Antipsychotic Medication for Prevention and Treatment of Delirium in Hospitalized Adults: A Systematic Review and Meta-Analysis

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OBJECTIVES: To evaluate the effectiveness of antipsychotic medications in preventing and treating delirium.

DESIGN: Systematic review and meta-analysis.

SETTING: PubMed, EMBASE, CINAHL, and ClinicalTrials.gov databases were searched from January 1, 1988, to November 26, 2013.

PARTICIPANTS: Adult surgical and medical inpatients.

INTERVENTION: Antipsychotic administration for delirium prevention or treatment in randomized controlled trials or cohort studies.

MEASUREMENTS: Two authors independently reviewed all citations, extracted relevant data, and assessed studies for potential bias. Heterogeneity was considered as chi-square $P < .1$ or $I^2 > 50\%$. Using a random-effects model ($I^2 > 50\%$) or a fixed-effects model ($I^2 < 50\%$), odds ratios (ORs) were calculated for dichotomous outcomes (delirium incidence and mortality), and mean or standardized mean difference for continuous outcomes (delirium duration, severity, hospital and intensive care unit (ICU) length of stay (LOS)). Sensitivity analyses included postoperative prevention studies only, exclusion of studies with high risk of bias, and typical versus atypical antipsychotics.

RESULTS: Screening of 10,877 eligible records identified 19 studies. In seven studies comparing antipsychotics with placebo or no treatment for delirium prevention after surgery, there was no significant effect on delirium incidence (OR = 0.56, 95% confidence interval (CI) = 0.23–1.34, $I^2 = 93\%$). Using data reported from all 19 studies, antipsychotic use was not associated with change in delirium duration, severity, or hospital or ICU LOS, with high heterogeneity among studies. No association with mortality was detected (OR = 0.90, 95% CI = 0.62–1.29, $I^2 = 0\%$).

CONCLUSION: Current evidence does not support the use of antipsychotics for prevention or treatment of delirium. Additional methodologically rigorous studies using standardized outcome measures are needed. **J Am Geriatr Soc 2016.**

Key words: delirium; pharmacological prevention; pharmacological treatment; adult

Delirium, a neuropsychiatric syndrome characterized by acute change in arousal and cognition arising from an underlying medical insult, is associated with poor clinical outcomes, including personal suffering, cognitive decline, institutionalization after hospitalization, economic costs, and risk of death.[1–4]

A major impetus for developing this guideline for postoperative delirium was the results of a survey given to participants in the American Geriatrics Society (AGS) Geriatrics-for-Specialists Initiative. Participants identified delirium as an essential area in the care of older adults that was poorly understood.[5] Having identified lack of knowledge of delirium as the area of greatest need, the AGS initiated the postoperative delirium clinical practice guideline project. A panel of experts was formed, and a system-

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atic review of the literature was conducted to develop these guidelines.[6,7] One major focus for the panel was evaluating whether current evidence supported use of antipsychotic medications in the perioperative period to prevent or treat delirium in older adults.

Although the focus was on older adults after surgery, the panel raised concerns that the existing literature was too limited; hence, the search included antipsychotic use to prevent or treat delirium in all hospitalized adults. The objectives of this article were to report a systematic review and meta-analysis addressing two questions: Does "preventive" antipsychotic administration reduce the incidence of postoperative delirium in adult patients? Does antipsychotic treatment in hospitalized adult medical or surgical patients with delirium improve outcomes, including duration and severity of delirium, hospital and intensive care unit (ICU) length of stay (LOS), institutionalization at hospital discharge, and mortality?

METHODS

Eligibility Criteria

This systematic review was conducted in accordance with the Institute of Medicine guidelines and reported in accordance with Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines.[8] The specific approach has been described in detail previously.[6,7,9] This systematic review included published and unpublished randomized controlled trials (RCTs) and prospective or historical cohort, case–control, and other observational studies. Inclusion criteria included a focus on prevention or treatment of delirium in adult medical or surgical inpatient settings, including ICU and general inpatient units. Exclusion criteria included non-English publications, narrative review articles, editorials, commentaries, letters, dissertations, and studies that focused exclusively on pediatric, alcohol or substance withdrawal, schizophrenia, dementia, stroke, neurosurgery or trauma populations, and nursing home and other nonhospital settings (e.g., rehabilitation, hospice, outpatient, emergency department). Articles were also excluded if delirium was not identified using a validated tool.

Search Strategy and Study Selection

A comprehensive review of the literature was performed, supplemented by additional targeted and focused searches. PubMed, Embase, and CINAHL electronic databases were searched for the period from January 1, 1988, to November 26, 2013, using the search terms "delirium," "organic brain syndrome," and "acute confusion" in combination with a variety of alternative terms for the prevention and treatment of delirium, including all variations of the words "prevention," "management," "treatment," "intervention," "therapy," "therapeutic," and "drug therapy." Two targeted searches using the U. S. National Library of Medicine PubMed Special Queries on Comparative Effectiveness Research and PubMed Clinical Queries were completed using the terms "delirium," "postoperative delirium," "acute confusion," and "organic brain syndrome." Trials containing the terms "quetiapine," "haloperidol," "olanzapine," "risperidone," "delirium," or "confusion" were retrieved from the registry of clinical trials, ClinicalTrials.gov, restricting the search to completed studies with available results. Reference lists from published narrative review articles and systematic reviews were reviewed to identify additional studies.

Data Extraction and Assessment of Risk of Bias

Two guideline project leaders (SKI, TNR) independently reviewed each title and abstract to determine eligibility for study inclusion. The full article was reviewed if there was any uncertainty regarding eligibility. A separate group of four trained reviewers created evidence tables using a standardized form. Information was collected from each eligible study on author, year, study design, population, sample size, intervention and control, delirium measure, outcomes, and adverse events. At least two independent reviewers evaluated each eligible article using Cochrane risk of bias assessment.[10] One of the authors (SKI) arbitrated discrepancies and independently reviewed a random 10% subsample of all articles to verify accuracy of the abstractions and risk-of-bias assessment ratings. Three authors (KJN, JY, DMN) reviewed the individual risk-of-bias ratings to select the final articles considered to be at low risk of bias.

Data Analysis

Meta-analyses were performed when two or more studies using similar interventions were identified. Dichotomous outcomes (e.g., incidence of delirium or mortality) were presented as odds ratios (ORs) with 95% confidence intervals (95% CIs). Continuous outcomes (e.g., duration and severity of delirium, hospital and ICU LOS) were analyzed using mean difference (MD) or, when different studies used different scales (e.g., delirium severity), standardized mean difference (SMD). Delirium severity was evaluated using the Delirium Rating Scale (DRS)[10] or the DRS Revised-98.[11] When specific data could not be obtained directly from the publications (n = 4), authors were contacted, with all providing additional statistics.[12–15]

Heterogeneity was assessed using the chi-square and I^2 statistics, with $P < .1$ and $I^2 > 50\%$ considered substantial heterogeneity. With high heterogeneity, a random-effects model was used for meta-analysis; otherwise a fixed-effect model was used.

The following sensitivity analyses were conducted: restricting to postoperative prevention studies, including studies with a low risk of bias, and comparing typical with atypical antipsychotics. A funnel plot was created to test for publication or other reporting biases for analyses that included more than 10 studies (e.g., mortality).[16]

RESULTS

Description of Studies

Of 10,877 citations screened for eligibility, 19 met criteria (Figure 1). The studies were divided into postoperative delirium prevention (n = 7),[17–23] which included

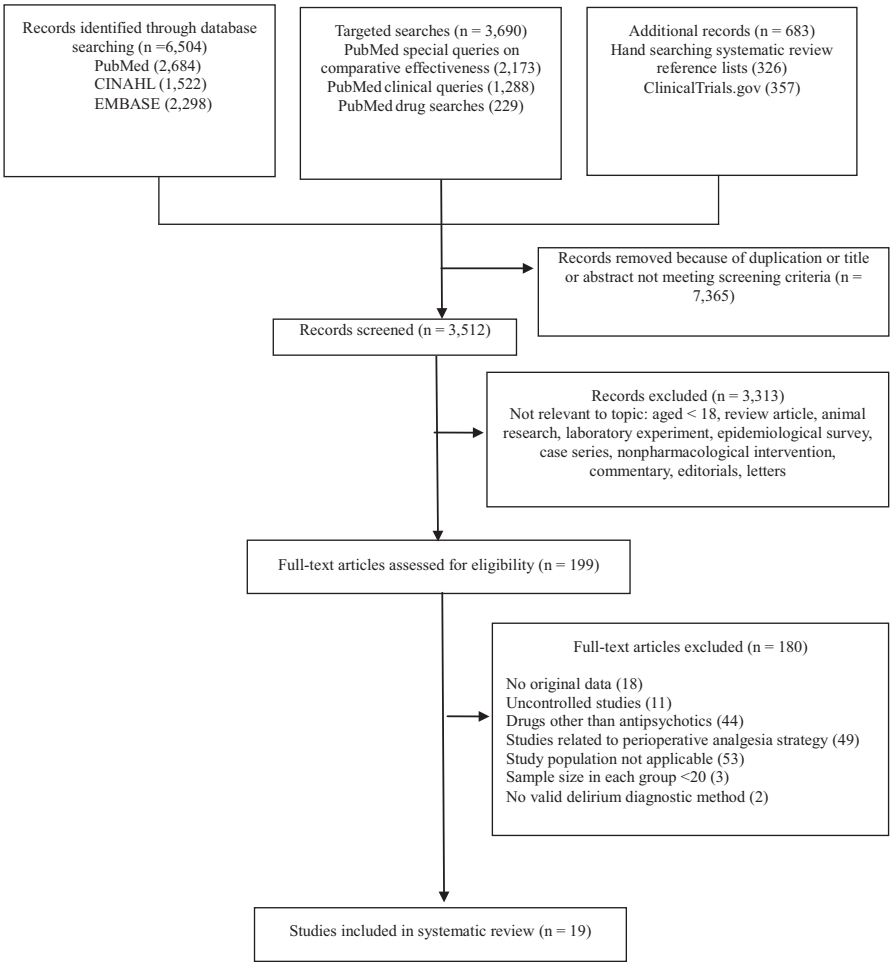

Figure 1. Flowchart of study selection process.

trials in which treatment was started in the perioperative period to prevent incident delirium, and studies that evaluated delirium treatment (n = 12) in mixed samples of hospitalized adults (medical and surgical admissions receiving treatment for prevalent delirium)[12–15,24–31] (Table 1). The seven postoperative delirium prevention studies focused on individuals undergoing surgery, who had an average age ranging from 61[21] to 87.[22] Six were RCTs comparing an antipsychotic agent with a placebo; two trials evaluated risperidone,[17,21] in one evaluated olanzapine,[20] and four evaluated haloperidol.[18,19,22,23] Administration of antipsychotics included pre- and postoperative administration in two of the seven studies,[18,20] with one dose given the day before surgery, followed by doses on postoperative day (POD) 1[20] or POD 1, 2, and 3;[18] the remainder administered postoperative doses only, with the duration ranging from POD 1[17,21–23] to POD 5.[19] Dosages ranged from 1.0 to 7.5 mg equivalents of haloperidol per day[32] with oral or intravenous routes of administration.

There were 12 treatment studies that included mixed surgical and nonsurgical populations, with average ages ranging from 39[24] to 84.[29] Five studies focused on an ICU population.[12–15,28] Of 12 studies comparing antipsychotics (including haloperidol and atypical antipsychotics) with placebo or no treatment (n = 5)[12–15,28] or comparisons between antipsychotic agents (n = 7),[24–28,31] 10 were RCTs.

Risk of Bias

Three postoperative prevention studies,[17,18,21] two treatment studies in ICU populations with medical and surgical patients,[13,14] and one treatment study in a non-ICU hospital setting with medical admissions[27] were included as low risk of bias (Appendix Table S1). A funnel plot for the mortality outcome did not suggest systematic bias in reporting (Appendix Figure S1).

Meta-Analysis Results

The effect of antipsychotic medication on incident delirium was derived from the seven postoperative prevention studies outlined in Table 1. The remaining meta-analyses were derived from all of the 19 studies in Table 1 reporting comparable data on the outcomes of interest. Outcomes are tabulated according to study in Appendix Table S2. The major findings are summarized below.

Delirium Prevention in the Postoperative Period

There was no significant association between antipsychotic administration and incidence of delirium in seven studies evaluating 1,970 individuals (OR = 0.56, 95% CI = 0.23–1.34, I^2 = 93%)[17–23] (Figure 2). A sensitivity analysis of

Table 1. Characteristics of Included Studies

Author, Year	Study Design	Population	Sample Size, n	Age, Mean ± SD	Intervention (I)	Control (C)	Delirium Diagnostic and Severity Instruments
Postoperative prevention trials							
Hakim, 2012[16]	RCT	Cardiac surgery	101 (51 I/50 C)	>65	Risperidone, oral 0.5 mg/12 h POD	Placebo	DSM-IV
Kalisvaart, 2005[17]	RCT	Orthopedic surgery	430 (212 I/218 C)	I, 79 ± 6; C, 80 ± 6	Haloperidol, oral 1 mg/d, preop—POD 3	Placebo	DSM-IV, CAM, DRS-R-98
Kaneko, 1999[18]	RCT	Abdominal surgery	78 (38 I/40 C)	I, 72 ± 8; C, 73 ± 9	Haloperidol, IV 5 mg/d, POD 1–5	Placebo	DSM-III-R
Larsen, 2010[19]	RCT	Orthopedic surgery	496 (246 I/252 C)	I, 73 ± 6; C, 74 ± 6	Olanzapine, oral 5 mg/d, pre and POD 1	Placebo	DSM-III-R, DRS-R-98, CAM
Prakanrattana, 2007[20]	RCT	Cardiac surgery	126 (63 I/63 C)	I, 61 ± 10; C, 61 ± 10	Risperidone, oral 1 mg/d, POD 1	Placebo	CAM-ICU
Vochteloo, 2011[21]	PCT	Hip fracture surgery	378 (173 I/205 C)	I, 87 ± 6; C, 81 ± 7	Haloperidol, oral 1 mg/12 h, Day 1	No haloperidol	DSM-IV
Wang, 2012[22]	RCT	Noncardiac surgery	457 (229 I/228 C)	I, 74 ± 6; C, 74 ± 7	Haloperidol, IV 1.7 mg/d, POD 1	Placebo	CAM-ICU
Treatment trials							
Breitbart, 1996[23]	RCT	Hospital medical-AIDS	30 (11 haloperidol, 13 chlorpromazine, 6 lorazepam)	39 ± 8.8	Haloperidol, oral and IM 1~9 mg/d	C1: chlorpromazine C2: lorazepam oral and IM, 1–9 mg/d	DSM-III-R, DRS
Devlin, 2010[24]	RCT	ICU, medical and surgical	36 (18 I/18 C)	I, 62 ± 14; C, 63 ± 15	Quetiapine, oral 50–200 mg/12 h	Placebo ≤ 10 d	ICDSC
Girard, 2010[12]	RCT	ICU, medical and surgical	101 (35 haloperidol, 30 ziprasidone, 36 placebo)	I1, 51 (35–59); I2, 54 (47–66); C, 56 (43–68)	I1: haloperidol, IM 5 mg/6 h, D1–14 I2: ziprasidone, IM 40 mg/6 h, D1–14	Placebo D1-D14	CAM-ICU
Grover, 2011[30]	RCT	Hospital, medical and surgical	64 (20 haloperidol, 21 risperidone, 23 olanzapine)	I, 44 ± 17; C1, 45 ± 19; C2, 46 ± 15	Haloperidol, po/IV 1.25–2.5 mg, 2–3 doses/d	Risperidone, oral 0.25–4 mg/d Olanzapine, oral 1.25–20 mg/d	CAM, DRS-R98
Han, 2004[13]	RCT	Hospital, medical and surgical	28 (12 I/12 C)	I, 67 ± 16; C, 66 ± 8	Haloperidol, oral 0.75 mg/d, D1–7	Risperidone, oral 0.5 mg/d D1–7	DRS, MDAS
Kim, 2010[25]	RCT	Hospital, medical and surgical	32 (17 I/15 C)	I, 67 ± 12; C, 68 ± 11	Risperidone, oral 0.25–2 mg/d, D1–7	Olanzapine, oral 1.25–7.5 mg/d, D1–7	DRS-R-98
Maneeton, 2013[26]	RCT	Hospital, medical	52 (28 I/24 C)	I, 57 ± 12; C, 57 ± 12	Haloperidol, oral 0.5–2 mg/d, D1–7	Quetiapine, oral 25–100 mg/d, D1–7	CAM, DRS-R-98
Page, 2013[a27]	RCT	ICU, medical and surgical	142 (71 I/71 C)	I, 68 ± 16; C, 69 ± 15	Haloperidol, IV 2.5 mg/8 h, ≤14 d	Placebo	CAM-ICU
Skrobik, 2004[14]	RCT	ICU, medical and surgical	73 (45I/28 C)	I, 63 ± 12; C, 68 ± 6	Haloperidol, oral 2.5–5 mg/8 h	Olanzapine, oral 5 mg/d	ICU-DSC, DI, DSM-IV
Tahir, 2010[28]	RCT	Hospital, medical	42 (21 I/21 C)	I, 84 ± 9; C, 84 ± 7	Quetiapine, oral 25–175 mg/d	Placebo ≤ 10 days	DSM-IV, DRS-R-98

(Continued)

Table 1 (Contd.)

Author, Year	Study Design	Population	Sample Size, n	Age, Mean ± SD	Intervention (I)	Control (C)	Delirium Diagnostic and Severity Instruments
van den Boogaard, 2013[a29]	HCT	ICU, medical and surgical	476 (177 I/299 C)	I, 63 ± 14; C, 64 ± 14	Haloperidol, IV 1 mg/8 h until discharge	No haloperidol	CAM-ICU
Yoon, 2013[15]	PCT	Hospital, medical and surgical	80 (23 haloperidol, 21 risperidone, 18 olanzapine, 18 quetiapine)	I1, 74 ± 10; I2, 70 ± 10; C1, 70 ± 16; C2, 73 ± 11	I1: haloperidol, oral 0.5–10 mg/d, D1–6 I2: risperidone, oral 0.25–4 mg/d, D1–6	C1: olanzapine, oral 1–20 mg/d C2: quetiapine, oral 25–200 mg/d D1–6	DSM-IV-TR, DRS- R-98

[a]Prevention and treatment study in the intensive care unit (ICU) setting.

RCT = randomized controlled trial, HCT = historical controlled trial, PCT = prospective cohort trial, IV = intravenous, IM = intramuscular, CAM = Confusion Assessment Method, DSM-III-R = *Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition, Revised*, DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition*, DRS = Delirium Rating Scale, DI = Delirium Index, ICU-DSC = Intensive Care Unit Delirium Screening Checklist, MDAS = Memorial Delirium Assessment Scale, POD = Postoperative Day.

three studies at low risk of bias (n = 657 patients)[17,18,21] did not change this finding (OR = 0.46, 95% CI = 0.19–1.08, I^2 = 71%).

Delirium Duration and Severity

Use of antipsychotics was not associated with a difference in duration of delirium in 581 individuals in seven postoperative prevention and treatment studies reporting this outcome (MD = −0.65 days, 95% CI = −1.59–0.29, I^2 = 80%)[12–14,17,18,20,25] (Figure 2). These findings were unchanged with sensitivity analyses including only postoperative prevention studies (n = 279 participants, 3 studies; MD = −0.71 days, 95% CI = −2.14–0.71, I^2 = 91%)[17,18,20] and including studies at low risk of bias (n = 411 participants, 4 studies; MD = −0.78 days, 95% CI = −2.23–0.68, I^2 = 77%).[13,14,17,18]

Severity of delirium was not associated with administration of antipsychotics in 464 participants in eight studies (SMD = −0.11, 95% CI = −0.43–0.22, I^2 = 61%)[18,20,24,25,27,29–31] (Figure 2). These findings were unchanged with sensitivity analyses including only postoperative prevention studies (n = 178 participants, 2 studies; SMD = −0.18, 95% CI = −1.80–1.43, I^2 = 96%)[18,19] and including studies at low risk of bias (n = 120 participants, 2 studies; SMD = −0.42, 95% CI = −1.59–0.74, I^2 = 90%).[18,27]

Hospital and ICU LOS

Administration of antipsychotics for the postoperative prevention or treatment of delirium was not associated with hospital LOS in 1,454 participants in eight studies (MD = −0.01 days, 95% CI = −0.16–0.14, I^2 = 42%)[12–14,17,18,21,23,29] (Figure 3). This finding was unchanged with sensitivity analyses based on only postoperative prevention studies (n = 752 patients, 4 studies; MD = 0 days, 95% CI = −0.15, 0.15 days, I^2 = 0%)[17,18,21,23] or including studies at low risk of bias (n = 485 patients, 5 studies; MD = –0.05 days, 95% CI = −0.74, 0.65 days, I^2 = 0%).[13,14,17,18,21]

There was no significant association with ICU LOS in 1,400 participants from seven studies (MD = −0.46 days, 95% CI = −1.15–0.24, I^2 = 91%)[12,16–19,21,25] (Figure 3). Sensitivity analysis of only postoperative prevention studies (n = 684 participants, 3 studies; MD = −0.36 days, 95% CI = −1.10–0.39, I^2 = 97%)[12,17,23] or studies at low risk of bias (n = 431 participants, 4 studies; MD = −0.55 days, 95% CI = −1.39–0.29, I^2 = 52%)[13,14,17,21] resulted in the same finding.

Institutionalization and Other Adverse Events

Three studies[12,20,22] reported outcomes related to institutionalization after hospitalization at different points in time (immediately after hospitalization vs at 3-month follow-up). A wide variety of adverse effects were monitored and reported (Appendix Table S2). Heterogeneity of outcomes prevented meta-analysis, but there was no apparent pattern of higher reported adverse events in intervention groups than in control groups.

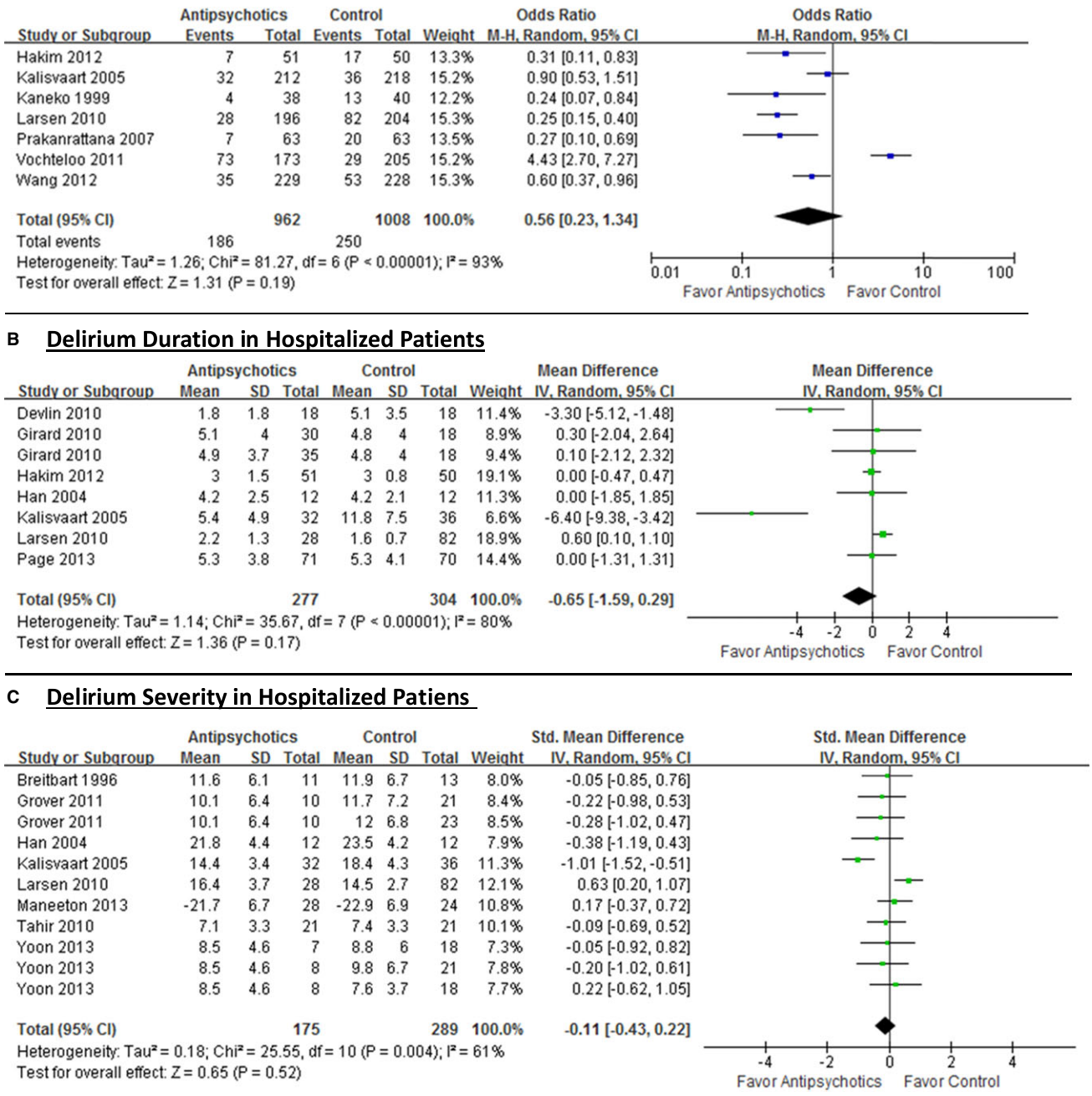

Figure 2. Forest plots of antipsychotic use and delirium prevention, duration, and severity reduction. (A) Delirium prevention in postoperative individuals (n = 1,970). (B) Delirium duration in hospitalized individuals (n = 581). (C) Delirium severity in hospitalized individuals (n = 464). SD = standard deviation; CI = confidence interval; df = degrees of freedom; M-H = Mantel-Haenszel; IV = inverse variance; Random = random effects model used to calculate estimate.

Mortality

There was no significant association between antipsychotics and mortality measured up to 30 days after hospital stay in 1,439 participants in 10 studies reporting this outcome (OR = 0.90, 95% CI = 0.62–1.29, I^2 = 0%) [12–15,17,22–24,27,29] (Figure 4). This finding remained consistent in sensitivity analyses including only postoperative prevention studies (n = 567 participants in 3 studies; OR = 1.65, 95% CI = 0.69–3.93, I^2 = 44%)[17,22,23] and including studies at low risk of bias (n = 395 participants in 4 studies; OR = 0.98, 95% CI = 0.54–1.76, I^2 = 0%).[13,14,17,27]

DISCUSSION

This systematic review and meta-analysis suggests that antipsychotic pharmacotherapy does not improve outcomes when used for prevention or treatment of delirium in hospitalized adults. Antipsychotics were not associated with lower short-term mortality, less-severe or shorter duration of delirium, or shorter ICU and hospital LOS.

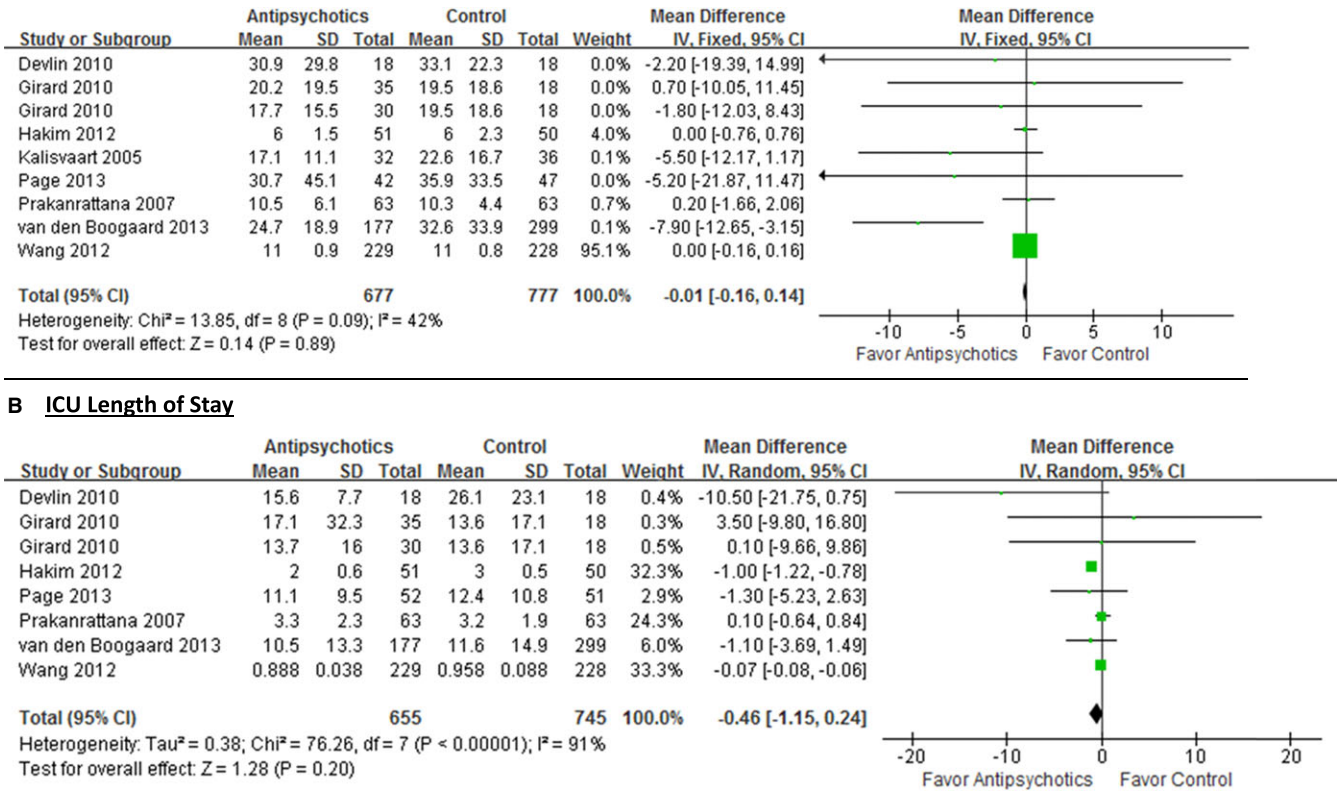

Figure 3. Forest plots of antipsychotic use and (A) hospital (n = 1,454) and (B) intensive care unit (ICU) (n = 1,400) length of stay. SD = standard deviation; CI = confidence interval; df = degrees of freedom; M-H = Mantel-Haenszel; IV = inverse variance; Random = random effects model used to calculate estimate; Fixed = fixed effects model used to calculate estimate.

Nevertheless, existing studies are heterogeneous in study design, including diverse populations, with few studies focused specifically on older adults after surgery. There was substantial variability in outcome measures, with few postoperative studies evaluating mortality and functional outcomes.

A number of other systematic reviews have examined the effect of antipsychotics on postoperative delirium and reached different conclusions.[33–39] One publication concluded that antipsychotics prevent delirium, but this analysis included unpublished RCT data of haloperidol versus placebo in individuals undergoing hip fracture repair surgery. Results for this study required imputation because of a lost randomization code.[39] The only systematic review to include all of the same studies identified in this review did not perform a meta-analysis.[33] An additional five meta-analyses included up to six of the same studies analyzed in this report and concluded that there was a modest postoperative delirium protective effect of antipsychotics.[35–39] The inclusion of an additional study focused on older adults undergoing surgery and the only study to include participants of significantly older average age (84)[24] contributed to the nonsignificant association in the meta-analysis of delirium prevention. This finding, based upon all postoperative studies of varying design and quality, was congruent with the sensitivity analysis excluding studies with high risk of bias, a comparison not provided in other published meta-analyses.

The current results were consistent with the findings of a meta-analysis[34] that included three RCTs of haloperidol versus placebo.[18,19,23] No association between antipsychotics and prevention of postoperative delirium was demonstrated. Other outcomes examined in this review, including delirium severity and duration, ICU and hospital LOS, and mortality, were consistent with other analyses that did not demonstrate a significant effect of antipsychotics on these outcomes.[33,37,38]

This systematic review and meta-analysis is the most comprehensive in coverage of published data. All available studies of hospitalized individuals were included. Merging postoperative prevention studies with treatment studies of individuals with delirium during surgical or medical admissions is warranted because of the limited available data in homogenous populations. Although this approach may increase the power to evaluate uncommon outcomes, it may also have limitations related to heterogeneity of the included studies. For example, data from critically ill individuals with sepsis may not be generalizable to infection-free older adults undergoing surgery. Combining trials that used very different methodologies and drugs for preventing delirium may have resulted in an erroneous conclusion that there is no difference in incidence of postoperative delirium when using antipsychotics as a preventive intervention. For example, one high-quality perioperative study[17] concluded that there was a significant difference in the incidence of postoperative delirium if individuals exhibiting any symptoms of delirium in the

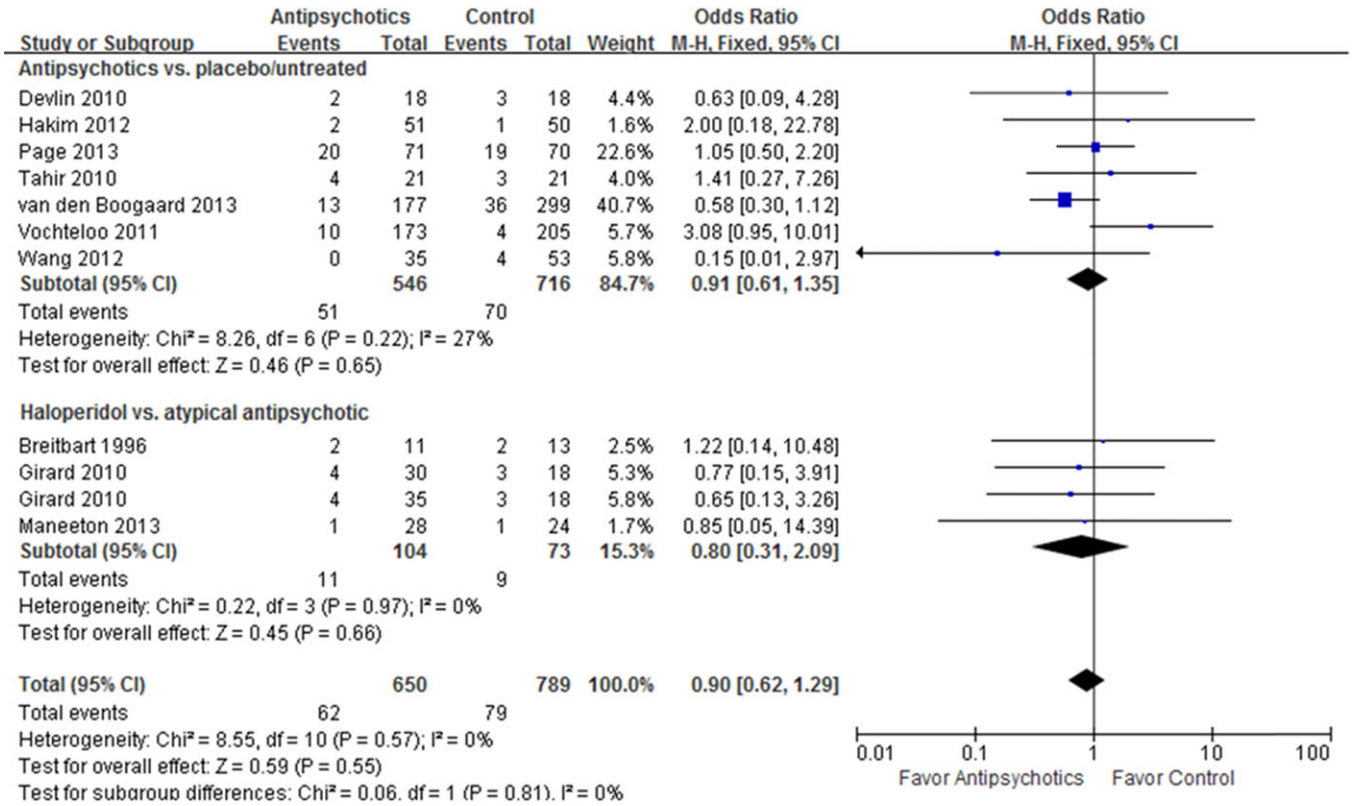

Figure 4. Forest plot of antipsychotic use and mortality in hospitalized individuals (N = 1,439; antispychotics vs placebo or no treatment: n = 1,262, antipsychotics vs. antipsychotics: n = 177). SD = standard deviation; CI = confidence interval; df = degrees of freedom; MH = Mantel-Haenszel; IV = inverse variance; Random = random effects model used to calculate estimate; Fixed = fixed effects model used to calculate estimate.

immediate postoperative recovery period on the day of cardiac surgery were treated every 12 hours with oral risperidone 0.5 mg. This design, which selected a subset of individuals at highest risk of developing delirium on subsequent hospital days, may not be comparable with other designs that treat all people regardless of risk.[40,41] Notwithstanding this criticism, the current findings are important to report given that they are consistent with the sensitivity analysis that compares more-homogeneous studies of preventive postoperative design, excluding those at high risk of bias.

Heterogeneity of outcome measures points to the great need for standardization.[42–44] Of the seven postoperative studies included in this review, only three collected mortality data and two reported on rehabilitation status following hospitalization for surgery at two differing time points. Consensus regarding collection of core outcome measures[43] in clinical trials for delirium would make comparison of studies and meta-analysis more feasible to help advance knowledge in this field.

Careful reflection on which outcomes are most meaningful to clinicians and patients should also inform future research. While antipsychotics in this review do not appear to decrease the incidence of delirium in the postoperative period, or improve other outcomes when used to treat delirious adult inpatients, none of the studies evaluated symptomatic relief attributable to these medications. Decreasing agitation and distress is a common reason for the prescription of antipsychotics in hospitalized adults, yet the field has no uniform data on those outcomes. Much more work in this area is needed to delineate the best strategies regarding delirium prevention, particularly in high-risk populations such as older adults after surgery. Well-powered randomized controlled evaluations, particularly in older at-risk individuals immediately after anesthesia, with well-defined outcomes are warranted to better understand whether there is any benefit from these medications.

CONCLUSIONS

There is insufficient evidence to support the routine use of antipsychotic pharmacotherapy to prevent or treat delirium in hospitalized adults, including in the postoperative setting. There is a great need to standardize outcome measures by creating a core outcome set for delirium prevention and treatment trials and conducting additional rigorous well-powered RCTs in high-risk populations.

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Author Contributions: All authors: study concept and design, acquisition of subjects and data, analysis and interpretation of data, preparation of manuscript. All authors have seen and approved the final version of this article.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. Risk of Bias Ratings of Included Studies.
Table S2. Outcomes of Included Studies.

Figure S1. Funnel plot for studies included in mortality outcome.

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