TECHNICAL COMMENTARY

NeuRA Discover. Conquer. Cure.
BIPOLAR DISORDERS LIBRARY

Cariprazine

Introduction

The treatment of bipolar disorder is complex due to the presence of varying configurations of symptoms in patients. The primary treatments for bipolar disorder are pharmacological, and often involve second generation antipsychotic drugs, such as cariprazine. Based on its high affinity for dopamine receptors, cariprazine has been proposed as a treatment for bipolar disorder.

Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2010 that report results separately for people with a diagnosis of bipolar or related disorders. Reviews were identified by searching the databases MEDLINE, EMBASE, and PsycINFO. Hand searching reference lists of identified reviews was also conducted. When multiple copies of review topics were found, the most recent and/or comprehensive review was included. Reviews with pooled data are prioritised for inclusion.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist that describes a preferred way to present a meta-analysis[1]. Reviews reporting less than 50% of items have been excluded from the library. The PRISMA flow diagram is a suggested way of providing information about studies included and excluded with reasons for exclusion. Where no flow diagram has been presented by individual reviews, but identified studies have been described in the text, reviews have been checked for this item. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that some reviews may have been limited by journal guidelines.

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach where high quality evidence such as that gained from randomised controlled trials (RCTs) may be downgraded to moderate or low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if risks associated with the intervention or other matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large or if there is a dose dependent response. We have also taken into account sample size and whether results are consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)[2]. The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

Results

We found six reviews that met our inclusion criteria[3-8].

- High quality evidence suggests cariprazine is associated with greater improvements in mania (medium-sized effect) and depression (small effect) than placebo, but is also associated with more adverse effects including akathisia, tremor, restlessness, and weight gain.
- Moderate quality evidence suggests similar improvement in depression symptoms with low (0.75-1.5 mg) and high (3 mg) dose cariprazine monotherapy.
- Moderate quality evidence finds a medium-sized effect of greater improvement in mania symptoms with cariprazine than with topiramate, but less improvement when compared to tamoxefin.

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

Bartoli F, Dell'Osso B, Crocamo C, Fiorillo A, Ketter TA, Suppes T, Clerici M, Carra G

Benefits and harms of low and high second-generation antipsychotics doses for bipolar depression: A meta-analysis

Journal of Psychiatric Research 2017; 88: 38-46

View review abstract online

Comparison	**High vs. low dose cariprazine monotherapy.**
Summary of evidence	**Moderate quality evidence (1 RCT, medium to large sample size, precise, direct) suggests no differences in depression symptoms between low (0.75-1.5 mg) and high (3 mg) dose cariprazine.**
Depression	
No significant differences between groups; Depression scores: 1 x 8 week RCT, N = 290, SMD = -0.137, 95%CI -0.367 to 0.094, $p > 0.05$ Response: 1 x 8 week RCT, N = 430, OR = 0.986, 95%CI 0.789 to 1.232, $p > 0.05$ Remission: 1 x 8 week RCT, N = 430, OR = 1.094, 95%CI 0.796 to 1.502, $p > 0.05$	
Risks	There were no significant differences between groups for discontinuation for any reason.
Consistency in results	Not applicable; 1 RCT
Precision in results	Precise for depression and response, imprecise for remission.
Directness of results	Direct

Citrome L

Cariprazine for bipolar depression: What is the number needed to treat, number needed to harm and likelihood to be helped or harmed?

International Journal of Clinical Practice 2019; 73: e13397

View review abstract online

Comparison	**Cariprazine vs. placebo.**

Summary of evidence	**Moderate quality evidence (large sample, unable to assess consistency or precision, direct) suggests higher rates of remission and response in people taking cariprazine for bipolar depression.**
Depression	
3 RCTs, N = 1,383 *There were higher rates of response and remission with cariprazine;* Response: 46.3% vs. 35.9% Remission: 30.2% vs. 20.9%	
Risks	There was a higher rate of discontinuation due to an adverse event (6.7% vs. 4.8%). Authors report that patients receiving cariprazine 3.0 mg/day were more likely to experience adverse events than those receiving 1.5 mg/d.
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

Kadakia A, Dembek C, Heller V, Singh R, Uyei J, Hagi K, Nosaka T, Loebel A

Efficacy and tolerability of atypical antipsychotics for acute bipolar depression: a network meta-analysis

BMC Psychiatry 2021; 21: 249

View review abstract online

Comparison	**Cariprazine vs. placebo or other second-generation antipsychotics.**
Summary of evidence	**Moderate to low quality evidence (unclear sample size, some inconsistencies, precise, direct) finds a small improvement in acute depression with cariprazine over placebo. Lower quality evidence (indirect) finds cariprazine was less efficacious than lurasidone and quetiapine, and there were no differences when compared to olanzapine or ziprasidone.**

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

Response for acute depression	
A small effect of improved response for acute depression with cariprazine over placebo; 4 studies, N not reported, OR = 1.47, 95%CI 1.25 to 1.75, $p < 0.05$ Network analysis showed no differences between cariprazine and olanzapine or ziprasidone. Cariprazine was less efficacious than lurasidone and quetiapine.	
Risks	There were no differences in all-cause discontinuation between cariprazine and placebe.
Consistency in results	Authors report some inconsistencies.
Precision in results	Precise
Directness of results	Direct for pairwise comparison with placebo only.

Lao KSJ, He Y, Wong ICK, Besag FMC, Chan EW

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

CNS Drugs 2016; 30: 1043-54

View review abstract online

Comparison	**Cariprazine vs. placebo.**
Summary of evidence	**Moderate to high quality evidence (large sample size, consistent, imprecise, direct) suggests cariprazine is associated with more akathisia, tremor, restlessness and weight gain than placebo (small to medium-sized effects).**
Adverse events	
Significant, small to medium-sized effects showed cariprazine was associated with higher risks of the following adverse events; Akathisia: 9 RCTs, N = 4,324, RR = 3.92, 95%CI 2.83 to 5.43, $p < 0.05$, $I^2 = 11\%$, $p = 0.31$ Tremor: 7 RCTs, N = 4,324, RR = 2.41, 95%CI 1.53 to 3.79, $p < 0.05$, $I^2 = 16\%$, $p = 0.31$ Restlessness: 7 RCTs, N = 4,324, RR = 2.17, 95%CI 1.38 to 3.40, $p < 0.05$, $I^2 = 22\%$, $p = 0.27$ Weight gain: 8 RCTs, N = 4,324, RR = 1.68, 95%CI 1.12 to 2.52, $p < 0.05$, $I^2 = 0\%$, $p = 0.52$ There were no significant differences between groups for discontinuation due to adverse events, or	

for metabolic/cardiovascular parameters.	
Consistency in results	Consistent
Precision in results	Imprecise
Directness of results	Direct

Pinto JV, Saraf G, Vigo D, Keramatian K, Chakrabarty T, Yatham LN

Cariprazine in the treatment of Bipolar Disorder: A systematic review and meta-analysis

Bipolar Disorders 2020; 22(4): 360-371

View review abstract online

Comparison	**Cariprazine vs. placebo in people with bipolar I disorder.**
Summary of evidence	**High quality evidence (large samples, consistent, precise, direct) suggests cariprazine is associated with greater improvements in mania and depression symptoms than placebo, but is also associated with more adverse effects.**
Mania	
A significant, medium-sized effect of greater improvement in mania symptoms with cariprazine; 3 RCTs (3-12mg/day), N = 870, SMD = -0.52, 95%CI -0.82 to -0.21 p = 0.018, I^2 = 6%	
Depression	
Small effects of greater improvement in depression symptoms with cariprazine; 4 RCTs (1.5mg/day), N = 1,035, SMD = -0.26, 95%CI -0.49 to -0.02, p = 0.040, I^2 = 29% 4 RCTs (3mg/day), N = 1,036, SMD = -0.21, 95%CI -0.41 to -0.01, p = 0.045, I^2 = 0%	
Psychotic symptoms	
No significant differences between groups; 3 RCTs, N = 870, SMD = -0.42, 95%CI -1.00 to 0.16, p = 0.090, I^2 = 74%	
Risks	Cariprazine was associated with more adverse effects.
Consistency in results	Consistent, apart from psychotic symptoms.

Precision in results	Precise, apart from psychotic symptoms.
Directness of results	Direct

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

Psychological Medicine 2015; 45: 299-317

View review abstract online

Comparison	**Cariprazine vs. placebo or other medications.**
Summary of evidence	**Moderate quality evidence (large sample, consistent, some imprecision and indirectness) suggests medium-sized effects of greater improvement in acute mania symptoms with cariprazine than placebo or topiramate, although there was greater improvement with tamoxefin than with cariprazine. There was also less all-cause discontinuation with olanzapine than with cariprazine.**

Mania symptoms

Network meta-analysis included 57 studies, N = 14,256

A significant, medium-sized effect of greater improvement with cariprazine than with placebo;

SMD = 0.47, 95%CrI 0.22 to 0.73, $p < 0.05$

A significant, medium-sized effect of greater improvement with cariprazine than with topiramate;

SMD = 0.54, 95%CrI 0.21 to 0.87, $p < 0.05$

A significant, large effect of greater improvement with tamoxefin than with cariprazine;

SMD = 2.44, 95%CrI 1.86 to 3.07, $p < 0.05$

Authors report no other significant differences between cariprazine and other medications.

Risks	There was less all-cause discontinuation with olanzapine than with cariprazine.
Consistency in results	Authors report data are consistent.
Precision in results	Precise for placebo and topiramate comparison, imprecise for tamoxefin comparison.

Directness of results	Some indirectness

Explanation of acronyms

CI = Confidence Interval, CrI = credible interval, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), N = number of participants, OR = odds ratio, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), RCT = randomised controlled trial, RR = risk ratio, SMD = standardised mean difference, vs. = versus

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias – selective reporting of results; publication bias - trials that are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small[9].

† Different effect measures are reported by different reviews.

Prevalence refers to how many existing cases there are at a particular point in time. Incidence refers to how many new cases there are per population in a specified time period. Incidence is usually reported as the number of new cases per 100,000 people per year. Alternatively some studies present the number of new cases that have accumulated over several years against a person-years denominator. This denominator is the sum of individual units of time that the persons in the population are at risk of becoming a case. It takes into account the size of the underlying population sample and its age structure over the duration of observation.

Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives that are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives that are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

Mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardised mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) which allows results from different scales to be combined and compared. Each study's mean difference is then given a weighting depending on the size of the sample and the variability in the data. Less than 0.4 represents a small effect, around 0.5 a medium effect, and over 0.8 represents a large effect[9].

Odds ratio (OR) or relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in a treatment group, or a group exposed to a risk factor, relative to the comparison group. For example, a RR of 0.75 translates to a reduction in risk of an outcome of 25% relative to those not receiving the treatment or not exposed to the risk factor. Conversely, a RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. A RR or OR of 1.00 means there is no difference between groups. A medium effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2[10]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios measure the effect of an explanatory variable on the hazard or risk of an event.

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

Correlation coefficients (eg, r) indicate the strength of association or relationship between variables. They can provide an indirect indication of prediction, but do not confirm causality due to possible and often unforseen confounding variables. An r of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardised (*b*) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the independent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

‡ Inconsistency refers to differing estimates of effect across studies (i.e. heterogeneity or variability in results) that is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. I^2 is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent considerable heterogeneity and over this is considerable heterogeneity. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula[9];

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%$$

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data (standardised mean differences, not weighted mean differences) is considered imprecise if the upper or lower confidence limit crosses an effect size of 0.5 in either direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, these criteria should be relaxed[11].

‖ Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared with C and B was compared with C that allows indirect comparisons of the magnitude of effect of A versus B. Indirectness of population, comparator and/or outcome can also occur when the available evidence regarding a particular population, intervention, comparator, or outcome is not available and is therefore inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-to-head comparisons of A and B.

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

References

1. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMAGroup (2009): Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *British Medical Journal* 151: 264-9.
2. GRADEWorkingGroup (2004): Grading quality of evidence and strength of recommendations. *British Medical Journal* 328: 1490.
3. Yildiz A, Vieta E, Leucht S, Baldessarini RJ (2011): Efficacy of antimanic treatments: meta-analysis of randomized, controlled trials. *Neuropsychopharmacology* 36: 375-89.
4. Bartoli F, Dell'Osso B, Crocamo C, Fiorillo A, Ketter TA, Suppes T*, et al.* (2017): Benefits and harms of low and high second-generation antipsychotics doses for bipolar depression: A meta-analysis. *Journal of Psychiatric Research* 88: 38-46.
5. Lao KSJ, He Y, Wong ICK, Besag FMC, Chan EW (2016): 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. *CNS Drugs* 30: 1043-54.
6. Citrome L (2019): Cariprazine for bipolar depression: What is the number needed to treat, number needed to harm and likelihood to be helped or harmed? *International Journal of Clinical Practice* 73: e13397.
7. Pinto JV, Saraf G, Vigo D, Keramatian K, Chakrabarty T, Yatham LN (2020): Cariprazine in the treatment of Bipolar Disorder: A systematic review and meta-analysis. *Bipolar Disorders* 22: 360-71.
8. Kadakia A, Dembek C, Heller V, Singh R, Uyei J, Hagi K*, et al.* (2021): Efficacy and tolerability of atypical antipsychotics for acute bipolar depression: a network meta-analysis. *BMC Psychiatry* 21: 249.
9. CochraneCollaboration (2008): Cochrane Handbook for Systematic Reviews of Interventions. Accessed 24/06/2011.
10. Rosenthal JA (1996): Qualitative Descriptors of Strength of Association and Effect Size. *Journal of Social Service Research* 21: 37-59.
11. GRADEpro (2008): [Computer program]. Jan Brozek, Andrew Oxman, Holger Schünemann. *Version 32 for Windows*