1mg)	Placebo	Oral	New institutionalization	13 / 118 (18.3%)	8 / 124 (11.9%)	1.71 (0.73 to 3.97)
Schrijver, 2018 ¹²	Medical and surgical patients	Haloperidol (Planned dose: 1mg),	Placebo	Oral	Not applicable	7 / 118 (6.1%)	6 / 124 (5%)	1.23 (0.42 to 3.54)
Schrijver, 2018 ¹²	Medical and surgical patients	Haloperidol (Planned dose: 1mg)	Placebo	Oral	New institutionalization	10 / 118 (16.1%)	8 / 124 (11.9%)	1.31 (0.54 to 3.21)
Second-generation antipsychotic vs. placebo								
Larsen, 2010 ⁹	Post-operative elderly joint replacement surgery patients	Olanzapine (Planned dose: 5mg)	Placebo (Planned dose: 5mg)	Oral	Discharge to rehabilitation facility (SNF or acute [hospital-level]) care	116 / 196 (59.2%)	143 / 204 (70.1%)	0.84 (0.73 to 0.98)

CI=confidence interval; ICU=intensive care unit; mg=milligram; MV=mechanical ventilation; n=sample size; SNF=skilled nursing facility

Evidence Table D-17. Fall outcomes in studies comparing interventions to prevent development of delirium

Author, year	Population	Intervention group	Control group	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
First-generation antipsychotic vs. placebo								
Fukata, 2014 ³	Delirium after abdominal or orthopedic surgery in elderly patients	Haloperidol (Planned dose: 2.5mg), 59	Placebo, 60	Intravenous	Number of patients fell	1 / 59 (2%)	0 / 60 (0%)	3.05 (0.13 to 73.39)

CI=confidence interval; ICU=intensive care unit; mg=milligram; n=sample size

Evidence Table D-18. Hospital readmission outcomes in studies comparing interventions to prevent development of delirium

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
First-generation antipsychotic vs. placebo								
Schrijver, 2018 ¹²	Medical and surgical patients	Haloperidol (Planned dose: 1mg), 118	Placebo, 124	Oral	Not applicable	27 / 118 (33.8%)	22 / 124 (27.2%)	1.29 (0.78 to 2.13)
Schrijver, 2018 ¹²	Medical and surgical patients	Haloperidol (Planned dose: 1mg), 118	Placebo, 124	Oral	Not applicable	17 / 118 (24.6%)	14 / 124 (18.2%)	1.28 (0.66 to 2.47)

CI=confidence interval; mg=milligram; n=sample size

Evidence Table D-19. Intensive care unit readmission outcomes in studies comparing interventions to prevent development of delirium

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
First-generation antipsychotic vs. placebo								
Page, 2013 ¹⁰	ICU patients needing MV within 72 hours of admission were enrolled	Haloperidol (Planned dose: 2.5mg), 71	Placebo (Planned dose: 0.5ml), 70	Intravenous	Readmission to ICU with sepsis	1 / 71 (3%)	1 / 70 (1%)	0.99 (0.06 to 15.45)
van den Boogaard, 2018 ¹⁵	ICU patients at high risk of delirium	Haloperidol (Planned dose: 2mg), 732	Placebo (Planned dose: 0.9% NaCl), 707	Intravenous	ICU readmission, No. (%)	65 / 732 (8.9%)	68 / 707 (9.6%)	0.92 (0.67 to 1.28)
van den Boogaard, 2018 ¹⁵	ICU patients at high risk of delirium	Haloperidol (Planned dose: 1mg), 350	Placebo (Planned dose: 0.9% NaCl), 707	Intravenous	ICU readmission, No. (%)	36 / 350 (10.3%)	68 / 707 (9.6%)	1.07 (0.73 to 1.57)

CI=confidence interval; ICU=intensive care unit; mg=milligram; MV=mechanical ventilation; n=sample size; NaCl=sodium chloride

Evidence Table D-20. Length of hospital stay outcomes in studies comparing interventions to prevent development of delirium

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	Mean (SD) days, intervention group	Mean (SD) days, control group	Mean between-group difference (95% CI)
First-generation antipsychotic vs. placebo								
Abdelgalel, 2016 ¹	Adult intensive care patients of ASA physical status III and IV aged between 26 and 70 years	Haloperidol (Planned dose: 0.5– 2 mg/h preceded by a loading dose of 2.5 mg intravenously over 10 min if needed (if RASS > 2+), 30	Placebo (Planned dose: 2-8ml, loading dose 10ml over 10 min if needed (if RASS > 2+)), 30	Intravenous	Length of stay in hospital (days)	13.5 (2)	15.5 (2.5)	-2 (-3.15 to -0.85)
Girard, 2010 ⁴	> 18 years MV medical and surgical ICU patients	Haloperidol (Planned dose: 5mg Median dose: 15mg (10.8-17mg), 35	Placebo (Planned dose: 5ml), 36	Oral	Length of stay, days in hospital	Median 13.8 (IQR 9.4 to NA)	Median 15.4 (IQR 8.9 to NA)	NA
Kalisvaart, 2005 ⁶	Acute or elective hip surgery patients ≥ 70 years is at risk of delirium: MMSE between less than or equal to 24; dehydration=BUN/creatinine> or = to 18, low visual acuity and/or increased severity of illness on APACHE II of 16 or greater.	Haloperidol (Planned dose: 0.5mg), 32	Placebo (Not applicable), 36	Oral	Hospital Days	17.1 (11.1)	22.6 (16.7)	-5.5 (-12.24 to 1.24)
Khan, 2018 ⁸	English speaking individuals undergoing thoracic surgery	Haloperidol (Planned dose: 0.5mg, Planned duration: 4 days (11 doses total)), 68	Placebo (Planned dose: NR, Planned duration: 4 days (11 doses total)), 67	Intravenous	Hospital length of stay, median, days	Median: 10 (IQR 8 to 11.5)	Median: 10 (IQR 8 to 12)	p=0.4
Page, 2013 ¹⁰	ICU patients needing MV within 72 hours of admission were enrolled	Haloperidol (Planned dose: 2.5mg), 42	Placebo (Planned dose: 0.5ml), 47	Intravenous	Length of hospital stay, Excluding patients who died in hospital	20.5 (14.9)	27 (19.8)	-6.5 (-13.78 to 0.78)
Schrijver, 2018 ¹²	Medical and surgical patients	Haloperidol (Planned dose: 1mg), 118	Placebo, 124	Oral	Not applicable	7.1 (4.9)	7.93 (5.4)	-0.83 (-2.13 to 0.47)
van den Boogaard, 2018 ¹⁵	ICU patients at high risk of delirium	Haloperidol (Planned dose: 1mg), 350	Placebo (Planned dose: 0.9% NaCl), 707	Intravenous	Length of stay, median (IQR), days	18.67 (17.3)	16.67 (13.5)	2 (0.13 to 3.87)
van den Boogaard, 2018 ¹⁵	ICU patients at high risk of delirium	Haloperidol (Planned dose: 2mg), 732	Placebo (Planned dose: 0.9% NaCl), 707	Intravenous	Length of stay, median (IQR), days	17.33 (14.9)	16.67 (13.5)	0.66 (-0.81 to 2.13)

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	Mean (SD) days, intervention group	Mean (SD) days, control group	Mean between-group difference (95% CI)
Wang, 2012 ¹⁶	Patients 65 or older admitted to the ICU after noncardiac surgery	Haloperidol (Planned dose: 0.5 mg followed by continuous infusion at a rate of 1 mL/hr (0.1 mg/hr haloperidol)), 35	Placebo (Planned dose: Normal saline), 53	Intravenous	Median Length of stay in hospital after surgery, in patients who developed post-operative delirium in days	14 (5.3)	12 (2.5)	2 (0.27 to 3.73)
Wang, 2012 ¹⁶	Patients 65 or older admitted to the ICU after noncardiac surgery	Haloperidol (Planned dose: 0.5 mg followed by continuous infusion at a rate of 1 mL/hr (0.1 mg/hr haloperidol)), 229	Placebo (Planned dose: Normal saline), 228	Intravenous	Median length of stay in hospital after surgery for all the patients in the group	11 (1.4)	11 (1.3)	0 (-0.25 to 0.25)
Second-generation antipsychotic vs. placebo								
Girard, 2010 ⁴	> 18 years MV medical and surgical ICU patients	Ziprasidone (Planned dose: 40mg Median dose: 113mg (81-140mg))	Placebo (Planned dose: 5ml),	Oral	Length of stay, days in Hospital	Not reported	Not reported	Median 15.4 (IQR 8.9 to NA)
Hakim, 2012 ⁵	Patients 65 years or older experiencing subsyndromal delirium after on-pump cardiac surgery	Risperidone (Planned dose: 0.5mg), 51	Placebo (Planned dose: given every 12 hours), 50	Oral	In study group	6 (1.6)	6.33 (2.4)	-0.33 (-1.13 to 0.47)
Prakanrattana, 2007 ¹¹	Elective Cardiac Surgery with cardiopulmonary bypass	Risperidone (Planned dose: 1mg), 63	Placebo (Not applicable), 63	Orally disintegrating tablet	Not applicable	10.5 (6.1)	10.3 (4.4)	0.2 (-1.66 to 2.06)
First-generation antipsychotic vs. second-generation antipsychotic								
Girard, 2010 ⁴	> 18 years MV medical and surgical ICU patients	Ziprasidone (Planned dose: 40mg Median dose: 113mg (81-140mg))	Haloperidol (Planned dose: 5mg Median dose: 15mg (10.8-17))	Oral	Length of stay, days in Hospital	Median 13.5 (IQR 9.3 to Not reported)	Median 13.8 (IQR 9.4 to Not reported)	p=0.68

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	Mean (SD) days, intervention group	Mean (SD) days, control group	Mean between-group difference (95% CI)
First-generation antipsychotic vs. other								
Abdelgalel, 2016 ¹	Adult intensive care patients of ASA physical status III and IV aged between 26 and 70 years	Dexmedetomidine (Planned dose: 0.2–0.7 ug/kg/h preceded by a loading dose of 1.0 ug/kg intravenously over 10 min if needed (if RASS > 2+)), 30	Haloperidol (Planned dose: 0.5– 2 mg/h preceded by a loading dose of 2.5 mg intravenously over 10 min if needed (if RASS > 2+), 30	Intravenous	Length of stay in hospital (days)	6.2 (0.9)	13.5 (2)	-7.3 (-8.08 to -6.52)

APACHE II= Acute Physiology and Chronic Health Evaluation 2; BUN=blood urea nitrogen ratio; ICU=intensive care unit; ICU=intensive care unit; Mg/hr=milligram per unit; ml/hr=milliliter per hour; MV=mechanical ventilation; NaCl=sodium chloride; RASS=Richmond Agitation and Sedation Scale; SD=standard deviation; Ug/kg/h=microgram per kilogram per hour

Evidence Table D-21. Length of intensive care unit stay outcomes in studies comparing interventions to prevent development of delirium

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	Mean (SD) days, intervention group	Mean (SD) days, control group	Mean between-group difference (95% CI)
First-generation antipsychotic vs. placebo								
Abdelgalel, 2016 ¹	Adult intensive care patients of ASA physical status III and IV aged between 26 and 70 years	Haloperidol (Planned dose: 0.5–2 mg/h preceded by a loading dose of 2.5 mg intravenously over 10 min if needed (if RASS > 2+), 30	Placebo (Planned dose: 2–8ml, loading dose 10ml over 10 min if needed (if RASS > 2+)), 30	Intravenous	Length of ICU stays (days)	6.5 (1)	6.9 (1.2)	-0.4 (-0.96 to 0.16)
Al-Qadheeb, 2016 ²	MV patients with subsyndromal delirium	Haloperidol (Planned dose: 1mg), 34	Placebo (Planned dose: 5% dextrose/ml), 34	Intravenous	Duration of ICU stay in days	6.17 (3.1)	6.67 (4)	-0.5 (-2.2 to 1.2)
Girard, 2010 ⁴	> 18 years MV medical and surgical ICU patients	Haloperidol (Planned dose: 5 Median dose: 15 (10.8-17), 35	Placebo (Planned dose: 5ml), 36	Oral	Length of stay, days in ICU	10.67 (8.7)	8.1 (6)	2.57 (-0.91 to 6.05)
Khan, 2018 ⁸	English speaking individuals undergoing thoracic surgery	Haloperidol (Planned dose: 0.5mg, Planned duration: 4 days (11 doses total)), 68	Placebo (Planned dose: NR, Planned duration: 4 days (11 doses total)), 67	Intravenous	ICU length of stay, median, days	Median: 2.2 (IQR 1 to 3.3)	Median: 2.3 (IQR 1 to 4)	p=0.29
Page, 2013 ¹⁰	ICU patients needing MV within 72 hours of admission were enrolled	Haloperidol (Planned dose: 2.5mg), 50	Placebo (Planned dose: 0.5ml), 52	Intravenous	Length of critical care stay, excluding patients who died in ICU	9.5 (7.1)	10.67 (10.3)	-1.17 (-4.6 to 2.26)
van den Boogaard, 2018 ¹⁵	ICU patients at high risk of delirium	Haloperidol (Planned dose: 2mg), 732	Placebo (Planned dose: 0.9% NaCl), 707	Intravenous	Length of stay, median (IQR), days	5.33 (5.5)	5 (5.6)	0.33 (-0.24 to 0.9)
van den Boogaard, 2018 ¹⁵	ICU patients at high risk of delirium	Haloperidol (Planned dose: 1mg), 350	Placebo (Planned dose: 0.9% NaCl), 707	Intravenous	Length of stay, median (IQR), days	5 (5.5)	5 (5.6)	0 (-0.67 to 0.67)
Wang, 2012 ¹⁶	Patients 65 or older admitted to the ICU after noncardiac surgery	Haloperidol (Planned dose: 0.5 mg followed by continuous infusion at a rate of 1 mL/hr (0.1 mg/hr haloperidol)), 229	Placebo (Planned dose: Normal saline), 228	Intravenous	Median Length of stay in ICU for all the patients in the group in hours	0.89 (0.06)	0.96 (0.14)	-0.07 (-0.09 to -0.05)
Wang, 2012 ¹⁶	Patients 65 or older admitted to the ICU after noncardiac surgery	Haloperidol (Planned dose: 0.5 mg followed by continuous infusion at a rate of 1 mL/hr (0.1 mg/hr haloperidol)), 35	Placebo (Planned dose: Normal saline), 53	Intravenous	Median Length of stay in ICU, in patients who developed post-operative delirium, in hours	0.82 (0.22)	1.73 (0.14)	-0.91 (-0.99 to -0.83)

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	Mean (SD) days, intervention group	Mean (SD) days, control group	Mean between-group difference (95% CI)
Second-generation antipsychotic vs. placebo								
Girard, 2010 ⁴	> 18 years MV medical and surgical ICU patients	Ziprasidone (Planned dose: 40 Median dose: 113 (81-140), 30	Placebo (Planned dose: 5ml), 36	Oral	Length of stay, days in ICU	9.3 (8.4)	8.1 (6)	1.2 (-2.32 to 4.72)
Hakim, 2012 ⁵	Patients 65 years or older experiencing subsyndromal delirium after on-pump cardiac surgery	Risperidone (Planned dose: 0.5mg), 51	Placebo (Planned dose: given every 12 hours), 50	Oral	In study group	2.33 (0.8)	2.67 (0.8)	-0.34 (-0.65 to -0.03)
Prakanrattana, 2007 ¹¹	Elective Cardiac Surgery with cardiopulmonary bypass	Risperidone (Planned dose: 1mg), 63	Placebo (Not applicable), 63	Orally disintegrating tablet	Not applicable	3.3 (2.3)	3.2 (1.9)	0.1 (-0.64 to 0.84)
First-generation antipsychotic vs. second-generation antipsychotic								
Girard, 2010 ⁴	> 18 years MV medical and surgical ICU patients	Ziprasidone (Planned dose: 40 Median dose: 113 (81-140), 30	Haloperidol (Planned dose: 5 Median dose: 15 (10.8-17), 35	Oral	Length of stay, days in ICU	9.3 (8.4)	10.67 (8.8)	-1.37 (-5.55 to 2.81)
First-generation antipsychotic vs. other								
Abdelgalel, 2016 ¹	Adult intensive care patients of ASA physical status III and IV aged between 26 and 70 years	Haloperidol (Planned dose: 0.5–2 mg/h preceded by a loading dose of 2.5 mg intravenously over 10 min if needed (if RASS > 2+), 30	Dexmedetomidine (Planned dose: 0.2–0.7 mcg/kg/h preceded by a loading dose of 1.0 ug/kg intravenously over 10 min if needed (if RASS > 2+)), 30	Intravenous	Length of ICU stays (days)	3.1 (0.4)	6.5 (1)	-3.4 (-3.79 to -3.01)

ASA=American Society of Anesthesiologists; CI=confidence interval; ICU=intensive care unit; Mg/hr=milligram per hour; mg=milligram; MV=mechanical ventilation; n=sample size; NaCl=sodium chloride; RASS=Richmond Agitation and Sedation Scale; SD=standard deviation

Evidence Table D-22. Sitter use outcomes in studies comparing interventions to prevent development of delirium

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
Second-generation antipsychotic vs. placebo								
Larsen, 2010 ⁹	Post-operative elderly joint replacement surgery patients	Olanzapine (Planned dose: 5mg), 196	Placebo (Planned dose: 5mg), 204	Oral	Sitter use	9 / 196 (4.6%)	4 / 204 (2%)	2.34 (0.73 o 7.48)

CI=confidence interval; Mg=milligram; N=sample size

Evidence Table D-23. Incidence of delirium outcomes in studies comparing interventions to prevent development of delirium

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
First-generation antipsychotic vs. placebo								
Abdelgalel, 2016 ¹	Adult intensive care patients of ASA physical status III and IV aged between 26 and 70 years	Haloperidol (Planned dose: 0.5– 2 mg/h preceded by a loading dose of 2.5 mg intravenously over 10 min if needed (if RASS > 2+), 30	Placebo (Planned dose: 2-8ml, loading dose 10ml over 10 min if needed (if RASS > 2+)), 30	Intravenous	Incidence of delirium based on CAM-ICU threshold	10 / 30 (33.3%)	13 / 30 (43.3%)	0.77 (0.40 to 1.47)
Al-Qadheeb, 2016 ²	MV patients with subsyndromal delirium	Haloperidol (Planned dose: 1mg), 34	Placebo (Planned dose: 5% dextrose/ml), 34	Intravenous	During study drug administration	12 / 34 (35.3%)	8 / 34 (23.5%)	1.50 (0.70 to 3.20)
Al-Qadheeb, 2016 ²	MV patients with subsyndromal delirium	Haloperidol (Planned dose: 1mg), 34	Placebo (Planned dose: 5% dextrose/ml), 34	Intravenous	During the ICU admission	12 / 34 (35.3%)	9 / 34 (26.5%)	1.33 (0.65 to 2.74)
Fukata, 2014 ³	Delirium after abdominal or orthopedic surgery in elderly patients	Haloperidol (Planned dose: 2.5mg), 59	Placebo (), 60	Intravenous	Patients were limited to those with a preoperative MMSE <25	31 / 59 (52.8%)	26 / 60 (43.52%)	1.21 (0.83 to 1.77)
Fukata, 2014 ³	Delirium after abdominal or orthopedic surgery in elderly patients	Haloperidol (Planned dose: 2.5mg), 59	Placebo (), 60	Intravenous	NEECHAM score < 20	25 / 59 (42.4%)	20 / 60 (33.3%)	1.27 (0.80 to 2.02)

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
Kalisvaart, 2005 ⁶	Acute or elective hip surgery patients ≥ 70 years is at risk of delirium: MMSE between less than or equal to 24; dehydration=BUN/creatinine> or = to 18, low visual acuity and/or increased severity of illness on APACHE II of 16 or greater.	Haloperidol (Planned dose: 0.5mg), 212	Placebo (Not applicable), 218	Oral	Not applicable	32 / 212 (15.1%)	36 / 218 (16.5%)	0.91 (0.59 to 1.42)
Kaneko, 1999 ⁷	Scheduled for elective gastrointestinal surgery and admitted to ICU	Haloperidol (Planned dose: 5mg), 38	Placebo (Planned dose: 1 ml (0.9% normal saline)ml), 40	Intravenous	based on DSM criteria (not specified)	4 / 38 (%)	13 / 40 (%)	0.32 (0.12 to 0.91)
Khan, 2018 ⁸	English speaking individuals undergoing thoracic surgery	Haloperidol (Planned dose: 0.5mg, Planned duration: 4 days (11 doses total)), 68	Placebo (Planned dose: NR, Planned duration: 4 days (11 doses total)), 67	Intravenous	Incidence of delirium, based on CAM-ICU	15 / 68 (22.1%)	19 / 67 (28.4%)	0.78 (0.43 to 1.40)
Schrijver, 2018 ¹²	Medical and surgical patients	Haloperidol (Planned dose: 1mg), 118	Placebo, 124	Oral	DOSS score ≥3, confirmed by DSM-IV criteria	23 / 118 (19.5%)	18 / 124 (14.5%)	1.34 (0.76 to 2.36)
van den Boogaard, 2018 ¹⁵	ICU patients at high risk of delirium	Haloperidol (Planned dose: 2mg), 732	Placebo (Planned dose: 0.9% NaCl), 707	Intravenous	Number of patients who scored positive at-least once for CAM-ICU or ICDSC during 28 days assessment	244 / 732 (33.3%)	233 / 707 (33%)	1.01 (0.87 to 1.17)
van den Boogaard, 2018 ¹⁵	ICU patients at high risk of delirium	Haloperidol (Planned dose: 1mg), 350	Placebo (Planned dose: 0.9% NaCl), 707	Intravenous	Number of patients who scored positive at-least once for CAM-ICU or ICDSC during 28 days assessment	139 / 350 (39.7%)	233 / 707 (33%)	1.21 (1.02 to 1.42)
Wang, 2012 ¹⁶	Patients 65 or older admitted to the ICU after noncardiac surgery	Haloperidol (Planned dose: 0.5 mg followed by continuous infusion at a rate of 1 mL/hr (0.1 mg/hr haloperidol)), 229	Placebo (Planned dose: Normal saline), 228	Intravenous	Occurrence of Delirium, based on CAM-ICU	35 / 229 (15.3%)	53 / 228 (23.2%)	0.66 (0.45 to 0.97)

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
Second-generation antipsychotic vs. placebo								
Hakim, 2012 ⁵	Patients 65 years or older experiencing subsyndromal delirium after on-pump cardiac surgery	Risperidone (Planned dose: 0.5mg), 51	Placebo (Planned dose: given every 12 hours), 50	Oral	DSM criteria	7 / 51 (13.7%)	17 / 50 (34%)	0.40 (0.18 to 0.89)
Hakim, 2012 ⁵	Patients 65 years or older experiencing subsyndromal delirium after on-pump cardiac surgery	Risperidone (Planned dose: 0.5mg),	Placebo (Planned dose: given every 12 hours),	Oral	Possible delirium: ICDSC ≥4	8 / 51 (15.7%)	19 / 50 (38%)	0.41 (0.20 to 0.86)
Larsen, 2010 ⁹	Post-operative elderly joint replacement surgery patients	Olanzapine (Planned dose: 5mg), 196	Placebo (Planned dose: 5mg), 204	Oral	DSM-III-R	28 / 196 (14.3%)	82 / 204 (40.2%)	0.36 (0.24 to 0.52)
Prakanrattana, 2007 ¹¹	Elective Cardiac Surgery with cardiopulmonary bypass	Risperidone (Planned dose: 1mg), 63	Placebo (Not applicable), 63	Orally disintegrating tablet	The presence of features 1 and 2 and either feature 3 or 4, of CAM-ICU	3 / 63 (%)	15 / 63 (%)	0.20 (0.06 to 0.66)
Prakanrattana, 2007 ¹¹	Elective Cardiac Surgery with cardiopulmonary bypass	Risperidone (Planned dose: 1mg), 63	Placebo (Not applicable), 63	Orally disintegrating tablet	The presence of features 1 and 2 and either feature 3 or 4, of CAM-ICU	7 / 63 (11.1%)	20 / 63 (31.7%)	0.35 (0.16 to 0.77)

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
First-generation antipsychotic vs. other								
Abdelgalel, 2016 ¹	Adult intensive care patients of ASA physical status III and IV aged between 26 and 70 years	Haloperidol (Planned dose: 0.5– 2 mg/h preceded by a loading dose of 2.5 mg intravenously over 10 min if needed (if RASS > 2+), 30	Dexmedetomidine (Planned dose: 0.2–0.7 mcg/kg/h preceded by a loading dose of 1.0 ug/kg intravenously over 10 min if needed (if RASS > 2+)), 30	Intravenous	incidence of delirium based on CAM-ICU threshold	10 / 30 (33.3%)	3 / 30 (10%)	3.33 (1.02 to 10.92)

APACHE II= Acute Physiology and Chronic Health Evaluation 2; BUN=blood urea nitrogen ratio; CAM-ICU=Confusion Assessment Method for the ICU; CI=confidence interval; DSM=Diagnostic and Statistical Manual of Mental Disorders; ICDSC=Intensive Care Delirium Screening Checklist; ICU=intensive care unit; ICU=intensive care unit; Mg/hr=milligram per hour; ml/hr=milliliter per hour; MMSE=Mini-Mental State Examination; MV=mechanical ventilation; NaCl=sodium chloride; NEECHAM=Neelon and Champagne Confusion Scale; RASS=Richmond Agitation and Sedation Scale; SD=standard deviation; Ug/kg/h=microgram per kilogram per hour

Evidence Table D-24. Sedation outcomes in studies comparing interventions to prevent development of delirium

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
First-generation antipsychotic vs. placebo								
Al-Qadheeb, 2016 ²	MV patients with subsyndromal delirium	Haloperidol (Planned dose: 1mg), 34	Placebo (Planned dose: 5% dextrose/ml), 34	Intravenous	Excessive sedation	1 / 34 (2.9%)	0 / 34 (0%)	3.00 (0.13 to 71.15)
Kalisvaart, 2005 ⁶	Acute or elective hip surgery patients ≥ 70 years is at risk of delirium: MMSE between less than or equal to 24; dehydration=BUN/creatinine > or = to 18, low visual acuity and/or increased severity of illness on APACHE II of 16 or greater.	Haloperidol (Planned dose: 0.5mg), 212	Placebo (Not applicable), 218	Oral	Sedation	0 / 212 (0%)	0 / 218 (0%)	
Page, 2013 ¹⁰	ICU patients needing MV within 72 hours of admission were enrolled	Haloperidol (Planned dose: 2.5mg), 71	Placebo (Planned dose: 0.5ml), 70	Intravenous	Oversedation	11 / 71 (15%)	6 / 70 (9%)	1.81 (0.71 to 4.62)
Schrijver, 2018 ¹²	Medical and surgical patients	Haloperidol (Planned dose: 1mg), 118	Placebo, 124	Oral	Somnolence	2 / 118 (1.7%)	0 / 124 (0%)	5.25 (0.25 to 108.27)

APACHE II= Acute Physiology and Chronic Health Evaluation 2; BUN=blood urea nitrogen ratio; CI=confidence interval; ICU=intensive care unit; Mg=milligram; MMSE=Mini-Mental State Examination; MV=mechanical ventilation; N=sample size

Evidence Table D-25. Binary cardiac outcomes in studies comparing interventions to prevent development of delirium

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
First-generation antipsychotic vs. placebo								
Abdelgalel, 2016 ¹	Adult intensive care patients of ASA physical status III and IV aged between 26 and 70 years	Haloperidol (Planned dose: 0.5– 2 mg/h preceded by a loading dose of 2.5 mg intravenously over 10 min if needed (if RASS > 2+), 30	Placebo (Planned dose: 2-8ml, loading dose 10ml over 10 min if needed (if RASS > 2+)), 30	Intravenous	Arrhythmia	3 / 30 (10%)	2 / 30 (7%)	1.50 (0.27 to 8.34)
Abdelgalel, 2016 ¹	Adult intensive care patients of ASA physical status III and IV aged between 26 and 70 years	Haloperidol (Planned dose: 0.5– 2 mg/h preceded by a loading dose of 2.5 mg intravenously over 10 min if needed (if RASS > 2+), 30	Placebo (Planned dose: 2-8ml, loading dose 10ml over 10 min if needed (if RASS > 2+)), 30	Intravenous	Bradycardia (Heart rate decreased to ≤60 beats/min)	2 / 30 (7%)	1 / 30 (3%)	2.00 (0.19 to 20.90)
Abdelgalel, 2016 ¹	Adult intensive care patients of ASA physical status III and IV aged between 26 and 70 years	Haloperidol (Planned dose: 0.5– 2 mg/h preceded by a loading dose of 2.5 mg intravenously over 10 min if needed (if RASS > 2+), 30	Placebo (Planned dose: 2-8ml, loading dose 10ml over 10 min if needed (if RASS > 2+)), 30	Intravenous	Hypotension	3 / 30 (10%)	3 / 30 (10%)	1.00 (0.22 to 4.56)
Abdelgalel, 2016 ¹	Adult intensive care patients of ASA physical status III and IV aged between 26 and 70 years	Haloperidol (Planned dose: 0.5– 2 mg/h preceded by a loading dose of 2.5 mg intravenously over 10 min if needed (if RASS > 2+), 30	Placebo (Planned dose: 2-8ml, loading dose 10ml over 10 min if needed (if RASS > 2+)), 30	Intravenous	Prolongation in the QTc interval >500ms	2 / 30 (7%)	0 / 30 (0%)	5.00 (0.25 to 99.95)
Al-Qadheeb, 2016 ²	MV patients with subsyndromal delirium	Haloperidol (Planned dose: 1mg), 34	Placebo (Planned dose: 5% dextrose/ml), 34	Intravenous	Hypotension	1 / 34 (2.9%)	1 / 34 (2.9%)	1.00 (0.07 to 15.34)
Al-Qadheeb, 2016 ²	MV patients with subsyndromal delirium	Haloperidol (Planned dose: 1mg), 34	Placebo (Planned dose: 5% dextrose/ml), 34	Intravenous	Prolongation in the QTc interval	4 / 34 (11.8%)	1 / 34 (2.9%)	4.00 (0.47 to 33.97)
Girard, 2010 ⁴	> 18 years MV medical and surgical ICU patients	Haloperidol (Planned dose: 5 Median dose: 15 (10.8-17), 35	Placebo (Planned dose: 5ml), 36	Oral	Prolongation in the QTc interval prolongation of the QTc > 500 ms while receiving study drug	2 / 35 (5.7%)	3 / 36 (8.3%)	0.69 (0.12 to 3.86)
Girard, 2010 ⁴	> 18 years MV medical and surgical ICU patients	Haloperidol (Planned dose: 5 Median dose: 15 (10.8-17), 35	Placebo (Planned dose: 5ml), 36	Oral	Ventricular arrhythmias	0 / 35 (%)	0 / 36 (%)	

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
Khan, 2018 ⁸	English speaking individuals undergoing thoracic surgery	Haloperidol (Planned dose: 0.5mg, Planned duration: 4 days (11 doses total)), 68	Placebo (Planned dose: NR, Planned duration: 4 days (11 doses total)), 67	Intravenous	Arrhythmia	9 / 68 (13.2%)	10 / 67 (14.9%)	0.89 (0.38 to 2.04)
Khan, 2018 ⁸	English speaking individuals undergoing thoracic surgery	Haloperidol (Planned dose: 0.5mg, Planned duration: 4 days (11 doses total)), 68	Placebo (Planned dose: NR, Planned duration: 4 days (11 doses total)), 67	Intravenous	QT prolongation	3 / 68 (4.4%)	4 / 67 (6%)	0.74 (0.17 to 3.18)
Khan, 2018 ⁸	English speaking individuals undergoing thoracic surgery	Haloperidol (Planned dose: 0.5mg, Planned duration: 4 days (11 doses total)), 68	Placebo (Planned dose: NR, Planned duration: 4 days (11 doses total)), 67	Intravenous	Deep venous thrombosis	1 / 68 (1.5%)	5 / 67 (7.5%)	0.2 (0.02 to 1.64)
Page, 2013 ¹⁰	ICU patients needing MV within 72 hours of admission were enrolled	Haloperidol (Planned dose: 2.5mg), 71	Placebo (Planned dose: 0.5ml), 70	Intravenous	Atrial fibrillation	7 / 71 (10%)	3 / 70 (4%)	2.30 (0.62 to 8.54)
Page, 2013 ¹⁰	ICU patients needing MV within 72 hours of admission were enrolled	Haloperidol (Planned dose: 2.5mg), 71	Placebo (Planned dose: 0.5ml), 70	Intravenous	Bradycardia	2 / 71 (3%)	0 / 70 (%)	4.93 (0.24 to 100.89)
Page, 2013 ¹⁰	ICU patients needing MV within 72 hours of admission were enrolled	Haloperidol (Planned dose: 2.5mg), 71	Placebo (Planned dose: 0.5ml), 70	Intravenous	Hypotension	3 / 71 (4%)	2 / 70 (3%)	1.48 (0.25 to 8.58)
Page, 2013 ¹⁰	ICU patients needing MV within 72 hours of admission were enrolled	Haloperidol (Planned dose: 2.5mg), 71	Placebo (Planned dose: 0.5ml), 70	Intravenous	Prolongation in the QTc interval > 500 ms	7 / 71 (10%)	6 / 70 (9%)	1.15 (0.41 to 3.25)
Page, 2013 ¹⁰	ICU patients needing MV within 72 hours of admission were enrolled	Haloperidol (Planned dose: 2.5mg), 71	Placebo (Planned dose: 0.5ml), 70	Intravenous	Supraventricular Tachycardia	4 / 71 (6%)	1 / 70 (1%)	3.94 (0.45 to 34.41)

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
Schrijver, 2018 ¹²	Medical and surgical patients	Haloperidol (Planned dose: 1mg), 118	Placebo, 124	Oral	Acute coronary syndrome	2 / 118 (1.7%)	2 / 124 (1.6%)	1.05 (0.15 to 7.34)
Schrijver, 2018 ¹²	Medical and surgical patients	Haloperidol (Planned dose: 1mg),	Placebo,	Oral	Prolongation in the QTc interval milliseconds	-8.5 (32.5%)	-5.5 (30%)	-2.92 (-12.42 to 6.59)
Schrijver, 2018 ¹²	Medical and surgical patients	Haloperidol (Planned dose: 1mg),	Placebo,	Oral	Prolongation in the QTc interval milliseconds	7.3 (35%)	-5.1 (45.5%)	12.45 (-12.26 to 37.17)
Schrijver, 2018 ¹²	Medical and surgical patients	Haloperidol (Planned dose: 1mg),	Placebo,	Oral	Prolongation in the QTc interval milliseconds	-6.4 (29.2)	7.3 (54.1)	-13.62 (-31.26 to 4.03)
van den Boogaard, 2018 ¹⁵	ICU patients at high risk of delirium	Haloperidol (Planned dose: 2mg), 732	Placebo (Planned dose: 0.9% NaCl), 707	Intravenous	Monomorphic ventricular tachycardia	1 / 732 (0.13%)	0 / 707 (0%)	2.90 (0.12 to 71.01)
van den Boogaard, 2018 ¹⁵	ICU patients at high risk of delirium	Haloperidol (Planned dose: 1mg), 350	Placebo (Planned dose: 0.9% NaCl), 707	Intravenous	Monomorphic ventricular tachycardia	2 / 350 (0.57%)	0 / 707 (0%)	10.09 (0.49 to 209.51)
van den Boogaard, 2018 ¹⁵	ICU patients at high risk of delirium	Haloperidol (Planned dose: 2mg),	Placebo (Planned dose: 0.9% NaCl),	Intravenous	Prolongation in the QTc interval Maximum QTc interval	Median of the maximum times, 465 (IQR, 446 to 483)	Median of the maximum times, 463 (IQR, 440 to 486)	1 (-2 to 5)
van den Boogaard, 2018 ¹⁵	ICU patients at high risk of delirium	Haloperidol (Planned dose: 1mg),	Placebo (Planned dose: 0.9% NaCl),	Intravenous	Prolongation in the QTc interval Maximum QTc interval	Median of the maximum times, 465 (IQR, 440 to 489)	Median of the maximum times, 463 (IQR, 440 to 486)	
van den Boogaard, 2018 ¹⁵	ICU patients at high risk of delirium	Haloperidol (Planned dose: 2mg), 732	Placebo (Planned dose: 0.9% NaCl), 707	Intravenous	Prolongation in the QTc interval Number of QTc time prolongations	33 / 732 (4.5%)	36 / 707 (5.1%)	0.89 (0.56 to 1.40)
van den Boogaard, 2018 ¹⁵	ICU patients at high risk of delirium	Haloperidol (Planned dose: 1mg), 350	Placebo (Planned dose: 0.9% NaCl), 707	Intravenous	Prolongation in the QTc interval Number of QTc time prolongations	31 / 350 (8.9%)	36 / 707 (5.1%)	1.74 (1.09 to 2.76)

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
Wang, 2012 ¹⁶	Patients 65 or older admitted to the ICU after noncardiac surgery	Haloperidol (Planned dose: 0.5 mg followed by continuous infusion at a rate of 1 mL/hr (0.1 mg/hr haloperidol)), 229	Placebo (Planned dose: Normal saline), 228	Intravenous	Arrhythmia during study drug infusion	6 / 229 (2.6%)	5 / 228 (2.2%)	1.19 (0.37 to 3.86)
Wang, 2012 ¹⁶	Patients 65 or older admitted to the ICU after noncardiac surgery	Haloperidol (Planned dose: 0.5 mg followed by continuous infusion at a rate of 1 mL/hr (0.1 mg/hr haloperidol)),	Placebo (Planned dose: Normal saline),	Intravenous	Change of heart rate-corrected QT interval after study drug infusion,, ms, mean +/- SD	1 (26%)	-1 (31%)	2 (-3.2 to 7.2)
Wang, 2012 ¹⁶	Patients 65 or older admitted to the ICU after noncardiac surgery	Haloperidol (Planned dose: 0.5 mg followed by continuous infusion at a rate of 1 mL/hr (0.1 mg/hr haloperidol)), 229	Placebo (Planned dose: Normal saline), 228	Intravenous	Prolongation in the QT interval Significant heart rate-corrected QT interval prolongation after study drug infusion	4 / 229 (1.7%)	5 / 228 (2.2%)	0.80 (0.22 to 2.93)

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
Second-generation antipsychotic vs. placebo								
Girard, 2010 ⁴	> 18 years MV medical and surgical ICU patients	Ziprasidone (Planned dose: 40 Median dose: 113 (81-140), 30	Placebo (Planned dose: 5ml), 36	Oral	Prolongation in the QTc interval prolongation of the QTc > 500 ms while receiving study drug	5 / 30 (%)	3 / 36 (%)	2.00 (0.52 to 7.69)
Girard, 2010 ⁴	> 18 years MV medical and surgical ICU patients	Ziprasidone (Planned dose: 40 Median dose: 113 (81-140), 30	Placebo (Planned dose: 5ml), 36	Oral	Ventricular arrhythmias	0 / 30 (%)	0 / 36 (%)	Not calculable
Hakim, 2012 ⁵	Patients 65 years or older experiencing subsyndromal delirium after on-pump cardiac surgery	Risperidone (Planned dose: 0.5mg), 51	Placebo (Planned dose: given every 12 hours), 50	Oral	Prolongation in the QT interval Abnormality	0 / 51 (%)	0 / 50 (%)	Not calculable
Larsen, 2010 ⁹	Post-operative elderly joint replacement surgery patients	Olanzapine (Planned dose: 5mg), 196	Placebo (Planned dose: 5mg), 204	Oral	Arrhythmia	2 / 196 (1%)	1 / 204 (0.5%)	2.08 (0.19 to 22.77)
Larsen, 2010 ⁹	Post-operative elderly joint replacement surgery patients	Olanzapine (Planned dose: 5mg), 196	Placebo (Planned dose: 5mg), 204	Oral	Atrial Fibrillation	6 / 196 (3.1%)	3 / 204 (1.5%)	2.08 (0.53 to 8.21)
Larsen, 2010 ⁹	Post-operative elderly joint replacement surgery patients	Olanzapine (Planned dose: 5mg), 196	Placebo (Planned dose: 5mg), 204	Oral	CHF	1 / 196 (0.5%)	1 / 204 (0.5%)	1.04 (0.07 to 16.53)
Prakanrattana, 2007 ¹¹	Elective Cardiac Surgery with cardiopulmonary bypass	Risperidone (Planned dose: 1mg), 63	Placebo (Not applicable), 63	Orally disintegrating tablet	Arrhythmia	6 / 63 (9.5%)	6 / 63 (9.5%)	1.00 (0.34 to 2.93)

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
First-generation antipsychotic vs. second-generation antipsychotic								
Girard, 2010 ⁴	> 18 years MV medical and surgical ICU patients	Ziprasidone (Planned dose: 40 Median dose: 113 (81-140), 30	Haloperidol (Planned dose: 5 Median dose: 15 (10.8-17), 35	Oral	Prolongation in the QTc interval prolongation of the QTc > 500 ms while receiving study drug	5 / 30 (%)	2 / 35 (%)	2.92 (0.61 to 13.96)
Girard, 2010 ⁴	> 18 years MV medical and surgical ICU patients	Ziprasidone (Planned dose: 40 Median dose: 113 (81-140), 30	Haloperidol (Planned dose: 5 Median dose: 15 (10.8-17), 35	Oral	Ventricular arrhythmias	0 / 30 (%)	0 / 35 (%)	Not calculable
First-generation antipsychotic vs. other								
Abdelgalel, 2016 ¹	Adult intensive care patients of ASA physical status III and IV aged between 26 and 70 years	Haloperidol (Planned dose: 0.5–2 mg/h preceded by a loading dose of 2.5 mg intravenously over 10 min if needed (if RASS > 2+), 30	Dexmedetomidine (Planned dose: 0.2–0.7 mcg/kg/h preceded by a loading dose of 1.0 ug/kg intravenously over 10 min if needed (if RASS > 2+)), 30	Intravenous	Arrhythmia	3 / 30 (10%)	2 / 30 (7%)	1.50 (0.27 to 8.34)
Abdelgalel, 2016 ¹	Adult intensive care patients of ASA physical status III and IV aged between 26 and 70 years	Haloperidol (Planned dose: 0.5–2 mg/h preceded by a loading dose of 2.5 mg intravenously over 10 min if needed (if RASS > 2+), 30	Dexmedetomidine (Planned dose: 0.2–0.7 mcg/kg/h preceded by a loading dose of 1.0 ug/kg intravenously over 10 min if needed (if RASS > 2+)), 30	Intravenous	Bradycardia (Heart rate decreased to <= 60 beats/min)	2 / 30 (7%)	8 / 30 (27%)	0.25 (0.06 to 1.08)
Abdelgalel, 2016 ¹	Adult intensive care patients of ASA physical status III and IV aged between 26 and 70 years	Haloperidol (Planned dose: 0.5–2 mg/h preceded by a loading dose of 2.5 mg intravenously over 10 min if needed (if RASS > 2+), 30	Dexmedetomidine (Planned dose: 0.2–0.7 mcg/kg/h preceded by a loading dose of 1.0 ug/kg intravenously over 10 min if needed (if RASS > 2+)), 30	Intravenous	Hypotension	3 / 30 (10%)	4 / 30 (13%)	0.75 (0.18 to 3.07)
Abdelgalel, 2016 ¹	Adult intensive care patients of ASA physical status III and IV aged between 26 and 70 years	Haloperidol (Planned dose: 0.5–2 mg/h preceded by a loading dose of 2.5 mg intravenously over 10 min if needed (if RASS > 2+), 30	Dexmedetomidine (Planned dose: 0.2–0.7 mcg/kg/h preceded by a loading dose of 1.0 ug/kg intravenously over 10 min if needed (if RASS > 2+)), 30	Intravenous	Prolongation in the QTc interval >500ms	2 / 30 (7%)	0 / 30 (0%)	5.00 (0.25 to 99.95)

ASA=American Society of Anesthesiologists; CI=confidence interval; ICU=intensive care unit; IQR=interquartile range; IV=intravenous; Mg=milligram; Mg=milligram; ml/hr=milliliter per hour; ml=milliliter; MV=mechanical ventilation; N=sample size; QT=Q and T wave interval; QTc=corrected QT interval; RASS=Richmond Agitation and Sedation Scale; SD=standard deviation; Ug/kg=microgram per kilogram

Evidence Table D-26. Continuous cardiac outcomes in studies comparing interventions to prevent development of delirium

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	Mean change from baseline (SD) in ms, intervention group	Mean change from baseline (SD) in ms, control group	Mean between-group difference (95% CI) in ms
First-generation antipsychotic vs. placebo								
Schrijver, 2018 ¹³	Medical and surgical patients age 70 and above, with at least three ECGs	Haloperidol (Planned dose: 1mg, bid, mean 7 days), 38	Placebo (Planned dose: dose NR, bid, mean 7 days), 34	Oral	QTc-automatic, ms	Baseline: Mean 435.4 (SD 25) Final: Mean 437.8 (SD 20)	Baseline: Mean 431.3 (SD 24.7) Final: Mean 437.8 (SD 32.9)	-4.10 (95% CI: -131.27 to 123.07)
Schrijver, 2018 ¹³	Medical and surgical patients age 70 and above, with at least three ECGs	Haloperidol (Planned dose: 1mg, bid, mean 7 days), 38	Placebo (Planned dose: dose NR, bid, mean 7 days), 34	Oral	QTc-Bazett, ms	Baseline: Mean 422.2 (SD 33.6) Final: Mean 424.7 (SD 53)	Baseline: Mean 430.8 (SD 33.4) Final: Mean 411.1 (SD 27.3)	22.20 (95% CI: -165.43 to 209.83)
Schrijver, 2018 ¹³	Medical and surgical patients age 70 and above, with at least three ECGs	Haloperidol (Planned dose: 1mg, bid, mean 7 days), 38	Placebo (Planned dose: dose NR, bid, mean 7 days), 34	Oral	QTc-Framingham, ms	Baseline: Mean 403.1 (SD 25.4) Final: Mean 400 (SD 43.5)	Baseline: Mean 414.9 (SD 29.3) Final: Mean 399.7 (SD 19.7)	12.10 (95% CI: -138.38 to 162.58)

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	Mean change from baseline (SD) in ms, intervention group	Mean change from baseline (SD) in ms, control group	Mean between-group difference (95% CI) in ms
Schrijver, 2018 ¹³	Medical and surgical patients age 70 and above, with at least three ECGs	Haloperidol (Planned dose: 1mg, bid, mean 7 days), 38	Placebo (Planned dose: dose NR, bid, mean 7 days), 34	Oral	QTc-Fridericia, ms	Baseline: Mean 402.9 (SD 28.9) Final: Mean 400 (SD 49)	Baseline: Mean 414.8 (SD 30.7) Final: Mean 398 (SD 21.6)	13.90 (95% CI: -153.24 to 181.04)
Schrijver, 2018 ¹³	Medical and surgical patients age 70 and above, with at least three ECGs	Haloperidol (Planned dose: 1mg, bid, mean 7 days), 38	Placebo (Planned dose: dose NR, bid, mean 7 days), 34	Oral	QTc-Hodges, ms	Baseline: Mean 405.4 (SD 25.9) Final: Mean 402 (SD 58.6)	Baseline: Mean 413.5 (SD 29.1) Final: Mean 388.5 (SD 13.5)	21.60 (95% CI: -150.46 to 193.66)

Bid=twice daily; CI=confidence interval; ECG=electrocardiogram; Mg=milligram; ms=millisecond; N=sample size; NR=not reported; QTc= QTc=corrected QT interval; SD=standard deviation

Evidence Table D-27. Cardiac outcomes in studies comparing interventions to prevent development of delirium: single arm studies

Author, year	Study design	Population	Intervention group, n	Route of administration	Outcome definition	n / N (%), intervention group
van den Boogaard, 2013 ¹⁴	Prospective cohort with a comparison group, analyzed as a single group	Patients in the ICU who are at a high risk of delirium	Haloperidol (Planned dose: 1 Median dose: 2mg),	Intravenous	Prolongation in the QTc interval stopped medication due to prolonged QTc-time	9 / 177 (5%)

Mg=milligram; N=sample size; QTc=corrected QT interval

Evidence Table D-28. Binary neurological outcomes in studies comparing interventions to prevent development of delirium

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
First-generation antipsychotic vs. placebo								
Al-Qadheeb, 2016 ²	MV patients with subsyndromal delirium	Haloperidol (Planned dose: 1mg), 34	Placebo (Planned dose: 5% dextrose/ml), 34	Intravenous	Extrapyramidal symptoms	1 / 34 (2.9%)	0 / 34 (0%)	3.00 (0.13 to 71.15)
Fukata, 2014 ³	Delirium after abdominal or orthopedic surgery in elderly patients	Haloperidol (Planned dose: 2.5mg), 59	Placebo (), 60	Intravenous	Convulsions and temporary loss of consciousness 2 days after completing the preventive administration of haloperidol and T-tube removal	1 / 59 (2%)	0 / 60 (0%)	3.05 (0.13 to 73.39)
Girard, 2010 ⁴	> 18 years MV medical and surgical ICU patients	Haloperidol (Planned dose: 5 Median dose: 15 (10.8-17), 35	Placebo (Planned dose: 5ml), 36	Oral	Akathisia	10 / 35 (29%)	7 / 36 (19%)	1.47 (0.63 to 3.43)
Girard, 2010 ⁴	> 18 years MV medical and surgical ICU patients	Haloperidol (Planned dose: 5 Median dose: 15 (10.8-17), 35	Placebo (Planned dose: 5ml), 36	Oral	Extrapyramidal symptoms	4 / 35 (11%)	6 / 36 (17%)	0.69 (0.21 to 2.22)
Girard, 2010 ⁴	> 18 years MV medical and surgical ICU patients	Haloperidol (Planned dose: 5 Median dose: 15 (10.8-17), 35	Placebo (Planned dose: 5ml), 36	Oral	Neuroleptic malignant syndrome	0 / 35 (%)	0 / 36 (%)	Not calculable

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
Kalisvaart, 2005 ⁶	Acute or elective hip surgery patients ≥ 70 years is at risk of delirium: MMSE between less than or equal to 24; dehydration=BUN/creatinine > or = to 18, low visual acuity and/or increased severity of illness on APACHE II of 16 or greater.	Haloperidol (Planned dose: 0.5mg), 212	Placebo (Not applicable), 218	Oral	Extrapyramidal symptoms	0 / 212 (%)	0 / 218 (%)	Not calculable
Kaneko, 1999 ⁷	Scheduled for elective gastrointestinal surgery and admitted to ICU	Haloperidol (Planned dose: 5mg), 38	Placebo (Planned dose: 1 ml (0.9% normal saline)ml), 40	Intravenous	Extrapyramidal symptoms	0 / 38 (%)	0 / 40 (%)	Not calculable
Khan, 2018 ⁸	English speaking individuals undergoing thoracic surgery	Haloperidol (Planned dose: 0.5mg, Planned duration: 4 days (11 doses total)), 68	Placebo (Planned dose: NR, Planned duration: 4 days (11 doses total)), 67	Intravenous	Elbow Rigidity	0 / 68 (0%)	2 / 67 (3%)	0.2 (0.01 to 4.03)
Khan, 2018 ⁸	English speaking individuals undergoing thoracic surgery	Haloperidol (Planned dose: 0.5mg, Planned duration: 4 days (11 doses total)), 68	Placebo (Planned dose: NR, Planned duration: 4 days (11 doses total)), 67	Intravenous	Wrist Rigidity	1 / 68 (1.5%)	2 / 67 (3%)	0.49 (0.05 to 5.31)

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
Khan, 2018 ⁸	English speaking individuals undergoing thoracic surgery	Haloperidol (Planned dose: 0.5mg, Planned duration: 4 days (11 doses total)), 68	Placebo (Planned dose: NR, Planned duration: 4 days (11 doses total)), 67	Intravenous	Resting Tremor	1 / 68 (1.5%)	4 / 67 (6%)	0.25 (0.03 to 2.15)
Khan, 2018 ⁸	English speaking individuals undergoing thoracic surgery	Haloperidol (Planned dose: 0.5mg, Planned duration: 4 days (11 doses total)), 68	Placebo (Planned dose: NR, Planned duration: 4 days (11 doses total)), 67	Intravenous	Dystonia	0 / 68 (0%)	0 / 67 (0%)	
Khan, 2018 ⁸	English speaking individuals undergoing thoracic surgery	Haloperidol (Planned dose: 0.5mg, Planned duration: 4 days (11 doses total)), 68	Placebo (Planned dose: NR, Planned duration: 4 days (11 doses total)), 67	Intravenous	Neuroleptic Malignant Syndrome	0 / 68 (0%)	0 / 67 (0%)	
Khan, 2018 ⁸	English speaking individuals undergoing thoracic surgery	Haloperidol (Planned dose: 0.5mg, Planned duration: 4 days (11 doses total)), 68	Placebo (Planned dose: NR, Planned duration: 4 days (11 doses total)), 67	Intravenous	Tardive Dyskinesia	0 / 68 (0%)	0 / 67 (0%)	
Khan, 2018 ⁸	English speaking individuals undergoing thoracic surgery	Haloperidol (Planned dose: 0.5mg, Planned duration: 4 days (11 doses total)), 68	Placebo (Planned dose: NR, Planned duration: 4 days (11 doses total)), 67	Intravenous	Pseudoparkinsonism	0 / 68 (0%)	0 / 67 (0%)	

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
Page, 2013 ¹⁰	ICU patients needing MV within 72 hours of admission were enrolled	Haloperidol (Planned dose: 2.5mg), 71	Placebo (Planned dose: 0.5ml), 70	Intravenous	Akathisia	1 / 71 (1%)	2 / 70 (3%)	0.49 (0.05 to 5.31)
Page, 2013 ¹⁰	ICU patients needing MV within 72 hours of admission were enrolled	Haloperidol (Planned dose: 2.5mg), 71	Placebo (Planned dose: 0.5ml), 70	Intravenous	Muscle Stiffness	1 / 71 (1%)	1 / 70 (3%)	0.99 (0.06 to 15.45)
Page, 2013 ¹⁰	ICU patients needing MV within 72 hours of admission were enrolled	Haloperidol (Planned dose: 2.5mg), 71	Placebo (Planned dose: 0.5ml), 70	Intravenous	Torticollis	0 / 71 (%)	1 / 70 (3%)	0.33 (0.01 to 7.93)

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
Schrijver, 2018 ¹²	Medical and surgical patients	Haloperidol (Planned dose: 1mg), 118	Placebo, 124	Oral	Extrapyramidal symptoms	2 / 118 (1.7%)	2 / 124 (1.6%)	1.05 (0.15 to 7.34)
Schrijver, 2018 ¹²	Medical and surgical patients	Haloperidol (Planned dose: 1mg), 118	Placebo, 124	Oral	Transient ischemic attack	2 / 118 (1.7%)	0 / 124 (0%)	5.25 (0.25 to 108.27)
van den Boogaard, 2018 ¹⁵	ICU patients at high risk of delirium	Haloperidol (Planned dose: 1mg), 350	Placebo (Planned dose: 0.9% NaCl), 707	Intravenous	Extrapyramidal symptoms	9 / 350 (2.6%)	11 / 707 (1.6%)	1.65 (0.69 to 3.95)
van den Boogaard, 2018 ¹⁵	ICU patients at high risk of delirium	Haloperidol (Planned dose: 2mg), 732	Placebo (Planned dose: 0.9% NaCl), 707	Intravenous	Extrapyramidal symptoms	11 / 732 (1.5%)	11 / 707 (1.6%)	0.97 (0.42 to 2.21)
van den Boogaard, 2018 ¹⁵	ICU patients at high risk of delirium	Haloperidol (Planned dose: 1mg), 350	Placebo (Planned dose: 0.9% NaCl), 707	Intravenous	Suspected malignant neuroleptic syndrome	0 / 350 (%)	1 / 707 (%)	0.67 (0.03 to 16.46)
van den Boogaard, 2018 ¹⁵	ICU patients at high risk of delirium	Haloperidol (Planned dose: 2mg), 732	Placebo (Planned dose: 0.9% NaCl), 707	Intravenous	Suspected malignant neuroleptic syndrome	0 / 732 (%)	1 / 707 (%)	0.32 (0.01 to 7.89)
Wang, 2012 ¹⁶	Patients 65 or older admitted to the ICU after noncardiac surgery	Haloperidol (Planned dose: 0.5 mg followed by continuous infusion at a rate of 1 mL/hr (0.1 mg/hr haloperidol)), 229	Placebo (Planned dose: Normal saline), 228	Intravenous	Extrapyramidal symptoms	0 / 229 (0%)	0 / 228 (0%)	Not calculable

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
Second-generation antipsychotic vs. placebo								
Girard, 2010 ⁴	> 18 years MV medical and surgical ICU patients	Ziprasidone (Planned dose: 40 Median dose: 113 (81-140), 30	Placebo (Planned dose: 5ml), 36	Oral	Akathisia	6 / 30 (20%)	7 / 36 (19%)	1.03 (0.39 to 2.73)
Girard, 2010 ⁴	> 18 years MV medical and surgical ICU patients	Ziprasidone (Planned dose: 40 Median dose: 113 (81-140), 30	Placebo (Planned dose: 5ml), 36	Oral	Extrapyramidal symptoms	2 / 30 (7%)	6 / 36 (17%)	0.40 (0.09 to 1.84)
Girard, 2010 ⁴	> 18 years MV medical and surgical ICU patients	Ziprasidone (Planned dose: 40 Median dose: 113 (81-140), 30	Placebo (Planned dose: 5ml), 36	Oral	Neuroleptic malignant syndrome	0 / 30 (0%)	0 / 36 (0%)	Not calculable
Hakim, 2012 ⁵	Patients 65 years or older experiencing subsyndromal delirium after on-pump cardiac surgery	Risperidone (Planned dose: 0.5mg), 51	Placebo (Planned dose: given every 12 hours), 50	Oral	Extrapyramidal symptoms	2 / 51 (3.9%)	0 / 50 (0%)	4.90 (0.24 to 99.66)

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
First-generation antipsychotic vs. second-generation antipsychotic								
Girard, 2010 ⁴	> 18 years MV medical and surgical ICU patients	Ziprasidone (Planned dose: 40 Median dose: 113 (81-140), 30	Haloperidol (Planned dose: 5 Median dose: 15 (10.8-17), 35	Oral	Akathisia	6 / 30 (20%)	10 / 35 (29%)	0.70 (0.29 to 1.70)
Girard, 2010 ⁴	> 18 years MV medical and surgical ICU patients	Ziprasidone (Planned dose: 40 Median dose: 113 (81-140), 30	Haloperidol (Planned dose: 5 Median dose: 15 (10.8-17), 35	Oral	Extrapyramidal symptoms	2 / 30 (7%)	4 / 35 (11%)	0.58 (0.11 to 2.96)
Girard, 2010 ⁴	> 18 years MV medical and surgical ICU patients	Ziprasidone (Planned dose: 40 Median dose: 113 (81-140), 30	Haloperidol (Planned dose: 5 Median dose: 15 (10.8-17), 35	Oral	Neuroleptic malignant syndrome	0 / 30 (0%)	0 / 35 (0%)	Not calculable

APACHE II= Acute Physiology and Chronic Health Evaluation 2; CI=confidence interval; ICU=intensive care unit; Mg/hr=milligram per hour; mg=milligram; ml/hr=milliliter per hour; ml=milliliter; MMSE=Mini-Mental State Examination; MV=mechanical ventilation; n=sample size; NaCl=sodium chloride; SD=standard deviation

Evidence Table D-29. Continuous neurological outcomes in studies comparing interventions to prevent development of delirium

Author, year	Study design	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	Mean score, intervention	Mean score, control group
First-generation antipsychotic vs. placebo								
Khan, 2018 ⁸	RCT	English speaking individuals undergoing thoracic surgery	Haloperidol (Planned dose: 0.5mg, Planned duration: 4 days (11 doses total)), 68	Placebo (Planned dose: NR, Planned duration: 4 days (11 doses total)), 67	Intravenous	Akathisia, mean score	Mean: 1.2 (SD 1.4)	Mean: 1.2 (SD 1.6)

mg=milligram; NR=not reported; RCT=randomized controlled trial; SD=standard deviation

Evidence Table D-30. Neurological outcomes in studies comparing interventions to prevent development of delirium: single arm studies

Author, year	Study design	Population	Intervention group, n	Route of administration	Outcome definition	n / N (%), intervention group
van den Boogaard, 2013 ¹⁴	Prospective cohort with a comparison group, analyzed as a single group	Patients in the ICU who are at a high risk of delirium	Haloperidol (Planned dose: 1 Median dose: 2mg),	Intravenous	Medication stopped due to suspected malignant neuroleptic syndrome (later not confirmed)	1 / 177 (1%)
van den Boogaard, 2013 ¹⁴	Prospective cohort with a comparison group, analyzed as a single group	Patients in the ICU who are at a high risk of delirium	Haloperidol (Planned dose: 1 Median dose: 2mg),	Intravenous	Medication stopped due to signs of Parkinsonism	1 / 177 (1%)

ICU=intensive care unit; mg=milligram; N=sample size

Evidence Table D-31. Short-term continuous delirium symptom outcomes for studies comparing interventions to treat delirium

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	Median (IQR) hours, intervention group	Median (IQR) hours, control group	Measure of association (95% CI)
Second-generation antipsychotic vs. placebo								
Devlin, 2010 ²⁶	Patients admitted to Medical & Surgical ICU with delirium.	Quetiapine (Mean dose: 50 Median dose: 110 (88-191 IQR) Max dose: 200 Dose range: 50 to 200mg), 18	Placebo (Mean dose: 50 Median dose: 210 (116 - 293) Max dose: 200mg), 18	Either orally or NG tube	Sedation Agitated Scale (SAS) score \geq 5, hours	6 (0 to 38)	36 (11 to 66)	p=0.02
Tahir, 2010 ⁵⁹	Patients in medical, surgical and orthopedic wards, who met the DSM-IV criteria for delirium on the same day if they had a DRS-R-98 total score of 15 or more	Quetiapine (Mean dose: 40 Dose range: 25 - 175mg), 21	Placebo (Mean dose: 25 Max dose: 175mg), 21	Oral	Brief Psychiatric Rating Scale	Not reported	Not reported	There were no significant differences found between treatment groups for MMSE, BPRS, or CGI Global scores.
First-generation antipsychotic vs. second-generation antipsychotic								
Lim, 2007 ⁴⁶	Patients from internal medicine, PMR, neurology, neurosurgery, orthopedic surgery, or general surgery that were referred to the psychiatric department	Olanzapine (Titrated (5 to 20 mg)	Haloperidol (Titrated (5 to 20 mg)	Intramuscular	Abnormal Involuntary Movement Scale	Not reported	Not reported	p=NS
Maneeton, 2013 ⁴⁹	General adult population (age 18-75) with hyperactive delirium, referred to psychiatry consult liaison service at tertiary care hospital in Thailand	Quetiapine (Mean dose: 67.6 (SD 9.7) Dose range: 25-100mg),	Haloperidol (Mean dose: 0.8 (SD 0.3) Dose range: 0.5-2.0mg),	Oral	Total sleep times (hours)	Change from baseline: Mean: 6.5 (SD: 3)	Change from baseline: Mean: 6.1 (SD: 3.4)	-0.40 (95% CI: -2.14 to 1.34)

BPRS= Brief Psychiatric Rating Scale; CGI=Clinical Global Impressions Scale; CI=confidence interval; DRS-R-98= Delirium Rating Scale Revised-98; DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th ed; ICU=intensive care unit; IQR=interquartile range; mg=milligram; MMSE=Mini-Mental State Examination; NG=nadogastric tube; p=p-value; SAS=Sedation Agitated Scale; SD=standard deviation

Evidence Table D-32. Short-term binary delirium symptom outcomes for studies comparing interventions to treat delirium

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
First-generation antipsychotic vs. placebo								
Page, 2013 ¹⁰	ICU patients needing MV within 72 hours of admission were enrolled	Haloperidol (Planned dose: 2.5mg), 71	Placebo (Planned dose: 0.5ml), 70	Intravenous	RASS +2	9 / 71 (13%)	14 / 70 (20%)	0.63 (0.29 to 1.37)
First-generation antipsychotic vs. second-generation antipsychotic								
Grover, 2011 ³⁰	Consecutive patients >-18 years old referred to psychiatry and diagnosed with delirium	Olanzapine (Mean dose: 3.05mg Dose range: 1.25-10 mg per day), 23	Haloperidol (Mean dose: 0.88 Dose range: 0.25-5mg per day), 21	Oral	Increased duration of sleep	0 / 23 (0%)	1 / 21 (5%)	0.31 (0.01 to 7.12)
Grover, 2011 ³⁰	Consecutive patients >-18 years old referred to psychiatry and diagnosed with delirium	Risperidone (Mean dose: 0.95mg Dose range: 0.5-2.0mg per day), 20	Haloperidol (Mean dose: 0.88 Dose range: 0.25-5mg per day), 21	Oral	Increased duration of sleep	1 / 20 (5%)	1 / 21 (5%)	1.05 (0.07 to 15.68)
Second-generation antipsychotic vs. second-generation antipsychotic								
Grover, 2011 ³⁰	Consecutive patients >-18 years old referred to psychiatry and diagnosed with delirium	Risperidone (Mean dose: 0.95mg Dose range: 0.5-2.0mg per day), 20	Olanzapine (Mean dose: 3.05mg Dose range: 1.25-10 mg per day), 23	Oral	Increased duration of sleep	1 / 20 (5%)	0 / 23 (0%)	3.43 (0.15 to 79.74)

CI=confidence interval; ICU=intensive care unit; mg=milligram; ml=milliliter; MV=mechanical ventilation; N=sample size; RASS=Richmond Agitation and Sedation Scale

Evidence Table D-33. Continuous delirium severity outcomes for studies comparing interventions to treat delirium

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	Severity score, intervention group	Severity score, control group	Mean between-group difference (95% CI)
First-generation antipsychotic vs. placebo								
Agar, 2017 ¹⁷	Patients in Hospice and palliative care with delirium	Haloperidol (Max dose: 4 mg/day), 59	Placebo (Max dose: 4 mg/day), 64	Oral	MDAS Scores	Baseline: Mean 15.99 (95% CI: 13.19 to 18.74) Final: Mean 13.61 (95% CI: 10.86 to 16.46)	Baseline: Mean 15.01 (95% CI: 12.21 to 17.81) Final: Mean 10.26 (95% CI: 7.41 to 13.05)	0.75 (95% CI: -0.03 to 1.51), p=0.06
Agar, 2017 ¹⁷	Patients in Hospice and palliative care with delirium	Haloperidol (Max dose: 4 mg/day),	Placebo (Max dose: 4 mg/day),	Oral	NuDESC (Scores 2, 3, 4)	Baseline: Mean 2.6 (SD 1.48) Final: Not reported	Baseline: Mean 2.54 (SD 1.43) Final: Not reported	0.24 (95% CI: 0.06 to 0.42), p=0.009
Hu, 2006 ³⁵	Inpatients with senile delirium aged 65-99	Haloperidol (Dose range: 2.5-10mg), 72	Not reported ²⁹	Intramuscular	CGI-GI (global improvement item of the clinical global impression scale)	Baseline: Mean 4.94 (SD 0.69) Final: Mean 1.79 (SD 1.12)	Baseline: Mean 5.21 (SD 0.77) Final: Mean 3.97 (SD 1.76)	-1.91 (95% CI: -2.85 to -0.97)
Hu, 2006 ³⁵	Inpatients with senile delirium aged 65-99	Haloperidol (Dose range: 2.5-10mg), 72	Not reported ²⁹	Intramuscular	DRS score	Baseline: Mean 24.3 (SD 2.5) Final: Mean 7.2 (SD 4.6)	Baseline: Mean 24.7 (SD 3.5) Final: Mean 17.6 (SD 9.3)	-10.00 (95% CI: -14.58 to -5.42)
Second-generation antipsychotic vs. placebo								
Agar, 2017 ¹⁷	Patients in Hospice and palliative care with delirium	Risperidone (Max dose: 4 mg/d), 46	Placebo (Max dose: 4 mg/day), 64	Oral	MDAS Scores	Baseline: Mean 16.97 (95% CI: 14.08 to 19.81) Final: Mean 14.69 (95% CI: 11.7 to 17.62)	Baseline: Mean 15.01 (95% CI: 12.21 to 17.81) Final: Mean 10.26 (95% CI: 7.41 to 13.05)	0.96 (95% CI: 0.16 to 1.77), p=0.001
Agar, 2017 ¹⁷	Patients in Hospice and palliative care with delirium	Risperidone (Max dose: 4 mg/d),	Placebo (Max dose: 4 mg/day),	Oral	NuDESC (Scores 2, 3, 4)	Baseline: Mean 2.54 (SD 1.23) Final: Not reported	Baseline: Mean 2.54 (SD 1.43) Final: Not reported	0.48 (95% CI: 0.09 to 0.86), p=0.02

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	Severity score, intervention group	Severity score, control group	Mean between-group difference (95% CI)
Hu, 2006 ³⁵	Inpatients with senile delirium aged 65-99	Olanzapine (Dose range: 1.25-20mg), 74	Not reported 29	Oral or sublingually	CGI-GI (global improvement item of the clinical global impression scale)	Baseline: Mean 4.85 (SD 0.95) Final: Mean 2.05 (SD 0.99)	Baseline: Mean 5.21 (SD 0.77) Final: Mean 3.97 (SD 1.76)	-1.56 (95% CI: -2.54 to -0.58)
Hu, 2006 ³⁵	Inpatients with senile delirium aged 65-99	Olanzapine (Dose range: 1.25-20mg), 74	Not reported 29	Oral or sublingually	DRS score	Change from baseline: Mean -17.2 (Not reported)	Change from baseline: Mean -7.1 (Not reported)	-10.10 (95% CI: -14.71 to -5.49)
Tahir, 2010 ⁵⁹	Patients in medical, surgical and orthopedic wards, who met the DSM-IV criteria for delirium on the same day if they had a DRS-R-98 total score of 15 or more	Quetiapine (Mean dose: 40 Dose range: 25 - 175mg), 21	Placebo (Mean dose: 25 Max dose: 175mg), 21	Oral	DRS-R-98	Baseline: Mean 19.07 (SE 2.921) Final: Mean 9.673 (SE 2.647)	Baseline: Mean 19.07 (SE 2.921) Final: Mean 12.255 (SE 2.204)	-2.58 (95% CI: -15.45 to 10.29)
Tahir, 2010 ⁵⁹	Patients in medical, surgical and orthopedic wards, who met the DSM-IV criteria for delirium on the same day if they had a DRS-R-98 total score of 15 or more	Quetiapine (Mean dose: 40mg Dose range: 25 - 175mg), 21	Placebo (Mean dose: 25mg Max dose: 175mg), 21	Oral	DRS-R-98	Baseline: Mean 19.07 (SE 2.921) Final: Mean 7.132 (SE 3.347)	Baseline: Mean 19.07 (SE 2.921) Final: Mean 7.387 (SE 3.264)	-0.26 (95% CI: -15.21 to 14.70)
First-generation antipsychotic vs. first-generation antipsychotic								
Breitbart, 1996 ²²	Medically hospitalized adult patients with AIDS and a DRS score of 13 or greater (delirium)	Haloperidol (Planned dose: oral: 0.25-5.0mg, Intramuscular: 0.125-3.0mg Mean dose: 1.4 Dose range: 0.4 - 3.6mg), 11	Chlorpromazine (Planned dose: Oral: 10-200mg, Intramuscular: 5-100mg Mean dose: 36 Dose range: 10-80mg), 13	Oral or intramuscular	Delirium Rating Scale (older version) score	Baseline: Mean 20.45 (SD 3.45) Final: Mean 11.64 (SD 6.1)	Baseline: Mean 20.62 (SD 3.88) Final: Mean 11.85 (SD 6.74)	-0.04 (95% CI: -6.17 to 6.09)

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	Severity score, intervention group	Severity score, control group	Mean between-group difference (95% CI)
First-generation antipsychotic vs. second-generation antipsychotic								
Grover, 2011 ³⁰	Consecutive patients >-18 years old referred to psychiatry and diagnosed with delirium	Risperidone (Mean dose: 0.95mg Dose range: 0.5-2.0mg per day), 20	Haloperidol (Mean dose: 0.88 Dose range: 0.25-5mg per day), 21	Oral	DRS-R-98	Baseline: Mean 23.8 (SD 5.16) Final: Mean 8 (SD 7.27)	Baseline: Mean 21.85 (SD 4.77) Final: Mean 6.09 (SD 7.19)	-0.04 (95% CI: -5.82 to 5.74)
Grover, 2011 ³⁰	Consecutive patients >-18 years old referred to psychiatry and diagnosed with delirium	Olanzapine (Mean dose: 3.05mg Dose range: 1.25-10 mg per day), 23	Haloperidol (Mean dose: 0.88 Dose range: 0.25-5mg per day), 21	Oral	DRS-R-98	Baseline: Mean 22.56 (SD 4.49) Final: Mean 9.17 (SD 8.65)	Baseline: Mean 21.85 (SD 4.77) Final: Mean 6.09 (SD 7.19)	2.37 (95% CI: -3.26 to 8.00)
Grover, 2016 ³¹	Patients >18 years old referred to Psychiatry who met DSM-IV criteria for delirium	Quetiapine (Mean dose: 26.63 ± 15.61 Dose range: 12.5-75mg), 31	Haloperidol (Mean dose: 0.67 ± 0.35 Dose range: 0.25-1.25mg), 32	Oral	DRS-R-98	Change from baseline: Mean 4.86 (Not reported)	Change from baseline: Mean 4.94 (Not reported)	-0.52 (95% CI: -3.57 to 2.53)
Han, 2004 ³²	All patients presenting with altered mental status (from both ICU and non-ICU units) who were referred to the consulting psychiatry division were evaluated.	Risperidone (Mean dose: 1.02 Dose range: 0.5 to 2.0mg), 12	Haloperidol (Mean dose: 1.7 Dose range: 1.0 to 3.0mg), 12	Oral	DRS-R-98 (MDAS)	Baseline: Mean 33.8 (SD 6.8) Final: Mean 20.94 (SD 8.9)	Baseline: Mean 32.82 (SD 6.66) Final: Mean 15.18 (SD 10.48)	4.78 (95% CI: -5.95 to 15.51)
Hu, 2006 ³⁵	Inpatients with senile delirium aged 65-99	Olanzapine (Dose range: 1.25-20mg), 74	Haloperidol (Dose range: 2.5-10mg), 72	Oral or sublingually	CGI-GI (global improvement item of the clinical global impression scale)	Baseline: Mean 4.85 (SD 0.95) Final: Mean 2.05 (SD 0.99)	Baseline: Mean 4.94 (SD 0.69) Final: Mean 1.79 (SD 1.12)	0.35 (95% CI: -0.14 to 0.84)
Hu, 2006 ³⁵	Inpatients with senile delirium aged 65-99	Olanzapine (Dose range: 1.25-20mg), 74	Haloperidol (Dose range: 2.5-10mg), 72	Oral or sublingually	DRS score	Change from baseline: Mean -17.2 (Not reported)	Change from baseline: Mean -17.1 (Not reported)	0.00 (95% CI: -1.78 to 1.78)

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	Severity score, intervention group	Severity score, control group	Mean between-group difference (95% CI)
Jain, 2017 ³⁸	Medical and surgical inpatients	Olanzapine (Mean dose: 5.49mg), 47	Haloperidol (Mean dose: 2.10mg), 53	Oral	MDAS	Baseline: Mean 18.49 (Not reported) Final: Mean 8.43 (Not reported)	Baseline: Mean 17.79 (Not reported) Final: Mean 8 (Not reported)	-0.27 (95% CI: Not reported)
Lim, 2007 ⁴⁶	Patients from internal medicine, PMR, neurology, neurosurgery, orthopedic surgery, or general surgery that were referred to the psychiatric department	Olanzapine (Titrated (5 to 20 mg)31	Haloperidol (Titrated (5 to 20 mg)31	Intramuscular	DRS-R-98	Baseline: Mean 27.2 (SD 4) Final: Mean 6.8 (SD 4)	Baseline: Mean 22.8 (SD 9.4) Final: Mean 8 (SD 4.4)	-5.60 (95% CI: -11.61 to 0.41)
Lin, 2008 ⁴⁷	Patients receiving hospice or palliative care with advanced cancer and met DSM-IV criteria for delirium	Olanzapine (Planned dose: start dose 5mg Max dose: 15mg), 5	Haloperidol (Planned dose: start dose 5mg Max dose: 15mg), 7	Oral	Clinical Global Impression - Severity	Baseline: Mean 5 (SD 1.03) Final: Mean 3.6 (SD 0.55)	Baseline: Mean 4.5 (SD 1.02) Final: Mean 3.57 (SD 0.98)	-0.47 (95% CI: -1.77 to 0.83)
Lin, 2008 ⁴⁷	Patients receiving hospice or palliative care with advanced cancer and met DSM-IV criteria for delirium	Olanzapine (Planned dose: start dose 5mg Max dose: 15mg), 10	Haloperidol (Planned dose: start dose 5mg Max dose: 15mg), 14	Oral	Clinical Global Impression - Severity	Baseline: Mean 5 (SD 1.03) Final: Mean 4.1 (SD 1.2)	Baseline: Mean 4.5 (SD 1.02) Final: Mean 3.79 (SD 0.89)	-0.19 (95% CI: -1.46 to 1.08)
Lin, 2008 ⁴⁷	Patients receiving hospice or palliative care with advanced cancer and met DSM-IV criteria for delirium	Olanzapine (Planned dose: start dose 5mg Max dose: 15mg), 14	Haloperidol (Planned dose: start dose 5mg Max dose: 15mg), 14	Oral	Clinical Global Impression-Severity	Baseline: Mean 5 (SD 1.03) Final: Mean 4.07 (SD 1.21)	Baseline: Mean 4.5 (SD 1.02) Final: Mean 3.57 (SD 0.65)	0.00 (95% CI: -1.20 to 1.20)

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	Severity score, intervention group	Severity score, control group	Mean between-group difference (95% CI)
Lin, 2008 ⁴⁷	Patients receiving hospice or palliative care with advanced cancer and met DSM-IV criteria for delirium	Olanzapine (Planned dose: start dose 5mg Max dose: 15mg), 14	Haloperidol (Planned dose: start dose 5mg Max dose: 15mg), 14	Oral	DRS-c	Baseline: Mean 17.56 (SD 5.18) Final: Mean 14.29 (SD 4.55)	Baseline: Mean 16.5 (SD 4.7) Final: Mean 11.93 (SD 3.81)	1.30 (95% CI: -4.62 to 7.22)
Lin, 2008 ⁴⁷	Patients receiving hospice or palliative care with advanced cancer and met DSM-IV criteria for delirium	Olanzapine (Planned dose: start dose 5mg Max dose: 15mg), 10	Haloperidol (Planned dose: start dose 5mg Max dose: 15mg), 14	Oral	DRS-c	Baseline: Mean 17.56 (SD 5.18) Final: Mean 14.9 (SD 3.48)	Baseline: Mean 16.5 (SD 4.7) Final: Mean 13 (SD 5.02)	0.84 (95% CI: -5.45 to 7.13)
Lin, 2008 ⁴⁷	Patients receiving hospice or palliative care with advanced cancer and met DSM-IV criteria for delirium	Olanzapine (Planned dose: start dose 5mg Max dose: 15mg), 5	Haloperidol (Planned dose: start dose 5mg Max dose: 15mg), 7	Oral	DRS-c	Baseline: Mean 17.56 (SD 5.18) Final: Mean 10.6 (SD 3.65)	Baseline: Mean 16.5 (SD 4.7) Final: Mean 12.29 (SD 5.59)	-2.75 (95% CI: -9.23 to 3.73)
Maneeton, 2013 ⁴⁹	General adult population (age 18-75) with hyperactive delirium, referred to psychiatry consult liaison service at tertiary care hospital in Thailand	Quetiapine (Mean dose: 67.6 (SD 9.7) Dose range: 25-100mg),	Haloperidol (Mean dose: 0.8 (SD 0.3) Dose range: 0.5-2.0mg),	Oral	Clinical global impression	Change from baseline: mean difference -1.1 (SD 1)	Change from baseline: mean difference -1.2 (SD 1.4)	-0.10 (95% CI: -0.75 to 0.55)

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	Severity score, intervention group	Severity score, control group	Mean between-group difference (95% CI)
Maneeton, 2013 ⁴⁹	General adult population (age 18-75) with hyperactive delirium, referred to psychiatry consult liaison service at tertiary care hospital in Thailand	Quetiapine (Mean dose: 67.6 (SD 9.7) Dose range: 25-100mg), 24	Haloperidol (Mean dose: 0.8 (SD 0.3) Dose range: 0.5-2.0mg), 28	Oral	DRS-R-98	Change from baseline: Mean -22.9 (SD 6.9)	Change from baseline: Mean -21.7 (SD 6.7)	1.20 (95% CI: -2.51 to 4.91)
Skrobik, 2004 ⁵⁷	Medical-surgical ICU	Olanzapine (Mean dose: 4.54 Dose range: 2.5 to 13.5mg), 28	Haloperidol (Mean dose: 6.5 Dose range: 1 to 28mg), 45	Oral	Delirium Index	Baseline: Mean 6.7 (Not reported) Final: Mean 5.4 (Not reported)	Baseline: Mean 7.4 (Not reported) Final: Mean 4.8 (Not reported)	1.30 (95% CI: Not reported) p=0.64
Second-generation antipsychotic vs. second-generation antipsychotic								
Grover, 2011 ³⁰	Consecutive patients >-18 years old referred to psychiatry and diagnosed with delirium	Risperidone (Mean dose: 0.95mg Dose range: 0.5-2.0mg per day), 20	Olanzapine (Mean dose: 3.05mg Dose range: 1.25-10 mg per day), 23	Oral	DRS-R-98	Baseline: Mean 23.8 (SD 5.16) Final: Mean 8 (SD 7.27)	Baseline: Mean 22.56 (SD 4.49) Final: Mean 9.17 (SD 8.65)	-2.41 (95% CI: -8.24 to 3.42)
Kim, 2010 ⁴²	General hospital inpatients who met DSM-IV diagnostic criteria for delirium	Risperidone (Mean dose: 0.9 ± 0.6 Dose range: 0.25 - 2mg), 17	Olanzapine (Mean dose: 2.4± 1.7 Dose range: 1.25 - 7.5mg), 15	Not reported	DRS-R-98	Baseline: Mean 25.8 (SD 5.2) Final: Mean 7.62 (Not reported)	Baseline: Mean 23.5 (SD 5.1) Final: Mean 7.52 (Not reported)	-2.2 (95% CI: Not reported)
Lee, 2005 ⁴⁵	Patients referred to the Psychiatric Consultation that met DSM-IV criteria for delirium	Amisulpride (Mean dose: 156.4±97.5 Dose range: 50–800mg), 16	Quetiapine (Mean dose: 113 ± 85.5 Dose range: 50–300mg), 15	Not reported	DRS-R-98	Baseline: Mean 10.5 (SD 4.1) Final: Mean 3.5 (1.4)	Baseline: Mean 10.1 (SD 4.1) Final: Mean 3.5 (2.6)	-0.40 (95% CI: -5.06 to 4.26)

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	Severity score, intervention group	Severity score, control group	Mean between-group difference (95% CI)
First-generation antipsychotic vs. other								
Bakri, 2015 ¹⁹	ICU trauma patients without severe injury, comatose, or moribund patients were excluded	Haloperidol (Planned dose: 5 mg), 32	Ondansetron (Planned dose: 8 mg), 32	Intravenous	ICDSC score	Baseline: Mean 6.5 (SD 1.6) Final: Mean 3.4 (SD 1.1)	Baseline: Mean 6.4 (SD 1.5) Final: Mean 3.5 (SD 1.3)	-0.20 (95% CI: -1.44 to 1.04)
Bakri, 2015 ¹⁹	ICU trauma patients without severe injury, comatose, or moribund patients were excluded	Haloperidol (Planned dose: 5 mg), 32	Dexmedetomidine (Planned dose: 1 ug/kg), 32	Intravenous	ICDSC score	Baseline: Mean 6.5 (SD 1.6) Final: Mean 3.4 (SD 1.1)	Baseline: Mean 6.7 (SD 1.3) Final: Mean 2.9 (SD 1.2)	0.70 (95% CI: -0.45 to 1.85)
Breitbart, 1996 ²²	Medically hospitalized adult patients with AIDS and a DRS score of 13 or greater (delirium)	Lorazepam (Planned dose: Oral: 0.50-4.0mg, Intramuscular: 0.2-2.0mg Mean dose: 4.6 Dose range: 1.3 - 7.9mg), 6	Chlorpromazine (Planned dose: Oral: 10-200mg, Intramuscular: 5-100mg Mean dose: 36 Dose range: 10-80mg), 13	Oral or intramuscular	Delirium Rating Scale (older version) score	Baseline: Mean 18.33 (SD 2.58) Final: Mean 17 (SD 4.98)	Baseline: Mean 20.62 (SD 3.88) Final: Mean 11.85 (SD 6.74)	7.44 (95% CI: 1.53 to 13.35)
Breitbart, 1996 ²²	Medically hospitalized adult patients with AIDS and a DRS score of 13 or greater (delirium)	Haloperidol (Planned dose: oral: 0.25-5.0mg, Intramuscular: 0.125-3.0mg Mean dose: 1.4 Dose range: 0.4 - 3.6mg), 11	Lorazepam (Planned dose: Oral: 0.50-4.0mg, Intramuscular: 0.2-2.0mg Mean dose: 4.6 Dose range: 1.3 - 7.9mg), 6	Oral or intramuscular	Delirium Rating Scale (older version) score	Baseline: Mean 20.45 (SD 3.45) Final: Mean 11.64 (SD 6.1)	Baseline: Mean 18.33 (SD 2.58) Final: Mean 17 (SD 4.98)	-7.48 (95% CI: -13.32 to -1.64)

AIDS=acquired immunodeficiency syndrome; CGI-GI=Clinical Global Impressions Scale-Global Impression; CI=confidence interval; DRS=Delirium Rating Scale; DRS-R-98= Delirium Rating Scale Revised-98; DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th ed; ICDSC=Intensive Care Delirium Screening Checklist; ICU=intensive care unit; MDAS=Memorial Delirium Assessment Scale; mg/day=milligram per day; mg=milligram; NuDESC=Nursing Delirium Screening Scale; SD=standard deviation; SE=standard error

Evidence Table D-34. Binary delirium severity outcomes for studies comparing interventions to treat delirium

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
First-generation antipsychotic vs. placebo								
Hu, 2006 ³⁵	Inpatients with senile delirium aged 65-99	Haloperidol (Dose range: 2.5-10mg), 72	Not reported	Intramuscular	CGI-GI score of "significantly improved" or "completely alleviated"	63 / 72 (87.5%)	9 / 29 (31%)	2.82 (1.62 to 4.88)
Second-generation antipsychotic vs. placebo								
Hu, 2006 ³⁵	Inpatients with senile delirium aged 65-99	Olanzapine (Dose range: 1.25-20mg), 74	Not reported	Oral or sublingually	CGI-GI score of "significantly improved" or "completely alleviated"	61 / 74 (82.4%)	9 / 29 (31%)	2.66 (1.53 to 4.62)
Tahir, 2010 ⁵⁹	Patients in medical, surgical and orthopedic wards, who met the DSM-IV criteria for delirium on the same day if they had a DRS-R-98 total score of 15 or more	Quetiapine (Mean dose: 40 Dose range: 25 - 175mg), 21	Placebo (Mean dose: 25 Max dose: 175mg), 21	Oral	Clinical Global Improvement			There were no significant differences found between treatment groups for MMSE, BPRS, or CGI Global scores.
First-generation antipsychotic vs. second-generation antipsychotic								
Grover, 2011 ³⁰	Consecutive patients >18 years old referred to psychiatry and diagnosed with delirium	Risperidone (Mean dose: 0.95mg Dose range: 0.5-2.0mg per day), 20	Haloperidol (Mean dose: 0.88 Dose range: 0.25-5mg per day), 21	Oral	DRS-R-98 score <10 on day 6	14 / 20 (70%)	17 / 21 (81%)	0.86 (0.61 to 1.23)
Grover, 2011 ³⁰	Consecutive patients >18 years old referred to psychiatry and diagnosed with delirium	Olanzapine (Mean dose: 3.05mg Dose range: 1.25-10 mg per day), 23	Haloperidol (Mean dose: 0.88 Dose range: 0.25-5mg per day), 21	Oral	DRS-R-98 score <10 on day 6	16 / 23 (69.56%)	17 / 21 (81%)	0.86 (0.61 to 1.21)

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
Grover, 2016 ³¹	Patients >18 years old referred to Psychiatry who met DSM-IV criteria for delirium	Quetiapine (Mean dose: 26.63 ± 15.61 Dose range: 12.5-75mg), 31	Haloperidol (Mean dose: 0.67 ± 0.35 Dose range: 0.25-1.25mg), 32	Oral	DRS-R-98 < 10	21 / 31 (67.74%)	22 / 32 (68.75%)	0.99 (0.70 to 1.38)
Hu, 2006 ³⁵	Inpatients with senile delirium aged 65-99	Olanzapine (Dose range: 1.25-20mg), 74	Haloperidol (Dose range: 2.5-10mg), 72	Oral or sublingually	CGI-GI score of "significantly improved" or "completely alleviated"	61 / 74 (82.4%)	63 / 72 (87.5%)	0.94 (0.82 to 1.08)
Maneeton, 2013 ⁴⁹	General adult population (age 18-75) with hyperactive delirium, referred to psychiatry consult liaison service at tertiary care hospital in Thailand	Quetiapine (Mean dose: 67.6 (SD 9.7) Dose range: 25-100mg), 24	Haloperidol (Mean dose: 0.8 (SD 0.3) Dose range: 0.5-2.0mg), 28	Oral	Remission rate, a DRS-R-98 severity score =<12 without relapse	18 / 24 (75%)	19 / 28 (67.9%)	1.11 (0.78 to 1.56)
Maneeton, 2013 ⁴⁹	General adult population (age 18-75) with hyperactive delirium, referred to psychiatry consult liaison service at tertiary care hospital in Thailand	Quetiapine (Mean dose: 67.6 (SD 9.7) Dose range: 25-100mg), 24	Haloperidol (Mean dose: 0.8 (SD 0.3) Dose range: 0.5-2.0mg), 28	Oral	Response rate, reduction in DRS-R-98 severity score ≥50% or more from baseline	19 / 24 (79.2%)	22 / 28 (78.6%)	1.01 (0.76 to 1.34)
Second-generation antipsychotic vs. second-generation antipsychotic								
Grover, 2011 ³⁰	Consecutive patients >18 years old referred to psychiatry and diagnosed with delirium	Risperidone (Mean dose: 0.95mg Dose range: 0.5-2.0mg per day), 20	Olanzapine (Mean dose: 3.05mg Dose range: 1.25-10 mg per day), 23	Oral	DRS-R-98 score <10 on day 6	14 / 20 (70%)	16 / 23 (69.56%)	1.01 (0.68 to 1.49)

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
First-generation antipsychotic vs. other								
Bakri, 2015 ¹⁹	ICU trauma patients without severe injury, comatose, or moribund patients were excluded	Haloperidol (Planned dose: 5 mg), 32	Dexmedetomidine (Planned dose: 1 ug/kg), 32	Intravenous	Patients who remained delirious, according to ICDSC score	2 / 32 (6%)	3 / 32 (9%)	0.67 (0.12 to 3.73)
Bakri, 2015 ¹⁹	ICU trauma patients without severe injury, comatose, or moribund patients were excluded	Haloperidol (Planned dose: 5 mg), 32	Ondansetron (Planned dose: 8 mg), 32	Intravenous	Patients who remained delirious, according to ICDSC score	2 / 32 (6%)	6 / 32 (19%)	0.33 (0.07 to 1.53)

BPRS= Brief Psychiatric Rating Scale; CGI=Clinical Global Impressions Scale; CGI-GI=Clinical Global Impressions Scale-Global Impression; CI=confidence interval; DRS-R-98= Delirium Rating Scale Revised-98; DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th ed; ICDSC=Intensive Care Delirium Screening Checklist; ICU=intensive care unit; mg=milligram; MMSE=Mini-Mental State Examination; N=sample size; SD=standard deviation

Evidence Table D-35. Delirium free days outcomes for studies comparing interventions to treat delirium

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	Median (IQR) days, intervention group	Median (IQR), days, control group	Measure of association (95% CI)
First-generation antipsychotic vs. placebo								
Girard, 2010 ⁴	> 18 years MV medical and surgical ICU patients	Haloperidol (Planned dose: 5 Median dose: 15 (10.8-17), 35	Placebo (Planned dose: 5ml), 36	Oral	delirium/coma-free days during the 21-day study period.	14 (6 to 18)	12.5 (1.2 to 17.2)	
Girard, 2018 ²⁹	Patients over 18 years of age in the medical or surgical ICU, with delirium	Haloperidol (Mean dose: 11mg Dose range: 2.5-20mg), 192	Placebo (Mean dose: Not reported), 184	Intravenous	Days alive without delirium or coma	8 (0 to 11)	7 (0 to 11)	OR 0.88 (95% CI: 0.64 to 1.21), p=0.26
Girard, 2018 ²⁹	Patients over 18 years of age in the medical or surgical ICU, with delirium	Haloperidol (Mean dose: 11mg Dose range: 2.5-20mg), 192	Placebo (Mean dose: Not reported), 184	Intravenous	Days alive without delirium or coma	Adjusted median: 7.9 (95% CI: 4.4 to 9.6)	Adjusted median: 8.5 (95% CI: 5.6 to 9.9)	OR 0.88 (95% CI: 0.64 to 1.21), p=0.26
Page, 2013 ^{10, 27}	ICU patients needing MV within 72 hours of admission were enrolled	Haloperidol (Planned dose: 2.5mg), 71	Placebo (Planned dose: 0.5ml), 70	Intravenous	Alive, delirium free, and coma free days in first 14 days, median (IQR)	5 (0 to 10)	6 (0 to 11)	Mean difference -0.48 (95% CI: -2.08 to 1.21), p=0.53
Page, 2013 ^{10, 27}	ICU patients needing MV within 72 hours of admission were enrolled	Haloperidol (Planned dose: 2.5mg), 71	Placebo (Planned dose: 0.5ml), 70	Intravenous	Alive, delirium free, and coma free days in first 28 days	19 (0 to 24)	19.5 (0 to 25)	Mean difference -0.26 (95% CI: -3.72 to 3.46), p=0.57
Second-generation antipsychotic vs. placebo								
Girard, 2010 ⁴	> 18 years MV medical and surgical ICU patients	Ziprasidone (Planned dose: 40 Median dose: 113 (81-140), 30	Placebo (Planned dose: 5ml), 36	Oral	Delirium/coma-free days during the 21-day study period.	15 (9.1 to 18)	12.5 (1.2 to 17.2)	
Girard, 2018 ²⁹	Patients over 18 years of age in the medical or surgical ICU, with delirium	Ziprasidone (Mean dose: 20mg Dose range: 5.0-40mg), 190	Placebo (Mean dose: Not reported), 184	Intravenous	Days alive without delirium or coma	8 (2 to 11)	7 (0 to 11)	OR 1.04 (95% CI: 0.73-1.48), p=0.26
Girard, 2018 ²⁹	Patients over 18 years of age in the medical or surgical ICU, with delirium	Ziprasidone (Mean dose: 20mg Dose range: 5.0-40mg), 190	Placebo (Mean dose: Not reported), 184	Intravenous	Days alive without delirium or coma	Adjusted median: 8.7 (95% CI: 5.9 to 10)	Adjusted median: 8.5 (95% CI: 5.6 to 9.9)	OR 1.04 (95% CI: 0.73-1.48), p=0.26

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	Median (IQR) days, intervention group	Median (IQR), days, control group	Measure of association (95% CI)
First-generation antipsychotic vs. second-generation antipsychotic								
Girard, 2010 ⁴	> 18 years MV medical and surgical ICU patients	Ziprasidone (Planned dose: 40 Median dose: 113 (81-140), 30	Haloperidol (Planned dose: 5 Median dose: 15 (10.8-17), 35	Oral	Delirium/coma-free days during the 21-day study period.	15 (9.1 to 18)	14 (6 to 18)	
Girard, 2018 ²⁹	Patients over 18 years of age in the medical or surgical ICU, with delirium	Ziprasidone (Mean dose: 20mg Dose range: 5.0-40mg), 190	Haloperidol (Mean dose: 11mg Dose range: 2.5-20mg), 192	Intravenous	Days alive without delirium or coma	8 (2 to 11)	8 (0 to 11)	
Girard, 2018 ²⁹	Patients over 18 years of age in the medical or surgical ICU, with delirium	Ziprasidone (Mean dose: 20mg Dose range: 5.0-40mg), 190	Haloperidol (Mean dose: 11mg Dose range: 2.5-20mg), 192	Intravenous	Days alive without delirium or coma	Adjusted median: 8.7 (95% CI: 5.9 to 10)	Adjusted median: 7.9 (95% CI: 4.4 to 9.6)	

CI=confidence interval; ICU=intensive care unit; IQR=interquartile range; MV=mechanical ventilation

Evidence Table D-36. Duration of delirium outcomes for studies comparing interventions to treat delirium

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	Median (IQR) days, intervention group	Median (IQR), days, control group	Measure of association (95% CI)
First-generation antipsychotic vs. placebo								
Girard, 2010 ⁴	> 18 years MV medical and surgical ICU patients	Haloperidol (Planned dose: 5 Median dose: 15 (10.8-17), 35	Placebo (Planned dose: 5ml), 36	Oral	Delirium days	4 (2 to 7)	4 (2 to 6)	
Girard, 2018 ²⁹	Patients over 18 years of age in the medical or surgical ICU, with delirium	Haloperidol (Mean dose: 11mg Dose range: 2.5-20mg), 192	Placebo (Not reported), 184	Intravenous	Days with delirium	4 (2 to 7)	4 (2 to 8)	OR 1.12 (95% CI: 0.86 to 1.46), p=Not reported
Girard, 2018 ²⁹	Patients over 18 years of age in the medical or surgical ICU, with delirium	Haloperidol (Mean dose: 11mg Dose range: 2.5-20mg), 192	Placebo (Not reported), 184	Intravenous	Days with hyperactive delirium (RASS >0)	0 (0 to 1)	0 (0 to 1)	OR 1.18 (95% CI: 0.86 to 1.61), p=Not reported
Girard, 2018 ²⁹	Patients over 18 years of age in the medical or surgical ICU, with delirium	Haloperidol (Mean dose: 11mg Dose range: 2.5-20mg), 192	Placebo (Not reported), 184	Intravenous	Days with hypoactive delirium (RASS ≤0)	4 (2 to 6)	3 (2 to 8)	OR 1.1 (95% CI: 0.81 to 1.48), p=Not reported
Page, 2013 ^{10, 27}	ICU patients needing MV within 72 hours of admission were enrolled	Haloperidol (Planned dose: 2.5mg), 71	Placebo (Planned dose: 0.5ml), 70	Intravenous	Days in delirium	5 (2 to 8)	5 (1 to 8)	Mean difference 0.01 (95% CI: -1.31 to 1.33), p=0.99
Page, 2013 ^{10, 27}	ICU patients needing MV within 72 hours of admission were enrolled	Haloperidol (Planned dose: 2.5mg), 71	Placebo (Planned dose: 0.5ml), 70	Intravenous	Days in delirium	5 (2 to 10)	5 (1 to 9)	Mean difference -0.38 (95% CI: -2.37 to 1.62), p=0.71
Second-generation antipsychotic vs. placebo								
Devlin, 2010 ²⁶	Patients admitted to Medical & Surgical ICU with delirium.	Quetiapine (Mean dose: 50 Median dose: 110 (88-191 IQR) Max dose: 200 Dose range: 50 to 200mg), 18	Placebo (Mean dose: 50 Median dose: 210 (116 - 293) Max dose: 200mg), 18	Either orally or NG tube	Percent of time in delirium, as the percentage of time subject was administered study drug	53 (16 to 67)	69 (58 to 100)	
Devlin, 2010 ²⁶	Patients admitted to Medical & Surgical ICU with delirium.	Quetiapine (Mean dose: 50 Median dose: 110 (88-191 IQR) Max dose: 200 Dose range: 50 to 200mg), 18	Placebo (Mean dose: 50 Median dose: 210 (116 - 293) Max dose: 200mg), 18	Either orally or NG tube	Time in delirium in hours	36 (12 to 87)	120 (60 to 195)	

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	Median (IQR) days, intervention group	Median (IQR), days, control group	Measure of association (95% CI)
Girard, 2010 ⁴	> 18 years MV medical and surgical ICU patients	Ziprasidone (Planned dose: 40 Median dose: 113 (81-140), 30	Placebo (Planned dose: 5ml), 36	Oral	Delirium days	4 (2 to 8)	4 (2 to 6)	
Girard, 2018 ²⁹	Patients over 18 years of age in the medical or surgical ICU, with delirium	Ziprasidone (Mean dose: 20mg Dose range: 5.0-40mg), 190	Placebo (Not reported), 184	Intravenous	Days with delirium	4 (2 to 6)	4 (2 to 8)	OR 1.02 (95% CI: 0.69 to 1.51), p=Not reported
Girard, 2018 ²⁹	Patients over 18 years of age in the medical or surgical ICU, with delirium	Ziprasidone (Mean dose: 20mg Dose range: 5.0-40mg), 190	Placebo (Not reported), 184	Intravenous	Days with hyperactive delirium (RASS >0)	0 (0 to 1)	0 (0 to 1)	OR 1.09 (95% CI: 0.7 to 1.7), p=Not reported
Girard, 2018 ²⁹	Patients over 18 years of age in the medical or surgical ICU, with delirium	Ziprasidone (Mean dose: 20mg Dose range: 5.0-40mg), 190	Placebo (Not reported), 184	Intravenous	Days with hypoactive delirium (RASS ≤0)	3 (2 to 6)	3 (2 to 8)	OR 1 (95% CI: 0.68 to 1.47), p=Not reported
First-generation antipsychotic vs. second-generation antipsychotic								
Girard, 2010 ⁴	> 18 years MV medical and surgical ICU patients	Ziprasidone (Planned dose: 40 Median dose: 113 (81-140), 30	Haloperidol (Planned dose: 5 Median dose: 15 (10.8-17), 35	Oral	Delirium days	Median: 4 (IQR: 2 to 8)	Median: 4 (IQR: 2 to 7)	
Girard, 2018 ²⁹	Patients over 18 years of age in the medical or surgical ICU, with delirium	Ziprasidone (Mean dose: 20mg Dose range: 5.0-40mg), 190	Haloperidol (Mean dose: 11mg Dose range: 2.5-20mg), 192	Intravenous	Days with delirium	4 (2 to 6)	4 (2 to 7)	OR 1.02 (95% CI: 0.69 to 1.51), p=Not reported
Girard, 2018 ²⁹	Patients over 18 years of age in the medical or surgical ICU, with delirium	Ziprasidone (Mean dose: 20mg Dose range: 5.0-40mg), 190	Haloperidol (Mean dose: 11mg Dose range: 2.5-20mg), 192	Intravenous	Days with hyperactive delirium (RASS >0)	0 (0 to 1)	0 (0 to 1)	OR 1.09 (95% CI: 0.7 to 1.7), p=Not reported
Girard, 2018 ²⁹	Patients over 18 years of age in the medical or surgical ICU, with delirium	Ziprasidone (Mean dose: 20mg Dose range: 5.0-40mg), 190	Haloperidol (Mean dose: 11mg Dose range: 2.5-20mg), 192	Intravenous	Days with hypoactive delirium (RASS ≤0)	3 (2 to 6)	4 (2 to 6)	OR 1 (95% CI: 0.68 to 1.47), p=Not reported

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	Median (IQR) days, intervention group	Median (IQR), days, control group	Measure of association (95% CI)
Han, 2004 ³²	All patients presenting with altered mental status (from both ICU and non-ICU units) who were referred to the consulting psychiatry division were evaluated.	Risperidone (Mean dose: 1.02 Dose range: 0.5 to 2.0mg), 12	Haloperidol (Mean dose: 1.7 Dose range: 1.0 to 3.0mg), 12	Oral	Period of time until MDAS < 13	Mean: 4.17 (SD: 2.14)	Mean: 4.22 (SD: 2.48)	Difference between means: -0.05 (95% CI: -1.45 to 1.35)
Jain, 2017 ³⁸	Medical and surgical inpatients	Olanzapine (Mean dose: 5.49mg), 47	Haloperidol (Mean dose: 2.10mg), 53	Oral	MDAS score <10	Mean: 3.57 (SD: 0.71)	Mean: 3.37 (SD: 0.92)	Difference between means: 0.20 (95% CI: -0.05 to 0.45)
Lim, 2007 ⁴⁶	patients from internal medicine, PMR, neurology, neurosurgery, orthopedic surgery, or general surgery that were referred to the psychiatric department	Olanzapine (Titrated (5 to 20 mg)31	Haloperidol (Titrated (5 to 20 mg)31	Intramuscular	Time to recovery	Mean: 3.22 (SD: 1.2)	Mean: 3.14 (SD: 1.1)	Difference between means: 0.08 (95% CI: -0.31 to 0.47)
Maneeton, 2013 ⁴⁹	General adult population (age 18-75) with hyperactive delirium, referred to psychiatry consult liaison service at tertiary care hospital in Thailand	Quetiapine (Mean dose: 67.6 (SD 9.7) Dose range: 25-100mg), 24	Haloperidol (Mean dose: 0.8 (SD 0.3) Dose range: 0.5-2.0mg), 28	Oral	Time to first remission (days)	Mean: 2.6 (SD: 1.9)	Mean: 1.8 (SD: 1.5)	Hazard ratio 1.15 (95% CI: 0.6 to 2.19), p=0.68
Second-generation antipsychotic vs. other								
Lee, 2005 ⁴⁵	Patients referred to the Psychiatric Consultation that met DSM-IV criteria for delirium	Amisulpride (Mean dose: 156.4±97.5 Dose range: 50–800mg), 16	Quetiapine (Mean dose: 113 ± 85.5 Dose range: 50–300mg), 15	Not reported	The mean duration of stabilization	Mean: 6.3 (SD: 4.4)	Mean: 7.4 (SD: 4.1)	Difference between means: -1.10 (95% CI: -3.17 to 0.97), p=0.4
First-generation antipsychotic vs. other								
Atalan, 2013 ¹⁸	Post cardiac surgery patients with hyperactive type delirium	Morphine sulfate (Max dose: 20mg), 27	Haloperidol (Max dose: 20mg), 26	Intramuscular	Delirium duration	Mean: 31.56 (SD: 16.6)	Mean: 33.92 (SD: 16.7)	Difference between means: -2.36 (95% CI: -8.78 to 4.06), p=0.607

CI=confidence interval; DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th ed; ICU=intensive care unit; IQR=interquartile range; mg=milligram; ml=milliliter; MV=mechanical ventilation; NG=nadogastric tube; OR=odds ratio; p=p-value; RASS=Richmond Agitation and Sedation Scale; SD=standard deviation

Evidence Table D-37. Use of rescue therapy outcomes for studies comparing interventions to treat delirium

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
First-generation antipsychotic vs. placebo								
Agar, 2017 ¹⁷	Patients in hospice and palliative care with delirium	Haloperidol (Max dose: 4 mg/d)	Placebo (Max dose: 4 mg/day)	Oral	Midazolam 2.5mg for both placebo and risperidone. 4mg for haloperidol group			Midazolam use was significantly lower among those in the placebo arm compared with the risperidone and haloperidol arms combined on each study day (13 of 75 [17.3%] vs 50 of 144 [34.7%] on day 1; P = .007; 11 of 68 [16.8%] vs 40 of 121 [33.1%] on day 2; P = .01; and 9 of 66 [13.6%] vs 32 of 108 [29.6%] on day 3; P = .02).
Girard, 2010 ⁴	> 18 years MV medical and surgical ICU patients	Haloperidol (Planned dose: 5 Median dose: 15 (10.8-17), 35	Placebo (Planned dose: 5ml), 36	Oral	Haloperidol varies for each group	6 / 35 (17%)	14 / 36 (39%)	0.44 (0.19 to 1.02)
Girard, 2018 ²⁹	Patients over 18 years of age in the medical or surgical ICU, with delirium	Haloperidol (Mean dose: 11mg Dose range: 2.5-20mg), 192	Placebo (Not reported), 184	Intravenous	Open label antipsychotic exposure	39 / 192 (20%)	38 / 184 (22%)	0.98 (0.66 to 1.47)
Page, 2013 ¹⁰	ICU patients needing MV within 72 hours of admission were enrolled	Haloperidol (Planned dose: 2.5mg), 71	Placebo (Planned dose: 0.5ml), 70	Intravenous	Any anti-psychotic	8 / 71 (11%)	18 / 70 (26%)	0.44 (0.20 to 0.94)
Page, 2013 ¹⁰	ICU patients needing MV within 72 hours of admission were enrolled	Haloperidol (Planned dose: 2.5mg), 71	Placebo (Planned dose: 0.5ml), 70	Intravenous	Open Label Haloperidol	6 / 71 (8%)	15 / 70 (21%)	0.39 (0.16 to 0.96)

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
Second-generation antipsychotic vs. placebo								
Agar, 2017 ¹⁷	Patients in Hospice and palliative care with delirium	Risperidone (Max dose: 4 mg/d)	Placebo (Max dose: 4 mg/day)	Oral	Midazolam 2.5mg for both placebo and risperidone. 4mg for haloperidol group			Midazolam use was significantly lower among those in the placebo arm compared with the risperidone and haloperidol arms combined on each study day (13 of 75 [17.3%] vs 50 of 144 [34.7%] on day 1; P = .007; 11 of 68 [16.8%] vs 40 of 121 [33.1%] on day 2; P = .01; and 9 of 66 [13.6%] vs 32 of 108 [29.6%] on day 3; P = .02).
Girard, 2010 ⁴	> 18 years MV medical and surgical ICU patients	Ziprasidone (Planned dose: 40 Median dose: 113 (81-140), 30	Placebo (Planned dose: 5ml), 36	Oral	Haloperidol varies for each group	9 / 30 (30%)	14 / 36 (39%)	0.77 (0.39 to 1.53)
Girard, 2018 ²⁹	Patients over 18 years of age in the medical or surgical ICU, with delirium	Ziprasidone (Mean dose: 20mg Dose range: 5.0-40mg), 190	Placebo (Not reported), 184	Intravenous	Open label antipsychotic exposure	41 / 190 (22%)	38 / 184 (22%)	1.05 (0.71 to 1.55)

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
First-generation antipsychotic vs. second-generation antipsychotic								
Agar, 2017 ¹⁷	Patients in hospice and palliative care with delirium	Risperidone (Max dose: 4 mg/d),	Haloperidol (Max dose: 4 mg/d),	Oral	Midazolam 2.5mg for both placebo and risperidone. 4mg for haloperidol group			Midazolam use was significantly lower among those in the placebo arm compared with the risperidone and haloperidol arms combined on each study day (13 of 75 [17.3%] vs 50 of 144 [34.7%] on day 1; P = .007; 11 of 68 [16.8%] vs 40 of 121 [33.1%] on day 2; P = .01; and 9 of 66 [13.6%] vs 32 of 108 [29.6%] on day 3; P = .02).
Girard, 2010 ⁴	> 18 years MV medical and surgical ICU patients	Ziprasidone (Planned dose: 40 Median dose: 113 (81-140), 30	Haloperidol (Planned dose: 5 Median dose: 15 (10.8-17), 35	Oral	Haloperidol varies for each group	9 / 30 (30%)	6 / 35 (17%)	1.75 (0.70 to 4.35)
Girard, 2018 ²⁹	Patients over 18 years of age in the medical or surgical ICU, with delirium	Ziprasidone (Mean dose: 20mg Dose range: 5.0-40mg), 190	Haloperidol (Mean dose: 11mg Dose range: 2.5-20mg), 192	Intravenous	Open label antipsychotic exposure	41 / 190 (22%)	39 / 192 (20%)	1.06 (0.72 to 1.57)

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
Lin, 2008 ⁴⁷	Patients receiving hospice or palliative care with advanced cancer and met DSM-IV criteria for delirium	Olanzapine (Planned dose: start dose 5mg Max dose: 15mg), 5	Haloperidol (Planned dose: start dose 5mg Max dose: 15mg), 7	Oral	Midazolam dose not reported, as needed			Only states midazolam intramuscular injection across time periods were found to be not significantly different statistically.
Skrobik, 2004 ⁵⁷	Medical-surgical ICU	Olanzapine (Mean dose: 4.54 Dose range: 2.5 to 13.5mg), 28	Haloperidol (Mean dose: 6.5 Dose range: 1 to 28mg), 45	Oral	IV Haloperidol 1-5 mg	10 / 28 (%)	19 / 45 (%)	0.85 (0.46 to 1.55)
Second-generation antipsychotic vs. second-generation antipsychotic								
Kim, 2010 ⁴²	General hospital inpatients who met DSM-IV diagnostic criteria for delirium	Risperidone (Mean dose: 0.9 ± 0.6 Dose range: 0.25 - 2mg), 17	Olanzapine (Mean dose: 2.4± 1.7 Dose range: 1.25 - 7.5mg), 15	Not reported	Haloperidol IM	3 / 17 (18%)	0 / 15 (0%)	6.22 (0.35 to 111.47)
Kim, 2010 ⁴²	General hospital inpatients who met DSM-IV diagnostic criteria for delirium	Risperidone (Mean dose: 0.9 ± 0.6 Dose range: 0.25 - 2mg), 17	Olanzapine (Mean dose: 2.4± 1.7 Dose range: 1.25 - 7.5mg), 15	Not reported	Benzodiazepine IM	7 / 17 (41.2%)	4 / 15 (26.7%)	1.54 (0.56 to 4.25)
First-generation antipsychotic vs. other								
Bakri, 2015 ¹⁹	ICU trauma patients without severe injury, comatose, or moribund patients were excluded	Haloperidol (Planned dose: 5 mg), 32	Ondansetron (Planned dose: 8 mg), 32	Intravenous	Haloperidol	3 / 32 (9%)	11 / 32 (34%)	0.27 (0.08 to 0.89)
Bakri, 2015 ¹⁹	ICU trauma patients without severe injury, comatose, or moribund patients were excluded	Haloperidol (Planned dose: 5 mg), 32	Dexmedetomidine (Planned dose: 1 ug/kg), 32	Intravenous	Haloperidol	3 / 32 (9%)	5 / 32 (16%)	0.60 (0.16 to 2.30)

CI=confidence interval; DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th ed; ICU=intensive care unit; IQR=interquartile range; IV=intravenous; mg/d=milligram per day; mg=milligram; ml=milliliter; MV=mechanical ventilation; NG=nadogastric tube; OR=odds ratio; p=p-value; p=p-value; RASS=Richmond Agitation and Sedation Scale; SD=standard deviation

Evidence Table D-38. Mortality outcomes for studies comparing interventions to treat delirium

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
First-generation antipsychotic vs. placebo								
Agar, 2017 ¹⁷	Patients in Hospice and palliative care with delirium	Haloperidol (Max dose: 4 mg/d), 81	Placebo (Max dose: 4 mg/day), 84	Oral	Died during study period	9 / 81 (11.1%)	9 / 84 (10.7%)	1.17 (0.47 to 2.88)
Girard, 2010 ⁴	> 18 years MV medical and surgical ICU patients	Haloperidol (Planned dose: 5 Median dose: 15 (10.8-17), 35	Placebo (Planned dose: 5ml), 36	Oral	21-day mortality, n (%)	4 / 35 (11%)	6 / 36 (17%)	0.69 (0.21 to 2.22)
Girard, 2018 ²⁹	Patients over 18 years of age in the medical or surgical ICU, with delirium	Haloperidol (Mean dose: 11mg Dose range: 2.5-20mg), 192	Placebo (Not reported), 184	Intravenous	Death at 30 days	50 / 192 (26%)	50 / 184 (27%)	0.96 (0.69 to 1.34)
Girard, 2018 ²⁹	Patients over 18 years of age in the medical or surgical ICU, with delirium	Haloperidol (Mean dose: 11mg Dose range: 2.5-20mg), 192	Placebo (Not reported), 184	Intravenous	Death at 90 days	73 / 192 (38%)	63 / 184 (34%)	1.11 (0.85 to 1.45)
Page, 2013 ¹⁰ Drinkwater, 2014 ²⁷	ICU patients needing MV within 72 hours of admission were enrolled	Haloperidol (Planned dose: 2.5mg), 71	Placebo (Planned dose: 0.5ml), 70	Intravenous		20 / 71 (28.2%)	19 / 70 (27.1%)	1.04 (0.61 to 1.77)
Second-generation antipsychotic vs. placebo								
Agar, 2017 ¹⁷	Patients in Hospice and palliative care with delirium	Risperidone (Max dose: 4 mg/d), 82	Placebo (Max dose: 4 mg/day), 84	Oral	died during study period	16 / 82 (19.5%)	9 / 84 (10.7%)	1.82 (0.85 to 3.89)
Devlin, 2010 ²⁶	Patients admitted to Medical & Surgical ICU with delirium.	Quetiapine (Mean dose: 50 Median dose: 110 (88-191 IQR) Max dose: 200 Dose range: 50 to 200mg), 18	Placebo (Mean dose: 50 Median dose: 210 (116 - 293) Max dose: 200mg), 18	Either orally or NG tube	%, Hospital Mortality	2 / 18 (11%)	3 / 18 (17%)	0.67 (0.13 to 3.53)
Girard, 2010 ⁴	> 18 years MV medical and surgical ICU patients	Ziprasidone (Planned dose: 40 Median dose: 113 (81-140), 30	Placebo (Planned dose: 5ml), 36	Oral	21-day mortality, n (%)	4 / 30 (13%)	6 / 36 (17%)	0.80 (0.25 to 2.57)
Girard, 2018 ²⁹	Patients over 18 years of age in the medical or surgical ICU, with delirium	Ziprasidone (Mean dose: 20mg Dose range: 5.0-40mg), 190	Placebo (Not reported), 184	Intravenous	Death at 30 days	53 / 190 (28%)	50 / 184 (27%)	1.03 (0.74 to 1.43)

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
Girard, 2018 ²⁹	Patients over 18 years of age in the medical or surgical ICU, with delirium	Ziprasidone (Mean dose: 20mg Dose range: 5.0-40mg), 190	Placebo (Not reported), 184	Intravenous	Death at 90 days	65 / 190 (34%)	63 / 184 (34%)	1.00 (0.75 to 1.32)
Tahir, 2010 ⁵⁹	Patients in medical, surgical and orthopedic wards, who met the DSM-IV criteria for delirium on the same day if they had a DRS-R-98 total score of 15 or more	Quetiapine (Mean dose: 40 Dose range: 25 - 175mg), 21	Placebo (Mean dose: 25 Max dose: 175mg), 21	Oral	Death within 30 days of entering the study	4 / 21 (19%)	3 / 21 (%)	1.33 (0.34 to 5.24)
Tahir, 2010 ⁵⁹	Patients in medical, surgical and orthopedic wards, who met the DSM-IV criteria for delirium on the same day if they had a DRS-R-98 total score of 15 or more	Quetiapine (Mean dose: 40 Dose range: 25 - 175mg), 21	Placebo (Mean dose: 25 Max dose: 175mg), 21	Oral	Deaths before the completion of study	3 / 21 (14.3%)	1 / 21 (4.8%)	3.00 (0.34 to 26.56)
First-generation antipsychotic vs. first-generation antipsychotic								
Breitbart, 1996 ²²	Medically hospitalized adult patients with AIDS and a DRS score of 13 or greater (delirium)	Haloperidol (Planned dose: oral: 0.25-5.0mg, Intramuscular: 0.125-3.0mg Mean dose: 1.4 Dose range: 0.4 - 3.6mg), 11	Chlorpromazine (Planned dose: Oral: 10-200mg, Intramuscular: 5-100mg Mean dose: 36 Dose range: 10-80mg), 13	Oral or intramuscular		2 / 11 (18.2%)	2 / 13 (15.4%)	1.18 (0.20 to 7.06)
First-generation antipsychotic vs. second-generation antipsychotic								
Agar, 2017 ¹⁷	Patients in Hospice and palliative care with delirium	Risperidone (Max dose: 4 mg/d), 82	Haloperidol (Max dose: 4 mg/d), 81	Oral	died during study period	16 / 82 (19.5%)	9 / 81 (11.1%)	1.76 (0.82 to 3.74)
Girard, 2010 ⁴	> 18 years MV medical and surgical ICU patients	Ziprasidone (Planned dose: 40 Median dose: 113 (81-140), 30	Haloperidol (Planned dose: 5 Median dose: 15 (10.8-17), 35	Oral	21-day mortality, n (%)	4 / 30 (13%)	4 / 35 (11%)	1.17(0.32 to 4.27)
Girard, 2018 ²⁹	Patients over 18 years of age in the medical or surgical ICU, with delirium	Ziprasidone (Mean dose: 20mg Dose range: 5.0-40mg), 190	Haloperidol (Mean dose: 11mg Dose range: 2.5-20mg), 192	Intravenous	Death at 30 days	53 / 190 (28%)	50 / 192 (26%)	1.07 (0.77 to 1.49)
Girard, 2018 ²⁹	Patients over 18 years of age in the medical or surgical ICU, with delirium	Ziprasidone (Mean dose: 20mg Dose range: 5.0-40mg), 190	Haloperidol (Mean dose: 11mg Dose range: 2.5-20mg), 192	Intravenous	Death at 90 days	65 / 190 (34%)	73 / 192 (38%)	0.90 (0.69 to 1.18)

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
Grover, 2011 ³⁰	Consecutive patients >-18 years old referred to psychiatry and diagnosed with delirium	Risperidone (Mean dose: 0.95mg Dose range: 0.5-2.0mg per day), 22	Haloperidol (Mean dose: 0.88 Dose range: 0.25-5mg per day), 26	Oral		0 / 22 (0%)	0 / 26 (0%)	
Grover, 2011 ³⁰	Consecutive patients >-18 years old referred to psychiatry and diagnosed with delirium	Olanzapine (Mean dose: 3.05mg Dose range: 1.25-10 mg per day), 26	Haloperidol (Mean dose: 0.88 Dose range: 0.25-5mg per day), 26	Oral		0 / 26 (0%)	0 / 26 (0%)	
Jain, 2017 ³⁸	Medical and surgical inpatients	Olanzapine (Mean dose: 5.49mg), 66	Haloperidol (Mean dose: 2.10mg), 66	Oral	Not applicable	9 / 66 (13.6%)	7 / 66 (10.6%)	1.29 (0.51 to 3.25)
Maneeton, 2013 ⁴⁹	General adult population (age 18-75) with hyperactive delirium, referred to psychiatry consult liaison service at tertiary care hospital in Thailand	Quetiapine (Mean dose: 67.6 (SD 9.7) Dose range: 25-100mg), 24	Haloperidol (Mean dose: 0.8 (SD 0.3) Dose range: 0.5-2.0mg), 28	Oral	Not applicable	1 / 24 (4.2%)	1 / 28 (3.6%)	1.17(0.08 to 17.67)
Second-generation antipsychotic vs. second-generation antipsychotic								
Grover, 2011 ³⁰	Consecutive patients >-18 years old referred to psychiatry and diagnosed with delirium	Risperidone (Mean dose: 0.95mg Dose range: 0.5-2.0mg per day), 22	Olanzapine (Mean dose: 3.05mg Dose range: 1.25-10 mg per day), 26	Oral		0 / 22 (0%)	0 / 26 (0%)	
First-generation antipsychotic vs. other								
Atalan, 2013 ¹⁸	Post cardiac surgery patients with hyperactive type delirium	Haloperidol (Max dose: 20mg), 26	Morphine sulfate (Max dose: 20mg), 27	Intramuscular	Hospital mortality	2 / 26 (7.7%)	1 / 27 (3.7%)	2.08 (0.20 to 21.55)
Breitbart, 1996 ²²	Medically hospitalized adult patients with AIDS and a DRS score of 13 or greater (delirium)	Chlorpromazine (Planned dose: Oral: 10-200mg, Intramuscular: 5-100mg Mean dose: 36 Dose range: 10-80mg), 13	Lorazepam (Planned dose: Oral: 0.50-4.0mg, Intramuscular: 0.2-2.0mg Mean dose: 4.6 Dose range: 1.3 - 7.9mg), 6	Oral or intramuscular		2 / 13 (%)	1 / 6 (16.7%)	0.92 (0.10 to 8.31)
Breitbart, 1996 ²²	Medically hospitalized adult patients with AIDS and a DRS score of 13 or greater (delirium)	Haloperidol (Planned dose: oral: 0.25-5.0mg, Intramuscular: 0.125-3.0mg Mean dose: 1.4 Dose range: 0.4 - 3.6mg), 11	Lorazepam (Planned dose: Oral: 0.50-4.0mg, Intramuscular: 0.2-2.0mg Mean dose: 4.6 Dose range: 1.3 - 7.9mg), 6	Oral or intramuscular		2 / 11 (%)	1 / 6 (16.7%)	1.09 (0.12 to 9.70)

AIDS=acquired immunodeficiency syndrome; CI=confidence interval; DRS-R-98= Delirium Rating Scale Revised-98; DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th ed; ICU=intensive care unit; mg=milligram; N=sample size

Evidence Table D-39. Survival outcomes for studies comparing interventions to treat delirium

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	Median (IQR) days, intervention group	Median (IQR) days, control group	Measure of association (95% CI)
First-generation antipsychotic vs. placebo								
Agar, 2017 ¹⁷	Patients in Hospice and palliative care with delirium	Haloperidol (Max dose: 4 mg/d), 81	Placebo (Max dose: 4 mg/day), 84	Oral	Median survival, days	16	26	
Second-generation antipsychotic vs. placebo								
Agar, 2017 ¹⁷	Patients in Hospice and palliative care with delirium	Risperidone (Max dose: 4 mg/d), 82	Placebo (Max dose: 4 mg/day), 84	Oral	Median survival, days	17	26	
First-generation antipsychotic vs. second-generation antipsychotic								
Agar, 2017 ¹⁷	Patients in Hospice and palliative care with delirium	Risperidone (Max dose: 4 mg/d), 82	Haloperidol (Max dose: 4 mg/d), 81	Oral	Median survival, days	17	16	

CI=confidence interval; IQR=interquartile range; mg/d=milligram per day; N=sample size

Evidence Table D-40. Cognitive outcomes for studies comparing interventions to treat delirium

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	MMSE, intervention group	MMSE, control group	Mean between-group difference (95% CI)
Second-generation antipsychotic vs. placebo								
Tahir, 2010 ⁵⁹	Patients in medical, surgical and orthopedic wards, who met the DSM-IV criteria for delirium on the same day if they had a DRS-R-98 total score of 15 or more	Quetiapine (Mean dose: 40 Dose range: 25 - 175mg), 21	Placebo (Mean dose: 25 Max dose: 175mg), 21	Oral	Mini Mental Status:	Baseline: Mean 11.829 (SE 4.08) Final: Mean 16.317 (SE 3.689)	Baseline: Mean 11.829 (SE 4.08) Final: Mean 16.773 (SE 3.838)	-0.46 (95% CI: -19.29 to 18.38)
Tahir, 2010 ⁵⁹	Patients in medical, surgical and orthopedic wards, who met the DSM-IV criteria for delirium on the same day if they had a DRS-R-98 total score of 15 or more	Quetiapine (Mean dose: 40 Dose range: 25 - 175mg), 21	Placebo (Mean dose: 25 Max dose: 175mg), 21	Oral	Mini Mental Status:	Baseline: Mean 11.829 (SE 4.08) Final: Mean 18.504 (SE 4.739)	Baseline: Mean 11.829 (SE 4.08) Final: Mean 18.534 (SE 4.757)	-0.03 (95% CI: -21.24 to 21.18)
First-generation antipsychotic vs. first-generation antipsychotic								
Breitbart, 1996 ²²	Medically hospitalized adult patients with AIDS and a DRS score of 13 or greater (delirium)	Haloperidol (Planned dose: oral: 0.25-5.0mg, Intramuscular: 0.125-3.0mg Mean dose: 1.4 Dose range: 0.4 - 3.6mg), 11	Chlorpromazine (Planned dose: Oral: 10-200mg, Intramuscular: 5-100mg Mean dose: 36 Dose range: 10-80mg), 13	Oral or intramuscular	Mini Mental Status:	Baseline: Mean 13.45 (SD 6.95) Final: Mean 17.18 (SD 12.12)	Baseline: Mean 10.92 (SD 8.87) Final: Mean 15.08 (SD 10.43)	-0.43 (95% CI: -12.20 to 11.34)
First-generation antipsychotic vs. second-generation antipsychotic								
Grover, 2011 ³⁰	Consecutive patients >-18 years old referred to psychiatry and diagnosed with delirium	Risperidone (Mean dose: 0.95mg Dose range: 0.5-2.0mg per day), 20	Haloperidol (Mean dose: 0.88 Dose range: 0.25-5mg per day), 21	Oral	Mini Mental Status:	Baseline: Mean 6.84 (SD 5.33) Final: Mean 22.31 (SD 6.63)	Baseline: Mean 6.38 (SD 5.02) Final: Mean 21.71 (SD 7.66)	0.14 (95% CI: -5.95 to 6.23)

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	MMSE, intervention group	MMSE, control group	Mean between-group difference (95% CI)
Grover, 2011 ³⁰	Consecutive patients >18 years old referred to psychiatry and diagnosed with delirium	Olanzapine (Mean dose: 3.05mg Dose range: 1.25-10 mg per day), 23	Haloperidol (Mean dose: 0.88 Dose range: 0.25-5mg per day), 21	Oral	Mini Mental Status:	Baseline: Mean 9.72 (SD 6.3) Final: Mean 20.77 (SD 8.14)	Baseline: Mean 6.38 (SD 5.02) Final: Mean 21.71 (SD 7.66)	-4.28 (95% CI: -10.61 to 2.05)
Grover, 2016 ³¹	Patients >18 years old referred to Psychiatry who met DSM-IV criteria for delirium	Quetiapine (Mean dose: 26.63 ± 15.61 Dose range: 12.5-75mg), 31	Haloperidol (Mean dose: 0.67 ± 0.35 Dose range: 0.25-1.25mg), 32	Oral	Mini Mental Status:	Change from baseline: Mean 12.23 (Not reported) Baseline: Mean 6.83 (SD 4.45) Final: Mean 22.54 (SD 5.34)	Change from baseline: Mean 12.38 (Not reported) Baseline: 7.5 SD (3.83 Not reported) Final: 23 SD (4.75 Not reported)	0.15 (95% CI: -3.43 to 3.73)
Second-generation antipsychotic vs. second-generation antipsychotic								
Grover, 2011 ³⁰	Consecutive patients >18 years old referred to psychiatry and diagnosed with delirium	Risperidone (Mean dose: 0.95mg Dose range: 0.5-2.0mg per day), 20	Olanzapine (Mean dose: 3.05mg Dose range: 1.25-10 mg per day), 23	Oral	Mini Mental Status:	Baseline: Mean 6.84 (SD 5.33) Final: Mean 22.31 (SD 6.63)	Baseline: Mean 9.72 (SD 6.3) Final: Mean 20.77 (SD 8.14)	4.42 (95% CI: -2.16 to 11.00)
First-generation antipsychotic vs. other								
Breitbart, 1996 ²²	Medically hospitalized adult patients with AIDS and a DRS score of 13 or greater (delirium)	Lorazepam (Planned dose: Oral: 0.50-4.0mg, Intramuscular: 0.2-2.0mg Mean dose: 4.6 Dose range: 1.3 - 7.9mg), 6	Chlorpromazine (Planned dose: Oral: 10-200mg, Intramuscular: 5-100mg Mean dose: 36 Dose range: 10-80mg), 13	Oral or intramuscular	Mini Mental Status:	Baseline: Mean 15.17 (SD 5.31) Final: Mean 11.5 (SD 8.69)	Baseline: Mean 10.92 (SD 8.87) Final: Mean 15.08 (SD 10.43)	-7.83 (95% CI: -19.15 to 3.49)
Breitbart, 1996 ²²	Medically hospitalized adult patients with AIDS and a DRS score of 13 or greater (delirium)	Lorazepam (Planned dose: Oral: 0.50-4.0mg, Intramuscular: 0.2-2.0mg Mean dose: 4.6 Dose range: 1.3 - 7.9mg), 6	Haloperidol (Planned dose: oral: 0.25-5.0mg, Intramuscular: 0.125-3.0mg Mean dose: 1.4 Dose range: 0.4 - 3.6mg), 11	Oral or intramuscular	Mini Mental Status:	Baseline: Mean 15.17 (SD 5.31) Final: Mean 11.5 (SD 8.69)	Baseline: Mean 13.45 (SD 6.95) Final: Mean 17.18 (SD 12.12)	-7.40 (95% CI: -19.11 to 4.31)

AIDS=acquired immunodeficiency syndrome; CI=confidence interval; DRS-R-98= Delirium Rating Scale Revised-98; DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th ed; mg=milligram; MMSE=Mini-Mental State Examination; SD=standard deviation; SE=standard error

Evidence Table D-41. Intensive care unit readmission outcomes for studies comparing interventions to treat delirium

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
First-generation antipsychotic vs. placebo								
Girard, 2018 ²⁹	Patients over 18 years of age in the medical or surgical ICU, with delirium	Haloperidol (Mean dose: 11mg Dose range: 2.5-20mg), 192	Placebo (Not reported), 184	Intravenous	ICU Readmission, % patients	27 / 192 (14%)	23 / 184 (12%)	1.13 (0.67 to 1.89)
Page, 2013 ¹⁰	ICU patients needing MV within 72 hours of admission were enrolled	Haloperidol (Planned dose: 2.5mg), 71	Placebo (Planned dose: 0.5ml), 70	Intravenous	Readmission to ICU with sepsis	1 / 71 (3%)	1 / 70 (1%)	0.99 (0.06 to 15.45)
Second-generation antipsychotic vs. placebo								
Girard, 2018 ²⁹	Patients over 18 years of age in the medical or surgical ICU, with delirium	Ziprasidone (Mean dose: 20mg Dose range: 5.0-40mg), 190	Placebo (Not reported), 184	Intravenous	ICU Readmission, % patients	18 / 190 (9%)	23 / 184 (12%)	0.76 (0.42 to 1.36)
First-generation antipsychotic vs. Second-generation antipsychotic								
Girard, 2018 ²⁹	Patients over 18 years of age in the medical or surgical ICU, with delirium	Ziprasidone (Mean dose: 20mg Dose range: 5.0-40mg), 190	Haloperidol (Mean dose: 11mg Dose range: 2.5-20mg), 192	Intravenous	ICU Readmission, % patients	18 / 190 (9%)	27 / 192 (14%)	0.67 (0.38 to 1.18)

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
First-generation antipsychotic vs. other								
Atalan, 2013 ¹⁸	Post cardiac surgery patients with hyperactive type delirium	Haloperidol (Max dose: 20mg), 26	Morphine sulfate (Max dose: 20mg), 27	Intramuscular	Duration of ICU stay	8 / 26 (30.8%)	7 / 27 (25.9%)	1.19 (0.50 to 2.80)

CI=confidence interval; ICU=intensive care unit; mg=milligram; ml=milliliter; n=sample size

Evidence Table D-42. Length of hospital stay outcomes for studies comparing interventions to treat delirium

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	Median (IQR) days, intervention group	Median (IQR), days, control group	Measure of association (95% CI)
First-generation antipsychotic vs. placebo								
Girard, 2010 ⁴	> 18 years MV medical and surgical ICU patients	Haloperidol (Planned dose: 5 Median dose: 15 (10.8-17), 35	Placebo (Planned dose: 5ml), 36	Oral	Length of stay, days in Hospital	13.8 (9.4 to Not reported)	15.4 (8.9 to Not reported)	
Girard, 2018 ²⁹	Patients over 18 years of age in the medical or surgical ICU, with delirium	Haloperidol (Mean dose: 11mg Dose range: 2.5-20mg), 192	Placebo (Not reported), 184	Intravenous	Days to hospital discharge	13 (8 to 22)	13 (8 to 23)	HR 1.03 (95% CI: 0.85 to 1.23), p=
Page, 2013 ^{10, 27}	ICU patients needing MV within 72 hours of admission were enrolled	Haloperidol (Planned dose: 2.5mg), 42	Placebo (Planned dose: 0.5ml), 47	Intravenous	Length of hospital stay, Excluding patients who died in hospital	18.5 (12 to 31)	26 (15 to 40)	Mean difference - 5.13 (95% CI: - 21.75 to 11.48), p=0.54
Second-generation antipsychotic vs. placebo								
Devlin, 2010 ²⁶	Patients admitted to Medical & Surgical ICU with delirium.	Quetiapine (Mean dose: 50 Median dose: 110 (88-191 IQR) Max dose: 200 Dose range: 50 to 200mg), 18	Placebo (Mean dose: 50 Median dose: 210 (116 - 293) Max dose: 200mg), 18	Either orally or NG tube	Duration of hospitalization, days	24 (11 to 33)	26 (17 to 49)	
Girard, 2010 ⁴	> 18 years MV medical and surgical ICU patients	Ziprasidone (Planned dose: 40 Median dose: 113 (81-140), 30	Placebo (Planned dose: 5ml), 36	Oral	Length of stay, days in Hospital	13.5 (9.3 to Not reported)	15.4 (8.9 to Not reported)	
Girard, 2018 ²⁹	Patients over 18 years of age in the medical or surgical ICU, with delirium	Ziprasidone (Mean dose: 20mg Dose range: 5.0-40mg), 190	Placebo (Not reported), 184	Intravenous	Days to hospital discharge	12 (8 to 21)	13 (8 to 23)	HR 1.05 (95% CI: 0.88 to 1.25), p=Not reported

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	Median (IQR) days, intervention group	Median (IQR), days, control group	Measure of association (95% CI)
First-generation antipsychotic vs. second-generation antipsychotic								
Girard, 2010 ⁴	> 18 years MV medical and surgical ICU patients	Ziprasidone (Planned dose: 40 Median dose: 113 (81-140), 30	Haloperidol (Planned dose: 5 Median dose: 15 (10.8-17), 35	Oral	Length of stay, days in Hospital	13.5 (9.3 to Not reported)	13.8 (9.4 to Not reported)	
Girard, 2018 ²⁹	Patients over 18 years of age in the medical or surgical ICU, with delirium	Ziprasidone (Mean dose: 20mg Dose range: 5.0-40mg), 190	Haloperidol (Mean dose: 11mg Dose range: 2.5-20mg), 192	Intravenous	Days to hospital discharge	12 (8 to 21)	13 (8 to 22)	HR 1.05 (95% CI: 0.88 to 1.25), p=Not reported
First-generation antipsychotic vs. other								
Atalan, 2013 ¹⁸	Post cardiac surgery patients with hyperactive type delirium	Morphine sulfate (Max dose: 20mg), 27	Haloperidol (Max dose: 20mg), 26	Intramuscular	length of hospital stay, in days	Mean: 8.93 (SD: 3.11)	Mean: 8.54 (SD: 3.44)	

CI=confidence interval; HR=Hazard ratio; ICU=intensive care unit; IQR=interquartile range; mg=milligram; ml=milliliter; MV=mechanical ventilation; n=sample size; NG=nadogastric tube; SD=standard deviation

Evidence Table D-43. Length of intensive care unit stay outcomes for studies comparing interventions to treat delirium

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	Median (IQR) days, intervention group	Median (IQR) days, control group	Measure of association (95% CI)
First-generation antipsychotic vs. placebo								
Girard, 2010 ⁴	> 18 years MV medical and surgical ICU patients	Haloperidol (Planned dose: 5 Median dose: 15 (10.8-17), 35	Placebo (Planned dose: 5ml), 36	Oral	Length of stay, days in ICU	11.7 (4.6 to 15.7)	7.3 (4.7 to 12.3)	
Girard, 2018 ²⁹	Patients over 18 years of age in the medical or surgical ICU, with delirium	Haloperidol (Mean dose: 11mg Dose range: 2.5-20mg), 192	Placebo (Not reported), 184	Intravenous	Days to ICU discharge	5 (3 to 13)	5 (3 to 14)	Hazard ratio 0.95 (95% CI: 0.81 to 1.12), p=Not reported
Page, 2013 ^{10, 27}	ICU patients needing MV within 72 hours of admission were enrolled	Haloperidol (Planned dose: 2.5mg), 50	Placebo (Planned dose: 0.5ml), 52	Intravenous	Length of critical care stay, excluding patients who died in ICU	9.5 (5 to 14)	9 (5 to 18)	Mean difference -1.45 (95% CI: -5.42 to 2.52), p=0.47
Second-generation antipsychotic vs. placebo								
Devlin, 2010 ²⁶	Patients admitted to Medical & Surgical ICU with delirium.	Quetiapine (Mean dose: 50 Median dose: 110 (88-191 IQR) Max dose: 200 Dose range: 50 to 200mg), 18	Placebo (Mean dose: 50 Median dose: 210 (116 - 293) Max dose: 200mg), 18	Either orally or NG tube	Duration of intensive care unit stay, days	16 (10 to 22)	16 (13 to 32)	
Girard, 2010 ⁴	> 18 years MV medical and surgical ICU patients	Ziprasidone (Planned dose: 40 Median dose: 113 (81-140), 30	Placebo (Planned dose: 5ml), 36	Oral	Length of stay, days in ICU	9.6 (3.8 to 14.5)	7.3 (4.7 to 12.3)	
Girard, 2018 ²⁹	Patients over 18 years of age in the medical or surgical ICU, with delirium	Ziprasidone (Mean dose: 20mg Dose range: 5.0-40mg), 190	Placebo (Not reported), 184	Intravenous	Days to ICU discharge	6 (3 to 10)	5 (3 to 14)	Hazard ratio 1.02 (95% CI: 0.88 to 1.17), p=Not reported

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	Median (IQR) days, intervention group	Median (IQR), days, control group	Measure of association (95% CI)
First-generation antipsychotic vs. second-generation antipsychotic								
Girard, 2010 ⁴	> 18 years MV medical and surgical ICU patients	Ziprasidone (Planned dose: 40 Median dose: 113 (81-140), 30	Haloperidol (Planned dose: 5 Median dose: 15 (10.8-17), 35	Oral	Length of stay, days in ICU	9.6 (3.8 to 14.5)	11.7 (4.6 to 15.7)	
Girard, 2018 ²⁹	Patients over 18 years of age in the medical or surgical ICU, with delirium	Ziprasidone (Mean dose: 20mg Dose range: 5.0-40mg), 190	Haloperidol (Mean dose: 11mg Dose range: 2.5-20mg), 192	Intravenous	Days to ICU discharge	6 (3 to 10)	5 (3 to 13)	
First-generation antipsychotic vs. other								
Atalan, 2013 ¹⁸	Post cardiac surgery patients with hyperactive type delirium	Morphine sulfate (Max dose: 20mg), 27	Haloperidol (Max dose: 20mg), 26	Intramuscular	ICU time (d)	Mean: 2.85 (SD: 1.48)	Mean: 3.31 (SD: 2.32)	

CI=confidence interval; ICU=intensive care unit; IQR=interquartile range; mg=milligram; ml=milliliter; MV=mechanical ventilation; n=sample size; NG=nadogastric tube; p=p-value; SD=standard deviation

Evidence Table D-44. Incidence of delirium outcomes for studies comparing interventions to treat delirium

Author, year	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
Second-generation antipsychotic vs. placebo								
Devlin, 2010 ²⁶	Patients admitted to Medical & Surgical ICU with delirium.	Quetiapine (Mean dose: 50 Median dose: 110 (88-191 IQR) Max dose: 200 Dose range: 50 to 200mg), 18	Placebo (Mean dose: 50 Median dose: 210 (116 - 293) Max dose: 200mg), 18	Either orally or NG tube	Delirium in the 14-day period after study drug discontinued, or until subject discharged/transferred from hospital.	4 / 18 (20%)	10 / 18 (56%)	0.40 (0.15 to 1.04)

CI=confidence interval; ICU=intensive care unit; IQR=interquartile range; mg=milligram; N=sample size; NG=nadogastric tube

Evidence Table D-45. Sedation outcomes for studies comparing interventions to treat delirium

Author, year	Study design	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
First-generation antipsychotic vs. placebo									
Girard, 2018 ²⁹	RCT	Patients over 18 years of age in the medical or surgical ICU, with delirium	Haloperidol (Mean dose: 11mg Dose range: 2.5-20mg), 192	Placebo (Not reported), 184	Intravenous	Reasons for temporary holds: Oversedation	42 / 192 (22%)	46 / 184 (25%)	RR 0.88 (95% CI: 0.61 to 1.26)
Page, 2013 ¹⁰	RCT	ICU patients needing MV within 72 hours of admission were enrolled	Haloperidol (Planned dose: 2.5mg), 71	Placebo (Planned dose: 0.5ml), 70	Intravenous	Oversedation	11 / 71 (15%)	6 / 70 (9%)	RR 1.81 (95% CI: 0.71 to 4.62)
Second-generation antipsychotic vs. placebo									
Devlin, 2010 ²⁶	RCT	Patients admitted to Medical & Surgical ICU with delirium.	Quetiapine (Mean dose: 50 Median dose: 110 (88-191 IQR) Max dose: 200 Dose range: 50 to 200mg),	Placebo (Mean dose: 50 Median dose: 210 (116 - 293) Max dose: 200mg),	Either orally or NG tube	Episodes of somnolence	Number of Events: 5	Number of Events: 2	
Devlin, 2010 ²⁶	RCT	Patients admitted to Medical & Surgical ICU with delirium.	Quetiapine (Mean dose: 50 Median dose: 110 (88-191 IQR) Max dose: 200 Dose range: 50 to 200mg), 18	Placebo (Mean dose: 50 Median dose: 210 (116 - 293) Max dose: 200mg), 18	Either orally or NG tube	Subjects experiencing somnolence, %	4 / 18 (22%)	2 / 18 (11%)	RR 2.00 (95% CI: 0.42 to 9.58)
Girard, 2018 ²⁹	RCT	Patients over 18 years of age in the medical or surgical ICU, with delirium	Ziprasidone (Mean dose: 20mg Dose range: 5.0-40mg), 190	Placebo (Not reported), 184	Intravenous	Reasons for temporary holds: Oversedation	50 / 190 (26%)	46 / 184 (25%)	RR 1.05 (95% CI: 0.75 to 1.49)
Tahir, 2010 ⁵⁹	RCT	Patients in medical, surgical and orthopedic wards, who met the DSM-IV criteria for delirium on the same day if they had a DRS-R-98 total score of 15 or more	Quetiapine (Mean dose: 40 Dose range: 25 - 175mg), 21	Placebo (Mean dose: 25 Max dose: 175mg), 21	Oral	Complained of sedation	1 / 21 (4.8%)	0 / 21 (%)	RR 3.00 (95% CI: 0.13 to 69.70)

Author, year	Study design	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
First-generation antipsychotic vs. second-generation antipsychotic									
Boettger, 2015 ²¹	Cohort w/ comparison group	Cancer patients	Olanzapine (Mean dose: 3.5 Dose range: 2.5 to 10mg), 21	Haloperidol (Mean dose: 4.9 Dose range: 1.5 to 16mg), 21	Not reported	Not applicable	6 / 21 (28.6%)	0 / 21 (0%)	RR 13.00 (95% CI: 0.78 to 217.03)
Boettger, 2015 ²¹	Cohort w/ comparison group	Cancer patients	Risperidone (Mean dose: 0.9 Dose range: 0.5 to 2mg), 21	Haloperidol (Mean dose: 4.9 Dose range: 1.5 to 16mg), 21	Not reported	Not applicable	0 / 21 (0%)	0 / 21 (0%)	
Boettger, 2015 ²¹	Cohort w/ comparison group	Cancer patients	Aripiprazole (Mean dose: 15.2 Dose range: 5 to 30mg), 21	Haloperidol (Mean dose: 4.9 Dose range: 1.5 to 16mg), 21	Not reported	Not applicable	0 / 21 (0%)	0 / 21 (0%)	
Charoenporn, 2018 ²⁵	Cohort w/ comparison group	Physically ill patients	Quetiapine (Mean dose: 26.7 Median dose: 25), 31	Haloperidol (Mean dose: 0.9 Median dose: 0.5mg), 11	Oral	Not applicable	3 / 31 (9.7%)	1 / 11 (9.1%)	RR 1.06 (95% CI: 0.12 to 9.19)
Charoenporn, 2018 ²⁵	Cohort w/ comparison group	Physically ill patients	Risperidone (Mean dose: 0.6 Median dose: 0.5mg), 14	Haloperidol (Mean dose: 0.9 Median dose: 0.5mg), 11	Oral	Not applicable	4 / 14 (28.6%)	1 / 11 (9.1%)	RR 3.14 (95% CI: 0.41 to 24.27)
Girard, 2018 ²⁹	RCT	Patients over 18 years of age in the medical or surgical ICU, with delirium	Ziprasidone (Mean dose: 20mg Dose range: 5.0-40mg), 190	Haloperidol (Mean dose: 11mg Dose range: 2.5-20mg), 192	Intravenous	Reasons for temporary holds: Oversedation	50 / 190 (26%)	42 / 192 (22%)	RR 1.20 (95% CI: 0.84 to 1.72)
Grover, 2011 ³⁰	RCT	Consecutive patients >-18 years old referred to psychiatry and diagnosed with delirium	Olanzapine (Mean dose: 3.05mg Dose range: 1.25-10 mg per day), 23	Haloperidol (Mean dose: 0.88 Dose range: 0.25-5mg per day), 21	Oral	Sleepiness/sedation	0 / 23 (0%)	1 / 21 (4.8%)	RR 0.31 (95% CI: 0.01 to 7.12)
Grover, 2011 ³⁰	RCT	Consecutive patients >-18 years old referred to psychiatry and diagnosed with delirium	Risperidone (Mean dose: 0.95mg Dose range: 0.5-2.0mg per day), 20	Haloperidol (Mean dose: 0.88 Dose range: 0.25-5mg per day), 21	Oral	Sleepiness/sedation	3 / 20 (15%)	1 / 21 (4.8%)	RR 3.15 (95% CI: 0.36 to 27.83)

Author, year	Study design	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
Han, 2004 ³²	RCT	All patients presenting with altered mental status (from both ICU and non-ICU units) who were referred to the consulting psychiatry division were evaluated.	Risperidone (Mean dose: 1.02 Dose range: 0.5 to 2.0mg), 14	Haloperidol (Mean dose: 1.7 Dose range: 1.0 to 3.0mg), 14	Oral	Withdrawal due to severe sedation	0 / 14 (0%)	1 / 14 (7.1%)	RR 0.33 (95% CI: 0.01 to 7.55)
Jain, 2017 ³⁸	RCT	Medical and surgical inpatients	Olanzapine (Mean dose: 5.49mg), 47	Haloperidol (Mean dose: 2.10mg), 53	Oral	Excessive sedation	1 / 47 (2.1%)	0 / 53 (0%)	RR 3.38 (95% CI: 0.14 to 80.91)
Kim, 2005 ⁴¹	Cohort w/ comparison group	Hospital patients referred to the psychiatry division	Risperidone (Not reported), 18	Haloperidol (Not reported), 24	Not reported	Drowsiness	0 / 18 (0%)	1 / 24 (4.2%)	RR 0.44 (95% CI: 0.02 to 10.18)
Lim, 2007 ⁴⁶	RCT	Patients from internal medicine, PMR, neurology, neurosurgery, orthopedic surgery, or general surgery that were referred to the psychiatric department	Olanzapine (Titrated (5 to 20 mg))	Haloperidol (Titrated (5 to 20 mg))	Intramuscular	Somnolence	2 / 31 (6.5%)	1 / 31 (3.2%)	RR 2.00 (95% CI: 0.19 to 20.93)
Maneeton, 2013 ⁴⁹	RCT	General adult population (age 18-75) with hyperactive delirium, referred to psychiatry consult liaison service at tertiary care hospital in Thailand	Quetiapine (Mean dose: 67.6 (SD 9.7) Dose range: 25-100mg), 24	Haloperidol (Mean dose: 0.8 (SD 0.3) Dose range: 0.5-2.0mg), 28	Oral	Hypersomnia	10 / 24 (41.7%)	8 / 28 (28.6%)	RR 1.46 (95% CI: 0.69 to 3.10)
Sipahimalani, 1998 ⁵⁶	Cohort w/ comparison group	Hospital patients	Olanzapine (Mean dose: 8.2 Max dose: 15mg), 11	Haloperidol (Dose range: 1.5 to 10mg), 11	Not reported	Excessively sedated	0 / 11 (0%)	2 / 11 (18.2%)	RR 0.20 (95% CI: 0.01 to 3.74)
Yoon, 2013 ⁶²	Cohort w/ comparison group	Referred to consultation-liaison psychiatric service for a mental status change	Quetiapine (Mean dose: 47.9 Dose range: 25-200mg), 18	Haloperidol (Mean dose: 1.2 Dose range: 0.5-10mg), 23	Not reported	Exacerbation of sedation or sleepiness	2 / 18 (11.1%)	4 / 23 (17.4%)	RR 0.64 (95% CI: 0.13 to 3.11)
Yoon, 2013 ⁶²	Cohort w/ comparison group	Referred to consultation-liaison psychiatric service for a mental status change	Olanzapine (Mean dose: 2.9 Dose range: 1-20mg), 18	Haloperidol (Mean dose: 1.2 Dose range: 0.5-10mg), 23	Not reported	Exacerbation of sedation or sleepiness	4 / 18 (22.2%)	4 / 23 (17.4%)	RR 1.28 (95% CI: 0.37 to 4.42)
Yoon, 2013 ⁶²	Cohort w/ comparison group	Referred to consultation-liaison psychiatric service for a mental status change	Risperidone (Mean dose: 1.1 Dose range: 0.25-4mg), 21	Haloperidol (Mean dose: 1.2 Dose range: 0.5-10mg), 23	Not reported	Exacerbation of sedation or sleepiness	3 / 21 (14.3%)	4 / 23 (17.4%)	RR 0.82 (95% CI: 0.21 to 3.25)

Author, year	Study design	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
Second-generation antipsychotic vs. second-generation antipsychotic									
Boettger, 2015 ²¹	Cohort w/ comparison group	Cancer patients	Olanzapine (Mean dose: 3.5 Dose range: 2.5 to 10mg), 21	Aripiprazole (Mean dose: 15.2 Dose range: 5 to 30mg), 21	Not reported	Not applicable	6 / 21 (28.6%)	0 / 21 (0%)	RR 13.00 (95% CI: 0.78 to 217.03)
Boettger, 2015 ²¹	Cohort w/ comparison group	Cancer patients	Risperidone (Mean dose: 0.9 Dose range: 0.5 to 2mg), 21	Aripiprazole (Mean dose: 15.2 Dose range: 5 to 30mg), 21	Not reported	Not applicable	0 / 21 (0%)	0 / 21 (0%)	
Boettger, 2015 ²¹	Cohort w/ comparison group	Cancer patients	Risperidone (Mean dose: 0.9 Dose range: 0.5 to 2mg), 21	Olanzapine (Mean dose: 3.5 Dose range: 2.5 to 10mg), 21	Not reported	Not applicable	0 / 21 (0%)	6 / 21 (28.6%)	RR 0.08 (95% CI: 0.00 to 1.28)
Charoenporn, 2018 ²⁵	Cohort w/ comparison group	Physically ill patients	Risperidone (Mean dose: 0.6 Median dose: 0.5mg), 14	Quetiapine (Mean dose: 26.7 Median dose: 25), 31	Oral	Not applicable	4 / 14 (28.6%)	3 / 31 (9.7%)	RR 2.95 (95% CI: 0.76 to 11.47)
Fox, 2018 ²⁸	Cohort w/ comparison group	Critically ill patients in the medical and cardiovascular ICU	Quetiapine (Mean dose: 153.8 Max dose: 800mg), 20	Lurasidone (Mean dose: 42.6 Max dose: 120mg), 20	Not reported	Discontinuation of study drug due to increased sedation	4 / 20 (20%)	2 / 20 (10%)	RR 2.00 (95% CI: 0.41 to 9.71)
Fox, 2018 ²⁸	Cohort w/ comparison group	Critically ill patients in the medical and cardiovascular ICU	Quetiapine (Mean dose: 153.8 Max dose: 800mg), 20	Lurasidone (Mean dose: 42.6 Max dose: 120mg), 20	Not reported	Percentage of time the patient was oversedated (RASS <= -3)	Median 2.7 (IQR 0.9 to 11.7)	Median 2.8 (IQR 0 to 29.8)	
Grover, 2011 ³⁰	RCT	Consecutive patients >-18 years old referred to psychiatry and diagnosed with delirium	Risperidone (Mean dose: 0.95mg Dose range: 0.5-2.0mg per day), 20	Olanzapine (Mean dose: 3.05mg Dose range: 1.25-10 mg per day), 23	Oral	Sleepiness/sedation	3 / 20 (15%)	0 / 23 (0%)	RR 8.00 (95% CI: 0.44 to 146.08)

Author, year	Study design	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
Kim, 2010 ⁴²	RCT	General hospital inpatients who met DSM-IV diagnostic criteria for delirium	Risperidone (Mean dose: 0.9 ± 0.6 Dose range: 0.25 - 2mg), 17	Olanzapine (Mean dose: 2.4 ± 1.7 Dose range: 1.25 - 7.5mg), 15	Not reported	Exacerbation of daytime somnolence or increased duration of sleep	5 / 17 (29.4%)	5 / 15 (33.3%)	RR 0.88 (95% CI: 0.32 to 2.46)
Lee, 2005 ⁴⁵	RCT	Patients referred to the Psychiatric Consultation that met DSM-IV criteria for delirium	Amisulpride (Mean dose: 156.4 ± 97.5 Dose range: 50–800mg), 16	Quetiapine (Mean dose: 113 ± 85.5 Dose range: 50–300mg), 15	Not reported	Oversedation	0 / 16 (0%)	0 / 15 (0%)	
Yoon, 2013 ⁶²	Cohort w/ comparison group	Referred to consultation-liaison psychiatric service for a mental status change	Quetiapine (Mean dose: 47.9 Dose range: 25-200mg), 18	Olanzapine (Mean dose: 2.9 Dose range: 1-20mg), 18	Not reported	Exacerbation of sedation or sleepiness	2 / 18 (11.1%)	4 / 18 (22.2%)	RR 0.50 (95% CI: 0.10 to 2.40)
Yoon, 2013 ⁶²	Cohort w/ comparison group	Referred to consultation-liaison psychiatric service for a mental status change	Risperidone (Mean dose: 1.1 Dose range: 0.25-4mg), 21	Olanzapine (Mean dose: 2.9 Dose range: 1-20mg), 18	Not reported	Exacerbation of sedation or sleepiness	3 / 21 (14.3%)	4 / 18 (22.2%)	RR 0.64 (95% CI: 0.17 to 2.50)
Yoon, 2013 ⁶²	Cohort w/ comparison group	Referred to consultation-liaison psychiatric service for a mental status change	Risperidone (Mean dose: 1.1 Dose range: 0.25-4mg), 21	Quetiapine (Mean dose: 47.9 Dose range: 25-200mg), 18	Not reported	Exacerbation of sedation or sleepiness	3 / 21 (14.3%)	2 / 18 (11.1%)	RR 1.29 (95% CI: 0.24 to 6.86)

CI=confidence interval; DRS-R-98= Delirium Rating Scale Revised-98; DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th ed; ICU=intensive care unit; IQR=interquartile range; mg=milligram; MV=mechanical ventilation; N=sample size; RCT=randomized controlled trial; RR=risk ratio

Evidence Table D-46. Sedation outcomes for studies comparing interventions to treat delirium: single arm studies

Author, year	Study design	Population	Intervention group, n	Route of administration	Outcome definition	n / N (%), intervention group
Breitbart, 2002 ²³	Cohort w/o comparison group	Cancer patients	Olanzapine (Mean dose: 3.0 Dose range: 2.5 to 10mg)	Oral	Not applicable	(30%)
Breitbart, 2002 ²³	Cohort w/o comparison group	Cancer patients	Olanzapine (Mean dose: 3.0 Dose range: 2.5 to 10mg)	Oral	Not applicable	(30%)
Breitbart, 2002 ²³	Cohort w/o comparison group	Cancer patients	Olanzapine (Mean dose: 3.0 Dose range: 2.5 to 10mg), 79	Oral	Dosage reduced due to sedation	8 / 79 (10%)
Horikawa, 2003 ³⁴	Cohort w/o comparison group	Medical and surgical inpatients	Risperidone (Planned dose: 0.5 Max dose: 1.7mg), 10	Oral	Daytime sleepiness	3 / 10 (30%)
Ikezawa, 2008 ³⁷	Open-label trial	Elderly patients with hyperactive-hypervalent delirium	Risperidone (Mean dose: 1.5 (0.7) Dose range: 0.5-3mg), 22	Oral	Somnolence	4 / 22 (18%)
Kim, 2001 ³⁹	Open label study	Medico-surgical patients from Neurology, Neurosurgery and BMT unit	Olanzapine (Mean dose: 5.9 (1.5) Max dose: 8.8 (2.2), 20	Oral	Mild sedation	2 / 20 (10%)
Kim, 2003 ⁴⁰	Cohort w/o comparison group	Patients in the acute medical units	Quetiapine (Planned dose: 25 Mean dose: 93.75mg), 12	Not reported	Not applicable	2 / 12 (17%)
Kishi, 2012 ⁴³	Cohort w/o comparison group	Delirious cancer patients	Risperidone (Mean dose: 1.4mg), 29	Oral	Mild sedation	0 / 29 (0%)
Maneeton, 2007 ⁴⁸	Open-label study	All physically ill in-patients whose pcp consulted psychiatrists	Quetiapine (Mean dose: 45.7 (28.7) Max dose: 100 Dose range: 25-100mg), 17	Oral	Daytime sleepiness	13 / 17 (76%)
Mittal, 2004 ⁵⁰	Cohort w/o comparison group	Hospitalized patients	Risperidone (Mean dose: 0.75mg), 10	Not reported	Mild sedation	2 / 10 (20%)

Author, year	Study design	Population	Intervention group, n	Route of administration	Outcome definition	n / N (%), intervention group
Omura, 2003 ⁵²	Cohort w/o comparison group	Hospitalized patients	Quetiapine (Mean dose: 54.7 Dose range: 25 to 125mg), 24	Not reported	Somnolence	3 / 24 (13%)
Omura, 2003 ⁵²	Cohort w/o comparison group	Hospitalized patients	Quetiapine (Mean dose: 54.7 Dose range: 25 to 125mg), 24	Not reported	Oversedation	0 / 24 (0%)
Pae, 2004 ⁵³	Cohort w/o comparison group	Delirious patients recruited from the departments of neurosurgery, orthopedic surgery, and oncology	Quetiapine (Mean dose: 127.1mg), 22	Oral	Stopped medication due to sedation	2 / 22 (9%)
Pae, 2004 ⁵³	Cohort w/o comparison group	Delirious patients recruited from the departments of neurosurgery, orthopedic surgery, and oncology	Quetiapine (Mean dose: 127.1mg), 22	Oral	Mild sedation	3 / 22 (14%)
Parellada, 2004 ⁵⁴	Cohort w/o comparison group	General hospital patients	Risperidone (Mean dose: day 1, 2.6; day 3, 2.6; day 7, 1.5mg), 64	Oral	Drowsiness	2 / 64 (3%)
Sasaki, 2003 ⁵⁵	Cohort w/o comparison group	Inpatients and outpatients	Quetiapine (Mean dose: 44.9 Max dose: 63.5mg), 12	Oral	Excessive sedation or somnolence in the daytime	0 / 12 (0%)
Toda, 2005 ⁶⁰	Cohort w/o comparison group	Hospital patients with delirium	Risperidone (Mean dose: 0.92 Max dose: 1.38), 10	Oral	Somnolence	2 / 10 (20%)

BMT=bone marrow transplant; Mg=milligram; N=sample size

Evidence Table D-47. Binary cardiac outcomes for studies comparing interventions to treat delirium

Author, year	Study design	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
First-generation antipsychotic vs. placebo									
Girard, 2010 ⁴	RCT	> 18 years MV medical and surgical ICU patients	Haloperidol (Planned dose: 5 Median dose: 15 (10.8-17), 35	Placebo (Planned dose: 5ml), 36	Oral	Prolongation in the QTc interval prolongation of the QTc > 500 ms while receiving study drug	2 / 35 (5.7%)	3 / 36 (8.3%)	RR 0.69 (95% CI: 0.12 to 3.86)
Girard, 2010 ⁴	RCT	> 18 years MV medical and surgical ICU patients	Haloperidol (Planned dose: 5 Median dose: 15 (10.8-17), 35	Placebo (Planned dose: 5ml), 36	Oral	Ventricular arrhythmias	0 / 35 (0%)	0 / 36 (0%)	
Girard, 2018 ²⁹	RCT	Patients over 18 years of age in the medical or surgical ICU, with delirium	Haloperidol (Mean dose: 11mg Dose range: 2.5-20mg), 192	Placebo (Not reported), 184	Intravenous	Reasons for temporary holds: Prolonged QTc	13 / 192 (7%)	10 / 184 (5%)	RR 1.25 (95% CI: 0.56 to 2.77)
Girard, 2018 ²⁹	RCT	Patients over 18 years of age in the medical or surgical ICU, with delirium	Haloperidol (Mean dose: 11mg Dose range: 2.5-20mg), 192	Placebo (Not reported), 184	Intravenous	Reasons for permanent discontinuation: Suspected torsades des pointes	0 / 192 (0%)	0 / 184 (0%)	
Page, 2013 ¹⁰	RCT	ICU patients needing MV within 72 hours of admission were enrolled	Haloperidol (Planned dose: 2.5mg), 71	Placebo (Planned dose: 0.5ml), 70	Intravenous	Atrial fibrillation	7 / 71 (10%)	3 / 70 (4%)	RR 2.30 (95% CI: 0.62 to 8.54)
Page, 2013 ¹⁰	RCT	ICU patients needing MV within 72 hours of admission were enrolled	Haloperidol (Planned dose: 2.5mg), 71	Placebo (Planned dose: 0.5ml), 70	Intravenous	Bradycardia	2 / 71 (2.8%)	0 / 70 (0%)	RR 4.93 (95% CI: 0.24 to 100.89)
Page, 2013 ¹⁰	RCT	ICU patients needing MV within 72 hours of admission were enrolled	Haloperidol (Planned dose: 2.5mg), 71	Placebo (Planned dose: 0.5ml), 70	Intravenous	Hypotension	3 / 71 (4%)	2 / 70 (3%)	RR 1.48 (95% CI: 0.25 to 8.58)
Page, 2013 ¹⁰	RCT	ICU patients needing MV within 72 hours of admission were enrolled	Haloperidol (Planned dose: 2.5mg), 71	Placebo (Planned dose: 0.5ml), 70	Intravenous	Prolongation in the QTc interval > 500 ms	7 / 71 (10%)	6 / 70 (9%)	RR 1.15 (95% CI: 0.41 to 3.25)
Page, 2013 ¹⁰	RCT	ICU patients needing MV within 72 hours of admission were enrolled	Haloperidol (Planned dose: 2.5mg), 71	Placebo (Planned dose: 0.5ml), 70	Intravenous	Supraventricular Tachycardia	4 / 71 (6%)	1 / 70 (1%)	RR 3.94 (95% CI: 0.45 to 34.41)

Author, year	Study design	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
Second-generation antipsychotic vs. placebo									
Devlin, 2010 ²⁶	RCT	Patients admitted to Medical & Surgical ICU with delirium.	Quetiapine (Mean dose: 50 Median dose: 110 (88-191 IQR) Max dose: 200 Dose range: 50 to 200mg), 18	Placebo (Mean dose: 50 Median dose: 210 (116 - 293) Max dose: 200mg), 18	Either orally or NG tube	Hypotension	1 / 18 (6%)	0 / 18 (0%)	RR 3.00 (95% CI: 0.13 to 69.09)
Devlin, 2010 ²⁶	RCT	Patients admitted to Medical & Surgical ICU with delirium.	Quetiapine (Mean dose: 50 Median dose: 110 (88-191 IQR) Max dose: 200 Dose range: 50 to 200mg)	Placebo (Mean dose: 50 Median dose: 210 (116 - 293) Max dose: 200mg)	Either orally or NG tube	Prolongation in the QTc interval Episodes of QTc interval > 60 m/sec above baseline	Number of events: 20	Number of events: 34	p=0.7
Devlin, 2010 ²⁶	RCT	Patients admitted to Medical & Surgical ICU with delirium.	Quetiapine (Mean dose: 50 Median dose: 110 (88-191 IQR) Max dose: 200 Dose range: 50 to 200mg)	Placebo (Mean dose: 50 Median dose: 210 (116 - 293) Max dose: 200mg)	Either orally or NG tube	Prolongation in the QTc interval Episodes of QTc interval > 500 m/sec	Number of events: 8	Number of events: 8	p=1
Devlin, 2010 ²⁶	RCT	Patients admitted to Medical & Surgical ICU with delirium.	Quetiapine (Mean dose: 50 Median dose: 110 (88-191 IQR) Max dose: 200 Dose range: 50 to 200mg)	Placebo (Mean dose: 50 Median dose: 210 (116 - 293) Max dose: 200mg)	Either orally or NG tube	Prolongation in the QTc interval Episodes of QTc interval prolongation	Number of events: 30	Number of events: 41	p=0.32
Devlin, 2010 ²⁶	RCT	Patients admitted to Medical & Surgical ICU with delirium.	Quetiapine (Mean dose: 50 Median dose: 110 (88-191 IQR) Max dose: 200 Dose range: 50 to 200mg), 18	Placebo (Mean dose: 50 Median dose: 210 (116 - 293) Max dose: 200mg), 18	Either orally or NG tube	Prolongation in the QTc interval Subjects experiencing QTc interval > 60 msec above baseline, %	7 / 18 (39%)	8 / 18 (44%)	RR 0.88 (95% CI: 0.40 to 1.90)
Devlin, 2010 ²⁶	RCT	Patients admitted to Medical & Surgical ICU with delirium.	Quetiapine (Mean dose: 50 Median dose: 110 (88-191 IQR) Max dose: 200 Dose range: 50 to 200mg), 18	Placebo (Mean dose: 50 Median dose: 210 (116 - 293) Max dose: 200mg), 18	Either orally or NG tube	Prolongation in the QTc interval Subjects experiencing QTc interval > 500 m/sec, %	4 / 18 (22%)	5 / 18 (28%)	RR 0.80 (95% CI: 0.26 to 2.50)

Author, year	Study design	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
Devlin, 2010 ²⁶	RCT	Patients admitted to Medical & Surgical ICU with delirium.	Quetiapine (Mean dose: 50 Median dose: 110 (88-191 IQR) Max dose: 200 Dose range: 50 to 200mg), 18	Placebo (Mean dose: 50 Median dose: 210 (116 - 293) Max dose: 200mg), 18	Either orally or NG tube	Prolongation in the QTc interval Subjects experiencing QTc prolongation, %	9 / 18 (50%)	13 / 18 (72%)	RR 0.69 (95% CI: 0.40 to 1.19)
Devlin, 2010 ²⁶	RCT	Patients admitted to Medical & Surgical ICU with delirium.	Quetiapine (Mean dose: 50 Median dose: 110 (88-191 IQR) Max dose: 200 Dose range: 50 to 200mg), 18	Placebo (Mean dose: 50 Median dose: 210 (116 - 293) Max dose: 200mg), 18	Either orally or NG tube	Torsades de pointes	0 / 18 (0%)	0 / 18 (0%)	
Girard, 2010 ⁴	RCT	> 18 years MV medical and surgical ICU patients	Ziprasidone (Planned dose: 40 Median dose: 113 (81-140)30	Placebo (Planned dose: 5ml), 36	Oral	Prolongation in the QTc interval prolongation of the QTc > 500 ms while receiving study drug	5 / 30 (16.7%)	3 / 36 (8.3%)	RR 2.00 (95% CI: 0.52 to 7.69)
Girard, 2010 ⁴	RCT	> 18 years MV medical and surgical ICU patients	Ziprasidone (Planned dose: 40 Median dose: 113 (81-140), 30	Placebo (Planned dose: 5ml), 36	Oral	Ventricular arrhythmias	0 / 30 (0%)	0 / 36 (0%)	
Girard, 2018 ²⁹	RCT	Patients over 18 years of age in the medical or surgical ICU, with delirium	Ziprasidone (Mean dose: 20mg Dose range: 5.0-40mg), 190	Placebo (Not reported), 184	Intravenous	Reasons for temporary holds: Prolonged QTc	20 / 190 (11%)	10 / 184 (5%)	RR 1.94 (95% CI: 0.93 to 4.03)
Girard, 2018 ²⁹	RCT	Patients over 18 years of age in the medical or surgical ICU, with delirium	Ziprasidone (Mean dose: 20mg Dose range: 5.0-40mg), 192	Placebo (Not reported), 184	Intravenous	Reasons for permanent discontinuation: Suspected torsades des pointes	0 / 192 (0%)	0 / 184 (0%)	
First-generation antipsychotic vs. second-generation antipsychotic									
Charoenporn, 2018 ²⁵	Cohort w/ comparison group	Physically ill patients	Quetiapine (Mean dose: 26.7 Median dose: 25), 31	Haloperidol (Mean dose: 0.9 Median dose: 0.5mg), 11	Oral	Arrhythmia	0 / 31 (0%)	1 / 11 (9.1%)	RR 0.13 (95% CI: 0.01 to 2.86)
Charoenporn, 2018 ²⁵	Cohort w/ comparison group	Physically ill patients	Risperidone (Mean dose: 0.6 Median dose: 0.5mg), 14	Haloperidol (Mean dose: 0.9 Median dose: 0.5mg), 11	Oral	Arrhythmia	1 / 14 (7.1%)	1 / 11 (9.1%)	RR 0.79 (95% CI: 0.06 to 11.20)

Author, year	Study design	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
Charoenporn, 2018 ²⁵	Cohort w/ comparison group	Physically ill patients	Quetiapine (Mean dose: 26.7 Median dose: 25), 31	Haloperidol (Mean dose: 0.9 Median dose: 0.5mg), 11	Oral	Orthostatic hypotension	1 / 31 (3.3%)	0 / 11 (0%)	RR 1.13 (95% CI: 0.05 to 25.76)
Charoenporn, 2018 ²⁵	Cohort w/ comparison group	Physically ill patients	Risperidone (Mean dose: 0.6 Median dose: 0.5mg), 14	Haloperidol (Mean dose: 0.9 Median dose: 0.5mg), 11	Oral	Orthostatic hypotension	0 / 14 (0%)	0 / 11 (0%)	
Girard, 2010 ⁴	RCT	> 18 years MV medical and surgical ICU patients	Ziprasidone (Planned dose: 40 Median dose: 113 (81-140), 30	Haloperidol (Planned dose: 5 Median dose: 15 (10.8-17), 35	Oral	Prolongation in the QTc interval prolongation of the QTc > 500 ms while receiving study drug	5 / 30 (16.7%)	2 / 35 (5.7%)	RR 2.92 (95% CI: 0.61 to 13.96)
Girard, 2010 ⁴	RCT	> 18 years MV medical and surgical ICU patients	Ziprasidone (Planned dose: 40 Median dose: 113 (81-140), 30	Haloperidol (Planned dose: 5 Median dose: 15 (10.8-17), 35	Oral	Ventricular arrhythmias	0 / 30 (0%)	0 / 35 (0%)	
Girard, 2018 ²⁹	RCT	Patients over 18 years of age in the medical or surgical ICU, with delirium	Ziprasidone (Mean dose: 20mg Dose range: 5.0-40mg), 190	Haloperidol (Mean dose: 11mg Dose range: 2.5-20mg), 192	Intravenous	Reasons for temporary holds: Prolonged QTc	20 / 190 (11%)	13 / 192 (7%)	RR 1.55 (95% CI: 0.80 to 3.03)
Girard, 2018 ²⁹	RCT	Patients over 18 years of age in the medical or surgical ICU, with delirium	Ziprasidone (Mean dose: 20mg Dose range: 5.0-40mg), 192	Haloperidol (Mean dose: 11mg Dose range: 2.5-20mg), 184	Intravenous	Reasons for permanent discontinuation: Suspected torsades des pointes	0 / 192 (0%)	0 / 184 (0%)	
Hatta, 2014 ³³	Cohort w/ comparison group	Patients in a general hospital who developed delirium and were managed by a psychiatrist	Olanzapine (Max dose: 10.2mg), 87	Haloperidol (Max dose: 6.40mg), 480	Not reported	Cardiovascular events (see below for details)	0 / 87 (0%)	0 / 480 (0%)	
Hatta, 2014 ³³	Cohort w/ comparison group	Patients in a general hospital who developed delirium and were managed by a psychiatrist	Quetiapine (Max dose: 71.8mg), 779	Haloperidol (Max dose: 6.40mg), 480	Not applicable	Cardiovascular events (see below for details)	1 / 779 (0.1%)	0 / 480 (0%)	RR 1.85 (95% CI: 0.08 to 45.32)
Hatta, 2014 ³³	Cohort w/ comparison group	Patients in a general hospital who developed delirium and were managed by a psychiatrist	Risperidone (Max dose: 1.35mg), 835	Haloperidol (Max dose: 6.40mg), 480	Not applicable	Cardiovascular events (see below for details)	1 / 835 (0.1%)	0 / 480 (0%)	RR 1.73 (95% CI: 0.07 to 42.29)

Author, year	Study design	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
Hatta, 2014 ³³	Cohort w/ comparison group	Patients in a general hospital who developed delirium and were managed by a psychiatrist	Risperidone (Max dose: 1.35mg), 835	Haloperidol (Max dose: 6.40mg), 480	Not applicable	Venous thromboembolism	0 / 835 (0%)	1 / 480 (0.2%)	RR 0.19 (95% CI: 0.01 to 4.70)
Hatta, 2014 ³³	Cohort w/ comparison group	Patients in a general hospital who developed delirium and were managed by a psychiatrist	Olanzapine (Max dose: 10.2mg), 87	Haloperidol (Max dose: 6.40mg), 480	Not reported	Venous thromboembolism	0 / 87 (0%)	1 / 480 (0.2%)	RR 1.82 (95% CI: 0.07 to 44.36)
Hatta, 2014 ³³	Cohort w/ comparison group	Patients in a general hospital who developed delirium and were managed by a psychiatrist	Quetiapine (Max dose: 71.8mg), 779	Haloperidol (Max dose: 6.40mg), 480	Not applicable	Venous thromboembolism	0 / 779 (0%)	1 / 480 (0.2%)	RR 0.21 (95% CI: 0.01 to 5.04)
Hatta, 2014 ³³	Cohort w/ comparison group	Patients in a general hospital who developed delirium and were managed by a psychiatrist	Aripiprazole (Max dose: 7.23mg), 61	Haloperidol (Max dose: 6.40mg), 480	Not reported	Cardiovascular events (see below for details)	0 / 61 (0%)	0 / 480 (0%)	
Hatta, 2014 ³³	Cohort w/ comparison group	Patients in a general hospital who developed delirium and were managed by a psychiatrist	Aripiprazole (Max dose: 7.23mg), 61	Haloperidol (Max dose: 6.40mg), 480	Not reported	Venous thromboembolism	0 / 61 (0%)	1 / 480 (0.2%)	RR 2.59 (95% CI: 0.11 to 62.79)
Lim, 2007 ⁴⁶	RCT	Patients from internal medicine, PMR, neurology, neurosurgery, orthopedic surgery, or general surgery that were referred to the psychiatric department	Olanzapine (Titrated (5 to 20 mg)	Haloperidol (Titrated (5 to 20 mg)	Intramuscular	Ventricular tachycardia	0 / 31 (0%)	0 / 31 (0%)	p=NS
Lim, 2007 ⁴⁶	RCT	Patients from internal medicine, PMR, neurology, neurosurgery, orthopedic surgery, or general surgery that were referred to the psychiatric department	Olanzapine (Titrated (5 to 20 mg)	Haloperidol (Titrated (5 to 20 mg)	Intramuscular	QT prolongation	0 / 31 (0%)	0 / 31 (0%)	p=NS
Lim, 2007 ⁴⁶	RCT	Patients from internal medicine, PMR, neurology, neurosurgery, orthopedic surgery, or general surgery that were referred to the psychiatric department	Olanzapine (Titrated (5 to 20 mg)	Haloperidol (Titrated (5 to 20 mg)	Intramuscular	Other serious cardiovascular complications	0 / 31 (0%)	0 / 31 (0%)	p=NS

Author, year	Study design	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
Maneeton, 2013 ⁴⁹	RCT	General adult population (age 18-75) with hyperactive delirium, referred to psychiatry consult liaison service at tertiary care hospital in Thailand	Quetiapine (Mean dose: 67.6 (SD 9.7) Dose range: 25-100mg), 24	Haloperidol (Mean dose: 0.8 (SD 0.3) Dose range: 0.5-2.0mg), 28	Oral	Withdrawal due to AV block	0 / 24 (0%)	1 / 28 (3.6%)	RR 0.39 (95% CI: 0.02 to 9.07)
Second-generation antipsychotic vs. second-generation antipsychotic									
Charoenporn, 2018 ²⁵	Cohort w/ comparison group	Physically ill patients	Risperidone (Mean dose: 0.6 Median dose: 0.5mg), 14	Quetiapine (Mean dose: 26.7 Median dose: 25), 31	Oral	Arrhythmia	1 / 14 (7.1%)	0 / 31 (0%)	RR 6.40 (95% CI: 0.28 to 148.06)
Charoenporn, 2018 ²⁵	Cohort w/ comparison group	Physically ill patients	Risperidone (Mean dose: 0.6 Median dose: 0.5mg), 14	Quetiapine (Mean dose: 26.7 Median dose: 25), 31	Oral	Orthostatic hypotension	0 / 14 (0%)	1 / 31 (3.3%)	RR 0.71 (95% CI: 0.03 to 16.45)
Fox, 2018 ²⁸	Cohort w/ comparison group	Critically ill patients in the medical and cardiovascular ICU	Quetiapine (Mean dose: 153.8 Max dose: 800mg), 20	Lurasidone (Mean dose: 42.6 Max dose: 120mg), 20	Not reported	Life-threatening arrhythmia or torsades de pointes	0 / 20 (0%)	0 / 20 (0%)	
Fox, 2018 ²⁸	Cohort w/ comparison group	Critically ill patients in the medical and cardiovascular ICU	Quetiapine (Mean dose: 153.8 Max dose: 800mg), 20	Lurasidone (Mean dose: 42.6 Max dose: 120mg), 20	Not reported	Prolongation in the QTc interval change from baseline QTc interval of >60 milliseconds	2 / 20 (10%)	2 / 20 (10%)	RR 1.00 (95% CI: 0.16 to 6.42)
Fox, 2018 ²⁸	Cohort w/ comparison group	Critically ill patients in the medical and cardiovascular ICU	Quetiapine (Mean dose: 153.8 Max dose: 800mg), 20	Lurasidone (Mean dose: 42.6 Max dose: 120mg), 20	Not reported	Prolongation in the QTc interval discontinuation of study drug due to an increase in the QTc interval	1 / 20 (5%)	0 / 20 (0%)	RR 3.00 (95% CI: 0.13 to 69.52)

Author, year	Study design	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
Hatta, 2014 ³³	Cohort w/ comparison group	Patients in a general hospital who developed delirium and were managed by a psychiatrist	Olanzapine (Max dose: 10.2mg), 87	Aripiprazole (Max dose: 7.23mg), 61	Not reported	Cardiovascular events (see below for details)	0 / 87 (0%)	0 / 61 (0%)	
Hatta, 2014 ³³	Cohort w/ comparison group	Patients in a general hospital who developed delirium and were managed by a psychiatrist	Quetiapine (Max dose: 71.8mg), 779	Aripiprazole (Max dose: 7.23mg), 61	Not applicable	Cardiovascular events (see below for details)	1 / 779 (0.1%)	0 / 61 (0%)	RR 0.24 (95% CI: 0.01 to 5.79)
Hatta, 2014 ³³	Cohort w/ comparison group	Patients in a general hospital who developed delirium and were managed by a psychiatrist	Quetiapine (Max dose: 71.8mg), 779	Olanzapine (Max dose: 10.2mg), 87,	Not applicable	Cardiovascular events (see below for details)	1 / 779 (0.1%)	0 / 87 (0%)	RR 0.34 (95% CI: 0.01 to 8.25)
Hatta, 2014 ³³	Cohort w/ comparison group	Patients in a general hospital who developed delirium and were managed by a psychiatrist	Risperidone (Max dose: 1.35mg), 835	Aripiprazole (Max dose: 7.23mg), 61	Not applicable	Cardiovascular events (see below for details)	1 / 835 (0.1%)	0 / 61 (0%)	RR 0.22 (95% CI: 0.01 to 5.40)
Hatta, 2014 ³³	Cohort w/ comparison group	Patients in a general hospital who developed delirium and were managed by a psychiatrist	Risperidone (Max dose: 1.35mg), 835	Olanzapine (Max dose: 10.2mg), 87	Not applicable	Cardiovascular events (see below for details)	1 / 835 (0.1%)	0 / 87 (0%)	RR 0.32 (95% CI: 0.01 to 7.69)

Author, year	Study design	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
Hatta, 2014 ³³	Cohort w/ comparison group	Patients in a general hospital who developed delirium and were managed by a psychiatrist	Risperidone (Max dose: 1.35mg), 835	Quetiapine (Max dose: 71.8mg), 779	Not applicable	Cardiovascular events (see below for details)	1 / 835 (0.1%)	1 / 779 (0.1%)	RR 0.93 (95% CI: 0.06 to 14.89)
Hatta, 2014 ³³	Cohort w/ comparison group	Patients in a general hospital who developed delirium and were managed by a psychiatrist	Risperidone (Max dose: 1.35mg), 835	Quetiapine (Max dose: 71.8mg), 779	Not applicable	Venous thromboembolism	0 / 835 (0%)	0 / 779 (0%)	
Hatta, 2014 ³³	Cohort w/ comparison group	Patients in a general hospital who developed delirium and were managed by a psychiatrist	Quetiapine (Max dose: 71.8mg), 779	Olanzapine (Max dose: 10.2mg), 87	Not applicable	Venous thromboembolism	0 / 779 (0%)	0 / 87 (0%)	
Hatta, 2014 ³³	Cohort w/ comparison group	Patients in a general hospital who developed delirium and were managed by a psychiatrist	Olanzapine (Max dose: 10.2mg), 87	Aripiprazole (Max dose: 7.23mg), 61	Not reported	Venous thromboembolism	0 / 87 (0%)	0 / 61 (0%)	
Hatta, 2014 ³³	Cohort w/ comparison group	Patients in a general hospital who developed delirium and were managed by a psychiatrist	Quetiapine (Max dose: 71.8mg), 779	Aripiprazole (Max dose: 7.23mg), 61	Not applicable	Venous thromboembolism	0 / 779 (0%)	0 / 61 (0%)	
Hatta, 2014 ³³	Cohort w/ comparison group	Patients in a general hospital who developed delirium and were managed by a psychiatrist	Risperidone (Max dose: 1.35mg), 835	Aripiprazole (Max dose: 7.23mg), 61	Not applicable	Venous thromboembolism	0 / 835 (0%)	0 / 61 (0%)	
Hatta, 2014 ³³	Cohort w/ comparison group	Patients in a general hospital who developed delirium and were managed by a psychiatrist	Risperidone (Max dose: 1.35mg), 835	Olanzapine (Max dose: 10.2mg), 87	Not applicable	Venous thromboembolism	0 / 835 (0%)	0 / 87 (0%)	

Author, year	Study design	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
First-generation antipsychotic vs. other									
Bakri, 2015 ¹⁹	RCT	ICU trauma patients without severe injury, comatose, or moribund patients were excluded	Haloperidol (Planned dose: 5 mg), 32	Dexmedetomidine (Planned dose: 1 ug/kg), 32	Intravenous	Hypotension	0 / 32 (0%)	0 / 32 (0%)	
Bakri, 2015 ¹⁹	RCT	ICU trauma patients without severe injury, comatose, or moribund patients were excluded	Haloperidol (Planned dose: 5 mg), 32	Dexmedetomidine (Planned dose: 1 ug/kg), 32	Intravenous	Incidence of bradycardia	0 / 32 (0%)	0 / 32 (0%)	
Bakri, 2015 ¹⁹	RCT	ICU trauma patients without severe injury, comatose, or moribund patients were excluded	Haloperidol (Planned dose: 5 mg), 32	Dexmedetomidine (Planned dose: 1 ug/kg), 32	Intravenous	Prolongation in the QTc interval prolonged QTc interval	0 / 32 (0%)	0 / 32 (0%)	
Bakri, 2015 ¹⁹	RCT	ICU trauma patients without severe injury, comatose, or moribund patients were excluded	Ondansetron (Planned dose: 8 mg), 32	Haloperidol (Planned dose: 5 mg), 32	Intravenous	Hypotension	0 / 32 (0%)	0 / 32 (0%)	
Bakri, 2015 ¹⁹	RCT	ICU trauma patients without severe injury, comatose, or moribund patients were excluded	Ondansetron (Planned dose: 8 mg), 32	Haloperidol (Planned dose: 5 mg), 32	Intravenous	Incidence of bradycardia	0 / 32 (0%)	0 / 32 (0%)	
Bakri, 2015 ¹⁹	RCT	ICU trauma patients without severe injury, comatose, or moribund patients were excluded	Ondansetron (Planned dose: 8 mg),	Haloperidol (Planned dose: 5 mg),	Intravenous	Prolongation in the QTc interval prolonged QTc interval	0 / 32 (0%)	0 / 32 (0%)	

CI=confidence interval; ICU=intensive care unit; Mg=milligram; Ml=milliliter; MV=mechanical ventilation; N=sample size; NG=nadogastric tube; QTc=corrected QT interval; RCT=randomized controlled trial; RR=risk ratio

Evidence Table D-48. Binary cardiac outcomes for studies comparing interventions to treat delirium: single arm studies

Author, year	Study design	Population	Control group, n	Route of administration	Outcome definition	n / N (%), control group	Measure of association
Kim, 2003 ⁴⁰	Cohort w/o comparison group	Patients in the acute medical units	Quetiapine (Planned dose: 25 Mean dose: 93.75mg), 12	Not reported	Fatal acute myocardial infarction	1/12(0.00%)	
Maneeton, 2007 ⁴⁸	Open-label study	All physically ill in-patients whose pcp consulted psychiatrists	Quetiapine (Mean dose: 45.7 (28.7) Max dose: 100 Dose range: 25-100mg), 17	Oral	Hypotension	2/17(11.76%)	
Mittal, 2004 ⁵⁰	Cohort w/o comparison group	Hospitalized patients	Risperidone (Mean dose: 0.75mg)	Not reported	QTc interval, ms	Baseline: Mean 436 (SE 10) Final: 432 (SE 15)	Change from baseline: -4
Mittal, 2004 ⁵⁰	Cohort w/o comparison group	Hospitalized patients	Risperidone (Mean dose: 0.75mg), 10	Not reported	Treatment discontinued because of severe, aggressively treated congestive heart failure, bradycardia, and worsening of hypotension	1/10(8.33%)	
Omura, 2003 ⁵²	Cohort w/o comparison group	Hospitalized patients	Quetiapine (Mean dose: 54.7 Dose range: 25 to 125mg), 24	Not reported	Hypotension	0/24(0.00%)	
Straker, 2006 ⁵⁸	Cohort w/o comparison group	Medically ill delirium patients	Aripiprazole (Mean dose: 8.9 Dose range: 5 to 15mg), 14	Not reported	Cardiac arrest	1/14(7.14%)	
Straker, 2006 ⁵⁸	Cohort w/o comparison group	Medically ill delirium patients	Aripiprazole (Mean dose: 8.9 Dose range: 5 to 15mg), 14	Not reported	Ventricular arrhythmias	0/14(0.00%)	
Straker, 2006 ⁵⁸	Cohort w/o comparison group	Medically ill delirium patients	Aripiprazole (Mean dose: 8.9 Dose range: 5 to 15mg)	Not reported	Prolongation in the qtc interval milliseconds	Baseline: Mean 442 (SD 44) Final: 434 (SD 22)	Change from baseline: -8
Straker, 2006 ⁵⁸	Cohort w/o comparison group	Medically ill delirium patients	Aripiprazole (Mean dose: 8.9 Dose range: 5 to 15mg), 14	Not reported	Prolongation in the qtc interval increase	3/14(0.00%)	

Mg=milligram; N=sample size; QTc=corrected QT interval; SD=standard deviation; SE=standard error

Evidence Table D-49. Continuous cardiac outcomes for studies comparing interventions to treat delirium

Author, year	Study design	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	MMSE, intervention group	MMSE, control group	Mean between-group difference (95% CI)
First-generation antipsychotic vs. placebo									
Naksuk, 2017 ⁵¹	Case control analyzed as cohort with comparison group	Patients admitted to the coronary care unit	Haloperidol (Median dose: 5.0 Dose range: 1.0 to 57.5mg), 124	Not Reported, 681	Not reported	Prolongation in the QTc interval milliseconds	Baseline: Mean 448 (SD 56) Final: Mean 471 (SD 52)	Baseline: Mean 459 (SD 60) Final: Mean (SD)	
Naksuk, 2017 ⁵¹	Case control analyzed as cohort with comparison group	Patients admitted to the coronary care unit	Haloperidol (Median dose: 5.0 Dose range: 1.0 to 57.5mg), 124	Not Reported, 681	Not reported	Prolongation in the QTc interval milliseconds	Baseline: Mean 448 (SD 56) Final: Mean 426 (SD 64)	Baseline: Mean 459 (SD 60) Final: Mean (SD)	
Naksuk, 2017 ⁵¹	Case control analyzed as cohort with comparison group	Patients admitted to the coronary care unit	Haloperidol (Median dose: 5.0 Dose range: 1.0 to 57.5mg), 124	Not Reported, 681	Not reported	Prolongation in the QTc interval milliseconds	Baseline: Mean 448 (SD 56) Final: Mean 442 (SD 34)	Baseline: Mean 459 (SD 60) Final: Mean 458 (SD 44)	-5.00 (95% CI: -194.06 to 184.06)
Naksuk, 2017 ⁵¹	Case control analyzed as cohort with comparison group	Patients admitted to the coronary care unit	Haloperidol (Median dose: 5.0 Dose range: 1.0 to 57.5mg), 124	Not Reported, 681	Not reported	Prolongation in the QTc interval milliseconds	Baseline: Mean 448 (SD 56) Final: Mean 458 (SD 57)	Baseline: Mean 459 (SD 60) Final: Mean (SD)	
Naksuk, 2017 ⁵¹	Case control analyzed as cohort with comparison group	Patients admitted to the coronary care unit	Haloperidol (Median dose: 5.0 Dose range: 1.0 to 57.5mg), 124	Not Reported, 681	Not reported	Prolongation in the QTc interval milliseconds	Baseline: Mean 448 (SD 56) Final: Mean 454 (SD 49)	Baseline: Mean 459 (SD 60) Final: Mean (SD)	

Author, year	Study design	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	MMSE, intervention group	MMSE, control group	Mean between-group difference (95% CI)
Second-generation antipsychotic vs. placebo									
Naksuk, 2017 ⁵¹	Case control analyzed as cohort with comparison group	Patients admitted to the coronary care unit	Quetiapine (Median dose: 25.0 Dose range: 4.2 to 150.0mg), 59	Not Reported, 681	Not reported	Prolongation in the QTc interval milliseconds	Baseline: Mean 470 (SD 66) Final: Mean 455 (SD 53)	Baseline: Mean 459 (SD 60) Final: Mean (SD)	
Naksuk, 2017 ⁵¹	Case control analyzed as cohort with comparison group	Patients admitted to the coronary care unit	Quetiapine (Median dose: 25.0 Dose range: 4.2 to 150.0mg), 59	Not Reported, 681	Not reported	Prolongation in the QTc interval milliseconds	Baseline: Mean 470 (SD 66) Final: Mean 451 (SD 51)	Baseline: Mean 459 (SD 60) Final: Mean (SD)	
Naksuk, 2017 ⁵¹	Case control analyzed as cohort with comparison group	Patients admitted to the coronary care unit	Quetiapine (Median dose: 25.0 Dose range: 4.2 to 150.0mg), 59	Not Reported, 681	Not reported	Prolongation in the QTc interval milliseconds	Baseline: Mean 470 (SD 66) Final: Mean 454 (SD 51)	Baseline: Mean 459 (SD 60) Final: Mean 458 (SD 44)	-15.00 (95% CI: -201.67 to 171.67)
Naksuk, 2017 ⁵¹	Case control analyzed as cohort with comparison group	Patients admitted to the coronary care unit	Quetiapine (Median dose: 25.0 Dose range: 4.2 to 150.0mg), 59	Not Reported, 681	Not reported	Prolongation in the QTc interval milliseconds	Baseline: Mean 470 (SD 66) Final: Mean 467 (SD 68)	Baseline: Mean 459 (SD 60) Final: Mean (SD)	
Naksuk, 2017 ⁵¹	Case control analyzed as cohort with comparison group	Patients admitted to the coronary care unit	Quetiapine (Median dose: 25.0 Dose range: 4.2 to 150.0mg), 59	Not Reported, 681	Not reported	Prolongation in the QTc interval milliseconds	Baseline: Mean 470 (SD 66) Final: 457 (41)	Baseline: Mean 459 (SD 60) Final: ()	

Author, year	Study design	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	MMSE, intervention group	MMSE, control group	Mean between-group difference (95% CI)
First-generation antipsychotic vs. second-generation antipsychotic									
Naksuk, 2017 ⁵¹	Case control analyzed as cohort with comparison group	Patients admitted to the coronary care unit	Quetiapine (Median dose: 25.0 Dose range: 4.2 to 150.0mg), 59	Haloperidol (Median dose: 5.0 Dose range: 1.0 to 57.5mg), 124	Median dose: 25.0 Dose range: 4.2 to 150.0mg	24 hours after last dose	Baseline: Mean 470 (SD 66) Final: Mean 455 (SD 53)	Baseline: Mean 448 (SD 56) Final: Mean 471 (SD 52)	-38.00 (95% CI: -268.46 to 192.46)
Naksuk, 2017 ⁵¹	Case control analyzed as cohort with comparison group	Patients admitted to the coronary care unit	Quetiapine (Median dose: 25.0 Dose range: 4.2 to 150.0mg), 59	Haloperidol (Median dose: 5.0 Dose range: 1.0 to 57.5mg), 124	Median dose: 25.0 Dose range: 4.2 to 150.0mg	48 hours after last dose	Baseline: Mean 470 (SD 66) Final: Mean 451 (SD 51)	Baseline: Mean 448 (SD 56) Final: Mean 426 (SD 64)	3.00 (95% CI: -242.80 to 248.80)
Naksuk, 2017 ⁵¹	Case control analyzed as cohort with comparison group	Patients admitted to the coronary care unit	Quetiapine (Median dose: 25.0 Dose range: 4.2 to 150.0mg), 59	Haloperidol (Median dose: 5.0 Dose range: 1.0 to 57.5mg), 124	Median dose: 25.0 Dose range: 4.2 to 150.0mg	During admission (mean QTc intervals during CCU admission, excluding baseline)	Baseline: Mean 470 (SD 66) Final: Mean 454 (SD 51)	Baseline: Mean 448 (SD 56) Final: Mean 442 (SD 34)	-10.00 (95% CI: -216.57 to 196.57)
Naksuk, 2017 ⁵¹	Case control analyzed as cohort with comparison group	Patients admitted to the coronary care unit	Quetiapine (Median dose: 25.0 Dose range: 4.2 to 150.0mg), 59	Haloperidol (Median dose: 5.0 Dose range: 1.0 to 57.5mg), 124	Median dose: 25.0 Dose range: 4.2 to 150.0mg	During therapy within 6 hours after each dose	Baseline: Mean 470 (SD 66) Final: Mean 467 (SD 68)	Baseline: Mean 448 (SD 56) Final: Mean 458 (SD 57)	-13.00 (95% CI: -260.81 to 234.81)
Naksuk, 2017 ⁵¹	Case control analyzed as cohort with comparison group	Patients admitted to the coronary care unit	Quetiapine (Median dose: 25.0 Dose range: 4.2 to 150.0mg), 59	Haloperidol (Median dose: 5.0 Dose range: 1.0 to 57.5mg), 124	Median dose: 25.0 Dose range: 4.2 to 150.0mg	During therapy within 6 hours after third dose	Baseline: Mean 470 (SD 66) Final: Mean 457 (SD 41)	Baseline: Mean 448 (SD 56) Final: Mean 454 (SD 49)	-19.00 (95% CI: -237.62 to 199.62)

CCU=coronary care unit; CI=confidence interval; mg=milligram; QTc=corrected QT interval

Evidence Table D-50. Binary neurological outcomes for studies comparing interventions to treat delirium

Author, year	Study design	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
First-generation antipsychotic vs. placebo									
Girard, 2010 ⁴	RCT	> 18 years MV medical and surgical ICU patients	Haloperidol (Planned dose: 5 Median dose: 15 (10.8-17), 35	Placebo (Planned dose: 5ml), 36	Oral	Akathisia	10 / 35 (29%)	7 / 36 (19%)	RR 1.47 (95% CI: 0.63 to 3.43)
Girard, 2010 ⁴	RCT	> 18 years MV medical and surgical ICU patients	Haloperidol (Planned dose: 5 Median dose: 15 (10.8-17), 35	Placebo (Planned dose: 5ml), 36	Oral	Extrapyramidal symptoms	4 / 35 (11%)	6 / 36 (17%)	RR 0.69 (95% CI: 0.21 to 2.22)
Girard, 2010 ⁴	RCT	> 18 years MV medical and surgical ICU patients	Haloperidol (Planned dose: 5 Median dose: 15 (10.8-17), 35	Placebo (Planned dose: 5ml), 36	Oral	Neuroleptic malignant syndrome	0 / 35 (0%)	0 / 36 (0%)	
Girard, 2018 ²⁹	RCT	Patients over 18 years of age in the medical or surgical ICU, with delirium	Haloperidol (Mean dose: 11mg Dose range: 2.5-20mg), 192	Placebo (Not reported), 184	Intravenous	Extrapyramidal symptoms or Dystonia	2 / 192 (1%)	1 / 184 (1%)	RR 1.92 (95% CI: 0.18 to 20.96)
Girard, 2018 ²⁹	RCT	Patients over 18 years of age in the medical or surgical ICU, with delirium	Haloperidol (Mean dose: 11mg Dose range: 2.5-20mg), 192	Placebo (Not reported), 184	Intravenous	Reasons for temporary holds: Extrapyramidal symptoms	0 / 192 (0%)	0 / 184 (0%)	
Girard, 2018 ²⁹	RCT	Patients over 18 years of age in the medical or surgical ICU, with delirium	Haloperidol (Mean dose: 11mg Dose range: 2.5-20mg), 192	Placebo (Not reported), 184	Intravenous	Reasons for temporary holds: Dystonia	0 / 192 (0%)	0 / 184 (0%)	
Girard, 2018 ²⁹	RCT	Patients over 18 years of age in the medical or surgical ICU, with delirium	Haloperidol (Mean dose: 11mg Dose range: 2.5-20mg), 192	Placebo (Not reported), 184	Intravenous	Reasons for permanent discontinuation: Suspected neuroleptic malignant syndrome	0 / 192 (0%)	0 / 184 (0%)	
Page, 2013 ¹⁰	RCT	ICU patients needing MV within 72 hours of admission were enrolled	Haloperidol (Planned dose: 2.5mg), 71	Placebo (Planned dose: 0.5ml), 70	Intravenous	Akathisia	1 / 71 (1%)	2 / 70 (3%)	RR 0.49 (95% CI: 0.05 to 5.31)
Page, 2013 ¹⁰	RCT	ICU patients needing MV within 72 hours of admission were enrolled	Haloperidol (Planned dose: 2.5mg), 71	Placebo (Planned dose: 0.5ml), 70	Intravenous	Muscle Stiffness	1 / 71 (1%)	1 / 70 (1.4%)	RR 0.99 (95% CI: 0.06 to 15.45)
Page, 2013 ¹⁰	RCT	ICU patients needing MV within 72 hours of admission were enrolled	Haloperidol (Planned dose: 2.5mg), 71	Placebo (Planned dose: 0.5ml), 70	Intravenous	Torticollis	0 / 71 (0%)	1 / 70 (1.4%)	RR 0.33 (95% CI: 0.01 to 7.93)

Author, year	Study design	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
Second-generation antipsychotic vs. placebo									
Devlin, 2010 ²⁶	RCT	Patients admitted to Medical & Surgical ICU with delirium.	Quetiapine (Mean dose: 50 Median dose: 110 (88-191 IQR) Max dose: 200 Dose range: 50 to 200mg)	Placebo (Mean dose: 50 Median dose: 210 (116 - 293) Max dose: 200mg)	Either orally or NG tube	Extrapyramidal symptoms	Number of events: 0	Number of events: 0	p=1
Girard, 2010 ⁴	RCT	> 18 years MV medical and surgical ICU patients	Ziprasidone (Planned dose: 40 Median dose: 113 (81-140), 30	Placebo (Planned dose: 5ml), 36	Oral	Akathisia	6 / 30 (20%)	7 / 36 (19%)	RR 1.03 (95% CI: 0.39 to 2.73)
Girard, 2010 ⁴	RCT	> 18 years MV medical and surgical ICU patients	Ziprasidone (Planned dose: 40 Median dose: 113 (81-140), 30	Placebo (Planned dose: 5ml), 36	Oral	Extrapyramidal symptoms	2 / 30 (7%)	6 / 36 (17%)	RR 0.40 (95% CI: 0.09 to 1.84)
Girard, 2010 ⁴	RCT	> 18 years MV medical and surgical ICU patients	Ziprasidone (Planned dose: 40 Median dose: 113 (81-140), 30	Placebo (Planned dose: 5ml), 36	Oral	Neuroleptic malignant syndrome	0 / 30 (0%)	0 / 36 (0%)	
Girard, 2018 ²⁹	RCT	Patients over 18 years of age in the medical or surgical ICU, with delirium	Ziprasidone (Mean dose: 20mg Dose range: 5.0-40mg), 190	Placebo (Not reported), 184	Intravenous	Extrapyramidal symptoms or Dystonia	1 / 190 (1%)	1 / 184 (1%)	RR 0.97 (95% CI: 0.06 to 15.37)
Girard, 2018 ²⁹	RCT	Patients over 18 years of age in the medical or surgical ICU, with delirium	Ziprasidone (Mean dose: 20mg Dose range: 5.0-40mg), 190	Placebo (Not reported), 184	Intravenous	Reasons for temporary holds: Extrapyramidal symptoms	0 / 190 (0%)	0 / 184 (0%)	
Girard, 2018 ²⁹	RCT	Patients over 18 years of age in the medical or surgical ICU, with delirium	Ziprasidone (Mean dose: 20mg Dose range: 5.0-40mg), 190	Placebo (Not reported), 184	Intravenous	Reasons for temporary holds: Dystonia	0 / 190 (0%)	0 / 184 (0%)	

Author, year	Study design	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
Girard, 2018 ²⁹	RCT	Patients over 18 years of age in the medical or surgical ICU, with delirium	Ziprasidone (Mean dose: 20mg Dose range: 5.0-40mg), 192	Placebo (Not reported), 184	Intravenous	Reasons for permanent discontinuation: Suspected neuroleptic malignant syndrome	0 / 192 (0%)	0 / 184 (0%)	
Tahir, 2010 ⁵⁹	RCT	Patients in medical, surgical and orthopedic wards, who met the DSM-IV criteria for delirium on the same day if they had a DRS-R-98 total score of 15 or more	Quetiapine (Mean dose: 40 Dose range: 25 - 175mg), 21	Placebo (Mean dose: 25 Max dose: 175mg), 21	Oral	Abnormal involuntary movements	1 / 21 (4.8%)	3 / 21 (14.3%)	RR 0.33 (95% CI: 0.04 to 2.95)
First-generation antipsychotic vs. second-generation antipsychotic									
Boettger, 2011 ²⁰	Cohort w/ comparison group	Cancer patients	Risperidone (Mean dose: 1.0 Dose range: 0.25 to 2), 32	Haloperidol (Mean dose: 4.6 Dose range: 1 to 10mg), 32	Not reported	Dystonia	1 / 32 (3.1%)	3 / 32 (9.4%)	RR 0.33 (95% CI: 0.04 to 3.04)
Boettger, 2011 ²⁰	Cohort w/ comparison group	Cancer patients	Risperidone (Mean dose: 1.0 Dose range: 0.25 to 2), 32	Haloperidol (Mean dose: 4.6 Dose range: 1 to 10mg), 32	Not reported	Parkinsonism	1 / 32 (3.1%)	7 / 32 (21.9%)	RR 0.14 (95% CI: 0.02 to 1.10)
Boettger, 2015 ²¹	Cohort w/ comparison group	Cancer patients	Risperidone (Mean dose: 0.9 Dose range: 0.5 to 2mg), 21	Haloperidol (Mean dose: 4.9 Dose range: 1.5 to 16mg), 21	Not reported	EPS - dystonia	0 / 21 (0%)	2 / 21 (9.5%)	RR 0.20 (95% CI: 0.01 to 3.93)
Boettger, 2015 ²¹	Cohort w/ comparison group	Cancer patients	Olanzapine (Mean dose: 3.5 Dose range: 2.5 to 10mg), 21	Haloperidol (Mean dose: 4.9 Dose range: 1.5 to 16mg), 21	Not reported	EPS - dystonia	0 / 21 (0%)	2 / 21 (9.5%)	RR 0.20 (95% CI: 0.01 to 3.93)
Boettger, 2015 ²¹	Cohort w/ comparison group	Cancer patients	Aripiprazole (Mean dose: 15.2 Dose range: 5 to 30mg), 21	Haloperidol (Mean dose: 4.9 Dose range: 1.5 to 16mg), 21	Not reported	EPS - dystonia	0 / 21 (0%)	2 / 21 (9.5%)	RR 0.20 (95% CI: 0.01 to 3.93)

Author, year	Study design	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
Boettger, 2015 ²¹	Cohort w/ comparison group	Cancer patients	Olanzapine (Mean dose: 3.5 Dose range: 2.5 to 10mg), 21	Haloperidol (Mean dose: 4.9 Dose range: 1.5 to 16mg), 21	Not reported	EPS - parkinsonism	0 / 21 (0%)	4 / 21 (19%)	RR 0.11 (95% CI: 0.01 to 1.94)
Boettger, 2015 ²¹	Cohort w/ comparison group	Cancer patients	Risperidone (Mean dose: 0.9 Dose range: 0.5 to 2mg), 21	Haloperidol (Mean dose: 4.9 Dose range: 1.5 to 16mg), 21	Not reported	EPS - parkinsonism	1 / 21 (4.8%)	4 / 21 (19%)	RR 0.25 (95% CI: 0.03 to 2.05)
Boettger, 2015 ²¹	Cohort w/ comparison group	Cancer patients	Aripiprazole (Mean dose: 15.2 Dose range: 5 to 30mg), 21	Haloperidol (Mean dose: 4.9 Dose range: 1.5 to 16mg), 21	Not reported	EPS - parkinsonism	0 / 21 (0%)	4 / 21 (19%)	RR 0.11 (95% CI: 0.01 to 1.94)
Boettger, 2015 ²¹	Cohort w/ comparison group	Cancer patients	Olanzapine (Mean dose: 3.5 Dose range: 2.5 to 10mg), 21	Haloperidol (Mean dose: 4.9 Dose range: 1.5 to 16mg), 21	Not reported	Extrapyramidal symptoms	0 / 21 (0%)	4 / 21 (19%)	RR 0.11 (95% CI: 0.01 to 1.94)
Boettger, 2015 ²¹	Cohort w/ comparison group	Cancer patients	Risperidone (Mean dose: 0.9 Dose range: 0.5 to 2mg), 21	Haloperidol (Mean dose: 4.9 Dose range: 1.5 to 16mg), 21	Not reported	Extrapyramidal symptoms	1 / 21 (4.8%)	4 / 21 (19%)	RR 0.25 (95% CI: 0.03 to 2.05)
Boettger, 2015 ²¹	Cohort w/ comparison group	Cancer patients	Aripiprazole (Mean dose: 15.2 Dose range: 5 to 30mg), 21	Haloperidol (Mean dose: 4.9 Dose range: 1.5 to 16mg), 21	Not reported	Extrapyramidal symptoms	0 / 21 (0%)	4 / 21 (19%)	RR 0.11 (95% CI: 0.01 to 1.94)
Charoenporn, 2018 ²⁵	Cohort w/ comparison group	Physically ill patients	Quetiapine (Mean dose: 26.7 Median dose: 25), 31	Haloperidol (Mean dose: 0.9 Median dose: 0.5mg), 11	Oral	Extrapyramidal symptoms	3 / 31 (9.7%)	1 / 11 (9.1%)	RR 1.06 (95% CI: 0.12 to 9.19)
Charoenporn, 2018 ²⁵	Cohort w/ comparison group	Physically ill patients	Risperidone (Mean dose: 0.6 Median dose: 0.5mg), 14	Haloperidol (Mean dose: 0.9 Median dose: 0.5mg), 11	Oral	Extrapyramidal symptoms	2 / 14 (14.2%)	1 / 11 (9.1%)	RR 1.57 (95% CI: 0.16 to 15.16)
Girard, 2010 ⁴	RCT	> 18 years MV medical and surgical ICU patients	Ziprasidone (Planned dose: 40 Median dose: 113 (81-140), 30	Haloperidol (Planned dose: 5 Median dose: 15 (10.8-17), 35	Oral	Akathisia	6 / 30 (20%)	10 / 35 (29%)	RR 0.70 (95% CI: 0.29 to 1.70)

Author, year	Study design	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
Girard, 2010 ⁴	RCT	> 18 years MV medical and surgical ICU patients	Ziprasidone (Planned dose: 40 Median dose: 113 (81-140), 30	Haloperidol (Planned dose: 5 Median dose: 15 (10.8-17), 35	Oral	Extrapyramidal symptoms	2 / 30 (7%)	4 / 35 (11%)	RR 0.58 (95% CI: 0.11 to 2.96)
Girard, 2010 ⁴	RCT	> 18 years MV medical and surgical ICU patients	Ziprasidone (Planned dose: 40 Median dose: 113 (81-140), 30	Haloperidol (Planned dose: 5 Median dose: 15 (10.8-17), 35	Oral	Neuroleptic malignant syndrome	0 / 30 (0%)	0 / 35 (0%)	
Girard, 2018 ²⁹	RCT	Patients over 18 years of age in the medical or surgical ICU, with delirium	Ziprasidone (Mean dose: 20mg Dose range: 5.0-40mg), 190	Haloperidol (Mean dose: 11mg Dose range: 2.5-20mg), 192	Intravenous	Extrapyramidal symptoms or Dystonia	1 / 190 (1%)	2 / 192 (1%)	RR 0.51 (95% CI: 0.05 to 5.53)
Girard, 2018 ²⁹	RCT	Patients over 18 years of age in the medical or surgical ICU, with delirium	Ziprasidone (Mean dose: 20mg Dose range: 5.0-40mg), 190	Haloperidol (Mean dose: 11mg Dose range: 2.5-20mg), 192	Intravenous	Reasons for temporary holds: Extrapyramidal symptoms	0 / 190 (0%)	0 / 192 (0%)	
Girard, 2018 ²⁹	RCT	Patients over 18 years of age in the medical or surgical ICU, with delirium	Ziprasidone (Mean dose: 20mg Dose range: 5.0-40mg), 190	Haloperidol (Mean dose: 11mg Dose range: 2.5-20mg), 192	Intravenous	Reasons for temporary holds: Dystonia	0 / 190 (0%)	0 / 192 (0%)	
Girard, 2018 ²⁹	RCT	Patients over 18 years of age in the medical or surgical ICU, with delirium	Ziprasidone (Mean dose: 20mg Dose range: 5.0-40mg), 192	Haloperidol (Mean dose: 11mg Dose range: 2.5-20mg), 184	Intravenous	Reasons for permanent discontinuation: Suspected neuroleptic malignant syndrome	0 / 192 (0%)	0 / 184 (0%)	
Grover, 2011 ³⁰	RCT	Consecutive patients >-18 years old referred to psychiatry and diagnosed with delirium	Olanzapine (Mean dose: 3.05mg Dose range: 1.25-10 mg per day), 23	Haloperidol (Mean dose: 0.88 Dose range: 0.25-5mg per day), 21	Oral	Jaw movement	0 / 23 (0%)	0 / 21 (0%)	

Author, year	Study design	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
Grover, 2011 ³⁰	RCT	Consecutive patients >-18 years old referred to psychiatry and diagnosed with delirium	Risperidone (Mean dose: 0.95mg Dose range: 0.5-2.0mg per day), 20	Haloperidol (Mean dose: 0.88 Dose range: 0.25-5mg per day), 21	Oral	Jaw movement	1 / 20 (5%)	0 / 21 (0%)	RR 3.14 (95% CI: 0.14 to 72.92)
Grover, 2011 ³⁰	RCT	Consecutive patients >-18 years old referred to psychiatry and diagnosed with delirium	Risperidone (Mean dose: 0.95mg Dose range: 0.5-2.0mg per day), 20	Haloperidol (Mean dose: 0.88 Dose range: 0.25-5mg per day), 21	Oral	Lips and perioral movements	1 / 20 (5%)	0 / 21 (0%)	RR 3.14 (95% CI: 0.14 to 72.92)
Grover, 2011 ³⁰	RCT	Consecutive patients >-18 years old referred to psychiatry and diagnosed with delirium	Olanzapine (Mean dose: 3.05mg Dose range: 1.25-10 mg per day), 23	Haloperidol (Mean dose: 0.88 Dose range: 0.25-5mg per day), 21	Oral	Lips and perioral movements	0 / 23 (0%)	0 / 21 (0%)	
Grover, 2011 ³⁰	RCT	Consecutive patients >-18 years old referred to psychiatry and diagnosed with delirium	Olanzapine (Mean dose: 3.05mg Dose range: 1.25-10 mg per day), 23	Haloperidol (Mean dose: 0.88 Dose range: 0.25-5mg per day), 21	Oral	Movements of the tongue	0 / 23 (0%)	0 / 21 (0%)	
Grover, 2011 ³⁰	RCT	Consecutive patients >-18 years old referred to psychiatry and diagnosed with delirium	Risperidone (Mean dose: 0.95mg Dose range: 0.5-2.0mg per day), 20	Haloperidol (Mean dose: 0.88 Dose range: 0.25-5mg per day), 21	Oral	Movements of the tongue	2 / 20 (10%)	0 / 21 (0%)	RR 5.24 (95% CI: 0.27 to 102.81)
Grover, 2011 ³⁰	RCT	Consecutive patients >-18 years old referred to psychiatry and diagnosed with delirium	Olanzapine (Mean dose: 3.05mg Dose range: 1.25-10 mg per day), 23	Haloperidol (Mean dose: 0.88 Dose range: 0.25-5mg per day), 21	Oral	Rigidity	0 / 23 (0%)	3 / 21 (14.3%)	RR 0.13 (95% CI: 0.01 to 2.39)
Grover, 2011 ³⁰	RCT	Consecutive patients >-18 years old referred to psychiatry and diagnosed with delirium	Risperidone (Mean dose: 0.95mg Dose range: 0.5-2.0mg per day), 20	Haloperidol (Mean dose: 0.88 Dose range: 0.25-5mg per day), 21	Oral	Rigidity	2 / 20 (10%)	3 / 21 (14.3%)	RR 0.70 (95% CI: 0.13 to 3.76)
Grover, 2011 ³⁰	RCT	Consecutive patients >-18 years old referred to psychiatry and diagnosed with delirium	Risperidone (Mean dose: 0.95mg Dose range: 0.5-2.0mg per day), 20	Haloperidol (Mean dose: 0.88 Dose range: 0.25-5mg per day), 21	Oral	Tremors	2 / 20 (10%)	4 / 21 (19%)	RR 0.53 (95% CI: 0.11 to 2.56)
Grover, 2011 ³⁰	RCT	Consecutive patients >-18 years old referred to psychiatry and diagnosed with delirium	Olanzapine (Mean dose: 3.05mg Dose range: 1.25-10 mg per day), 23	Haloperidol (Mean dose: 0.88 Dose range: 0.25-5mg per day), 21	Oral	Tremors	2 / 23 (8.7%)	4 / 21 (19%)	RR 0.46 (95% CI: 0.09 to 2.24)

Author, year	Study design	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
Han, 2004 ³²	RCT	All patients presenting with altered mental status (from both ICU and non-ICU units) who were referred to the consulting psychiatry division were evaluated.	Risperidone (Mean dose: 1.02 Dose range: 0.5 to 2.0mg), 12	Haloperidol (Mean dose: 1.7 Dose range: 1.0 to 3.0mg), 12	Oral	Extrapyramidal symptoms	0 / 12 (0%)	1 / 12 (8.3%)	RR 0.33 (95% CI: 0.01 to 7.45)
Hatta, 2014 ³³	Cohort w/ comparison group	Patients in a general hospital who developed delirium and were managed by a psychiatrist	Quetiapine (Max dose: 71.8mg), 779	Haloperidol (Max dose: 6.40mg), 480	Not applicable	Extrapyramidal symptoms	34 / 779 (4.4%)	30 / 480 (6.3%)	RR 0.70 (95% CI: 0.43 to 1.13)
Hatta, 2014 ³³	Cohort w/ comparison group	Patients in a general hospital who developed delirium and were managed by a psychiatrist	Olanzapine (Max dose: 10.2mg), 87	Haloperidol (Max dose: 6.40mg), 480	Not reported	Extrapyramidal symptoms	4 / 87 (4.6%)	30 / 480 (6.3%)	RR 0.74 (95% CI: 0.27 to 2.04)
Hatta, 2014 ³³	Cohort w/ comparison group	Patients in a general hospital who developed delirium and were managed by a psychiatrist	Risperidone (Max dose: 1.35mg), 835	Haloperidol (Max dose: 6.40mg), 480	Not applicable	Extrapyramidal symptoms	53 / 835 (6.3%)	30 / 480 (6.3%)	RR 1.02 (95% CI: 0.66 to 1.57)
Hatta, 2014 ³³	Cohort w/ comparison group	Patients in a general hospital who developed delirium and were managed by a psychiatrist	Aripiprazole (Max dose: 7.23mg), 61	Haloperidol (Max dose: 6.40mg), 480	Not reported	Extrapyramidal symptoms	2 / 61 (3.3%)	30 / 480 (6.3%)	RR 0.52 (95% CI: 0.13 to 2.14)
Jain, 2017 ³⁸	RCT	Medical and surgical inpatients	Olanzapine (Mean dose: 5.49mg), 47	Haloperidol (Mean dose: 2.10mg), 53	Oral	Akathisia	1 / 47 (2.1%)	0 / 53 (0%)	RR 3.38 (95% CI: 0.14 to 80.91)
Jain, 2017 ³⁸	RCT	Medical and surgical inpatients	Olanzapine (Mean dose: 5.49mg), 47	Haloperidol (Mean dose: 2.10mg), 53	Oral	Drug-induced parkinsonism	0 / 47 (0%)	3 / 53 (5.7%)	RR 0.16 (95% CI: 0.01 to 3.03)
Kim, 2005 ⁴¹	Cohort w/ comparison group	Hospital patients referred to the psychiatry division	Risperidone (Not reported), 18	Haloperidol (Not reported), 24	Not reported	Extrapyramidal symptoms	0 / 18 (0%)	0 / 24 (0%)	

Author, year	Study design	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
Lim, 2007 ⁴⁶	RCT	Patients from internal medicine, PMR, neurology, neurosurgery, orthopedic surgery, or general surgery that were referred to the psychiatric department	Olanzapine (Titrated (5 to 20 mg))	Haloperidol (Titrated (5 to 20 mg))	Intramuscular	EPS	0 / 31 (0%)	3 / 31 (9.6%)	RR 0.14 (95% CI: 0.01 to 2.66)
Lim, 2007 ⁴⁶	RCT	Patients from internal medicine, PMR, neurology, neurosurgery, orthopedic surgery, or general surgery that were referred to the psychiatric department	Olanzapine (Titrated (5 to 20 mg))	Haloperidol (Titrated (5 to 20 mg))	Intramuscular	Akathisia	0 / 31 (0%)	2 / 31 (6.4%)	RR 0.20 (95% CI: 0.01 to 4.00)
Lin, 2008 ⁴⁷	RCT	Patients receiving hospice or palliative care with advanced cancer and met DSM-IV criteria for delirium	Olanzapine (Planned dose: start dose 5mg Max dose: 15mg)	Haloperidol (Planned dose: start dose 5mg Max dose: 15mg)	Oral	Extrapyramidal symptoms			p=no significant findings
Maneeton, 2013 ⁴⁹	RCT	General adult population (age 18-75) with hyperactive delirium, referred to psychiatry consult liaison service at tertiary care hospital in Thailand	Quetiapine (Mean dose: 67.6 (SD 9.7) Dose range: 25-100mg), 24	Haloperidol (Mean dose: 0.8 (SD 0.3) Dose range: 0.5-2.0mg), 28	Oral	Akathisia	0 / 24 (0%)	1 / 28 (3.6%)	RR 0.39 (95% CI: 0.02 to 9.07)
Maneeton, 2013 ⁴⁹	RCT	General adult population (age 18-75) with hyperactive delirium, referred to psychiatry consult liaison service at tertiary care hospital in Thailand	Quetiapine (Mean dose: 67.6 (SD 9.7) Dose range: 25-100mg), 24	Haloperidol (Mean dose: 0.8 (SD 0.3) Dose range: 0.5-2.0mg), 28	Oral	Tics	0 / 24 (0%)	1 / 28 (3.6%)	RR 0.39 (95% CI: 0.02 to 9.07)
Maneeton, 2013 ⁴⁹	RCT	General adult population (age 18-75) with hyperactive delirium, referred to psychiatry consult liaison service at tertiary care hospital in Thailand	Quetiapine (Mean dose: 67.6 (SD 9.7) Dose range: 25-100mg), 24	Haloperidol (Mean dose: 0.8 (SD 0.3) Dose range: 0.5-2.0mg), 28	Oral	Tremor	0 / 24 (0%)	1 / 28 (3.6%)	RR 0.39 (95% CI: 0.02 to 9.07)
Maneeton, 2013 ⁴⁹	RCT	General adult population (age 18-75) with hyperactive delirium, referred to psychiatry consult liaison service at tertiary care hospital in Thailand	Quetiapine (Mean dose: 67.6 (SD 9.7) Dose range: 25-100mg), 24	Haloperidol (Mean dose: 0.8 (SD 0.3) Dose range: 0.5-2.0mg), 28	Oral	Withdrawal due to seizures	1 / 24 (4.2%)	0 / 28 (0%)	RR 3.48 (95% CI: 0.15 to 81.66)

Author, year	Study design	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
Sipahimalani, 1998 ⁵⁶	Cohort w/ comparison group	Hospital patients	Olanzapine (Mean dose: 8.2 Max dose: 15mg), 11	Haloperidol (Dose range: 1.5 to 10mg), 11	Not reported	Extrapyramidal symptoms	0 / 11 (0%)	3 / 11 (27.3%)	RR 0.14 (95% CI: 0.01 to 2.48)
Skrobik, 2004 ⁵⁷	Cohort w/ comparison group	Medical-surgical ICU	Olanzapine (Mean dose: 4.54 Dose range: 2.5 to 13.5mg), 28	Haloperidol (Mean dose: 6.5 Dose range: 1 to 28mg), 45	Oral	Extrapyramidal symptoms	0 / 28 (0%)	6 / 45 (13.3%)	RR 0.12 (95% CI: 0.01 to 2.09)
Yoon, 2013 ⁶²	Cohort w/ comparison group	Referred to consultation-liaison psychiatric service for a mental status change	Olanzapine (Mean dose: 2.9 Dose range: 1-20mg), 18	Haloperidol (Mean dose: 1.2 Dose range: 0.5-10mg), 23	Not reported	Akathisia	0 / 18 (0%)	1 / 23 (4.3%)	RR 0.42 (95% CI: 0.02 to 9.76)
Yoon, 2013 ⁶²	Cohort w/ comparison group	Referred to consultation-liaison psychiatric service for a mental status change	Quetiapine (Mean dose: 47.9 Dose range: 25-200mg), 18	Haloperidol (Mean dose: 1.2 Dose range: 0.5-10mg), 23	Not reported	Akathisia	0 / 18 (0%)	1 / 23 (4.3%)	RR 0.42 (95% CI: 0.02 to 9.76)
Yoon, 2013 ⁶²	Cohort w/ comparison group	Referred to consultation-liaison psychiatric service for a mental status change	Risperidone (Mean dose: 1.1 Dose range: 0.25-4mg), 21	Haloperidol (Mean dose: 1.2 Dose range: 0.5-10mg), 23	Not reported	Akathisia	0 / 21 (0%)	1 / 23 (4.3%)	RR 0.36 (95% CI: 0.02 to 8.47)

Author, year	Study design	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
Yoon, 2013 ⁶²	Cohort w/ comparison group	Referred to consultation-liaison psychiatric service for a mental status change	Quetiapine (Mean dose: 47.9 Dose range: 25-200mg), 18	Haloperidol (Mean dose: 1.2 Dose range: 0.5-10mg), 23	Not reported	Bradykinesia	0 / 18 (0%)	1 / 23 (4.3%)	RR 0.42 (95% CI: 0.02 to 9.76)
Yoon, 2013 ⁶²	Cohort w/ comparison group	Referred to consultation-liaison psychiatric service for a mental status change	Risperidone (Mean dose: 1.1 Dose range: 0.25-4mg), 21	Haloperidol (Mean dose: 1.2 Dose range: 0.5-10mg), 23	Not reported	Bradykinesia	1 / 21 (4.8%)	1 / 23 (4.3%)	RR 1.10 (95% CI: 0.07 to 16.43)
Yoon, 2013 ⁶²	Cohort w/ comparison group	Referred to consultation-liaison psychiatric service for a mental status change	Olanzapine (Mean dose: 2.9 Dose range: 1-20mg), 18	Haloperidol (Mean dose: 1.2 Dose range: 0.5-10mg), 23	Not reported	Bradykinesia	1 / 18 (5.6%)	1 / 23 (4.3%)	RR 1.28 (95% CI: 0.09 to 19.06)
Yoon, 2013 ⁶²	Cohort w/ comparison group	Referred to consultation-liaison psychiatric service for a mental status change	Olanzapine (Mean dose: 2.9 Dose range: 1-20mg), 18	Haloperidol (Mean dose: 1.2 Dose range: 0.5-10mg), 23	Not reported	Dystonia	0 / 18 (0%)	0 / 23 (0%)	
Yoon, 2013 ⁶²	Cohort w/ comparison group	Referred to consultation-liaison psychiatric service for a mental status change	Quetiapine (Mean dose: 47.9 Dose range: 25-200mg), 18	Haloperidol (Mean dose: 1.2 Dose range: 0.5-10mg), 23	Not reported	Dystonia	0 / 18 (0%)	0 / 23 (0%)	
Yoon, 2013 ⁶²	Cohort w/ comparison group	Referred to consultation-liaison psychiatric service for a mental status change	Risperidone (Mean dose: 1.1 Dose range: 0.25-4mg), 21	Haloperidol (Mean dose: 1.2 Dose range: 0.5-10mg), 23	Not reported	Dystonia	0 / 21 (0%)	0 / 23 (0%)	
Yoon, 2013 ⁶²	Cohort w/ comparison group	Referred to consultation-liaison psychiatric service for a mental status change	Quetiapine (Mean dose: 47.9 Dose range: 25-200mg), 18	Haloperidol (Mean dose: 1.2 Dose range: 0.5-10mg), 23	Not reported	Rigidity	1 / 18 (5.6%)	2 / 23 (8.7%)	RR 0.64 (95% CI: 0.06 to 6.50)
Yoon, 2013 ⁶²	Cohort w/ comparison group	Referred to consultation-liaison psychiatric service for a mental status change	Olanzapine (Mean dose: 2.9 Dose range: 1-20mg), 18	Haloperidol (Mean dose: 1.2 Dose range: 0.5-10mg), 23	Not reported	Rigidity	1 / 18 (5.6%)	2 / 23 (8.7%)	RR 0.64 (95% CI: 0.06 to 6.50)
Yoon, 2013 ⁶²	Cohort w/ comparison group	Referred to consultation-liaison psychiatric service for a mental status change	Risperidone (Mean dose: 1.1 Dose range: 0.25-4mg), 21	Haloperidol (Mean dose: 1.2 Dose range: 0.5-10mg), 23	Not reported	Rigidity	1 / 21 (4.8%)	2 / 23 (8.7%)	RR 0.55 (95% CI: 0.05 to 5.61)

Author, year	Study design	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
Yoon, 2013 ⁶²	Cohort w/ comparison group	Referred to consultation-liaison psychiatric service for a mental status change	Olanzapine (Mean dose: 2.9 Dose range: 1-20mg), 18	Haloperidol (Mean dose: 1.2 Dose range: 0.5-10mg), 23	Not reported	Tremors	1 / 18 (5.6%)	3 / 23 (13%)	RR 0.43 (95% CI: 0.05 to 3.76)
Yoon, 2013 ⁶²	Cohort w/ comparison group	Referred to consultation-liaison psychiatric service for a mental status change	Quetiapine (Mean dose: 47.9 Dose range: 25-200mg), 18	Haloperidol (Mean dose: 1.2 Dose range: 0.5-10mg), 23	Not reported	Tremors	1 / 18 (5.6%)	3 / 23 (13%)	RR 0.43 (95% CI: 0.05 to 3.76)
Yoon, 2013 ⁶²	Cohort w/ comparison group	Referred to consultation-liaison psychiatric service for a mental status change	Risperidone (Mean dose: 1.1 Dose range: 0.25-4mg), 21	Haloperidol (Mean dose: 1.2 Dose range: 0.5-10mg), 23	Not reported	Tremors	2 / 21 (9.5%)	3 / 23 (13%)	RR 0.73 (95% CI: 0.13 to 3.95)
Second-generation antipsychotic vs. second-generation antipsychotic									
Boettger, 2015 ²¹	Cohort w/ comparison group	Cancer patients	Risperidone (Mean dose: 0.9 Dose range: 0.5 to 2mg), 21	Olanzapine (Mean dose: 3.5 Dose range: 2.5 to 10mg), 21	Not reported	EPS - dystonia	0 / 21 (0%)	0 / 21 (0%)	
Boettger, 2015 ²¹	Cohort w/ comparison group	Cancer patients	Risperidone (Mean dose: 0.9 Dose range: 0.5 to 2mg), 21	Aripiprazole (Mean dose: 15.2 Dose range: 5 to 30mg), 21	Not reported	EPS - dystonia	0 / 21 (0%)	0 / 21 (0%)	
Boettger, 2015 ²¹	Cohort w/ comparison group	Cancer patients	Olanzapine (Mean dose: 3.5 Dose range: 2.5 to 10mg), 21	Aripiprazole (Mean dose: 15.2 Dose range: 5 to 30mg), 21	Not reported	EPS - dystonia	0 / 21 (0%)	0 / 21 (0%)	
Boettger, 2015 ²¹	Cohort w/ comparison group	Cancer patients	Olanzapine (Mean dose: 3.5 Dose range: 2.5 to 10mg), 21	Aripiprazole (Mean dose: 15.2 Dose range: 5 to 30mg), 21	Not reported	EPS - parkinsonism	0 / 21 (0%)	0 / 21 (0%)	

Author, year	Study design	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
Boettger, 2015 ²¹	Cohort w/ comparison group	Cancer patients	Risperidone (Mean dose: 0.9 Dose range: 0.5 to 2mg), 21	Aripiprazole (Mean dose: 15.2 Dose range: 5 to 30mg), 21	Not reported	EPS - parkinsonism	1 / 21 (4.8%)	0 / 21 (0%)	RR 3.00 (95% CI: 0.13 to 69.70)
Boettger, 2015 ²¹	Cohort w/ comparison group	Cancer patients	Risperidone (Mean dose: 0.9 Dose range: 0.5 to 2mg), 21	Olanzapine (Mean dose: 3.5 Dose range: 2.5 to 10mg), 21	Not reported	EPS - parkinsonism	1 / 21 (4.8%)	0 / 21 (0%)	RR 3.00 (95% CI: 0.13 to 69.70)
Boettger, 2015 ²¹	Cohort w/ comparison group	Cancer patients	Olanzapine (Mean dose: 3.5 Dose range: 2.5 to 10mg), 21	Aripiprazole (Mean dose: 15.2 Dose range: 5 to 30mg), 21	Not reported	Extrapyramidal symptoms	0 / 21 (0%)	0 / 21 (0%)	
Boettger, 2015 ²¹	Cohort w/ comparison group	Cancer patients	Risperidone (Mean dose: 0.9 Dose range: 0.5 to 2mg), 21	Aripiprazole (Mean dose: 15.2 Dose range: 5 to 30mg), 21	Not reported	Extrapyramidal symptoms	1 / 21 (4.8%)	0 / 21 (0%)	RR 3.00 (95% CI: 0.13 to 69.70)
Boettger, 2015 ²¹	Cohort w/ comparison group	Cancer patients	Risperidone (Mean dose: 0.9 Dose range: 0.5 to 2mg), 21	Olanzapine (Mean dose: 3.5 Dose range: 2.5 to 10mg), 21	Not reported	Extrapyramidal symptoms	1 / 21 (4.8%)	0 / 21 (0%)	RR 3.00 (95% CI: 0.13 to 69.70)
Charoenporn, 2018 ²⁵	Cohort w/ comparison group	Physically ill patients	Risperidone (Mean dose: 0.6 Median dose: 0.5mg), 14	Quetiapine (Mean dose: 26.7 Median dose: 25), 31	Oral	Extrapyramidal symptoms	2 / 14 (14.2%)	3 / 31 (9.7%)	RR 1.48 (95% CI: 0.28 to 7.87)
Grover, 2011 ³⁰	RCT	Consecutive patients >-18 years old referred to psychiatry and diagnosed with delirium	Risperidone (Mean dose: 0.95mg Dose range: 0.5-2.0mg per day), 20	Olanzapine (Mean dose: 3.05mg Dose range: 1.25-10 mg per day), 23	Oral	Jaw movement	1 / 20 (5%)	0 / 23 (0%)	RR 3.43 (95% CI: 0.15 to 79.74)
Grover, 2011 ³⁰	RCT	Consecutive patients >-18 years old referred to psychiatry and diagnosed with delirium	Risperidone (Mean dose: 0.95mg Dose range: 0.5-2.0mg per day), 20	Olanzapine (Mean dose: 3.05mg Dose range: 1.25-10 mg per day), 23	Oral	Lips and perioral movements	1 / 20 (5%)	0 / 23 (0%)	RR 3.43 (95% CI: 0.15 to 79.74)

Author, year	Study design	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
Grover, 2011 ³⁰	RCT	Consecutive patients >-18 years old referred to psychiatry and diagnosed with delirium	Risperidone (Mean dose: 0.95mg Dose range: 0.5-2.0mg per day), 20	Olanzapine (Mean dose: 3.05mg Dose range: 1.25-10 mg per day), 23	Oral	Movements of the tongue	2 / 20 (10%)	0 / 23 (0%)	RR 5.71 (95% CI: 0.29 to 112.43)
Grover, 2011 ³⁰	RCT	Consecutive patients >-18 years old referred to psychiatry and diagnosed with delirium	Risperidone (Mean dose: 0.95mg Dose range: 0.5-2.0mg per day), 20	Olanzapine (Mean dose: 3.05mg Dose range: 1.25-10 mg per day), 23	Oral	Rigidity	2 / 20 (10%)	0 / 23 (0%)	RR 5.71 (95% CI: 0.29 to 112.43)
Grover, 2011 ³⁰	RCT	Consecutive patients >-18 years old referred to psychiatry and diagnosed with delirium	Risperidone (Mean dose: 0.95mg Dose range: 0.5-2.0mg per day), 20	Olanzapine (Mean dose: 3.05mg Dose range: 1.25-10 mg per day), 23	Oral	Tremors	2 / 20 (10%)	2 / 23 (8.7%)	RR 1.15 (95% CI: 0.18 to 7.43)
Hatta, 2014 ³³	Cohort w/ comparison group	Patients in a general hospital who developed delirium and were managed by a psychiatrist	Olanzapine (Max dose: 10.2mg), 87	Aripiprazole (Max dose: 7.23mg), 61	Not reported	Extrapyramidal symptoms	4 / 87 (4.6%)	2 / 61 (3.3%)	RR 1.40 (95% CI: 0.27 to 7.42)
Hatta, 2014 ³³	Cohort w/ comparison group	Patients in a general hospital who developed delirium and were managed by a psychiatrist	Quetiapine (Max dose: 71.8mg), 779	Aripiprazole (Max dose: 7.23mg), 61	Not applicable	Extrapyramidal symptoms	34 / 779 (4.4%)	2 / 61 (3.3%)	RR 1.33 (95% CI: 0.33 to 5.41)
Hatta, 2014 ³³	Cohort w/ comparison group	Patients in a general hospital who developed delirium and were managed by a psychiatrist	Risperidone (Max dose: 1.35mg), 835	Quetiapine (Max dose: 71.8mg), 779	Not applicable	Extrapyramidal symptoms	53 / 835 (6.3%)	34 / 779 (4.4%)	RR 1.45 (95% CI: 0.96 to 2.21)
Hatta, 2014 ³³	Cohort w/ comparison group	Patients in a general hospital who developed delirium and were managed by a psychiatrist	Risperidone (Max dose: 1.35mg), 835	Aripiprazole (Max dose: 7.23mg), 61	Not applicable	Extrapyramidal symptoms	53 / 835 (6.3%)	2 / 61 (3.3%)	RR 1.94 (95% CI: 0.48 to 7.75)
Hatta, 2014 ³³	Cohort w/ comparison group	Patients in a general hospital who developed delirium and were managed by a psychiatrist	Risperidone (Max dose: 1.35mg), 835	Olanzapine (Max dose: 10.2mg), 87	Not applicable	Extrapyramidal symptoms	53 / 835 (6.3%)	4 / 87 (4.6%)	RR 1.38 (95% CI: 0.51 to 3.72)
Hatta, 2014 ³³	Cohort w/ comparison group	Patients in a general hospital who developed delirium and were managed by a psychiatrist	Quetiapine (Max dose: 71.8mg), 779	Olanzapine (Max dose: 10.2mg), 87	Not applicable	Extrapyramidal symptoms	34 / 779 (4.4%)	4 / 87 (4.6%)	RR 0.95 (95% CI: 0.35 to 2.61)

Author, year	Study design	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
Kim, 2010 ⁴²	RCT	General hospital inpatients who met DSM-IV diagnostic criteria for delirium	Risperidone (Mean dose: 0.9 ± 0.6 Dose range: 0.25 - 2mg), 17	Olanzapine (Mean dose: 2.4± 1.7 Dose range: 1.25 - 7.5mg), 15	Not reported	Akathisia	0 / 17 (0%)	2 / 15 (13.3%)	RR 0.18 (95% CI: 0.01 to 3.43)
Kim, 2010 ⁴²	RCT	General hospital inpatients who met DSM-IV diagnostic criteria for delirium	Risperidone (Mean dose: 0.9 ± 0.6 Dose range: 0.25 - 2mg), 17	Olanzapine (Mean dose: 2.4± 1.7 Dose range: 1.25 - 7.5mg), 15	Not reported	Tremor and bradykinesia	2 / 17 (11.8%)	1 / 15 (6.7%)	RR 1.76 (95% CI: 0.18 to 17.56)
Lee, 2005 ⁴⁵	RCT	Patients referred to the Psychiatric Consultation that met DSM-IV criteria for delirium	Amisulpride (Mean dose: 156.4±97.5 Dose range: 50–800mg), 16	Quetiapine (Mean dose: 113 ± 85.5 Dose range: 50–300mg), 15	Not reported	Acute dystonia	0 / 16 (0%)	0 / 15 (0%)	
Lee, 2005 ⁴⁵	RCT	Patients referred to the Psychiatric Consultation that met DSM-IV criteria for delirium	Amisulpride (Mean dose: 156.4±97.5 Dose range: 50–800mg), 16	Quetiapine (Mean dose: 113 ± 85.5 Dose range: 50–300mg), 15	Not reported	Dyskinesia	0 / 16 (0%)	0 / 15 (0%)	
Yoon, 2013 ⁶²	Cohort w/ comparison group	Referred to consultation-liaison psychiatric service for a mental status change	Quetiapine (Mean dose: 47.9 Dose range: 25-200mg), 18	Olanzapine (Mean dose: 2.9 Dose range: 1-20mg), 18	Not reported	Akathisia	0 / 18 (0%)	0 / 18 (0%)	
Yoon, 2013 ⁶²	Cohort w/ comparison group	Referred to consultation-liaison psychiatric service for a mental status change	Risperidone (Mean dose: 1.1 Dose range: 0.25-4mg), 21	Olanzapine (Mean dose: 2.9 Dose range: 1-20mg), 18	Not reported	Akathisia	0 / 21 (0%)	0 / 18 (0%)	
Yoon, 2013 ⁶²	Cohort w/ comparison group	Referred to consultation-liaison psychiatric service for a mental status change	Risperidone (Mean dose: 1.1 Dose range: 0.25-4mg), 21	Quetiapine (Mean dose: 47.9 Dose range: 25-200mg), 18	Not reported	Akathisia	0 / 21 (0%)	0 / 18 (0%)	
Yoon, 2013 ⁶²	Cohort w/ comparison group	Referred to consultation-liaison psychiatric service for a mental status change	Risperidone (Mean dose: 1.1 Dose range: 0.25-4mg), 21	Quetiapine (Mean dose: 47.9 Dose range: 25-200mg), 18	Not reported	Bradykinesia	1 / 21 (4.8%)	0 / 18 (0%)	RR 2.59 (95% CI: 0.11 to 59.93)
Yoon, 2013 ⁶²	Cohort w/ comparison group	Referred to consultation-liaison psychiatric service for a mental status change	Quetiapine (Mean dose: 47.9 Dose range: 25-200mg), 18	Olanzapine (Mean dose: 2.9 Dose range: 1-20mg), 18	Not reported	Bradykinesia	0 / 18 (0%)	1 / 18 (5.6%)	RR 0.33 (95% CI: 0.01 to 7.68)

Author, year	Study design	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
Yoon, 2013 ⁶²	Cohort w/ comparison group	Referred to consultation-liaison psychiatric service for a mental status change	Risperidone (Mean dose: 1.1 Dose range: 0.25-4mg), 21	Olanzapine (Mean dose: 2.9 Dose range: 1-20mg), 18	Not reported	Bradykinesia	1 / 21 (4.8%)	1 / 18 (5.6%)	RR 0.86 (95% CI: 0.06 to 12.75)
Yoon, 2013 ⁶²	Cohort w/ comparison group	Referred to consultation-liaison psychiatric service for a mental status change	Quetiapine (Mean dose: 47.9 Dose range: 25-200mg), 18	Olanzapine (Mean dose: 2.9 Dose range: 1-20mg), 18	Not reported	Dystonia	0 / 18 (0%)	0 / 18 (0%)	
Yoon, 2013 ⁶²	Cohort w/ comparison group	Referred to consultation-liaison psychiatric service for a mental status change	Risperidone (Mean dose: 1.1 Dose range: 0.25-4mg), 21	Quetiapine (Mean dose: 47.9 Dose range: 25-200mg), 18	Not reported	Dystonia	0 / 21 (0%)	0 / 18 (0%)	
Yoon, 2013 ⁶²	Cohort w/ comparison group	Referred to consultation-liaison psychiatric service for a mental status change	Risperidone (Mean dose: 1.1 Dose range: 0.25-4mg), 21	Olanzapine (Mean dose: 2.9 Dose range: 1-20mg), 18	Not reported	Dystonia	0 / 21 (0%)	0 / 18 (0%)	
Yoon, 2013 ⁶²	Cohort w/ comparison group	Referred to consultation-liaison psychiatric service for a mental status change	Quetiapine (Mean dose: 47.9 Dose range: 25-200mg), 18	Olanzapine (Mean dose: 2.9 Dose range: 1-20mg), 18	Not reported	Rigidity	1 / 18 (5.6%)	1 / 18 (5.6%)	RR 1.00 (95% CI: 0.07 to 14.79)
Yoon, 2013 ⁶²	Cohort w/ comparison group	Referred to consultation-liaison psychiatric service for a mental status change	Risperidone (Mean dose: 1.1 Dose range: 0.25-4mg), 21	Olanzapine (Mean dose: 2.9 Dose range: 1-20mg), 18	Not reported	Rigidity	1 / 21 (4.8%)	1 / 18 (5.6%)	RR 0.86 (95% CI: 0.06 to 12.75)
Yoon, 2013 ⁶²	Cohort w/ comparison group	Referred to consultation-liaison psychiatric service for a mental status change	Risperidone (Mean dose: 1.1 Dose range: 0.25-4mg), 21	Quetiapine (Mean dose: 47.9 Dose range: 25-200mg), 18	Not reported	Rigidity	1 / 21 (4.8%)	1 / 18 (5.6%)	RR 0.86 (95% CI: 0.06 to 12.75)
Yoon, 2013 ⁶²	Cohort w/ comparison group	Referred to consultation-liaison psychiatric service for a mental status change	Risperidone (Mean dose: 1.1 Dose range: 0.25-4mg), 21	Olanzapine (Mean dose: 2.9 Dose range: 1-20mg), 18	Not reported	Tremors	2 / 21 (9.5%)	1 / 18 (5.6%)	RR 1.71 (95% CI: 0.17 to 17.38)
Yoon, 2013 ⁶²	Cohort w/ comparison group	Referred to consultation-liaison psychiatric service for a mental status change	Quetiapine (Mean dose: 47.9 Dose range: 25-200mg), 18	Olanzapine (Mean dose: 2.9 Dose range: 1-20mg), 18	Not reported	Tremors	1 / 18 (5.6%)	1 / 18 (5.6%)	RR 1.00 (95% CI: 0.07 to 14.79)
Yoon, 2013 ⁶²	Cohort w/ comparison group	Referred to consultation-liaison psychiatric service for a mental status change	Risperidone (Mean dose: 1.1 Dose range: 0.25-4mg), 21	Quetiapine (Mean dose: 47.9 Dose range: 25-200mg), 18	Not reported	Tremors	2 / 21 (9.5%)	1 / 18 (5.6%)	RR 1.71 (95% CI: 0.17 to 17.38)

CI=confidence interval; DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th ed; EPS=extrapyramidal symptoms; ICU=intensive care unit; mg=milligram; ml=milliliter; MV=mechanical ventilation; n=sample size; RCT=randomized controlled trial; RR=risk ratio; SD=standard deviation

Evidence Table D-51. Binary neurological outcomes for studies comparing interventions to treat delirium: single arm studies

Author, year	Study design	Population	Intervention group, n	Route of administration	Outcome definition	n / N (%), intervention group
Horikawa, 2003 ³⁴	Cohort w/o comparison group	Medical and surgical inpatients	Risperidone (Planned dose: 0.5 Max dose: 1.7mg), 10	Oral	Mild parkinsonism	1 / 10 (10%)
Ikezawa, 2008 ³⁷	Open-label trial	Elderly patients with hyperactive-hypervalent delirium	Risperidone (Mean dose: 1.5 (0.7) Dose range: 0.5-3mg), 22	Oral	Extrapyramidal symptoms	1 / 22 (5%)
Kim, 2003 ⁴⁰	Cohort w/o comparison group	Patients in the acute medical units	Quetiapine (Planned dose: 25 Mean dose: 93.75mg), 12	Not reported	Extrapyramidal symptoms	0 / 12 (0%)
Kishi, 2012 ⁴³	Cohort w/o comparison group	Delirious cancer patients	Risperidone (Mean dose: 1.4mg), 29	Oral	Extrapyramidal symptoms	0 / 29 (0%)
Maneeton, 2007 ⁴⁸	Open-label study	All physically ill in-patients whose pcp consulted psychiatrists	Quetiapine (Mean dose: 45.7 (28.7) Max dose: 100 Dose range: 25-100mg), 17	Oral	Extrapyramidal symptoms	2 / 17 (12%)
Mittal, 2004 ⁵⁰	Cohort w/o comparison group	Hospitalized patients	Risperidone (Mean dose: 0.75mg), 10	Not reported	ESRS dyskinesia scale	Baseline: Mean 0.2 (SE 0.6) Final: Mean 0 (Not reported)
Mittal, 2004 ⁵⁰	Cohort w/o comparison group	Hospitalized patients	Risperidone (Mean dose: 0.75mg), 10	Not reported	ESRS dystonia scores	Baseline: Mean 0 (Not reported) Final: Mean 0 (Not reported)
Mittal, 2004 ⁵⁰	Cohort w/o comparison group	Hospitalized patients	Risperidone (Mean dose: 0.75mg), 10	Not reported	ESRS Parkinsonism scale	Baseline: Mean 1.9 (SE 2.7) Final: Mean 0.6 (SE 0.4)
Omura, 2003 ⁵²	Cohort w/o comparison group	Hospitalized patients	Quetiapine (Mean dose: 54.7 Dose range: 25 to 125mg), 24	Not reported	Extrapyramidal symptoms	0 / 24 (0%)
Pae, 2004 ⁵³	Cohort w/o comparison group	Delirious patients recruited from the departments of neurosurgery, orthopedic surgery, and oncology	Quetiapine (Mean dose: 127.1mg), 22	Oral	Extrapyramidal symptoms	0 / 22 (0%)
Parellada, 2004 ⁵⁴	Cohort w/o comparison group	General hospital patients	Risperidone (Mean dose: day 1, 2.6; day 3, 2.6; day 7, 1.5mg), 64	Oral	Neurologic subscale of the UKU	Baseline: Mean 1.2 (SE 0.3) Final: Mean 1 (SE 0.1)
Parellada, 2004 ⁵⁴	Cohort w/o comparison group	General hospital patients	Risperidone (Mean dose: day 1, 2.6; day 3, 2.6; day 7, 1.5mg), 64	Oral	Neurologic subscale of the UKU	Baseline: Mean 1.2 (SE 0.3) Final: Mean 1.1 (SE 0.1)
Parellada, 2004 ⁵⁴	Cohort w/o comparison group	General hospital patients	Risperidone (Mean dose: day 1, 2.6; day 3, 2.6; day 7, 1.5mg), 64	Oral	Cerebrovascular events	0 / 64 (0%)

Author, year	Study design	Population	Intervention group, n	Route of administration	Outcome definition	n / N (%), intervention group
Sasaki, 2003 ⁵⁵	Cohort w/o comparison group	Inpatients and outpatients	Quetiapine (Mean dose: 44.9 Max dose: 63.5mg), 10	Oral	DIEPSS score	Baseline: Mean 1.5 (SD 1.7) Final: Mean 0.7 (SD 1.3)
Straker, 2006 ⁵⁸	Cohort w/o comparison group	Medically ill delirium patients	Aripiprazole (Mean dose: 8.9 Dose range: 5 to 15mg), 14	Not reported	Cerebrovascular accidents	0 / 14 (0%)
Yoon, 2011 ⁶¹	Open-label pilot trial	Patients who were referred to psychiatrists at Korea University Ansan Hospital	Paliperidone (Mean dose: 3.75 (1.06) Max dose: 9mg), 15	Oral	Akathisia	2 / 15 (13%)

ESRS=Extrapyramidal Symptom Rating Scale; Mg=milligram; N=sample size; SD=standard deviation; UKU= Udvalg for Kliniske Undersøgelser Scale

Evidence Table D-52. Continuous neurological outcomes for studies comparing interventions to treat delirium

Author, year	Study design	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	Mean score, intervention	Mean score, control group	Relative risk (95% CI)
First-generation antipsychotic vs. placebo									
Agar, 2017 ¹⁷	RCT	Patients in hospice and palliative care with delirium	Haloperidol (Max dose: 4 mg/d),	Placebo (Max dose: 4 mg/day),	Oral	Mean of Extra pyramidal symptom rating scale.	Not reported	Not reported	Mean difference 0.79 (95% CI: 0.17 to 1.41), p=0.01
Second-generation antipsychotic vs. placebo									
Agar, 2017 ¹⁷	RCT	Patients in hospice and palliative care with delirium	Risperidone (Max dose: 4 mg/d),	Placebo (Max dose: 4 mg/day),	Oral	Mean of Extra pyramidal symptom rating scale.	Not reported	Not reported	Mean difference 0.73 (95% CI: 0.09 to 1.37), p=0.03
First-generation antipsychotic vs. first-generation antipsychotic									
Breitbart, 1996 ²²	RCT	Medically hospitalized adult patients with AIDS and a DRS score of 13 or greater (delirium)	Haloperidol (Planned dose: oral: 0.25-5.0mg, Intramuscular: 0.125-3.0mg Mean dose: 1.4 Dose range: 0.4 - 3.6mg), 11	Chlorpromazine (Planned dose: Oral: 10-200mg, Intramuscular: 5-100mg Mean dose: 36 Dose range: 10-80mg), 13	Oral or intramuscular	Extrapyramidal Symptom Rating Scale: Parkinson's subscale	Baseline: Mean 7 (SD 6.8) Final: Mean 5.54 (SD 6.76)	Baseline: Mean 7.42 (SD 8.08) Final: Mean 5.08 (SD 4.48)	0.88 (95% CI: -29.37 to 31.13)

Author, year	Study design	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	Mean score, intervention	Mean score, control group	Relative risk (95% CI)
First-generation antipsychotic vs. second-generation antipsychotic									
Maneeton, 2013 ⁴⁹	RCT	General adult population (age 18-75) with hyperactive delirium, referred to psychiatry consult liaison service at tertiary care hospital in Thailand	Quetiapine (Mean dose: 67.6 (SD 9.7) Dose range: 25-100mg), 24	Haloperidol (Mean dose: 0.8 (SD 0.3) Dose range: 0.5-2.0mg), 28	Oral	MSAS score	Baseline: Mean 0.1 (SD 0.5) Final: Mean 0.3 (SD 0.7)	Baseline: Mean 0.2 (SD 0.8) Final: Mean 0.3 (SD 1.1)	0.10 (95% CI: -3.65 to 3.85)
Maneeton, 2013 ⁴⁹	RCT	General adult population (age 18-75) with hyperactive delirium, referred to psychiatry consult liaison service at tertiary care hospital in Thailand	Quetiapine (Mean dose: 67.6 (SD 9.7) Dose range: 25-100mg), 24	Haloperidol (Mean dose: 0.8 (SD 0.3) Dose range: 0.5-2.0mg), 28	Oral	MSAS score	Baseline: Mean 0.1 (SD 0.5) Final: Mean 0.3 (SD 0.7)	Baseline: Mean 0.2 (SD 0.8) Final: Mean 0.3 (SD 1.1)	0.10 (95% CI: -3.65 to 3.85)
First-generation antipsychotic vs. other									
Breitbart, 1996 ²²	RCT	Medically hospitalized adult patients with AIDS and a DRS score of 13 or greater (delirium)	Lorazepam (Planned dose: Oral: 0.50-4.0mg, Intramuscular: 0.2-2.0mg Mean dose: 4.6 Dose range: 1.3 - 7.9mg), 6	Chlorpromazine (Planned dose: Oral: 10-200mg, Intramuscular: 5-100mg Mean dose: 36 Dose range: 10-80mg), 13	Oral or intramuscular	Extrapyramidal Symptom Rating Scale: Parkinson's subscale	Baseline: Mean 7.6 (SD 10.11) Final: Mean 12.2 (SD 8.93)	Baseline: Mean 7.42 (SD 8.08) Final: Mean 5.08 (SD 4.48)	6.94 (95% CI: -23.88 to 37.76)
Breitbart, 1996 ²²	RCT	Medically hospitalized adult patients with AIDS and a DRS score of 13 or greater (delirium)	Lorazepam (Planned dose: Oral: 0.50-4.0mg, Intramuscular: 0.2-2.0mg Mean dose: 4.6 Dose range: 1.3 - 7.9mg), 6	Haloperidol (Planned dose: oral: 0.25-5.0mg, Intramuscular: 0.125-3.0mg Mean dose: 1.4 Dose range: 0.4 - 3.6mg), 11	Oral or intramuscular	Extrapyramidal Symptom Rating Scale: Parkinson's subscale	Baseline: Mean 7.6 (SD 10.11) Final: Mean 12.2 (SD 8.93)	Baseline: Mean 7 (SD 6.8) Final: Mean 5.54 (SD 6.76)	6.06 (95% CI: -27.11 to 39.23)

AIDS=acquired immunodeficiency syndrome; CI=confidence interval; DRS=Delirium Rating Scale; Mg/day=milligram per day; Mg=milligram; P=p-value; SD=standard deviation

Evidence Table D-53. Aspiration pneumonia outcomes for studies comparing interventions to treat delirium

Author, year	Study design	Population	Intervention group, n	Control group, n	Route of administration	Outcome definition	n / N (%), intervention group	n / N (%), control group	Relative risk (95% CI)
First-generation antipsychotic vs. second-generation antipsychotic									
Hatta, 2014 ³³	Cohort w/ comparison group	Patients in a general hospital who developed delirium and were managed by a psychiatrist	Quetiapine (Max dose: 71.8mg),	Haloperidol (Max dose: 6.40mg),	Not applicable	serious	4 / 779 (0.5%)	3 / 480 (0.6%)	0.82 (0.18 to 3.65)
Hatta, 2014 ³³	Cohort w/ comparison group	Patients in a general hospital who developed delirium and were managed by a psychiatrist	Olanzapine (Max dose: 10.2mg),	Haloperidol (Max dose: 6.40mg),	Not reported	serious	2 / 87 (2.3%)	3 / 480 (0.6%)	3.68 (0.62 to 21.69)
Hatta, 2014 ³³	Cohort w/ comparison group	Patients in a general hospital who developed delirium and were managed by a psychiatrist	Risperidone (Max dose: 1.35mg),	Haloperidol (Max dose: 6.40mg),	Not applicable	serious	7 / 835 (0.8%)	3 / 480 (0.6%)	1.34 (0.35 to 5.16)
Hatta, 2014 ³³	Cohort w/ comparison group	Patients in a general hospital who developed delirium and were managed by a psychiatrist	Haloperidol (Max dose: 6.40mg),	Aripiprazole (Max dose: 7.23mg),	Intravenous	serious	3 / 480 (0.6%)	0 / 61 (0%)	0.90 (0.05 to 17.26)
Second-generation antipsychotic vs. second-generation antipsychotic									
Hatta, 2014 ³³	Cohort w/ comparison group	Patients in a general hospital who developed delirium and were managed by a psychiatrist	Risperidone (Max dose: 1.35mg),	Quetiapine (Max dose: 71.8mg),	Not applicable	serious	7 / 835 (0.8%)	4 / 779 (0.5%)	1.63 (0.48 to 5.56)
Hatta, 2014 ³³	Cohort w/ comparison group	Patients in a general hospital who developed delirium and were managed by a psychiatrist	Quetiapine (Max dose: 71.8mg),	Olanzapine (Max dose: 10.2mg),	Not applicable	serious	4 / 779 (0.5%)	2 / 87 (2.3%)	0.22 (0.04 to 1.20)
Hatta, 2014 ³³	Cohort w/ comparison group	Patients in a general hospital who developed delirium and were managed by a psychiatrist	Risperidone (Max dose: 1.35mg),	Olanzapine (Max dose: 10.2mg),	Not applicable	serious	7 / 835 (0.8%)	2 / 87 (2.3%)	0.36 (0.08 to 1.73)
Hatta, 2014 ³³	Cohort w/ comparison group	Patients in a general hospital who developed delirium and were managed by a psychiatrist	Quetiapine (Max dose: 71.8mg),	Aripiprazole (Max dose: 7.23mg),	Not applicable	serious	4 / 779 (0.5%)	0 / 61 (0%)	0.72 (0.04 to 13.14)
Hatta, 2014 ³³	Cohort w/ comparison group	Patients in a general hospital who developed delirium and were managed by a psychiatrist	Olanzapine (Max dose: 10.2mg),	Aripiprazole (Max dose: 7.23mg),	Not reported	serious	2 / 87 (2.3%)	0 / 61 (0%)	3.52 (0.17 to 72.11)
Hatta, 2014 ³³	Cohort w/ comparison group	Patients in a general hospital who developed delirium and were managed by a psychiatrist	Risperidone (Max dose: 1.35mg),	Aripiprazole (Max dose: 7.23mg),	Not applicable	serious	7 / 835 (0.8%)	0 / 61 (0%)	1.11 (0.06 to 19.25)

CI=confidence interval; N=sample size; mg=milligram

Evidence Table D-54. Aspiration pneumonia outcomes for studies comparing interventions to treat delirium: single arm studies

Author, year	Study design	Population	Intervention group, n	Route of administration	Outcome definition	n / N (%), intervention group
Straker, 2006 ⁵⁸	Cohort w/o comparison group	Medically ill delirium patients	Aripiprazole (Mean dose: 8.9 Dose range: 5 to 15mg),	Not reported	Not applicable	1 / 14 (7%)

N=sample size; Mg=milligram

Evidence Table D-55. Cochrane Risk of Bias assessment for randomized controlled trials comparing interventions to prevent development of delirium

Author, year	Risk of Bias in Sequence Generation is:	Risk of Bias in Allocation Concealment is:	Risk of Bias in binding of participants, personnel and outcomes assessors is:	Risk of Bias from missing outcome data	Risk of Bias from Selective Outcome Reporting	The study appears to be free of other sources of bias.	Overall risk of bias
Abdelgalel, 2016 ¹	Low	Low	Unclear	Unclear	Unclear	Unclear	Unclear
Al-Qadheeb, 2016 ²	Low	Low	Low	Low	Low	Yes	Low
Fukata, 2014 ³	Low	High	High	Unclear	Unclear	Yes	High
Girard, 2010 ⁴	Low	Low	Low	Low	Low	Yes	Low
Hakim, 2012 ⁵	Low	Low	Low	Low	Unclear	Yes	Low
Kalisvaart, 2005 ⁶	Low	Low	Low	Low	Low	Yes	Low
Kaneko, 1999 ⁷	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Khan, 2018 ⁸	Low	Low	Low	Unclear	Low	Low	Low
Larsen, 2010 ⁹	Low	Low	Low	Unclear	Low	Yes	Low
Page, 2013 ¹⁰	Low	Low	Unclear	Low	Low	No	Low
Prakanrattana, 2007 ¹¹	Low	Low	High	Low	Unclear	Yes	High
Schrijver, 2018 ^{12, 13}	Low	Low	Low	Low	Low	Yes	Low
van den Boogaard, 2018 ¹⁵	Low	Low	Low	Low	Low	Yes	Low
Wang, 2012 ¹⁶	Low	Unclear	Low	Low	Unclear	Unclear	Unclear

High=high risk of bias; Low=low risk of bias; Unclear=unclear risk of bias

Evidence Table D-56. Cochrane Risk of Bias assessment for randomized controlled trials comparing interventions to treat delirium

Author, year	Risk of Bias in Sequence Generation is:	Risk of Bias in Allocation Concealment is:	Risk of Bias in binding of participants, personnel and outcomes assessors is:	Risk of bias from missing outcome data	Risk of Bias from Selective Outcome Reporting	The study appears to be free of other sources of bias.	Overall risk of bias
Agar, 2017 ¹⁷	Low	Low	Low	Low	Low	Yes	Low
Atalan, 2013 ¹⁸	Unclear	Unclear	Low	Unclear	Unclear	Unclear	Unclear
Bakri, 2015 ¹⁹	Low	Low	Low	Unclear	Unclear	Unclear	Low
Breitbart, 1996 ²²	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Devlin, 2010 ²⁶	Low	Low	Low	Low	Unclear	Unclear	Low
Girard, 2010 ⁴	Low	Low	Low	Low	Low	Yes	Low
Girard, 2018 ²⁹	Low	Low	Low	Low	Low	Unclear	Low
Grover, 2011 ³⁰	Low	Unclear	Low	Unclear	Unclear	Unclear	Unclear
Grover, 2016 ³¹	Low	Unclear	Low	Low	Unclear	Unclear	Low
Han, 2004 ³²	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Hu, 2006 ³⁵	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Jain, 2017 ³⁸	Low	Unclear	High	High	Unclear	Unclear	High
Kim, 2010 ⁴²	Unclear	Unclear	Low	High	Unclear	Unclear	High
Lee, 2005 ⁴⁵	Unclear	Unclear	High	Unclear	Unclear	Unclear	High
Lim, 2007 ⁴⁶	Low	Low	Unclear	Low	Low	Low	Low
Lin, 2008 ⁴⁷	Unclear	Unclear	High	High	Unclear	Yes	High
Maneeton, 2013 ⁴⁹	Low	Unclear	Low	Low	Low	Unclear	Low
Page, 2013 ¹⁰	Low	Low	Unclear	Low	Low	No	Low
Tahir, 2010 ⁵⁹	Low	Low	Low	Unclear	Unclear	Unclear	Low

High=high risk of bias; Low=low risk of bias; Unclear=unclear risk of bias

Evidence Table D-57. Cochrane Risk of Bias in non-randomized studies assessing interventions to prevent development of delirium

Author, year	Domain 1: Bias Due to Confounding	Domain 2: Bias in Selection of Participants into Study	Domain 3: Bias in Classification of Interventions	Domain 4: Bias Due to Deviations from Intended Interventions	Domain 5: Bias Due to Missing Data	Domain 6: Bias in Measurement of Outcomes	Domain 7: Bias in Selection of Reported Results	Overall Risk of Bias Judgment
van den Boogaard, 2013 ¹⁴	Low	Low	Low	Low	Low	Moderate	Low	Moderate

Low=low risk of bias; Moderate=moderate risk of bias; Unclear=unclear risk of bias

Evidence Table D-58. Cochrane Risk of Bias in non-randomized studies assessing interventions to treat delirium

Author, year	Domain 1: Bias Due to Confounding	Domain 2: Bias in Selection of Participants into Study	Domain 3: Bias in Classification of Interventions	Domain 4: Bias Due to Deviations from Intended Interventions	Domain 5: Bias Due to Missing Data	Domain 6: Bias in Measurement of Outcomes	Domain 7: Bias in Selection of Reported Results	Overall Risk of Bias Judgment
Boettger, 2011 ²⁰	Serious	Serious	Serious	Moderate	Moderate	Serious	Moderate	Serious
Boettger, 2015 ²¹	Serious	Moderate	Moderate	Serious	Moderate	Serious	Moderate	Serious
Breitbart, 2002 ²³	Moderate	Moderate	Serious	Moderate	Moderate	Serious	Moderate	Moderate
Carrasco, 2016 ²⁴	Serious	Serious	Moderate	Serious	Moderate	Serious	Moderate	Serious
Charoenporn, 2018 ²⁵	Moderate	Moderate	Serious	Moderate	Moderate	Serious	Moderate	Moderate
Fox, 2018 ²⁸	Serious	Low	Low	Moderate	Low	Moderate	Low	Moderate
Hatta, 2014 ³³	Serious	Low	Moderate	Moderate	Low	Serious	Low	Serious
Horikawa, 2003 ³⁴	Serious	Moderate	Serious	Serious	Moderate	Serious	Moderate	Serious
Hui, 2017 ³⁶	Low	Low	Low	Low	Low	Low	Low	Low
Ikezawa, 2008 ³⁷	Serious	Serious	Serious	Moderate	Moderate	Serious	Moderate	Serious
Kim, 2001 ³⁹	Serious	Serious	Moderate	Moderate	Moderate	Low	Moderate	Serious
Kim, 2003 ⁴⁰	Serious	Moderate	Moderate	Moderate	Moderate	Serious	Moderate	Moderate
Kim, 2005 ⁴¹	Serious	Serious	Moderate	Moderate	Low	Moderate	Moderate	Serious
Kishi, 2012 ⁴³	Serious	Serious	Low	Low	Low	Moderate	Low	Serious
Maneeton, 2007 ⁴⁸	Serious	Moderate	Low	Low	Moderate	Moderate	Low	Serious
Mittal, 2004 ⁵⁰	Serious	Low	Low	Low	Low	Moderate	Low	Moderate
Naksuk, 2017 ⁵¹	Serious	Moderate	Serious	Moderate	Moderate	Serious	Low	Serious
Omura, 2003 ⁵²	Serious	Serious	Serious	Serious	Moderate	Serious	Moderate	Serious
Pae, 2004 ⁵³	Serious	Serious	Serious	Serious	Moderate	Serious	Moderate	Serious
Parellada, 2004 ⁵⁴	Serious	Moderate	Moderate	Moderate	Moderate	Serious	Moderate	Moderate
Sasaki, 2003 ⁵⁵	Serious	Serious	Serious	Serious	Moderate	Serious	Moderate	Serious
Sipahimalani, 1998 ⁵⁶	Serious	Serious	Serious	Moderate	Moderate	Serious	Moderate	Serious
Skrobik, 2004 ⁵⁷	Low	Low	Low	Low	Low	Low	Low	Low
Straker, 2006 ⁵⁸	Serious	Serious	Low	Moderate	Low	Moderate	Low	Serious
Toda, 2005 ⁶⁰	Serious	Serious	Moderate	Low	Low	Moderate	Low	Serious
Yoon, 2011 ⁶¹	Serious	Low	Low	Low	Low	Moderate	Low	Serious
Yoon, 2013 ⁶²	Serious	Low	Serious	Low	Low	Serious	Low	Serious

Low=low risk of bias; Moderate=moderate risk of bias; Serious=serious risk of bias

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