Antipsychotics for Primary Alcohol Dependence: A Systematic Review and Meta-Analysis of Placebo-Controlled Trials

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ABSTRACT

Objective: We sought to meta-analytically assess the utility of antipsychotics in patients with primary alcohol dependence.

Data Sources: We searched PubMed, Cochrane Library, and PsycINFO without language restrictions from database inception until December 2012, using the following keywords: (*randomized*, *random*, OR *randomly*) AND (*placebo*) AND (*alcohol dependence*) AND (*neuroleptic* OR *antipsychotic* OR *antidopaminergic* OR the names of 34 individual antipsychotics).

Study Selection: Included in this study were randomized, placebo-controlled trials of antipsychotics lasting ≥ 2 weeks in patients with primary alcohol dependence and without schizophrenia or bipolar disorder.

Data Extraction: Two independent evaluators extracted data. Standardized mean difference (SMD), risk ratio (RR), and numbers needed to harm (NNH) ± 95% confidence intervals (CIs) were calculated.

Results: Across 13 double-blind studies, 1,593 patients were randomly assigned to one of the following: amisulpride (1 study, n = 37), aripiprazole (2 studies, n = 163), flupenthixol decanoate (1 study, n = 142), olanzapine (2 studies, n = 62), quetiapine (4 studies, n = 174), tiapride (3 studies, n = 212), or placebo (13 studies, n = 803). Neither pooled nor individual antipsychotics outperformed placebo regarding relapse prevention (pooled RR = 1.05 [95% CI, 0.95 to 1.16], $P = .38$, 9 studies, n = 1,405). Antipsychotics were similar to placebo regarding heavy drinking days ($P = .15$), craving ($P = .82$), and first alcohol consumption time ($P = .94$). Placebo outperformed pooled antipsychotics regarding number or percentage of abstinent days/lack of drinking days (SMD = 0.17 [95% CI, 0.01 to 0.33], $P = .04$, 5 studies, n = 918), without significant group differences after removal of 1 outlying flupenthixol decanoate study ($P = .24$). Individually, flupenthixol decanoate (1 study, n = 281) was inferior to placebo regarding abstinence/drinking days ($P = .004$), whereas aripiprazole (1 study, n = 30) was superior regarding heavy drinking days ($P < .00001$). Antipsychotics caused greater all-cause discontinuation than placebo (RR = 1.24 [95% CI, 1.07 to 1.45], $P = .005$, NNH = 14), especially aripiprazole ($P = .01$) and flupenthixol decanoate ($P = .001$). Discontinuation due to intolerability was similar between antipsychotics and placebo ($P = .12$), but aripiprazole's risk was higher ($P = .003$). Drowsiness/sedation ($P < .0001$, NNH = 9), increased appetite ($P = .02$, NNH = 14), and dry mouth ($P < .0001$, NNH = 7) occurred more frequently with pooled antipsychotics.

Conclusions: Except for 1 isolated outcome, the studied antipsychotics did not improve abstinence or reduce drinking or craving in patients with primary alcohol dependence.

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Alcohol is the most common cause of substance abuse and dependence worldwide.[1,2] Alcohol dependence is a chronic disorder with high risk of relapses, progressive worsening, co-occurring psychiatric and neurologic disorders, and medical complications, such as liver cirrhosis, cardiovascular diseases, and cancer.[1–5] Alcohol dependence is responsible for 4% of global deaths.[3–5] In the United States, excessive alcohol consumption is associated with approximately 75,000 deaths per year and accounts for approximately 40% of all deaths related to traffic accidents.[3–5] Excessive alcohol consumption is also associated with major cost to society due to violence, lost productivity, and health care expenditure. Alcohol dependence contributes to a wide range of social problems, including family disruption and loss of work productivity.[6,7]

The treatment for alcohol dependence includes pharmacotherapy, psychotherapy, and self-help groups such as Alcoholics Anonymous, which are frequently administered in combination. Disulfiram, naltrexone, and acamprosate, but not antipsychotics, have US Food and Drug Administration (FDA) approval for the pharmacologic treatment of alcohol dependence.[8] However, antipsychotics, antidepressants, mood stabilizers, and benzodiazepines are widely utilized in real-world practice for the treatment of primary alcohol dependence, despite lacking regulatory approval for this indication.[8]

Abnormalities in dopaminergic neural transmission are strongly hypothesized to contribute to the pathophysiology of alcohol dependence through an amplification of drug-seeking and drug-taking behaviors.[9–12] The mesolimbic dopamine pathway that projects from the ventral tegmental area to a structure within the ventral striatum, the nucleus accumbens, has been implicated as a major site for the reinforcing actions of many addictive drugs including alcohol.[13–15]

For example, a neuroimaging study demonstrated a decrease in striatal dopamine type 2 receptor availability in the limbic, associative, and sensorimotor regions in alcohol dependence subjects compared with healthy controls.[16] In recent years, several randomized controlled trials (RCTs) compared antipsychotics, especially second-generation antipsychotics (SGAs), against placebo in patients with alcohol dependence.

Clinical Points

- Both individually and pooled together, antipsychotics did not differ from placebo regarding relapse prevention of alcohol dependence.
- Placebo outperformed pooled antipsychotics regarding number or percentage of abstinent days/lack of drinking days, without significant group differences after removing 1 outlying flupenthixol decanoate study.
- Antipsychotics caused greater all-cause discontinuation than placebo, especially aripiprazole and flupenthixol decanoate.

Although dopamine blockade may further decrease dopamine transmission beyond already proposed deficits, SGAs might also block the craving and reinforcing effects of alcohol in alcohol dependence and reduce symptoms that may increase drinking behaviors and relapse, such as anxiety, depression, and impulsivity.[17–19] However, efficacy results of SGAs for alcohol dependence have been mixed. While olanzapine and quetiapine were superior to placebo regarding alcohol craving in 2 trials,[20,21] other studies found no statistical differences between olanzapine or quetiapine and placebo.[22,23] Moreover, in 2 studies,[15,24] biological cue reactivity was investigated in non–help-seeking subjects. In 1 of these studies,[24] quetiapine reduced cue-induced alcohol craving following the alcohol administration session compared with placebo, while in the other study[15] aripiprazole was not superior to placebo. Two additional studies[25,26] comparing amisulpride or flupenthixol decanoate to placebo for relapse prevention after detoxification or abstinence reported a significant difference favoring placebo. Two studies[27,28] reported that tiapride was superior to placebo for relapse prevention in alcohol dependence, but another study[29] reported inferiority to placebo. Conversely, alcohol dependence patients receiving aripiprazole showed a significant reduction in Alcohol Dependence Scale scores compared to placebo.[30] In addition, quetiapine was superior to placebo in relapse prevention.[20] Reasons for these discrepant results may be related to the small sample sizes of these trials, which had less than 50 participants in each treatment arm and disparate outcome measures.

A meta-analysis can increase the statistical power for group comparisons and can overcome the limitation of sample size in conditions where larger trials are lacking.[31] Moreover, using random-effects models and standardized mean difference analyses, outcomes with different metrics can be combined. To our knowledge, no meta-analysis addressing the efficacy and effectiveness of antipsychotics in alcohol dependence has been published to date. To address this gap and synthesize the available trial evidence, we carried out a systematic review and meta-analysis of RCTs of antipsychotic monotherapy for patients with primary alcohol dependence. Given the involvement of dopamine mechanisms in the reinforcing effects of alcohol consumption and the beneficial effects of some SGAs on factors associated with alcohol use, such as anxiety, depression, and impulsivity, we hypothesized that antipsychotics would be superior to placebo in 1 or more efficacy outcomes.

METHOD

Inclusion Criteria, Search Strategy, Data Extraction, and Outcomes

We included in the meta-analysis RCTs lasting ≥ 2 weeks that investigated antipsychotics in patients with a primary diagnosis of alcohol dependence and without comorbid major psychiatric disorders (eg, schizophrenia or bipolar disorder). We searched PubMed, Cochrane Library databases, and PsycINFO from inception of the databases until December 2012 using the following keywords: (*randomized*, *random*, OR *randomly*) AND (*placebo*) AND (*alcohol dependence*) AND (*neuroleptic* OR *antipsychotic* OR *antidopaminergic* OR the names of 34 individual antipsychotics). The 34 individual antipsychotics were risperidone, olanzapine, aripiprazole, quetiapine, perospirone, ziprasidone, clozapine, amisulpride, asenapine, blonanserin, clotiapine, iloperidone, lurasidone, mosapramine, paliperidone, remoxipride, sertindole, sulpiride, tiapride, chlorpromazine, thioridazine, mesoridazine, loxapine, molindone, perphenazine, thiothixene, trifluoperazine, haloperidol, fluphenazine, droperidol, zuclopenthixol, pimozide, flupenthixol, and prochlorperazine. Since antipsychotics have a benefit for the treatment of major psychiatric disorders, such as bipolar disorder or psychotic disorders, we did not include patients with comorbid major psychiatric disorders, aiming to reveal whether antipsychotics have independent benefits for the treatment of the patients with primary alcohol dependence.[32–35] To complement the electronic search, pertinent review articles and reference lists from identified studies were hand-searched for additional studies.

Three authors (T.K., S.S., and C.U.C.) checked eligibility of the identified studies. When data required for the meta-analysis were missing or available data were significantly skewed (ie, standard deviation more than double the mean, especially frequent regarding change scores), first/corresponding authors were contacted for additional information (including endpoint scores). Two authors (T.K. and R.C.) independently extracted and entered data. To verify accuracy of the work, 2 authors (T.K. and R.C.) independently extracted and entered data. Discrepancies in the extracted data were resolved by discussion between both authors; when no consensus was reached, a third author decided (C.U.C.).

Data Synthesis and Statistical Analysis

We conducted meta-analyses of outcomes for which ≥ 3 studies contributed data. The primary efficacy outcome was "relapse" in patients who were abstinent for ≥ 1 day, defined as either the number of patients not maintaining abstinence (8 trials)[15,20,23,25,26,28–30] or the number of patients drinking heavily (1 trial).[22] Secondary outcomes included dropout rate due to any cause and due to adverse events, first alcohol consumption time point, number/percentage of abstinent drinking days, heavy drinking days, and adherence. To

analyze the combined outcomes of abstinent/drinking days, we used percentage of abstinent days from 3 studies,[22,23,30] total abstinent days from 1 study,[25] and total drinking days from 1 study.[26] Since lower numbers are worse for percentage and number of abstinent days and higher numbers are worse for drinking days, and since higher numbers are categorically considered a bad outcome in the meta-analytic program Review Manager (see below), we reversed the algebraic sign of the outcomes for which higher numbers are positive (ie, for percentage and number of abstinent days). This allowed us to combine these 3 outcomes that measure the same dimension pooling standardized mean differences (SMDs). Since only effect sizes in individual studies comparing antipsychotics with placebo are combined, the difference between the study arms is not altered and the final pooled effect size is not affected by the change of the algebraic sign. We analyzed heavy drinking days by combining the percentage of heavy drinking days from 2 studies[15,23] and the number of heavy drinking days from 1 study.[26] We evaluated craving by combining 2[26,30] of 3 studies using Obsessive Compulsive Drinking Scale total scores[36] and 1 study[23] using the Penn Alcohol Craving Scale.[37] We evaluated adherence by combining 1[26] of 3 studies using pill counts, 1 study[22] counting patients who completed the study and attended all weekly medical visits, and 1 study[25] that did not provide any details. In addition, we analyzed reported adverse effects, as long as ≥ 3 studies contributed data to the analyses.

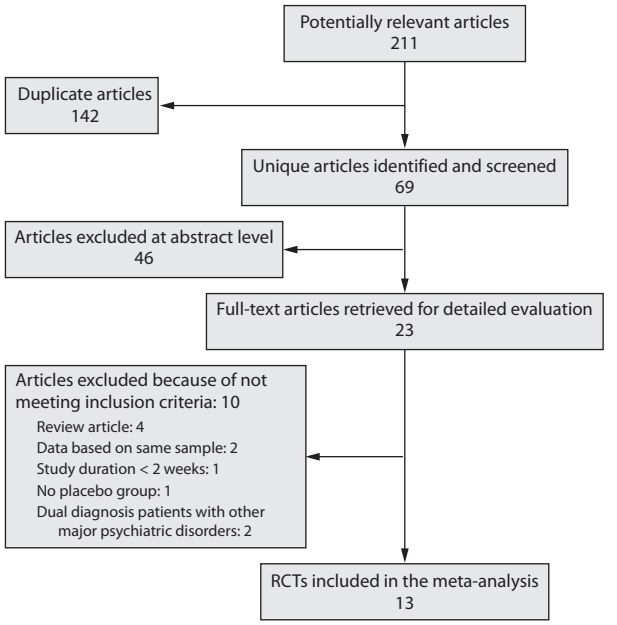
We based the analyses solely on intent-to-treat (ITT) or modified ITT data (ie, at least 1 dose taken or at least 1 follow-up assessment obtained, respectively); no observed cases data were allowed. The meta-analysis was performed using Review Manager (RevMan) Version 5.1 for Windows (Nordic Cochrane Centre, Cochrane Collaboration; Copenhagen, Denmark; http://ims.cochrane.org/revman). When studies were combined, a random-effects model[38] was used to account for study heterogeneity. For continuous data, SMD was used, combining the effect size (Hedges *g*) data. For dichotomous data, relative risk (RR) was estimated with 95% confidence intervals (CIs). In the case of significant group differences, the number needed to treat (NNT) or number needed to harm (NNH) was calculated by dividing 1 by the risk difference between the rates in each treatment, with the 95% CIs of NNT/NNH being the inverse of the upper and lower limits of the 95% CI of the risk difference. Study heterogeneity was measured using the χ^2 and I^2 statistics, with χ^2 $P < .05$ and $I^2 \geq 50\%$ indicating heterogeneity.[39] In cases of $I^2 \geq 50\%$, sensitivity analyses were conducted to seek reasons for the heterogeneity. Funnel plots were inspected visually to assess the possibility of publication bias.

RESULTS

Study, Patient, and Treatment Characteristics

The search in PubMed, Cochrane Library databases, and PsycINFO yielded 211 hits. We excluded 142 duplicate studies across the 3 databases as well as 46 studies based on title or abstract review. An additional 10 full-text articles were excluded because they were review papers (4 studies), they were not placebo-controlled (1 study), the study duration was < 2 weeks (1 study), data were based on the same sample (2 studies), or studies were conducted in dual diagnosis patients with psychiatric disorders (2 studies), yielding 13 eligible studies (Figure 1).[15,20–30,40] We did not find any additional studies to include in the meta-analysis from review articles.

Figure 1. PRISMA Flow Diagram



Abbreviations: PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, RCT = randomized controlled trial.

In total, we identified 13 randomized trials with 1,593 patients that compared an antipsychotic to placebo in patients with primary alcohol dependence (Table 1). All studies were of high methodological quality on the basis of the Cochrane Risk of Bias Criteria (Cochrane Collaboration, http://www.cochrane.org/), as all studies were double-blind and placebo-controlled and mentioned the required details of the study design. In addition, we based the analyses solely on ITT or modified ITT data (ie, at least 1 dose taken or at least 1 follow-up assessment obtained, respectively); no observed-cases data were allowed. All studies were published in English. Eight of 13 studies were industry sponsored. Six of 13 studies were conducted in the United States. The mean study duration was 18.5 weeks; 8 trials lasted 2–12 weeks, and 5 trials lasted 26–52 weeks. Sample sizes ranged from 20 to 299, with 10–150 participants in each of the randomized groups. Except for 2 studies[27,28] in which no criteria were mentioned, alcohol dependence was diagnosed according to standardized diagnostic criteria, including *DSM-IV* (9 trials), *DSM-III-R* (1 trial), or *ICD-10* (1 trial). The mean patient age was 43.7 years, 73.3% were male, and 77.2% were white. Alcohol intake characteristics at baseline included completed detoxification (6 studies), complete abstinence (1 study), abstinent for 1–7 days (3 studies), heavy drinker with blood alcohol content = 0.00 at informed consent (1 study), detoxification not completed (1 study), and using alcohol (1 study).

Table 1. Study and Patient Characteristics of Double-Blind, Placebo-Controlled Trials of Antipsychotics for Alcohol Dependence

Study, Country, Sponsor	N	Duration	Alcohol Dependence Criteria	Alcohol Intake at Baseline	Comorbid Disorders (%, if available)	White, %
Amisulpride						
Marra et al, 2002,[26] France, industry	71	26 weeks	*DSM-IV*	Completed detox	Nicotine abuse (NR), depressive symptoms (12.7), GAD (14.1)	NR
Aripiprazole						
Anton et al, 2008,[30] United States, industry	295	12 weeks	*DSM-IV*	Maintained abstinence ≥ 3 days in the screening period	Marijuana abuse	84.4
Myrick et al, 2010,[15] United States, nonindustry	30	2 weeks	*DSM-IV*	Using alcohol; had to abstain from drinking for 24 hours before imaging session on day 14 only	Marijuana abuse, no psychiatric disorders	90
Flupenthixol decanoate						
Wiesbeck et al, 2001,[25] Germany, nonindustry	281	52 weeks	*DSM-III-R*	Moderate or severe alcohol dependence, complete abstinence	Depression, anxiety	NR
Olanzapine						
Guardia et al, 2004,[22] Spain, industry	60	12 weeks	*DSM-IV*	Completed detox	Nicotine abuse	100
Hutchison et al, 2006,[21] United States, industry	64	12 weeks	*DSM-IV*	Instructed to remain abstinent for ≥ 4 days	Marijuana and nicotine abuse	84.3
Quetiapine						
Kampman et al, 2007,[20] United States, industry	61	12 weeks	*DSM-IV*	Abstinent (≥ 3 days) and free from significant alcohol withdrawal symptoms	Nicotine abuse (NR), MDD (14.7), APD (11.5), PTSD (8.2), panic disorder (4.9), SP (4.9), GAD (3.3), OCD (1.6)	54.1
Guardia et al, 2011,[40] Spain, industry	62	12 weeks	*DSM-IV*	Completed detox	Nicotine abuse (29.0), anxiety disorders (27.4), MDD (11.3), other (29.0)	NR
Litten et al, 2012,[23] United States, industry	218	12 weeks	*DSM-IV*	Heavy drinker, BAC = 0.00 at informed consent, no restriction about alcohol intake at baseline	Nicotine abuse, no psychiatric disorders	82.1
Ray et al, 2011,[24] United States, nonindustry	20	12 weeks	*DSM-IV*	Detox not completed; on target dose single-blind, placebo-controlled IV alcohol to assess subjective response to alcohol during cue exposure	Nicotine abuse, no psychiatric disorders	45
Tiapride						
Shaw et al, 1987,[27] United Kingdom, nonindustry	32	26 weeks	NR	Completed detox	None	NR
Shaw et al, 1994,[28] United Kingdom, nonindustry	100	26 weeks	NR	Completed detox	No psychotic disorders	NR
Bender et al, 2007,[29] Germany, industry	299	24 weeks	*ICD-10*	Completed detox ≤ 1 month and no alcohol intake for ≥ 7 days	None	NR
TOTAL						
United States = 6 Germany = 2 United Kingdom = 2 France = 1 Spain = 2 Industry = 8 Nonindustry = 5	1,593	18.5 ± 12.5 weeks[c]	*DSM-IV* = 9, *DSM-III-R* = 1, *ICD-10* = 1, NR = 2	Completed detox = 6, complete abstinence = 1, abstinent for 1–7 days = 3, heavy drinker—BAC = 0.00 at informed consent = 1, detox not completed = 1, using alcohol = 1	None = 2, no psychotic disorders = 4	77.2 ± 18.4[c]

[a]Riboflavin as a compliance measure. [b]Primary outcome is underlined. [c]Data presented as mean ± SD.
Abbreviations: ADS = Alcohol Dependence Scale, APD = antisocial personality disorder, BAC = blood alcohol concentration; CBT = cognitive-behavioral therapy, *DRD4* = D_4 dopamine receptor gene, *DSM-III-R* = *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition, Revised, *DSM-IV* = *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, GAD = generalized anxiety disorder,

Age, Mean (range), y	Male, %	Treatment (n)	Total Dropout, %	Dose, Mean (range/fixed), mg/d	CBT and/or Concomitant Drugs (%)[a]	Efficacy Outcomes[b]
43.5 (28–63)	69.0	Amisulpride (37) Placebo (34)	62.2 50.0	50 (fixed) 50 (fixed)	Psychotherapy (100) and benzodiazepines (NR)	Amisulpride = placebo: drinking days, first alcohol consumption time, heavy drinking days, OCDS score, craving
47.3 (21–65)	68.5	Aripiprazole (149) Placebo (146)	40.9 26.7	23.3 (5–30) 27.4 (5–30)	Psychotherapy (100), benzodiazepines (aripiprazole: 19.9, placebo: 19.6), antidepressants (aripiprazole: 18.5, placebo: 16.8)	Aripiprazole > placebo: ADS score, drinks/drinking day, aripiprazole = placebo: % abstinence days, OCDS score, aripiprazole < placebo: no. patients completely abstinent
29	73.3	Aripiprazole (14) Placebo (16)	0.00 0.00	15 (fixed) 15 (fixed)	NR	Aripiprazole = placebo: craving, no. patients remaining completely abstinent
41.7 (22–55)	72.6	Flupenthixol decanoate (142) Placebo (139)	76.8 58.3	10, IM injection 10, IM injection	Psychotherapy (NR)	Flupenthixol depot < placebo: relapse, craving, abstinent days, no. patients with "loss of control"
43.5 (18–60)	73.3	Olanzapine (29) Placebo (31)	41.4 22.6	7.5 (5–15) 7.5	Psychotherapy (100), benzodiazepines and antidepressants (NR)	Olanzapine = placebo: relapse, craving, first alcohol consumption time, drinks/drinking day, % abstinent days, OCDS score
44.2	67.1	Olanzapine (33) Placebo (31)	18.2 22.6	5 (fixed) NR	Psychotherapy (100), riboflavin (100)	Olanzapine > placebo: craving (*DRD4 L* genotype)
47.2 (> 18)	77	Quetiapine (29) Placebo (32)	20.7 25.0	303 (25–400) NR	Psychotherapy (100)	Quetiapine > placebo: relapse, % days drinking (only patients with an early age at onset of problem drinking)
43.8 (18–65)	80.6	Quetiapine + naltrexone (30) Placebo + naltrexone (32)	36.7 12.5	Quetiapine: 127.5 (100.7–154.3) + naltrexone: 50 Placebo: 172.5 (155.6–189.4) + naltrexone: 50	Zolpidem (NR), sertraline (NR)	Quetiapine = placebo: no. days abstinent, drinks/drinking day, no. patients with relapse, craving
45.4 (18–64)	80.3	Quetiapine (105) Placebo (113)	24.8 28.3	327.7 (50–400) 370.4	Psychotherapy (100)	Quetiapine = placebo: % heavy drinking days, drinks/day, drinks/drinking day, no. patients abstinent
32.8 (11.3)	80.0	Quetiapine (10) Placebo (10)	40 10	400 (0–400) NR	Riboflavin (100)	Quetiapine > placebo: craving, OCDS score
(25–60)	NR	Tiapride (13) Placebo (19)	38.5 36.8	100 (fixed) NR	NR	Tiapride > placebo: total abstinence days
(25–60)	NR	Tiapride (50) Placebo (50)	52.0 40.0	100 (fixed) NR	Vitamins (100)	Tiapride > placebo: total abstinence days
42.0 (24–65)	73.2	Tiapride (149) Placebo (150)	20.8 23.3	300 (fixed) NR	Psychotherapy (100)	Tiapride = placebo: time to first relapse
43.7 ± 5.77[c]	73.3	Amisulpride (1 study) Aripiprazole (2 studies) Flupenthixol decanoate (1 study) Olanzapine (2 studies) Quetiapine (4 studies) Tiapride (3 studies) Placebo (13 studies)	36.4 ± 20.2[c] 28.6 ± 15.3[c]		Psychotherapy (8 studies; 100%, 7 studies), benzodiazepines (4 studies), antidepressants (3 studies), riboflavin (2 studies), vitamins (1 study)	Primary outcomes: Craving (3 studies), relapse (3 studies), no. abstinence days (3 studies), time to relapse (1 study), no. drinking days (1 study), % heavy drinking days (1 study), % abstinence days (1 study)

ICD-10 = *International Statistical Classification of Diseases, 10th Revision*, IM = intramuscular, IV = intravenous, *L* = long allele, MDD = major depressive disorder, NR = not reported, OCD = obsessive-compulsive disorder, OCDS = Obsessive Compulsive Drinking Scale, PTSD = posttraumatic stress disorder, SP = social phobia.

Two studies[15,24] were biological cue reactivity studies in non–help-seeking subjects; the remaining 10 studies were clinical trials investigating the efficacy of antipsychotics for alcohol dependence. Nine trials evaluated SGAs, and 4 trials evaluated first-generation antipsychotics (FGAs), including 1 depot antipsychotic (flupenthixol decanoate). Specific treatment arms included amisulpride (1 study, n = 37), aripiprazole (2 studies, n = 163), flupenthixol decanoate (1 study, n = 142), olanzapine (2 studies, n = 62), quetiapine (4 studies, n = 174), tiapride (3 studies, n = 212), and placebo (13 studies, n = 803). Seven of 13 trials provided psychotherapy for the patients with alcohol dependence as cotreatment, 4 allowed benzodiazepines, and 3 trials allowed antidepressants. One study[40] randomly assigned patients to either quetiapine or placebo in addition to naltrexone following a single-blind lead-in with naltrexone plus placebo for 1 week. Patients were treated with riboflavin as a compliance measure in 2 trials, and in 1 trial, patients received vitamins adjunctively. Four of 13 trials allowed alcohol dependence patients with comorbid depressive symptoms or major depressive disorder; however, no studies included alcohol dependence patients with comorbid psychotic or bipolar spectrum disorders.

Relapse

Nine studies provided relapse rates. Eight of them defined relapse as the proportion of patients who did not maintain abstinence during study. One study defined relapse as the proportion of patients who drank heavily during the study. Pooled together, antipsychotics were not different from placebo regarding relapse (RR = 1.05 [95% CI, 0.95 to 1.16], $P = .38$, n = 1,405, 9 studies), but results were heterogeneous ($\chi^2 = 24.97$, $P = .002$, $I^2 = 68\%$) (Figure 2). Except for flupenthixol decanoate, which had higher relapse rates than placebo (RR = 1.14 [95% CI, 1.03 to 1.27], $P = .01$, I^2 = not applicable, NNT = 9, n = 281, 1 study), none of the other antipsychotics differed significantly from placebo (Figure 2).

To identify potential moderator variables, sensitivity analyses across 14 study design and patient variables were performed (Table 2). Across all analyses involving 23 different study/patient characteristics, antipsychotics continued to be similar to placebo regarding relapse, with I^2 values continuing to indicate significant heterogeneity ($I^2 = 57\%–81\%$). Visual inspection of the funnel plot for relapse did not suggest presence of publication bias.

Abstinence/Drinking Days

Pooled antipsychotics were inferior to placebo regarding abstinence/drinking days ($P = .04$, SMD = 0.17 [95% CI, 0.01 to 0.33], n = 918, 5 studies) (Figure 3). Although results were not heterogeneous ($I^2 = 29\%$), this significant difference was driven by 1 study with flupenthixol decanoate (n = 281) that alone was inferior to placebo (SMD = 0.34 [95% CI, 0.11 to 0.58], $P = .004$) (Figure 3). Removal of this study eliminated the placebo-antipsychotic difference ($P = .24$).

Heavy Drinking Days

Pooled antipsychotics and placebo were similar regarding their effect on heavy drinking days (SMD = −0.85 [95% CI, −2.00 to 0.31], $P = .15$, $I^2 = 94\%$, n = 319, 3 studies). Individually, aripiprazole was superior to placebo regarding heavy drinking days (SMD = −3.24 [95% CI, −4.37 to −2.10], $P < .00001$, n = 30, 1 study). When this study was excluded from the meta-analysis, the significant heterogeneity disappeared ($I^2 = 0\%$), and the trend toward an antipsychotic-placebo difference disappeared ($P = .85$).

Craving

There was no difference between pooled and individual antipsychotics and placebo regarding craving (pooled SMD = −0.02 [95% CI, −0.18 to 0.14], $P = .82$, $I^2 = 0\%$, n = 572, 3 studies).

First Alcohol Consumption Time

First alcohol consumption time was similar for pooled and individual antipsychotics and placebo (pooled SMD = −0.01 [95% CI, −0.20 to 0.19], $P = .94$, $I^2 = 0\%$, n = 412, 3 studies).

Dropout Rate

Dropout due to any cause. Pooled together, antipsychotics were associated with significantly higher dropout rates due to any cause compared to placebo (RR = 1.24 [95% CI, 1.07 to 1.45], $P = .005$, $I^2 = 17\%$, NNH = 14, $P = .02$, n = 1,593, 13 studies) (Figure 4). Individually, patients receiving aripiprazole or flupenthixol decanoate had a significantly higher risk of all-cause dropout than those receiving placebo (aripiprazole: RR = 1.53 [95% CI, 1.10 to 2.13], $P = .01$, I^2 = not applicable, NNH = nonsignificant, n = 325, 2 studies; flupenthixol decanoate: RR = 1.32 [95% CI, 1.11 to 1.56], $P = .001$, I^2 = not applicable, NNH = 6, $P = .0007$, n = 281, 1 study) (Figure 4).

Dropout due to adverse events. There was no difference in the dropout rate due to adverse events between pooled antipsychotics and placebo (RR = 1.63 [95% CI, 0.88 to 3.01], $P = .12$, $I^2 = 28\%$, n = 1,311, 11 studies). Individually, only aripiprazole had a higher risk of dropout due to adverse events than placebo (RR = 20.85 [95% CI, 2.80 to 150.99], $P = .003$, I^2 = not applicable, NNH = nonsignificant, n = 325, 2 studies).

Adherence

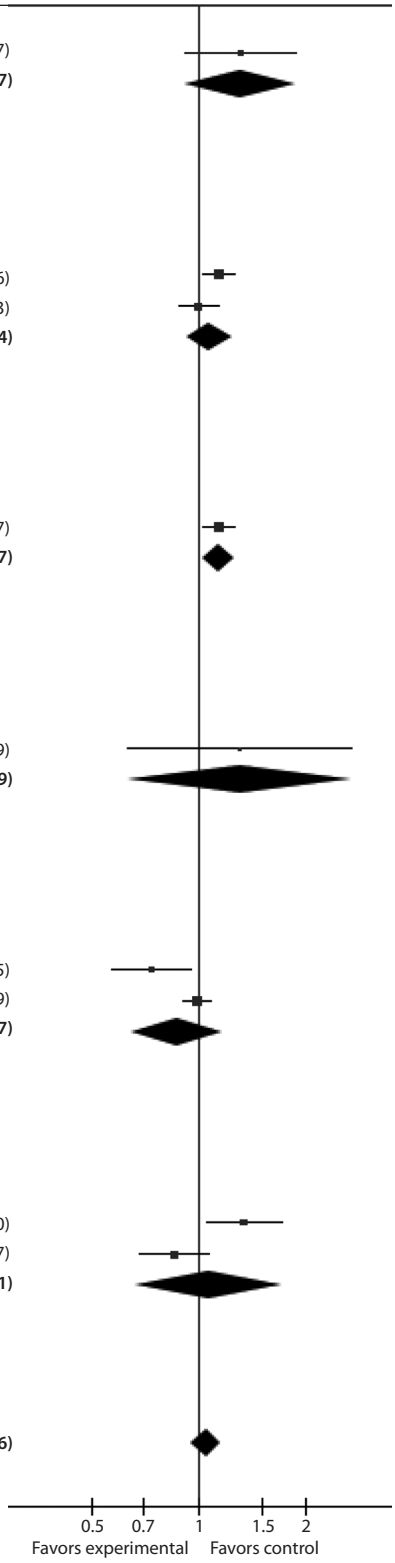
Treatment adherence did not differ between all and individual antipsychotics and placebo (pooled RR = 1.00 [95% CI, 0.64 to 1.56], $P = .99$, $I^2 = 31\%$, n = 412, 3 studies).

Adverse Effects

Limited results based on data from ≥ 3 studies indicated no pooled antipsychotic-placebo group differences for the following adverse events: ≥ 1 adverse event, dizziness, headache, skin problem, anxiety/depression, gastrointestinal adverse events, and insomnia. Among individual antipsychotics, insomnia, ≥ 1 adverse event, and anxiety/depression were significantly more frequent with aripiprazole

Figure 2. Forest Plot of Relapse

Study or Subgroup	Antipsychotic Events	Antipsychotic Total	Placebo Events	Placebo Total	Weight	Risk Ratio Mantel-Haenszel, Random Effects, 95% CI
Amisulpride						
Marra et al, 2002[26]	27	37	19	34	5.6%	1.31 (0.91–1.87)
Subtotal (95% CI)		**37**		**34**	**5.6%**	**1.31 (0.91–1.87)**
Total events	27		19			
Heterogeneity: not applicable						
Test for overall effect: $z = 1.46$ ($P = .14$)						
Aripiprazole						
Anton et al, 2008[30]	130	146	111	142	16.4%	1.14 (1.03–1.26)
Myrick et al, 2010[15]	14	14	16	16	15.2%	1.00 (0.88–1.13)
Subtotal (95% CI)		**160**		**158**	**31.6%**	**1.07 (0.92–1.24)**
Total events	144		127			
Heterogeneity: $\tau^2 = 0.01$; $\chi^2_1 = 3.34$ ($P = .07$), $I^2 = 70\%$						
Test for overall effect: $z = 0.91$ ($P = .36$)						
Flupenthixol decanoate						
Wiesbeck et al, 2001[25]	127	142	109	139	16.4%	1.14 (1.03–1.27)
Subtotal (95% CI)		**142**		**139**	**16.4%**	**1.14 (1.03–1.27)**
Total events	127		109			
Heterogeneity: not applicable						
Test for overall effect: $z = 2.48$ ($P = .01$)						
Olanzapine						
Guardia et al, 2004[22]	11	29	9	31	1.8%	1.31 (0.64–2.69)
Subtotal (95% CI)		**29**		**31**	**1.8%**	**1.31 (0.64–2.69)**
Total events	11		9			
Heterogeneity: not applicable						
Test for overall effect $z = 0.73$ ($P = .47$)						
Quetiapine						
Kampman et al, 2007[20]	20	29	30	32	8.5%	0.74 (0.57–0.95)
Litten et al, 2012[23]	90	102	101	113	16.9%	0.99 (0.90–1.09)
Subtotal (95% CI)		**131**		**145**	**25.4%**	**0.87 (0.65–1.17)**
Total events	110		131			
Heterogeneity: $\tau^2 = 0.04$; $\chi^2_1 = 4.65$ ($P = .03$); $I^2 = 78\%$						
Test for overall effect: $z = 0.90$ ($P = .37$)						
Tiapride						
Bender et al, 2007[29]	81	149	61	150	9.2%	1.34 (1.05–1.70)
Shaw et al, 1994[28]	35	50	41	50	10.0%	0.85 (0.68–1.07)
Subtotal (95% CI)		**199**		**200**	**19.2%**	**1.07 (0.67–1.71)**
Total events	116		102			
Heterogeneity: $\tau^2 = 0.10$; $\chi^2_1 = 8.15$ ($P = .004$), $I^2 = 88\%$						
Test for overall effect: $z = 0.27$ ($P = .79$)						
Total (95% CI)		**698**		**707**	**100.0%**	**1.05 (0.95–1.16)**
Total events	535		497			
Heterogeneity: $\tau^2 = 0.01$; $\chi^2_8 = 24.97$ ($P = .002$), $I^2 = 68\%$						
Test for overall effect: $z = 0.89$ ($P = .38$)						
Test for subgroup differences: $\chi^2_5 = 4.05$ ($P = .54$), $I^2 = 0\%$						



Abbreviation: CI = confidence interval.

Table 2. Sensitivity Analysis Between Antipsychotics and Placebo With Respect to Relapse Prevention

Variable	Subgroup	No. of Studies	n	RR[a]	95% CI	*P* Value	I^2	NNT/ NNH	95% CI	*P* Value
Location	United States	4	594	0.99	0.88–1.12	.89	73%	…	…	…
	Europe	5	811	1.13	0.96–1.34	.15	57%	…	…	…
Type of trial[b]	Clinical trials	7	1,160	1.07	0.93–1.23	.33	68%	…	…	…
	Nonclinical trials	2	245	0.99	0.92–1.07	.83	0%	…	…	…
Trial duration, wk	≤ 12	5	654	1.00	0.89–1.13	.99	65%	…	…	…
	> 12	4	751	1.12	0.94–1.35	.21	67%	…	…	…
Number of participants	≤ 100	4	222	0.99	0.78–1.27	.97	64%	…	…	…
	> 100	5	1,183	1.08	0.96–1.28	.19	71%	…	…	…
Publication year	Prior to and including 2000	1	100	0.85	0.68–1.07	.16	NA	…	…	…
	From 2001 onward	8	1,305	1.07	0.96–1.19	.20	69%	…	…	…
Sponsorship	Industry sponsored	7	1,275	1.09	0.96–1.22	.18	70%	…	…	…
	Non–industry sponsored	2	130	0.94	0.75–1.18	.57	69%	…	…	…
Patient population	Only heavy/moderate drinkers	2	496	1.06	0.92–1.22	.43	76%	…	…	…
	Not only heavy/moderate drinkers	7	909	1.04	0.89–1.21	.60	71%	…	…	…
Comorbid depressive or anxiety disorders	Comorbidity	3	413	1.03	0.75–1.39	.87	81%	…	…	…
	None	6	992	1.05	0.94–1.18	.40	66%	…	…	…
Alcohol use at baseline[c]	Complete detox + abstinence	7	1,160	1.07	0.93–1.23	.33	68%	…	…	…
	Alcohol use + no restriction of alcohol intake	2	245	0.99	0.92–1.07	.83	0%	…	…	…
	Complete detox	4	530	1.15	0.86–1.53	.36	68%	…	…	…
	Abstinence	3	630	1.03	0.86–1.23	.74	80%	…	…	…
Antipsychotic class	Second-generation antipsychotic	6	725	1.02	0.91–1.15	.74	64%	…	…	…
	First-generation antipsychotic	3	680	1.09	0.88–1.36	.42	75%	…	…	…
Type of antipsychotic	D_2 partial agonist	2	318	1.07	0.92–1.24	.36	70%	…	…	…
	D_2 antagonist	7	1,087	1.04	0.90–1.20	.62	72%	…	…	…
Administration route	Oral	8	1,124	1.03	0.91–1.16	.63	69%	…	…	…
	Depot injection[d]	**1**	**281**	**1.14**	**1.01–1.28**	**.01**	**NA**	**NNH = 9**	**5–33**	**.01**
Definition of relapse	Patients did not stay abstinent	8	1,345	1.04	0.94–1.15	.43	71%	…	…	…
	Patients drank heavily	1	60	1.31	0.64–2.69	.47	NA	…	…	…
Dropout rate	> 50% (either arm)	3	452	1.07	0.86–1.33	.56	68%	…	…	…
	≤ 50% (either arm)	6	953	1.04	0.91–1.18	.59	73%	…	…	…

[a]RR < 1 favors second-generation antipsychotic; RR > 1 favors placebo.
[b]The studies by Myrick et al[15] and Ray et al[24] were biological cue reactivity studies in non–help-seeking subjects.
[c]Complete detox = Marra et al,[26] Guardia et al,[22] Shaw et al,[28] and Bender et al.[29] Abstinence = Anton et al,[30] Wiesbeck et al,[25] and Kampman et al.[20] Alcohol use = Myrick et al.[15] No restriction of alcohol intake = Litten et al.[23]
[d]Boldface in this row indicates significance.
Abbreviations: CI = confidence interval, NA = not applicable, NNH = number needed to harm, NNT = number needed to treat, RR = risk ratio.
Symbol: … = missing information/no data.

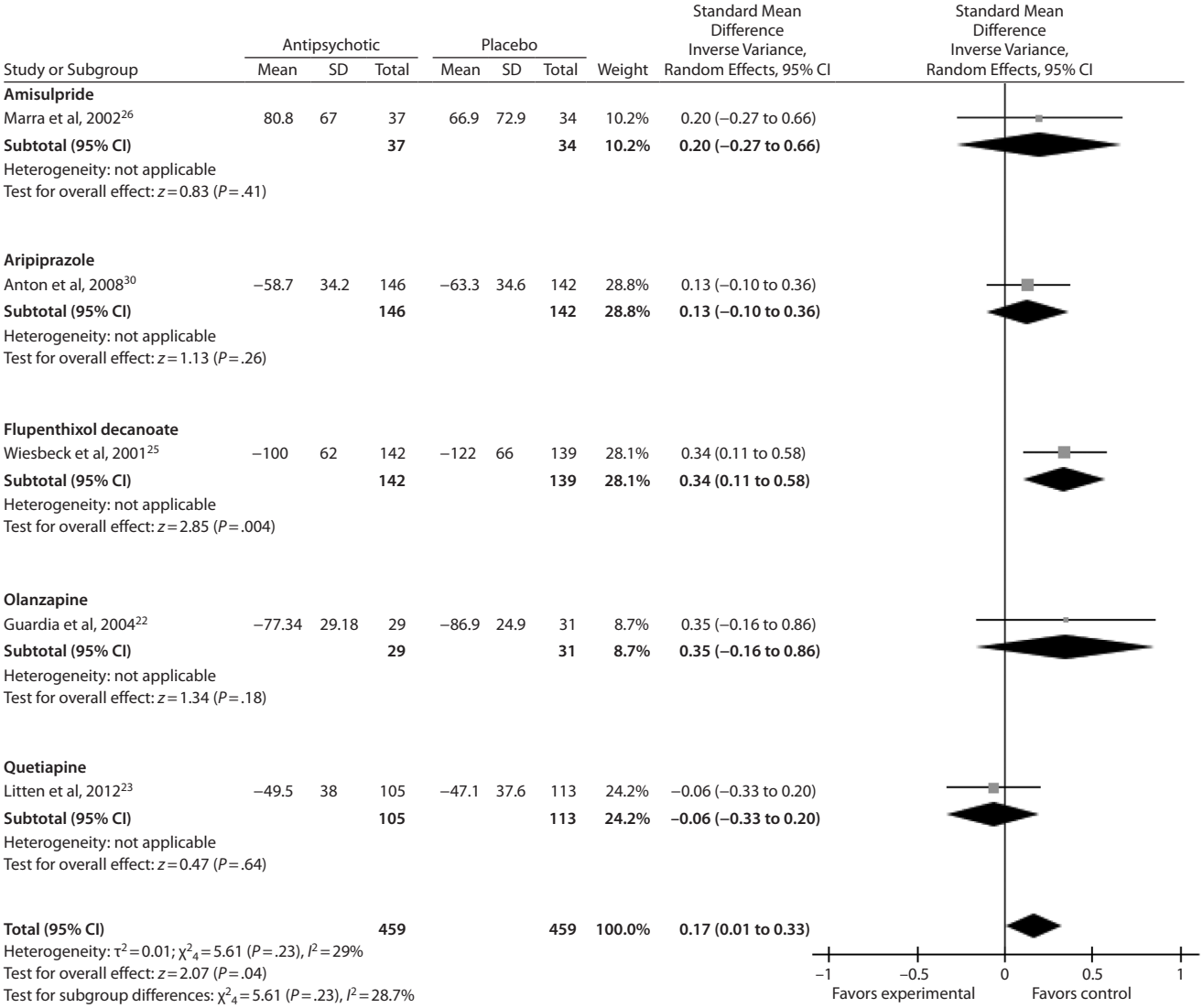
compared to placebo (insomnia, RR = 1.95, $P = .02$; ≥ 1 adverse event, RR = 1.31, $P = .003$; anxiety/depression, RR = 4.62, $P = .004$).

Drowsiness, increased appetite, and dry mouth were significantly more frequent with pooled antipsychotics than with placebo in pooled analyses; results were as follows: drowsiness, RR = 2.69 [95% CI, 1.68 to 4.31], $P < .0001$, $I^2 = 7\%$, NNH = 9, $P = .0001$, n = 689, 5 studies; increased appetite, RR = 3.07 [95% CI, 1.17 to 8.08], $P = .02$, $I^2 = 29\%$, NNH = 14, $P = .05$ n = 566, 3 studies; and dry mouth, RR = 3.47 [95% CI, 1.95 to 6.19], $P < .0001$, $I^2 = 0\%$, NNH = 7, $P = .04$, n = 401, 4 studies. Among individual antipsychotics, drowsiness was significantly more frequent with aripiprazole and quetiapine compared to placebo (aripiprazole, RR = 3.04, $P = .004$; quetiapine, RR = 3.33, $P = .0002$). Increased appetite and dry mouth were significantly more frequent with quetiapine compared to placebo (increased appetite, RR = 12.9, $P = .01$; dry mouth, RR = 3.83, $P < .0001$).

DISCUSSION

To our knowledge, this is the first meta-analysis of efficacy, effectiveness, and adverse effects of antipsychotics in the treatment of patients with primary alcohol dependence. For this meta-analysis, 13 placebo-controlled trials involving 1,593 subjects and 6 different antipsychotics were included. Although we hypothesized that antipsychotics would be beneficial in patients with alcohol dependence, we found no significant differences between pooled or individual antipsychotics and placebo in analyses including at least 3 trials regarding any efficacy outcomes, such as relapse prevention, heavy drinking days, craving, and first alcohol consumption time. Actually, pooled together, antipsychotics were inferior to placebo regarding abstinence/drinking days, although results became nonsignificant after removing 1 outlier trial. Individually, relapse prevention and abstinence/drinking days were significantly worse in patients treated with flupenthixol decanoate compared to placebo. Conversely, aripiprazole was associated with significantly fewer heavy drinking days compared to placebo, but results were based on 1 study only. It is possible that the strong antidopaminergic activity of the first-generation antipsychotic flupenthixol decanoate[25] led to greater discontinuation than placebo. Conversely, aripiprazole, which has intrinsic dopamine partial agonist activity,[15,30] may have decreased craving through partially restoring inefficient dopamine transmission.

Figure 3. Forest Plot of Abstinence/Drinking Days



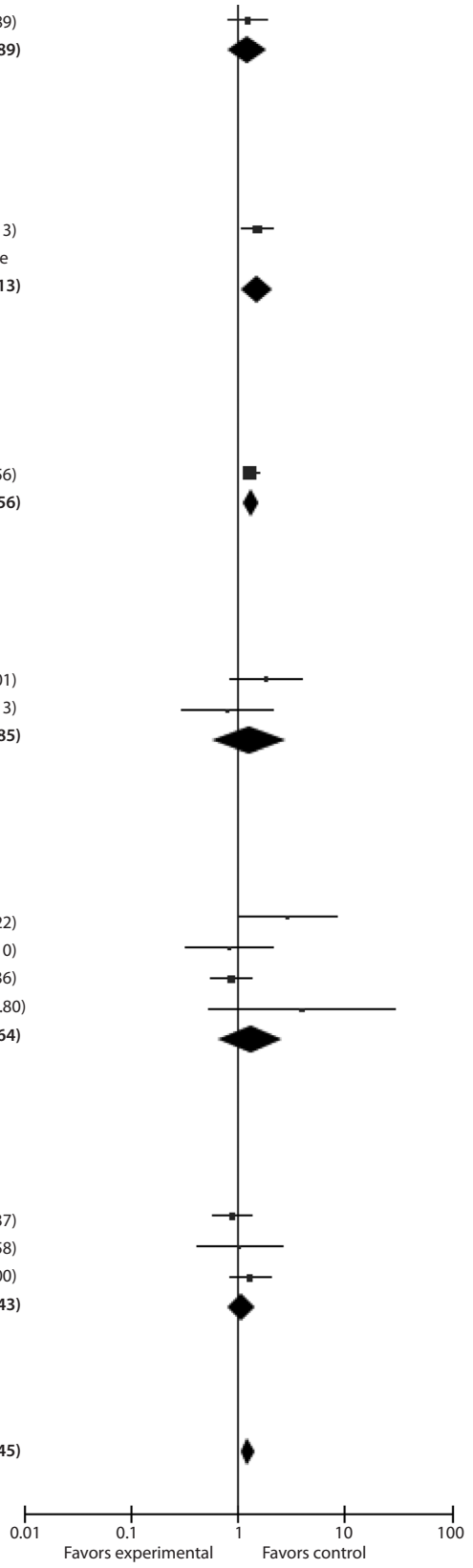
Abbreviations: CI = confidence interval, SD = standard deviation.

Dropout due to any cause and selected adverse effects was significantly more likely with antipsychotics than with placebo. The mean ± SD pooled dropout rates due to any cause were 36.4% ± 20.2% in the antipsychotic group and 28.6% ± 15.3% in the placebo group, translating into an NNT of 14. Individually, aripiprazole and flupenthixol decanoate were associated with greater all-cause dropout compared to placebo. Conversely, the dropout rates due to adverse events did not differ significantly between pooled antipsychotics and placebo, but aripiprazole had a higher dropout rate due to adverse events than placebo. Drowsiness, increased appetite, and dry mouth were significantly higher with antipsychotics than placebo. Although concomitant use of benzodiazepines could have influenced the results, drowsiness was significantly more frequent in patients treated with aripiprazole and quetiapine compared with placebo. Increased appetite and dry mouth were significantly more frequent in patients treated with quetiapine compared with placebo. Although there was no significant difference regarding ≥ 1 adverse event, anxiety/depression, and insomnia between pooled antipsychotics and placebo, these were significantly more frequent with aripiprazole compared to placebo.

Although patients with alcohol dependence were reported to have poor adherence to medication regimens, which may limit the effectiveness of pharmacologic interventions,[41] in this meta-analysis, adherence did not differ between pooled or individual antipsychotics and placebo. However, the reviewed studies used self-report measures of adherence, which are unreliable.[42] None of the trials included pill count, informant reporting, clinician ratings, the Medication Event Monitoring System, or blood drug levels. Although depot antipsychotics are thought to facilitate adherence, flupenthixol decanoate did not have benefits in relapse prevention in alcohol dependence patients compared with placebo. Rather, flupenthixol decanoate was associated

Figure 4. Forest Plot of Dropout Rate Due to Any Cause

Study or Subgroup	Antipsychotic Events	Antipsychotic Total	Placebo Events	Placebo Total	Weight	Risk Ratio Mantel-Haenszel, Random Effects, 95% CI
Amisulpride						
Marra et al, 2002[26]	23	37	17	34	10.4%	1.24 (0.82–1.89)
Subtotal (95% CI)		**37**		**34**	**10.4%**	**1.24 (0.82–1.89)**
Total events	23		17			
Heterogeneity: not applicable						
Test for overall effect: $z = 1.02$ ($P = .31$)						
Aripiprazole						
Anton et al, 2008[30]	61	149	39	146	14.9%	1.53 (1.10–2.13)
Myrick et al, 2010[15]	0	14	0	16		Not estimable
Subtotal (95% CI)		**163**		**162**	**14.9%**	**1.53 (1.10–2.13)**
Total events	61		39			
Heterogeneity: not applicable						
Test for overall effect: $z = 2.53$ ($P = .01$)						
Flupenthixol decanoate						
Wiesbeck et al, 2001[25]	109	142	81	139	31.7%	1.32 (1.11–1.56)
Subtotal (95% CI)		**142**		**139**	**31.7%**	**1.32 (1.11–1.56)**
Total events	109		81			
Heterogeneity: not applicable						
Test for overall effect: $z = 3.23$ ($P = .001$)						
Olanzapine						
Guardia et al, 2004[22]	12	29	7	31	3.5%	1.83 (0.84–4.01)
Hutchison et al, 2006[21]	6	33	7	31	2.3%	0.81 (0.30–2.13)
Subtotal (95% CI)		**62**		**62**	**5.8%**	**1.28 (0.58–2.85)**
Total events	18		14			
Heterogeneity: $\tau^2 = 0.14$; $\chi^2_1 = 1.670$ ($P = .20$), $I^2 = 40\%$						
Test for overall effect: $z = 0.61$ ($P = .54$)						
Quetiapine						
Guardia et al, 2011[40]	11	30	4	32	2.1%	2.93 (1.05–8.22)
Kampman et al, 2007[20]	6	29	8	32	2.5%	0.83 (0.33–2.10)
Litten et al, 2012[23]	26	105	32	113	9.5%	0.87 (0.56–1.36)
Ray et al, 2011[24]	4	10	1	10	0.6%	4.00 (0.54–29.80)
Subtotal (95% CI)		**174**		**187**	**14.6%**	**1.32 (0.66–2.64)**
Total events	47		45			
Heterogeneity: $\tau^2 = 0.25$; $\chi^2_3 = 6.50$ ($P = .09$), $I^2 = 54\%$						
Test for overall effect: $z = 0.80$ ($P = .43$)						
Tiapride						
Bender et al, 2007[29]	31	149	35	150	10.1%	0.89 (0.58–1.37)
Shaw et al, 1987[27]	5	13	7	19	2.6%	1.04 (0.42–2.58)
Shaw et al, 1994[28]	26	50	20	50	9.9%	1.30 (0.84–2.00)
Subtotal (95% CI)		**212**		**219**	**22.7%**	**1.07 (0.80–1.43)**
Total events	62		62			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_2 = 1.52$ ($P = .47$), $I^2 = 0\%$						
Test for overall effect: $z = 0.47$ ($P = .64$)						
Total (95% CI)		**790**		**803**	**100.0%**	**1.24 (1.07–1.45)**
Total events	320		258			
Heterogeneity: $\tau^2 = 0.01$; $\chi^2_{11} = 13.31$ ($P = .27$), $I^2 = 17\%$						
Test for overall effect: $z = 2.82$ ($P = .005$)						
Test for subgroup differences: $\chi^2_5 = 2.74$ ($P = .74$), $I^2 = 0\%$						



Abbreviation: CI = confidence interval.

with a greater number of days without abstinence/days with drinking. This negative finding may have to do with the constant dopamine blockade unmodulated by other receptor activity seen with first-generation antipsychotics as opposed to second-generation antipsychotics.[43] These results are consistent with the findings of an RCT comparing the safety and efficacy of long-acting injectable risperidone (RIS-LAI) versus zuclopenthixol depot in schizophrenia patients with substance use disorders. In this trial, RIS-LAI patients had a lower frequency of substance use, including nicotine, alcohol, cannabis, cocaine, and opiates, and better compliance with the Substance Abuse Management program compared with zuclopenthixol depot patients.[44] However, Loebl and colleagues[45] showed that RIS-LAI was not superior to placebo in reducing cocaine use or craving in nonpsychotic cocaine dependence patients. These results suggest that the effects of an SGA-LAI on substance use outcomes may differ between abused substances and that future studies with an SGA-LAI in patients with primary alcohol dependence should be considered to rule out that the lack of efficacy is mediated by nonadherence to antipsychotic treatment.

There is no RCT (antipsychotic vs placebo or other comparators) in dually diagnosed alcohol dependence patients with schizophrenia. Two RCTs (quetiapine vs placebo) in dually diagnosed patients with alcohol dependence and bipolar disorder did not find differences for alcohol use between patients treated with quetiapine or placebo.[46,47] In nonrandomized clinical trials, clozapine was superior for relapse prevention in dually diagnosed alcohol dependence patients with psychosis compared with FGAs and other SGAs (olanzapine and risperidone).[48–50]

The main limitation of this meta-analysis is the paucity of studies and subjects. There was only 1 study with amisulpride or flupenthixol decanoate, and the other antipsychotics were tested in only 2 or 3 individual trials. Moreover, no study investigated clozapine, which has shown particular promise in dual diagnosis patients with schizophrenia[51]; yet, owing to its side effect pattern, clozapine will not be a viable treatment option in substance abuse patients without a refractory psychotic or bipolar disorder. Furthermore, only 4 of 13 studies randomized more than 100 patients. Nevertheless, in the 4 studies with 105–150 patients per treatment arm, substance use outcomes did not differ between antipsychotics and placebo.

In addition, studies were heterogeneous, and, especially, primary outcomes as well as alcohol dependence–related efficacy measures differed quite substantially between studies. For example, 2 studies[15,24] investigated biological cue reactivity as the primary outcome in non–help-seeking subjects, although there is no consistent literature linking cue reactivity to predictability of treatment outcome in patients with alcohol dependence. The lack of consistent assessments across studies underscores the need for standardizing outcomes in future studies. In particular, relevant primary outcome measures need to be applied in the evaluation of medications that are aimed at treating alcohol dependence. Of note, the FDA defined "percent subjects with no heavy drinking days" as the primary end point of phase 3 alcohol dependence trials.[52] This outcome has become a regulatory requirement for pharmaceutical companies in order to receive an FDA indication for alcohol dependence. However, this outcome was assessed in only 1[23] of the 6 trials published after 2006. In addition, the primary results were significantly heterogeneous. Notably, however, the heterogeneity was caused only by studies disfavoring antipsychotics. This finding indicates that although the similarity of antipsychotics compared to placebo in the primary outcome is not entirely clear due to the heterogeneous result, the potential bias in the available studies is toward an overestimation of the antipsychotic effects, not toward an underestimation. In addition, the lack of superiority of antipsychotics for relapse prevention was confirmed in 14 sensitivity analyses that assessed the moderating effect of potentially relevant study design, patient, and treatment variables, with 1 analysis showing greater relapse in a single FGA depot study. Moreover, with the exception of 1 analysis in nonclinical studies, all other subgroup analysis results remained heterogeneous.

Another limitation is that most of the studies did not report important outcomes such as psychiatric symptoms and adverse events. In addition, alcohol dependence patients often have comorbid symptoms such as depressive and/or anxiety symptoms, and these psychiatric symptoms can further aggravate alcohol dependence.[53] However, although some SGAs have antidepressive and antianxiety efficacy,[17–19] data on the effects of antipsychotics on these dimensions in patients with primary alcohol dependence were lacking. In this context, it is also unclear to what degree the allowed psychotherapeutic and pharmacologic cotreatment in both the placebo arm and the antipsychotic arm could have attenuated any potential antipsychotic effects. However, since in primary alcohol dependence antipsychotics are unlikely to be given without accompanying therapies, this design feature rather increases the generalizability of the findings.

Recently, substance use disorders are considered to be disorders involving both impulsivity and compulsivity psychopathology that produces an interactive addiction cycle leading to the following 3 stages: binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation (craving).[13,14] Future antipsychotic trials for patients with primary alcohol dependence should evaluate the outcomes in each stage of the addiction cycle (ie, intoxication, withdrawal affect, and craving) as well as relevant psychiatric symptoms. While relapse may still be an appropriate overall efficacy measure of pharmacologic interventions for alcohol dependence, definitions should be standardized. Moreover, studies should be conducted in subgroups of patients with varying durations of abstinence and ongoing drinking behaviors. In the available studies, baseline alcohol use status varied and data on the duration of abstinence were lacking, further limiting the inferences that can be derived from these studies. Finally, 8 of the 13 trials included in this meta-analysis lasted 12 weeks or less and longer-term efficacy and safety data are needed, although there was no

difference in the primary efficacy outcome in short- versus longer-term studies.

CONCLUSION

Our results suggest that the use of antipsychotics in patients with primary alcohol dependence is not associated with a decrease in relapse rates, heavy drinking days, or craving or an increase in days without abstinence/drinking days or first alcohol consumption time. In addition, drowsiness/sedation, increased appetite, and dry mouth occurred more frequently with pooled antipsychotics than placebo, further tilting the cost-benefit balance against antipsychotics. Thus, our study suggests that, unless additional data refute these findings, antipsychotics should most likely not be used in patients with primary alcohol dependence. Rather, other therapeutic options should be utilized and explored in this challenging patient population.

Drug names: acamprosate (Campral), aripiprazole (Abilify), asenapine (Saphris), clozapine (Clozaril, FazaClo, and others), disulfiram (Antabuse), haloperidol (Haldol and others), iloperidone (Fanapt), loxapine (Loxitane and others), lurasidone (Latuda), molindone (Moban), naltrexone (Vivitrol, ReVia, and others), olanzapine (Zyprexa), paliperidone (Invega), pimozide (Orap), prochlorperazine (Compro and others), quetiapine (Seroquel), risperidone (Risperdal and others), sertraline (Zoloft and others), thiothixene (Navane and others), ziprasidone (Geodon), zolpidem (Ambien, Edluar, and others).

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Author contributions: Dr Kishi 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 (Drs Correll and Sevy); acquisition of data (Drs Kishi and Chekuri); analysis and interpretation of data (Drs Kishi and Correll); drafting of the manuscript (all authors); statistical analysis (Drs Kishi and Correll); and study supervision (Dr Correll).

Potential conflicts of interest: **Dr Kishi** has received speakers honoraria from Astellas, Dainippon Sumitomo, Eli Lilly, Yoshitomi, Otsuka, Meiji, Shionogi, Novartis, and Pfizer. **Dr Correll** has been a consultant and/or advisor to or has received honoraria from Actelion, Alexza, American Academy of Child and Adolescent Psychiatry, AstraZeneca, Biotis, Bristol-Myers Squibb, Cephalon, Desitin, Eli Lilly, Gerson Lehrman Group, GlaxoSmithKline, IntraCellular Therapies, Lundbeck, Medavante, Medscape, Merck, National Institute of Mental Health, Novartis, Ortho-McNeil/Janssen/Johnson & Johnson, Otsuka, Pfizer, ProPhase, Sunovion, Takeda, and Teva and has received grant support from Bristol-Myers Squibb, Feinstein Institute for Medical Research, Janssen/Johnson & Johnson, National Institute of Mental Health, National Alliance for Research on Schizophrenia and Depression, and Otsuka. **Drs Sevy** and **Chekuri** have nothing to disclose.

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