Title:

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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Tolerability/safety of cariprazine

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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 data analysis.

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Abstract (299 words)

Background Cariprazine is a novel antipsychotic agent recently approved for treating schizophrenia and bipolar mania in the US. 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 A meta-analysis of published RCTs was conducted to systematically review the tolerability and safety of cariprazine versus placebo.

Methods Clinical trials registers (the metaRegister of controlled trials, the Clinical trials government and the World Health Organisation International Clinical Trials Registry Platform) and electronic databases (PubMed, Embase, PsycINFO and Cochrane library) were searched up to June 2016 to identify phase II/III RCTs of cariprazine in patients with schizophrenia, bipolar disorder or major depressive disorder. A meta-analysis was conducted 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.

*Result*s Nine RCTs were included with a total of 4,324 subjects. The risk of discontinuation due to AEs for cariprazine was similar to placebo (risk ratio [RR] =1.13, 95% confidence interval [95%CI] 0.77-1.66). Cariprazine was associated with higher risks of EPS-related events compared to 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 adverse events and a slight increase in mean body weight with cariprazine. There were no statistically significant effects on prolactin level or cardiovascular parameters. EPS 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.

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 were 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 lower risk of extrapyramidal side effects (EPS) and tardive dyskinesia compared to first generation antipsychotics [6]. However, the claims of better efficacy have been questioned and, although SGAs are associated with less EPS, they have been shown to be associated with higher risks of weight gain [7], metabolic syndrome (including dyslipidemia, hyperglycemia) [8-10], arrhythmia [11] and hyperprolactinemia [12]. Drug-induced adverse events are the major cause of APD discontinuation [12]. It is consequently important for prescribing clinicians to have sound knowledge of the tolerability/safety profile of APDs and closely monitor patients on 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 approved by the U.S. Food and Drug Administration (FDA) to treat schizophrenia and bipolar mania in adults on September 17, 2015 [13].

Data on efficacy, tolerability and safety in adult patients with acute exacerbations of schizophrenia [14-17], acute or mixed mania associated with bipolar I disorder [18-20], bipolar I depression [21] and MDD [22] have been reported in phase II and III RCTs. Compared with placebo, superiority in efficacy and general tolerability of cariprazine has been demonstrated in these RCTs. With regard to safety, the sample sizes of these RCTs are not adequate to provide definitive data.

As a dopamine D_2 and D_3 receptors partial agonist, cariprazine has preference for D_3 receptors [23, 24]. Its high affinity to D_3 receptor 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 [25-27]. 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 low affinity for 5-HT_{2A}, 5-HT_{2C}, adrenergic α_1 and histamine H_1 receptors [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 distinct tolerability/safety profile from other marketed SGAs might be anticipated.

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

134 analysis.

135 2. Methods

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

140 2.1.Study population

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

144 2.2.Data sources and search strategy

145 A literature search for any RCTs of cariprazine was performed using PubMed, Embase,
146 PsycINFO, the Cochrane library and trial registries including the metaRegister of
147 controlled trials (www.controlled-trials.com), the Clinical trials government
148 (http://www.ClinicalTrials.gov) and the World Health Organisation International
149 Clinical Trials Registry Platform (ICTRP) (http://www.who.int/ictrp/en/). The latest
150 search was conducted on 13th June 2016. The search strategy was “Vraylar OR (trans-
151 4-(2-(4-(2,3-dichlorophenyl)piperazine-1-yl)-ethyl)-N,N-dimethylcarbamoyl-
152 cyclohexyl-amine) OR RGH-188 OR cariprazine”. No restrictions were set on
153 publication time, study size, treatment duration or language. Duplicates were removed.
154 Titles, abstracts and full texts were screened to determine whether the studies met the
155 inclusion/exclusion criteria. The bibliographies of relevant review articles were also

screened 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. Full texts were evaluated for assessing the inclusion criteria. Conference abstracts were excluded due to the unknown quality of studies. Studies without double-blind design applied were excluded due to unknown risk of bias.

2.4. Evaluation of bias

The methodological quality of included RCTs was assessed using the Cochrane Collaboration tool for assessing the risk of bias [35]. Assessment was conducted and cross-checked by two independent reviewers (KSJL and YH). Any discrepancies were addressed by 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]. 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 adverse events (AEs), (2) EPS related outcomes, (3) metabolic syndrome related outcomes, and (4) cardiovascular adverse effects related outcomes. Details of the risks of discontinuation, treatment-emergent adverse effects (TEAEs), use of rescue medication and mean changes of laboratory parameters analysed in the four categories are described and defined below. A TEAE was defined as an adverse event that

178 occurred or deteriorated during the treatment period.

179 (1) Discontinuation due to total AEs.

180 (2) EPS outcomes: akathisia, tremor and restlessness, reported as adverse events during
181 treatment period; treatment-emergent akathisia (based on a Barnes Akathisia Rating
182 Scale, BARS score ≤2 at baseline and >2 after baseline); treatment-emergent
183 Parkinsonism (based on a Simpson-Angus Scale, SAS score ≤3 at baseline and >3 after
184 baseline); and use of anti-Parkinson medication or beta-blockers.

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

192 (4) Cardiovascular outcomes: orthostatic hypotension (defined as ≥20 mmHg systolic
193 or ≥10 mmHg diastolic reduction in blood pressure from supine to standing position
194 [14, 18, 21]), blood pressure, and creatine kinase levels. In addition, as important
195 parameters of cardiovascular outcomes, changes in QTcB (QT interval, *Bazett's*
196 formula corrected) were also reviewed narratively as data was unavailable for meta-
197 analysis.

198 Secondary outcomes included other individual types of TEAEs, serious adverse events
199 (SAEs), laboratory parameters of liver function and vital signs. The term SAE was used

in all included RCTs but not explicitly defined. In addition, discontinuations due to other causes were analysed.

2.6.Data extraction

The initial literature search and screening for eligible RCTs were independently performed by two researchers (KSJL and YH). Primary and secondary outcome data were also extracted from included RCTs by both reviewers independently and cross-checked for accuracy. Data not used in the statistical analyses including characteristics of studies and patients were extracted and summarized.

2.7.Statistical methods

The Mantel-Haenszel method [39, 40] with random effects model [41] was used to calculate the risk ratios (RRs) for all dichotomous outcomes (adverse events, PCS changes of scales or parameters). Laboratory parameters were analysed 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]. Standardized mean difference (SMD) was calculated for continuous outcomes to compare with results from other meta-analyses investigating safety profiles of APDs. For the calculation of SMD, the difference in mean outcomes between groups was divided by the standard deviation of outcomes among studies. Heterogeneity was assessed 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]. The I^2 statistic was also calculated to estimate the proportion of total variation among studies, where values of 25%, 50% and 75% were regarded as low, moderate and high heterogeneity, retrospectively [43]. 95% prediction intervals (95%PI) were calculated

for primary outcomes reported in at least 5 RCTs by using tau-squared [44]. Range and width of 95%PI reflect heterogeneity [45, 46].

Review Manager 5.3 [47] was used to conduct all statistical analyses. P-values (two-tailed) <0.05 were 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

Subgroup analyses of the nine included RCTs were conducted based on different indications of cariprazine use and various doses of cariprazine. Subgroup analyses were performed to investigate the source of heterogeneity in assessing primary outcomes. All primary outcomes were analysed in subgroups. Results were compared with those of the main analysis, where all cariprazine users belong to one treatment group. Results were also compared 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 (low dose group was defined as dose 6mg/day or below and high dose group was defined as above 6mg/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], while in the other eight RCTs it was cariprazine alone. Hence a *post-hoc* sensitivity analysis was conducted where this study was excluded in 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 flowchart in accordance with the PRISMA statement. The search of electronic databases including PubMed, Embase, PsycINFO and Cochrane library yielded a total of 563 studies. Twenty-two records were found registered at clinicaltrial.gov and 41 at ICTRP. After removing duplicates and screening abstracts, 29 full-texts were further assessed for eligibility. Overall nine RCTs met the inclusion criteria and were included in the systematic review.

3.2.Characteristics and quality of included RCTs

Table 1 summarizes the characteristics of included studies. Of the nine RCTs included, four [14-17] investigated the use of cariprazine in patients with schizophrenia, three [18-20] 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 three to eight weeks. Daily cariprazine doses investigated in these RCTs ranged from 0.75 mg to 12 mg. Antidepressants (including but not limited to sertraline, citalopram, escitalopram, venlafaxine and duloxetine) were used in combination with placebo or cariprazine in one RCT [22].

The included RCTs were rated as “low risk of bias” or “unclear” with respect to sequence generation, allocation concealment, blinding setting and outcome data reporting (**Supplementary Table 1**). As reported in the evidence profile table (**Supplementary Table 2**) and the summary of findings table (**Supplementary Table 3**), with the exception of the outcomes of discontinuation due to AEs and use of anti-

Parkinson medication being rated as “Low”, the quality of a body of evidence for primary outcomes were rated as “High” or “Moderate”.

3.3.Discontinuation of treatment

There was no statistically significant difference between discontinuation due to AEs in the cariprazine treatment group compared to the placebo group, RR 1.13 (95%CI 0.77-1.66, 95%PI 0.32-3.93) (**Figure 2**).

3.4.Extrapyramidal symptoms (EPS)

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**). Cariprazine-treated patients had greater than a 3-fold increase in the risk than placebo-treated patients 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 of SAS (≤3 at baseline and >3 after baseline) and BARS (≤2 at baseline and >2 after baseline) respectively (**Figure 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) for treating akathisia (**Figure 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**.

3.5.Metabolic outcomes

From the eight RCTs which had reported the PCS change in weight, the meta-analysis showed that the cariprazine group were more likely to have a clinically significant weight gain compared to the placebo group (RR 1.68, 95%CI 1.12-2.52, 95%PI 1.01-2.79) (**Figure 2**). Furthermore, the cariprazine-treated group had an increased mean weight of 0.61kg (95%CI 0.39-0.82, 95%PI 0.02-1.20) compared to the placebo group (**Table 2**). There was no PCS change in fasting glucose (glucose levels less than 100 mg/dL at baseline to 126 mg/dL or above at the end of treatment). In addition, there was 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 with the aripiprazole arm as an active control, mean change in fasting glucose in the cariprazine group was statistically significantly elevated compared with aripiprazole (mean difference 4.21 mg/dL, 95%CI 1.24-7.17), however this was not statistically different from 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 cariprazine group (**Table 2**). The mean creatine kinase level was higher in the cariprazine group compared to placebo, with a statistically significant difference of 17.49 U/L (95%CI 1.63-33.35,

95%PI -17.33 to 52.31). Data was inadequate for QTc intervals and hence was not included in meta-analysis; however three adverse events of QTcB interval >500 msec were reported in two RCTs (two in the placebo group and one in the cariprazine-treated group) [18, 20].

3.7.Secondary outcomes

Three deaths were reported in the cariprazine-treated group from two RCTs [17, 20] and no death was reported in the placebo 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 Columbia-Suicide Severity Rating Scale (C-SSRS) and use of benzodiazepines mostly yielded statistically non-significant differences between the cariprazine and placebo groups. Detailed results are presented in the **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 to 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**). Forest plots for all outcomes were shown in **Supplementary Figure 1**.

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 of the risk ratios of PCS weight change in high-dose group (>6mg/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 compared to the low-dose group (**Supplementary Table 5**).

When stratifying by indication, cariprazine was associated with a statistically significant higher risk of PCS weight change in patients with schizophrenia; however, it 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 bipolar mania patients compared with patients with schizophrenia (**Supplementary Table 6**).

Sensitivity analysis showed similar results to the primary analysis except the mean change of LDL level was marginally lower in cariprazine group with statistically significant difference (-2.11 mg/dL, 95%CI -4.09, -0.13), while in the primary analysis, no statistically significant difference was detected.

4. Discussion

To our knowledge this is the first systematic review and meta-analysis to investigate 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 (three to eight weeks) and long-term safety data was not reported. An 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 similar to the recommended doses in the manufacturer's product information (1.5–6 mg/d for schizophrenia and 3–6 mg/d for bipolar mania [49]) or doses higher than recommended. Notably, the included patients were relatively young (average age approximately 40 years). Whether similar results will 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: only nine RCTs were included in our study. 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 to placebo. This suggests that the tolerability of cariprazine was generally good. Additional analysis of the data on discontinuation due to AEs and SAEs (**Tables 2** and **supplementary table 4**) did not reveal statistically significant differences between cariprazine and placebo, also suggesting that cariprazine was well tolerated by the patients. However, the meta-analysis is not adequately powered to detect a difference in some of the individual adverse effects between cariprazine and placebo. There were more patients in the placebo group who discontinued treatment due to insufficient drug response, which indirectly suggests superior efficacy of cariprazine when compared to placebo. This result is consistent with results of previous RCTs and meta-analyses suggesting better efficacy of cariprazine compared to placebo [29-31]. However, additional RCTs are required for adequate power to detect a difference in tolerability and safety outcomes

between cariprazine and placebo.

As with some of the other SGAs, akathisia was a common TEAE. Statistically significant higher risks of EPS-related TEAEs, including akathisia, tremor, restlessness and overall extrapyramidal disorder were reported in the cariprazine than in the placebo group. The use of rescue medications is also an indicator reflecting clinically significant EPS-related events. The odds ratios (ORs) versus placebo of at least one occasion of the prescription of anti-Parkinson drugs for other marketed antipsychotics in the study by Leucht et al. 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 risk ratios 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 to placebo. Although cariprazine has a different pharmacological profile from other SGAs, the risk of EPS appears to be similar. Although 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 in **Table 2**), the results should still be interpreted with caution, as the analysis may have been underpowered for some of the other outcomes due to 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 adverse effects. Compared to the standardized mean difference 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 similar risk of PCS weight gain as aripiprazole and ziprasidone [51-53]. Weight gain, hyperglycaemia and dyslipidaemia (elevated total cholesterol and LDL, and decreased HDL level) are the main risk factors contributing to cardiovascular diseases in patients with schizophrenia and can be frequently observed in users of SGAs [54]. In our results, levels of total cholesterol, LDL and HDL did not differ statistically significantly between the placebo and cariprazine groups – generally this shows a more favourable metabolic profile than other SGAs. No statistically significant elevation of prolactin level was revealed in our analysis.

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 and in these short-term RCTs. However, these results should be interpreted in the 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 and this result appears unlikely to be clinically significant. Marginally statistical significant changes in blood

pressure were observed, however there was no difference 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.

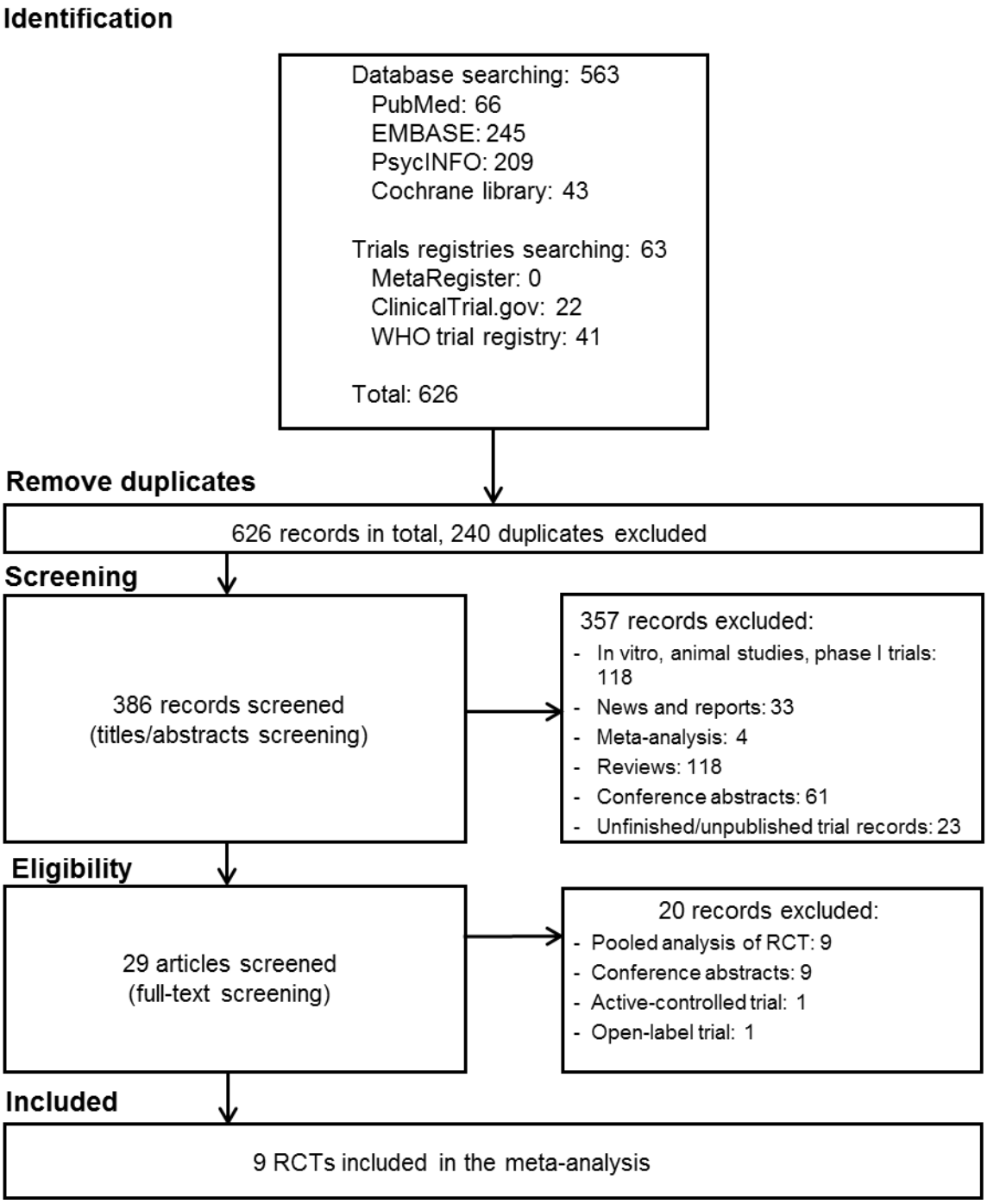
Using a 6mg/day cut-off, seven of the nine RCTs had a low-dose cariprazine treatment group and four of nine RCTs had a high-dose cariprazine treatment group. Although results of subgroup analysis are not statistically significant, no conclusion regarding the dose response relationship can be drawn with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

Among the nine included RCTs, an active-control design was used in two studies where cariprazine was also compared with risperidone and aripiprazole, respectively [16, 17]. However, the sample sizes of direct comparison with active comparators were too limited to allow conclusions to be drawn. Another RCT where cariprazine was compared with risperidone [50] was excluded as there was no placebo arm. Future studies are needed for comparative safety. However, as some of the outcomes were not reported in all nine RCTs, results should be interpreted with caution due to the small sample size.

5. Conclusions

Our meta-analysis of short-term RCTs suggested that cariprazine was generally well tolerated, as indicated by similar discontinuation rates due to adverse events between drug and placebo groups. Cariprazine was associated with a higher risk of EPS-related

adverse events, 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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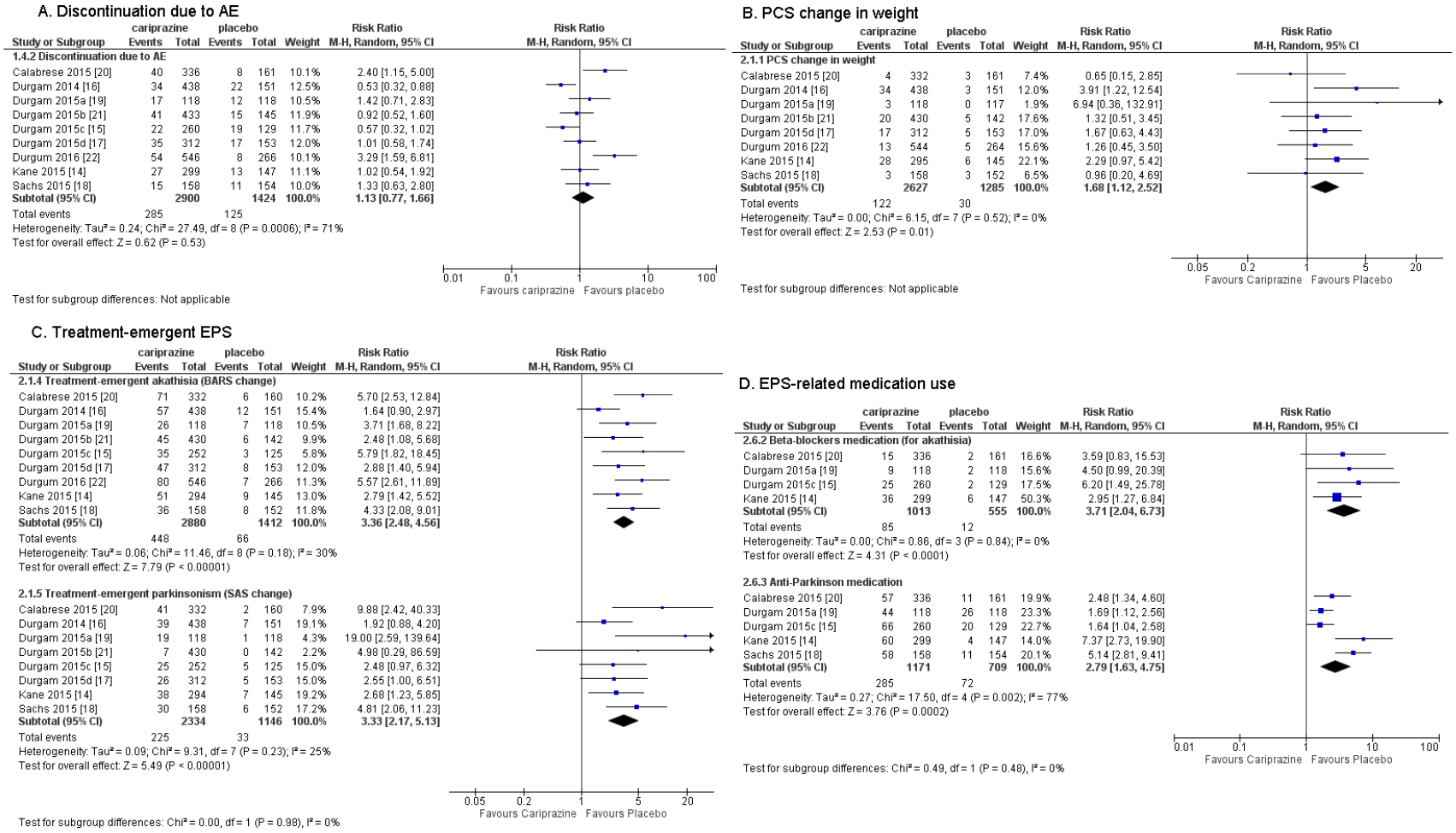
455 **Figure 1** PRISMA flowchart summarizing study identification and selection

Figure 2 Forest plots of primary safety outcomes: (A) discontinuation due to AEs; (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.



Abbreviations: EPS, extrapyramidal side effects; PCS, potential clinically significant.
Tau-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.

462 **Table 1** Characteristics of randomized controlled studies included in this meta-analysis

Article	Region	Study design	Indication	Treatment Duration (weeks)	Intervention, (dose, [mg/d])	Number of patients (safety population)	Male		Age (years)	
							n	%	mean	SD
Calabrese 2015 [20]	U.S, Romania, Russia, Croatia, Ukraine & Serbia	Double-blind, placebo-controlled	bipolar I mania	3	placebo	161	89	55.3	41.5	11.4
					cariprazine (3-6)	167	90	53.9	43.1	12.2
					cariprazine (6-12)	169	85	50.3	41.2	11.3
Durgam 2014 [16]	U.S, India, Russia, Ukraine & Malaysia	Double-blind, placebo- and active-controlled	schizophrenia	6	placebo	151	101	66.9	36	10.8
					cariprazine (1.5)	145	93	64.1	36.8	9.6
					cariprazine (3.0)	146	107	73.3	37.1	10.4
					cariprazine (4.5)	147	103	70.1	35.8	10.8
					risperidone (4.0)	140	98	70.0	36.5	11.1
Durgam 2015a [19]	U.S, Russia & India	Double-blind, placebo-controlled	bipolar I mania	3	placebo	118	77	65.3	38.7	11.0
					cariprazine (3-12)	118	80	67.8	38	10.3
Durgam 2015b [21]	U.S, Canada, Colombia, Russia & Ukraine	Double-blind, placebo-controlled	bipolar I depression	8	placebo	148	59	39.6	43.6	12.0
					cariprazine (0.75)	143	52	35.5	40.1	11.2
					cariprazine (1.5)	147	55	37.0	40.9	11.4
					cariprazine (3.0)	146	58	39.7	42.8	10.8
Durgam 2015c [15]	U.S	Double-blind, placebo-controlled	schizophrenia	6	placebo	129	103	79.8	41.1	9.9
					cariprazine (1.5-4.5)	127	105	82.7	40.3	11.1
					cariprazine (6-12)	133	101	75.9	42.4	9.0
Durgam 2015d [17]	U.S, Romania, Russia & Ukraine	Double-blind, placebo- and active-controlled	schizophrenia	6	placebo	153	97	63.4	38.2	11.3
					cariprazine (3)	155	99	63.9	37.9	10.6
					cariprazine (6)	157	100	63.7	38.6	10.6
					aripiprazole (10)	152	94	61.8	39.3	10.8
Kane 2015 [14]	U.S, India, Colombia & South Africa	Double-blind, placebo-controlled	schizophrenia	6	placebo	147	110	74.8	36.7	11.3
					cariprazine (3-6)	151	118	78.1	36.6	10.5
					cariprazine (9-12)	148	113	76.4	35.5	9.3
Sachs 2015 [18]	U.S & India	Double-blind, placebo-controlled	bipolar I mania	3	placebo	154	95	61.7	36.7	11.8
					cariprazine (3-12)	158	105	66.5	35.8	11.4
Durgam 2016. [22]	U.S & Europe	Double-blind, placebo-controlled	major depressive disorder	8	placebo, antidepressants	266	76	28.6	46.4	11.6

	cariprazine (1-2), antidepressant	273	86	31.5	45.5	11.9
	cariprazine (2-4.5), antidepressant	273	72	26.4	45.1	11.4

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464 **Table** 2 Primary tolerability/safety outcomes of included RCTs

Outcome		**No. of studies**	**RR/Mean difference[#] (95%CI)**	**Heterogeneity (95%PI)**
Discontinuation due to AEs		9	1.13 (0.77, 1.66)	P=0.07, I^2=71% (0.32, 3.93)
EPS-related outcomes	Discontinuation due to EPS-related TEAE	5	3.31 (1.06, 10.32)	P=0.68, I^2=0% (0.52, 21.00)
	Discontinuation due to akathisia	4	8.71 (2.08, 36.49)	P=0.95, I^2=0% (NA)
	Akathisia	9	3.92 (2.83, 5.43)	P=0.31, I^2=11% (2.12, 7.25)
	Tremor	7	2.41 (1.52, 3.79)	P=0.31, I^2=16% (1.01, 5.75)
	Restlessness	7	2.17 (1.38, 3.40)	P=0.27, I^2=21% (0.85, 5.54)
	BARS, mean change	5	0.32 (0.21, 0.43)	P=0.04, I^2=60% (-0.04, 0.68)
	SAS, mean change	5	0.45 (0.27, 0.64)	P=0.02, I^2=65% (-0.18, 1.08)
	AIMS, mean change	5	0.04 (-0.05, 0.13)	P=0.003, I^2=75% (-0.31, 0.39)
Metabolic outcomes	Body weight (kg)	9	0.61 (0.39, 0.82)	P=0.07, I^2=46% (0.02, 1.20)
	Total cholesterol (mg/dL)	9	-0.59 (-1.86, 0.68)	P=0.34, I^2=12% (-3.00, 1.82)
	LDL (mg/dL)	9	-1.61 (-3.31, 0.09)	P=0.11, I^2=39% (-5.65, 2.43)
	HDL (mg/dL)	9	0.02 (-0.06, 0.10)	P=0.50, I^2=0% (-0.08, 0.12)
	Triglycerides (mg/dL)	9	-0.04 (-0.25, 0.16)	P=0.80, I^2=0% (-0.29, 0.21)
	Fasting glucose (mg/dL)	9	1.31 (-0.19, 2.82)	P=0.02, I^2=57% (-2.74, 5.36)
	PCS change in glucose*	3	1.38 (0.47, 4.08)	P=0.38, I^2=0% (NA)

	Prolactin (ng/mL)	7	-0.53 (-3.30, 2.23)	P<0.001, I^2=75% (-9.11, 8.05)
Cardiovascular outcomes	Orthostatic hypotension	7	0.93 (0.76, 1.13)	P=0.74, I^2=0% (0.72, 1.21)
	SBP (mmHg)	9	0.83 (0.02, 1.65)	P=0.17, I^2=31% (-1.05, 2.71)
	DBP (mmHg)	9	0.68 (0.04, 1.32)	P=0.15, I^2=34% (-0.86, 2.22)
	Creatine kinase (U/L)	4	17.49 (1.63, 33.35)	P=0.60, I^2=0% (NA)

[#] Results underlined were mean difference.

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

***** 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.

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