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REVIEW

Antipsychotics for Preventing Delirium in Hospitalized Adults

A Systematic Review

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Background: Delirium is an acute disorder marked by impairments in attention and cognition, caused by an underlying medical problem. Antipsychotics are used to prevent delirium, but their benefits and harms are unclear.

Purpose: To conduct a systematic review evaluating the benefits and harms of antipsychotics for prevention of delirium in adults.

Data Sources: PubMed, Embase, CENTRAL, CINAHL, and PsycINFO from inception through July 2019, without restrictions based on study setting, language of publication, or length of follow-up.

Study Selection: Randomized, controlled trials (RCTs) that compared an antipsychotic with placebo or another antipsychotic, and prospective observational studies with a comparison group.

Data Extraction: One reviewer extracted data and graded the strength of the evidence, and a second reviewer confirmed the data. Two reviewers independently assessed the risk of bias.

Data Synthesis: A total of 14 RCTs were included. There were no differences in delirium incidence or duration, hospital length of stay (high strength of evidence [SOE]), and mortality between haloperidol and placebo used for delirium prevention. Little to no evidence was found to determine the effect of haloperidol on cognitive function, delirium severity (insufficient SOE), inappropriate continuation, and sedation (insufficient SOE). There is limited evidence that second-generation antipsychotics may lower delirium incidence in the postoperative setting. There is little evidence that short-term use of antipsychotics was associated with neurologic harms. In some of the trials, potentially harmful cardiac effects occurred more frequently with antipsychotic use.

Limitations: There was significant heterogeneity in antipsychotic dosing, route of antipsychotic administration, assessment of outcomes, and adverse events. There were insufficient or no data available to draw conclusions for many of the outcomes.

Conclusion: Current evidence does not support routine use of haloperidol or second-generation antipsychotics for prevention of delirium. There is limited evidence that second-generation antipsychotics may lower the incidence of delirium in postoperative patients, but more research is needed. Future trials should use standardized outcome measures.

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Delirium is a clinical syndrome marked by an acute and fluctuating disturbance in attention and cognition developing over a short period as a consequence of an underlying medical perturbation (1). Delirium commonly occurs after an acute illness or surgery. It may affect up to 50% of hospitalized older adults, and annual health care costs associated with delirium and its complications are estimated to be over $38 billion in the United States (2). Beyond its economic impact, delirium is also associated with poor clinical outcomes, including physical and cognitive decline, as well as increased institutionalization and mortality. In older adults undergoing major elective surgery, postoperative delirium was associated with impairment in functional recovery lasting up to 18 months after surgery (3). Delirium was also associated with long-term cognitive decline in studies conducted in intensive care unit (ICU) (4) and postoperative settings (5).

The prevalence of delirium varies by patient population and setting, ranging from 1% to 2% in the community to 82% in the ICU (6). Delirium has multiple causes; once it develops, it can be difficult to treat. Delirium may be preventable in up to 30% to 40% of cases (7, 8). Hence, interventions to prevent delirium may provide an important opportunity to reduce the morbidity and mortality associated with this condition.

At this time, multicomponent nonpharmacologic interventions, including such therapeutic activities as reminiscing, interacting with family and friends, sleep enhancement, and early mobilization (9, 10), are effective (11) and are recommended for delirium prevention (12). Despite the efficacy and cost-effectiveness of multicomponent nonpharmacologic interventions in delirium prevention (13), pharmacologic interventions, including antipsychotic medications, continue to be evaluated for potential benefit in preventing delirium.

A prior systematic review examined the evidence for use of antipsychotics to prevent delirium in adult medical and surgical inpatients up to 2013 and determined that the evidence does not support the use of antipsychotics for prevention or treatment of delirium (14). Since then, additional important studies have

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been published. Moreover, questions about antipsychotics still remain, including about mortality, cardiac, and extrapyramidal harms. Therefore, we conducted a systematic review of the benefits and harms of antipsychotics for the prevention of delirium.

METHODS

We report part of a larger systematic review on the effectiveness and safety of antipsychotics for the prevention and treatment of delirium (15). Our findings on delirium treatment are reported separately (16). In this review, we report our assessment of the effectiveness and safety of antipsychotics for preventing delirium, and the available evidence for 10 outcomes: cognitive functioning, hospital length of stay (LOS), delirium severity, sedation, inappropriate continuation of antipsychotics, delirium incidence, delirium duration, mortality, and cardiac and neurologic harms. The full evidence report includes additional details on methods and other results, including search strategies, comparison of antipsychotics with other medications, and subgroup analyses of patient populations (such as critically ill patients; those older than 65 years; the postoperative, palliative care, and hospice care settings; and patients with dementia) (15).

With input from a technical expert panel and representatives from the Agency for Healthcare Research and Quality (AHRQ) and the American Geriatrics Society, we developed a protocol that was posted 6 September 2018 at www.effectivehealthcare.ahrq.gov and registered on PROSPERO (CRD42018109552) on 28 September 2018. With the exception of finalizing the critical outcomes and adding the sensitivity analyses, we did not deviate from the protocol. We followed the methods outlined in the AHRQ's Methods Guide for Effectiveness and Comparative Effectiveness Reviews (17).

Data Sources and Searches

We searched PubMed, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), the Cumulative Index to Nursing and Allied Health Literature (CINAHL), and PsycINFO through 11 July 2019, with no restrictions on language. Our search was peer-reviewed by a medical librarian with experience in developing literature searches in the field of delirium. We hand-searched the reference lists of included articles and relevant reviews. We also hand-searched the references included in delirium-specific bibliographic repositories (18, 19).

Study Selection

Two reviewers independently screened abstracts and full-text articles for inclusion. We tracked and resolved differences between reviewers through consensus. We included randomized controlled trials (RCTs) that compared an antipsychotic with placebo or another antipsychotic for the prevention of delirium and evaluated relevant outcomes among adults at risk for delirium. The inclusion and exclusion criteria to define adults at risk for delirium varied across studies. We also included prospective observational studies with a comparison group. We had no restrictions based on study setting (inpatient or outpatient), language of publication, or length of follow-up. We excluded studies that did not use a validated instrument to diagnose delirium (18). We also included prospective observational studies with comparison groups that reported adverse events.

Data Extraction, Quality, and Applicability Assessment

We used standardized forms created in DistillerSR database (Evidence Partners Inc.) to extract data on general study characteristics, study participants, interventions, comparisons, and outcomes. One reviewer extracted data, with confirmation by a second reviewer. We contacted authors for missing data.

Two reviewers independently assessed the risk of bias (ROB) for each trial by using the Cochrane Handbook for Systematic Reviews of Interventions (20). Disagreements were resolved through discussion.

Data Synthesis and Analysis

We used the total sample size to describe the included studies; the sample size of each group is reported separately in the tables of the **Supplement** (available at Annals.org). We conducted meta-analyses of RCTs when data were sufficient (≥3 studies) and studies were homogenous enough with respect to key variables (such as population characteristics, study duration, measurement of outcomes, and treatment). We separately evaluated studies of haloperidol and second-generation antipsychotics, but combined studies evaluating different types of second-generation antipsychotics. Because we anticipated that most drugs within a class would have similar effects on the outcomes of interest, we combined studies of unique medications within classes when reporting outcomes. When an RCT had multiple study groups, we selected for the meta-analysis the study groups that were most similar to the other studies in terms of study drugs and dosing, or we combined study groups where possible.

For continuous outcomes, we calculated a mean between-group difference via a random-effects model, with the DerSimonian and Laird formula in settings of low heterogeneity (I^2 < 50%) (21) or with profile likelihood analyses when heterogeneity was not low (22). As a sensitivity analysis, we also calculated a pooled mean between-group difference by using the Hartung–Knapp–Sidik–Jonkman approach, because this provides a more conservative estimate for meta-analysis with few studies (23). For dichotomous outcomes, we calculated a pooled effect estimate of the relative risk between RCT groups, with each study weighted by the inverse variance, using a random-effects model with the DerSimonian and Laird formula in settings of low statistical heterogeneity (21) and profile likelihood analysis when heterogeneity was not low (22). When there were 0 events, we also calculated pooled odds ratios by using the Peto method and pooled relative risks by using the treatment-group continuity correction (inverse of the sample size of the other treatment group in cells with 0 events) (24, 25). For each meta-analysis, we planned to examine publication bias by using the Begg test and the Egger test, including evaluation of the asymmetry of

funnel plots, when there were more than 9 (26, 27). Publication bias was qualitatively considered as part of the strength of evidence determination. We used the admetan package in Stata (Intercooled, version 14.2 [StataCorp]) for all meta-analyses.

Grading of the Evidence

We graded the strength of evidence (SOE) by using the grading scheme recommended by the AHRQ's Guide for Conducting Comparative Effectiveness (28). We applied evidence grades to the bodies of evidence for each critical outcome.

Critical outcomes were determined before data extraction but after protocol registration. We asked each member of our technical expert panel to select the 5 most important outcomes, with at least 1 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 prevention of delirium. Results were compiled and outcomes with the most votes were designated "critical outcomes"; these were cognitive functioning, delirium severity, hospital LOS, inappropriate continuation of antipsychotic medication, and sedation.

We assessed domains of study limitations (by using individual-study ROB assessments), consistency, directness, precision, and reporting bias. We classified evidence into 4 categories: high, moderate, low, and insufficient (Supplement Table 1, available at Annals.org) (28).

Role of the Funding Source

The AHRQ reviewed the protocol and report but did not participate in the literature search, determination of study eligibility, analysis, interpretation of findings, or preparation of the manuscript for publication.

RESULTS

We identified 9427 unique citations, of which 14 RCTs met eligibility criteria (4281 participants) (Table); the ROB was low for 9, high for 2, and unclear for 3 RCTs (Supplement Table 2, available at Annals.org). The most commonly used delirium diagnosis or screening tools or algorithms were the Confusion Assessment Method for the ICU (CAM-ICU) and the *Diagnostic and Statistical Manual of Mental Disorders* (Table). All 14 RCTs were conducted in the inpatient setting (7 mainly in the ICU), with 4 having an unclear funding source, 4 with no funding or nonprofit sources, 5 with government funding, and 1 with industry funding.

Effects of Antipsychotics on Critical Outcomes

Figure 1 shows a summary of the SOE and conclusions for the effect of antipsychotics on critical outcomes.

Cognitive Functioning

No trial evaluated this outcome.

Delirium Severity

Five RCTs with low ROB (29–33) (1308 participants), evaluating various patient populations, reported delirium severity. Four trials used Delirium Rating Scale-Revised-98 (DRS-R-98) to determine delirium severity and 1 trial (31) used the Intensive Care Delirium Screening Checklist.

Haloperidol was compared with placebo in 3 RCTs with low ROB (29, 32, 33) (807 participants), but we were unable to draw conclusions owing to inconsistency and methodological limitations (insufficient SOE) (Supplement Tables 3 and 4, available at Annals.org).

Two second-generation antipsychotics (olanzapine, risperidone) were compared with placebo in 2 RCTs with low ROB (30, 31) (501 participants), but we were unable to draw conclusions owing to inconsistent results and nonrepresentativeness (insufficient SOE) (Supplement Tables 3 and 4).

We found no RCTs on delirium prevention that evaluated delirium severity between haloperidol and second-generation antipsychotics or between 2 different second-generation antipsychotics.

Hospital Length of Stay

A total of 10 RCTs reported on hospital LOS ROB ratings: 7 low (29, 31–36) (2939 participants), 2 unclear (37, 38) (547 participants), and 1 high (39) (126 participants).

Eight RCTs (3385 participants), in different patient populations and inpatient settings, reported the effect of haloperidol compared with placebo on hospital LOS (29, 32–38). One RCT, with unclear ROB (38) (90 participants), reported shorter hospital LOS for haloperidol, with a mean between-group difference of 2 days (mean difference [MD], −2.0 days [95% CI, −3.2 to −0.9 day]). However, the other 7 RCTs, with varying ROB (29, 32–37) (3295 participants), reported no statistically significant difference in hospital LOS for the overall trial population: 3 of these 7 trials favored haloperidol (33–35), with mean between-group differences ranging from 0.8 day (MD, −0.8 day [CI, −2.1 to 0.5 day]) (33) to 6.5 days (MD, −6.5 days [CI, −13.8 to 0.8 day]) (35). One of the largest trials (36) (1789 participants) in this review favored placebo, with a mean between-group difference of 0.7 day (MD, 0.7 day [CI, −0.8 to 2.1 days]) in the 2-mg haloperidol group vs. placebo. Considering the overall body of evidence, we concluded that there was no effect of haloperidol compared with placebo on hospital LOS (high SOE) (Supplement Tables 5 and 6, available at Annals.org).

Three RCTs with varying ROB (31, 34, 39) (328 participants) reported no effect on hospital LOS for second-generation antipsychotics (ziprasidone, risperidone) compared with placebo (low SOE) (Supplement Tables 5 and 6). One RCT with low ROB (34) (101 participants) reported no effect on hospital LOS for haloperidol compared with ziprasidone (insufficient SOE) (Supplement Tables 5 and 6). We found no delirium prevention RCTs evaluating hospital LOS between 2 different second-generation antipsychotics.

Inappropriate Continuation of Antipsychotic Drugs

No trial evaluated this outcome.

Table. Characteristics of Included Randomized Controlled Trials

Author, Year (Reference)	Study Sample	Participants, *n*	Comparison Groups	Mean Age, *y*	Men, %	Delirium Diagnosis Tool	Outcome Assessed	Risk of Bias
Abdelgalel, 2016 (38)	Patients in ICU	90	Placebo Haloperidol	49 51	70 73	CAM-ICU	Delirium incidence, mortality, hospital LOS, ICU LOS, cardiac effects	Unclear
Al-Qadheeb et al, 2016 (40)	Patients in medical and surgical ICU	68	Placebo Haloperidol	59 62	59 53	ICDSC, DSM	Delirium incidence, duration of delirium, mortality, ICU LOS, sedation, cardiac effects, neurologic effects	Low
Fukata et al, 2014 (42)	Elective abdominal or orthopedic surgery	121	No intervention Haloperidol	80 81	52 54	NEECHAM	Delirium incidence, duration of delirium, falls	High
Girard et al, 2010 (34)	Mechanically ventilated patients in medical and surgical ICU	101	Placebo Haloperidol Ziprasidone	56 51 54	61 57 70	CAM-ICU	Delirium- and coma-free days, duration of delirium, use of rescue therapy, mortality, hospital LOS, ICU LOS, cardiac effects, neurologic effects	Low
Hakim et al, 2012 (31)	Patients undergoing on-pump cardiac surgery	101	Placebo Risperidone	NR* NR	72 65	ICDSC, DSM	Delirium incidence, delirium severity, duration of delirium, mortality, hospital LOS, ICU LOS, cardiac effects, neurologic effects	Low
Kalisvaart et al, 2005 (29)	Acute or elective hip surgery	430	Placebo Haloperidol	80 79	22 19	CAM, DRS-R-98, DSM	Delirium incidence, delirium severity, duration of delirium, hospital LOS, sedation, neurologic effects	Low
Kaneko et al, 1999 (41)	Elective GI surgery	80	Placebo Haloperidol	73 72	65 60	DSM	Delirium incidence, short-term delirium symptoms, neurologic effects	Unclear
Khan et al, 2018 (32)	Noncardiac thoracic surgery patients in ICU	135	Placebo Haloperidol	63† 60	81 68	CAM-ICU, DRS-R-98	Delirium incidence, delirium severity, duration of delirium, mortality, hospital LOS, ICU LOS, cardiac effects, neurologic effects	Low
Larsen et al, 2010 (30)	Elective orthopedic surgery	400	Placebo Olanzapine	74 73	40 52	CAM, DRS-R-98, DSM	Delirium incidence, delirium severity, duration of delirium, use of physical restraint, institutionalization, safety attendant use, cardiac effects	Low
Page et al, 2013 (35)	Mechanically ventilated patients in ICU	141	Placebo Haloperidol	69 68	64 52	CAM-ICU	Delirium- and coma-free days, duration of delirium, short-term delirium symptoms, use of rescue therapy, mortality, hospital LOS, ICU LOS, sedation, cardiac effects, neurologic effects	Low
Prakanrattana and Prapaitrakool, 2007 (39)	Patients undergoing on-pump cardiac surgery	126	Placebo Risperidone	61 61	60 57	CAM-ICU	Delirium incidence, hospital LOS, ICU LOS, cardiac effects	High
Schrijver et al, 2018 (33)	Inpatients in medical or surgical wards	242	Placebo Haloperidol	83 84	41 48	DOSS, DRS-R-98, DSM	Delirium incidence, delirium severity, duration of delirium, use of rescue therapy, mortality, institutionalization, readmission to hospital, hospital LOS, sedation, cardiac effects, neurologic effects	Low
Van den Boogaard et al, 2018 (36)	ICU	1789	Placebo Haloperidol, 1 mg Haloperidol, 2 mg	67 66 67	61 59 63	CAM-ICU, ICDSC	Delirium incidence, delirium- and coma-free days, use of physical restraint, mortality, hospital LOS, ICU LOS, cardiac effects, neurologic effects	Low
Wang et al, 2012 (37)	Surgical ICU	457	Placebo Haloperidol	74 74	63 63	CAM-ICU	Delirium incidence, delirium- and coma-free days, use of rescue therapy, mortality, hospital LOS, ICU LOS, cardiac effects, neurologic effects	Unclear

CAM = Confusion Assessment Method; CAM-ICU = Confusion Assessment Method-ICU; DOSS = Delirium Observation Screening Scale; DRS-R-98 = Delirium Rating Scale-Revised-98; DSM = *Diagnostic and Statistical Manual of Mental Disorders*; GI = gastrointestinal; ICDSC = Intensive Care Delirium Screening Checklist; ICU = intensive care unit; LOS = length of stay; NEECHAM = Neelon and Champagne Confusion Scale; NR = not reported.
* All participants were aged ≥65 y.
† Median age.

Sedation

Four RCTs with low ROB (29, 33, 35, 40) (881 participants) compared haloperidol with placebo for prevention of delirium and reported sedation (for example, excessive or oversedation, or daytime somnolence).

One RCT (29) (430 participants) had no report of sedation and was excluded from the pooled analysis. We found no difference in sedation between haloperidol and placebo (pooled relative risk [RR], 2.05 [CI, 0.86 to 4.85] (Figure 2; Supplement Figure 2, available at Annals.org). However, there were too few events to draw conclusions about the clinical effects of haloperidol on sedation (insufficient SOE) (Supplement Tables 7 to 9, available at Annals.org).

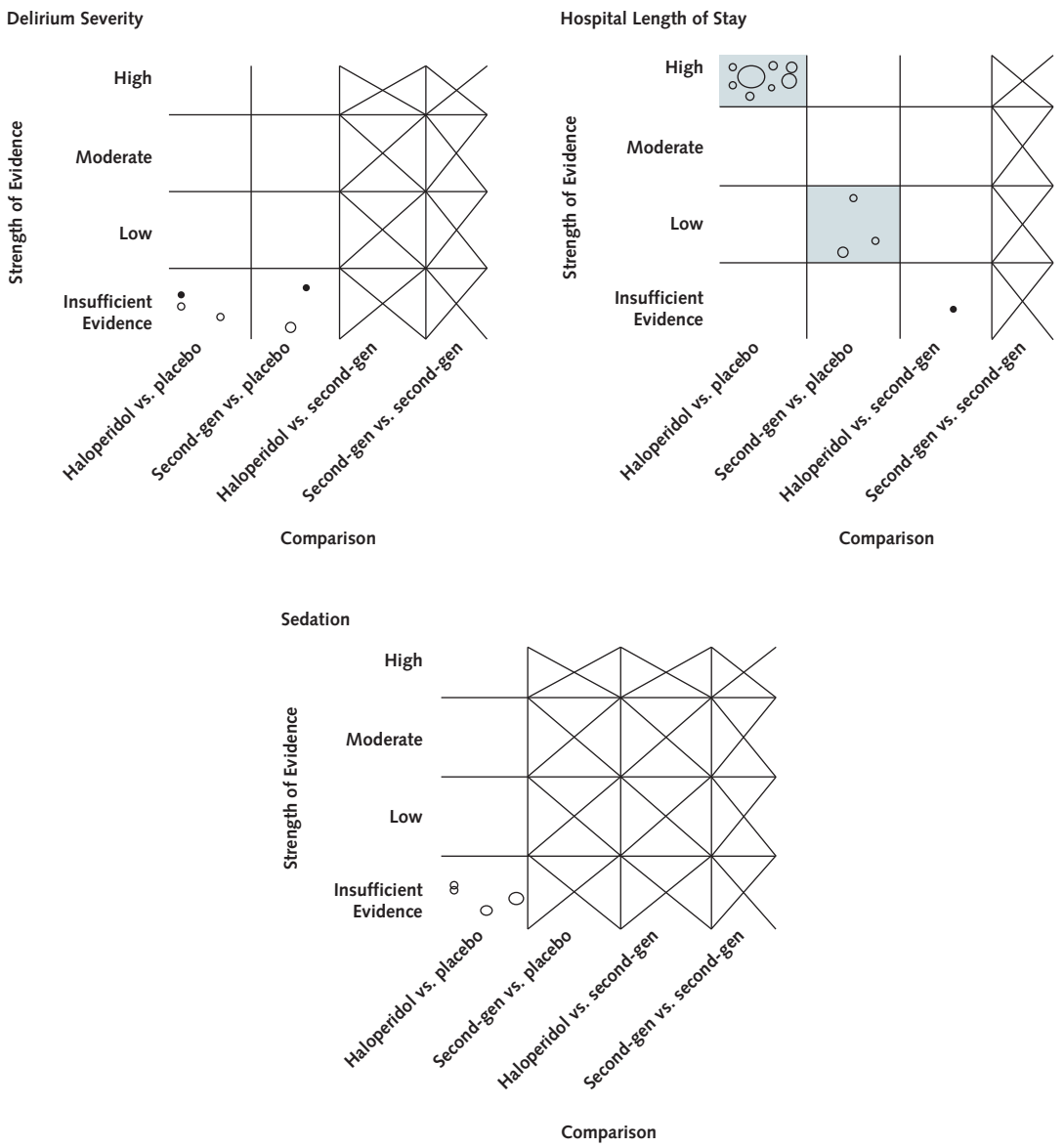
We found no RCTs evaluating sedation that compared second-generation antipsychotics and placebo, haloperidol and second-generation antipsychotics, or 2 different second-generation antipsychotics.

Effects of Antipsychotics on Other Outcomes

Delirium Incidence

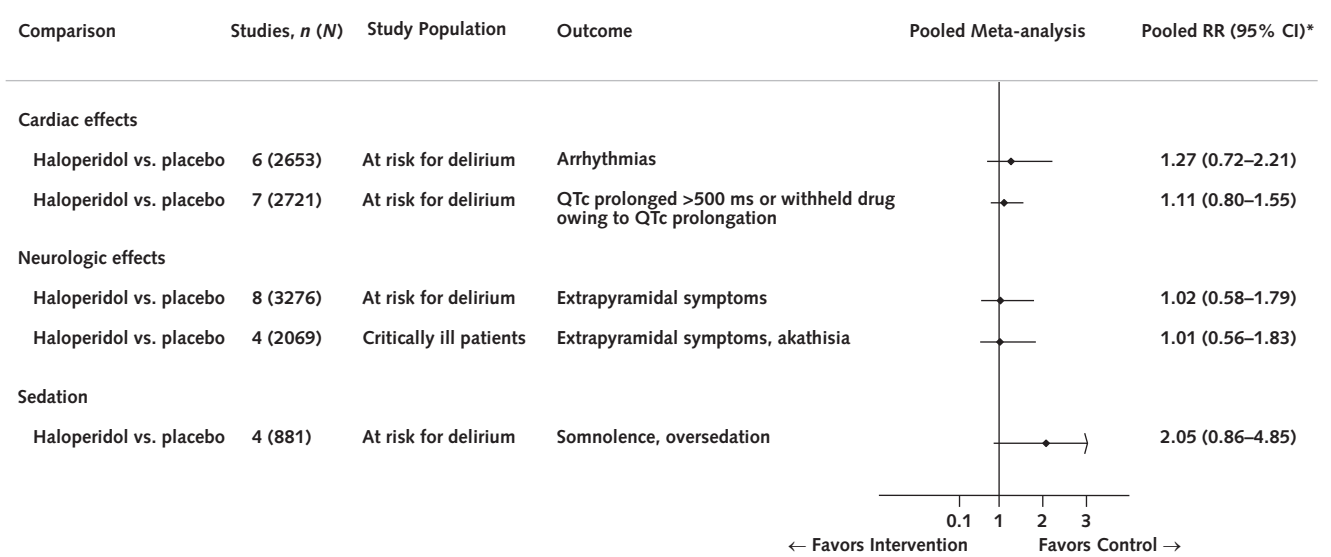
A total of 12 RCTs reported on delirium incidence ROB ratings: 6 low (29, 30, 32, 33, 36, 40) (3064 partic-

Figure 1. Summary of the strength of evidence and conclusions for the effect of antipsychotics on critical outcomes.



Each circle represents a study; the size of the circle corresponds to the study sample size. Shaded areas indicate specific comparisons for which we concluded there was little to no difference. Crossed-out columns indicate no evidence identified for the specific comparison. "Insufficient evidence" means we concluded that evidence was insufficient to make a conclusion, because of unknown consistency due to single trials, small sample size (imprecision), high risk of bias, or inconsistency in study results. We found no randomized controlled trials evaluating the role of antipsychotics for the critical outcome of cognitive function and inappropriate continuation of antipsychotics. Second-gen = second-generation antipsychotic.

Figure 2. Meta-analysis of difference in the incidence of adverse events in studies evaluating effect of antipsychotics.



RR = relative risk; QTc = corrected QT interval.
* I^2 for all the meta-analysis was 0.0%.

ipants), 4 unclear (31, 37, 38, 41) (728 participants), and 2 high (39, 42) (247 participants).

Nine RCTs with varying ROB (29, 32, 33, 36–38, 40–42) (3412 participants) compared delirium incidence between haloperidol and placebo groups. These RCTs included patients in both surgical and medical ICU and non-ICU settings, and used a variety of validated instruments for diagnosis of delirium. We found no difference in the RR for delirium with haloperidol compared with placebo (0.94 [CI, 0.77 to 1.16]) (**Figure 3**; **Supplement Figure 3** and **Supplement Table 9**, available at Annals.org).

Three RCTs with varying ROB (30, 31, 39) (627 participants) compared delirium incidence with second-generation antipsychotics (olanzapine, risperidone) versus placebo in on-pump cardiac or joint-replacement surgery. We found a statistically significant and clinically meaningful difference favoring second-generation antipsychotics in the pooled analysis (RR, 0.36 [CI, 0.26 to 0.50]) (**Figure 3**; **Supplement Figure 3** and **Supplement Table 9**).

We found no delirium prevention RCTs that evaluated the incidence of delirium between haloperidol and second-generation antipsychotics, or between 2 different second-generation antipsychotics.

Duration of Delirium

A total of 9 RCTs reported on duration of delirium ROB ratings: 8 low (29–35, 40) (1618 participants) and 1 high (42) (121 participants).

Seven RCTs (29, 32–35, 40, 42) (1238 participants) compared haloperidol with placebo in medical or surgical patients in both ICU and non-ICU settings. We did not perform meta-analysis because the data were skewed. Although 1 perioperative trial found an effect favoring haloperidol, with a mean between-group difference of 6.4 days (MD, −6.4 days [CI, −8.0 to −4.0 days]) (29), the other trials reported no difference in delirium duration. We concluded that haloperidol has no effect on duration of delirium (**Supplement Table 10**, available at Annals.org).

Three RCTs with low ROB (30, 31, 34) (602 participants) compared second-generation antipsychotics (risperidone, olanzapine, ziprasidone) with placebo in medical and surgical patients in ICU and postsurgical acute inpatient wards. Two trials (31, 34) did not show differences in delirium duration between second-generation antipsychotics (ziprasidone, risperidone) and placebo, and 1 trial (30) reported longer duration of delirium in the second-generation antipsychotic group (olanzapine) compared with placebo. We concluded that evidence is insufficient regarding the effect of second-generation antipsychotics compared with placebo. One RCT (34) comparing haloperidol with ziprasidone did not show a difference in duration of delirium (**Supplement Table 10**).

We found no RCTs evaluating delirium duration between 2 different second-generation antipsychotics.

Mortality

A total of 9 RCTs reported on mortality ROB ratings: 7 low (31–36, 40) (2577 participants) and 2 unclear (37, 38) (547 participants).

Eight RCTs (32–38, 40) (3023 participants) comparing haloperidol with placebo reported mortality. There was no between-group differences in short-term mortality (up to 30 days after randomization) (pooled RR, 0.98 [CI, 0.82 to 1.17]) (**Figure 3**; **Supplement Figure 4** and **Supplement Tables 9** and **11**, available at Annals.org). Two of these RCTs (33, 36) (2031 participants) examined 90-day mortality, with no between-group dif-

ferences (pooled RR, 0.97 [CI, 0.81 to 1.16]) (**Supplement Figure 4** and **Supplement Tables 9** and **11**). One RCT (33) (242 participants) examining 180-day mortality also reported no between-group differences (RR, 1 [CI, 0.5 to 1.7]) (**Supplement Table 11**).

Two RCTs with low ROB (31, 34) (202 participants) compared second-generation antipsychotics (risperidone, ziprasidone) with placebo in medical and surgical ICU patients. Both trials reported no between-group differences in short-term mortality. One RCT (34) (101 participants), comparing ziprasidone with haloperidol, reported no between-group differences in short-term mortality (**Supplement Table 11**).

We found no RCTs evaluating mortality between 2 different second-generation antipsychotics.

Cardiac Effects

A total of 11 RCTs (30–40) (3650 participants) reported on a variety of cardiac outcomes (**Supplement Tables 12** and **13**, available at Annals.org).

Four RCTs with low ROB (32, 34–36) (2166 participants) and 2 RCTs with unclear ROB (37, 38) (547 participants) compared haloperidol with placebo and reported on arrhythmias. One RCT (34) reported no occurrence of arrhythmia and was not included in the meta-analysis. There was no between-group difference in arrhythmias (RR, 1.27 [CI, 0.72 to 2.21] (**Figure 2** and **Supplement Figure 5** and **Supplement Tables 9** and **12**, available at Annals.org).

Two RCTs with low ROB (30, 34) (501 participants) and 1 RCT with high ROB (39) (126 participants) compared second-generation antipsychotics (ziprasidone, olanzapine, and risperidone) with placebo. One RCT (34) (101 participants) reported no occurrence of arrhythmia. In the other 2 RCTs, there were no between-group differences in arrhythmias (**Supplement Table 12**).

Five RCTs with low ROB (32, 34–36, 40) (2234 participants) and 2 RCTs with unclear ROB (37, 38) (547 participants) compared haloperidol with placebo and reported on corrected QT interval (QTc) prolongation. There were no between-group differences in QTc prolongation (pooled RR, 1.11 [CI, 0.80 to 1.55]) (**Figure 2**; **Supplement Figure 5** and **Supplement Tables 9**, **12**, and **13**, available at Annals.org).

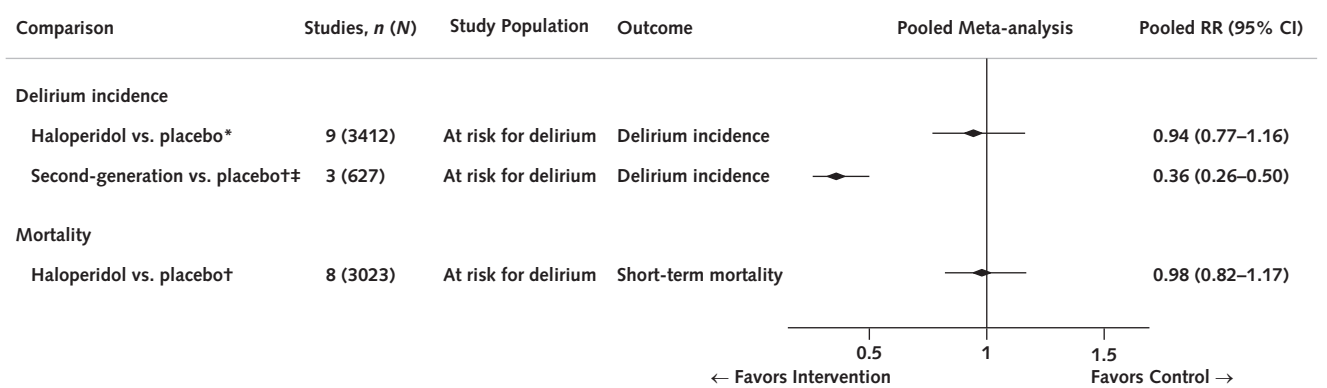
Two RCTs with low ROB (31, 34) (202 participants) compared second-generation antipsychotics (ziprasidone and risperidone) with placebo. One trial using ziprasidone (34) found no between-group differences in QTc prolongation (RR, 2.0 [CI, 0.5 to 7.7]), and the other trial (31) reported no occurrence of QTc prolongation. One RCT (34) comparing ziprasidone with haloperidol reported no between-group differences in QTc prolongation (**Supplement Tables 12** and **13**).

Neurologic Effects

Ten RCTs (29, 32–37, 40, 41) (3544 participants) reported on neurologic outcomes (**Supplement Table 14**, available at Annals.org). Seven RCTs with low ROB (29, 32–36, 40) (2906 participants) and 2 RCTs with unclear ROB (37, 41) (537 participants) compared haloperidol with placebo and reported on extrapyramidal side effects. Three RCTs (29, 37, 41) reporting no occurrence of extrapyramidal symptoms and 1 RCT (32) reporting individual symptoms of extrapyramidal side effects were not included in the meta-analysis. There was no between-group difference in extrapyramidal symptoms (pooled RR, 1.02 [CI, 0.58 to 1.79] (**Figure 2**, **Supplement Figure 6**, and **Supplement Table 9**).

Two RCTs with low ROB (31, 34) (202 participants) compared second-generation antipsychotics (risperidone, ziprasidone) with placebo and reported no between-group differences in extrapyramidal symptoms (**Supplement Table 14**, available at Annals.org). Because of the low number of events in both studies, the results are imprecise. One RCT (34) compared ziprasidone with haloperidol and found no statistically significant between-group differences in extrapyramidal symptoms (**Supplement Table 14**).

Figure 3. Pooled outcome meta-analysis for delirium incidence and mortality.



RR = relative risk.
* I^2 for the meta-analysis was 44%.
† I^2 for the meta-analysis was 0%.
‡ Olanzapine or risperidone.

Three RCTs with low ROB (32, 34, 36) (2025 participants) comparing haloperidol with placebo reported neuroleptic malignant syndrome. Two RCTs (32, 34) reported no occurrence, and 1 (36) reported no between-group differences (**Supplement Table 14**). There was no instance of neuroleptic malignant syndrome in 1 RCT (34) that compared ziprasidone with haloperidol (**Supplement Table 14**).

DISCUSSION

Our systematic review of 14 RCTs (4281 participants) found insufficient or no evidence supporting the routine use of antipsychotics for the prevention of delirium in adult inpatients.

Delirium severity provides a sensitive continuous measure of delirium (43). Delirium severity is often associated with worse clinical outcome and may be a more important outcome than incident delirium (44). Although all of the included RCTs measuring delirium severity had low ROB and most used the same delirium severity scale (DRS-R-98), because of inconsistent results and methodological limitations, evidence was insufficient to determine the effect of haloperidol and second-generation antipsychotics on delirium severity.

Hospital LOS is often examined to determine the cost-effectiveness of an intervention, including delirium prevention methods (13). In our review, which included 8 RCTs from different populations and care settings, there was no effect of haloperidol compared with placebo on hospital LOS. Three RCTs of second-generation antipsychotics compared with placebo also reported no effect on hospital LOS.

We also examined the effect of antipsychotics on sedation and found no statistically significant differences comparing haloperidol with placebo, but because of imprecision of the estimates and methodological heterogeneity of the studies, we concluded that evidence was insufficient to determine the effect of antipsychotics on sedation. We found no RCTs that examined cognitive functioning or inappropriate continuation of antipsychotic drugs as study outcomes.

In comparing haloperidol with placebo, we found no differences in incident delirium in the meta-analysis that included a large RCT with low ROB (1789 participants) (36). Exclusion of any one trial did not change the inference of the meta-analysis. However, in 3 RCTs that compared second-generation antipsychotics with placebo in postoperative settings, we found a statistically significant lower RR for incident delirium. Two trials were in cardiac surgery (risperidone) and 1 in elective orthopedic surgery (olanzapine). However, our finding should be interpreted with caution; further research is required for several reasons. One of the RCTs had high ROB due to lack of blinding (39). Even though the delirium incidence was lower in another trial, delirium duration was longer and delirium severity was higher in the antipsychotic group compared with placebo (30).

Finally, it would be important to directly compare the effectiveness of antipsychotics with that of nonpharmacologic interventions, because 1 study showed that a nonpharmacologic intervention was able to reduce the odds of postoperative delirium by 56% in a surgical population (45). At this time, important guidelines either suggest not using antipsychotics for prevention of delirium in ICU (12) or note insufficient evidence to recommend antipsychotics in all settings (46), including the postoperative setting (47).

Duration of delirium is another important outcome, given its associations with poor clinical outcomes. In 1 study of elective cardiac surgery patients, longer duration of delirium was associated with slower cognitive recovery after surgery (48), and another study showed that longer duration of delirium is associated with higher 6-month mortality in a population of patients with hip fractures (49). In our systematic review, compared with placebo, haloperidol did not have an effect on the delirium duration in the overall population, and evidence was insufficient regarding the effect of second-generation antipsychotics.

Because delirium is associated with higher mortality (50), it is important to evaluate whether delirium prevention strategies reduce mortality. Both first-generation (such as haloperidol) and second-generation antipsychotics have a U.S. Food and Drug Administration black-box warning for their association with higher mortality when used on a long-term basis in individuals with dementia (51). In our systematic review, haloperidol did not have an effect on mortality up to 30, 90, or 180 days, but few studies reported on 90- and 180-day outcomes. We found similar outcomes with second-generation antipsychotics, but only 2 RCTs examined short-term mortality. Notably, individuals with advanced dementia were excluded from the trials included in this review.

Finally, we examined harms of antipsychotics, including cardiac and neurologic side effects. Overall, there were no significant differences between haloperidol and placebo in episodes of arrhythmia and QTc prolongation. Similar findings were seen in comparisons of second-generation antipsychotics with placebo. Despite the lack of statistically significant between-group differences when comparing haloperidol and second-generation antipsychotics with placebo, in some of the studies, potentially harmful cardiac effects occurred more frequently in the antipsychotic group.

Among the 10 trials that examined neurologic outcomes, overall few neurologic events were reported. Most studies in our review excluded individuals who had underlying neurologic disorders or cardiovascular problems, and therefore the reported cardiac and neurologic harms in our review may underrepresent the event rate in routine clinical practice that includes higher-risk patients.

In recent years, several systematic reviews have examined the role of antipsychotics in delirium prevention. Most systematic reviews have been on a specific population, such as ICU patients (52–54). Our results differ from those of a prior systematic review, which found that haloperidol prophylaxis reduced the incidence of delirium in critically ill patients (52). Of note, since the end of literature search in that study (November 2015), several larger studies have been published

(32, 36, 38, 40) comparing haloperidol with placebo for prevention of delirium in critically ill patients. Our findings are consistent with more recent systematic reviews (53, 54) that have included some of the more recent studies. We performed sensitivity analysis by using alternative statistical methods, which did not change the interpretation of our primary findings (Supplement Table 9). We also searched the PubMed, Embase, CINAHL, and PsycINFO databases through 11 July 2019 and did not identify any new relevant systematic reviews. Taking this information together, we can conclude that haloperidol is most likely not effective in delirium prevention compared with placebo, especially in the ICU.

Our systematic review has limitations. First, the existing data were limited for some of the critical outcomes. Second, there was heterogeneity in dosing; route of administration; and assessment of outcomes, including adverse events. There was also heterogeneity in patient populations and settings; however, additional details of subgroup analyses of patient populations (such as critically ill patients; those aged ≥65 years; the postoperative, palliative care, or hospice care setting; and patients with dementia) are available in the full AHRQ report (15). Finally, we had few or no data on other high-risk populations (for example, patients in acute inpatient medicine units, palliative care, or nursing homes, or patients with acute stroke, other neurologic event, or advanced dementias) (6). Hence, the generalizability of our findings may be limited, and future research should evaluate these populations by using standardized outcomes assessment tools. An international effort to establish core outcomes and harmonize delirium assessment tools in intervention trials to prevent and/or treat delirium are ongoing (55–57).

In conclusion, evidence was insufficient to support the routine use of antipsychotics for preventing delirium in adult patients. Second-generation antipsychotics may lower delirium incidence in postoperative patients, but more research is needed to confirm this finding. Although statistically significant differences were not detected in cardiac side effects when antipsychotics were compared with placebo, in some of the trials, events were more common in patients receiving an antipsychotic.

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