Tolerability and Safety Profile of Cariprazine in Treating Psychotic Disorders, Bipolar Disorder and Major Depressive Disorder: A Systematic Review with Meta-Analysis of Randomized Controlled Trials

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Abstract

Background

Cariprazine is a novel antipsychotic agent recently approved for treating schizophrenia and bipolar mania in the USA. The sample sizes of published randomized controlled trials (RCTs) of the drug are small; previous meta-analyses included few RCTs and did not specifically investigate the tolerability/safety profile of cariprazine.

Objective

Our objective was to conduct a meta-analysis of published RCTs to systematically review the tolerability and safety of cariprazine versus placebo.

Methods

We searched the clinical trial registers (the metaRegister of controlled trials, ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform) and electronic databases (PubMed, Embase, PsycINFO and Cochrane library) up to June 2016 to identify phase II/III RCTs of cariprazine in patients with schizophrenia, bipolar disorder or major depressive disorder. We conducted a meta-analysis to investigate outcomes, including risks of discontinuation due to adverse events (AEs), extrapyramidal side effects (EPS) or related events, metabolic syndrome and cardiovascular-related events.

Results

We included nine RCTs, with a total of 4324 subjects. The risk of discontinuation due to AEs for cariprazine was similar to that for placebo (risk ratio [RR] 1.13, 95 % confidence interval [CI] 0.77–1.66). Cariprazine was associated with higher risks of EPS-related events than was placebo, including risk of akathisia (RR 3.92, 95 % CI 2.83–5.43), tremor (RR 2.41, 95 % CI 1.53–3.79) and restlessness (RR 2.17, 95 % CI 1.38–3.40). The cariprazine treatment group was more likely to have clinically significant weight gain (RR 1.68, 95 % CI 1.12–2.52). No statistically significant differences in results were found in other metabolic parameters or cardiovascular-related events.

Conclusion

There was a statistically significant higher risk of EPS-related AEs and a slight increase in mean body weight with cariprazine. There were no statistically significant effects on prolactin level or cardiovascular parameters. EPSs were the main short-term adverse reactions reported in the limited number of patients studied. Further clinical and post-marketing pharmacovigilance studies are needed to investigate the long-term safety of cariprazine.

K. S. J. Lao and Y. He contributed equally to this work.

Electronic supplementary material

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1. Introduction

Antipsychotic drugs (APDs) have been the mainstay for the management of schizophrenia for more than 60 years [1]. In recent decades, they have also become established in the treatment of bipolar disorder, for episodes of both mania and depression [2], and are also recommended as combination treatment with antidepressants for major depressive disorder (MDD) [3]. Dopamine D_2 receptor antagonism appears to be a key mechanism in the efficacy of APDs [4]. Second-generation antipsychotics (SGAs) also have affinity to other receptors, including—but not limited to—dopamine (other than D_2), serotonin, muscarinic, cholinergic and histamine receptors [5]. The affinity to multiple receptors was thought to contribute to better efficacy and a lower risk of extrapyramidal side effects (EPSs) and tardive dyskinesia compared with first-generation antipsychotics [6]. However, the claims of better efficacy have been questioned, and although SGAs are associated with fewer EPSs, they have been shown to be associated with higher risks of weight gain [7], metabolic syndrome (including dyslipidaemia, hyperglycaemia) [8, 9, 10], arrhythmia [11] and hyperprolactinemia [12]. Drug-induced adverse events (AEs) are the major cause of APD discontinuation [12]. Consequently, it is important that prescribing clinicians have a sound knowledge of the tolerability/safety profile of APDs and closely monitor patients receiving APD treatment.

Cariprazine (Vraylar™, also previously known as RG-188 or trans-4-(2-(4-(2,3-dichlorophenyl)piperazine-1-yl)-ethyl)-*N*,*N*-dimethylcarbamoyl-cyclohexyl-amine

hydrochloride) is a new APD for the treatment of schizophrenia and bipolar mania in adults that was approved by the ~~US FDA~~Food and Drug Administration (FDA, USA) on 17 September 2015 [13]. Data on efficacy, tolerability and safety in adult patients with acute exacerbations of schizophrenia [14, 15, 16, 17], acute or mixed mania associated with bipolar I disorder [18, 19, 20], bipolar I depression [21] or MDD [22] have been reported in phase II and III randomized controlled trials (RCTs). These RCTs have demonstrated that the efficacy and general tolerability of cariprazine is superior to that of placebo; however, the sample sizes have not been large enough to provide definitive safety data.

As a dopamine D_2 and D_3 receptor partial agonist, cariprazine has preference for D_3 receptors [23, 24]. Its high affinity to D_3 receptors has been shown both in vitro and in vivo [23, 24]. In contrast, D_3 receptor occupancy is low or negligible with other SGAs, as reported in positron emission tomography studies [25, 26, 27]. With regard to other receptors, cariprazine shows partial agonism at 5-HT_{1A} receptors and acts as an antagonist of 5-HT_{2B} receptors with high affinity and of 5-HT_{2A}, 5-HT_{2C}, adrenergic α_1 and histamine H_1 receptors with low affinity [24]. In animal studies, cariprazine has been shown to have antipsychotic-like activity, including (but not limited to) inhibition of amphetamine-induced climbing and hyperactivity in vivo [23]. Based on the pharmacological actions, a tolerability/safety profile distinct from those of other marketed SGAs might be anticipated.

Previous cariprazine meta-analyses or post hoc analyses have focused on efficacy [28, 29, 30, 31, 32] but have not investigated tolerability and safety. Given the unique pharmacological profile of cariprazine, there is a need for a systematic review of its tolerability/safety data. The objective of this study was to investigate the tolerability/safety outcomes of cariprazine compared with placebo in adult patients with schizophrenia, bipolar mania, bipolar depression or MDD from phase II/III RCTs via a meta-analysis.

2. Methods

This systematic review was conducted following guidance provided in the Cochrane Handbook [33] and is reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement [34]. The protocol for the meta-analysis is available at ~~http://www.pharma.hku.hk/sweb/CSMPR/~~http://www.pharma.hku.hk/sweb/CSMPR/fileC

2.1. Study Population

The study population included adult patients (aged ≥18 years) in phase II/III RCTs allocated to cariprazine (treatment group) or placebo for the management of any mental disorder. Details of outcome measures are provided in Sect. 2.5.

2.2. Data Sources and Search Strategy

We performed a literature search for any RCTs investigating cariprazine in PubMed, Embase, PsycINFO, the Cochrane library and trial registries, including the metaRegister of controlled trials (www.controlled-trials.com), ClinicalTrials.gov (http://www.ClinicalTrials.gov) and the World Health Organization International Clinical Trials Registry Platform (ICTRP) (http://www.who.int/ictrp/en/). The latest search was conducted on 13 June 2016. The search strategy was "Vraylar OR (trans-4-(2-(4-(2,3-dichlorophenyl)piperazine-1-yl)-ethyl)-*N*,*N*-dimethylcarbamoyl-cyclohexyl-amine) OR RGH-188 OR cariprazine". We set no restrictions on publication time, study size, treatment duration or language. We removed duplicates and screened the titles, abstracts and full texts to determine whether the studies met the inclusion/exclusion criteria. We also screened the bibliographies of relevant review articles to identify any potentially relevant studies.

2.3. Inclusion and Exclusion Criteria

Published randomized placebo-controlled phase II and III trials investigating the tolerability and safety of cariprazine in patients with mental disorders were eligible; we evaluated full texts to ensure they met inclusion criteria. Conference abstracts were excluded because the quality of studies was unknown, and studies without double-blind design were excluded because the risk of bias was unknown.

2.4. Evaluation of Bias

Two independent reviewers (KSJL and YH) conducted and cross-checked the methodological quality of included RCTs using the Cochrane Collaboration tool for assessing the risk of bias [35]. Any discrepancies were addressed via re-evaluation and discussion to reach consensus. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) guidelines were applied to assess the quality of a body of evidence [36, 37]. An evidence profile table and summary of findings table were generated using GRADEpro [38].

2.5. Outcome Measures

The primary outcomes for assessing tolerability/safety were (1) discontinuation due to AEs, (2) EPS-related outcomes, (3) metabolic syndrome-related outcomes and (4) cardiovascular AE-related outcomes. A treatment-emergent AE (TEAE) was defined as an AE that occurred or deteriorated during the treatment period. Details of the risks of discontinuation, TEAEs, use of rescue medication and mean changes in laboratory parameters analysed in the four categories are as follows:

1. EPS outcomes: akathisia, tremor and restlessness, reported as AEs during the treatment period; treatment-emergent akathisia (based on a Barnes Akathisia Rating Scale [BARS] score ≤2 at baseline and >2 after baseline); treatment-emergent Parkinsonism (based on a Simpson–Angus Scale [SAS] score ≤3 at baseline and >3 after baseline); and use of anti-Parkinson medication or beta-blockers.

2. Metabolic outcomes: potential clinically significant (PCS) changes in weight (defined as 7 % weight gain) from baseline in original studies [14, 16, 17, 18, 19, 20, 21]) and PCS changes in fasting glucose (defined as a shift from normal glucose levels [<100 mg/dl] at baseline to high glucose levels [≥126 mg/dl] at the end of treatment [18, 19, 21]). In addition, all changes in body weight (from baseline to the end of treatment), total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides and prolactin were pooled and reported, where available.

3. Cardiovascular outcomes: orthostatic hypotension (defined as ≥20 mmHg systolic or ≥10 mmHg diastolic reduction in blood pressure from supine to standing position [14, 18, 21]), blood pressure and creatine kinase levels. In addition, as important parameters of cardiovascular outcomes, changes in QTcB (QT interval, Bazett's formula corrected) were also reviewed narratively as data were unavailable for meta-analysis.

Secondary outcomes included other individual types of TEAEs, serious AEs (SAEs), laboratory parameters of liver function and vital signs. The term SAE was used but not explicitly defined in all included RCTs. In addition, discontinuations due to other causes were analysed.

2.6. Data Extraction

Two researchers (KSJL and YH) independently conducted the initial literature search and screened for eligible RCTs. Both reviewers also independently extracted primary and secondary outcome data from included RCTs, and cross-checked these data for accuracy, as well as extracted and summarized data not used in the statistical analyses, including study and patient characteristics.

2.7. Statistical Methods

We used the Mantel–Haenszel method [39, 40] with random effects model [41] to calculate the risk ratios (RRs) for all dichotomous outcomes (AEs, PCS changes of scales or parameters). We analysed laboratory parameters as continuous data. The inverse variance method with random effects model was used to estimate the pooled mean difference of continuous outcomes from baseline to the end of treatment [41]. The standardized mean difference (SMD) was calculated for continuous outcomes to allow comparison with results from other meta-analyses investigating the safety profiles of APDs. To calculate the SMD, we divided the difference in mean outcomes between groups by the standard deviation of outcomes among studies. We assessed heterogeneity using Cochran's Q statistics, I^2 statistics and prediction intervals; Cochran's Q statistical test was considered statistically significant when $p < 0.10$ [42]. We also calculated the I^2 statistic to estimate the proportion of total variation among studies, and regarded values of 25, 50 and 75 % as low, moderate and high heterogeneity, respectively [43]. We calculated the 95 % prediction intervals (PIs) for primary outcomes reported in at least five RCTs using τ-squared [44]; the range and width of the 95 % PIs reflect heterogeneity [45, 46].

We used Review Manager 5.3 [47] to conduct all statistical analyses. Any p value~~s~~ (two-tailed) <0.05 ~~were~~was regarded as statistically significant, except for heterogeneity tests. Online module (statstodo.com) was used to combine means and standard deviations of continuous variables from multiple groups [48].

2.8. Subgroup and Sensitivity Analyses

We conducted subgroup analyses of the nine included RCTs based on different indications for the use of cariprazine and various doses to investigate the source of heterogeneity in assessing primary outcomes. All primary outcomes were analysed in subgroups. We compared results with those of the main analysis, where all cariprazine users belong to one treatment group, as well as between subgroups. Subgroup analysis (by indication) was conducted for indications including schizophrenia and manic episodes of bipolar disorder. Subgroup analysis by dose

was stratified by cariprazine dose (a low dose was defined as ≤6 mg/day and a high dose was defined as >6 mg/day, based on the treatment dose range recommended by the FDA [49]).

The treatment intervention in one of the included RCTs was a combination of cariprazine and antidepressant [22], whereas it was cariprazine alone in the other eight RCTs. Hence, we conducted a post hoc sensitivity analysis with this study excluded from the primary analysis to investigate the impact of the adjunctive antidepressant on the outcomes of interest in this study.

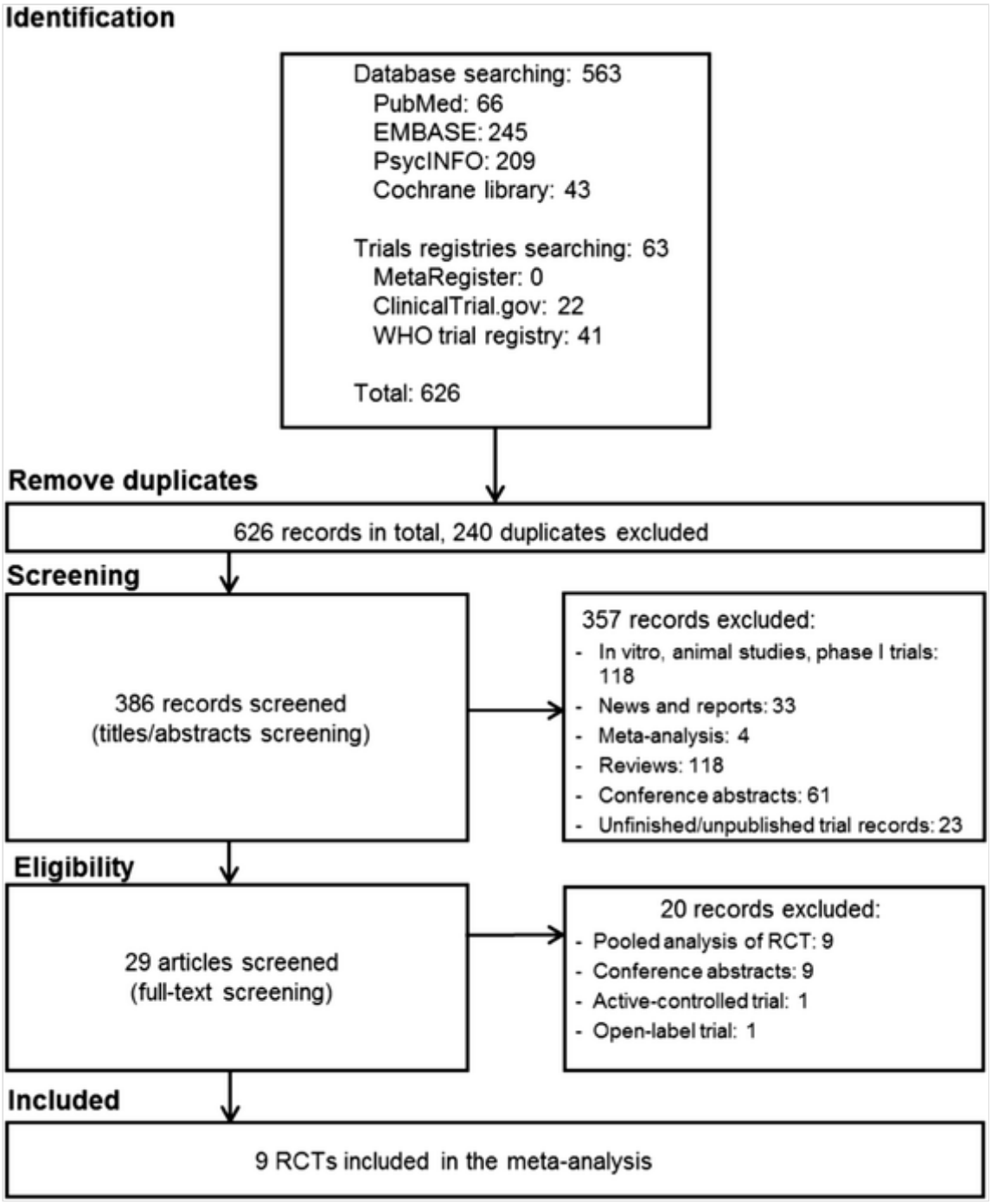
3. Results

3.1. Search Results

Figure 1 summarizes the review process in accordance with the PRISMA statement. The search of electronic databases, including PubMed, Embase, PsycINFO and the Cochrane library, yielded a total of 563 studies. We found a further 22 records registered at clinicaltrial.gov and 41 at ICTRP. After removing duplicates and screening abstracts, we assessed 29 full texts for eligibility. Overall, nine RCTs met the inclusion criteria and were included in the systematic review.

Fig. 1

PRISMA flowchart summarizing study identification and selection. *RCT* randomized controlled trial, *WHO* World Health Organization



3.2. Characteristics and Quality of Included Randomized Controlled Trials

Table 1 summarizes the characteristics of included studies. Of the nine RCTs included, four [14, 15, 16, 17] investigated the use of cariprazine in patients with schizophrenia, three [18, 19, 20] investigated the use of cariprazine in mania associated with bipolar I disorder, one [21] focused on patients with bipolar I depression and one recruited patients with MDD [22]. Treatment duration ranged from 3 to 8 weeks, and daily cariprazine doses ranged from 0.75 to 12 mg. One RCT [22] investigated antidepressants (including but not limited to sertraline,

citalopram, escitalopram, venlafaxine and duloxetine) in combination with placebo or cariprazine.

Table 1

Characteristics of randomized controlled studies included in this meta-analysis

Study	Region	Study design	Indication	Tx duration (weeks)	Intervention (dose[a])	Patients (safety populatio (*n*)
Calabrese et al. [20]	USA, Romania, Russia, Croatia, Ukraine and Serbia	Double-blind, PL-controlled	Bipolar I mania	3	PL	161
					CAR (3–6)	167
					CAR (6–12)	169
Durgam et al. [16]	USA, India, Russia, Ukraine and Malaysia	Double-blind, PL- and active-controlled	Schizophrenia	6	PL	151
					CAR (1.5)	145
					CAR (3.0)	146
					CAR (4.5)	147
					RIS (4.0)	140
Durgam et al. [19]	USA, Russia and India	Double-blind, PL-controlled	Bipolar I mania	3	PL	118
					CAR (3–12)	118
Durgam et al. [21]	USA, Canada, Colombia, Russia and Ukraine	Double-blind, PL-controlled	Bipolar I depression	8	PL	148
					CAR (0.75)	143
					CAR (1.5)	147
					CAR (3.0)	146
					PL	129

Durgam et al. [15]	USA	Double-blind, PL-controlled	Schizophrenia	6	CAR (1.5–4.5)	127
					CAR (6–12)	133
Durgam et al. [17]	USA, Romania, Russia and Ukraine	Double-blind, PL- and active-controlled	Schizophrenia	6	PL	153
					CAR (3)	155
					CAR (6)	157
					ARI (10)	152
Kane et al. [14]	USA, India, Colombia and South Africa	Double-blind, PL-controlled	Schizophrenia	6	PL	147
					CAR (3–6)	151
					CAR (9–12)	148
Sachs et al. [18]	USA and India	Double-blind, PL-controlled	Bipolar I mania	3	PL	154
					CAR (3–12)	158
Durgam et al. [22]	USA and Europe	Double-blind, PL-controlled	MDD	8	PL, ADs	266
					CAR (1–2), AD	273
					CAR (2–4.5), AD	273

AD(s) antidepressant(s), *ARI* aripiprazole, *CAR* cariprazine, *MDD* major depressive disorder, risperidone, *SD* standard deviation, *tx* treatment

[a]Doses are presented in mg/day

The included RCTs were rated as “low risk of bias” or “unclear risk of bias” in terms of sequence generation, allocation concealment, blinding setting and reporting of outcome data (Supplementary Table 1 in the Electronic Supplementary Material [ESM]). As shown in the evidence profile table (Supplementary Table 2) and the summary of findings table (Supplementary Table 3), the quality of the body of evidence for primary outcomes was rated as “high” or “moderate”, with the

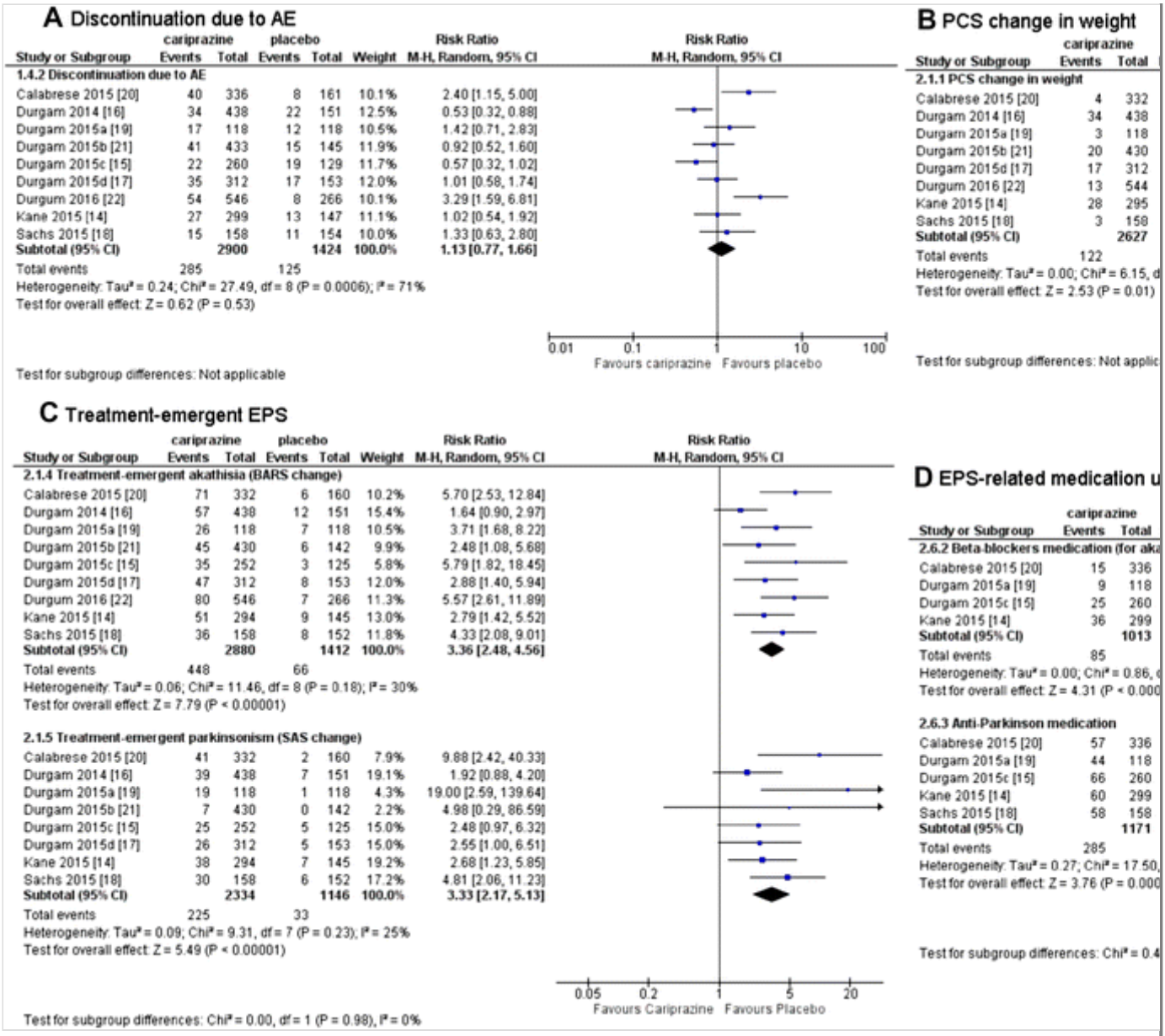
exception of the outcomes discontinuation due to AEs and use of anti-Parkinson medication, which were rated as “low”.

3.3. Discontinuation of Treatment

There was no statistically significant difference between discontinuation due to AEs in the cariprazine treatment group compared with the placebo group (RR 1.13; 95 % confidence interval [CI] 0.77–1.66; 95 % prediction interval [PI] 0.32–3.93) (Fig. 2).

Fig. 2

Forest plots of primary safety outcomes: (**a**) discontinuation due to adverse effects; (**b**) potential clinically significant change in weight; (**c**) risks of treatment-emergent extrapyramidal side effects and (**d**) use of rescue medication for extrapyramidal side effects. τ-squared statistics were used to calculate prediction intervals (by default as generated by RevMan). *PCS change in weight was defined as a 7 % weight gain from baseline. *AE* adverse effect, *CI* confidence interval, *EPS* extrapyramidal side effects, *PCS* potential clinically significant



3.4. Extrapyramidal Symptoms

Discontinuation due to EPS-related TEAEs was more likely in the cariprazine group (RR 3.31; 95 % CI 1.06–10.32; 95 % PI 0.52–21.00) (Table 2). Compared with placebo-treatment patients, those treated with cariprazine had ~~a~~ more than threefold increased risk of treatment-emergent Parkinsonism (RR 3.33; 95 % CI 2.17–5.13; 95 % PI 1.34–8.27) and treatment-emergent akathisia (RR 3.36; 95 % CI 2.48–4.56; 95 % PI 1.69–6.67), defined as change in SAS (≤3 at baseline and >3 after baseline) and BARS (≤2 at baseline and >2 after baseline), respectively (Fig. 2). Similarly, the cariprazine-treated group was more likely to receive anti-Parkinson medication (RR 2.79; 95 % CI 2.04–6.73; 95 % PI 0.35–22.18) and beta-blocking medication (RR 3.71; 95 % CI 2.04–6.73; 95 % PI not applicable) to treat akathisia (Fig. 2). Cariprazine-treated patients had a higher risk of EPS-related

AEs, including akathisia (RR 3.92; 95 % CI 2.83–5.43; 95 % PI 2.12–7.25), tremor (RR 2.41; 95 % CI 1.52–3.79; 95 % PI 1.01–5.75) and restlessness (RR 2.17; 95 % CI 1.38–3.40; 95 % PI 0.85–5.54) (Table 2). There was a statistically significant increase in the mean change in BARS scale (for akathisia) and SAS scale (for Parkinsonism), as shown in Table 2.

Table 2

Primary tolerability/safety outcomes of included randomized controlled trials

Outcome	Studies (*n*)	RR/mean difference[a] (95 % CI)	Heterogeneity (95 % PI)
Discontinuation due to AEs	9	1.13 (0.77 to 1.66)	$p = 0.07$, $I^2 = 71$ % (0.32 to 3.93)
EPS-related outcomes			
Discontinuation due to EPS-related TEAE	5	3.31 (1.06 to 10.32)	$p = 0.68$, $I^2 = 0$ % (0.52 to 21.00)
Discontinuation due to akathisia	4	8.71 (2.08 to 36.49)	$p = 0.95$, $I^2 = 0$ % (NA)
Akathisia	9	3.92 (2.83 to 5.43)	$p = 0.31$, $I^2 = 11$ % (2.12 to 7.25)
Tremor	7	2.41 (1.52 to 3.79)	$p = 0.31$, $I^2 = 16$ % (1.01 to 5.75)
Restlessness	7	2.17 (1.38 to 3.40)	$p = 0.27$, $I^2 = 21$ % (0.85 to 5.54)
BARS, mean change	5	**0.32** (0.21 to 0.43)	$p = 0.04$, $I^2 = 60$ % (–0.04 to 0.68)
SAS, mean change	5	**0.45** (0.27 to 0.64)	$p = 0.02$, $I^2 = 65$ % (−0.18 to 1.08)
AIMS, mean change	5	**0.04** (−0.05 to 0.13)	$p = 0.003$, $I^2 = 75$ % (−0.31 to 0.39)
Metabolic outcomes			
Body weight (kg)	9	**0.61** (0.39 to 0.82)	$p = 0.07$, $I^2 = 46$ % (0.02 to 1.20)
Total cholesterol (mg/dl)	9	−**0.59** (−1.86 to 0.68)	$p = 0.34$, $I^2 = 12$ % (−3.00 to 1.82)
LDL (mg/dl)	9	−**1.61** (−3.31 to 0.09)	$p = 0.11$, $I^2 = 39$ % (−5.65 to 2.43)
HDL (mg/dl)	9	**0.02** (−0.06 to 0.10)	$p = 0.50$, $I^2 = 0$ % (–0.08 to 0.12)

			(−0.08 to 0.12)
Triglycerides (mg/dl)	9	−**0.04** (−0.25 to 0.16)	$p = 0.80$, $I^2 = 0$ % (−0.29 to 0.21)
Fasting glucose (mg/dl)	9	**1.31** (−0.19 to 2.82)	$p = 0.02$, $I^2 = 57$ % (−2.74 to 5.36)
PCS change in glucose[b]	3	1.38 (0.47 to 4.08)	$p = 0.38$, $I^2 = 0$ % (NA)
Prolactin (ng/ml)	7	−**0.53** (−3.30 to 2.23)	$p < 0.001$, $I^2 = 75$ % (−9.11 to 8.05)
Cardiovascular outcomes			
Orthostatic hypotension	7	0.93 (0.76 to 1.13)	$p = 0.74$, $I^2 = 0$ % (0.72 to 1.21)
SBP (mmHg)	9	**0.83** (0.02 to 1.65)	$p = 0.17$, $I^2 = 31$ % (−1.05 to 2.71)
DBP (mmHg)	9	**0.68** (0.04 to 1.32)	$p = 0.15$, $I^2 = 34$ % (−0.86 to 2.22)
Creatine kinase (U/L)	4	**17.49** (1.63 to 33.35)	$p = 0.60$, $I^2 = 0$ % (NA)

AE adverse events, *AIMS* Abnormal Involuntary Movement Scale, *BARS* Barnes Akathisia Rating Scale, *CI* confidence interval, *DBP* diastolic blood pressure, *EPS* extrapyramidal side effects, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *NA* not applicable., *PCS* potentially clinically significant, *PI* prediction interval, *RR* relative risk, *SAE* serious adverse events, *SAS* Simpson–Angus Scale, *SBP* systolic blood pressure, *TEAE* treatment-emergent adverse events

[a]Results presented in bold indicate mean differences

[b]PCS change in fasting glucose was defined as the shift from normal glucose levels (<100 mg/dl) at baseline to high glucose levels (≥126 mg/dl) at the end of treatment

3.5. Metabolic Outcomes

From the eight RCTs that reported a PCS change in weight, the meta-analysis showed that the cariprazine-treated group was more likely to have a clinically significant weight gain than the placebo-treated group (RR 1.68; 95 % CI 1.12–2.52; 95 % PI 1.01–2.79) (Fig. 2). Furthermore, the cariprazine-treated group had a mean weight increase of 0.61 kg (95 % CI 0.39–0.82; 95 % PI 0.02–1.20) compared with the placebo group (Table 2). There was no PCS change in fasting glucose (glucose levels <100 mg/dl at baseline to ≥126 mg/dl at the end of treatment), and no statistically significant difference between the cariprazine and placebo groups in

the mean change from baseline to the end of treatment of total cholesterol, LDL, HDL, triglycerides, prolactin and fasting glucose.

The mean change in body weight for cariprazine was statistically significantly lower (mean change −0.73 kg; 95 % CI −1.34 to −0.13) than for risperidone [16]. In the study where the aripiprazole arm was the active control, mean change in fasting glucose in the cariprazine group was statistically significantly elevated compared with that in the aripiprazole group (mean difference 4.21 mg/dl; 95 % CI 1.24–7.17); however, this was not statistically different from that in the placebo group (mean difference −1.59 mg/dl, 95 % CI −8.01 to 4.83) [17].

3.6. Cardiovascular Outcomes

The risk of orthostatic hypotension was similar between cariprazine and placebo groups. Both systolic and diastolic blood pressure were marginally higher in the cariprazine group (Table 2). The mean creatine kinase level was higher in the cariprazine group than in the placebo group, with a statistically significant difference of 17.49 U/l (95 % CI 1.63–33.35; 95 % PI −17.33 to 52.31). Data were inadequate for QTc intervals and therefore were not included in the meta-analysis; however, two RCTs reported three AEs of a QTcB interval >500 ms (two in the placebo-treated group and one in the cariprazine-treated group) [18, 20].

3.7. Secondary Outcomes

Two RCTs [17, 20] reported three deaths in the cariprazine-treated group, and no deaths were reported in the placebo-treated group. Meta-analysis of other tolerability/safety outcomes, including risks of other reasons for discontinuation, risks of specific AEs and SAEs, mean change in parameters for liver function, vital signs, suicidal ideation defined by the Columbia–Suicide Severity Rating Scale (C-SSRS) and use of benzodiazepines, mostly yielded statistically non-significant differences between cariprazine and placebo groups. Detailed results are presented in Supplementary Table 4. There was a lower risk of total SAEs (RR 0.62; 95 % CI 0.42–0.91) in the cariprazine group compared with the placebo group. However, the following AEs were more frequently reported in the cariprazine group than in the placebo group, with statistically significant results: nausea, extrapyramidal disorder, vomiting, constipation, dizziness, somnolence and blurred vision (Supplementary Table 4). Supplementary Figure 1 in the ESM shows forest plots for all outcomes.

3.8. Subgroup and Sensitivity Analyses

In the subgroup analysis stratified by dose, most of the results were similar/consistent with the main analysis, with the exception that the RRs for PCS weight change in the high-dose group (>6 mg/day) did not reach statistical significance (Supplementary Table 5). In comparisons between subgroups, the mean change in the SAS scale was larger in the high-dose group than in the low-dose group (Supplementary Table 5).

When ~~stratifying~~stratified by indication, cariprazine was associated with a statistically significant higher risk of PCS weight change in patients with schizophrenia; however, this did not reach statistical significance in patients with bipolar mania disorder (Supplementary Table 6). The mean change in SAS scale between the cariprazine and placebo groups was statistically significantly higher in patients with bipolar mania compared with patients with schizophrenia (Supplementary Table 6).

Results from the sensitivity analysis were similar to those of the primary analysis, except that the mean change of LDL level was marginally lower in the cariprazine group, with a statistically significant difference (−2.11 mg/dl; 95 % CI −4.09, −0.13). No statistically significant difference was detected in the primary analysis.

4. Discussion

To our knowledge, this is the first systematic review and meta-analysis to investigate the tolerability and safety of cariprazine by combining all available RCTs to date. This review provides a comprehensive and evidence-based overview of the tolerability/safety profiles of cariprazine used for different indications, including schizophrenia, bipolar mania, bipolar depression and MDD.

Our results should be interpreted with caution, as the treatment periods were relatively short (3–8 weeks), and long-term safety data were not reported. ~~An~~One RCT with a 6-month treatment period was conducted; however, this study was excluded as it was not placebo controlled [50]. Patients in the treatment arms received daily doses that were either similar to the recommended doses in the manufacturer's product information (1.5–6 mg/day for schizophrenia and 3–6 mg/day for bipolar mania [49]) or higher than recommended doses. Notably, the included patients were relatively young (average age approximately 40 years). Whether similar results would be seen in older or younger patients remains to be explored, as extensive data on these age groups are currently not available. The

number of available RCTs was limited: our study included only nine RCTs. Some of the outcomes were not consistently reported in all the RCTs; therefore, results presented in this study should be interpreted with caution as it may not be adequately powered.

Discontinuation of treatment is a composite outcome measure of tolerability/safety and efficacy. There was no statistically significant difference in the all-cause discontinuation of cariprazine treatment compared with placebo. This suggests that the tolerability of cariprazine was generally good. Additional analysis of the data on discontinuation due to AEs and SAEs (Table 2 and Supplementary Table 4) did not reveal statistically significant differences between cariprazine and placebo, also suggesting that patients tolerated cariprazine well. However, the meta-analysis is not adequately powered to detect a difference in some of the individual AEs between cariprazine and placebo. More patients in the placebo group discontinued treatment because of insufficient drug response, which indirectly suggests superior efficacy of cariprazine when compared with placebo. This result is consistent with the results of previous RCTs and meta-analyses suggesting better efficacy of cariprazine compared with placebo [29, 30, 31]. However, additional RCTs are required for adequate power to detect a difference in tolerability and safety outcomes between cariprazine and placebo.

As with some other SGAs, akathisia was a common TEAE in cariprazine-treated patients. Risks of EPS-related TEAEs, including akathisia, tremor, restlessness and overall extrapyramidal disorder, were statistically significantly higher in the cariprazine than in the placebo group. The use of rescue medications ~~is~~was also an indicator reflecting clinically significant EPS-related events. Leucht et al. [51] found the odds ratios (ORs) for other marketed APDs versus placebo of at least one occasion of anti-Parkinson drugs being prescribed varied from 0.3 (clozapine, 95 % CI 0.12–0.62) to 4.76 (haloperidol, 95 % CI 3.70–6.04) [51]. The result in our analysis (OR 3.49, 95 % CI 1.91–6.38) overlapped with the range reported by Leucht et al. [51]. Pooled RRs of treatment-emergent akathisia, defined by BARS, was 3.36 (95 % CI 2.48–4.56), which was similar to the results for other SGAs (RR 5.37, 95 % CI 3.38–8.53), as reported in previous meta-analyses [52, 53]. The available data indicate that cariprazine is consistently associated with a higher risk of EPS compared with placebo. Although the pharmacological profile of cariprazine differs from those of other SGAs, the risk of EPS appears to be similar. While there was a statistically significant difference between cariprazine and placebo in several of the outcomes (e.g. discontinuation due to akathisia; risk of tremor; risk of restlessness; mean change in BARS, SAS and AIMS scores

[Table 2]), the results should still be interpreted with caution because the analysis may have been underpowered for some of the other outcomes given the small number of studies/patients included.

Our analysis revealed that cariprazine was associated with a marginally increased risk of PCS weight gain compared with placebo. The pooled mean change of body weight was only 0.61 kg (standard mean difference 0.25; 95 % CI 0.17–0.34) during the study period. However, it should be noted that this is a mean result and does not indicate whether some individuals gained weight excessively, nor do these relatively brief studies give any indication of the long-term effects on weight or other AEs. Compared with the SMD in weight gain or risk reduction in PCS weight gain of other SGAs, cariprazine was associated with less mean weight gain than olanzapine, quetiapine, risperidone and clozapine [51, 52], with a risk of PCS weight gain similar to that of aripiprazole and ziprasidone [51, 52, 53]. Weight gain, hyperglycaemia and dyslipidaemia (elevated total cholesterol and LDL, and decreased HDL) are the main risk factors contributing to cardiovascular diseases in patients with schizophrenia and can be frequently observed in patients receiving SGAs [54]. In our results, levels of total cholesterol, LDL and HDL were not statistically significantly different between the placebo and cariprazine groups. Generally, this indicates that the metabolic profile of cariprazine is more favourable than that of other SGAs. Our analysis did not reveal a statistically significant elevation of prolactin level.

In summary, the cariprazine-treated group had a PCS change in weight, but the overall magnitude of changes of metabolic parameters was mild or benign in these short-term RCTs. However, these results should be interpreted cautiously in light of the relatively short treatment period, as some of the metabolic problems may take time to become established.

Cariprazine was associated with a statistically significant but mild elevation of creatine kinase. However, no acute myocardial infarction was reported, so this result appears unlikely to be clinically significant. Marginally statistically significant changes in blood pressure were observed; however, there were no differences in reports of orthostatic hypotension between cariprazine and placebo. No cardiovascular safety concerns were reported in the short periods of treatment. QTcB prolongation remains to be further explored. Again, data on long-term drug use in large numbers of patients are needed to provide a complete evaluation of the cardiovascular safety profile.

Using a cut-off of 6 mg/day, seven of the nine RCTs had a low-dose cariprazine treatment group and four had a high-dose cariprazine treatment group. Although the results of our subgroup analysis were not statistically significant, no conclusion regarding a dose–response relationship can be drawn given the limited published data available. Further studies are required to confirm the dose–response relationship.

Among the nine included RCTs, an active-control design was used in two studies, wherein cariprazine was also compared with risperidone [16] and aripiprazole [17]. However, the sample sizes in direct comparisons with active comparators were too limited to allow conclusions to be drawn. Another RCT in which cariprazine was compared with risperidone [50] was excluded as it did not include a placebo arm. Studies of comparative safety are needed. However, as not all nine RCTs reported all outcomes, results should be interpreted with caution due to the small sample sizes.

5. Conclusions

Our meta-analysis of short-term RCTs suggests that cariprazine is generally well tolerated, as indicated by similar discontinuation rates due to AEs between drug and placebo groups. Cariprazine was associated with a higher risk of EPS-related AEs, particularly akathisia, and a slight increase in mean body weight. No statistically significant effects on prolactin level or the cardiovascular system were evident. It is important that patients are informed of the potential EPS. More clinical and post-marketing pharmacovigilance studies are needed to investigate the long-term tolerability and safety of cariprazine.

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Compliance with Ethical Standards

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Conflicts of Interest ~~:~~KSJL, YH, ICKW, FMCB and EWC declare no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous

3 years; and no other relationships or activities that could appear to have influenced the submitted study.

Author Contributions KSJL, ICKW and EWC had the original idea for this study and contributed to the development of the idea and study design. KSJL and YH independently conducted a systematic review and reviewed the literature for relevance. KSJL and YH undertook the analysis. KSJL, YH, ICKW and EWC contributed to interpretation of the analysis. KSJL and YH wrote the first draft of the paper. KSJL, YH, ICKW and EWC critically reviewed the results and the manuscript. FMCB reviewed the data and presentation of the paper and provided clinical input. ICKW and EWC provided oversight to all aspects of this project. KSJL and EWC are the guarantors. All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

6. Electronic supplementary material

Below is the link to the electronic supplementary material.

Supplementary material 1 (DOCX 3299 kb)

References

1. Kuipers E, Yesufu-Udechuku A, Taylor C, Kendall T. Management of psychosis and schizophrenia in adults: summary of updated NICE guidance. BMJ. 2014;348:g1173. doi:10.1136/bmj.g1173.

2. Kendall T, Morriss R, Mayo-Wilson E, Marcus E, Guideline Development Group of the National Institute for H, Care E. Assessment and management of bipolar disorder: summary of updated NICE guidance. BMJ. 2014;349:g5673. doi: 10.1136/bmj.g5673.

3. Publication No. WO/2009/104739 Published on Aug. 27, Assigned to Mitsubishi Tanabe Pharma for Oral Administration Solid Preparation (Japanese Inventors). US Fed News Service, Including US State News. 3 September 2009.

4. Nord M, Farde L. Antipsychotic occupancy of dopamine receptors in schizophrenia. CNS Neurosci Ther. 2011;17(2):97–103. doi:10.1111/j.1755-5949.2010.00222.x.

5. Kusumi I, Boku S, Takahashi Y. Psychopharmacology of atypical antipsychotic drugs: from the receptor binding profile to neuroprotection and neurogenesis. Psychiatry Clin Neurosci. 2015;69(5):243–58. doi:10.1111/pcn.12242.

6. Miyamoto S, Duncan GE, Marx CE, Lieberman JA. Treatments for schizophrenia: a critical review of pharmacology and mechanisms of action of antipsychotic drugs. Mol Psychiatry. 2005;10(1):79–104. doi:10.1038/sj.mp.4001556.

7. Allison DB, Mentore JL, Heo M, Chandler LP, Cappelleri JC, Infante MC, et al. Antipsychotic-induced weight gain: a comprehensive research synthesis. Am J Psychiatry. 1999;156(11):1686–96. doi:10.1176/ajp.156.11.1686.

8. McEvoy JP, Meyer JM, Goff DC, Nasrallah HA, Davis SM, Sullivan L, et al. Prevalence of the metabolic syndrome in patients with schizophrenia: baseline results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial and comparison with national estimates from NHANES III. Schizophr Res. 2005;80(1):19–32. doi:10.1016/j.schres.2005.07.014.

9. Henderson DC, Cagliero E, Copeland PM, Borba CP, Evins E, Hayden D, et al. Glucose metabolism in patients with schizophrenia treated with atypical antipsychotic agents: a frequently sampled intravenous glucose tolerance test and minimal model analysis. Arch Gen Psychiatry. 2005;62(1):19–28. doi:10.1001/archpsyc.62.1.19.

10. Koro CE, Fedder DO, L'Italien GJ, Weiss S, Magder LS, Kreyenbuhl J, et al. An assessment of the independent effects of olanzapine and risperidone exposure on the risk of hyperlipidemia in schizophrenic patients. Arch Gen Psychiatry. 2002;59(11):1021–6.

11. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. Lancet. 2005;365(9468):1415–28. doi:10.1016/S0140-6736(05)66378-7.

12. Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med. 2005;353(12):1209–23. doi:10.1056/NEJMoa051688.

13. US Department of Health and Human Services; US Food and Drug Administration. FDA approves new drug to treat schizophrenia and bipolar disorder. Available at http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm463103.htm. Accessed 29 Dec 2015.

14. Kane JM, Zukin S, Wang Y, Lu K, Ruth A, Nagy K, et al. Efficacy and safety of cariprazine in acute exacerbation of schizophrenia: results from an international, phase III clinical trial. J Clin Psychopharmacol. 2015;35(4):367–73. doi:10.1097/JCP.0000000000000346.

15. Durgam S, Litman RE, Papadakis K, Li D, Nemeth G, Laszlovszky I. Cariprazine in the treatment of schizophrenia: a proof-of-concept trial. Int Clin Psychopharmacol. 2015;. doi:10.1097/YIC.0000000000000110.

16. Durgam S, Starace A, Li D, Migliore R, Ruth A, Nemeth G, et al. An evaluation of the safety and efficacy of cariprazine in patients with acute exacerbation of schizophrenia: a phase II, randomized clinical trial. Schizophr Res. 2014;152(2–3):450–7. doi:10.1016/j.schres.2013.11.041.

17. Durgam S, Cutler AJ, Lu K, Migliore R, Ruth A, Laszlovszky I, et al. Cariprazine in acute exacerbation of schizophrenia: a fixed-dose, phase 3, randomized, double-blind, placebo- and active-controlled trial. J Clin Psychiatry. 2015;76(12):e1574–82. doi:10.4088/JCP.15m09997.

18. Sachs GS, Greenberg WM, Starace A, Lu K, Ruth A, Laszlovszky I, et al. Cariprazine in the treatment of acute mania in bipolar I disorder: a double-blind, placebo-controlled, phase III trial. J Affect Disord. 2015;174:296–302. doi:10.1016/j.jad.2014.11.018.

19. Durgam S, Starace A, Li D, Migliore R, Ruth A, Nemeth G, et al. The efficacy and tolerability of cariprazine in acute mania associated with bipolar I disorder: a phase II trial. Bipolar Disord. 2015;17(1):63–75. doi:10.1111/bdi.12238.

20. Calabrese JR, Keck PE Jr, Starace A, Lu K, Ruth A, Laszlovszky I, et al. Efficacy and safety of low- and high-dose cariprazine in acute and mixed mania associated with bipolar I disorder: a double-blind, placebo-controlled study. J Clin Psychiatry. 2015;76(3):284–92. doi:10.4088/JCP.14m09081.

21. Durgam S, Earley W, Lipschitz A, Guo H, Laszlovszky I, Nemeth G, et al. An 8-week randomized, double-blind, placebo-controlled evaluation of the safety and efficacy of cariprazine in patients with bipolar I depression. Am J Psychiatry. 2015;. doi:10.1176/appi.ajp.2015.15020164.

AQ1

22. Durgam S, Earley W, Guo H, Li D, Nemeth G, Laszlovszky I, et al. Efficacy and safety of adjunctive cariprazine in inadequate responders to antidepressants: a randomized, double-blind, placebo-controlled study in adult patients with major depressive disorder. J Clin Psychiatry. 2016;77(3):371–8. doi:10.4088/JCP.15m10070.

23. Gyertyan I, Kiss B, Saghy K, Laszy J, Szabo G, Szabados T, et al. Cariprazine (RGH-188), a potent D3/D2 dopamine receptor partial agonist, binds to dopamine D3 receptors in vivo and shows antipsychotic-like and procognitive effects in rodents. Neurochemist Int. 2011;59(6):925–35. doi:10.1016/j.neuint.2011.07.002.

24. Kiss B, Horvath A, Nemethy Z, Schmidt E, Laszlovszky I, Bugovics G, et al. Cariprazine (RGH-188), a dopamine D(3) receptor-preferring, D(3)/D(2) dopamine receptor antagonist-partial agonist antipsychotic candidate: in vitro and neurochemical profile. J Pharmacol Exp Ther. 2010;333(1):328–40. doi:10.1124/jpet.109.160432.

25. Girgis RR, Xu X, Gil RB, Hackett E, Ojeil N, Lieberman JA, et al. Antipsychotic binding to the dopamine-3 receptor in humans: a PET study with [(11)C]-(+)-PHNO. Schizophr Res. 2015;168(1–2):373–6. doi:10.1016/j.schres.2015.06.027.

26. Mizrahi R, Agid O, Borlido C, Suridjan I, Rusjan P, Houle S, et al. Effects of antipsychotics on D3 receptors: a clinical PET study in first episode antipsychotic naive patients with schizophrenia using [11C]-(+)-PHNO. Schizophr Res. 2011;131(1–3):63–8. doi:10.1016/j.schres.2011.05.005.

27. Graff-Guerrero A, Mamo D, Shammi CM, Mizrahi R, Marcon H, Barsoum P, et al. The effect of antipsychotics on the high-affinity state of D2 and D3 receptors: a positron emission tomography study With [11C]-(+)-PHNO. Arch Gen Psychiatry. 2009;66(6):606–15. doi:10.1001/archgenpsychiatry.2009.43.

28. Yildiz A, Nikodem M, Vieta E, Correll CU, Baldessarini RJ. A network meta-analysis on comparative efficacy and all-cause discontinuation of antimanic treatments in acute bipolar mania. Psychol Med. 2015;45(2):299–317. doi:10.1017/S0033291714001305.

29. Citrome L, Durgam S, Lu K, Ferguson P, Laszlovszky I. The effect of cariprazine on hostility associated with schizophrenia: post hoc analyses from 3 randomized controlled trials. J Clin Psychiatry. 2016;77(1):109–15. doi:10.4088/JCP.15m10192.

30. Vieta E, Durgam S, Lu K, Ruth A, Debelle M, Zukin S. Effect of cariprazine across the symptoms of mania in bipolar I disorder: analyses of pooled data from phase II/III trials. Eur Neuropsychopharmacol. 2015;25(11):1882–91. doi:10.1016/j.euroneuro.2015.08.020.

31. Yildiz A, Vieta E, Leucht S, Baldessarini RJ. Efficacy of antimanic treatments: meta-analysis of randomized, controlled trials. Neuropsychopharmacology. 2011;36(2):375–89. doi:10.1038/npp.2010.192.

32. Zukin S, Lu K, Ruth A, Debelle M, Durgam S, D'Souza I. Categorical improvement across mania symptoms: pooled analyses of cariprazine phase II/III trials. Bipolar Disord. 2015;17:89.

33. Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org. Accessed 15 June 2014.

34. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009;339:b2535. doi:10.1136/bmj.b2535 (**Epub 2009/07/23**).

35. Higgins JPT, Altman DG, Sterne JAC (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org. Accessed 8 Aug 2014.

36. Sterne JA, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ. 2011;343:d4002. doi:10.1136/bmj.d4002.

37. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011;64(4):383–94. doi:10.1016/j.jclinepi.2010.04.026.

38. GRADEpro GDT: GRADEpro Guideline Development Tool [Software]. McMaster University dbEP, Inc.). Available from gradepro.org.

39. Greenland S, Robins JM. Estimation of a common effect parameter from sparse follow-up data. Biometrics. 1985;41(1):55–68.

40. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst. 1959;22(4):719–48.

41. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7(3):177–88.

42. Cochran WG. The combination of estimates from different experiments. Biometrics. 1954;10(1):101–29.

43. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557–60. doi:10.1136/bmj.327.7414.557 (**Epub 2003/09/06**).

44. Rosenblad A. Chapter 17: introduction to meta-analysis by Michael Borenstein, Larry V. Hedges, Julian PT Higgins, Hannah R. Rothstein. Int Stat Rev. 2009;77(3):478–9.

45. Higgins JP, Green S. Cochrane handbook for systematic reviews of interventions. Wiley Online Library; 2008.

46. Higgins JP, Thompson SG, Spiegelhalter DJ. A re-evaluation of random-effects meta-analysis. J R Stat Soc Ser A. 2009;172(1):137–59. doi:10.1111/j.1467-985X.2008.00552.x.

47. Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012.

48. StatsToDo. Computer Program to Combine Means and Standard Deviations from Multiple Groups [cited Jan 2016]. Available from: https://www.statstodo.com/ComMeans_Pgm.php.

49. US Food and Drug Administration. Full Prescribing information for VRAYLAR (cariprazine). 2015. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/204370lbl.pdf.

50. Nemeth G, Debelle M, Laszlovszky I, Szalai E, Szatmari B, Harsanyi J, et al. Monotherapy treatment with cariprazine for the treatment of predominant negative symptoms of patients with schizophrenia: a double-blind, active comparator-controlled trial. Eur Psychiatry. 2016;33:S256–7.

51. Leucht S, Cipriani A, Spineli L, Mavridis D, Orey D, Richter F, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. Lancet. 2013;382(9896):951–62. doi:10.1016/S0140-6736(13)60733-3.

52. De Fruyt J, Deschepper E, Audenaert K, Constant E, Floris M, Pitchot W, et al. Second generation antipsychotics in the treatment of bipolar depression: a systematic review and meta-analysis. J Psychopharmacol. 2012;26(5):603–17. doi:10.1177/0269881111408461.

53. Correll CU, Sheridan EM, DelBello MP. Antipsychotic and mood stabilizer efficacy and tolerability in pediatric and adult patients with bipolar I mania: a comparative analysis of acute, randomized, placebo-controlled trials. Bipolar Disord. 2010;12(2):116–41. doi:10.1111/j.1399-5618.2010.00798.x.

54. Osby U, Correia N, Brandt L, Ekbom A, Sparen P. Mortality and causes of death in schizophrenia in Stockholm county, Sweden. Schizophr Res. 2000;45(1–2):21–8.