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REVIEW

Antipsychotics for Treating Delirium in Hospitalized Adults

A Systematic Review

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Background: Delirium is common in hospitalized patients and is associated with worse outcomes. Antipsychotics are commonly used; however, the associated benefits and harms are unclear.

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

Data Sources: PubMed, Embase, CENTRAL, CINAHL, and PsycINFO from inception to July 2019 without language restrictions.

Study Selection: Randomized controlled trials (RCTs) of antipsychotic versus placebo or another antipsychotic, and prospective observational studies reporting harms.

Data Extraction: One reviewer extracted data and assessed strength of evidence (SOE) for critical outcomes, with confirmation by another reviewer. Risk of bias was assessed independently by 2 reviewers.

Data Synthesis: Across 16 RCTs and 10 observational studies of hospitalized adults, there was no difference in sedation status (low and moderate SOE), delirium duration, hospital length of stay (moderate SOE), or mortality between haloperidol and second-generation antipsychotics versus placebo. There was no difference in delirium severity (moderate SOE) and cognitive functioning (low SOE) for haloperidol versus second-generation antipsychotics, with insufficient or no evidence for antipsychotics versus placebo. For direct comparisons of different second-generation antipsychotics, there was no difference in mortality and insufficient or no evidence for multiple other outcomes. There was little evidence demonstrating neurologic harms associated with short-term use of antipsychotics for treating delirium in adult inpatients, but potentially harmful cardiac effects tended to occur more frequently.

Limitations: Heterogeneity was present in terms of dose and administration route of antipsychotics, outcomes, and measurement instruments. There was insufficient or no evidence regarding multiple clinically important outcomes.

Conclusion: Current evidence does not support routine use of haloperidol or second-generation antipsychotics to treat delirium in adult inpatients.

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Delirium is a common syndrome in hospitalized patients, with a prevalence of approximately 20% in general populations of inpatients and up to 80% in mechanically ventilated patients in the intensive care unit (ICU) setting (1, 2). The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5), criteria for delirium include an abrupt onset of inattention, decreased awareness and disorientation, and cognitive disturbance (such as impairment in memory and/or perception), with fluctuation throughout the day (3).

Delirium is associated with worse short- and long-term patient outcomes, including increased length of stay, institutionalization, long-term cognitive impairment, and mortality (4, 5). Among older adults in the United States, the 1-year health care costs of delirium are estimated to be at least $38 billion (6, 7).

Multiple predisposing factors are associated with the incidence of delirium; these include older age and preexisting cognitive impairment. Precipitating factors include benzodiazepines and other sedative medications, severity of illness, and infection (8). Usually, more than one etiologic factor simultaneously contributes to the development of delirium (9).

In clinical practice, multiple strategies, including pharmacologic and nonpharmacologic therapy, are used to treat delirium (9). There is no medication approved by the U.S. Food and Drug Administration for treating delirium. However, haloperidol and second-generation antipsychotics are commonly used to treat delirium, especially in critically ill patients (10). The effectiveness of routinely using antipsychotics in managing delirium has been questioned, especially given the potential for adverse effects (such as medication interactions [9, 11]). Whereas some previous systematic reviews have evaluated the role of antipsychotics in treating delirium and found no clear benefit (12–16), another systematic review reported some beneficial role for antipsychotics (for example, lower delirium severity) (17). However, these reviews were generally focused on a limited number of beneficial outcomes or harms, or they were conducted among only specific patient populations, with language restrictions. An up-to-date, comprehensive systematic review across all adult patients is not available. Hence, we conducted a systematic review of randomized controlled trials (RCTs) and prospective observational studies to evaluate the

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benefits and harms of haloperidol and second-generation antipsychotics compared with placebo and with other antipsychotics for treating delirium in adult patients.

METHODS

This report is part of a larger systematic review on the effectiveness and safety of antipsychotics for preventing and treating delirium (18). This review reports on the benefits and harms of antipsychotics for treating delirium, with a focus on 5 outcomes that were identified, on an a priori basis, as "critical outcomes": cognitive functioning, hospital length of stay, delirium severity, sedation, and inappropriate continuation of antipsychotics, along with 2 additional clinical outcomes (delirium duration and mortality) and 2 safety outcomes (cardiac and neurologic harms). Our findings regarding antipsychotics for preventing delirium are reported separately (19). The full evidence report has additional details on the methods and other results, including search strategies, comparison of antipsychotics with other medications, subgroup analyses of specific patient populations (such as critically ill patients, those aged ≥65 years, postoperative patients, the palliative and hospice care settings, and patients with dementia), data from observational studies without comparison groups, and data on other outcomes and harms (18).

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 (https://effectivehealthcare.ahrq.gov/topics/antipsychotics/research-protocol) that was registered on PROSPERO (CRD42018109552) on 28 September 2018. With the exception of finalizing the process for selecting critical outcomes and adding sensitivity analyses using alternative statistical methods, we did not deviate from the protocol. We followed AHRQ's Methods Guide for Effectiveness and Comparative Effectiveness Reviews (20).

Data Sources and Searches

We searched the PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Cumulative Index to Nursing and Allied Health Literature (CINAHL), and PsycINFO databases 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 several delirium-specific bibliographic repositories (21–23).

Study Selection

Two reviewers independently screened abstracts and full-text articles for inclusion. We tracked and resolved differences between reviewers through consensus. We included RCTs that compared an antipsychotic with placebo or with another antipsychotic, evaluated outcomes relevant to this review, and were conducted in adults with delirium. We also included prospective observational studies with comparison groups that reported adverse events. We had no restrictions based on study setting (such as inpatient or outpatient), language, or duration of follow-up. We excluded studies that did not use a validated instrument to diagnose delirium (24).

Data Extraction, Quality, and Applicability Assessment

We used standardized forms, created in the 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 study. For RCTs, we used the Cochrane Risk of Bias Tool (25). For observational studies, we used the Cochrane Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) tool (26). Disagreements were resolved through consensus.

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 applicable tables in the **Supplement** (available at Annals.org). We conducted meta-analyses of RCTs when there were sufficient data (≥3 studies) and studies were sufficiently homogeneous with respect to key variables (such as population characteristics, study duration, measurement of outcome, and treatment). We separately evaluated studies of haloperidol and second-generation antipsychotics but combined studies evaluating different types of second-generation antipsychotics. When an RCT had multiple study groups, for the meta-analysis, we selected the study groups that were most similar to the other studies in terms of medications and dosing, or we combined study groups were possible. We did not conduct a meta-analysis if study results were only reported as median (rather than mean) values.

We calculated a pooled effect estimate of the relative risk between the RCT groups for dichotomous outcomes, with each study weighted by the inverse variance. 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) (27, 28). We calculated a pooled mean between-group difference for continuous outcomes via a random-effects model with the DerSimonian and Laird formula in settings of low statistical heterogeneity (defined as I^2 < 50%) (29) and planned to use other appropriate analyses if there was greater heterogeneity (30). As a sensitivity analysis, we calculated a pooled mean between-group difference by using the Hartung–Knapp–Sidik–Jonkman approach because it provides a more conservative estimate for meta-analysis with few studies (31).

For the outcome of delirium severity, we used an existing conversion for the Memorial Delirium Assessment Scale and Confusion Assessment Method-

Severity scores to the Delirium Rating Scale-Revised-98 (DRS-R-98) score (32, 33).

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 studies (34, 35). Publication bias was qualitatively considered as part of the strength of evidence (SOE) determination.

We used the admetan package in Stata statistical software (Intercooled, version 14.2 [StataCorp]) for all meta-analyses.

Grading of the Evidence

We graded SOE as recommended by the AHRQ's Guide for Conducting Comparative Effectiveness Reviews (36). We applied evidence grades to the bodies of evidence for each comparison for each critical outcome. One reviewer assessed SOE, with confirmation from a second reviewer.

Critical outcomes were determined before data extraction but after protocol registration. We asked the 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 with the greatest relevance to decision making about the use of antipsychotics for treating or preventing delirium.

We assessed domains of study limitations (by using individual 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) (36).

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 a total of 9427 unique citations, of which 26 (5607 participants) met eligibility criteria (Supplement Figure 1, available at Annals.org). Of these, 16 were RCTs (1768 participants; 9 trials with low ROB) (37–52) and 10 were observational studies (3839 participants; 9 studies with moderate or serious ROB) (Supplement Tables 2 and 3, available at Annals.org). Details of the SOE assessment for critical outcomes reported in Supplement Tables 4 to 7 (available at Annals.org). The most commonly used delirium diagnosis or screening tools were the DSM and the Confusion Assessment Method for the ICU (CAM-ICU) (Table; Supplement Table 8, available at Annals.org). All 26 studies were conducted in the inpatient setting (7 exclusively in the intensive care unit); 8 had an unclear funding source, 9 had no funding or funding from nonprofit sources, 5 had governmental funding, and 4 had at least partial industry funding.

Effect of Antipsychotics on Critical Outcomes

Cognitive Functioning

Three RCTs of non–critically ill inpatients (169 participants) reported on cognitive functioning by using the Mini-Mental State Examination. No RCT compared haloperidol with placebo. Evidence was insufficient to compare the effect of second-generation antipsychotics with placebo (Figure 1; Supplement Table 9, available at Annals.org). Three different second-generation antipsychotics (olanzapine, risperidone, and quetiapine) were compared with haloperidol in 2 RCTs (64 and 63 participants; unclear and low ROB, respectively) (41, 42), with no effect (low SOE) (Supplement Table 9). Finally, evidence was insufficient to evaluate the difference between second-generation antipsychotics on cognitive functioning (Figure 1 and Supplement Table 9).

Delirium Severity

Twelve RCTs (924 participants) with various ROB, evaluating various inpatient populations, reported delirium severity by using 8 different instruments. Haloperidol was compared with placebo in two 3-group RCTs (424 participants; unclear and low ROB) (37, 44), with inconsistent findings (insufficient SOE) (Supplement Table 10, available at Annals.org). Three RCTs (466 participants; 2 low and 1 unclear ROB), including two 3-group RCTs, compared 3 different second-generation antipsychotics (risperidone, quetiapine, and olanzapine) with placebo and reported inconsistent findings (insufficient SOE) (Supplement Table 10) (37, 44, 52).

Three different second-generation antipsychotics (olanzapine, risperidone, and quetiapine) were compared with haloperidol in 8 RCTs (570 participants) (41–45, 48–50), showing no difference (moderate SOE) (Figure 1). Meta-analysis of the 5 RCTs (265 participants; unclear and low ROB) with the DRS-R-98 (41–43, 48, 50) demonstrated no difference in improvement of delirium severity (pooled mean difference, 0.0 [95% CI, −2.0 to 2.0]) (Supplement Figure 2, available at Annals.org). There also was no significant difference across 3 RCTs (257 participants; variable ROB) (44, 49, 50) by using Delirium Rating Scale (DRS) or different measures of Clinical Global Impression (CGI) (Supplement Tables 10 and 11, available at Annals.org).

Evidence was insufficient to evaluate differences between second-generation antipsychotics in terms of delirium severity.

Hospital Length of Stay

Four RCTs with low ROB, including two 3-group RCTs, reported on hospital length of stay (38–40, 51). These RCTs were conducted in medical or surgical ICUs. Three RCTs (808 participants) (39, 40, 51) comparing haloperidol with placebo showed no significant effect (moderate SOE) (Figure 1; Supplement Table 12, available at Annals.org). Two different second-generation antipsychotics (ziprasidone and quetiapine) were compared with placebo in 3 RCTs (703 participants) (38–40), with no significant effect on hospital length of stay (moderate SOE) (Supplement Table 12). Two RCTs (101 and 566 partici-

Table. Characteristics of Included Randomized Controlled Trials

Study, Year (Reference)	Study Sample	Participants, *n*	Comparison Groups	Mean Age, *y*	Men, %	Delirium Diagnosis Tool	Outcome Assessed	Risk of Bias
Agar et al, 2017 (37)	Patients in hospice and palliative care	249	Placebo Haloperidol Risperidone	74 77 75	68 59 70	DSM MDAS Nu-DESC	Delirium severity, mortality and survival, neurologic effects, use of rescue therapy	Low
Devlin et al, 2010 (38)	Patients in medical and surgical ICU	36	Placebo Quetiapine	64 62	56 56	ICDSC	Cardiac effects, delirium incidence, duration of delirium, hospital LOS, ICU LOS, mortality, neurologic effects, sedation, short-term delirium symptoms	Low
Girard et al, 2010 (39)	Mechanically ventilated patients in medical and surgical ICU	101	Placebo Haloperidol Ziprasidone	56 51 54	61 57 70	CAM-ICU	Cardiac effects, delirium- and coma-free days, duration of delirium, hospital LOS, ICU LOS, mortality, neurologic effects, use of rescue therapy	Low
Girard et al, 2018 (40)	Patients in medical and surgical ICU	566	Placebo Haloperidol Ziprasidone	59 61 61	58 56 57	CAM-ICU	Cardiac effects, delirium- and coma-free days, duration of delirium, hospital LOS, ICU LOS, ICU readmission, mortality, neurologic effects, sedation, use of rescue therapy	Low
Grover et al, 2011 (41)	Non–critically ill inpatients	64	Haloperidol Olanzapine Risperidone	44 45 47	62 61 90	DRS-R-98	Cognitive functioning, delirium severity, mortality, neurologic effects, sedation, short-term delirium symptoms	Unclear
Grover et al, 2016 (42)	Non–critically ill inpatients	63	Haloperidol Quetiapine	44 49	88 68	DSM	Cognitive functioning, delirium severity	Low
Han and Kim, 2004 (43)	Inpatients with and without critical illness	24	Haloperidol Risperidone	67 66	58 50	SCID	Delirium severity, duration of delirium, neurologic effects, sedation	Unclear
Hu et al, 2006 (44)	Inpatients with senile delirium	175	Placebo Haloperidol Olanzapine	73 74 74	62 67 61	DSM	Delirium severity	Unclear
Jain et al, 2017 (45)	Non–critically ill inpatients	100	Haloperidol Olanzapine	NR NR	NR NR	MDAS	Delirium severity, duration of delirium, mortality, neurologic effects, sedation	High
Kim et al, 2010 (46)	Inpatients	32	Olanzapine Risperidone	68 67	60 53	DSM	Delirium severity, neurologic effects, sedation, use of rescue therapy	High
Lee et al, 2005 (47)	Inpatients	31	Quetiapine Amisulpride	63 61	53 75	DSM	Delirium severity, duration of delirium, neurologic effects, sedation	High
Lim et al, 2007 (48)	Inpatients	62	Haloperidol Olanzapine	67 66	48 56	DRS-R-98 DSM	Cardiac effects, delirium severity, duration of delirium, neurologic effects, sedation	Low
Lin et al, 2008 (49)	Patients with cancer receiving hospice or palliative care	30	Haloperidol Olanzapine	68 61	29 56	DRS-c	Delirium severity, neurologic effects, use of rescue therapy	High
Maneeton et al, 2013 (50)	Inpatients with hyperactive delirium	52	Haloperidol Quetiapine	57 57	71 63	CAM-ICU DSM	Cardiac effects, delirium severity, duration of delirium, mortality, neurologic effects, sedation, short-term delirium symptoms	Low
Page et al, 2013 (51)	Mechanically ventilated patients in ICU	141	Placebo Haloperidol	69 68	64 52	CAM-ICU	Cardiac effects, delirium- and coma-free days, duration of delirium, hospital LOS, ICU LOS, mortality, neurologic effects, ICU readmissions, sedation, short-term delirium symptoms, use of rescue therapy	Low
Tahir et al, 2010 (52)	Non–critically ill inpatients	42	Placebo Quetiapine	84 84	29 29	DRS-R-98 DSM	Cognitive functioning, delirium severity, mortality, neurologic effects, sedation, short-term delirium symptoms	Low

CAM-ICU = Confusion Assessment Method for the Intensive Care Unit; DRS-R-98 = Delirium Rating Scale-Revised-98; DRS-c = Delirium Rating Scale (Chinese version); DSM = *Diagnostic and Statistical Manual of Mental Disorders*; ICDSC = Intensive Care Delirium Screening Checklist; ICU = intensive care unit; LOS = length of stay; MDAS = Memorial Delirium Assessment Scale; NR = not reported; NuDESC = Nursing Delirium Screening Scale; SCID = Structured Clinical Interview for DSM-III-R.

pants) (39, 40) compared a second-generation antipsychotic (ziprasidone) with haloperidol, with no difference (moderate SOE) (Supplement Table 12). No trial directly compared different second-generation antipsychotics.

Inappropriate Continuation of Antipsychotics

No study evaluated this outcome.

Sedation

Eleven RCTs (1150 participants), with various ROB ratings, and 6 observational studies (324 participants; moderate to serious ROB) reported on sedation-related outcomes. Two RCTs (141 and 566 participants; low ROB) (40, 51) of critically ill patients compared haloperidol with placebo, showing no statistically significant ef-

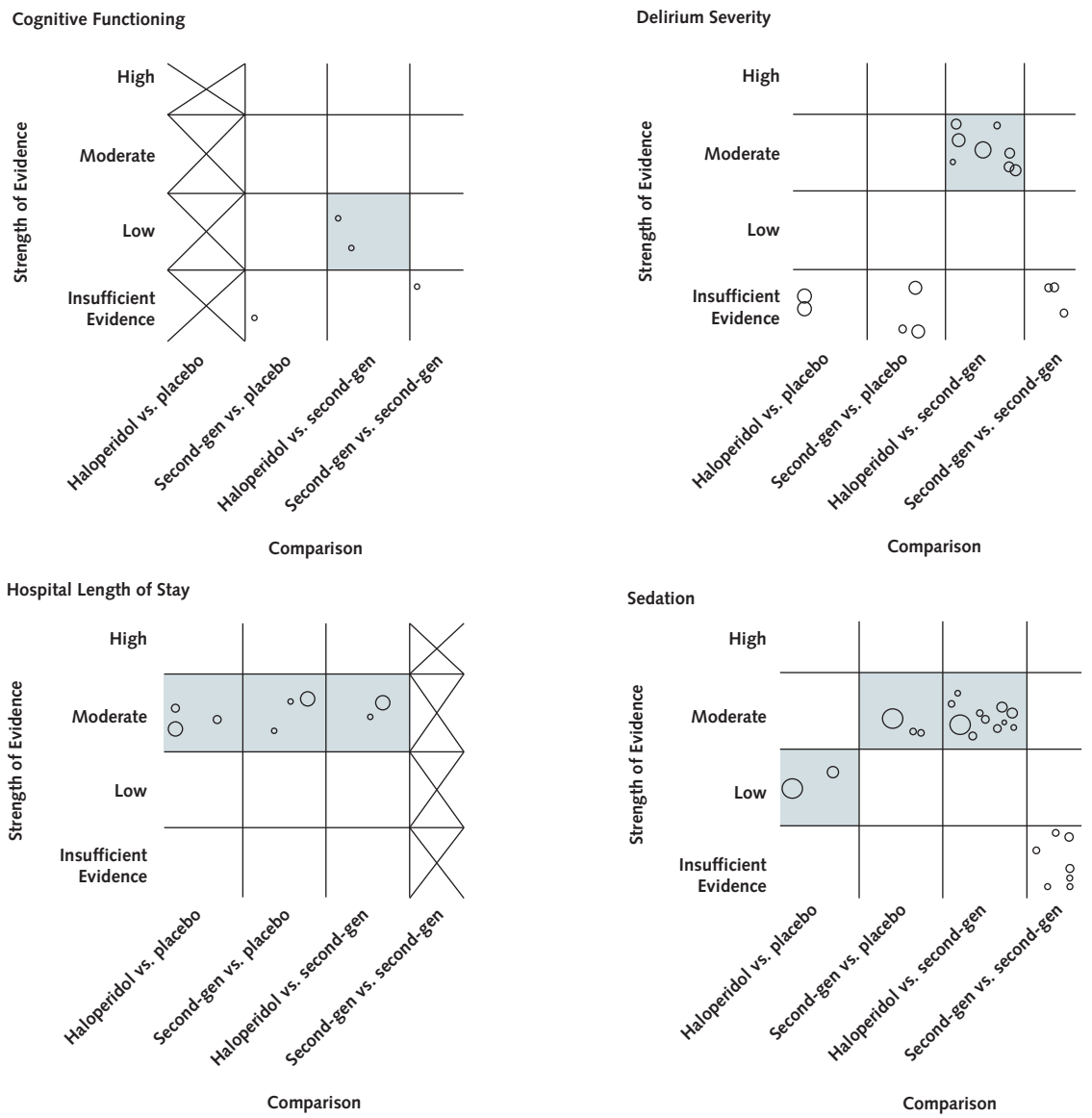
fect on sedation-related outcomes (low SOE) (**Figure 1**), including oversedation (relative risk [RR], 1.81 [CI, 0.71 to 4.62]) or holding haloperidol because of oversedation (RR, 0.88 [CI, 0.61 to 1.26]) (**Supplement Table 13**, available at Annals.org).

Two second-generation antipsychotics (quetiapine and ziprasidone) were compared with placebo in 3 RCTs of inpatients with and without critical illness (644 participants; low ROB) (38, 40, 52), with no effect on the onset of sedation (pooled RR, 1.10 [CI, 0.78 to 1.53; moderate SOE) (**Figure 2**; **Supplement Figure 3**, available at Annals.org).

Eleven studies of inpatients with and without critical illness (1316 participants; various ROB), including 6 RCTs (40, 41, 43, 45, 48, 50) (872 participants) and 5 observational studies (53–57) (444 participants), compared second-generation antipsychotics with haloperidol. These studies showed no difference in sedation-related outcomes (pooled RR across 6 RCTs, 1.26 [CI, 0.92 to 1.72]; moderate SOE) (**Figures 1** and **2**; **Supplement Figure 4**, available at Annals.org).

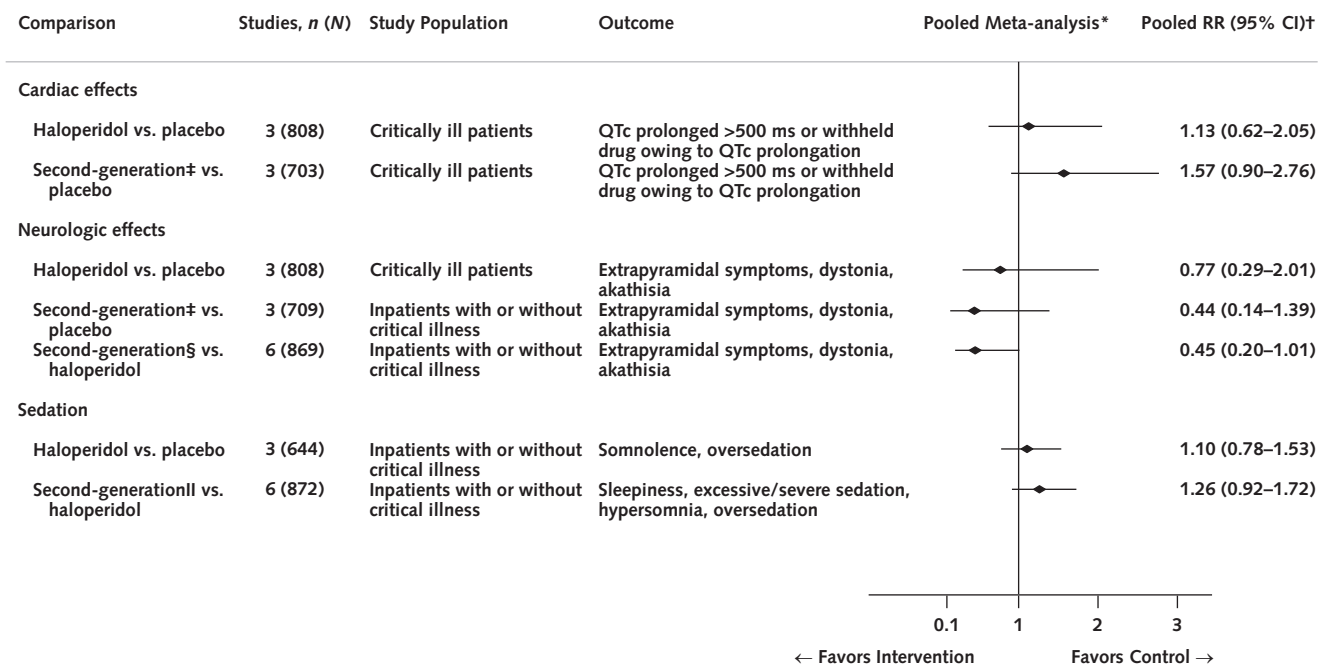
Evidence was insufficient to evaluate direct comparison of different second-generation antipsychotics on sedation (**Figure 1** and **Supplement Table 13**).

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 antipsychotics for the critical outcome of inappropriate continuation of antipsychotics. Second-gen = second-generation antipsychotic.

Figure 2. Meta-analysis of trials evaluating the effect of antipsychotics on the incidence of adverse effects.



RR = relative risk; QTc = corrected QT interval.
* Effect sizes and 95% CI for each individual study within the comparison groups are provided in Supplement Figures 3, 4, 9, 10, 11, and 12 (available at Annals.org).
† I^2 for all was 0%.
‡ Ziprasidone or quetiapine.
§ Any second-generation antipsychotic, ziprasidone, quetiapine, or risperidone.
‖ Any second-generation antipsychotic, olanzapine, ziprasidone, or risperidone.

Effect of Antipsychotics on Other Outcomes

Delirium Duration

Nine RCTs (1113 participants), with a variety of ROB ratings, reported on delirium duration. Three RCTs (808 participants; low ROB) of critically ill patients compared haloperidol with placebo, reporting no effect on delirium duration (39, 40, 51) (**Supplement Table 14**, available at Annals.org). Two second-generation antipsychotics (ziprasidone and quetiapine) were compared with placebo in 3 RCTs (703 participants; low ROB) of critically ill patients (38–40), with no effect (**Supplement Table 14**). Six RCTs (905 participants) of inpatients with and without critical illness compared 4 second-generation antipsychotics (quetiapine, ziprasidone, risperidone, and olanzapine) with haloperidol (**Supplement Table 14**) (39, 40, 43, 45, 48, 50), with 2 RCTs (667 participants) of critically ill patients reporting no difference (39, 40) and meta-analysis of the other 4 RCTs (238 participants) of predominantly non–critically ill patients (43, 45, 48, 50) demonstrating slightly longer delirium duration for second-generation antipsychotics (pooled mean difference, 0.2 day [CI, 0.0 to 0.4 day]) (**Supplement Table 14** and **Supplement Figure 5**, available at Annals.org). Evidence was insufficient to evaluate different effects of second-generation antipsychotics on delirium duration (**Supplement Table 14**).

Mortality

There were 8 RCTs (1102 participants; various ROB) of inpatients with and without critical illness (38–41, 45, 50–52) (**Table**; **Supplement Table 15**, available at Annals.org), and 1 RCT of patients receiving palliative care (37) (249 participants; low ROB) reporting on short-term mortality (death in hospital or up to 30 days after randomization).

In comparing haloperidol with placebo, 4 RCTs (1057 participants; low ROB) (37, 39, 40, 51) demonstrated no effect (pooled RR, 0.98 [CI, 0.75 to 1.27]) (**Supplement Figure 6**, available at Annals.org). However, 1 of the 4 RCTs, evaluating palliative care patients (37), also performed a time-to-event analysis and reported decreased survival for haloperidol (hazard ratio [HR], 1.73 [CI, 1.20 to 2.50]).

Three second-generation antipsychotics (quetiapine, ziprasidone, and risperidone) were compared with placebo in 5 RCTs (994 participants; low ROB) (37–40, 52), with no effect on mortality (pooled RR, 1.09 [CI, 0.83 to 1.45]) (**Supplement Figure 7**, available at Annals.org). One of the 5 RCTs, evaluating palliative care patients (37), reported a non–statistically significant decrease in survival for risperidone (HR, 1.29 [CI, 0.91 to 1.84]). The largest RCT, evaluating critically ill patients (566 participants; low ROB), also evaluated 90-day mortality and reported no effect for ziprasidone versus pla-

cebo (RR, 1.00 [CI, 0.75 to 1.32]) (**Supplement Table 15**) (40).

Six RCTs (1132 participants; various ROB) (**Table**), including four 3-group RCTs, compared 4 second-generation antipsychotics (quetiapine, ziprasidone, olanzapine, and risperidone) with haloperidol (37, 39–41, 45, 50), showing no effect on mortality (pooled RR, 1.17 [CI, 0.89 to 1.55]) (**Supplement Figure 8**, available at Annals.org). The largest RCT, evaluating critically ill patients (566 participants; low ROB), also evaluated 90-day mortality and reported no effect for ziprasidone versus haloperidol (RR, 0.90 [CI, 0.69 to 1.18]) (**Supplement Table 15**) (40).

Two second-generation antipsychotics (risperidone and olanzapine) were directly compared in 1 RCT (64 participants; unclear ROB) of non–critically ill inpatients, with no death in either group (41) (**Supplement Table 15**).

Cardiac Effects

A total of 6 RCTs (958 participants) and 4 observational studies (3474 participants) reported on variety of cardiac outcomes (**Supplement Tables 16** and **17**, available at Annals.org).

Three RCTs (39, 40, 51) (808 participants; low ROB) and 1 observational study (58) (925 participants; serious ROB) compared haloperidol with placebo among critically ill patients and reported on variety of cardiac outcomes (**Supplement Table 16**). There was no difference in prolongation of the corrected QT interval in 1 observational study and in meta-analysis of the 3 RCTs (pooled RR, 1.13 [CI, 0.62 to 2.05]) (**Figure 2**; **Supplement Figure 9**, available at Annals.org).

Two second-generation antipsychotics were compared with placebo among critically ill patients in 3 RCTs (703 participants; low ROB) (38–40) and 1 observational study (925 participants; serious ROB) (58) (**Supplement Table 16**). Meta-analysis of the 3 RCTs of ziprasidone and quetiapine demonstrated an increase in prolongation of the corrected QT interval (pooled RR; 1.57 [CI, 0.90 to 2.76]) (**Figure 2** and **Supplement Figure 9**), with removal of the single RCT (36 participants) of quetiapine (38) resulting in a stronger association (pooled RR, 1.95 [CI, 1.03 to 3.71]).

Four RCTs (781 participants; low ROB) (39, 40, 48, 50) and 3 observational studies (3434 participants; moderate or serious ROB) (54, 58, 59) compared 5 second-generation antipsychotics (quetiapine, olanzapine, risperidone, ziprasidone, and aripiprazole) with haloperidol among patients with and without critical illness for a variety of cardiac outcomes. Three RCTs and 1 observational study with serious ROB reported data for QT prolongation (39, 40, 48, 58). Whereas 1 RCT (62 participants) reported no incidence of QT prolongation in the haloperidol or the olanzapine group (48) and the observational study (925 participants) reported no difference for quetiapine (58), 2 RCTs (667 participants) of ziprasidone (39, 40) reported a potentially important, but imprecise, increase in the incidence of QT prolongation or temporary discontinuation of drug due to QT prolongation (**Supplement Table 16**). The largest RCT (566 participants) reported no incidence of permanent discontinuation of ziprasidone due to torsades de pointes (40).

Five second-generation antipsychotics (risperidone, aripiprazole, olanzapine, quetiapine, and lurasidone) were directly compared in 3 observational studies (2549 participants; moderate or serious ROB), with no between-group difference for a variety of cardiac outcomes (54, 59, 60) (**Supplement Table 16**).

Neurologic Effects

Fourteen RCTs (1530 participants; mostly low ROB) (**Table**) and 8 observational studies (2874 participants; mostly with serious ROB) (**Supplement Table 8**) reported on neurologic outcomes (**Supplement Tables 18** and **19**, available at Annals.org).

Haloperidol was compared with placebo in 4 RCTs (1057 participants; low ROB). Meta-analysis of the 3 RCTs of critically ill patients (808 participants) (39, 40, 51) demonstrated no increase in extrapyramidal symptoms (pooled RR, 0.77 [CI, 0.29 to 2.02] (**Figure 2**; **Supplement Figure 10**, available at Annals.org). However, the RCT of palliative care patients (249 participants) reported increased extrapyramidal symptoms for patients receiving haloperidol compared with placebo (37) (**Supplement Table 19**).

Three second-generation antipsychotics (quetiapine, ziprasidone, and risperidone) were compared with placebo in 5 RCTs (994 participants; low ROB) (37–40, 52). Meta-analysis of the 3 RCTs (709 participants) of inpatients with and without critical illness demonstrated no increase in extrapyramidal symptoms (pooled RR, 0.44 [CI, 0.14 to 1.38]) (**Figure 2**; **Supplement Figure 11**, available at Annals.org) (39, 40, 52). However, one RCT of palliative care patients reported increased extrapyramidal symptoms for risperidone (37) (**Supplement Table 19**).

Five second-generation antipsychotics (quetiapine, ziprasidone, aripiprazole, olanzapine, and risperidone) were compared with haloperidol in 8 RCTs (999 participants) (39–41, 43, 45, 48–50) and 8 observational studies (2874 participants) (53–57, 59, 61, 62) (**Supplement Table 18**). Meta-analysis of the 6 RCTs (869 participants; low or unclear ROB) of inpatients with and without critical illness (39–41, 43, 48, 50) demonstrated a lower incidence of extrapyramidal symptoms for second-generation antipsychotics (pooled RR, 0.45 [CI, 0.20 to 1.01]) (**Figure 2**; **Supplement Figure 12**, available at Annals.org). Seven RCTs (39–41, 45, 48–50) and 8 observational studies (53–57, 59, 61, 62) reported on specific extrapyramidal symptoms, with results ranging from no difference to a potentially important difference across heterogeneous outcomes (all $P > 0.05$) (**Supplement Table 18**). There was no incidence of neuroleptic malignant syndrome or permanent holding of drug because of neuroleptic malignant syndrome in 2 RCTs (667 participants; low ROB) (39, 40).

Five second-generation antipsychotics (aripiprazole, olanzapine, quetiapine, risperidone, and amisulpride) were directly compared in 3 RCTs (127 partici-

pants; unclear or high ROB) (41, 46, 47) and 4 observational studies (2673 participants; moderate or serious ROB) (53, 54, 57, 59), with results ranging from no difference to a potentially important difference across heterogeneous neurologic outcomes (all $P > 0.05$) (Supplement Table 18).

DISCUSSION

Our systematic review of 26 RCTs and observational studies, evaluating 5607 adult inpatients with delirium, does not support routine use of haloperidol or second-generation antipsychotics for treating delirium in adult inpatients. We found no differences for haloperidol and second-generation antipsychotics, compared with placebo, in hospital length of stay, sedation status, delirium duration and mortality, and insufficient or no evidence regarding the effect on cognitive functioning and delirium severity. We also found no difference between haloperidol compared with different second-generation antipsychotics in cognitive functioning, delirium severity, hospital length of stay, sedation status and mortality, with little or no difference for delirium duration. Directly comparing different second-generation antipsychotics demonstrated no difference in mortality, with insufficient or no evidence for other outcomes. Cardiac and neurologic harms were studied mainly in critically ill patients. For neurologic harms, there was little evidence of harm for haloperidol and second-generation antipsychotics with short-term use for treating delirium in adult inpatients. However, potentially harmful cardiac effects tended to occur more frequently with use of antipsychotics, particularly prolongation of the QT interval with second-generation antipsychotics versus placebo or haloperidol. Moreover, a single RCT in 249 palliative care patients (37) reported that haloperidol and risperidone had less improvement in delirium severity and more extrapyramidal symptoms compared with placebo, with haloperidol (versus placebo) demonstrating significantly worse survival. Notably, the sensitivity analysis using alternative statistical methods did not change the inferences arising from our primary results (Supplement Table 20, available at Annals.org).

We searched the PubMed, Embase, CENTRAL, CINAHL, and PsycINFO databases through 11 July 2019 for relevant systematic reviews. Findings of our review are consistent with those of recent systematic reviews (12–16). A meta-analysis of inpatients with and without critical illness (12) reported no benefit for antipsychotics in treating delirium and no association with mortality, with little evidence of harms among a variety of adverse effects evaluated. Notably, this review ended its literature search (limited to English-language articles only) in 2013, and important RCTs have been published since then. Our review included 16 additional studies (with 4962 additional patients) and systematically considered more outcomes, including potential harms. A more recent Cochrane review (literature search ending July 2017), focusing only on RCTs of non–critically ill inpatients, also demonstrated no beneficial effect for antipsychotics in reducing the delirium severity or resolving delirium-related symptoms and reported no differences in extrapyramidal symptoms or mortality (13). A systematic review of RCTs until October 2018, comparing haloperidol versus placebo solely in critically ill patients, reported no difference in delirium incidence, ICU length of stay, delirium- and coma-free days, short-term mortality, risk for QT interval prolongation, or extrapyramidal symptoms (16).

A network meta-analysis evaluating 20 RCTs of different pharmacologic treatments, including antipsychotics, for delirium among adult inpatient with and without critical illness reported a lack of superiority of monotherapy with any antipsychotic, compared with placebo or a control group, for resolution of delirium and all-cause mortality (15). Notably, this network meta-analysis only evaluated mortality, delirium duration, and delirium response rate, without evaluation of other clinically important outcomes or cardiac and neurologic harms.

Finally, a Cochrane systematic review and network meta-analysis (literature search ending March 2019) of RCTs conducted solely in critically ill patients showed no difference between typical and atypical antipsychotics versus placebo, or among antipsychotics compared directly with one another, for 10 outcomes (14). However, this Cochrane review reported a higher incidence of arrhythmia for haloperidol versus placebo among 3 RCTs (588 participants) that individually demonstrated no statistically significant difference and were not pooled in our systemic review.

Our findings are also consistent with recent clinical practice guidelines that do not recommend routine use of antipsychotics for treating delirium. These include the 2018 Society of Critical Care Medicine guidelines for critically ill patients (63) (conditional recommendation with low quality of evidence) and the 2019 Scottish Intercollegiate Guidelines Network guideline for inpatients with and those without critical illness (insufficient evidence) (64).

Our findings contradict an older meta-analysis (literature search ended 2014) of inpatients with and without critical illness (17) that reported a superior delirium response rate, lower delirium severity, and greater sedation for antipsychotics compared with placebo or usual care. Unlike our review, this prior meta-analyses pooled first- and second-generation antipsychotics, pooled scores from different delirium severity instruments (DRS and DRS-R-98), and pooled different groups of a single study in the meta-analysis. Moreover, our review also included more recently published RCTs.

The majority of studies in our systematic review are small RCTs or observational studies with unclear or high/serious ROB. We found insufficient or no evidence for multiple outcomes, including long-term cognitive functioning, use of physical restraints, and inappropriate continuation of antipsychotics. Moreover, the included studies did not rigorously evaluate the effect of antipsychotics on patient distress in-hospital or patient functioning after hospital discharge. Hence, additional

large, rigorous studies are needed, including greater focus on these outcomes. A search of ClinicalTrials.gov (through 11 July 2019) for ongoing trials found 4 RCTs, of which 2 are large (1000 participants [NCT03392376] and 742 participants [NCT03628391]) and focus on haloperidol in the ICU and 2 are smaller (NCT03021486 and NCT03743649), evaluating haloperidol in refractory agitated delirium in palliative care.

Our systematic review has limitations. Some large studies in this review were conducted in critically ill patients, which may affect generalizability of the findings. Moreover, most RCTs excluded patients with underlying neurologic or cardiovascular issues, which can potentially underestimate the harms in routine clinical practice. However, as described above, our findings are consistent with those of multiple other meta-analyses and clinical practice guidelines for both critically ill and non–critically ill populations. Among the included studies, there was heterogeneity in the drug dose, frequency, and route of administration; the outcomes evaluated; and the measurement instruments used, limiting the ability to synthesize results. This limitation emphasizes the importance of ongoing international efforts to establish core outcomes and associated measurement instruments, along with harmonization of delirium instruments, for use in all studies evaluating antipsychotics for treating delirium (32, 65, 66). We also combined different second-generation antipsychotics in comparison with placebo or haloperidol despite differences in mechanism of actions. Finally, we could not evaluate the benefits and harms of antipsychotics in the context of different types of delirium and agitation status.

In conclusion, antipsychotics for treatment of delirium in adult inpatients did not improve patient outcomes, with little evidence of neurologic harms but a tendency for more frequent potentially harmful cardiac effects. For some clinically important outcomes and specific patient subgroups (such as older adults and palliative care patients), there was insufficient or no evidence, emphasizing the need for continued future research in the field.

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