Prophylactic Antipsychotic Use for Postoperative Delirium: A Systematic Review and Meta-Analysis

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ABSTRACT

Objective: Although antipsychotics have been used empirically to prevent the development of postoperative delirium, there has been no confirming evidence to support their use. Thus, we conducted a systematic review and a meta-analysis to elucidate their efficacy and tolerability in surgical patients.

Data Sources: MEDLINE, EMBASE, the Cochrane Library databases, CINAHL, and PsycINFO were searched up to February 2013 without language restrictions, using the following keywords: (*antipsychotics* OR [nonproprietary name of each antipsychotic medication, separated by OR]) AND *delirium* AND (*randomized* OR *random* OR *randomly*).

Study Selection: Randomized controlled trials comparing prophylactic use of antipsychotics with placebo in surgical patients were included.

Data Extraction: Two authors extracted and scrutinized the data. The risk ratio (RR), 95% confidence interval (CI), number needed to treat (NNT), and standardized mean difference were used.

Results: Six studies (3 haloperidol, 1 olanzapine, and 2 risperidone) including 1,689 surgical patients were identified. The results showed significant efficacy in reducing the occurrence of delirium (RR = 0.50, 95% CI = 0.34 to 0.73, $P = .0003$; NNT = 7, $P = .001$, 6 studies). Sensitivity analysis showed that second-generation antipsychotics were superior to placebo (RR = 0.36, $P < .00001$; NNT = 4, $P < .00001$), whereas haloperidol failed to show superiority to placebo. There were no statistically significant differences between groups in severity of delirium, discontinuation rate, or rates of several adverse events.

Conclusions: Our results suggest that second-generation antipsychotics are more beneficial than placebo for preventing the incidence of delirium. Among patients who do develop delirium, the severity of delirium is not reduced in those who received prophylactic antipsychotics.

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Delirium, defined by the acute onset of fluctuating cognitive impairment and a disturbance of consciousness (*Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision [*DSM-IV-TR*]), commonly occurs in acutely ill hospitalized patients. The occurrence rate of delirium varies between 11% and 42% in medically ill patients[1] and is higher in postoperative elderly patients.[2–4] This rate increases up to 70%–87% in postoperative elderly patients who require intensive care unit (ICU) stays.[5,6] Postoperative delirium is a poor prognostic sign that leads to a cascade of postoperative complications and subsequent prolonged hospital stays, impaired functional recovery, and higher mortality rates.[7,8] Given the lack of evidence supporting antipsychotics and other medications for the treatment of patients with delirium,[9,10] prevention of delirium is undoubtedly desirable in acute hospital settings.

Although nonpharmacologic interventions focusing on risk factors for delirium, such as sleep deprivation, cognitive impairment, immobility, sensory impairment, nutrition, and dehydration, have resulted in significant reduction in the incidence of delirium,[11,12] the role of pharmacologic intervention for prevention of delirium is unclear. Further, the administration of pharmacologic agents to prevent postoperative delirium has not been included in most practice guidelines.[13] A previous randomized controlled trial (RCT) comparing prophylactic use of haloperidol with placebo in patients undergoing orthopedic surgery failed to show efficacy in reducing incidence of delirium, although haloperidol was significantly superior to placebo in reducing duration of delirium, severity of delirium, and length of hospital stay.[14] More recent trials including haloperidol and second-generation antipsychotics (SGAs), however, report the superiority of these medications in the prevention of delirium in surgical patients.[15–18] A meta-analysis has been considered to resolve these discrepant results by aggregating the data from the individual studies. Moreover, a meta-analysis produces a weighted summary result, with more weight given to larger studies. Combining results from more than 1 study has the advantage of increasing statistical power, which is often inadequate in studies with a small sample size.[19] Accordingly, the objectives of this meta-analysis were (1) to determine whether prophylactic antipsychotic use reduces incidence of delirium and (2) to evaluate how prophylactic antipsychotic use affects severity of delirium and other outcomes should delirium occur.

METHOD

This meta-analysis was performed according to the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009.

Inclusion Criteria and Search Strategy, Data Extraction, and Outcomes

Studies were included in our meta-analysis if they were randomized, placebo-controlled clinical trials comparing prophylactic use of antipsychotic medication with placebo or another antipsychotic

Clinical Points

- Prevention of postoperative delirium is desirable in surgical patients due to its contribution to prolonged hospital stays, impaired functional recovery, and higher mortality rates.
- Meta-analysis of pooled antipsychotics showed significant reduction in the incidence of delirium in comparison to placebo. Individually, although second-generation antipsychotics were superior to placebo on this outcome, haloperidol was not.
- Both individually and pooled together, prophylactic antipsychotics did not differ from placebo regarding severity of delirium, duration of delirium, or length of hospital or intensive care unit stay.

medication in adult patients (aged >18 years) with no delirium at the time of administration of trial medication. Studies involving substance-induced/withdrawal delirium were excluded. To identify relevant studies, we searched MEDLINE, the Cochrane Library databases, CINAHL, EMBASE, and PsycINFO citations up to February 2013 using the following keywords: (*antipsychotics* OR *aripiprazole* OR *amisulpride* OR *asenapine* OR *blonanserin* OR *clozapine* OR *iloperidone* OR *lurasidone* OR *olanzapine* OR *paliperidone* OR *risperidone* OR *sulpiride* OR *ziprasidone* OR *zotepine* OR *chlorpromazine* OR *clotiapine* OR *droperidol* OR *haloperidol* OR *loxapine* OR *mosapramine* OR *mesoridazine* OR *molindone* OR *fluphenazine* OR *flupenthixol* OR *pimozide* OR *perospirone* OR *perphenazine* OR *prochloperazine* OR *tiapride* OR *thioridazine* OR *thiothixene* OR *trifluoperazine* OR *zuclopenthixol*) AND *delirium* AND (*randomized* OR *random* OR *randomly*). Both authors scrutinized the inclusion and exclusion criteria of the identified studies. The references of included articles and review articles in this area were also searched for citations of further relevant published and unpublished research. When data required for the meta-analysis were missing, we contacted the corresponding authors to acquire unpublished information. Both authors independently extracted, checked, and entered the data into Review Manager (RevMan) for Windows, version 5.1 (Nordic Cochrane Centre, Cochrane Collaboration; Copenhagen, Denmark).

Data Synthesis and Statistical Analysis

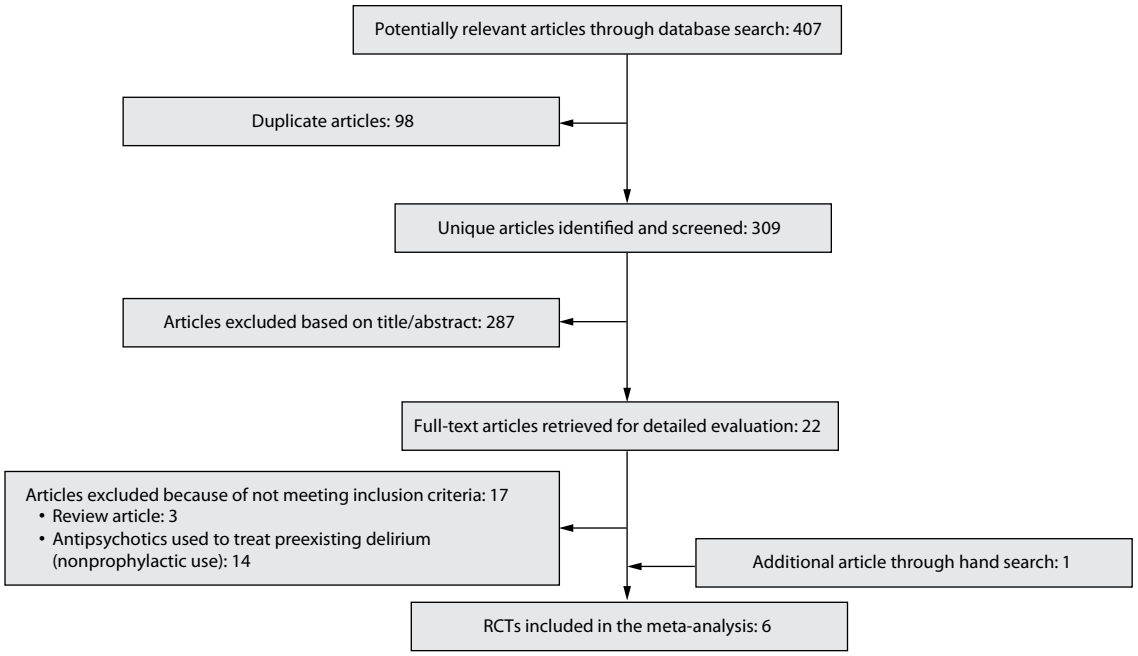
To perform a meta-analysis, we required at least 3 studies with the same outcome measure. The primary outcome measure was incidence of delirium. The secondary outcome measures were as follows: duration of delirium, length of ICU stay, length of hospital stay, and severity of delirium, as measured using highest scores of Delirium Rating Scale-Revised-98 and Intensive Care Delirium Screening Checklist. Further secondary outcome measures included adverse effects, discontinuation due to all causes, and discontinuation due to adverse effects. We based the analyses on intention-to-treat (ITT) or modified ITT data (ie, at least 1 dose or at least 1 follow-up assessment). If such data were unavailable, completer analysis data were extracted in order to include more data in the meta-analysis (Supplementary eTable 1). To combine studies, the random-effects model by DerSimonian and Laird[20] was used in all cases because subjects in this meta-analytic study tended to be heterogeneous and because methodological differences across studies could generate effect size differences. Since it was considered likely a priori that not all trials would produce exactly equal underlying effect sizes, a random-effects model was considered preferable to a fixed-effects model. The random-effects model incorporates both within-study and between-study variance into the estimate of average treatment effects and is therefore usually more realistic and conservative than the fixed-effects model. For dichotomous outcomes, the relative risk (RR) was estimated along with its 95% confidence interval (CI), whereas for continuous outcomes standardized mean difference (SMD) was used, combining the effect size data (Hedges *g*). A *P* value (from a directional zero-effect test) of .05 or less was considered statistically significant. When the random-effects model showed significant differences between groups, the number needed to treat (NNT) was calculated. NNT values were derived from the risk differences using the following formula: NNT = 1/risk difference, with the 95% CIs of the NNTs being the inverse of the upper and lower limits of the 95% CIs of the risk differences. We explored study heterogeneity using the Cochran *Q* statistic or the I^2 statistic, a measure estimating how much of the variance is explained by study heterogeneity.[21] In cases of I^2 values ≥50% for primary outcomes, we planned to conduct sensitivity analyses to determine the reasons for heterogeneity. Finally, funnel plots were constructed in RevMan for the primary outcome and visually inspected to assess for publication bias.

RESULTS

Study Characteristics

The computerized search yielded 309 references after 98 duplicates were removed. We excluded 287 studies on the basis of title and abstract review because they were neither a study of antipsychotics for delirium nor an RCT. Of the remaining 22 studies, 17 additional articles were excluded after full-text review because 3 were review articles and 14 were RCTs comparing antipsychotics with placebo or active medications in patients with delirium, yielding 5 eligible studies. One additional publication[22] was identified through hand-searching all review articles. In total, we included 6 RCTs comparing prophylactic antipsychotic use with placebo for 1,689 surgical patients[14–18,22] (Figure 1). These studies evaluated 3 antipsychotic medications (3 haloperidol studies,[14,17,22] 1 olanzapine study,[16] and 2 risperidone studies[15,18]) in 4 types of operations (2 cardiac surgeries,[15,18] 2 orthopedic surgeries,[14,16] 1 gastrointestinal surgery,[22] and 1 noncardiac surgery[17]). Among the studies included, 3 studies[15,17,18] were conducted in ICU settings. One study[22] was a nonblind, placebo-controlled RCT, and the remaining 5 studies[14–18] were double-blind, placebo-controlled RCTs. Included studies were conducted in China,[17] Egypt,[18] Japan,[22] Netherlands,[14] Thailand,[15] and the United States,[16] and all studies were published in English. None of the studies were

Figure 1. Included and Excluded Studies Flowchart



Abbreviation: RCT = randomized controlled trial.

industry-sponsored. Sample sizes varied from 80 to 495 subjects. The mean age of the study population ranged from 61.0 to 79.1 years. The duration of prophylactic antipsychotic administration was variable in each study. Only 1 study[22] reported premorbid cognitive impairment, in 7.7% of subjects. In 1 study,[18] all participants were diagnosed with subsyndromal delirium, a clinical phase with some but not all symptoms of delirium, prior to randomization. Regarding the primary outcome measure, 5 of 6 studies (2 haloperidol studies, 1 olanzapine study, 2 risperidone studies) reported the effectiveness of experimental medications in comparison to placebo.[15–18,22] Three studies[14,18,22] reported the switch to standard treatment (ie, haloperidol and/or lorazepam as needed for both treatment arms) when patients developed delirium during trials. In the other 2 studies,[16,17] blind treatment was continued and standard treatment was added if patients with delirium became agitated (these unpublished data were obtained via direct contact with authors of each study). A summary of included studies is shown in Table 1.

Incidence of Delirium

Six RCTs compared antipsychotics including haloperidol,[14,17,22] olanzapine,[16] and risperidone[15,18] with placebo with regard to incidence of delirium. Data from these studies indicated that prophylactic antipsychotic use was significantly effective in reducing incidence of delirium compared with placebo (RR = 0.50, 95% CI = 0.34 to 0.73, $P = .0003$; $I^2 = 64\%$, NNT = 7, $P = .001$; 6 studies, n = 1,594) (Figure 2). When individual antipsychotic medications were analyzed separately, olanzapine and risperidone were superior to placebo in preventing the incidence of delirium (olanzapine: RR = 0.36, 95% CI = 0.24 to 0.52, $P < .00001$; NNT = 4, $P < .00001$; 1 study, n = 400, risperidone: RR = 0.38, 95% CI = 0.22 to 0.66, $P = .0006$; NNT = 5, $P = .0001$; 2 studies, n = 227), whereas there was no significant difference between haloperidol and placebo (RR = 0.68, $P = .08$, $I^2 = 50\%$; 3 studies, n = 967) (Figure 2). No publication bias was apparent (Supplementary eFigure 1).

To determine the reason for significant heterogeneity in primary outcome measure between both treatment groups, we conducted sensitivity analyses (Table 2), summarized below.

Study design. Excluding the nonblind RCT[22] did not alter the results.

First- vs second-generation antipsychotics. When studies of first-generation antipsychotic (FGA) medication (ie, haloperidol[14,17,22]) were excluded, SGAs (olanzapine[16] and risperidone[15,18]) were superior to placebo with no significant heterogeneity (RR = 0.36, $P < .00001$, $I^2 = 0\%$, NNT = 4).

Subsyndromal delirium. Excluding the study that included patients with subsyndromal delirium did not alter the results.

Operation type. In studies with cardiopulmonary surgeries,[15,18] prophylactic antipsychotic use was significantly more efficacious than placebo on the primary outcome measure with no heterogeneity (RR = 0.38, $P = .0001$, $I^2 = 0\%$, NNT = 5). In studies with orthopedic surgeries,[14,16] no significant difference was observed from original results.

Duration of Delirium

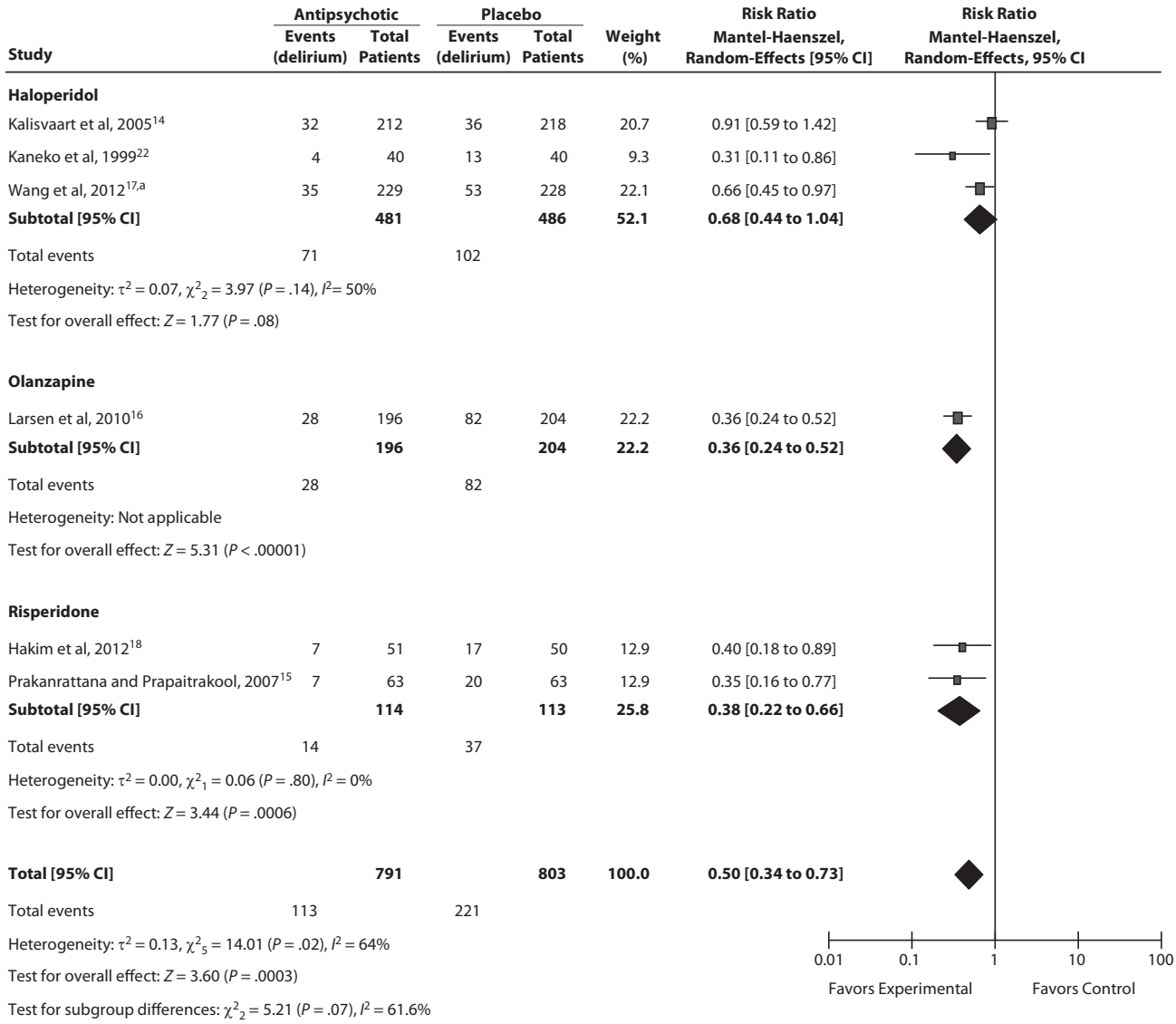
Three RCTs[14,16,18] compared antipsychotics with placebo regarding duration of delirium in postoperative patients exhibiting defined delirium. Data from these studies suggested that patients who received prophylactic antipsychotics

Table 1. Study, Patient, and Treatment Characteristics of Included Randomized Controlled Trials

Study	N	Study Design	Population	Intervention	Diagnostic Criteria	Outcome Measures[a]	Comments
Hakim et al,[18] 2012 (Egypt)	101	DBPCT parallel	Age ≥ 65 y, male: 68.3% On-pump cardiac surgery NYHA class III or IV: 62.4% MMSE score ≥ 25 ICU setting All patients had subsyndromal delirium prior to randomization	RIS: n = 51, 0.5 mg bid until incidence of delirium PLA: n = 50	ICDSC ≥ 3 every 8 h *DSM-IV-TR*	**Incidence of delirium: RIS > PLA** Duration of delirium: RIS = PLA Severity of delirium: RIS = PLA (highest score on the ICDSC) Length of ICU stay: RIS = PLA Length of hospital stay: RIS = PLA	Switched to standard treatment (RIS up to 4 mg/d and HAL as needed)
Kalisvaart et al,[14] 2005 (Netherlands)	430	DBPCT parallel	Mean age = 79.1 y, male: 20.2% Orthopedic (hip) surgery APACHE II mean score = 13.4 MMSE mean score = 24.7 Non-ICU setting	HAL: n = 212, 0.5 mg tid until postoperative day 3 PLA: n = 218	*DSM-IV-TR* CAM	**Incidence of delirium: HAL = PLA** Duration of delirium: HAL > PLA Severity of delirium: HAL > PLA (maximum DRS-R-98 score) Length of hospital stay: HAL > PLA	Switched to standard treatment (HAL and/or lorazepam) when delirium was diagnosed
Kaneko et al,[22] 1999 (Japan)	80	Nonblind parallel	Mean age = 72.8 y, male: 64.1% Gastrointestinal surgery Cognitive impairment: 7.7% Non-ICU setting	HAL: n = 40, 5 mg IV until postoperative day 5 PLA (normal saline): n = 40	*DSM-III-R*	**Incidence of delirium: HAL > PLA**	Switched to standard treatment (HAL and/or lorazepam) when delirium was diagnosed
Larsen et al,[16] 2010 (United States)	495	DBPCT parallel	Mean age = 73.7 y, male: 45.7% Orthopedic surgery (knee and hip joint replacement) ASA class ≥ 3: 42.0% No dementia Non-ICU setting	OLA: n = 243, 5 mg twice perioperative administration PLA: n = 252	*DSM-III-R* MMSE DRS-R-98 CAM	**Incidence of delirium: OLA > PLA** Time to onset of delirium: OLA > PLA Duration of delirium: OLA < PLA Severity of delirium: OLA < PLA (maximum DRS-R-98 score) Length of hospital stay: OLA = PLA	Continued blind treatment and additional standard treatment (nonpharmacologic and/or HAL/OLA as needed) when delirium was diagnosed
Prakanrattana and Prapaitrakool,[15] 2007 (Thailand)	126	DBPCT parallel	Mean age = 61.0 y, male: 58.7% On-pump cardiac surgery NYHA class III or IV: 33.3% ICU setting	RIS: n = 63, 1 mg when regained consciousness from surgery PLA: n = 63	CAM-ICU	**Incidence of delirium: RIS > PLA** Length of ICU stay: RIS > PLA Length of hospital stay: RIS = PLA	
Wang et al,[17] 2012 (China)	457	DBPCT parallel	Mean age = 74.2 y, male: 63.0% Noncardiac surgery ASA class ≥ 3: 38.7% ICU setting	HAL: n = 229, 0.5 mg IV within 1 h after enrollment, followed by 0.1 mg/h for 12 h PLA: n = 228	Richmond Agitation Sedation Scale CAM-ICU	**Incidence of delirium: HAL > PLA** Time to onset of delirium: HAL = PLA Length of ICU stay: HAL > PLA Length of hospital stay: HAL = PLA	Continued blind treatment and additional standard treatment (nonpharmacologic and/or IV HAL 0.5–1.0 mg every 20 min) when delirium was diagnosed

[a]In Outcome Measures column, boldface indicates primary outcome measure of each study, ">" indicates superiority of experimental drug to placebo, and "=" indicates no significant difference between 2 groups.
Abbreviations: APACHE II = Acute Physiology and Chronic Health Evaluation II, ASA = American Society of Anesthesiology, CAM = Confusion Assessment Method, DBPCT = double-blind, placebo-controlled trial, DRS-R-98 = Delirium Rating Scale-Revised-98, HAL = haloperidol, ICDSD = Intensive Care Delirium Screening Checklist, ICU = intensive care unit, IV = intravenous, MMSE = Mini-Mental State Examination, NYHA = New York Heart Association, OLA = olanzapine, PLA = placebo, RASS = Richmond Agitation Sedation Scale, RIS = risperidone.

Figure 2. Incidence of Delirium



[a]Injectable haloperidol.
Abbreviations: CI = confidence interval, HAL = haloperidol, OLA = olanzapine, RIS = risperidone.

showed no significant reduction in duration of delirium as compared with patients who received placebo (SMD = −0.18, 95% CI = −1.06 to 0.71, $P = .70$, $I^2 = 92\%$; 3 studies, n = 279) (Supplementary eFigure 2). When each antipsychotic medication was compared with placebo separately, however, haloperidol[14] showed a significant difference in shortening duration of delirium compared with placebo (SMD = −0.99, 95% CI = −1.49 to −0.48, $P = .0001$; 1 study, n = 68). Moreover, olanzapine[16] was inferior to placebo on this outcome measure (SMD = 0.67, 95% CI = 0.23 to 1.11, $P = .003$; 1 study, n = 110). Risperidone[18] showed no significant difference compared to placebo on this outcome measure (SMD = −0.23, 95% CI = −0.62 to 0.16, $P = .25$; 1 study, n = 101).

Severity of Delirium

Three RCTs[14,16,18] comparing antipsychotics with placebo indicated no significant reduction of severity of delirium in patients who received prophylactic antipsychotics as compared with patients who received placebo (SMD = 0.07, 95% CI = −0.90 to 1.04, $P = .88$, $I^2 = 93\%$; 3 studies, n = 280) (Supplementary eFigure 3). When an individual antipsychotic medication was compared with placebo, however, haloperidol[14] was superior to placebo (SMD = −1.00, 95% CI = −1.51 to −0.50, $P = .0001$; 1 study, n = 68), whereas olanzapine[16] and risperidone[18] were inferior to placebo (olanzapine: SMD = 0.63, 95% CI = 0.20 to 1.07, $P = .005$; 1 study, n = 110, risperidone: SMD = 0.56, 95% CI = 0.16 to 0.95, $P = .006$; 1 study, n = 101).

Length of Stay (hospital stay and ICU stay)

Data from 5 RCTs[14–18] showed no significant difference between antipsychotics and placebo in length of hospital stay (SMD = −0.09, 95% CI = −0.28 to 0.10, $P = .37$, $I^2 = 37\%$; 5 studies, n = 862). Additionally, none of the antipsychotic

Table 2. Sensitivity Analyses of Incidence of Delirium

Variable	No. of Studies	N	RR	95% CI	P^a	I^2 (%)	RD	95% CI	NNT	95% CI	P^a	I^2 (%)
Total	6	1,594	0.50	0.34 to 0.37	**.0003**	64	−0.15	−0.25 to −0.06	7	4 to 17	**.001**	80
Antipsychotic												
Second-generation	3	627	0.36	0.26 to 0.50	**<.00001**	0	−0.24	−0.30 to −0.17	4	4 to 6	**<.00001**	0
First-generation	3	967	0.68	0.44 to 1.04	.08	50	…	…	…	…	…	…
Drug formulation												
Oral	5	1,137	0.45	0.28 to 0.73	**.001**	67	−0.18	−0.30 to −0.05	6	4 to 20	**.005**	83
Injection	1	457	0.66	0.45 to 0.97	**.03**	NA	−0.08	−0.15 to −0.01	13	7 to 100	**.03**	NA
Study design												
Double-blind	5	1,514	0.52	0.35 to 0.78	**.002**	69	−0.14	−0.25 to −0.04	7	4 to 25	**.006**	83
Others	1	80	0.31	0.11 to 0.86	**.03**	NA	−0.23	−0.40 to −0.05	4	3 to 20	**.01**	NA
Year												
2001 or after	5	1,514	0.52	0.35 to 0.78	**.002**	69	−0.14	−0.25 to −0.04	7	4 to 25	**.006**	83
Before 2001	1	80	0.31	0.11 to 0.86	**.03**	NA	−0.23	−0.40 to −0.05	4	3 to 20	**.01**	NA
Control												
Placebo	5	1,514	0.52	0.35 to 0.78	**.002**	69	−0.14	−0.25 to −0.04	7	4 to 25	**.006**	83
Nonplacebo	1	80	0.31	0.11 to 0.86	**.03**	NA	−0.23	−0.40 to −0.05	4	3 to 20	**.01**	NA
Subsyndromal delirium prior to randomization												
Yes	1	101	0.40	0.18 to 0.89	**.02**	NA	−0.20	−0.36 to −0.04	5	3 to 25	**.01**	NA
No	5	1,493	0.51	0.33 to 0.78	**.002**	70	−0.15	−0.25 to −0.04	7	4 to 25	**.006**	83
Setting												
ICU	3	684	0.52	0.34 to 0.77	**.001**	25	−0.14	−0.24 to −0.05	7	5 to 20	**.003**	46
Non-ICU	3	910	0.49	0.23 to 1.03	.06	82	…	…	…	…	…	…
Operation type, analysis 1												
Cardiopulmonary	2	227	0.38	0.22 to 0.66	**.0001**	0	−0.20	−0.31 to −0.10	5	3 to 10	**.0001**	0
Others	4	1,367	0.54	0.33 to 0.89	**.01**	76	−0.14	−0.26 to −0.02	7	4 to 50	**.03**	87
Operation type, analysis 2												
Orthopedic	2	830	0.57	0.22 to 1.43	.23	90	…	…	…	…	…	…
Others	4	764	0.49	0.33 to 0.71	**.0002**	21	−0.16	−0.24 to −0.07	6	5 to 15	**.0002**	40

[a]Boldface indicates significance.
Abbreviations: ICU = intensive care unit, NA = not applicable, NNT = number needed to treat, RD = risk difference, RR = relative risk.

medications, when analyzed individually, was superior to placebo on this outcome measure. With regard to length of ICU stay, an aggregated report of 3 studies[15,17,18] showed no significant difference between antipsychotics and placebo (SMD = −0.01, 95% CI = −0.16 to 0.14, $P = .94$, $I^2 = 0\%$; 3 studies, n = 684). No individual antipsychotic medication was superior to placebo on this outcome measure.

Safety Measures: Discontinuation and Adverse Events

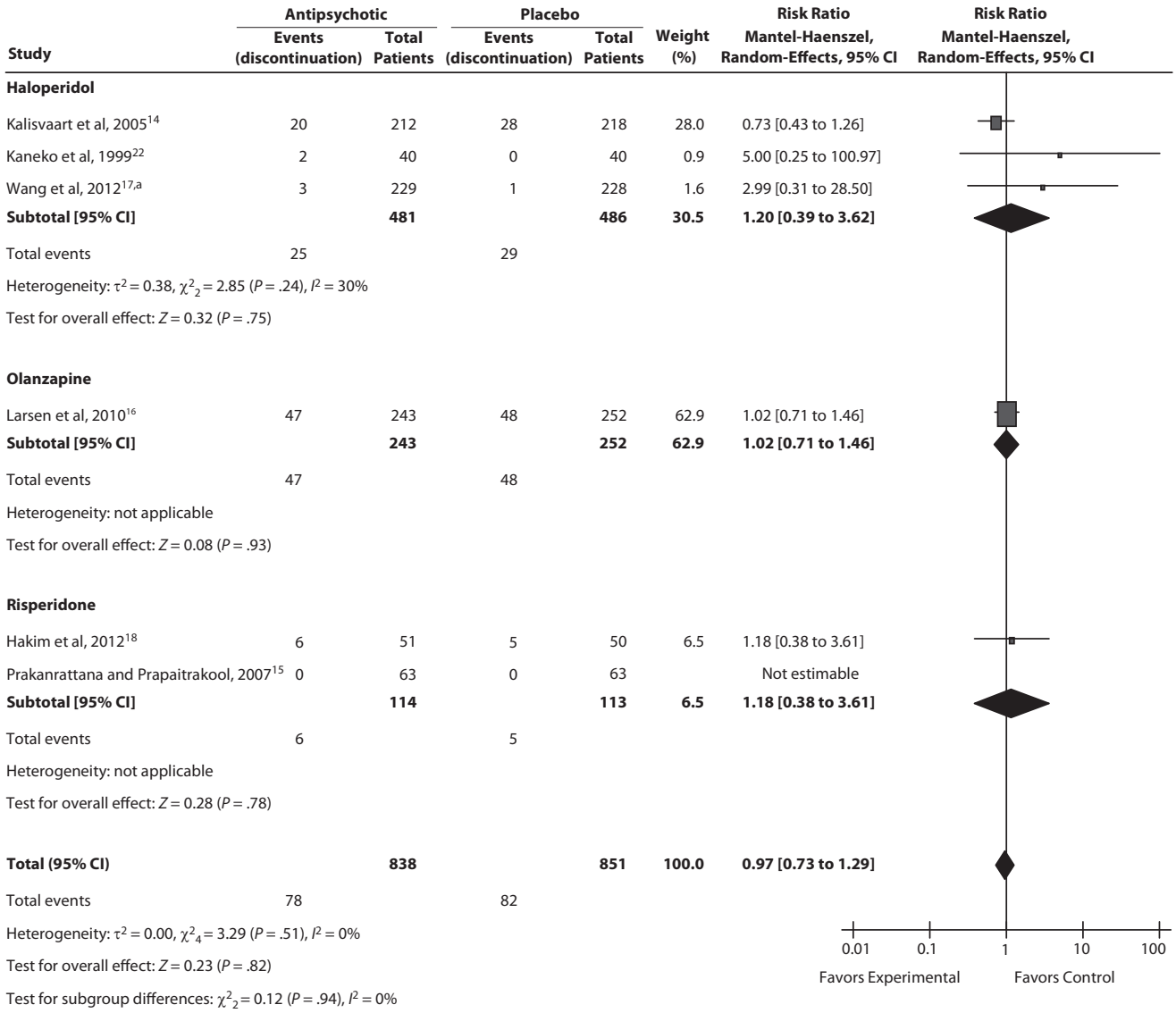
Patients who received prophylactic antipsychotics did not have a significantly higher rate of discontinuation either due to all causes (RR = 0.97, 95% CI = 0.73 to 1.29, $P = .82$, $I^2 = 0\%$; 6 studies,[14–18,22] n = 1,689) (Figure 3) or due to adverse effects (RR = 0.79, 95% CI = 0.26 to 2.33, $P = .66$, $I^2 = 25\%$; 5 studies,[14,15,17,18,22] n = 1,194) as compared with patients treated with placebo. For 2 of the adverse effects examined in this meta-analysis, no significant differences were observed: arrhythmia (RR = 1.45, 95% CI = 0.53 to 3.94, $P = .47$, $I^2 = 0\%$; 4 studies,[14,16,17,22] n = 1,365) and extrapyramidal symptoms (RR = 1.96, 95% CI = 0.18 to 20.94, $P = .58$, I^2 = not applicable; 5 studies,[14,15,17,18,22] n = 1,192). No significant differences in the frequency of these side effects were found between individual antipsychotics and placebo.

DISCUSSION

In this study, we have established that prophylactic antipsychotic use reduces the incidence of postoperative delirium in surgical patients. The effect was more robust when comparing SGAs with placebo (NNT = 4, 95% CI = 4 to 6, $P < .00001$) than when comparing pooled antipsychotic medications with placebo (NNT = 7, 95% CI = 4 to 17, $P = .001$). On the other hand, our results showed that haloperidol had no beneficial effect in preventing delirium. Given the results of our meta-analyses, SGAs may be beneficial for preventing postoperative delirium in surgical patients, although the adequate amount of caution and monitoring of side effects are necessary. When comparing the receptor-binding profile of trial medications, haloperidol mainly blocks dopamine receptors and has little affinity for serotonergic, muscarinic, cholinergic, or histaminergic receptors, whereas SGAs including olanzapine and risperidone show higher affinity for serotonin (5-HT) receptors than dopamine receptors.[23–25] Serotonin has been known to play an important role in altering the sleep and wakefulness pattern.[26] Moreover, there has been a hypothesis that decreased slow-wave sleep contributes to the development of delirium, although the cause-effect relationship has not been completely understood.[27] Recently, several animal studies reported that administering 5-HT_{2A} antagonists to laboratory animals decreased their wakefulness and increased their slow-wave sleep.[28,29] Taken together, it is worth suggesting that SGAs are superior to FGAs in preventing delirium through their affinities for 5-HT_{2A} receptors, which cause beneficial effects on sleep and wakefulness patterns in postoperative patients.

Olanzapine is considered to have a complex multireceptor-binding profile, including receptors for dopamine, serotonin, epinephrine, histamine, and acetylcholine.[30]

Figure 3. Discontinuation due to All Causes



[a]Injectable haloperidol.
Abbreviations: CI = confidence interval, HAL = haloperidol, OLA = olanzapine, RIS = risperidone.

Using olanzapine, which blocks the muscarinic cholinergic receptor, seems paradoxical in light of the acetylcholine deficiency hypothesis for the development of delirium,[31] although this medication undoubtedly reduced the incidence of delirium in Larsen and coworkers' trial.[16] Collectively, the imbalance between several neurotransmitters is more explanatory of the pathophysiology that contributes to the development of delirium[32] than only decreased acetylcholine and elevated dopamine concentrations. Furthermore, the negative results of prophylactic use of cholinesterase inhibitors including donepezil and rivastigmine support this concept.[33,34] In view of this pathophysiology of delirium, other SGAs with complex receptor-binding profiles, such as quetiapine, can become possible alternative prophylactic antipsychotic treatments, although further research is required. Future research comparing FGAs with SGAs and comparing different SGAs in the prevention of delirium is also desirable given the variety of receptor-binding profiles per antipsychotic medication.

Dosage of each study medication could be a potential key factor that influenced the results of our study. Oral haloperidol 1.5 mg/d (0.5 mg 3 times per day) was not effective in preventing delirium in comparison to placebo in Kalisvaart and colleagues' study.[14] Although the low doses of experimental medication may have contributed to the negative results of this study in prevention of postoperative delirium, more RCTs are needed to determine this relationship given the fact that Hakim et al[18] showed superiority of risperidone 0.5 mg twice a day (equivalent to oral haloperidol 1.4 mg/d based on formulas by Andreasen et al[35]) to placebo on this outcome measure.

Moreover, antipsychotics were superior to placebo in preventing postoperative delirium in patients undergoing cardiopulmonary surgery[15,18] but not in patients undergoing

orthopedic surgery.[14,16] This discrepancy may be attributed to the results of our meta-analysis of individual antipsychotics (Figure 2). Haloperidol, which failed to show superiority to placebo in preventing delirium, was used in 1[14] of the 2 studies[14,16] involving orthopedic patients (olanzapine was used in the other study). On the other hand, risperidone, which showed significant efficacy in the prevention of delirium, was used in the 2 studies involving cardiopulmonary surgery.[15,18]

Our results do not support the assumption that prophylactic use of antipsychotic medication positively affects severity of delirium and other outcomes, such as duration of delirium, length of ICU stay, and length of hospital stay. These results, however, should be interpreted with a careful consideration of differences in treatments that participants received when they developed delirium in the included studies. For example, in Kalisvaart and colleagues' study,[14] in which all patients received standard treatment (haloperidol and/or lorazepam as needed) when they developed delirium, regardless of their study group, outcome measures such as duration of delirium and severity of delirium were superior in patients who had received prophylactic haloperidol compared to patients who received placebo. However, Hakim and colleagues' study,[18] in which both groups of patients received standard treatment after they developed delirium, was not consistent with Kalisvaart and colleagues' study[14] with regard to delirium severity. Moreover, in the study by Larsen et al,[16] in which patients continued blind treatment and as-needed standard treatment (nonpharmacologic intervention and haloperidol or olanzapine), the results of patients who received prophylactic olanzapine were inferior to those of patients treated with placebo on these outcome measures. Furthermore, 2[14,16] of 3 studies used delirium duration data based on the completer analysis. Given the fact that the efficacy of antipsychotics in the treatment of delirium lacks extensive evidence, further research using similar methodology is required to elucidate how prophylactic antipsychotic use affects severity of delirium and length of hospital stay, which contribute substantially to cost of health care as well.

Further, our results show no significant differences between antipsychotics and placebo in either discontinuation rates or adverse effects. These findings are probably due to the low-dose and short-term use of each antipsychotic medication. It is notable that low-dose and short-term use of prophylactic antipsychotic medications showed significant reduction in the incidence of delirium in comparison to placebo in all studies except the study by Kalisvaart et al,[14] in which each participant received prophylactic haloperidol 0.5 mg 3 times per day. Higher dosage of antipsychotics, especially first-generation antipsychotics, is not desirable in light of the increased risks of extrapyramidal symptoms and QT interval prolongation.[36,37]

Our meta-analysis does not include mortality rates due to the paucity of available data. Although only 1 study[22] reported premorbid cognitive impairment, in 7.7% of participants, in our meta-analysis delirium is frequently superimposed in patients with dementia in clinical settings.[38] Caution is required when administering antipsychotics to these populations given the US Food and Drug Administration black-box warning that atypical antipsychotics potentially increase the risk of sudden death in elderly patients with dementia.[39] Additionally, a recent meta-analysis regarding atypical antipsychotic medications for off-label uses reported that olanzapine and risperidone significantly increased the risk of cardiovascular events in comparison to placebo in elderly patients with dementia.[40,41]

The main limitation of our study is the small number of included studies, which raises concerns regarding whether our results will affect clinical practice. Despite this limitation, however, our results are considered to have external validation because the included studies consist of relatively representative populations in clinical settings where postoperative delirium tends to become problematic. The second limitation is that this meta-analysis includes a study (Hakim et al[18]) consisting of subjects with subsyndromal delirium, which is considered a potential predisposition to delirium in several articles.[42,43] It is worth noting, however, there are currently no definitions of subsyndromal delirium in diagnostic criteria, including *DSM-IV-TR*. Furthermore, a systematic review of subsyndromal delirium in elderly people reported it as a continuum between no symptoms and delirium but failed to conclude its definite development to delirium.[44] It was therefore appropriate to include this study[18] in our meta-analysis given the current inconsistency regarding the definition and concept of subsyndromal delirium. Another limitation of this meta-analysis is that we were unable to compare the timing of administration of individual experimental medications due to heterogeneity, as described in Table 1. More research is required to elucidate the relationship between the timing of administration and efficacy as well as tolerability of prophylactic antipsychotics in surgical patients.

Drug names: aripiprazole (Abilify), asenapine (Saphris), clozapine (Clozaril, FazaClo, and others), donepezil (Aricept and others), haloperidol (Haldol and others), iloperidone (Fanapt), lorazepam (Ativan and others), loxapine (Loxitane and others), lurasidone (Latuda), molindone (Moban), olanzapine (Zyprexa), paliperidone (Invega), pimozide (Orap), quetiapine (Seroquel), risperidone (Risperdal and others), rivastigmine (Exelon and others), thiothixene (Navane and others), ziprasidone (Geodon).

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Author contributions: Dr Hirota had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Hirota. Analysis and interpretation of data, statistical analysis, acquisition of data, and drafting of the manuscript: Hirota and Kishi. Study supervision: Kishi.

Potential conflicts of interest: **Dr Kishi** declares no direct conflict of interest or grant support that is directly related to the content of the study. He has received speaker's honoraria from Astellas, Daiichi Sankyo, Dainippon Sumitomo, Eli Lilly, GlaxoSmithKline, Janssen, Meiji, Novartis, Otsuka, Pfizer, Shionogi, Mitsubishi Tanabe, and Yoshitomi. **Dr Hirota** reports no potential conflict of interest.

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Supplementary material: See accompanying pages.

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Supplementary material follows this article.

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Supplementary Material

Article Title: Prophylactic Antipsychotic Use for Postoperative Delirium: A Systematic Review and Meta-Analysis

Authors: Tomoya Hirota, MD, and Taro Kishi, MD, PhD

DOI Number: 10.4088/JCP.13r08512

List of Supplementary Material for the article

1. eTable 1 Data Synthesis
2. eFigure 1 Publication Bias for Incidence of Delirium
3. eFigure 2 Duration of Delirium
4. eFigure 3 Severity of Delirium

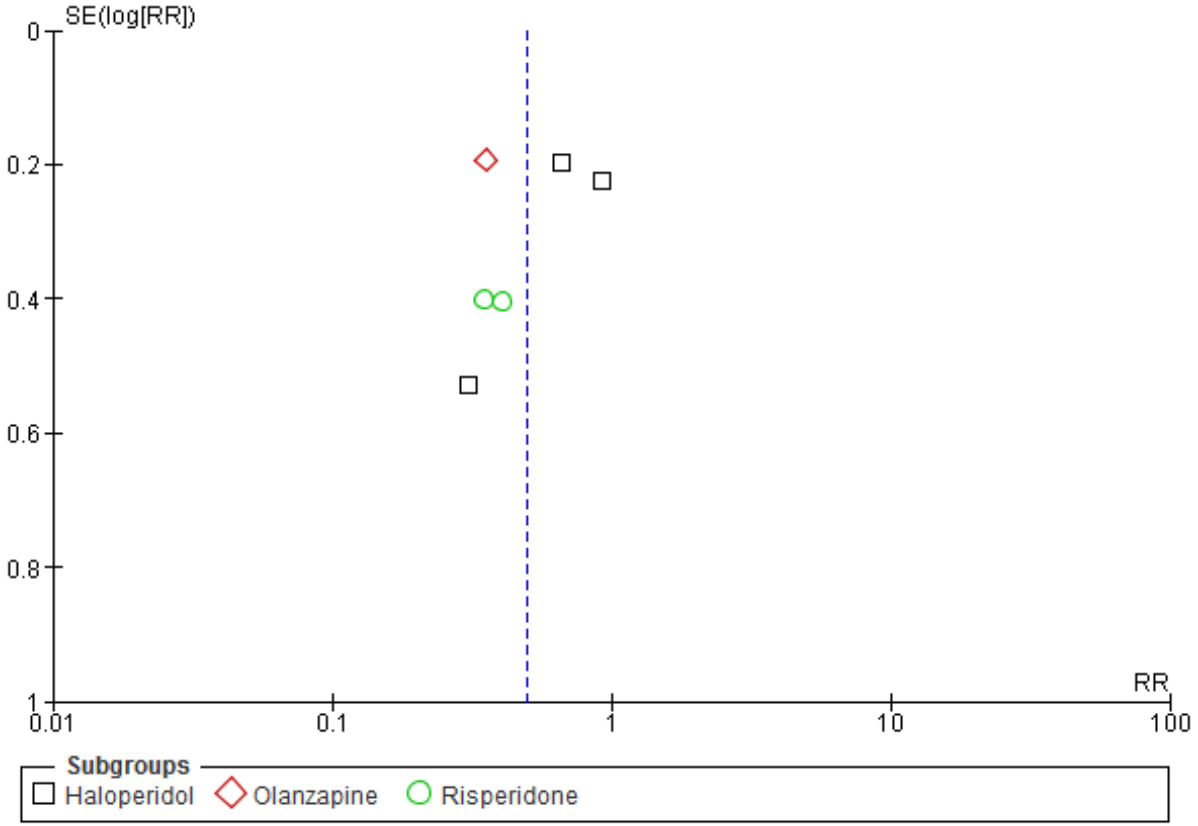
Disclaimer

	Hakim 2012	Kalisvaart 2005	Kaneko 1999	Larsen 2010	Prakanrattana 2007	Wang 2012
Incidence of delirium	✓	✓	✓	✓	✓	✓
Severity of delirium	ICDSC*	DRS-R-98 MAX		DRS-R-98 MAX		
Duration of delirium	✓	✓*		✓*		
Length of ICU stay	✓				✓	✓
Hospital days	✓	✓*		✓	✓	✓
Discontinuation due to all cause	✓	✓	✓	✓	✓	✓
Discontinuation due to side effects	✓	✓	✓		✓	✓
Arrhythmia		✓	✓	✓		✓
Extrapyramidal symptoms	✓	✓	✓		✓	✓

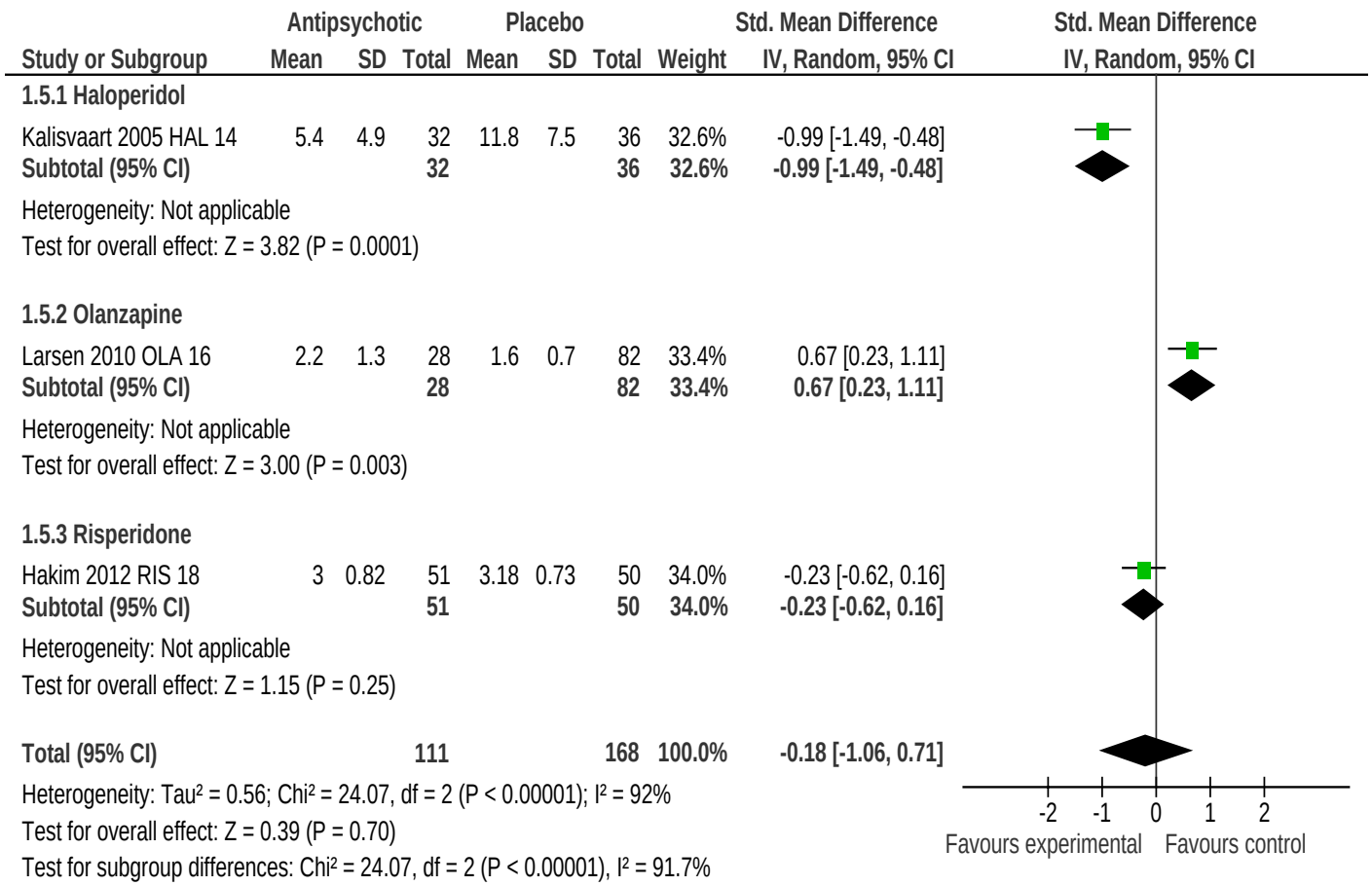
Supplementary eTable 1: Data synthesis

ICDSC: Intensive Care Delirium Screening Checklist, ICU: Intensive Care Unit, DRS-R-98 MAX:Delirium Rating Scale-Revised 98

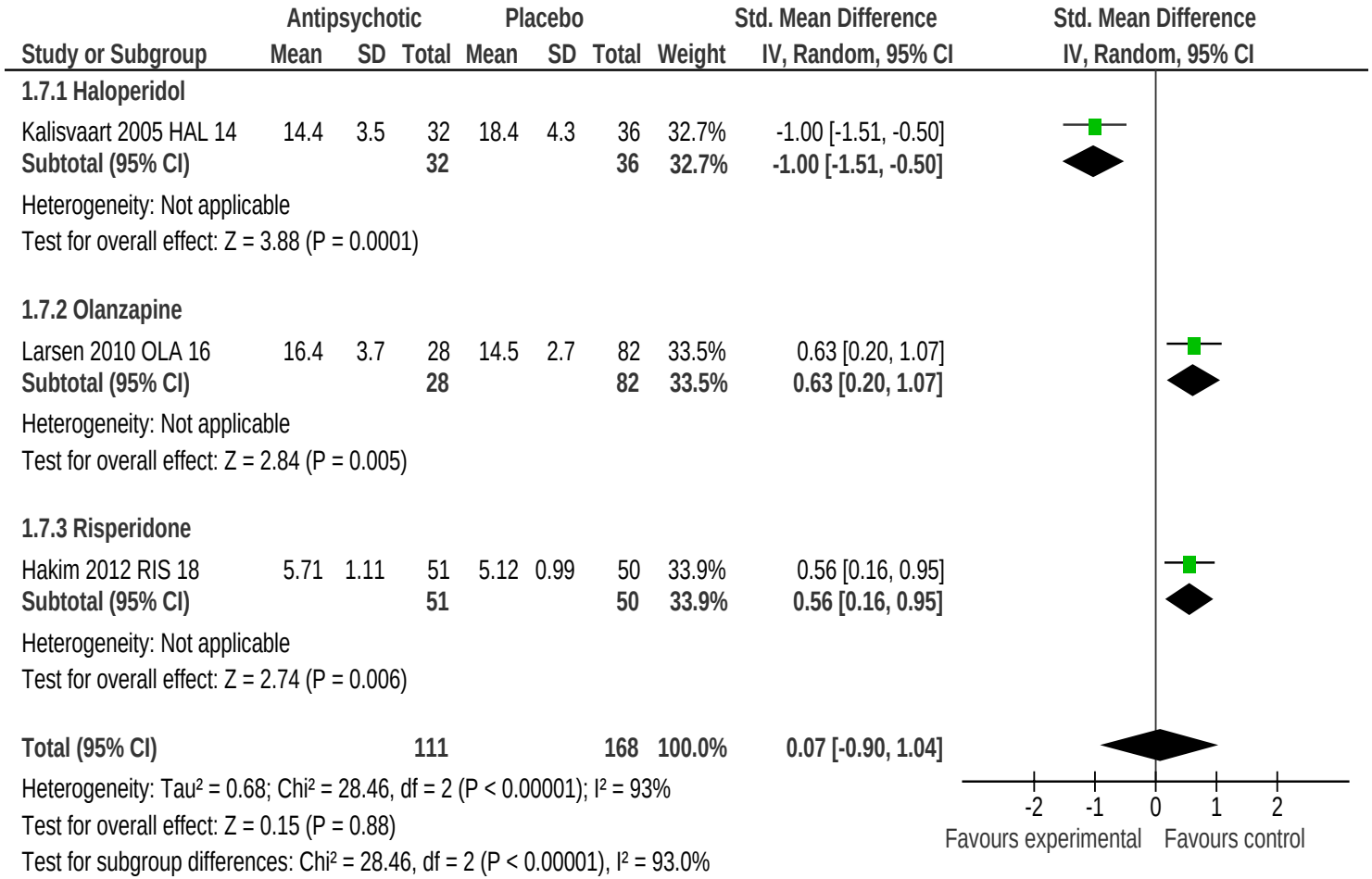
* completer analysis



Supplementary eFigure 1. Publication bias for Incidence of delirium



Supplementary eFigure 2. Duration of delirium. CI = confidence interval, HAL = haloperidol, OLA = olanzapine, RIS = risperidone



Supplementary eFigure 3. Severity of delirium. CI = confidence interval, HAL = haloperidol, OLA = olanzapine, RIS = risperidone