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Psychiatric–Medical Comorbidity

The Psychiatric–Medical Comorbidity section will focus on the prevalence and impact of psychiatric disorders in patients with chronic medical illness as well as the prevalence and impact of medical disorders in patients with chronic psychiatric illness.

# Antipsychotic prophylaxis in surgical patients modestly decreases delirium incidence — but not duration — in high-incidence samples: A meta-analysis ☆

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ABSTRACT

*Objective:* The objective was to examine whether prophylactic treatment with antipsychotics can decrease the incidence and severity of postsurgical delirium.
*Method:* A meta-analysis of existing trials comparing delirium incidence between patients given prophylactic antipsychotic and placebo was performed. Secondary outcomes were total hospital days, total days of delirium and severity. Pooled odds ratios (ORs) and mean differences were calculated using a random-effects model.
*Results:* Five randomized placebo-controlled trials comprising a total of 1491 patients were included. In the pooled analysis, prophylactic antipsychotic administration showed a reduction in delirium incidence (OR: 0.42; 95% confidence interval (CI): 0.24, 0.74). Among the studies reporting other outcomes, patients receiving antipsychotics prophylactically showed no differences in total hospital days (0.1; 95% CI: −0.73, 0.94), days of delirium (−1.17; 95% CI: −5.22, 2.88) or delirium severity (−1.02; 95% CI: −6.81, 4.76).
*Conclusions:* Prophylactic antipsychotic treatment in surgical patients modestly decreases the incidence of delirium, but not the length of hospital stay, duration of delirium or its severity. Given the modest protective effect of antipsychotics and their potential adverse reactions, there is insufficient evidence to support its universal use as a preventive agent, though potential benefit may be seen in populations at high risk of developing delirium.


## 1. Introduction

Delirium, an acute change in mental status marked by impairment of attention, remains a common and serious medical complication among hospitalized patients. The full syndrome of delirium often involves hallucinations, agitation, sleep disturbance, affective symptoms and other disruptions in cognition, causing patients risk of injury as well as subjective distress.

In the elderly, the prevalence of delirium in the hospital ranges between 14% and 56% and at least doubles the likelihood of mortality over the subsequent year [1–3]. One particularly vulnerable period for developing delirium is in the days following surgery, where rates as high as 70% have been reported [4]. Reviews of delirium in patients following orthopedic or cardiac surgeries have found heterogeneous incidence rates ranging from 3.6% to 53.3% and 13.5% to 41.7%, respectively [5,6].

Differences in the patient population, surgical procedure, anesthesia and method of neuropsychiatric assessment all likely contribute to this variation, though it is clear that delirium remains a significant problem and not solely in the immediate postoperative period. A large prospective study of patients undergoing coronary artery bypass grafting revealed that delirium was a significant, independent predictor of hospitalization for stroke and all-cause mortality over the subsequent 5 years [7]. In patients with dementia at baseline, evidence suggests that episodes of postoperative delirium are even more likely, last longer and accelerate the rate of cognitive decline [7–11].

With an aging population and an increasing number of elderly patients undergoing surgery, there is a growing need to understand the risk factors associated with delirium as well as potential interventions to prevent it [12]. Multidisciplinary interventions such as the Hospital Elder Life Program (HELP), which involves baseline screening of patients and management of hospital-associated risk factors, led to a reduction in delirium incidence (9.9% versus 15.0%) and duration (105 versus 161 total days), but not severity [13].

Similar reductions were found in other studies employing non-pharmacologic interventions such as staff education, systematic monitoring of mental status, attention to nutrition and other risk

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factor reduction [14,15]. A recent study in patients undergoing elective abdominal surgery employed a modified, proactive HELP program consisting of early mobilization, attention to nutritional needs and cognitive activities, which led to a significantly lower rate of delirium (0%) compared to the usual care group (16.7%) [16]. A proactive, structured consultation with a geriatrician reduced delirium incidence by about one third among elderly patients undergoing surgical repair of hip fracture, though this study was not powered to demonstrate which specific recommendations were effective for prevention [17]. Variability in the findings of these studies suggests that patient population and other factors are significantly influencing delirium incidence as well, leading to a limited consensus over which interventions are most preventive in routine practice.

The notion that medications alone can serve as prophylaxis against delirium remains under investigation. Drawing on the observation that decreased acetylcholine was associated with delirium, there was initial hope for the role of cholinesterase inhibitors in prevention [18]. Trials of donepezil and rivastigmine failed to yield significant, positive results in brief perioperative courses, though these studies had relatively low incidence rates and were generally underpowered to demonstrate small treatment effects [19–21]. In the case of Sampson et al., a trend towards lower incidence and shorter hospital stay was seen with donepezil, though only 33 patients completed the study, and the overall delirium incidence rate (21.2%) was lower than anticipated by the authors. The timing and duration of treatment may also be important, however; over a 24-month study period, standing rivastigmine decreased the incidence and severity of delirium in patients with vascular dementia [22].

A small pilot study of gabapentin 900 mg daily given before and after surgery showed a significant decrease in delirium incidence compared to placebo, with a trend towards lower opiate requirements in the gabapentin arm [23]. Rubino et al. found that a postoperative bolus and subsequent infusion of clonidine reduced delirium severity — though not incidence — in 30 intensive-care patients following aortic dissection repair [24]. A preliminary trial using melatonin to prevent delirium has shown promise, and a larger study has been proposed [25,26].

While antipsychotics, primarily haloperidol, are routinely used to treat the symptoms of delirium — such as agitation, anxiety, sleep disturbance and hallucinations — there are few studies examining their potential role in actually preventing it [27–29]. The present meta-analysis reviews the available randomized placebo-controlled trials conducted to date that address this question.

## 2. Methods

### 2.1. Search strategy and selection of studies

The PubMed, Cochrane Library and Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases were searched for studies published between 1984 and 2012 with the following key words: “delirium,” “prevention” and “trial.” Of these results, studies were included if they employed a randomized controlled trial design, comparing delirium incidence in surgical patients given prophylactic antipsychotic or placebo. All patients had to be nondelirious at baseline and subject to a discrete surgical procedure during the study period. In addition, studies were included only if they were published in English and represented original research.

Excluding review articles, the search using PubMed provided references for 130 studies, 5 of which met the selection criteria for the meta-analysis. Of the excluded studies, 43 did not study delirium as an outcome, 15 were solely descriptive, 30 involved a nonmedication intervention, 28 were medication trials using nonantipsychotic agents, 8 examined a treatment (as opposed to prevention) intervention, and 2 were reanalyses of previously reported data. Twenty-one trials were identified in the Cochrane library, one of which met inclusion criteria and did not appear in PubMed. The search using CINAHL yielded a total of four studies, all of which were among the results from PubMed.

### 2.2. Data extraction

For the study characteristics, the following data were extracted: year of publication, number of subjects, study design, study intervention, type of surgery, mean age and standard deviation of the study arms, outcomes assessed and the diagnostic definition used for the outcome. To perform the meta-analysis, the counts of patients in each arm with and without delirium were tabulated for each study.

When reported, the mean and standard deviation for the length of hospital stay among all study subjects in both arms were recorded. For the studies that reported the duration of delirium in days, these values were similarly extracted. In the case of one study (Wang et al.), the duration of delirium needed to be estimated by subtracting the mean number of “Delirium-Free” days from the total mean length of hospital stay for each group. In this instance, the standard deviation was calculated from the square root of the summed variances of the two means.

### 2.3. Data analysis

The odds ratios (ORs) for dichotomous outcomes and 95% confidence intervals (CIs) for delirium incidence between the antipsychotic and placebo groups were calculated for each study. For continuous variables, the mean difference and 95% CIs were calculated. Assuming that additional factors could explain the differential outcomes among the studies, a random-effects (Mantel–Haenszel) model was used to calculate the pooled ORs and means. Forest plots were generated to depict graphically the pooled effect sizes for each variable.

The incidence rate in the placebo group, assumed to be representative of the population at each hospital, was calculated to establish an indicator of baseline risk for developing delirium. Linear regression analysis was used to explore across studies the relationship between the observed effect of antipsychotic prophylaxis (OR) and delirium risk in the placebo group. A separate linear regression was used to examine the relationship between mean age of the study participants and the observed effect of antipsychotic prophylaxis.

Statistical analyses were performed using Review Manager 5.1.6 (RevMan, Cochrane Collaboration) [30] and SAS 4.3 (SAS Institute, Inc., Cary, NC, USA), both running in Microsoft Windows.

## 3. Results

### 3.1. Study characteristics

Five randomized placebo-controlled trials comprising a total of 1413 patients were eligible for inclusion (Table 1). In the first published study of its kind, Kaneko et al. randomized 78 patients undergoing gastrointestinal surgery to placebo or haloperidol 5 mg iv each night for five nights. During the study period, 10.5% of the experimental arm became delirious compared to 32.5% in the placebo group ($P<.05$), and no significant adverse events were reported [31].

Kalisvaart et al. randomized patients to placebo or haloperidol 1.5 mg daily prior to and following hip surgery. Among the 430 participants, all of whom were over the age of 70, the impact of haloperidol on delirium incidence was nonsignificant when compared to placebo (15.1% versus 16.5%; RR: 0.91; 95% CI: 0.6, 1.3), though the authors concluded that the intervention did reduce length of hospital stay (17.1 versus 22.6 days; $P<.001$) as well as the severity [peak Delirium Rating Scale (DRS-R-98) score 14.4 versus 18.4; $P<.001$] and duration (5.4 versus 11.8; $P<.001$) of delirium [32].

Prakanrattana et al. studied the potential benefit of a single dose of risperidone 1 mg po (oral disintegrating form) given immediately