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Antipsychotics for Prevention and Treatment of Delirium in Hospitalized Adults: A Systematic Review and Meta-analysis

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Abstract

Background—Prevention and treatment of delirium is critical due to its common occurrence and associated poor outcomes.

Objectives—To evaluate antipsychotic medications for preventing and treating delirium.

Design—Systematic review and meta-analysis.

Setting—PubMed, EMBASE, and CINAHL and ClinicalTrials.gov databases were searched from January 1, 1988 and November 26, 2013.

Participants—Adult surgical or medical inpatients.

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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 $p<0.1$ or and I^2 >50%. Using a random effects model ($I^2 > 50\%$) or a fixed effects model ($I^2 < 50\%$) we calculated odds ratios (OR) for dichotomous outcomes (delirium incidence and mortality), and mean/standardized mean difference for continuous outcomes (delirium duration, severity, hospital/ICU length of stay (LOS)). Sensitivity analyses included 1) postoperative prevention studies only, 2) exclusion of studies with high risk-of-bias, and 3) typical versus atypical antipsychotics.

Results—Screening of 10,877 eligible records identified 19 studies. In seven studies comparing antipsychotics to placebo or no treatment for delirium prevention in postoperative patients, there was no significant effect on delirium incidence (OR 0.56; 95% 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, 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—Antipsychotics for prevention or treatment of delirium is not supported by current evidence. Additional methodologically rigorous studies using standardized outcome measures are needed.

Keywords

Delirium; Pharmacologic Prevention; Pharmacologic Treatment; Adult

Introduction

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, increased costs, and increased risk of death.[1–4]

A major impetus for developing this guideline for postoperative delirium was the result of a survey given to participants in the American Geriatrics Society Geriatrics-for-Specialists Initiative (AGS GSI). Participants identified delirium as an essential area in the care of older adults that was the least understood.[5] Having identified lack of knowledge of delirium as the area of greatest need, the American Geriatrics Society (AGS) initiated the postoperative delirium clinical practice guideline project. A panel of experts was formed and a systematic 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 post-operative patients, 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. Therefore, the objectives of this paper were to report a systematic review and meta-analysis addressing two questions: (1) Does “preventive” antipsychotic administration reduce the incidence of postoperative delirium in adult

patients? and (2) Does antipsychotic treatment in hospitalized adult medical or surgical patients with delirium improve outcomes, including: duration and severity of delirium, hospital and 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 (Reference) and reported in accordance with PRISMA guidelines.[8] The specific approach has been described in detail previously.[6, 7] (http://geriatricscareonline.org/toc/american-geriatrics-society-clinical-practice-guideline-for-postoperative-delirium-in-older-adults/CL018). 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 an adult medical or surgical inpatient settings, including ICU or general inpatient units. Exclusion criteria included non-English publications, narrative review articles, editorials, commentaries, letters, dissertations, and studies that focused exclusively on pediatric, alcohol/substance withdrawal, schizophrenia, dementia, stroke, neurosurgery or trauma patient populations, or nursing home, and other non-hospital settings (e.g., rehabilitation, hospice, outpatient and emergency department). Articles were also excluded if delirium identification was not conducted using a validated tool.

Search Strategy and Study Selection

We performed a comprehensive review of the literature, 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 following 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”, or “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”, and “risperidone”, “delirium” or “confusion” were retrieved from the registry of clinical trials, ClinicalTrials.gov, restricting the search to completed studies with available results. Review of reference lists from published narrative review articles and systematic reviews were used to identify additional studies.

Data Extraction and Assessment of Risk of Bias

Two guideline project leaders (SKI and TNR) independently reviewed each title and abstract to determine eligibility for study inclusion. The full article was reviewed if any uncertainty was present regarding eligibility. A separate group of 4 trained reviewers created evidence tables using a standardized form. The following data were collected from each eligible study: author, year, study design, patient population, sample size, intervention and control,

delirium measure, outcomes, and adverse events. Each eligible article was evaluated using Cochrane risk of bias assessment,[9] by at least 2 independent reviewers. Discrepancies were arbitrated by one of the authors (SKI), who also independently reviewed a random 10% subsample of all articles to verify accuracy of the abstractions and risk of bias assessment ratings. Moreover, 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. the incidence of delirium or mortality) were presented as odds ratios (OR) with 95% confidence intervals (95%CIs). Continuous outcomes (e.g. duration and severity of delirium, length of hospital and ICU stay) were analyzed using mean difference (MD), or standardized mean difference (SMD) when different scales were used across studies (e.g., delirium severity). Delirium severity was evaluated using the Delirium Rating Scale (DRS)[9] or the DRS-98R.[10] When specific data could not be obtained directly from the publications (n=4), authors were contacted with all providing additional statistics.[20,21,25,28]

Heterogeneity was assessed using the chi-square and I^2 statistics, with $p < 0.1$ 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.

We undertook the following relevant sensitivity analyses: (1) restricting to only postoperative prevention studies, (2) including studies with a low risk of bias, and 3) comparing typical versus 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).[11]

RESULTS

Description of Studies

A total of 10,877 citations were screened for eligibility with 19 meeting criteria. (Figure 1) The studies were divided into postoperative delirium prevention (n=7),[12–18] and included those trials where treatment was started in the perioperative period to prevent incident delirium, and studies that evaluated delirium treatment (n=12) in mixed samples of hospitalized adult patients (i.e., medical and surgical admissions receiving treatment for prevalent delirium)[19–30] (Table 1) The 7 postoperative delirium prevention studies focused on surgical patients with average age ranging from age 61[16] to 87 years[17], and 6 were randomized controlled trials (RCT) of an antipsychotic agent versus placebo, evaluating risperidone in two trials,[12, 16] olanzapine in one trial,[15] and haloperidol in four.[13, 14, 17, 18] Administration of antipsychotics included pre- and postoperative administration in 2 of the 7 studies[13, 15] with one dose given the day prior to surgery, followed by doses on postoperative day (POD) 1[15] or POD 1, 2 and 3[13]; the remainder administered postoperative doses only with the duration ranging from POD 1[12, 16–18] to POD 5.[14] Dosages ranged from 1.0 to 7.5

mg equivalents of haloperidol per day[31] with either oral or intravenous routes of administration.

There were 12 treatment studies that included mixed surgical and non-surgical populations, with average ages ranging from 39[19] to 84[27] years across studies. Five studies focused on an ICU population.[20, 21, 25, 26, 28] RCT design was used in 10 of 12 studies, comparing antipsychotics (including both haloperidol and atypical antipsychotics) to placebo or no treatment (n=5)[20, 21, 25, 27, 28] or comparisons between antipsychotic agents (n=7).[19, 22–24, 26, 29, 30]

Risk of Bias

Three postoperative prevention studies,[12, 13, 16] two treatment studies in ICU patient populations with both medical and surgical patients[21, 25] and one treatment study in a non-ICU hospital setting with medical admissions[24] were included as low risk of bias (Appendix Table 1). A funnel plot for the mortality outcome did not suggest systematic bias in reporting (Appendix Figure).

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 by study are tabulated in the Appendix Table 2. The major findings are summarized below.

Delirium Prevention in the Postoperative Period

There was no significant association of antipsychotic administration with the incidence of delirium in the seven studies evaluating 1,970 patients (OR 0.56; 95% CI 0.23, 1.34; I^2 = 93%).[12–18] (Figure 2) A sensitivity analysis of three studies at low risk of bias (n=657 patients)[12, 13, 16] 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 among 581 patients in seven postoperative prevention and treatment studies reporting this outcome (MD −0.65 days; 95% CI −1.59, 0.29; I^2 = 80%).[12, 13, 15, 20–22, 25] (Figure 2) These findings were unchanged with sensitivity analyses including only postoperative prevention studies (n=279 patients, 3 studies)[12, 13, 15] and including studies at low risk of bias (n=411 patients, 4 studies)[12, 13, 21, 25] (MD = −0.71 days; 95% CI: −2.14, 0.71; I^2 = 91%; and MD = −0.78 days; 95% CI: −2.23, 0.68; I^2 = 77%, respectively).

Severity of delirium was not associated with administration of antipsychotics in 464 patients in 8 studies (SMD −0.11; 95% CI −0.43, 0.22; I^2 = 61%).[13, 15, 19, 22, 24, 27, 29, 30] (Figure 2) These findings were unchanged with sensitivity analyses including only postoperative prevention studies (n=178 patients, 2 studies)[13, 15] and including studies at low risk of bias (n=120 patients, 2 studies)[13, 24] (SMD = −0.18; 95% CI: −1.80, 1.43; I^2 = 96%; and SMD = −0.42; 95% CI: −1.59, 0.74; I^2 = 90% respectively).

Hospital and ICU Length of Stay

Antipsychotics administered for the postoperative prevention or treatment of delirium was not associated with hospital LOS in 1,454 patients in eight studies (MD = −0.01 days; 95%CI: −0.16, 0.14; I^2= 42%).[12, 13, 16, 18, 20, 21, 25, 28] (Figure 3) This finding was unchanged with sensitivity analyses based on only postoperative prevention studies (n=752 patients, 4 studies)[12, 13, 16, 18] or including studies at low risk of bias (n=485 patients, 5 studies)[12, 13, 16, 21, 25] (MD = 0 days; 95% CI: −0.15, 0.15 days; I^2 = 0% and MD = −0.05 days; 95%CI: −0.74, 0.65 days; I^2 = 0% respectively).

There was no significant association with ICU LOS in 1,400 patients from seven studies (MD = −0.46 days; 95% CI: −1.15, 0.24; I^2 = 91%).[12, 16, 18, 20, 21, 25, 28] (Figure 3) Sensitivity analysis of only postoperative prevention studies (n=684 patients, 3 studies)[12, 16, 18] or studies at low risk of bias (n=431 patients, 4 studies)[12, 16, 21, 25] resulted in the same finding (MD = −0.36 days; 95% CI: −1.10, 0.39; I^2 = 97%; and MD = −0.55 days; 95% CI: −1.39, 0.29; I^2 = 52% respectively).

Institutionalization and Other Adverse Events

Three studies[15, 17, 20] reported outcomes related to institutionalization after hospitalization at different points in time (immediately following hospitalization vs. at 3 months follow-up). A wide variety of adverse effects were monitored and reported (Appendix Table 2). Heterogeneity of outcomes prevented meta-analysis. However, there was no apparent pattern of higher reported adverse events in intervention versus control groups.

Mortality

Among all studies, there was no significant association of antipsychotics with mortality measured up to 30 days following hospital stay in 1,439 patients in 10 studies reporting this outcome (OR 0.90; 95% CI 0.62, 1.29; I^2 = 0%).[12, 17, 18, 19, 20, 21, 24, 25, 27, 28] (Figure 4) This finding remained consistent in the following sensitivity analyses: including only postoperative prevention studies (n= 567 patients in 3 studies),[12, 17, 18], or including studies at low risk of bias (n = 395 patients in 4 studies)[12, 21, 24, 25] (OR = 1.65; 95% CI 0.69, 3.93; I^2 = 44%; and OR = 0.98; 95% CI 0.54, 1.76; I^2 = 0% respectively).

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 adult patients. Antipsychotics were not associated with improvements short-term mortality, severity or duration of delirium, and length of ICU and hospital stay. However, existing studies demonstrate heterogeneity in study design, including diverse populations, with few studies focused specifically on older postoperative patients. 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 with different conclusions.[32–38] One publication concluded that

antipsychotics do prevent delirium: however this analysis included unpublished RCT data of haloperidol versus placebo in patients undergoing hip fracture repair surgery. Results for this study required imputation due to a lost randomization code.[38] The only systematic review to include all of the same studies identified in this review did not perform a meta-analysis.[32] An additional 5 meta-analyses included up to 6 of the same studies analyzed in this report, and concluded that there *was* a modest postoperative delirium protective effect of antipsychotics.[34–38] 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 years)[19] contributed to the non-significant 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.

Our results were consistent with the findings of a meta-analysis[33] that included three RCTS of haloperidol vs. placebo.[13, 14, 18] No association between antipsychotics and the prevention of post-operative delirium was demonstrated. Other outcomes examined in this review, including delirium severity and duration, length of ICU and hospital stay, and mortality were consistent with other analyses that did not demonstrate a significant effect of antipsychotics on these outcomes.[32, 36, 37]

To-date, this systematic review and meta-analysis is the most comprehensive in coverage of published data. We included all available studies of hospitalized patients. Merging postoperative prevention studies with treatment studies of patients with delirium during surgical or medical admissions is warranted due to the limited available data in homogenous populations. While this approach may increase the power for evaluating uncommon outcomes, it may also have limitations related to heterogeneity of the included studies. For example, data from critically ill septic patients 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[12] concluded that there was a significant difference in the incidence of postoperative delirium, if patients exhibiting any symptoms of delirium in the immediate postoperative recovery period on the day of cardiac surgery were treated every 12 hours with an oral dose of risperidone 0.5 mg. This design, which selects a subset of patients at highest risk for the development of delirium on subsequent hospital days, may not be comparable to other designs that treat all patients regardless of risk.[39, 40] Not-with-standing this criticism, we believe that our findings are important to report, given that they are consistent with the sensitivity analyses after comparing more homogeneous studies, restricted to the preventive postoperative designs and excluding those at high risk of bias.

Heterogeneity of outcome measures points to the great need for standardization.[41–43] Of the seven postoperative studies included in this review, only 3 collected mortality data and 2 reported on rehabilitation status following hospitalization for surgery at two differing time points. Consensus regarding collection of core outcome measures[42] 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 patient agitation and distress is a common reason for the prescription of antipsychotics in hospitalized adults and yet the field has no uniform data on those outcomes. Much more work in this area is needed to delineate the best strategies around delirium prevention, particularly in high-risk populations such as older postoperative patients. Well-powered randomized controlled evaluations, particularly among older at-risk patients immediately post-anesthesia, with well-defined outcomes are warranted in order to better understand whether there is any benefit from these medications.

CONCLUSIONS

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

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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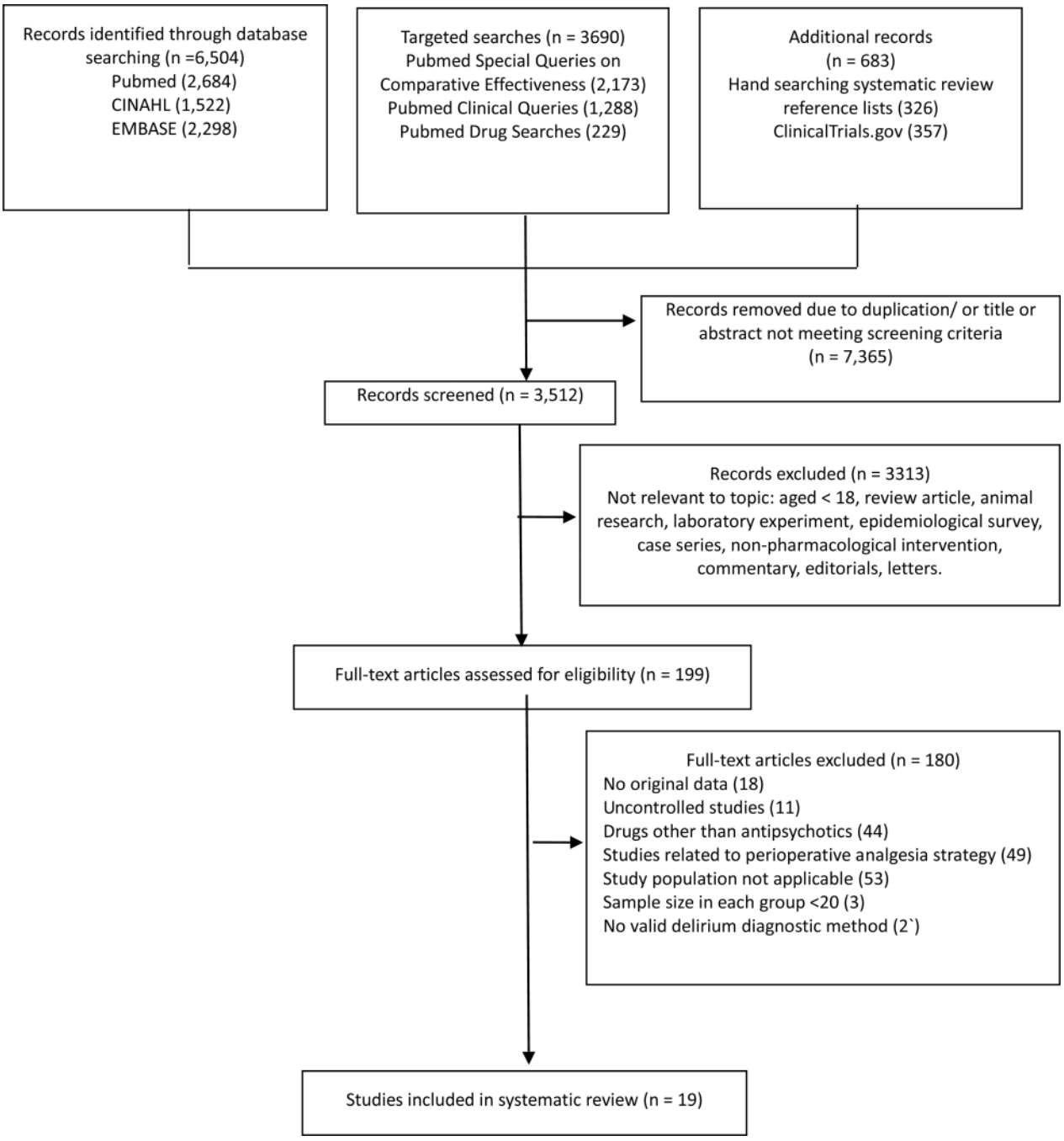
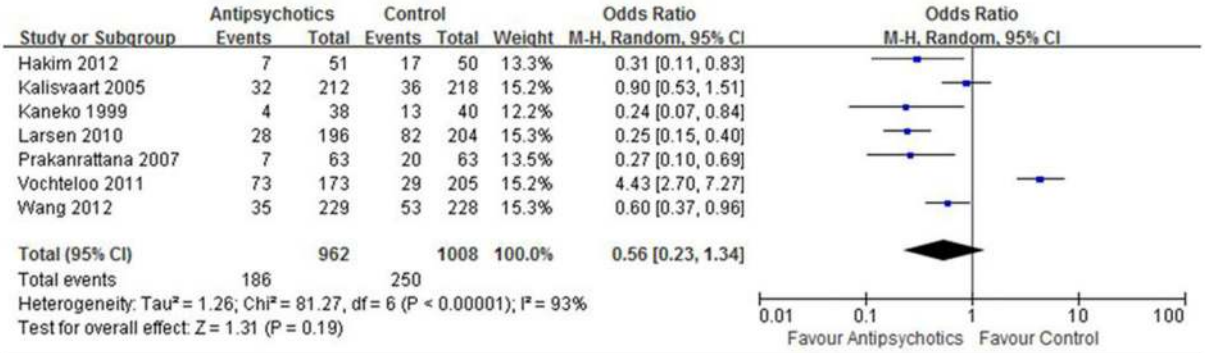
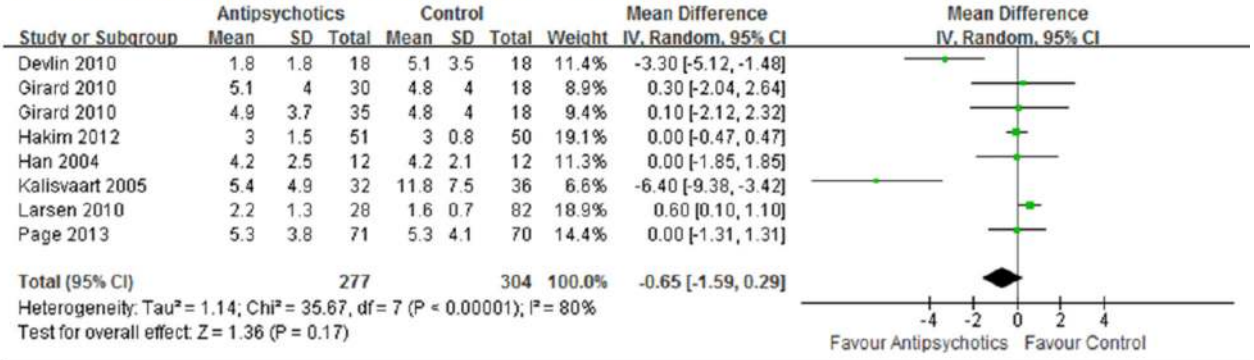


Figure 1.
Flow chart of study selection process

A. Delirium Prevention in Postoperative Patients



B. Delirium Duration in Hospitalized Patients



C. Delirium Severity in Hospitalized Patients

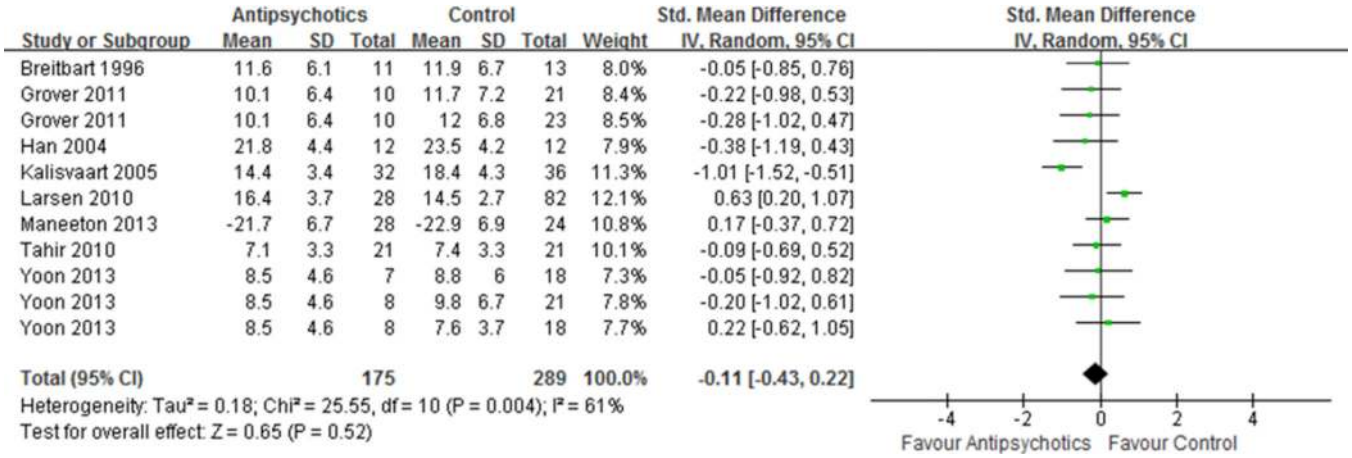


Figure 2.

Forest Plots of Antipsychotic Use and Delirium Prevention, Duration and Severity Reduction

Abbreviations: SD = Standard Deviation; 95% CI –95% Confidence Interval; df = degrees of freedom; MH = Mantel-Heanzel Odds Ratio IV = Inverse Variance; Random = Random Effects Model used to calculate estimate

Total Number of Patients Combined for each Meta-analysis:

A. n = 1,970 for Delirium Prevention

B. n = 581 for Delirium Duration

C. n = 464 for Delirium Severity

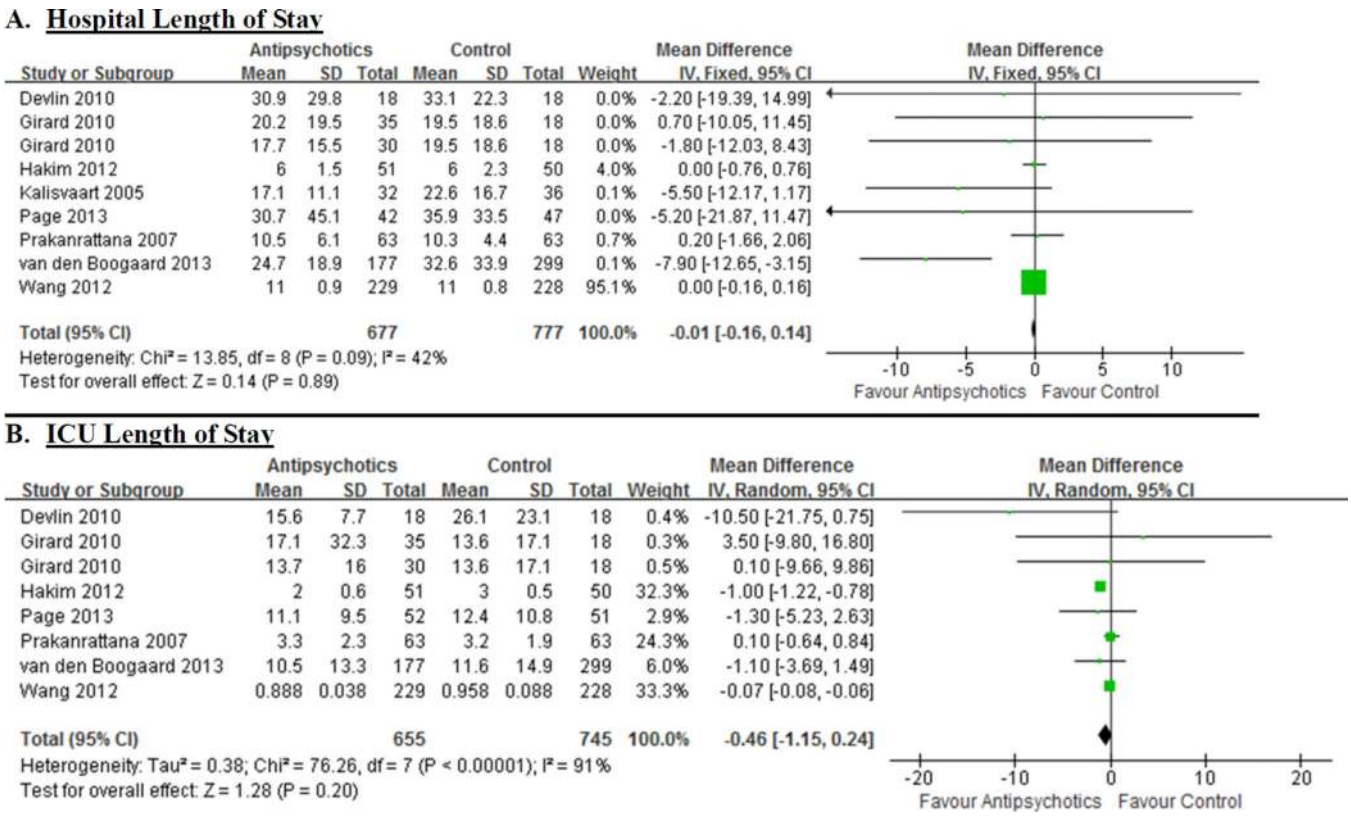


Figure 3.

Forest Plots of Antipsychotic Use and Hospital and Intensive Care Unit (ICU) Length of Stay

Abbreviations: SD = Standard Deviation; 95% CI – 95% Confidence Interval; df = degrees of freedom; MH = Mantel-Heanzel Odds Ratio IV = Inverse Variance; Random = Random Effects Model used to calculate estimate; Fixed = Fixed Effects Model used to calculatethe estimate.

Total Number of Patients Combined for each Meta-analysis:

A. n = 1,454 for Hospital Length of Stay

B. n = 1,400 for ICU Length of Stay

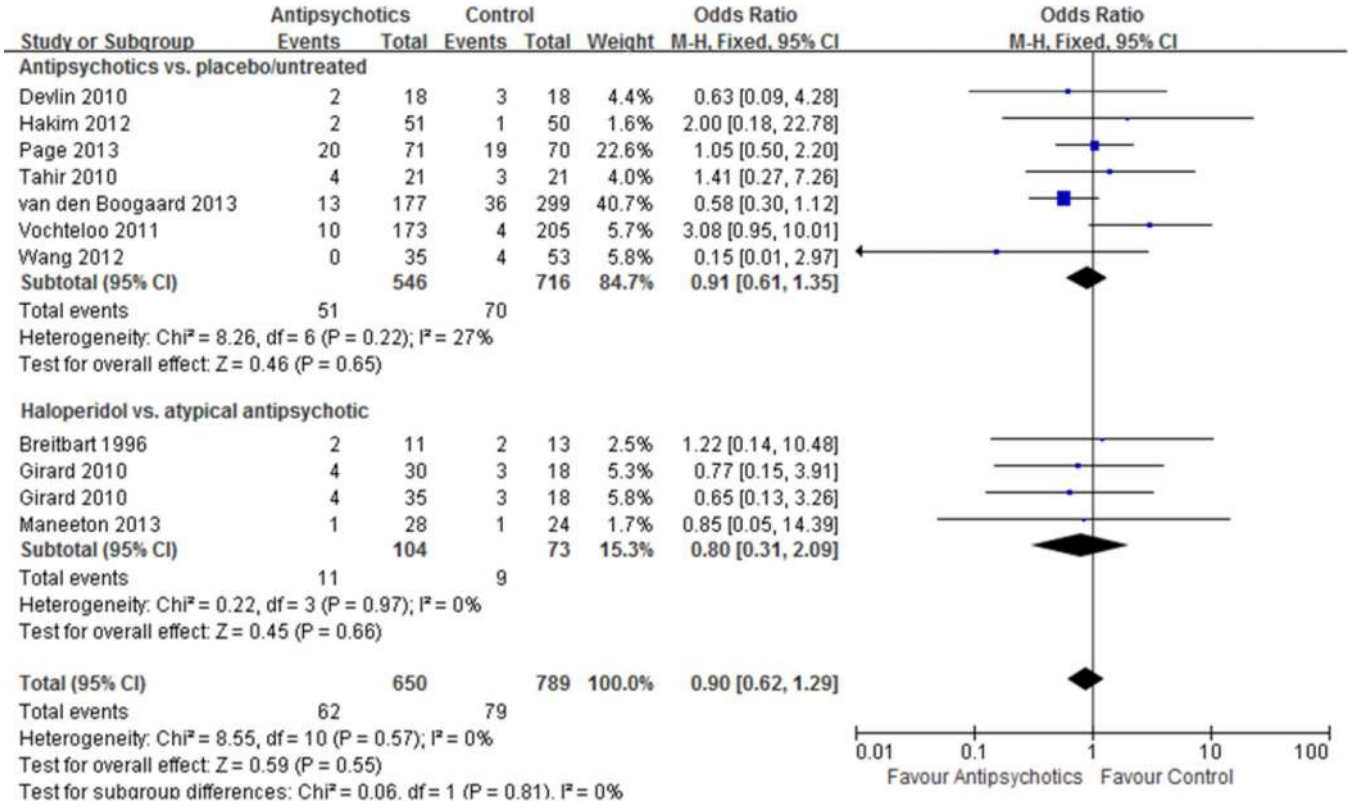


Figure 4.

Forest Plot of Antipsychotic Use and Mortality in Hospitalized Patients

Abbreviations: SD = Standard Deviation; 95% CI – 95% Confidence Interval; df = degrees of freedom; MH = Mantel-Heanzel Odds Ratio; IV = Inverse Variance; Random = Random Effects Model used to calculate estimate; Fixed = Fixed Effects Model used to calculate the estimate.

Total Number of Patients Combined for each Meta-analysis:

Antispychotics vs. Placebo or No Treamtment: n = 1,262

Antipsychotics vs. Antipsychotics: n = 177

Total: n= 1,439

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Table 1

Characteristics of Included Studies

First Author, Year	Study Design	Population	Sample Size Intervention (I) /Control (C)	Age (mean ± SD)	Intervention	Control	Delirium Diagnostic & Severity Instruments
Postoperative Prevention Trials							
Hakim 2012[12]	RCT	Cardiac surgery	101(51 I /50 C)	> 65	Risperidone, oral0.5 mg /12h POD	Placebo	DSM-IV
Kalisvaart 2005[13]	RCT	Orthopedic surgery	430(212 I /218 C)	I:79 ± 6;C: 80 ± 6	Haloperidol, oral 1 mg/day, preop - POD 3	Placebo	DSM-IV; CAM, DRS-R-98
Kaneko 1999[14]	RCT	Abdominal surgery	78(38 I /40 C)	I:72 ± 8; C: 73 ± 9	Haloperidol, iv 5mg/d, POD 1–5	Placebo	DSM-III-R
Larsen 2010[15]	RCT	Orthopedic surgery	496(246 I /252 C)	I:73 ± 6; C: 74 ± 6	Olanzapine, oral 5 mg/d, pre & POD 1	Placebo	DSM-III-R; DRS-R-98, CAM
Prakanrattana 2007[16]	RCT	Cardiac surgery	126(63 I /63 C)	I:61±10; C: 61±10	Risperidone, oral 1mg/d, POD 1	Placebo	CAM-ICU
Vochteloo 2011[17]	PCT	Hip fracture surgery	378(173 I /205 C)	I:87 ± 6; C:81± 7	Haloperidol, oral 1 mg/12h, D 1	No haloperidol	DSM-IV
Wang 2012[18]	RCT	Non-cardiac 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[19]	RCT	Hospital medical-AIDS	30(11 Haloperidol 13 Chlorpromazine 6 Lorazepam)	39± 8.8	Haloperidol, oral & im 1~ 9 mg/d	C1:Chlorpromazine C2:Lorazepam oral & IM, 1–9 mg/d	DSM-III-R DRS
Devlin 2010[20]	RCT	ICU, medical & surgical	36 (18 I /18 C)	I :62 ± 14 C: 63 ± 15	Quetiapine, oral 50–200mg/12h	Placebo ≤10 d	ICDSC
Girard 2010[21]	RCT	ICU, medical & 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/6h, D1–D14 I2: Ziprasidone, im 40mg/6h, D1–D14	Placebo D1–D14	CAM-ICU
Grover 2011[30]	RCT	Hospital, medical & 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[22]	RCT	Hospital, medical & surgical	28 (12 I /12 C)	I : 67 ± 16 C: 66 ± 8	Haloperidol, oral 0.75 mg/d, D1–D7	Risperidone, oral 0.5 mg/d D1–D7	DRS MDAS
Kim 2010[23]	RCT	Hospital, medical & surgical	32 (17 I /15 C)	I : 67 ± 12 C: 68 ± 11	Risperidone, oral 0.25–2 mg/d, D1–D7	Olanzapine, oral 1.25–7.5mg/d, D1–D7	DRS-R-98

First Author, Year	Study Design	Population	Sample Size Intervention (I) /Control (C)	Age (mean ± SD)	Intervention	Control	Delirium Diagnostic & Severity Instruments
Maneeton 2013[24]	RCT	Hospital, medical	52 (28 I /24 C)	I : 57 ± 12 C: 57 ± 12	Haloperidol, oral 0.5–2mg/d, D1–D7	Quetiapine, oral 25–100 mg/d, D1–D7	CAM DRS-R-98
Page 2013 *[25]	RCT	ICU, medical & surgical	142(71 I /71 C)	I:68±16; C:69±15	Haloperidol, iv 2.5 mg/8h, ≤14d	Placebo	CAM-ICU
Skrobik 2004[26]	RCT	ICU, medical & surgical	73 (45I /28 C)	I: 63 ± 12 C: 68 ± 6	Haloperidol, oral 2.5–5 mg /8h	Olanzapine, oral 5 mg/d	ICU-DSC, DI, DSM-IV
Tahir 2010[27]	RCT	Hospital, medical	42 (21 I /21 C)	I: 84 ± 9 C: 84 ± 7	Quetiapine, oral 25–175 mg/d	Placebo ≤10 D	DSM-IV DRS-R-98
van den Boogaard 2013 *[28]	HCT	ICU, medical & surgical	476(177 I /299 C)	I:63±14; C:64±14	Haloperidol, iv 1mg/8h, until discharge	No haloperidol	CAM-ICU
Yoon 2013[29]	PCT	Hospital, medical & 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 0.5–10mg/d,D1–D6 I2:Risperidone,oral 0.25–4mg/d,D1–D6	C1: Olanzapine, oral1–20 mg/d C2: Quetiapine,oral 25–200 mg/d D1–6	DSM-IV-TR DRS- R-98

Abbreviation: RCT= randomized control trial, HCT= historical control trial, PCT= prospective cohort trial, iv= intravenous, im= intramuscular injection, CAM-ICU= confusion assessment method for the ICU, 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= ICU Delirium Screening Checklist, MDAS = Memorial Delirium Assessment Scale, POD= Postoperative Day; D=day; mg/d = milligrams per day;

*prevention and treatment study in the ICU setting