

1 **Title:**

2 Tolerability and safety profile of cariprazine in treating psychotic disorders, bipolar
3 disorder and major depressive disorder: a systematic review with meta-analysis of
4 randomized controlled trials

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19 KSJL, ICKW and EWC had the original idea for this study and contributed to the
20 development of the idea and study design. KSJL and YH independently conducted a
21 systematic review and reviewed the literature for relevance. KSJL and YH undertook
22 the analysis. KSJL, YH, ICKW and EWC contributed to interpretation of the analysis.
23 KSJL and YH wrote the first draft of the paper. KSJL, YH, ICKW and EWC critically
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56

57 **Abstract (299 words)**

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

62 *Objective* A meta-analysis of published RCTs was conducted to systematically review
63 the tolerability and safety of cariprazine versus placebo.

64 *Methods* Clinical trials registers (the metaRegister of controlled trials, the Clinical trials
65 government and the World Health Organisation International Clinical Trials Registry
66 Platform) and electronic databases (PubMed, Embase, PsycINFO and Cochrane library)
67 were searched up to June 2016 to identify phase II/III RCTs of cariprazine in patients
68 with schizophrenia, bipolar disorder or major depressive disorder. A meta-analysis was
69 conducted to investigate outcomes, including risks of discontinuation due to adverse
70 events (AEs), extrapyramidal side effects (EPS) or related events, metabolic syndrome
71 and cardiovascular-related events.

72 *Results* Nine RCTs were included with a total of 4,324 subjects. The risk of
73 discontinuation due to AEs for cariprazine was similar to placebo (risk ratio [RR]=1.13,
74 95% confidence interval [95%CI] 0.77-1.66). Cariprazine was associated with higher
75 risks of EPS-related events compared to placebo, including risk of akathisia (RR=3.92,
76 95%CI 2.83-5.43), tremor (RR=2.41, 95%CI 1.53-3.79) and restlessness (RR=2.17,
77 95%CI 1.38-3.40). The cariprazine treatment group was more likely to have clinically
78 significant weight gain (RR=1.68, 95%CI 1.12-2.52). No statistically significant

79 differences in results were found in other metabolic parameters or cardiovascular-
80 related events.

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

87

88 **1. Introduction**

89 Antipsychotic drugs (APDs) have been the mainstay for the management of
90 schizophrenia for more than 60 years [1]. In recent decades they have also become
91 established in the treatment of bipolar disorder, for episodes of both mania and
92 depression [2], and were also recommended as combination treatment with
93 antidepressants for major depressive disorder (MDD) [3]. Dopamine D₂ receptor
94 antagonism appears to be a key mechanism in the efficacy of APDs [4]. Second
95 generation antipsychotics (SGAs) also have affinity to other receptors, including but
96 not limited to, dopamine (other than D₂), serotonin, muscarinic, cholinergic and
97 histamine receptors [5]. The affinity to multiple receptors was thought to contribute to
98 better efficacy and lower risk of extrapyramidal side effects (EPS) and tardive
99 dyskinesia compared to first generation antipsychotics [6]. However, the claims of
100 better efficacy have been questioned and, although SGAs are associated with less EPS,
101 they have been shown to be associated with higher risks of weight gain [7], metabolic
102 syndrome (including dyslipidemia, hyperglycemia) [8-10], arrhythmia [11] and
103 hyperprolactinemia [12]. Drug-induced adverse events are the major cause of APD
104 discontinuation [12]. It is consequently important for prescribing clinicians to have
105 sound knowledge of the tolerability/safety profile of APDs and closely monitor patients
106 on APD treatment.

107 Cariprazine (Vraylar™, also previously known as RG-188 or trans-4-(2-(4-(2,3-
108 dichlorophenyl)piperazine-1-yl)-ethyl)-N,N-dimethylcarbamoyl-cyclohexyl-amine
109 hydrochloride) is a new APD approved by the U.S. Food and Drug Administration
110 (FDA) to treat schizophrenia and bipolar mania in adults on September 17, 2015 [13].

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

117 As a dopamine D₂ and D₃ receptors partial agonist, cariprazine has preference for D₃
118 receptors [23, 24]. Its high affinity to D₃ receptor has been shown both *in vitro* and *in*
119 *vivo* [23, 24]. In contrast, D₃ receptor occupancy is low or negligible with other SGAs,
120 as reported in positron emission tomography studies [25-27]. With regard to other
121 receptors, cariprazine shows partial agonism at 5-HT_{1A} receptors and acts as an
122 antagonist of 5-HT_{2B} receptors with high affinity, and low affinity for 5-HT_{2A}, 5-HT_{2C},
123 adrenergic α_1 and histamine H₁ receptors [24]. In animal studies, cariprazine has been
124 shown to have antipsychotic-like activity, including (but not limited to) inhibition of
125 amphetamine-induced climbing and hyperactivity *in vivo* [23]. Based on the
126 pharmacological actions, a distinct tolerability/safety profile from other marketed
127 SGAs might be anticipated.

128 Previous cariprazine meta-analyses or post-hoc analyses have focused on efficacy [28-
129 32] but did not investigate its tolerability and safety. Due to its unique pharmacological
130 profile, there is a need for a systematic review of the tolerability/safety data of
131 cariprazine. The objective of this study was to investigate the tolerability/safety
132 outcomes of cariprazine compared to placebo in adult patients with schizophrenia,
133 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

156 screened to identify any potentially relevant studies.

157 **2.3. Inclusion and exclusion criteria**

158 Published randomized, placebo-controlled phase II and III trials investigating the
159 tolerability and safety of cariprazine in patients with mental disorders were eligible.
160 Full texts were evaluated for assessing the inclusion criteria. Conference abstracts were
161 excluded due to the unknown quality of studies. Studies without double-blind design
162 applied were excluded due to unknown risk of bias.

163 **2.4. Evaluation of bias**

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

171 **2.5. Outcome measures**

172 The primary outcomes for assessing tolerability/safety were (1) discontinuation due to
173 adverse events (AEs), (2) EPS related outcomes, (3) metabolic syndrome related
174 outcomes, and (4) cardiovascular adverse effects related outcomes. Details of the risks
175 of discontinuation, treatment-emergent adverse effects (TEAEs), use of rescue
176 medication and mean changes of laboratory parameters analysed in the four categories
177 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

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

202 **2.6.Data extraction**

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

208 **2.7.Statistical methods**

209 The Mantel-Haenszel method [39, 40] with random effects model [41] was used to
210 calculate the risk ratios (RRs) for all dichotomous outcomes (adverse events, PCS
211 changes of scales or parameters). Laboratory parameters were analysed as continuous
212 data. The inverse variance method with random effects model was used to estimate the
213 pooled mean difference of continuous outcomes from baseline to the end of treatment
214 [41]. Standardized mean difference (SMD) was calculated for continuous outcomes to
215 compare with results from other meta-analyses investigating safety profiles of APDs.
216 For the calculation of SMD, the difference in mean outcomes between groups was
217 divided by the standard deviation of outcomes among studies. Heterogeneity was
218 assessed using Cochran's Q statistics, I^2 statistics and prediction intervals. Cochran's
219 Q statistical test was considered statistically significant when $P < 0.10$ [42]. The I^2
220 statistic was also calculated to estimate the proportion of total variation among studies,
221 where values of 25%, 50% and 75% were regarded as low, moderate and high
222 heterogeneity, retrospectively [43]. 95% prediction intervals (95%PI) were calculated

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

225 Review Manager 5.3 [47] was used to conduct all statistical analyses. P-values (two-
226 tailed) <0.05 were regarded as statistically significant, except for heterogeneity tests.
227 Online module (statstodo.com) was used to combine means and standard deviations of
228 continuous variables from multiple groups [48].

229 **2.8.Subgroup and sensitivity analyses**

230 Subgroup analyses of the nine included RCTs were conducted based on different
231 indications of cariprazine use and various doses of cariprazine. Subgroup analyses were
232 performed to investigate the source of heterogeneity in assessing primary outcomes.
233 All primary outcomes were analysed in subgroups. Results were compared with those
234 of the main analysis, where all cariprazine users belong to one treatment group. Results
235 were also compared between subgroups. Subgroup analysis (by indication) was
236 conducted for indications including schizophrenia and manic episodes of bipolar
237 disorder. Subgroup analysis by dose was stratified by cariprazine dose (low dose group
238 was defined as dose 6mg/day or below and high dose group was defined as above
239 6mg/day, based on the treatment dose range recommended by the FDA [49]).

240 The treatment intervention in one of the included RCTs was a combination of
241 cariprazine and antidepressant [22], while in the other eight RCTs it was cariprazine
242 alone. Hence a *post-hoc* sensitivity analysis was conducted where this study was
243 excluded in the primary analysis to investigate the impact of the adjunctive
244 antidepressant on the outcomes of interest in this study.

245 **3. Results**

246 **3.1. Search results**

247 **Figure 1** summarizes the review flowchart in accordance with the PRISMA statement.
248 The search of electronic databases including PubMed, Embase, PsycINFO and
249 Cochrane library yielded a total of 563 studies. Twenty-two records were found
250 registered at clinicaltrial.gov and 41 at ICTRP. After removing duplicates and screening
251 abstracts, 29 full-texts were further assessed for eligibility. Overall nine RCTs met the
252 inclusion criteria and were included in the systematic review.

253 **3.2. Characteristics and quality of included RCTs**

254 baseline.

255 **Table 1** Table 1 summarizes the characteristics of included studies. Of the nine RCTs
256 included, four [14-17] investigated the use of cariprazine in patients with schizophrenia,
257 three [18-20] investigated the use of cariprazine in mania associated with bipolar I
258 disorder, one [21] focused on patients with bipolar I depression and one recruited
259 patients with MDD [22]. Treatment duration ranged from three to eight weeks. Daily
260 cariprazine doses investigated in these RCTs ranged from 0.75 mg to 12 mg.
261 Antidepressants (including but not limited to sertraline, citalopram, escitalopram,
262 venlafaxine and duloxetine) were used in combination with placebo or cariprazine in
263 one RCT [22].

264 The included RCTs were rated as “low risk of bias” or “unclear” with respect to
265 sequence generation, allocation concealment, blinding setting and outcome data
266 reporting (**Supplementary Table 1**). As reported in the evidence profile table

267 (Supplementary Table 2) and the summary of findings table (Supplementary Table
268 3), with the exception of the outcomes of discontinuation due to AEs and use of anti-
269 Parkinson medication being rated as “Low”, the quality of a body of evidence for
270 primary outcomes were rated as “High” or “Moderate”.

271 3.3. Discontinuation of treatment

272 There was no statistically significant difference between discontinuation due to AEs in
273 the cariprazine treatment group compared to the placebo group, RR 1.13 (95%CI 0.77-
274 1.66, 95%PI 0.32-3.93) (Figure 2).

275 3.4. Extrapyrarnidal symptoms (EPS)

276 Discontinuation due to EPS-related TEAEs was more likely in the cariprazine group
277 (RR 3.31, 95%CI 1.06-10.32, 95%PI 0.52-21.00) (Table 2). Cariprazine-treated
278 patients had greater than a 3-fold increase in the risk than placebo-treated patients of
279 treatment-emergent Parkinsonism (RR 3.33, 95%CI 2.17-5.13, 95%PI 1.34-8.27) and
280 treatment-emergent akathisia (RR 3.36, 95%CI 2.48-4.56, 95%PI 1.69-6.67), defined
281 as change of SAS (≤ 3 at baseline and >3 after baseline) and BARS (≤ 2 at baseline
282 and >2 after baseline) respectively (Figure 2). Similarly, the cariprazine-treated group
283 was more likely to receive anti-Parkinson medication (RR 2.79, 95%CI 2.04-6.73,
284 95%PI 0.35-22.18) and beta-blocking medication (RR 3.71, 95%CI 2.04-6.73, 95%PI
285 not applicable) for treating akathisia (Figure 2). Cariprazine-treated patients had a
286 higher risk of EPS-related AEs including akathisia (RR 3.92, 95%CI 2.83-5.43, 95%PI
287 2.12-7.25), tremor (RR 2.41, 95%CI 1.52-3.79, 95%PI 1.01-5.75) and restlessness (RR
288 2.17, 95%CI 1.38-3.40, 95%PI 0.85-5.54) (Table 2). There was a statistically
289 significant increase in the mean change in BARS scale (for akathisia) and SAS scale

290 (for Parkinsonism) as shown in **Table 2**.

291 **3.5. Metabolic outcomes**

292 From the eight RCTs which had reported the PCS change in weight, the meta-analysis
293 showed that the cariprazine group were more likely to have a clinically significant
294 weight gain compared to the placebo group (RR 1.68, 95%CI 1.12-2.52, 95%PI 1.01-
295 2.79) (**Figure 2**). Furthermore, the cariprazine-treated group had an increased mean
296 weight of 0.61kg (95%CI 0.39-0.82, 95%PI 0.02-1.20) compared to the placebo group
297 (**Table 2**). There was no PCS change in fasting glucose (glucose levels less than 100
298 mg/dL at baseline to 126 mg/dL or above at the end of treatment). In addition, there
299 was no statistically significant difference between the cariprazine and placebo groups
300 in the mean change from baseline to the end of treatment of total cholesterol, LDL,
301 HDL, triglycerides, prolactin and fasting glucose.

302 The mean change in body weight for cariprazine was statistically significantly lower
303 (mean change -0.73 kg, 95%CI -1.34 to -0.13) than for risperidone [16]. In the study
304 with the aripiprazole arm as an active control, mean change in fasting glucose in the
305 cariprazine group was statistically significantly elevated compared with aripiprazole
306 (mean difference 4.21 mg/dL, 95%CI 1.24-7.17), however this was not statistically
307 different from the placebo group (mean difference -1.59 mg/dL, 95%CI -8.01 to 4.83)
308 [17].

309 **3.6. Cardiovascular outcomes**

310 The risk of orthostatic hypotension was similar between cariprazine and placebo groups.
311 Both systolic and diastolic blood pressure were marginally higher in cariprazine group

312 (Table 2). The mean creatine kinase level was higher in the cariprazine group compared
313 to placebo, with a statistically significant difference of 17.49 U/L (95%CI 1.63-33.35,
314 95%PI -17.33 to 52.31). Data was inadequate for QTc intervals and hence was not
315 included in meta-analysis; however three adverse events of QTcB interval >500 msec
316 were reported in two RCTs (two in the placebo group and one in the cariprazine-treated
317 group) [18, 20].

318 3.7.Secondary outcomes

319 Three deaths were reported in the cariprazine-treated group from two RCTs [17, 20]
320 and no death was reported in the placebo group. Meta-analysis of other
321 tolerability/safety outcomes, including risks of other reasons for discontinuation, risks
322 of specific AEs and SAEs, mean change in parameters for liver function, vital signs,
323 suicidal ideation defined by Columbia-Suicide Severity Rating Scale (C-SSRS) and use
324 of benzodiazepines mostly yielded statistically non-significant differences between the
325 cariprazine and placebo groups. Detailed results are presented in the **Supplementary**
326 **Table 4**. There was a lower risk of total SAEs (RR 0.62, 95%CI 0.42-0.91) in the
327 cariprazine group compared to the placebo group. However, the following AEs were
328 more frequently reported in the cariprazine group than in the placebo group, with
329 statistically significant results: nausea, extrapyramidal disorder, vomiting, constipation,
330 dizziness, somnolence and blurred vision (**Supplementary Table 4**). Forest plots for
331 all outcomes were shown in **Supplementary Figure 1**.

332 3.8.Subgroup and sensitivity analyses

333 In the subgroup analysis stratified by dose, most of the results were similar/consistent
334 with the main analysis, with the exception of the risk ratios of PCS weight change in

335 high-dose group (>6mg/day) did not reach statistical significance (**Supplementary**
336 **Table 5**). In comparisons between subgroups, the mean change in the SAS scale was
337 larger in the high-dose group compared to the low-dose group (**Supplementary Table**
338 **5**).

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

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

349

350 **4. Discussion**

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

356 Our results should be interpreted with caution as the treatment periods were relatively
357 short (three to eight weeks) and long-term safety data was not reported. An RCT with
358 a 6-month treatment period was conducted; however this study was excluded as it was
359 not placebo-controlled [50]. Patients in the treatment arms received daily doses similar
360 to the recommended doses in the manufacturer's product information (1.5–6 mg/d for
361 schizophrenia and 3–6 mg/d for bipolar mania [49]) or doses higher than recommended.
362 Notably, the included patients were relatively young (average age approximately 40
363 years). Whether similar results will be seen in older or younger patients remains to be
364 explored as extensive data on these age groups are currently not available. The number
365 of available RCTs was limited: only nine RCTs were included in our study. Some of
366 the outcomes were not consistently reported in all the RCTs. Therefore results presented
367 in this study should be interpreted with caution as it may not be adequately powered.

368 Discontinuation of treatment is a composite outcome measure of tolerability/safety and
369 efficacy. There was no statistically significant difference in the all-cause
370 discontinuation of cariprazine treatment compared to placebo. This suggests that the
371 tolerability of cariprazine was generally good. Additional analysis of the data on
372 discontinuation due to AEs and SAEs (**Tables 2** and **supplementary table 4**) did not
373 reveal statistically significant differences between cariprazine and placebo, also
374 suggesting that cariprazine was well tolerated by the patients. However, the meta-
375 analysis is not adequately powered to detect a difference in some of the individual
376 adverse effects between cariprazine and placebo. There were more patients in the
377 placebo group who discontinued treatment due to insufficient drug response, which
378 indirectly suggests superior efficacy of cariprazine when compared to placebo. This
379 result is consistent with results of previous RCTs and meta-analyses suggesting better

380 efficacy of cariprazine compared to placebo [29-31]. However, additional RCTs are
381 required for adequate power to detect a difference in tolerability and safety outcomes
382 between cariprazine and placebo.

383 As with some of the other SGAs, akathisia was a common TEAE. Statistically
384 significant higher risks of EPS-related TEAEs, including akathisia, tremor, restlessness
385 and overall extrapyramidal disorder were reported in the cariprazine than in the placebo
386 group. The use of rescue medications is also an indicator reflecting clinically significant
387 EPS-related events. The odds ratios (ORs) versus placebo of at least one occasion of
388 the prescription of anti-Parkinson drugs for other marketed antipsychotics in the study
389 by Leucht et al. varied from 0.3 (clozapine, 95%CI 0.12-0.62) to 4.76 (haloperidol,
390 95%CI 3.70-6.04) [51]. The result in our analysis (OR 3.49, 95%CI 1.91-6.38)
391 overlapped with the range reported by Leucht et al. [51]. Pooled risk ratios of treatment-
392 emergent akathisia, defined by BARS was 3.36 (95%CI 2.48-4.56), which was similar
393 to the results for other SGAs (RR 5.37, 95%CI 3.38-8.53), as reported in previous meta-
394 analyses [52, 53]. The available data indicate that cariprazine is consistently associated
395 with a higher risk of EPS compared to placebo. Although cariprazine has a different
396 pharmacological profile from other SGAs, the risk of EPS appears to be similar.
397 Although there was a statistically significant difference between cariprazine and
398 placebo in several of the outcomes (e.g. discontinuation due to akathisia, risk of tremor,
399 risk of restlessness, mean change in BARS, SAS and AIMS scores in **Table 2**), the
400 results should still be interpreted with caution, as the analysis may have been
401 underpowered for some of the other outcomes due to the small number of
402 studies/patients included.

403 Our analysis revealed that cariprazine was associated with a marginally increased risk
404 of PCS weight gain compared with placebo. The pooled mean change of body weight
405 was only 0.61 kg (standard mean difference=0.25, 95%CI 0.17-0.34) during the study
406 period. However, it should be noted that this is a mean result and does not indicate
407 whether some individuals gained weight excessively nor do these relatively brief
408 studies give any indication of the long-term effects on weight or other adverse effects.
409 Compared to the standardized mean difference in weight gain or risk reduction in PCS
410 weight gain of other SGAs, cariprazine was associated with less mean weight gain than
411 olanzapine, quetiapine, risperidone and clozapine [51, 52], with similar risk of PCS
412 weight gain as aripiprazole and ziprasidone [51-53]. Weight gain, hyperglycaemia and
413 dyslipidaemia (elevated total cholesterol and LDL, and decreased HDL level) are the
414 main risk factors contributing to cardiovascular diseases in patients with schizophrenia
415 and can be frequently observed in users of SGAs [54]. In our results, levels of total
416 cholesterol, LDL and HDL did not differ statistically significantly between the placebo
417 and cariprazine groups – generally this shows a more favourable metabolic profile than
418 other SGAs. No statistically significant elevation of prolactin level was revealed in our
419 analysis.

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

425 Cariprazine was associated with a statistically significant but mild elevation of creatine

426 kinase. However, no acute myocardial infarction was reported and this result appears
427 unlikely to be clinically significant. Marginally statistical significant changes in blood
428 pressure were observed, however there was no difference in reports of orthostatic
429 hypotension between cariprazine and placebo. No cardiovascular safety concerns were
430 reported in the short periods of treatment. QTcB prolongation remains to be further
431 explored. Again, data on long-term drug use in large numbers of patients are needed to
432 provide a complete evaluation of the cardiovascular safety profile.

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

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

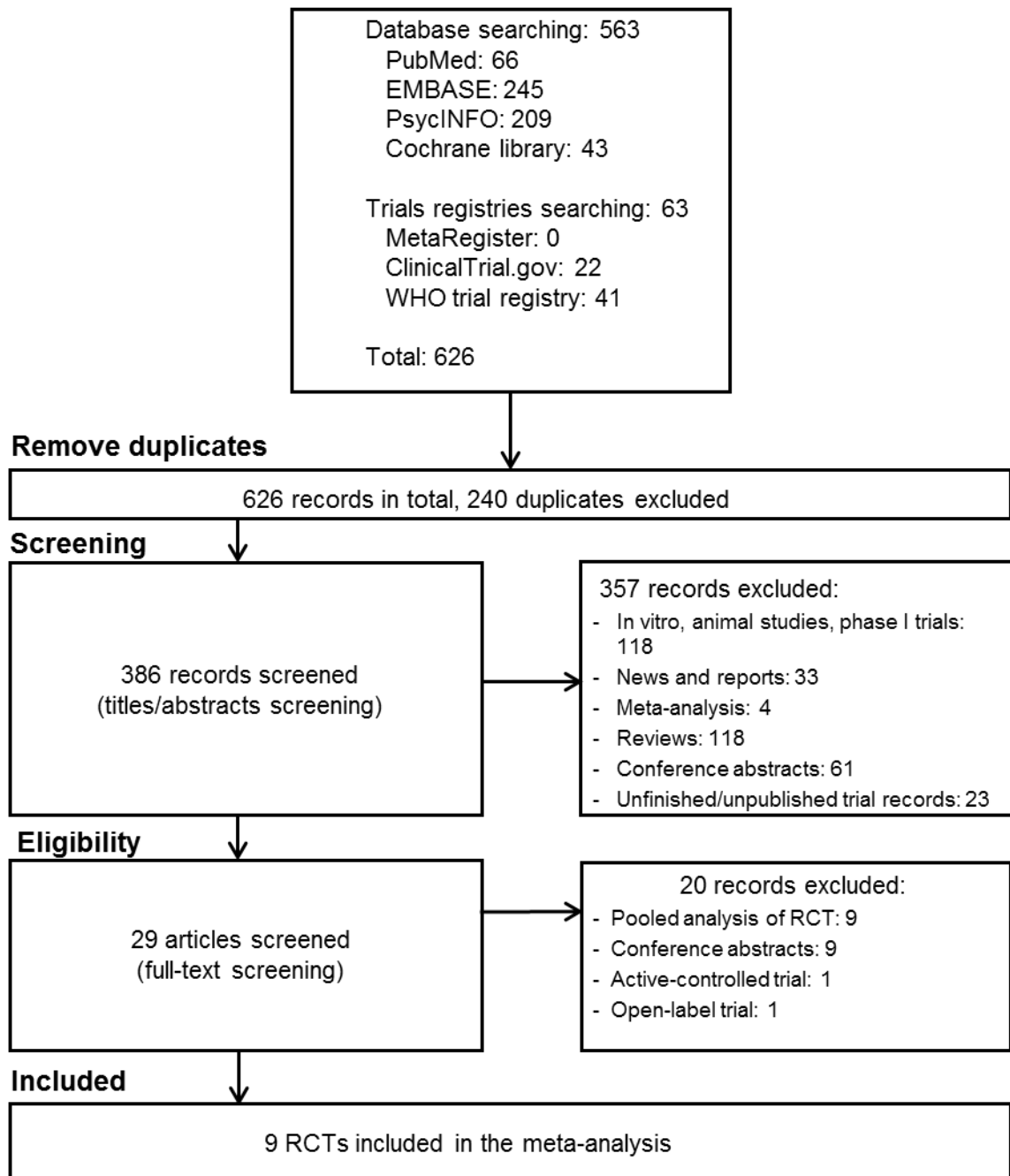
446 **5. Conclusions**

447 Our meta-analysis of short-term RCTs suggested that cariprazine was generally well

448 tolerated, as indicated by similar discontinuation rates due to adverse events between
449 drug and placebo groups. Cariprazine was associated with a higher risk of EPS-related
450 adverse events, particularly akathisia, and a slight increase in mean body weight. No
451 statistically significant effects on prolactin level or the cardiovascular system were
452 evident. It is important that patients are informed of the potential EPS. More clinical
453 and post-marketing pharmacovigilance studies are needed to investigate the long-term
454 tolerability and safety of cariprazine.

455

Identification

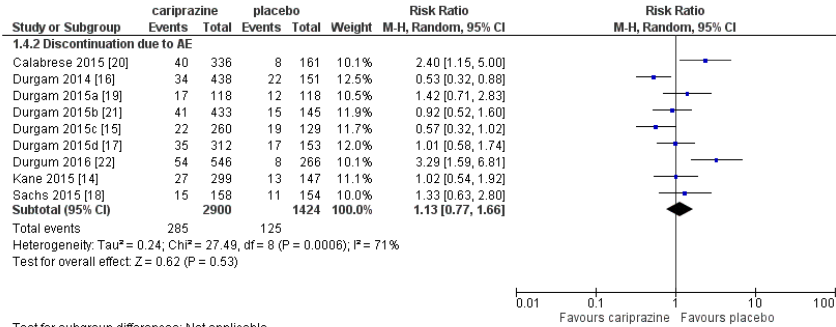


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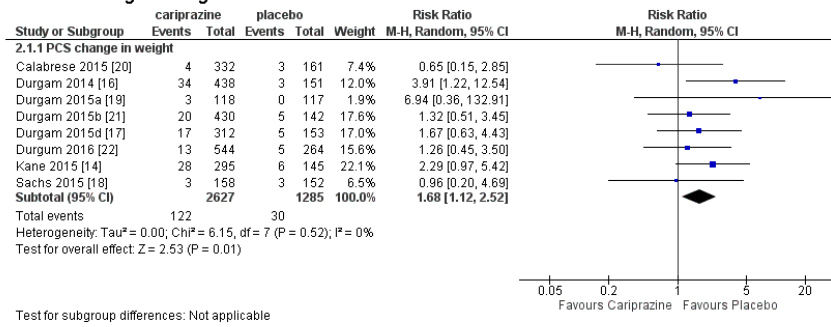
457 **Figure 1** PRISMA flowchart summarizing study identification and selection

458 **Figure 2** Forest plots of primary safety outcomes: (A) discontinuation due to AEs; (B) potential clinically significant change in weight; (C) risks of
 459 treatment-emergent extrapyramidal side effects and (D) use of rescue medication for extrapyramidal side effects.

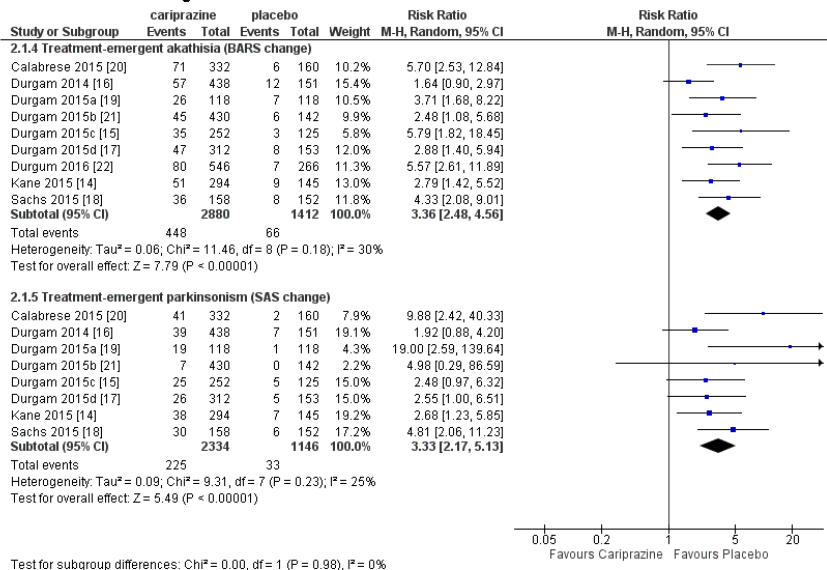
A. Discontinuation due to AE



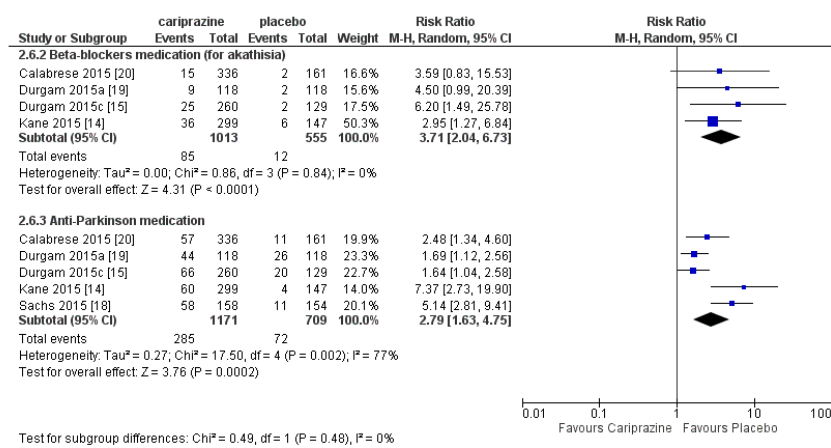
B. PCS change in weight



C. Treatment-emergent EPS



D. EPS-related medication use



460

461 Abbreviations: EPS, extrapyramidal side effects; PCS, potential clinically significant.
 462 Tau-squared statistics were used to calculate prediction intervals (by default as generated by RevMan).
 463 *PCS change in weight was defined as a 7% weight gain from baseline.

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

465

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

466 **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	<u>0.32</u> (0.21, 0.43)	P=0.04, I ² =60% (-0.04, 0.68)
	SAS, mean change	5	<u>0.45</u> (0.27, 0.64)	P=0.02, I ² =65% (-0.18, 1.08)
	AIMS, mean change	5	<u>0.04</u> (-0.05, 0.13)	P=0.003, I ² =75% (-0.31, 0.39)
Metabolic outcomes	Body weight (kg)	9	<u>0.61</u> (0.39, 0.82)	P=0.07, I ² =46% (0.02, 1.20)
	Total cholesterol (mg/dL)	9	<u>-0.59</u> (-1.86, 0.68)	P=0.34, I ² =12% (-3.00, 1.82)
	LDL (mg/dL)	9	<u>-1.61</u> (-3.31, 0.09)	P=0.11, I ² =39% (-5.65, 2.43)
	HDL (mg/dL)	9	<u>0.02</u> (-0.06, 0.10)	P=0.50, I ² =0% (-0.08, 0.12)
	Triglycerides (mg/dL)	9	<u>-0.04</u> (-0.25, 0.16)	P=0.80, I ² =0% (-0.29, 0.21)
	Fasting glucose (mg/dL)	9	<u>1.31</u> (-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	<u>-0.53</u> (-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	<u>0.83</u> (0.02, 1.65)	P=0.17, I ² =31% (-1.05, 2.71)
	DBP (mmHg)	9	<u>0.68</u> (0.04, 1.32)	P=0.15, I ² =34% (-0.86, 2.22)
	Creatine kinase (U/L)	4	<u>17.49</u> (1.63, 33.35)	P=0.60, I ² =0% (NA)

467

468 # Results underlined were mean difference.

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

476 * PCS change in fasting glucose was defined as the shift from normal glucose levels
477 (<100 mg/dL) at baseline to high glucose levels (≥126 mg/dL) at the end of treatment.

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