Comparative Effectiveness Review
Number 219

Antipsychotics for the Prevention and Treatment of Delirium

Evidence Summary

Introduction

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

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.

AHRQ Agency for Healthcare Research and Quality

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;				
	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-general 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.

References

1. American Psychiatric Association. DSM-5 Task Force. Diagnostic and Statistical Manual of Mental Disorders. DSM-5. 5th ed. Arlington, VA: American Psychiatric Association; 2013.

2. Leslie DL, Marcantonio ER, Zhang Y, et al. One-year health care costs associated with delirium in the elderly population. Arch Intern Med. 2008 Jan 14;168(1):27-32. doi: 10.1001/archinternmed.2007.4. PMID: 18195192.

3. Sakusic A, O'Horo JC, Dziadzko M, et al. Potentially Modifiable Risk Factors for Long-Term Cognitive Impairment After Critical Illness: A Systematic Review. Mayo Clin Proc. 2018 Jan;93(1):68-82. doi: 10.1016/j.mayocp.2017.11.005. PMID: 29304923.

4. Devlin JW, Bhat S, Roberts RJ, et al. Current perceptions and practices surrounding the recognition and treatment of delirium in the intensive care unit: a survey of 250 critical care pharmacists from eight states. Ann Pharmacother. 2011 Oct;45(10):1217-29. doi: 10.1345/aph.1Q332. PMID: 21934036.

5. Neufeld KJ, Yue J, Robinson TN, et al. Antipsychotic Medication for Prevention and Treatment of Delirium in Hospitalized Adults: A Systematic Review and Meta-Analysis. J Am Geriatr Soc. 2016 Apr;64(4):705-14. doi: 10.1111/jgs.14076. PMID: 27004732.

6. Kishi T, Hirota T, Matsunaga S, et al. Antipsychotic medications for the treatment of delirium: a systematic review and meta-analysis of randomised controlled trials. J Neurol Neurosurg Psychiatry. 2016 Jul;87(7):767-74. doi: 10.1136/jnnp-2015-311049. PMID: 26341326.

7. Yang C, Hao Z, Tian J, et al. Does antipsychotic drug use increase the risk of long term mortality? A systematic review and meta-analysis of observational studies. Oncotarget. 2018 Mar 13;9(19):15101-10. doi: 10.18632/oncotarget.24120. PMID: 29599930.

8. Chen WY, Chen LY, Liu HC, et al. Antipsychotic medications and stroke in schizophrenia: A case-crossover study. PLoS One. 2017;12(6):e0179424. doi: 10.1371/journal.pone.0179424. PMID: 28614417.

9. Wu CS, Wu KY, Lo YR, et al. Psychotropic use and risk of stroke among patients with bipolar disorders: 10-year nationwide population based study. J Affect Disord. 2018 Jan 15;226:77-84. doi: 10.1016/j.jad.2017.09.020. PMID: 28964996.

10. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(14)-EHC063-EF. Agency for Healthcare Research and Quality. Rockville, MD. January 2014. 2014. www.effectivehealthcare.ahrq.gov.

11. Girard TD, Pandharipande PP, Carson SS, et al. Feasibility, efficacy, and safety of antipsychotics for intensive care unit delirium: the MIND randomized, placebo-controlled trial. Crit Care Med. 2010 Feb;38(2):428-37. PMID: 20095068.

12. Page VJ, Ely EW, Gates S, et al. Effect of intravenous haloperidol on the duration of delirium and coma in critically ill patients (Hope-ICU): a randomised, double-blind, placebo-controlled trial. Lancet Respir Med. 2013 Sep;1(7):515-23. doi: 10.1016/s2213-2600(13)70166-8. PMID: 24461612.

Full Report

This Evidence Summary is part of the following document: Neufeld KJ, Needham DM, Oh ES, Wilson LM, Nikooie R, Zhang A, Koneru M, Balagani A, Singu S, Aldabain L, Robinson KA. Antipsychotics for the Prevention and Treatment of Delirium. Comparative Effectiveness Review No. 219. (Prepared by the Johns Hopkins University Evidence-based Practice Center under Contract No. 290-2015-00006-I-2.) AHRQ Publication No. 19-EHC019-EF. Rockville, MD: Agency for Healthcare Research and Quality; September 2019. Posted final reports are located on the Effective Health Care Program search page.
DOI: https://doi.org/10.23970/AHRQEPCCER219.