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Prophylaxis with Antipsychotic Medication Reduces the Risk of Post-Operative Delirium in Elderly Patients: A Meta-Analysis

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Background: *Delirium commonly occurs in hospitalized elderly patients, resulting in increased morbidity and mortality. Although evidence for treatment of delirium exists, evidence supporting pharmacologic prevention of delirium in high risk patients is limited.* **Objective:** *This review examined whether delirium in at-risk patients can be prevented with antipsychotic prophylaxis in the inpatient setting.* **Data sources:** *A systematic literature review of articles from January 1950 to April 2012 was conducted in PubMed, PsychInfo, and Cochrane Controlled Trials and databases.* **Study selection:** *Five studies (1491 participants) met our inclusion criteria for analysis. Medication administered included haloperidol (three studies), risperidone (one study), and olanzapine (1 study). All five studies examined older post-surgical patients, spanning five different countries.* **Data extraction:** *Only RCTs of antipsychotic medication used to prevent delirium were included. Key words used in the search were: "delirium," "encephalopathy," "ICU psychosis," "prevention," and "prophylaxis." Studies had to include a validated method of diagnosing delirium. Data analysis was performed using the Metan command in Stata (Stata Corp LP, College Station, TX).* **Results:** *The pooled relative risk of the five studies resulted in a 50% reduction in the relative risk of delirium among those receiving antipsychotic medication compared with placebo (RR(95% CI): 0.51 (0.33–0.79; heterogeneity, $p < 0.01$, random effects model). Examination of the funnel plot did not indicate publication bias.* **Conclusions:** *Although few studies have examined prophylactic use of antipsychotics, this analysis suggests that perioperative use of prophylactic antipsychotics may effectively reduce the overall risk of postoperative delirium in elderly patients.*

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Delirium is a serious, but common, postoperative complication in older adults and is associated with numerous adverse outcomes.[1,2] Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision (DSM IV-TR) defines delirium as a disturbance of consciousness and attention that develops over a short period of time, tends to fluctuate during the course of day, and is typically the consequence of a general medical condition. It is present in 10% of emergency room patients, 10%–30% of patients hospitalized in medical units, 15%–53% of elderly surgical patients, 30%–50% of non-intubated ICU patients, and 80% of patients in ICU who are on mechanical ventilation. Those at greatest risk are 70 and older, have preexisting cognitive impairments, have pre-

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operative exposure to narcotics and benzodiazepines, and have a previous history of postoperative delirium.[3–6]

The sequelae of delirium can include prolonged hospital stay, increased morbidity and mortality, and an increased likelihood to be discharged to a nursing home.[5,7,8] A meta-analysis of over 2000 patients over 65 years old found the risk of death increased from 27.5% to 38% in patients who developed delirium, the risk of institutionalization increased from 10.7% to 33.4%, and the risk of developing dementia increased from 8.1% to 62.5%.[8] Leslie et al. estimated that delirium is responsible for $16,303 to $64,421 in additional costs per delirious patient per year with total 1-year health-attributable cost between $38 billion to $152 billion nationally.[9]

Given its frequency and its association with an increased morbidity and mortality, the need for primary and secondary prevention of delirium is critical. To date, several studies have demonstrated various non-pharmacologic measures that can be implemented to reduce the incidence of delirium by addressing specific risk factors. These measures include reorientation of the patient, nonpharmacologic enhancement of sleep, addressing sensory limitations, early recognition of dehydration, pain management, early mobilization, and modification of the hospital environment.[10] Nonpharmacologic interventions are shown to lower incidence of delirium by approximately one-third.[11,12]

Currently, there is no FDA approved pharmacologic prevention of delirium. Numerous studies have been undertaken to support the use of antipsychotic medication for the treatment of delirium.[13–15] The putative mechanism for antipsychotic action involves dopaminergic blockage as it relates to the dopamine excess and acetylcholine deficiency hypothesis of delirium.[16,17] Intravenous haloperidol is currently recommended by APA guidelines.[18]

However, the majority of pharmacologic investigations have focused on treatment rather than prevention. Indeed, evaluations of pharmacologic prophylaxis are scant. Although short-term administration of antipsychotic medication minimizes the potential of associated longer-term metabolic consequences and may decrease incidence of delirium, their routine use as prophylaxis in medically and surgically ill patients warrants more careful evaluation. The purpose of this meta-analysis is to determine whether delirium in at-risk patients can be prevented by prophylaxis with antipsychotic medication when compared to placebo control.

METHODS

A systematic literature review of English language articles published between January 1950 and April 2012 pertaining to the prophylaxis of delirium using antipsychotic medication was conducted in PubMed, PsychInfo, and the Cochrane Controlled Trials and Database. The following search terms were used to search each database: delirium, encephalopathy, ICU psychosis, prevention, antipsychotic, and prophylaxis. Abstracts were reviewed and only randomized placebo controlled trials of typical or atypical antipsychotic medication used to prevent the onset of delirium were included for analysis. In addition, studies had to use a validated method of diagnosing delirium to be included for analysis. Studies were excluded if they were not randomized, were not placebo controlled, did not investigate the use of antipsychotic medication for the prevention (not treatment) of delirium, or did not use a validated method for diagnosing delirium. To improve generalizability, we did not restrict location of studies to ICUs, to the elderly, or to surgical patients. Of note, the only literature we found currently in publication is of elderly surgical patients.

Searches were conducted independently by four authors (P.T., V.S., C.W., and U.C.) with identical results (inter-rater agreement, indexed with κ, was 1.0). The authors then reviewed all of citations for those articles that met the criteria for inclusion to identify any additional articles that may not have been identified through the database search. The quality of the articles that were retrieved was assessed using Cochrane collaborative quality assessment method. Tables that were published in each of the articles provided the number of incident cases with and without delirium, as defined by a validated method for diagnosing delirium, e.g., Larsen et al. used DSM-III-R clinical diagnosis aided by Mini Mental State Exam (MMSE),[19] Confusion Assessment Method (CAM),[20] and the Delirium Rating Scale (DRS-R-98);[21,22] Prakanrattana and Prapaitrakool used clinical assessment and the CAM-ICU;[23] Kaneko et al. used DSM-III-R clinical diagnosis;[24] Kalisvaart used DSM-IV criteria aided by MMSE, CAM, and DRS-R-98;[25] Wang used CAM-ICU.[26] These data (i.e., the presence or absence of delirium), stratified by active vs. placebo arm, were then extracted for analysis by two of the study authors (P.T., V.S.) from the information that was contained in the articles. Inter-rater agreement in this case was indexed with κ, which was also 1.0, indicating perfect agreement.

Although equivalency data between the second and first generation antipsychotics is not well established, we converted each study drug to oral haloperidol dosing equivalents based on the work published by Andreasen et al[27] because three of the five studies used haloperidol as the investigational agent. This information can be found in Table 1. Two of the three haloperidol studies used intravenous rather than oral administration; we converted these doses to oral equivalents based on the oral dose having approximately half the potency of intravenous because of lower bioavailability.[28]

TABLE 1. Description of Studies Included for Analysis

Author (Date) Country	Description of Study		Control Group		Intervention Group		Outcomes	
	Study Setting	Intervention	Total (*n*)	Delirium (*n*)	Total (*n*)	Delirium (*n*)	% Retained	Intervention Outcomes
Prakanrattana and Prapaitrakool (2007) Thailand	Elective cardiac surgery with use of cardiopulmonary bypass, ages >40 years	Risperidone 1 mg po (ODT) in ICU at the moment of emergence from anesthesia (one dose total)[1.4 OHE*/d]	63	20	63	7	100	Incidence of delirium was significantly reduced from 31.7% to 11.1% (NNT 4.85), severity of delirium was significantly lower in the treatment group
Larsen et al. (2010) United States	Hip/knee replacement, ages >65 years or <65 if already had history of delirium	Olanzapine 5 mg po (ODT) preoperatively and postoperatively (2 doses for total 10 mg po) [4 OHE*/d]	204	82	196	28	80.8	Incidence of delirium was significantly reduced from 40.2% to 14.3% (NNT 4), more patients discharged to home rather than to another institution
Kalisvaart et al. (2005) The Netherlands	Hip surgery with patients moderate to high risk for delirium (excluded low risk), ages >70 years	Haloperidol 1.5 mg/d po, for 1 to 6 days, preoperatively and postoperatively (at 0.5 mg po tid) + non-pharmacologic intervention for all subjects	218	36	212	32	91.9	No statistically significant reduction of delirium incidence (16.5% vs. 15.1%), however among those who did become delirious, there was a reduction in duration and intensity
Kaneko et al. (1999) Japan	Gastrointestinal surgery, mean age >70 years	Haloperidol 5 mg IV daily for 5 days [10 OHE*/d]	40	13	38	4	100	Incidence of delirium was significantly reduced from 32.5% to 10.5% (NNT 4.55)
Wang et al. (2012) China	Noncardiac surgery, ages >65 years	Haloperidol 1.7 mg IV post operatively + non-pharmacologic intervention for all subjects [3.4 OHE*/d]	228	53	229	35	100	Incidence of delirium was significantly reduced from 23.2% to 15.3% (NNT 12), length of stay in ICU reduced in treatment arm, time to onset of delirium, and delirium free days increased in treatment arm

* OHE = oral haloperidol equivalents.[27,28]

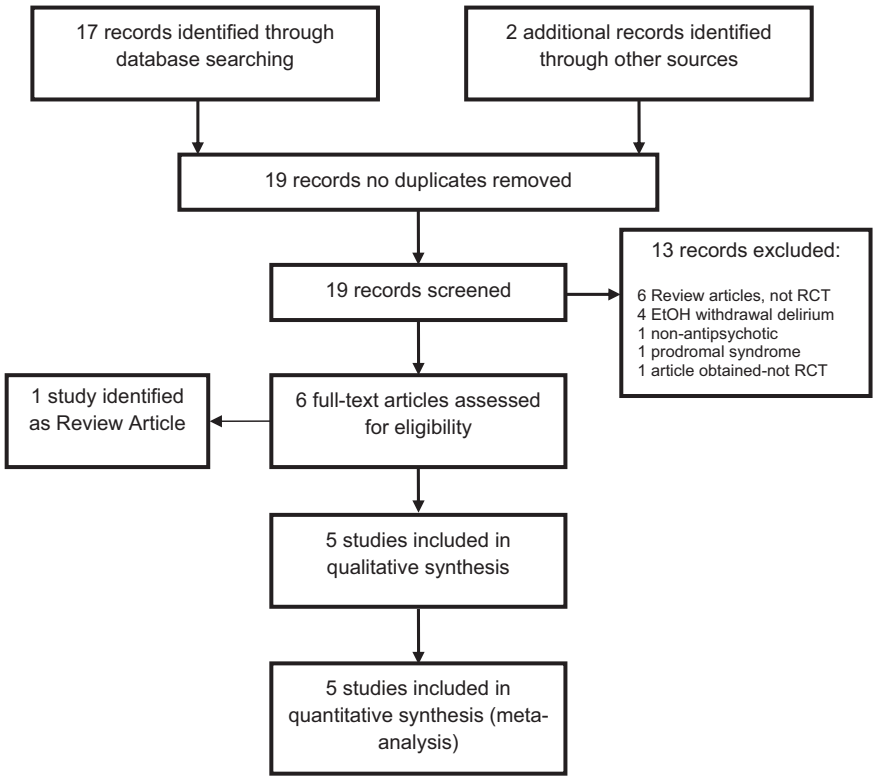
We calculated the relative risk ratios and the weighted pooled relative risk ratios across studies (Metan command; Stata 10.0, College Station, TX). A random effects model was used. The Q statistic and I^2 statistic were used to evaluate heterogeneity. The Q statistic quantifies the magnitude of heterogeneity, whereas the I^2 statistic quantifies the total variation due to between-study variance. Publication bias was evaluated using a funnel plot.

RESULTS

Qualitative Analysis

The initial search identified 126 citations from MEDLINE, 281 from PsychINFO database, and 17 from the Cochrane Controlled Trials database. One additional citation was identified after review of secondary references. After a review of the abstracts, 19 articles were identified as potential candidates and reviewed in detail. Of those, five studies met inclusion criteria (exclusion rationale are presented in the PRISMA flow diagram, see Figure 1),[22–26] and were included for review (see Table 1 for a summary of the included studies). All included studies were randomized, placebo-controlled, clinical trials spanning five different countries: Japan,[24] The Netherland,[25] Thailand,[23] China,[26] and the USA.[22] All five studies examined elderly patients undergoing surgery. Study medications included haloperidol,[24–26] risperidone,[23] and olanzapine,[22] and the prevention of postoperative delirium was the primary outcome. The methodological quality of

FIGURE 1. PRISMA Flow Diagram of Study Inclusion and Exclusion.



each study was evaluated using Cochrane criteria,[29] and a summary of this evaluation is presented in Table 2.

Prakanrattana and Prapaitrakool[23] included 126 patients undergoing elective cardiac surgery in their study, with 63 participants in each arm. Patients were randomly assigned to receive risperidone 1mg orally or placebo immediately after surgery by staff not directly involved in patient care. Among 126 randomized patients, the occurrence of postoperative delirium in the risperidone group was significantly less common than in the placebo group (11.1% vs. 31.7%, respectively, $p = 0.01$, (RR [95% CI]: 0.35 [0.16–0.77]). Other postoperative outcomes such as presence of postoperative complications and the length of hospital or ICU stay were not statistically different between the groups. The number need to treat (NNT) in this study was 4.85.

In a study evaluating the use of olanzapine, Larsen et al.[22] included 400 patients undergoing simple or complex hip or knee surgery in a randomized, double-blind placebo trial: 196 patients received olanzapine 5 mg orally immediately pre- and postoperatively (a total of 10 mg of olanzapine) and 204 patients received placebo. Delirium was identified using DSM-III-R criteria in conjunction with the MMSE, the DRS-R-98 and the CAM. Compared with the placebo group, the incidence of postoperative delirium was lower in the olanzapine group (14.3% vs. 40.2%; 95% CI 17.6–34.2, $p < 0.0001$). Despite this lower incidence,

TABLE 2. Cochrane Quality Analysis of Studies Included in the Analysis

Study	Adequate Sequence Generation	Allocation Concealment	Blinding	Incomplete Outcome Data Reporting	Free of Selective Outcome Reporting	Free of Other Sources of Bias
Prakanrattana and Prapaitrakool	Yes	Yes	Yes	Yes	Yes	Yes
Larsen et al.	Yes	Yes	Yes	No	Unclear	No
Kalisvaart et al.	Yes	Yes	Yes	Yes	Yes	No
Kaneko et al.	Unclear	Yes	Unclear	Yes	No	No
Wang et al.	Yes	Yes	Yes	Yes	Yes	Yes

among those who developed delirium, the duration of delirium was longer in the olanzapine group compared with the placebo group (2.2 days vs. 1.6 days [SD 0.7] days; $p = 0.02$). Moreover, delirium was more severe in the olanzapine group compared with the placebo group (mean DRS total scores were 16.44 in the olanzapine group compared with 14.5 in the placebo group, $p = 0.02$). The calculated NNT in this study was 4.

Kalisvaart et al.[25] included 430 patients admitted for acute or elective hip surgery in their study with patients randomized to a prophylaxis group haloperidol 0.5 mg po three times daily, for a total of 1.5 mg po daily. The study drug was administered from the initial day of their hospital admission and continued through the postoperative day 3 (for a maximum of 6 days). All of the clinical staff in contact with study participants were blinded to the treatment conditions, as were the participants of the study. Of the 382 patients who completed the protocol, 55 patients (15.8%) developed delirium diagnosed using DSM-IV and CAM criteria. Fisher's exact test was used to evaluate differences between the groups for the presence of postoperative delirium, Student's *t*-tests were used to evaluate parametric variables, and Mann-Whitney U-tests were used to evaluate nonparametric variables. There was no significant difference between the prophylaxis and the placebo group in the incidence of postsurgical delirium. There were, however, differences in the secondary outcomes of severity and duration: participants in the prophylaxis arm scored lower on the DRS-R-98 delirium severity scale (14.4 ± 3.4 vs. 18.4 ± 4.3, with a mean difference of 4.0, 95% CI 5 2.0–5.8; $p < 0.001$), had a lower duration of delirium (5.4 vs. 11.8 days, with a mean difference of 6.4 days, 95% CI 4.0–8.0; $p < 0.001$) and had shorter hospital stays (17.1 vs. 22.6 days, with a mean difference of 5.5 days, 95% CI 1.4–2.3; $p < 0.001$). There were no noted drug related side effects.

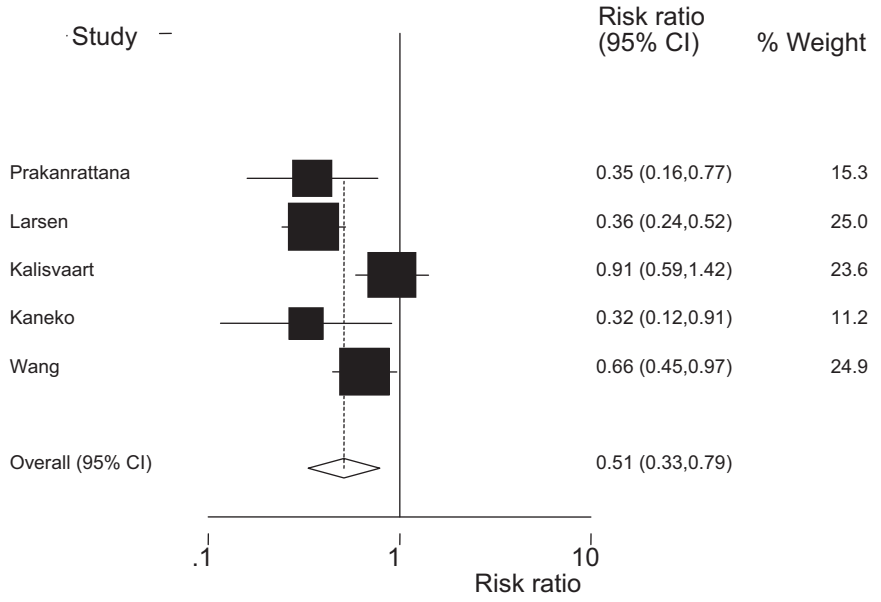
In another study evaluating the use of haloperidol, Kaneko et al.[24] included 78 patients undergoing elective gastrointestinal surgery. Patients were randomly allocated to two groups; 38 patients received prophylaxis with 5 mg intravenous haloperidol on postoperative days 1 through 5, and 40 patients received normal saline under the same conditions. The authors report that patients were randomly selected using a "closed envelope system," but the specifics of the blinding procedures were not clarified. DSM-III-R criteria were used to diagnose postoperative delirium, which developed in 17 of 78 patients (21.8%). However, only 4 (10.5%) patients developed delirium in the study group compared with 13 (32.5%) in the placebo group (χ^2 not reported, but the authors report a p value of <0.05). The intensity and duration of the delirium were noted to be worse in the control group. There were no complications or adverse outcomes noted with haloperidol treatment except that 1 patient developed transient tachycardia. The calculated NNT in this study was 4.55.

Wang et al.[26] also investigated the use of haloperidol to prevent delirium among patients after non-cardiac surgery. Their study enrolled 457 patients above the age of 65 years who were admitted to the intensive care unit after non-cardiac surgery: 229 patients were randomized to receive 0.5 mg IV bolus of haloperidol followed by continuous infusion at a rate to 0.1 mg/h for 12 hours (for a total dose of 1.7 mg of haloperidol IV) postoperatively vs. 228 patient who received normal saline placebo. The study was a prospective, randomized, double-blind, placebo-controlled two-center study. The study drug was identical in appearance to placebo and was mixed by a nurse not involved in other aspects of the study. Nonpharmacologic environmental approaches to reduce incidence of delirium were implemented for all patients irrespective of study arm. The primary outcome measured was incidence of delirium during first 7 postoperative days as measured by the CAM-ICU. Secondary outcomes included time to extubation, length of stay in ICU and hospital, as well as all-cause mortality in the first 28 postoperative days. Assessments were performed daily by research team members not involved in the care of the patients using the CAM-ICU and the Richmond Agitation Sedation Scale. The study was an intention-to-treat analyses and *t*-tests were used to evaluate parametric variables, and Mann-Whitney U-tests were used to evaluate nonparametric variables. The incidence of delirium in the haloperidol study arm was significantly lower with 35 out of 229 subjects (15.3%) of participants developing delirium in the treatment arm compared with 53 out of 228 subjects (23.2%) of participants in the control arm. After adjusting for the differences between the two groups, the odds ratio of delirium in the haloperidol vs. placebo group was 0.57 (95% CI 0.35–0.94, $p = 0.03$). The length of ICU stay was also significantly shorter (21.3 vs. 23 hours), but the length of hospitalization did not significantly differ between the two groups. Importantly, no adverse events were identified, no EPS occurred, and changes in QTc prolongation were similar in both arms. The NNT in this study was 12.

Quantitative Analysis

A Forest plot with corresponding relative risk ratios, confidence intervals, and weighting coefficients are pre-

FIGURE 2. Forest Plot.



sented in Figure 2. Four of five studies showed a significant decrease in incidence of postoperative delirium in elderly patients receiving antipsychotic medication prior to or immediately after surgery. The pooled relative risk of the five studies resulted in a 50% reduction in the relative risk of the incidence of delirium among those receiving antipsychotic medication compared with placebo (RR [95% CI]: 0.51 [0.33–0.79]). All but one study[25] concluded that if delirium in prophylaxis group develops, it is milder with a shorter duration. No study reported any serious or statistically significant adverse outcome, including adverse cardiac outcomes.

There was significant heterogeneity associated with the five studies analyzed in this meta-analysis (Q statistic = 13.33 [$p < 0.01$]; $I^2 = 0.15$). In order to account for random factors across studies that cannot be adequately modeled, we used a random effects model. Additionally our meta-analysis sought to evaluate different possible variables across studies that may have contributed to heterogeneity. Because the quality of the Kaneko[24] study was limited, we repeated the analysis excluding this study from the analysis. When the Kaneko study was excluded from the meta-analysis, heterogeneity remained statistically significant (Q statistic = 12.33 [$p < 0.01$]; $I^2 = 0.17$). Exclusion of the study did not significantly alter the results of the meta-analysis (RR [95% CI]: 0.54, [0.34–0.87]). Next we evaluated the Kalisvaart study as the overall incidence of delirium in this study was lower than that found in the other studies and lower than the incidence rate the authors assumed in their power analysis (15.8% vs. 40%). As a result, this study may have been underpowered to detect a difference. When the Kalisvaart[25] study was excluded from the meta-analysis, heterogeneity was no longer statistically significant (Q statistic = 5.97, $p = 0.13$). Exclusion of the study did not alter the results of the meta-analysis (RR [95% CI]: 0.49, [0.29–0.65]).

Examination of the funnel plot did not indicate publication bias. However, it is important to note that the overall number of studies in this analysis was small, which may limit inferences that can be made about the symmetry of the plot.

DISCUSSION

When taken together, the five clinical trials comprised 1491 participants and demonstrated that antipsychotic medication as a class may protect against postoperative delirium. Four of the five studies[21–23,25] showed that prophylaxis with antipsychotics resulted in a clear reduction in the incidence of delirium, with NNT ranging from 4.00 to 12.6. The overall effect, as indexed with a relative risk ratio of 0.51 (RR [95% CI]: 0.51 [0.33–0.79]) suggests that patients using antipsychotic prophylaxis were approximately half as likely to develop delirium compared with those who did not use antipsychotic prophylaxis.

There was significant heterogeneity associated with the five studies analyzed in this meta-analysis. The pri-

mary source of this heterogeneity appeared to be the Kalisvaart[25] study. The overall incidence of delirium in that study was significantly lower than the incidence rate the authors assumed in their power analysis raising the possibility of a type II error. When the Kalisvaart[25] study was excluded from the meta-analysis, heterogeneity was no longer statistically significant (Q statistic = 5.97, p = 0.13) suggesting that issues relating to power may be one source of heterogeneity. It is important to note that whether the meta-analysis was conducted including the Kalisvaart study (RR [95% CI]: 0.51 [0.33–0.79]) or excluding the Kalisvaart study (RR [95% CI]: 0.49, [0.29–0.65]) the effect size associated with the meta-analysis remained largely the same, thus limiting the impact of heterogeneity as it is typically conceived.

Another difference among the five articles pertained to the severity and length of delirium between the intervention and control arms. The Larsen et al.[22] study of olanzapine was the only study showing that despite a significantly lower incidence of delirium in the treatment arm, the patients who developed delirium had a longer duration and more severe symptoms of delirium compared with those in the control arm. This may, in part, be explained by a confounding factor: five of the 28 patients (17.9%) with delirium in the olanzapine group developed unanticipated postoperative alcohol withdrawal during the study (compared with one of the 82 [1.2%] in the control arm) despite the fact that alcohol dependence, alcohol abuse, and the use of more than 10 drinks per week were exclusion criteria for the study. The authors also note that more patients in the olanzapine arm who developed delirium had abnormally low albumin levels (<3.5 g/dL). The authors hypothesized that the hypoalbuminemia may have led to "more severe delirium due to higher available levels of the active drug." It is also notable that this study showed a slight nonsignificant trend toward a greater proportion of cardiac complications in the prophylaxis arm. Also of interest is the finding that significantly more patients in the treatment arm were able to be discharged to home as opposed to a rehabilitation facility compared with the placebo group.

Our conclusions differ from another review that has recently been published by Devlin and Skrobik,[15] in part because they restricted the treatment setting to the ICU. They conclude that although none of the studies they evaluated identified serious safety concerns with the use of antipsychotic medications, there was a lack of evidence supporting the use of these medications to treat delirium in the ICU setting. Their narrative review, however, examined a completely different set of clinical trials.[6,21,30] Common to all of them is that they examined the most critically ill patients in the ICU setting who may be more treatment refractory compared with those undergoing scheduled surgeries and, most importantly, all were treatment (not prophylaxis) studies. However, consistent with the conclusion of Devlin and Skrobik regarding safety, our study suggests that short-term use of antipsychotic medications to prevent delirium appears to be safe. No study reported any serious or statistically significant adverse outcome. Of the adverse events that are most feared with antipsychotic use such as death, cardiac events, or metabolic complications; none were found with any statistical significance in the five trials.

The literature, and therefore this meta-analysis, is limited by the small number of randomized, placebo controlled clinical trials examining the use of antipsychotics as prophylaxis against delirium. Indeed, we were only able to definitively identify five published randomized control trials meeting inclusion criteria, and these were of varying quality. However, those five studies encompassed 1491 participants. Although all were randomized placebo controlled clinical trials, the studies were conducted in five different countries, evaluated delirium using multiple (though validated) methods, examined three different antipsychotic medications with different dose equivalents and perioperative dosing strategies, and evaluated the use of these medications among patients with varying levels of disease burden. Yet, this analysis demonstrates a protective effect conferred by the use of antipsychotic prophylaxis. Moreover, although this meta-analysis of five studies comprising 1491 participants (738 of whom were exposed to an antipsychotic medication) was substantially powered, it remains possible that very rare adverse effects are still possible if undetected with this sample.

Though we could not identify which antipsychotic might offer the optimal prophylaxis against delirium. These results suggest that brief, limited use of antipsychotic prophylaxis in the elderly who are at risk for delirium may markedly reduce the incidence of delirium, thereby potentially reducing mortality, disease burden, length of hospital stay, and associated healthcare costs. The NNT for all studies was very small, ranging between four and 12. Future research should focus on determining if a reduction in the incidence of delirium actually reduces associated morbidity and mortality, as well as identifying the optimal agent and dose to maximize benefits while minimizing risk.

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