Antipsychotics for Cocaine or Psychostimulant Dependence: Systematic Review and Meta-Analysis of Randomized, Placebo-Controlled Trials

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ABSTRACT

Objective: Since cocaine and psychostimulant dependence are related to increased dopamine release, antipsychotics have been tried to reduce their reinforcing properties. A meta-analysis was undertaken to assess the efficacy and tolerability of antipsychotics in cocaine- or stimulant-dependent patients.

Data Sources: We searched PubMed, Cochrane Library databases, and PsycINFO from database inception until June 24, 2013, using the following keywords: (*randomized* OR *random* OR *randomly*) AND (*placebo*) AND (*methylphenidate* OR *cocaine* OR *methamphetamine* OR *amphetamine* OR *3,4-methylenedioxymethamphetamine*) AND (*dependence* OR *abuse*) AND (*antipsychotic* OR *neuroleptic* OR 34 specific antipsychotic names).

Study Selection: Included were randomized, placebo-controlled trials of antipsychotics lasting at least 2 weeks in patients with primary cocaine or psychostimulant dependence. Of 363 hits, we removed 316 duplicates, 20 references based on abstract/title, and 13 ineligible full-text articles, retaining 14 trials for this meta-analysis.

Data Extraction: Two authors independently extracted the data. Coprimary outcomes included degree of substance use and lack of abstinence. Risk ratio (RR), 95% CI, and standardized mean difference were calculated.

Results: Ten studies in patients with primary cocaine dependence (risperidone = 5, olanzapine = 3, reserpine = 2; n = 562) and 4 in those with amphetamine/methamphetamine dependence (aripiprazole = 4; n = 179) were meta-analyzed (14 studies, total n = 741). When study results were pooled together, antipsychotics did not differ from placebo in regard to cocaine use days and lack of cocaine or amphetamine/methamphetamine abstinence, severity of addiction, cocaine or amphetamine/methamphetamine craving, Clinical Global Impressions-Severity of Illness (CGI-S) scores, depression, anxiety, compliance, all-cause discontinuation, and several side effects. However, antipsychotics caused more intolerability-related discontinuation than placebo ($P = .0009$). Individually, aripiprazole was superior to placebo in regard to CGI-S ($P = .001$), while olanzapine was inferior to placebo in regard to cocaine craving ($P = .03$) and risperidone was inferior to placebo in regard to depression ($P = .002$).

Conclusions: Antipsychotics had no advantages over placebo in regard to cocaine use and cocaine or psychostimulant abstinence or craving, while causing more intolerability-related discontinuations.

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Cocaine and psychostimulant abuse and dependence are a serious public health problem because of the high addictive properties of these agents, association with a variety of neuropsychological complications,[1,2] and their often chronic, relapsing, and progressive course.[3] Agents with prodopaminergic activity include foremost cocaine, psychostimulants (methylphenidate, methamphetamine, amphetamine) and 3,4-methylenedioxymethamphetamine, but nicotine, cannabis, and caffeine all also have some prodopaminergic properties.[4] Among these substances, cocaine has the most addictive property, but psychostimulants that are indicated for use in attention-deficit/hyperactivity disorder are also abused. The possible effects of cocaine and, less so, of psychostimulants include increased alertness, cognitive abilities, excitation, libido, pulse rate, and blood pressure, as well as euphoria, insomnia, and loss of appetite.[5,6] Moreover, stimulation or exacerbation of motor tics and psychosis can occur.[7] Effects of overdosing on cocaine, methylphenidate, or amphetamine/methamphetamine include agitation, increased body temperature, hallucinations, convulsions, and possible death. Withdrawal symptoms may include apathy, long periods of sleep, irritability, depression, and disorientation.[8]

The effects during cocaine and psychostimulant ingestion described above are considered to be produced by dopamine receptor stimulation in the mesocorticolimbic system, via either dopamine reuptake inhibition (cocaine, methylphenidate, and amphetamine derivates) or release (amphetamine derivates).[6,9,10] Dopamine transporter inhibition causes an increase of dopamine in the ventral tegmental area, the nucleus accumbens, and prefrontal cortex.[11] Furthermore, dopamine-related behaviors, such as levels of pretreatment impulsivity, aggression, and sensation seeking have been associated with poor treatment outcome in cocaine-dependent patients receiving intensive outpatient treatment.[12] On the basis of these physiologic and behavioral data, antipsychotics, whose therapeutic targets are mainly the blockade of dopamine receptors, have been tried in the treatment of cocaine and psychostimulant dependence.

Recently, Amato and colleagues[13] conducted a meta-analysis of the efficacy and tolerability of antipsychotics in cocaine dependence (n = 293, 7 studies). However, this meta-analysis included 1 study in dual-diagnosis patients (schizophrenia plus cocaine dependence, n = 31)[14] and another study with a very short duration (5 days, n = 20).[15] The authors reported that no significant differences were found for any of the efficacy measures (craving, severity of dependence and depressive symptoms) comparing

Clinical Points

- Although the number of studies and participants was relatively small, antipsychotics had no advantages over placebo in regard to cocaine use as well as cocaine or psychostimulant abstinence or craving.
- Despite lacking evidence for efficacy in primary cocaine and psychostimulant dependence, antipsychotics caused more intolerability-related discontinuations compared to placebo.
- Strategies other than blocking dopamine transmission need to be utilized to treat primary cocaine and psychostimulant dependence.

antipsychotics with placebo.[13] Additionally, the number of studies and sample sizes were limited, and, since 2007, a number of additional randomized controlled trials (RCTs) have been published. Moreover, despite methylphenidate and amphetamine preparations sharing the same mechanism of action as cocaine, RCTs of antipsychotic use for psychostimulant dependence were not included. Therefore, the aim of the current study was to update and synthesize the evidence for the efficacy and tolerability of antipsychotics in patients with cocaine or psychostimulant dependence.

METHOD

This meta-analysis was performed according to the guidelines of preferred reporting items for systematic reviews and meta-analyses (PRISMA) 2009.[16]

Inclusion Criteria

We included RCTs of antipsychotics lasting ≥ 2 weeks in patients with a primary diagnosis of dependence to cocaine or psychostimulants, based on *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*) or *International Classification of Diseases* (*ICD*) criteria. Since antipsychotics have a benefit for the treatment of major psychiatric disorders, such as bipolar disorder or psychotic disorders,[17–20] we did not include patients with comorbid major psychiatric disorders, aiming to assess whether antipsychotics have independent benefits for the treatment of patients with primary cocaine or psychostimulant dependence.

Data Sources

To identify relevant studies, we searched PubMed, the Cochrane Library databases, and PsycINFO citations from database inception until June 24, 2013, without language restriction, using the following keywords: (*randomized* OR *random* OR *randomly*) AND (*placebo*) AND (*methylphenidate* OR *cocaine* OR *methamphetamine* OR *amphetamine* OR *3,4-methylenedioxymethamphetamine* [*MDMA*]) AND (*dependence* OR *abuse*) AND (*antipsychotic* OR *neuroleptic* OR *risperidone* OR *olanzapine* OR *aripiprazole* OR *quetiapine* OR *perospirone* OR *ziprasidone* OR *clozapine* OR *amisulpride* OR *asenapine* OR *blonanserin* OR *clotiapine* OR *iloperidone* OR *lurasidone* OR *mosapramine* OR *paliperidone* OR *remoxipride* OR *sertindole* OR *sulpiride* OR *tiapride* OR *chlorpromazine* OR *thioridazine* OR *mesoridazine* OR *loxapine* OR *molindone* OR *perphenazine* OR *thiothixene* OR *trifluoperazine* OR *haloperidol* OR *fluphenazine* OR *droperidol* OR *zuclopenthixol* OR *pimozide* OR *flupenthixol* OR *prochlorperazine*). Complementing the electronic search, pertinent review articles, prior reviews, and reference lists from identified studies were hand searched for additional studies eligible for inclusion in this meta-analysis. Two authors (T.K. and C.U.C.) checked the inclusion and exclusion criteria of the identified studies.

Data Extraction

When data required for the meta-analysis were missing or available data were significantly skewed (ie, value of standard deviation (SD) was more than double that of the mean, especially in change scores), first/corresponding authors were contacted for additional information (including endpoint scores). Two researchers (T.K. and Y.M.) independently extracted, checked, and entered data into Review Manager. Any discrepancies were resolved by discussion and consensus.

Outcome and Data Synthesis

To increase precision of the estimates, we included only outcomes in this meta-analysis for which ≥ 3 studies contributed data. Coprimary outcomes included degree of substance use and lack of abstinence. To analyze days of cocaine use, we combined days of use in the past 30 days from 1 study,[21] percentage of days of cocaine use from 1 study,[22] percent change in cocaine use (days/wk) from 1 study,[23] percentage of reduction in cocaine use per day in the past 30 days from 1 study,[24] and days of use during the study from other 1 study.[25] To analyze lack of abstinence, we combined the number of patients who did not maintain negative cocaine or methamphetamine screens throughout the treatment period[24,26–28] with the number of those without negative cocaine or methamphetamine screens at the last visit.[25,29] Secondary outcomes included addiction/dependence severity (combining scores from the Addiction Severity Index-drug composite scores [ASI-DCS][30] and the Severity of Dependence Scale [SDS]),[31] craving, depressive symptoms, the Hamilton Anxiety Rating Scale (HARS),[32] Clinical Global Impressions-Severity of Illness scale (CGI-S),[33] all-cause and specific-cause discontinuation (we included the number of patients who reduced or stopped the study drug due to side effects in the outcome "discontinuation due to side effects" from 1 study[28]), average compliance, presence of at least 1 side effect, severe side effects, dizziness/postural hypotension, and drowsiness. To analyze craving, 5 of 7 studies[21,22,25,29,34] used the Brief Substance Craving Scale,[35] and 2 other studies used a Visual Analog Scale (1 study[23] used percent change in cocaine craving to compare the first 2 weeks in treatment to the last 2 weeks in treatment and 1 other study[28] used endpoint scores). To assess depressive symptoms, 5 studies[21,22,24,25,34] used the Hamilton Depression Rating Scale (HDRS),[36] 1 study[37] used the Beck Depression Inventory (BDI),[38] and 1 other study[28] used the Center for Epidemiologic Studies

Depression Scale (CES-D).[39] To analyze average compliance, 1 study[28] used medication event monitoring system, and 2 other studies[21,26] used pill count.

Analyses were basically of the full intention-to-treat trial populations. However, data of completer analyses (ASI-DCS, HDRS, and CGI-S from 1 study[34]) were also included in order to obtain as much information as possible. Further, since Kampman et al[21] did not report the SD of average compliance, we imputed the SD from Hamilton et al,[26] as has been done before.[40]

Statistical Analysis

We combined outcome data across trials with standard meta-analytic methods. When SDs or number of participants in the experimental or control groups were missing, we contacted the trial authors. The meta-analysis was performed using Review Manager (RevMan) version 5.1 for Windows (Review Manager version 5.0, Cochrane Collaboration: http://ims.cochrane.org/revman). To combine studies, we used the random-effects model by DerSimonian and Laird[41] in all cases. For continuous data, we analyzed the standardized mean difference (SMD) with its 95% confidence interval (CI), combining the effect size (Hedges *g*) data. For dichotomous data, the risk ratio (RR) was estimated, again with its 95% CI. In the case of significant between-group differences, the number needed to treat (NNT) or number needed to harm (NNH) among participants was calculated by dividing 1 by the risk difference, with the 95% CIs of NNT being the inverse of the upper and lower limits of the 95% CI of the risk difference.

Study heterogeneity was measured by using the χ^2 and I^2 statistics, with $P < .05$ for χ^2 and $I^2 < 50\%$ indicating heterogeneity (Cochrane Handbook, version 5.1.0; http://cochrane-handbook.org/).[42] In cases in which I^2 was $\geq 50\%$ in the primary outcome, sensitivity analyses were conducted to seek reasons for the heterogeneity. Finally, funnel plots were constructed in RevMan for the primary outcome and visually inspected to assess for publication bias. We also assessed the methodological quality of the articles included in the meta-analysis based on Cochrane Risk of Bias Criteria (Cochrane Collaboration: http://bmg.cochrane.org/assessing-risk-bias-included-studies).

RESULTS

Search Results

The search in PubMed, Cochrane Library databases, and PsycINFO yielded 363 hits. We excluded 316 duplicate studies across the 3 databases as well as 20 studies based on title or abstract review, leaving a total of 27 articles. An additional 13 full-text articles were excluded because they were reviews (6 articles), were studies of non-antidopaminergic drugs (4 articles),[43–46] included patients with dual diagnosis (1 article),[47] or had a study duration of < 2 weeks (2 articles),[15,48] yielding 14 eligible studies (Supplementary eFigure 1).[21–29,34,37,49–51] We did not find any additional studies from review articles[13,52–54] or reference lists of included trials.

Study Characteristics

The 14 randomized placebo-controlled trials of antipsychotics for cocaine or psychostimulant dependence (n = 741) included 10 cocaine dependence studies (n = 562)[21–27,34,49,50] and 4 amphetamine/methamphetamine dependence studies (n = 179)[28,29,37,51] (Table 1). All included studies were double-blind RCTs, and all were published in English. One study[51] was conducted in Finland, another study[29] was conducted in Malaysia, and the remaining 12 studies were all conducted in the United States.

With the exception of 2 studies,[29,34] all studies were of high methodological quality based on Cochrane Risk of Bias Criteria, as all studies were double-blind, placebo-controlled, and mentioned the required details of the study design (Supplementary eFigure 2). Data of completer analyses (ASI-DCS, HDRS, and CGI-S) from 1 study[34] and number of patients who were negative methamphetamine screens at the last visit from 1 other study[29] were also included in the analyses in order to obtain as much information as possible. Four studies[25,29,37,50] were of short study duration (< 10 weeks); 9 studies[21–26,29,37,50,51] had small sample sizes (total n < 50) (Table 1). Antipsychotics studied in the RCTs included aripiprazole (4 trials, n = 179: 2 trials with 15-mg fixed dose, 1 trial with 20-mg fixed dose, 1 trial with 5- to 10-mg dose, all amphetamine/methamphetamine dependence),[28,29,37,51] olanzapine (3 trials, n = 112: 2 trials with 10-mg fixed dose; 1 trial with flexible dose [2.5–20 mg/d], all cocaine dependence),[21,25,26] reserpine (2 trials, n = 149: fixed dose [0.5 mg/d], all cocaine dependence),[22,34] and risperidone (5 trials, n = 301: 3 trials with fixed oral dose [1, 2, 4, and 8 mg/d], 1 trial with fixed long-acting injectable dose [25 mg every 2 weeks; oral dose equivalent = 2 mg/d], and 1 trial with flexible dose [1–6 mg/d], all cocaine dependence)[23,24,27,49,50] (Table 1). Patients in all included studies did not need to be abstinent at baseline.

Substance Use

Only data from studies on cocaine dependence, but none from those on methamphetamine dependence, were analyzable. When study results were both pooled together (SMD = 0.19; 95% CI, −0.18 to 0.56; $P = .32$; 5 studies, n = 136) and assessed individually, antipsychotics were not superior to placebo in regard to cocaine use (Figure 1). No significant heterogeneity was observed ($\chi^2 = 4.70$, $P = .32$ and $I^2 = 15\%$), and no publication bias was apparent (Supplementary eFigure 3).

Lack of Abstinence

When study results were both pooled together (RR = 0.98; 95% CI, 0.82 to 1.16; $P = .78$; 6 studies, n = 362) and assessed individually, antipsychotics were not different from placebo in regard to lack of abstinence (Figure 2). Although results were marginally significantly heterogeneous ($\chi^2 = 9.94$, $P = .08$, $I^2 = 50\%$), we did not find significant subgroup differences when we subdivided these studies based on antipsychotic ($P = .79$, $I^2 = 0\%$). Therefore, we performed a sensitivity analysis. When dividing studies by the substance

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

Study, Country, Sponsor	Total n	Duration, wk	Dependence Criteria	Drug of Abuse	Comorbid Disorders (%)	White, %	Age, Mean (SD), y	Male, %	Treatment, n	Total Drop Out, %	Dose, Mean (range/fixed), mg/d	Psychotherapy and/or Concomitant Drugs, %	Efficacy Outcomes[a]
Psychostimulant dependence													
Aripiprazole													
Coffin et al 2013[28] United States Nonindustry	90	12	*DSM-IV-TR*	Methamphetamine dependence (patients had interest in reducing or stopping methamphetamine use and had methamphetamine metabolite–positive urine results at screening)	No acute medical or psychiatric illness	50	Aripiprazole: 37.4 (12.3) Placebo: 40 (8.9) [range, 18–60]	Aripiprazole: 86.7 Placebo: 88.9	Aripiprazole: 45 Placebo: 45	22.0 40.0	20 (fixed) Not reported	Psychotherapy (100)	Aripiprazole = placebo: methamphetamine use, CES-D, Craving (VAS), SDS
Newton et al 2008[37] United States Nonindustry	16	2	*DSM-IV-TR*	Amphetamine/methamphetamine dependence (all patients not seeking treatment)	Nicotine abuse	75	Aripiprazole: 32.5 (6.4) Placebo: 28.3 (7.9) [range, 18–45]	Aripiprazole: 100 Placebo: 87.5	Aripiprazole: 8 Placebo: 8	0 0	15 (fixed) Not reported	No	Aripiprazole = placebo: craving (VAS), BSCS, BDI
Sulaiman et al 2013[29] Malaysia Nonindustry	37	8	*DSM-IV*	Methamphetamine dependence (methamphetamine use at least once a week for the prior 3 mo) (all patients from a previously completed 2-wk open-label trial with aripiprazole 10 mg were included)	Nicotine abuse (83.8), alcohol abuse (5.41), cannabis abuse (37.8)	Not reported	Aripiprazole: 35.5 (8.5) Placebo: 32.9 (8.4) [range, 18–60]	Aripiprazole: 94.7 Placebo: 94.4	Aripiprazole: 19 Placebo: 18	15.8 55.6	Not reported (5–10)	Lorazepam (21.6) Zolpidem (2.7) Escitalopram (2.7)	Aripiprazole = placebo: methamphetamine use Aripiprazole > placebo: PANSS
Tiihonen et al 2007[51] Finland Nonindustry	36	20	*DSM-IV*	Amphetamine/methamphetamine dependence (recent use confirmed by urine test)	Not reported	100	Aripiprazole: 32.2 (6.1) Placebo: 40.0 (10.1) [range, 18–65]	33.3	Aripiprazole: 19 Placebo: 17	89.5 76.4	15 (fixed) Not reported	Psychotherapy (100)	Aripiprazole < placebo: amphetamine/methamphetamine use
Cocaine dependence													
Olanzapine													
Hamilton et al 2009[26] United States Industry	48	16	*DSM-IV*	Cocaine dependence (active use of cocaine within the past 30 d)	Alcohol abuse (85.1), heroin abuse (6.4), methadone abuse (10.6), other opioid abuse (8.5), hypnotics abuse (14.9), cannabis abuse (25.5), dysthymia (2.1%), PTSD (2.1%), OCD (4.2%)	14.6	45.8 (6.8) [range, 33–60]	100	Olanzapine: 23 Placebo: 25	Not reported Not reported	6.8 (2.5–20) Not reported	Psychotherapy (100)	Olanzapine = placebo: cocaine use, ASI, Craving Questionnaire
Kampman et al 2003[21,b] United States Industry	30	12	*DSM-IV*	Cocaine dependence (≥ $100 worth of cocaine use in the month prior to study entry)	Nicotine dependence, alcohol dependence (not requiring benzodiazepines for detoxification)	3.3	Olanzapine: 42 (6.26) Placebo: 40.58 (5.79) [range, 18–60]	73.3	Olanzapine: 15 Placebo: 15	13.3 6.67	10 (fixed) Not reported	Psychotherapy (100)	Olanzapine < placebo: cocaine use Olanzapine = placebo: ASI, BSCS, HARS, HDRS
Reid et al 2005[25,b] United States Nonindustry	34	8	*DSM-IV*	Cocaine dependence (≥ 2 positive urine benzoylecgonine specimens [> 300 ng/mL] within the 2-wk baseline period prior to randomization with ≥ 4 samples tested)	None	9.68	Olanzapine: 38.9 (5.1) Placebo: 40.1 (4.6)	80.6	Olanzapine: 18 Placebo 16	50.0 43.8	10 (fixed) Not reported	Psychotherapy (100) Amitriptyline (4.41) Zolpidem (1.47) Alprazolam (1.47)	Olanzapine = placebo: cocaine use, ASI, HARS, HDRS Olanzapine < placebo: BSCS, CCQ

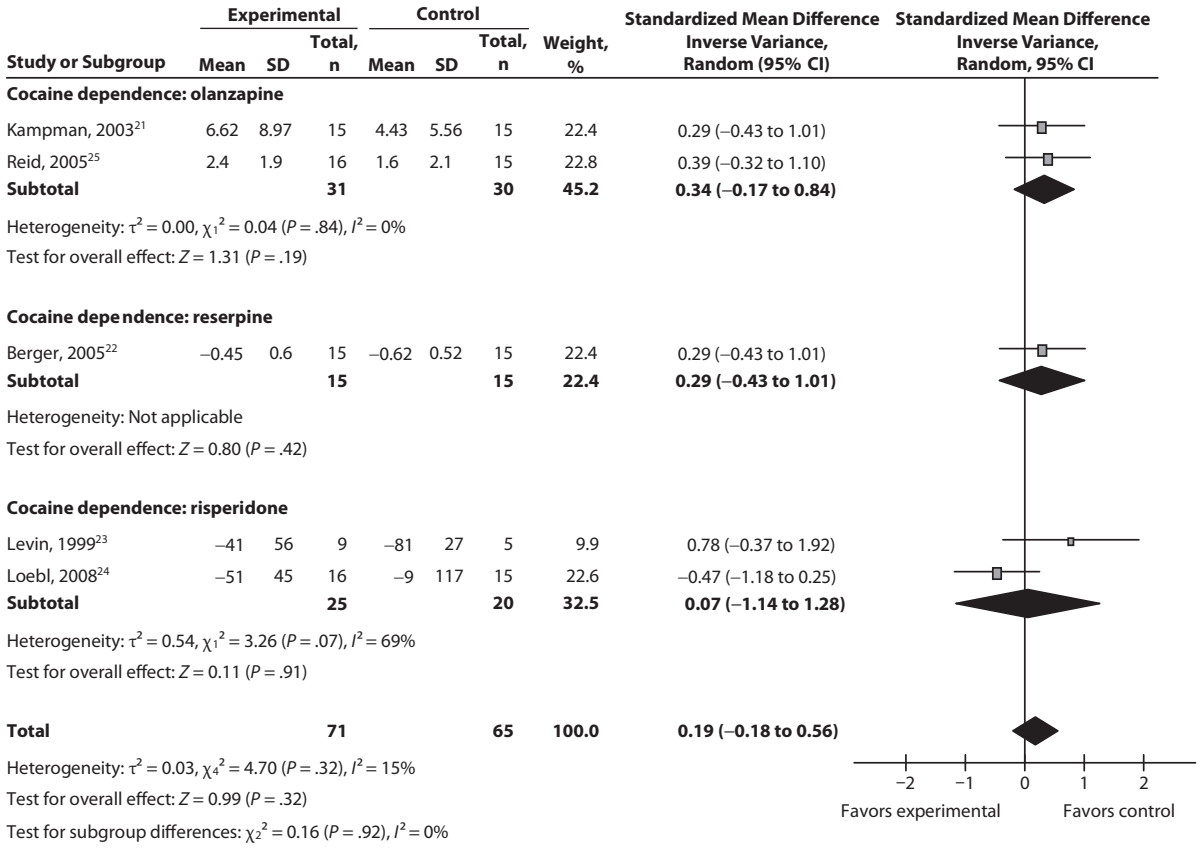
(continued)

Table 1 (continued). Study and Patient Characteristics of Randomized Double-Blind, Placebo-Controlled Trials of Antipsychotics for Amphetamine and Cocaine Dependence

Study, Country, Sponsor	Total n	Duration, wk	Dependence Criteria	Drug of Abuse	Comorbid Disorders (%)	White, %	Age, Mean (SD), y	Male, %	Treatment, n	Total Drop Out, %	Dose, Mean (range/fixed), mg/d	Psychotherapy and/or Concomitant Drugs, %	Efficacy Outcomes[a]
Reserpine													
Berger et al 2005[22] United States Nonindustry	30	10	*DSM-IV*	Cocaine dependence (≥ 2 positive urine benzoylecgonine specimens [> 300 ng/mL] within the 2-wk baseline period prior to randomization with ≥ 4 samples tested)	None	13.3	Reserpine: 39.5 (5.2) Placebo: 39.5 (6.5)	63.3	Reserpine:15 Placebo:15	26.6 6.7	0.5 (fixed) Not reported	Psychotherapy (100)	Reserpine > placebo: <u>cocaine use</u>
Winhusen et al 2007[34] United States Nonindustry	119	12	*DSM-IV*	Cocaine dependence (≥ 1 positive urine test during screening)	Alcohol dependence (not requiring detoxification from alcohol)	18.5	Reserpine: 41.2 (7.4) Placebo: 40.7 (7.9)	70.6	Reserpine: 60 Placebo: 59	30.0 37.3	0.5 (fixed) Not reported	Psychotherapy (100)	Reserpine = placebo: <u>cocaine use</u>, ASI, BSCS, HDRS
Risperidone													
Grabowski et al 2000[27] United States Nonindustry	125	12	*DSM-IV*	Cocaine dependence (all patients in good medical health and without other psychiatric diagnoses)	Nicotine dependence	43	34.8 (7.0)	74	Risperidone 2 mg: 30 Risperidone 4 mg: 38 Risperidone 8 mg: 12 Placebo: 45	76.7 92.1 100.0 93.3	2 (fixed) 4 (fixed) 8 (fixed) Not reported	Psychotherapy (100) Riboflavin (100)	Risperidone 2 mg = risperidone 4 mg = risperidone 8 mg = placebo: <u>cocaine use</u>
Grabowski et al 2004[49,b] United States Nonindustry	96	24	*DSM-IV*	Cocaine dependence (all patients in good medical health and without other psychiatric diagnoses)	Nicotine dependence	79.2	36.9 (7.5) [range, 18–50]	59.4	Risperidone 2 mg: 32 Risperidone 4 mg: 31 Placebo: 33	65.6 54.4 78.8	2 (fixed) 4 (fixed) Not reported	Psychotherapy (100) Riboflavin (100)	Risperidone 2 mg = risperidone 4 mg = placebo: <u>cocaine use</u>
Levin et al 1999[23,b] United States Nonindustry	14	12	*DSM-IV*	Cocaine dependence (all patients without any other Axis I disorder requiring psychiatric treatment)	None	14.3	Risperidone: 37.8 (5.5) Placebo: 42.0 (7.5)	82.1	Risperidone: 9 Placebo: 5	33.3 20.0	2.1 (1.1) (1–6) Not reported	Psychotherapy (100)	Risperidone = placebo: <u>cocaine use</u>, craving (VAS)
Loebl et al 2008[24] United States Industry	31	12	*DSM-IV*	Cocaine dependence (cocaine use ≥ once every other wk confirmed by self-report)	Alcohol dependence (29), depressive disorder (22.6), anxiety disorder (25.9)	38.7	Risperidone-LAI: 44.1 (5.9) Placebo: 42.4 (6.4) [range, 18–60]	100	Risperidone-LAI: 16 Placebo: 15	50.0 60.0	25 (fixed) Not reported	Psychotherapy (100)	Risperidone = placebo: <u>cocaine use</u>, ASI, MCCS Risperidone < placebo: HDRS
Smelson et al 2004[50,b] United States Industry	35	2	*DSM-IV*	Cocaine dependence (≥ 6 g cocaine in the past mo)	None	Not reported	Risperidone: 41.1 (8.1) Placebo: 41.3 (6.1)	Not reported	Risperidone: 19 Placebo: 16	5.26 12.5	1 (fixed) Not reported	Psychotherapy (100)	Risperidone = placebo: <u>VCCQ</u>

[a]Primary outcomes were underlined.
[b]Included in the previous meta-analysis of 5 studies (Amato et al[13]).
Abbreviations: ASI = Addiction Severity Index, BDI = Beck Depression Inventory, BSCS = Brief Substance Craving Scale, CCQ = Cocaine Craving Questionnaire, CES-D = Center for Epidemiologic Studies Depression Scale, CQ = Craving Questionnaire, HARS = Hamilton Anxiety Rating Scale, HDRS = Hamilton Depression Rating Scale, MCCS = Minnesota Cocaine Craving Scale, OCD = obsessive-compulsive disorder, PANSS = Positive and Negative Symptoms Scale, PTSD = posttraumatic stress disorder, LAI = long-acting injection, SDS = Severity of Dependence Scale, Stim = stimulant, VAS = Visual Analog Scale, VCCQ = Voris Cocaine Craving Questionnaire.

Figure 1. Cocaine Use



of dependence, the significant heterogeneity of cocaine dependence disappeared ($P = .29$, $I^2 = 20\%$), whereas that of methamphetamine remained significant, at least based on the I^2 value ($P = .15$, $I^2 = 52\%$). Nevertheless, results remained nonsignificant in both subgroups. Antipsychotic treatment was not superior to placebo in regard to lack of abstinence for cocaine (RR = 0.91, $P = .19$) as well as for methamphetamine (RR = 1.06, $P = .80$). No publication bias was apparent (Supplementary eFigure 4).

ASI-DCS and SDS Scores

When study results were both pooled together (SMD = –0.06; 95% CI, –0.43 to 0.32; $P = .77$; 6 studies, n = 269) and assessed individually, antipsychotics did not differ from placebo in regard to ASI-DCS and SDS scores, but results were heterogeneous ($\chi^2 = 11.15$, $P = .05$, $I^2 = 55\%$). When the data based on completer analysis were excluded,[34] the result did not change (SMD = –0.08; 95% CI, –0.56 to 0.41; $P = .76$; $I^2 = 64\%$).

Craving

When study results were pooled together, antipsychotics did not differ significantly from placebo in regard to cocaine craving (SMD = 0.04; 95% CI, –0.38 to 0.47; $P = .84$; 7 studies, n = 297), but results were heterogeneous ($\chi^2 = 17.72$, $P = .007$, $I^2 = 66\%$) (Figure 3). However, the overall trend level was due to the fact that, individually, olanzapine was inferior to placebo in regard to the reduction in craving (SMD = 0.59; 95% CI, 0.07 to 1.10; $P = .03$; 2 studies, n = 61) (Figure 3). When data from the completer analysis were excluded,[34] the pooled result remained nonsignificant (SMD = 0.11; 95% CI, –0.40 to 0.62; $P = .67$; $I^2 = 69\%$).

Depressive Symptoms

When study results were pooled together, antipsychotics did not affect depressive symptom scores differently than placebo (SMD = 0.23; 95% CI, –0.22 to 0.67; $P = .32$; 7 studies, n = 285), but results were heterogeneous ($\chi^2 = 18.99$, $P = .004$, $I^2 = 68\%$). However, individually, risperidone was inferior in regard to depression compared to placebo (SMD = 1.26, 95% CI, 0.48 to 2.04; $P = .002$; 1 study, n = 31). Excluding data from the completer analysis[34] did not change the result (SMD = 0.34; 95% CI, –0.14 to 0.82; $P = .16$; $I^2 = 64\%$).

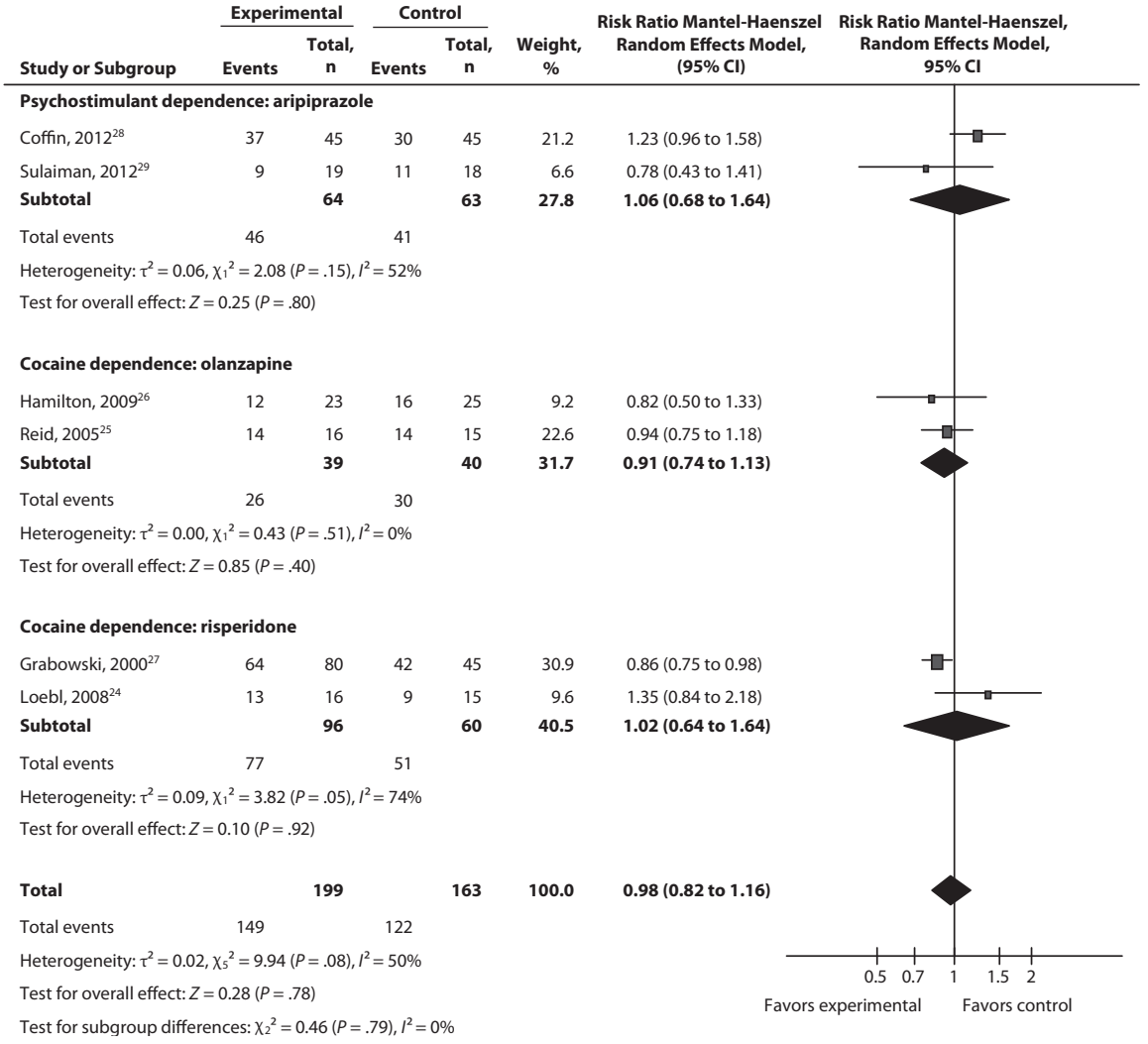
HARS Scores

When study results were pooled together, antipsychotics were not superior to placebo in regard to HARS scores (SMD = 0.25; 95% CI, –0.62 to 1.11; $P = .58$; 3 studies, n = 91), but results were heterogeneous ($\chi^2 = 8.36$, $P = .02$, $I^2 = 76\%$).

CGI-S Scores

When study results were pooled together, antipsychotics were not superior to placebo in regard to CGI-S scores (SMD = –0.14; 95% CI, –0.62 to 0.34; $P = .56$; 5 studies,

Figure 2. Lack of Abstinence



n = 195), but results were heterogeneous ($\chi^2 = 10.59$, $P = .03$, $I^2 = 62\%$). However, individually, aripiprazole was superior to placebo in CGI-S scores (SMD = −1.14; 95% CI, −1.85 to −0.44; $P = .001$; 1 study, n = 37). Excluding data from the completer analysis[34] did not change the result (SMD = −0.17; 95% CI, −0.83 to 0.50; $P = .62$; $I^2 = 71\%$).

Average Compliance

When study results were both pooled together and assessed individually, antipsychotics and placebo did not differ in regard to compliance (SMD = −0.12; 95% CI, −0.47 to 0.24; $P = .52$; 3 studies, n = 168), and results were not heterogeneous ($\chi^2 = 2.58$, $P = .28$, $I^2 = 22\%$).

Treatment Discontinuation

All-cause discontinuation. When study results were pooled together, antipsychotics and placebo did not differ in regard to all-cause discontinuation (RR = 0.94; 95% CI, 0.81 to 1.08; $P = .37$; 14 studies, n = 741), and results were homogeneous ($\chi^2 = 14.71$, $P = .26$, $I^2 = 18\%$). When the results were assessed individually, risperidone was associated with a marginally higher risk of all-cause discontinuation than placebo (RR = 0.91; 95% CI, 0.82 to 1.01; $P = .06$; 5 studies, n = 301). Other antipsychotics did not significantly differ from placebo.

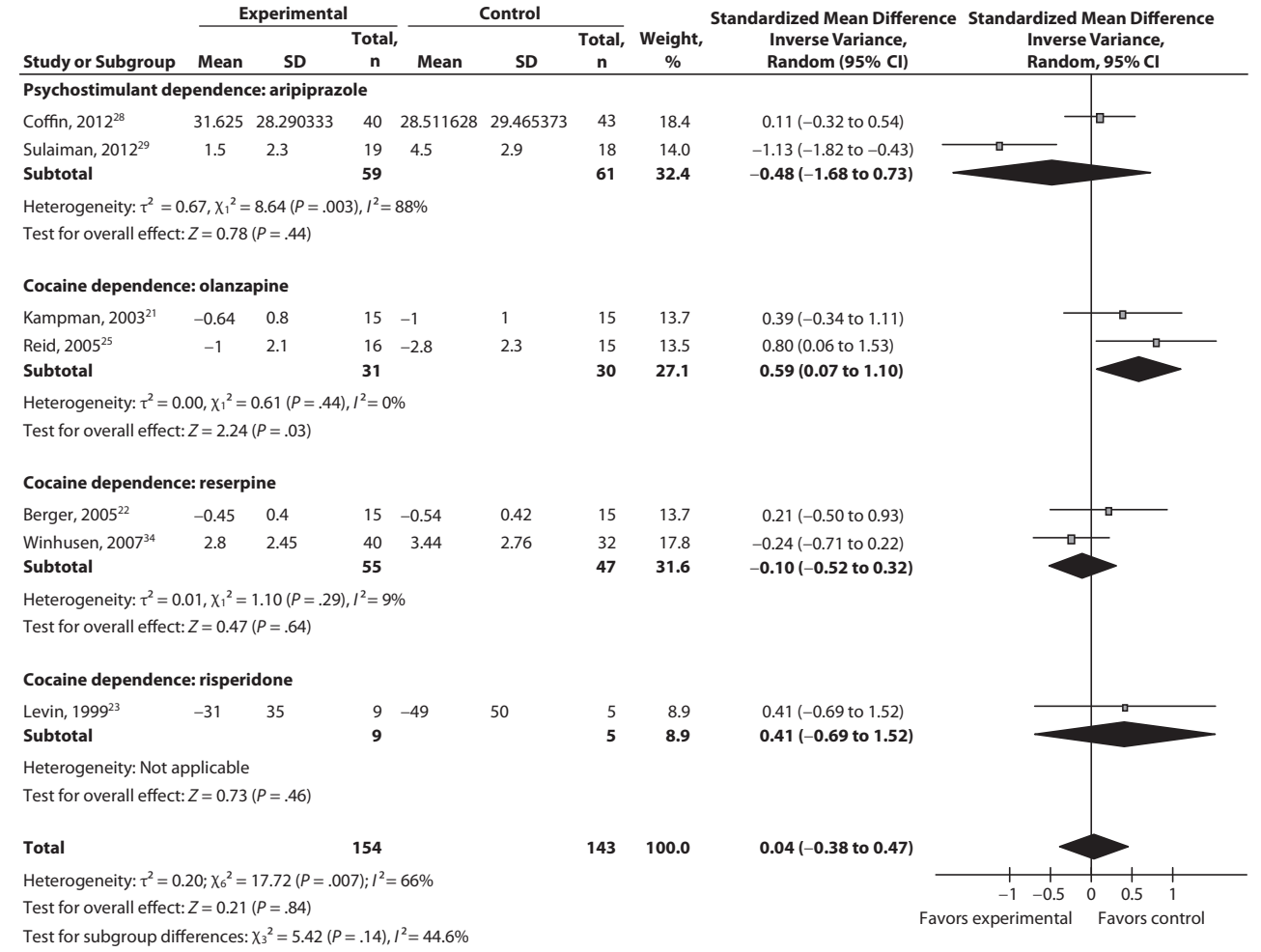
Discontinuation Due to Side Effects

When study results were pooled together, antipsychotics were associated with significantly greater rates of discontinuation due to side effects than placebo (RR = 4.48; 95% CI = 1.85 to 10.85; $P = .0009$; $I^2 = 0\%$; NNH = 14; $P = .02$; 8 studies, n = 378), and results were homogeneous ($\chi^2 = 0.14$, $P = 1.00$, $I^2 = 0\%$) (Figure 4). When study results were assessed individually, aripiprazole was associated with more discontinuation due to side effects than placebo (RR = 4.64; 95% CI, 1.56 to 13.86; $P = .006$; $I^2 = 0\%$; NNH = not significant; 4 studies, n = 179).

Side Effects

Limited results based on 3–4 studies showed no group differences for the following side effects: at least 1 side effect ($P = .73$, $I^2 = 0\%$), severe side effects ($P = .93$, $I^2 = 0\%$),

Figure 3. Craving



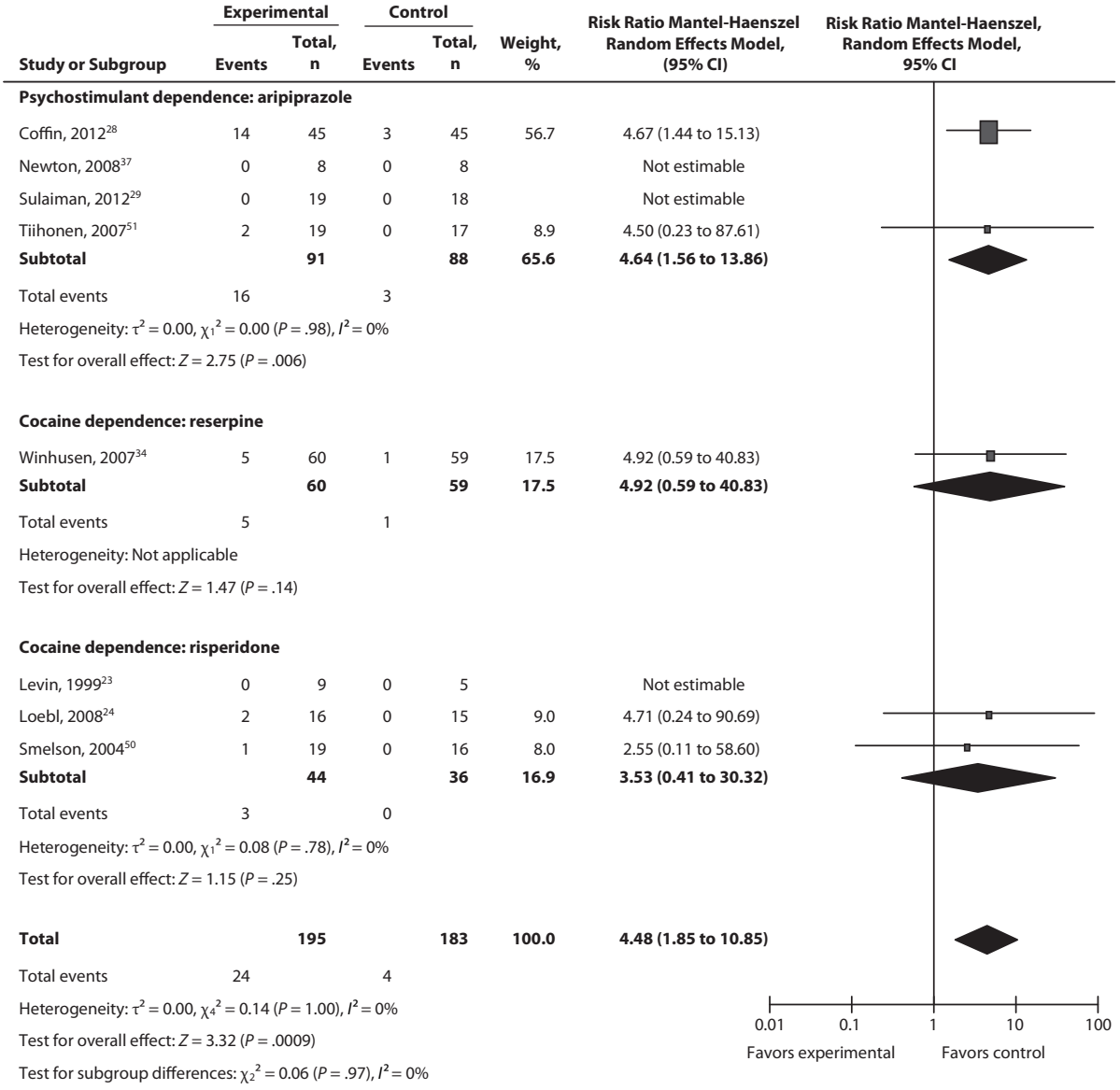
dizziness/postural hypotension ($P = .91$, $I^2 = 0\%$), infection ($P = .68$, $I^2 = 0\%$), and drowsiness ($P = .12$, $I^2 = 9\%$). Akathisia was significantly more common with antipsychotics than placebo (RR = 2.80; 95% CI, 1.12 to 6.98; $P = .03$; $I^2 = 31\%$; NNH = 5; $P = .0001$; 4 studies, n = 191). When study results were assessed individually, aripiprazole was associated with more frequent akathisia than placebo (RR = 5.47; 95% CI, 1.84 to 16.27; $P = .002$; $I^2 = 0\%$; NNH = 5; $P = .0001$; 3 studies, n = 143).

DISCUSSION

Findings from this comprehensive meta-analysis of 14 studies and 741 randomized subjects with either cocaine dependence (10 studies, n = 562) or psychostimulant dependence (4 studies, n = 179) suggest lack of efficacy of antipsychotics for reducing cocaine use and for achieving abstinence from cocaine or methamphetamine. Across several secondary efficacy outcomes, antipsychotics were also not superior to placebo. Moreover, olanzapine was associated with a significantly weaker reduction in cocaine craving than placebo. Conversely, although rates of all-cause discontinuation were similar to those of placebo, antipsychotics pooled together were associated with greater levels of intolerability-related discontinuation than placebo. Moreover, antipsychotics (especially aripiprazole) were associated with significantly more akathisia than placebo. Unfortunately, except for dizziness/postural hypotension, no other individual adverse events relevant for antipsychotic use, such as extrapyramidal side effects, weight gain, or effects on glucose and lipid parameters, were reported by at least 3 studies. Although the overall conclusions are similar to the only prior meta-analysis on this topic,[13] the current meta-analysis included 4 additional placebo-controlled trials conducted in primary cocaine dependence lasting at least 2 weeks, which also enables the meta-analysis of additional outcomes, increasing the confidence in the findings. Moreover, 4 studies in psychostimulant dependence were meta-analyzed for the first time, showing the same results, lending further support to the interpretation of the data in that antipsychotics are not effective for primary dependence to dopamine agonistic agents.

The findings from this meta-analysis are in contrast to our hypothesis that dopamine blockade would counter the effects of substances of abuse that are reinforcing due to increased dopamine transmission. However, although studies of antipsychotics that were both pooled together

Figure 4. Discontinuation Due to Side Effects



and assessed individually did not affect average compliance differently than placebo in the meta-analysis, most patients were actively using either cocaine or psychostimulants, and, since adherence was not formally assessed or assured across these studies, results could be due to both a lack of effect of antipsychotics or decreased efficacy secondary to covert nonadherence. Moreover, there were only 3 studies that reported meta-analyzable data for compliance. In fact, 1 study included in the meta-analysis showed a discrepancy between average compliance measured via self-report (aripiprazole = 69%, placebo = 79%) and medication event monitoring system (aripiprazole = 46%, placebo = 39%).[28] However, at least, the lack of any effect of risperidone in the 1 study[24] that used a long-acting injectable antipsychotic with assured adherence argues against a relevant mediating effect of nonadherence, yet the sample was small, so that a type II error cannot be excluded. Alternatively, it is possible that reinforcing or, at least, substance use–maintaining biological pathways are partially independent of dopamine transmission that is blocked with antipsychotic agents. For example, glutamatergic and GABAergic pathways have also been implicated in substance use behaviors in general and in cocaine dependence in particular.[55,56] Moreover, habit formation or anticipated highs due to substance use or lows due to stopping drug use may maintain substance use behaviors, even if the actual effect of the substance is attenuated.[55,56]

Our finding that blocking dopamine D_2 receptors was ineffective for countering continued abuse of substances stimulating that same receptor system raises the general question whether "blockade" of rewarding effects of a substance is the sole or best treatment strategy for addiction. While this general discussion is beyond the scope of this article, it is of interest that opioid dependence can be treated

successfully with an antagonist, such as naltrexone, as well as with an agonist treatment strategy, such as methadone. In this context, it is noteworthy that, in a recent RCT, aripiprazole was superior to ropinirole, a dopamine agonist at D_2, D_3, and D_4 receptors, for reducing cocaine use in cocaine dependent individuals.[57]

Although not related to substance use itself, craving was reduced significantly less with olanzapine than with placebo when results from 2 trials including this outcome were pooled. However, given that a small number of studies contributed to this outcome, the results should be interpreted with caution. In fact, in 2 head-to-head trials of antipsychotics, olanzapine was associated with some favorable outcomes in regard to substance use craving. For example, Machielsen and colleagues[58] reported that psychotic disorder patients with comorbid cannabis dependence treated with olanzapine and clozapine experienced significantly less craving compared with patients treated with risperidone. Moreover, Akerele and Levin[59] also reported that the proportion of cocaine-positive urine tests decreased, with a trend for a greater reduction in the olanzapine group compared to the risperidone group, while marijuana craving was significantly less likely for the olanzapine group compared to the risperidone group. Olanzapine has high affinity for serotonin $(5\text{-HT})_{2A}$, 5-HT_6, dopamine D_2, muscarinic M_1–M_5, and histamine $(H)_1$ receptors.[60] Risperidone has high affinity for the 5-HT_{2A}, 5-HT_7, D_2, D_3, α_1- and α_2-adrenergic, and H_1 receptors.[60] However, although both olanzapine and risperidone are serotonin-dopamine antagonists, the binding of risperidone to the dopamine D_2 receptors is stronger than that with olanzapine,[61] which may explain the finding of inferiority compared to placebo for depressive symptoms found in our meta-analysis. While it was based on only 1 small study with risperidone long-acting injectable,[24] this finding is consistent with a lack of significant antidepressant effects of risperidone in major depressive disorder.[62,63] While the link between depression and substance use craving is less clear,[64] it is possible that ongoing depressive symptoms, even at subsyndromal levels, can fuel substance use craving and self-medicating behaviors. Of note, a recent genetic study[65] reported that a polymorphism in 5-HT_6 receptor gene was associated with methamphetamine-induced psychosis. Thus, the 5-HT_6 receptor may be a therapeutic target for patients with substance dependence, possibly particularly for agents strongly and directly enhancing dopamine transmission.

Furthermore, in dually diagnosed patients with bipolar disorder or schizophrenia, quetiapine and olanzapine were reported to decrease craving for cocaine or psychostimulants significantly more than first-generation antipsychotics or placebo.[14,66,67] However, we did not combine results from studies of antipsychotic effects for cocaine or psychostimulants in dually diagnosed patients with those in patients with primary substance dependence in order to obtain conclusive results on the effects of dopamine blocking agents for substance dependence independent of effects on schizophrenia or bipolar disorder symptoms.

The results of this meta-analysis have to be interpreted within its limitations. These include predominantly the small number of included studies with mostly small sample sizes, the heterogeneity of primary and secondary outcome measures, and the lack of adequate adherence measures. The heterogeneous endpoints used in the identified studies point to the need to develop a consensus on useful study endpoints that should be included across RCTs targeting dopamine agonist (and other substance) dependence. Moreover, a limited number of different antipsychotics were studied in the available RCTs. Furthermore, most trials did not provide sufficient data to comprehensively evaluate efficacy and, especially, tolerability outcomes, and data on the important extrapyramidal and cardiometabolic effects[68–71] were almost absent (Supplementary eFigure 2). In this context, we cannot exclude the possibility of selective reporting in some trials. In addition, although we included an inpatient laboratory study,[37] results did not change when excluding this study. Finally, most studies did not report results of relevant outcomes, such as craving and psychiatric symptoms, although cocaine and psychostimulant dependence are considered to be disorders that involve psychopathology of both impulsivity and compulsivity[72–74] and that are associated with depressive and/or anxiety symptoms, which can further aggravate cocaine and psychostimulant dependence.[75] However, data on these psychopathological domains were largely absent, except for some studies that reported on depressive symptom changes. Although future studies should evaluate antipsychotic effects on psychiatric symptoms in cocaine- and psychostimulant-dependent patients as well, the lack of a primary effect on substance use and achievement of abstinence observed across the included studies reduces the hope that antipsychotics could be useful for these disorders.

CONCLUSION

Results from this meta-analysis suggest that antipsychotics have no efficacy advantages over placebo in regard to cocaine use and in regard to cocaine or methamphetamine abstinence or craving; they, in fact, cause more intolerability-related discontinuations in cocaine- or amphetamine/methamphetamine-dependent patients. Interventions other than antidopaminergic agents need to be studied for the treatment of patients with primary cocaine and psychostimulant dependence. Moreover, consensus development is needed to define useful study endpoints that should be included in all RCTs targeting dopamine agonist (and other substance) dependence.

Drug names: alprazolam (Xanax, Niravam, and others), aripiprazole (Abilify), asenapine (Saphris), clozapine (Clozaril, FazaClo, and others), droperidol (Inapsine and others), escitalopram (Lexapro and others), haloperidol (Haldol and others), iloperidone (Fanapt), lorazepam (Ativan and others), lurasidone (Latuda), methadone (Methadose and others), methylphenidate (Focalin, Daytrana, and others), naltrexone (Vivitrol, ReVia, and others), olanzapine (Zyprexa and others), paliperidone (Invega), pimozide (Orap), prochlorperazine (Compro, Procomp, and others), quetiapine (Seroquel and others), risperidone (Risperdal and others), ropinirole (Requip and others), thiothixene (Navane and others), ziprasidone (Geodon and others), 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: Dr Correll. Acquisition of data and analysis and interpretation of data: Drs Kishi and Matsuda. Drafting of the manuscript: Drs Kishi, Iwata, and Correll. Statistical analysis: Drs Kishi and Correll. Study supervision: Dr Correll.

Potential conflicts of interest: **Dr Kishi** has received speaker's honoraria from Abbott, Astellas, Daiichi Sankyo, Dainippon Sumitomo, Eli Lilly, GlaxoSmithKline, Janssen, Eisai, Yoshitomi, Otsuka, Meiji, Shionogi, Tanabe-Mitsubishi, Tsumura, Novartis, and Pfizer. **Dr Matsuda** has received speaker's honoraria from Eli Lilly and Otsuka. **Dr Iwata** has received speaker's honoraria from Astellas, Dainippon Sumitomo, Eli Lilly, GlaxoSmithKline, Janssen, Yoshitomi, Otsuka, Meiji, Shionogi, Novartis, and Pfizer. **Dr Correll** has been a consultant and/or advisor to or has received honoraria from Actelion, Alexza, Bristol-Myers Squibb, Cephalon, Eli Lilly, Genetech, Gerson Lehrman Group, IntraCellular Therapies, Janssen/Johnson & Johnson, Lundbeck, Medavante, Medscape, Merck, Otsuka, Pfizer, ProPhase, Roche, Sunovion, Takeda, Teva, and Vanda; and has received grant/research support from Bristol-Myers Squibb, Janssen/Johnson & Johnson, and Otsuka.

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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: Antipsychotics for Cocaine or Psychostimulant Dependence: Systematic Review and Meta-Analysis of Randomized, Placebo-Controlled Trials

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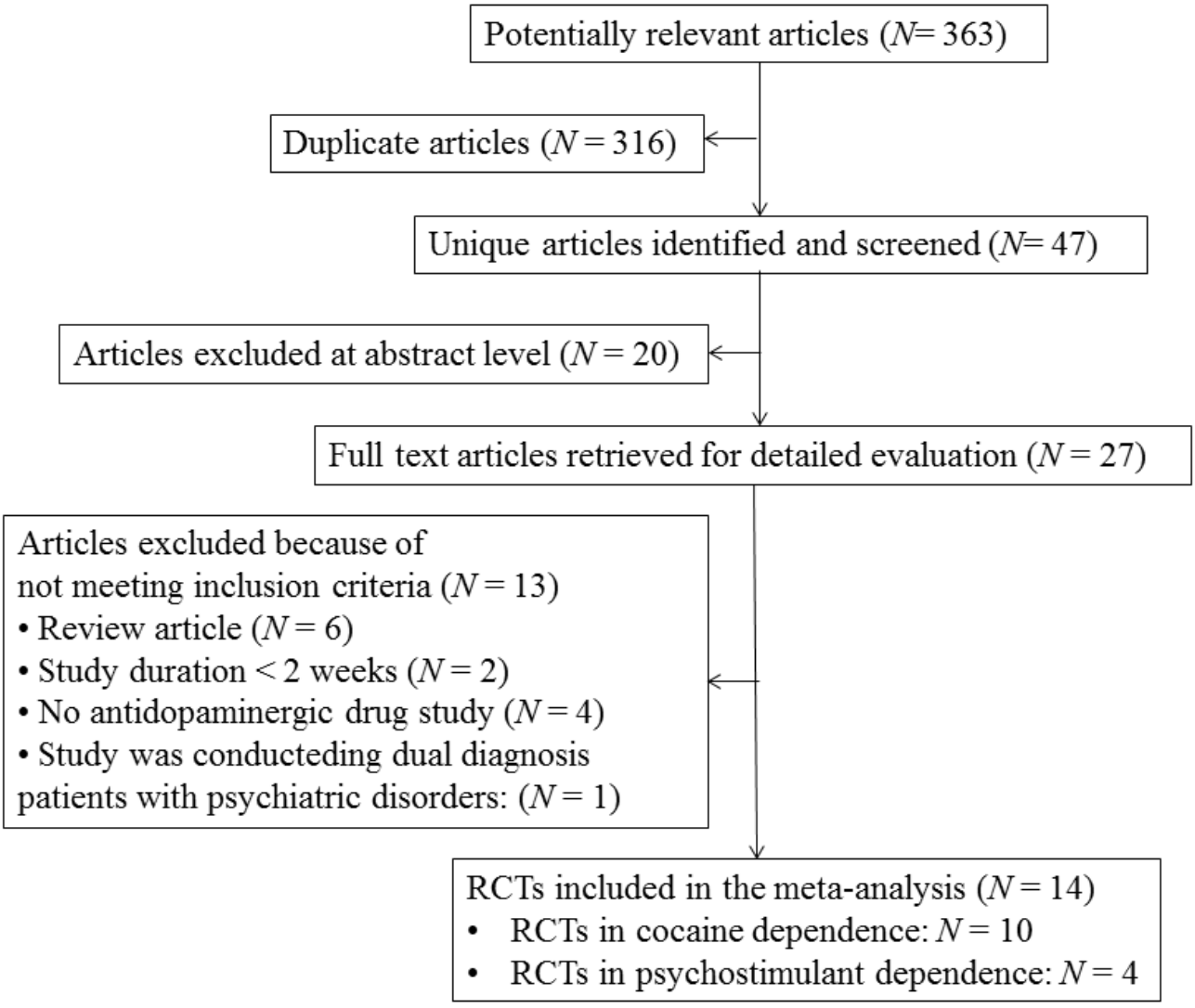
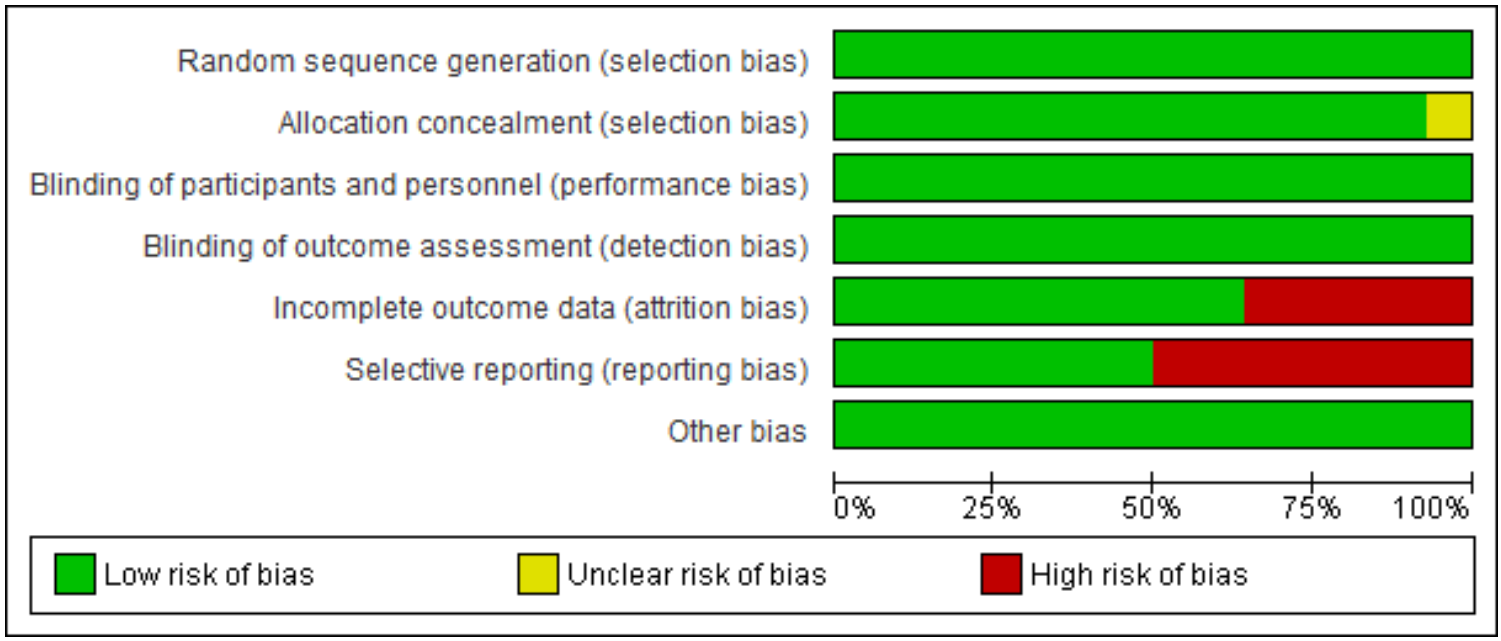
List of Supplementary Material for the article

Disclaimer

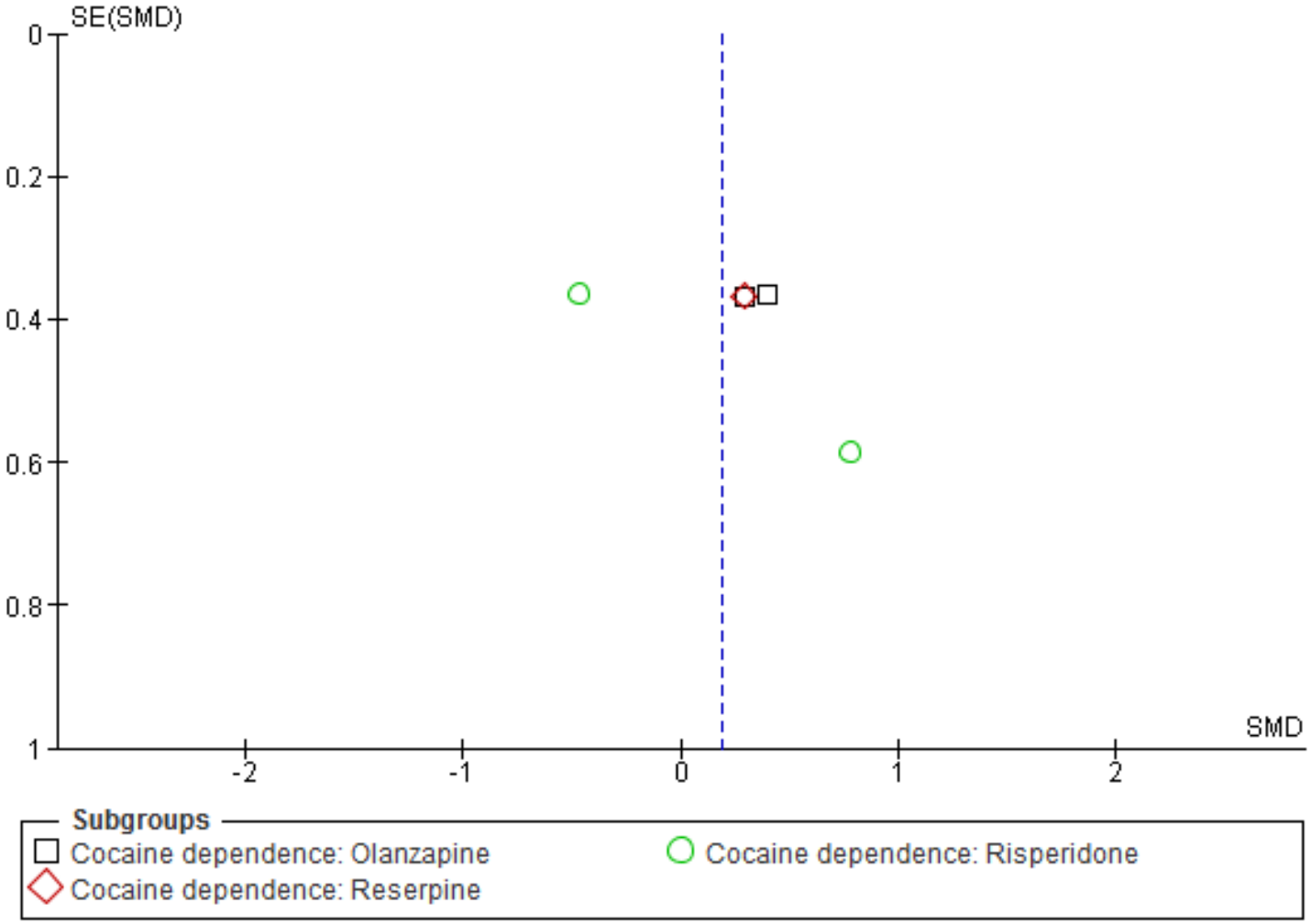
Supplementary eFigure 1. PRISMA flow diagram



Supplementary eFigure 2. Risk of Bias Graph



Supplementary eFigure 3. Funnel Plot of Cocaine Use



Supplementary eFigure 4. Funnel Plot of Lack of Abstinence