Efficacy of Cariprazine in the Psychosis Spectrum: A Systematic Review and Network Meta-Analysis of Randomised Controlled Trials

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SYSTEMATIC REVIEW

Efficacy of Cariprazine in the Psychosis Spectrum: A Systematic Review and Network Meta-Analysis of Randomised Controlled Trials in Schizophrenia and Bipolar Disorder

Livio Tarchi[1] · Susan Bugini[1] · Cristiano Dani[1] · Emanuele Cassioli[1] · Eleonora Rossi[1] · Stefano Lucarelli[2] · Valdo Ricca[1] · Saverio Caini[3] · Giovanni Castellini[1]

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Abstract

Background and Objective Psychosis represents one of the most challenging clinical presentations in psychiatry. Schizophrenia and bipolar disorder may both present psychotic features, and cariprazine may offer improvement in the treatment and care of these conditions. Therefore, the objective of the current work was to synthesise results of efficacy for cariprazine in these disorders.

Methods In total, five electronic databases were searched for randomized controlled trials enrolling patients across the psychosis spectrum, using the search term 'Cariprazine' (PubMed, Embase, clinicaltrials.gov, EUDRACT, Cochrane—last search January 2024). No filter or limits were employed. Effect sizes were extracted, by the mean difference in psychometric variables before and after the intervention (Clinical Global Impression Scale, Positive and Negative Symptom Scale, Montgomery–Asberg Depression Rating Scale, Young Mania Rating Scale, Hamilton Anxiety Rating Scale).

Results In total, 12 studies enrolling either patients with schizophrenia or bipolar disorder were included (total $n = 6477$; $n = 4814$ patients treated with cariprazine, $n = 1663$ controls treated with placebo). Cariprazine was effective in reducing global clinical severity, and higher improvements were observed at increasing dosages (− 0.25 at ≤ 1.5 mg/day, − 0.45 at ≥ 3 mg/day). Cariprazine also effectively reduced psychotic total scores: − 6.74, [95% confidence interval (CI) − 8.31; − 5.17], depression: − 1.78, [95% CI − 2.54; − 1.02], mania: − 5.72, [95% CI – 6.95; – 4.49], and anxiety symptoms: – 1.24, [95% CI – 1.92; – 0.56].

Conclusions Cariprazine was observed as efficacious across retrieved studies, offering a potential for tailored treatments across the psychosis spectrum.

Registration Number https://osf.io/pmyhq.

Key Points

Cariprazine effectively reduces global clinical severity in patients along the psychosis spectrum.

Higher doses of cariprazine were associated with better treatment responses for global clinical severity.

Cariprazine also reduced depressive, manic and anxiety symptoms.

✉ Giovanni Castellini
giovanni.castellini@unifi.it

[1] Psychiatry Unit, Department of Health Sciences, University of Florence, Largo Brambilla, 3, 50134 Florence, Italy

[2] UFS Eating Disorders ASL Toscana Centro, 50122 Florence, Italy

[3] Cancer Risk Factors and Lifestyle Epidemiology Unit, Institute for Cancer Research, Prevention, and Clinical Network (ISPRO), 50139 Florence, Italy

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1 Introduction

Cariprazine is an atypical antipsychotic, originally approved by the Food and Drug Administration (FDA) [1] and the European Medicine Agency (EMA) [2] for the acute and maintenance treatment of schizophrenia. In the USA, the FDA approved the use of cariprazine for acute episodes in bipolar disorder (either mania, or with mixed features) [1], as well as for the treatment of depressive episodes in bipolar disorder (type I) and as adjunctive therapy in treatment-resistant major depressive disorder [3].

To the current day, a limited number of meta-analyses have assessed the use of cariprazine in the treatment of schizophrenia or bipolar disorder. In particular, two meta-analyses by Corponi and colleagues in 2017 [4] and by Zhao and colleagues in 2018 [5] underscored the efficacy and tolerability of cariprazine in the treatment of acute schizophrenia. The efficacy and tolerability of cariprazine in acute schizophrenia was evidenced by the significant reduction in positive and negative symptoms after cariprazine intake, accompanied by a reduction in global clinical severity. Nonetheless, no evidence has been synthesised on the effect of cariprazine on anxiety symptoms, which is a common clinical concern in both schizophrenia and bipolar disorder [6, 7].

On this remark, a third meta-analysis showed that cariprazine may be effective in managing acute and mixed episodes in bipolar disorder [8]. Cariprazine was assessed as significantly associated with reductions in the burden of affective symptoms in bipolar disorder, namely manic and depressive symptoms [8]. A further additional meta-analysis, conducted in 2020 [9], extended its scope beyond schizophrenia and bipolar disorder. This fourth meta-analysis by Cooper and colleagues reported that cariprazine may be well-tolerated irrespective of psychiatric diagnoses (schizophrenia, bipolar disorder and major depressive disorder), although associated with a higher risk of extrapyramidal side effects in comparison to placebo [9].

However, grouping together schizophrenia, bipolar disorder and major depressive disorder may not fully inform clinical practice. In fact, although major depression and bipolar disorder may share affective components, the inclusion of patients with major depression may bias meta-analytic results when assessing evidence in favour of a reduction in depressive symptoms after its intake. A more accurate investigation of antidepressive effects of cariprazine when used as an antipsychotic agent is therefore timely.

For this scope, the current work adopts a transdiagnostic approach and moves beyond single diagnostic categories when assessing the potential efficacy of cariprazine across the spectrum of psychosis, while trying to maintain caution in delineating psychopathological boundaries between these different conditions [10]. Indeed, schizophrenia and bipolar disorder may be appraised as representing different disorders across a spectrum of continuity, rather than being distinct clinical entities, as evidenced by accumulating evidence on shared biological components and prospective clinical transitions during the life-time between these diagnostic categories [11–14]. Schizophrenia and bipolar disorders do not only share positive symptoms of psychosis (i.e. delirium and hallucinations), but also a reduction or absence of normal emotional or behavioural functions—i.e. negative symptoms of psychosis [15]. While historically associated primarily with schizophrenia, negative symptoms have been described as also shared across the psychosis spectrum [15], suggesting that a dimensional approach to psychosis may aid in addressing its impact on functional outcomes in affected individuals across a spectrum of continuum.

To enrich previous research, the present study thus proposed an updated systematic review and meta-analysis of existing literature, adopting a transdiagnostic perspective.

2 Methods

The methodology of this systematic review is in accordance with the PRISMA 2020 guidelines [16]. Included articles were all randomised controlled trials (RCT). Inclusion criteria were as follows: (1) enrolled patients with either a diagnosis of schizophrenia, schizoaffective disorder or bipolar disorder—irrespective of acute psychotic feature, according to DSM-IV, DSM-IV-TR, DSM-5, DSM-5-TR, ICD-9, ICD-10 or ICD-11; (2) evaluating at least one psychometric domain between depression, mania, anxiety, psychotic symptoms (either positive, negative, or general) and general clinical severity; (3) comparing cariprazine with either a different dosage of cariprazine versus placebo or two different dosages of cariprazine. Exclusion criteria were as follows: (1) the article being a systematic review, a meta-analysis or an opinion article; (2) animal studies; (3) methodological or technical contributions with no analysis of clinical data. The following data were extracted from selected articles: study description, drug dosage, comparator, psychometric instrument used duration of treatment.

2.1 Information Sources and Search Strategy

The research of selected articles was conducted on the electronic databases PubMed, Embase, clinicaltrials.gov, and Cochrane to select RCT studies investigating cariprazine. EUDRACT was also included to ensure the inclusion of each trial only once, excluding derivative studies. The search term 'cariprazine' was used, and results were manually screened to apply inclusion/exclusion criteria. No filter or limits were employed. The search was conducted in January 2024.

2.2 Data Selection Process

Two authors (L.T. and S.B.) assessed the published abstracts of potentially eligible studies independently. Eligibility assessment was performed in a standardised manner by two authors (L.T., S.B.). If there were doubts concerning potential eligibility, reviewers examined the full text of the articles. The two authors independently extracted relevant data from each included paper: NCT identification string, population (number of subjects), dosage of cariprazine (quantitatively reported, and also categorically reported according to the following code: low—up to 1.5 mg daily, medium—up to 3 mg daily, high—more than 3 mg daily) psychometric instrument used, outcome evaluated, estimate of intervention effect [calculated as mean difference (MD); comparing outcomes before and after treatment] along with its 95% confidence interval (CI) and standard error. MD was used as the estimate for intervention effect owing to insufficient data in published reports to derive the standardised mean difference (SMD). In case of multiple groups of intervention (different dosages), an estimate of effect was derived for each contrast. As recommended by Cochrane [17], the standard error of the MD was calculated as:

$$\frac{\text{Upper} - \text{Lower } 95\%\text{ CI}}{3.92}. \quad (1)$$

SMD was not calculated, as studies did not report the standard deviation of both the control and exposed group, and the standard error of the term could thus not be derived from the retrieved information [17].

2.3 Risk of Bias

Two authors (L.T., S.B.) independently assessed risk of bias for individual papers using the RoB2 [18]. Risk of bias scores are reported, in detail, in Supplementary Materials (Fig. S1).

2.4 Statistical Analysis

As study participants are nested within studies, and data derived may also be influenced by between-study variances, a multilevel data structure can be described for retrieved effect sizes [19]. Therefore, to address this dependency within and between effect sizes [20], and to better account for the above-mentioned multilevel structure, we assessed overall effect sizes by applying a three-level model, accounting for three sources of variance: sampling variance (level 1, variance between participants), within-study variance (level 2, variance owing to outcomes), and between-study variance (level 3, variance owing to study conditions; see Table S1 in Supplementary Materials). While multilevel models in meta-analyses have long been described (two-level models, equivalent to random effects models) [19], more recently the scientific literature has attempted to better assess uncertainty in meta-analyses. In this regard, specific three-level models, constructed as explained above, have gained prominence and have started to be considered as a standard tool in meta-analytic research [21]. In other words, while standard meta-analyses move beyond pooling effect sizes from individual studies (level one) pooling them (level two) to obtain an estimate of effect size across studies, three-level meta-analyses also control for the dependencies between observed results, namely that one study may have contributed for more than one observation, or that different effect sizes may be derived from similar participants or overlapping samples.

A large heterogeneity between studies was found when meta-analysing effect sizes by outcomes (i.e. $I^2 > 25\%$). Therefore, only random effect models were computed for each outcome [22, 23]. Forest plots were illustrated for each psychological construct. Funnel plots were visually inspected to check for the risk of inclusion due to publication bias. Results were also tested for publication bias by Egger's test [24].

If at least one observation for each dose category was retrieved, a network meta-analysis was also performed, to compare these interventions. The network meta-analysis was conducted following Cochrane guidelines [25]. Multiple interventions (categories of drug dosage) were then ranked according to available evidence, according to the degree of effect (from highest to lowest) estimated using the surface under the cumulative ranking (SUCRA) with n simulations = 10,000 [26, 27].

Sensitivity analyses were conducted, analysing each outcome leveraging standard, non-network, multi-level meta-analytical approaches (MD as treatment effect, NCT number as cluster effect), excluding (1) RCTs conducted in a non-double-blind manner (i.e. MP-241, Nakamura et al. 2016) and (2) RCTs conducted in a non-double-blind manner and studies collecting patients without psychotic features.

All analyses were performed with R (version 4.3.3) [28] and RStudio (version 2023.12.1, build 402) [29], with the support of the following libraries: *meta* [30], *netmeta*, [31], *metafor* [32], *PRISMA2020* [33] and *tidyverse* [34].

3 Results

A total of 773 papers were found after searching: 597 were screened after removing duplicates, of which 471 were excluded after application of inclusion/exclusion criteria. Consequently, 126 studies were selected for full-text examination. Overall, 23 studies were included after full-text examination. The NCT string identifier for RCT was then manually searched on EUDRACT, and 23 unique RCT

identifiers were retrieved. Of these, 11 were excluded, as the study was ongoing at the time of retrieval (2 studies: CTRI/2019/04/018793 and CTRI/2018/09/015741), data were not yet published (8 studies: NCT03593213, NCT03573297, NCT04771299, NCT05913947, NCT05168007, NCT03817502, CTRI/2023/09/057293 and CTRI/2023/09/058092), or the study was conducted following open-label stabilisation after 20 weeks (one study: NCT01412060). In total, 12 studies were finally included (total $n = 6477$; $n = 4814$ patients treated with cariprazine, $n = 1663$ controls treated with placebo) [35–46]. See Fig. 1 for a flowchart of study retrieval (Fig. 1).

In total, 24 pairwise comparisons were retrieved for clinical severity [Clinical Global Impression Scale (CGI)], 14 for general psychotic symptoms [Positive and Negative Symptom Scale (PANSS), total score], 12 for depression [Montgomery–Asberg Depression Rating Scale (MADRS)], 9 negative and positive psychotic symptoms [9 PANSS positive subscales, 9 PANSS negative subscales], 3 for anxiety [Hamilton Anxiety Rating Scale (HAM-A)] and 3 for manic symptoms [Young Mania Rating Scale (YMRS)]. Notably, no study enrolling patients with a diagnosis of bipolar disorder and assessing PANNS subscores, nor assessing MADRS, HAM-A or YMRS in patients with a diagnosis of schizophrenia were retrieved (Table 1). See Table 1 for further

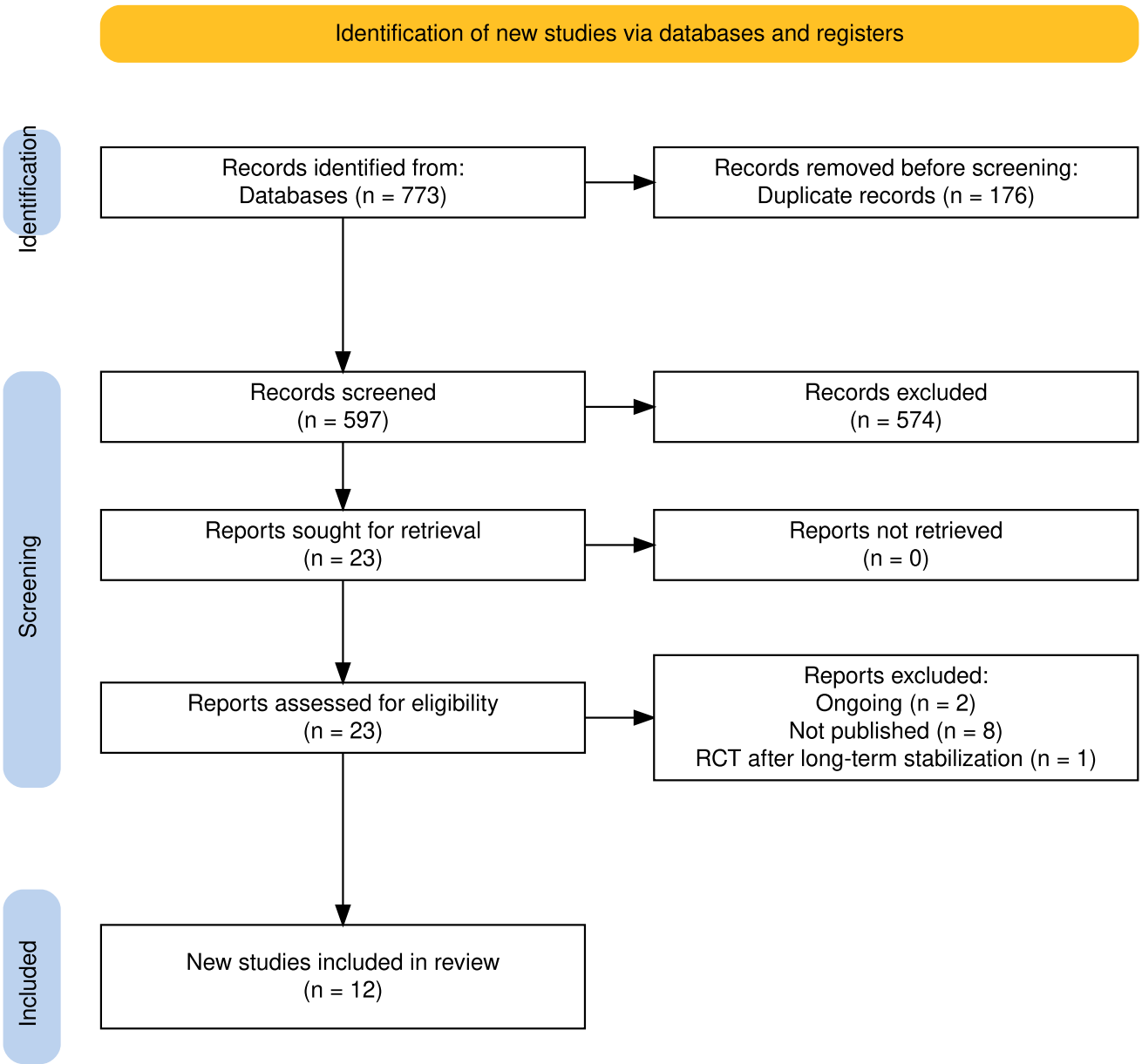

Fig. 1 Flowchart of the inclusion and exclusion procedures

Table 1 Included studies

NCT	Publication (first author, year)	Diagnosis	Diagnostic criteria	Psychotic symptoms	Sample size, cariprazine	Sample size, placebo	Duration of treatment	Outcome	Psychometric instrument	Countries	Blinding
NCT02670538	Earley, 2020a [35]	Bipolar disorder, type I	DSM-V	No acute psychotic symptoms at the time of enrolment	1.5 mg = 168 3 mg = 158	167	6 weeks	Depression, general clinical severity	MADRS, CGI, HAMA	United States, Bulgaria, Croatia, Romania, Serbia, Slovakia, Ukraine	Double blind
NCT02670551	Earley, 2019 [37]	Bipolar disorder, type I	DSM-V	No acute psychotic symptoms at the time of enrolment	1.5 mg = 157 3 mg = 165	158	6 weeks	Depression, general clinical severity	MADRS, CGI, HAMA	United States, Bulgaria, Estonia, Lithuania	Double blind
NCT01104766	Durgam, 2015a [38]	Schizophrenia	DSM-IV-TR	Yes, current psychotic symptoms at time of enrolment	3 mg = 155 6 mg = 157	153	6 weeks	Psychotic symptoms, general clinical severity	PANSS, CGI	United States, Romania, Russia, Ukraine	Double blind
NCT01104779	Kane, 2015 [40]	Schizophrenia	DSM-IV-TR	Yes, current psychotic symptoms at time of enrolment	4.5 mg = 151 7.5 mg = 148	147	6 weeks	Psychotic symptoms, general clinical severity	PANSS, CGI	United States, Colombia, India, South Africa	Double blind
NCT00694707	Durgam, 2014 [41]	Schizophrenia	DSM-IV-TR	Yes, current psychotic symptoms at time of enrolment	1.5 mg = 145 3.0 mg = 146 4.5 mg = 147	151	6 weeks	Psychotic symptoms, general clinical severity	PANSS, CGI	United States, India, Malaysia, Russia, Ukraine	Double blind
NCT00488618	Durgam, 2015b [39]	Bipolar disorder, type I	DSM-IV-TR	Yes, patients enrolled with and without current psychotic symptoms	7.5 mg = 118	118	3 weeks	Depression, psychotic symptoms, general clinical severity, manic symptoms	MADRS, PANSS, CGI, YMRS	United States	Double blind
NCT01058096	Sachs, 2015 [42]	Bipolar disorder, type I	DSM-IV-TR	Yes, patients enrolled with and without current psychotic symptoms	7.5 mg = 158	154	3 weeks	General clinical severity, manic symptoms	CGI, YMRS	United States, India	Double blind

Table 1 (continued)

NCT	Publication (first author, year)	Diagnosis	Diagnostic criteria	Psychotic symptoms	Sample size, cariprazine	Sample size, placebo	Duration of treatment	Outcome	Psychometric instrument	Countries	Blinding
NCT01058668	Calabrese, 2015 [43]	Bipolar disorder, type I	DSM-IV-TR	Yes, patients enrolled with and without current psychotic symptoms	4.5 mg = 167 9.0 mg = 169	161	3 weeks	Depression, psychotic symptoms, general clinical severity, manic symptoms	MADRS, PANSS, CGI, YMRS	United States, Croatia, Romania, Russia, Serbia, Ukraine	Double blind
NCT01396447	Durgam, 2016 [44]	Bipolar disorder, type I	DSM-IV-TR	No acute psychotic symptoms at the time of enrolment	0.75 mg = 143 1.5 mg = 147 3.0 mg = 146	148	6 weeks	Depression, general clinical severity	MADRS, CGI	United States, Argentina, Bulgaria, Canada, Colombia, Russia, Ukraine	Double blind
NCT00852202	Earley, 2020b [36]	Bipolar disorder, type I, with a current depressive episode	DSM-IV-TR	No acute psychotic symptoms at the time of enrolment	0.5 mg = 75 2.25 mg = 75	77	8 weeks	Depression, general clinical severity	MADRS, CGI	United States	Double blind
NCT00404573	Earley, 2017 [45]	Schizophrenia	DSM-IV-TR	Yes, current psychotic symptoms at time of enrolment	3 mg = 128 9 mg = 134	130	6 weeks	Psychotic symptoms, general clinical severity	PANSS, CGI	United States	Double blind
MP-214	Nakamura, 2016 [46]	Schizophrenia	DSM-IV-TR	Yes, patients enrolled with and without current psychotic symptoms	3 mg = 11 6 mg = 16 9 mg = 11	/	12 weeks	Psychotic symptoms, general clinical severity	PANSS, CGI	Japan	Open label

CGI Clinical Global Impression Scale, *DSM* diagnostic and statistical manual of mental disorders, *HAMA* Hamilton Anxiety Rating Scale, *MADRS* Montgomery–Asberg Depression Rating Scale, *PANSS* Positive and Negative Symptom Scale, *YMRS* Young Mania Rating Scale

details on each study, and Supplementary Fig. S1 for further information on the assessment of each clinical trial for risk of bias and Results S1 for further details on tests related to publication bias.

Cariprazine was significantly associated with better outcomes across the psychosis spectrum (Table S1, estimated effect in MD). However, a high within-study variance was found (88.40% of variance explained), suggesting that outcomes may explain most of the variance between effect sizes. For this reason, further results describe effect size estimates for each outcome. See Supplementary Materials Table S1 for further details.

3.1 Clinical Severity

Cariprazine was observed as effective in improving global clinical severity, as evaluated by CGI (MD reduction in comparison with placebo: low dosage – 0.249, 95% confidence interval – 0.370; – 0.128, medium dosage – 0.274, 95% CI – 0.384; – 0.163, high dosage – 0.445, 95% CI – 0.545; – 0.345; $I^2 = 26.2\%$, $\text{tau}^2 = 0.007$; number of pairwise comparisons = 24; Fig. 2a). SUCRA analysis confirmed that cariprazine was associated with better outcomes, in a dose-response fashion (see Supplementary Materials Table S2).

3.2 Psychotic Symptoms

Cariprazine was observed as effective in improving global psychotic symptoms, as evaluated by PANSS total scores (MD reduction in comparison to placebo: low dosage – 7.123, 95% CI – 8.270; – 5.975], medium dosage – 6.733, 95% CI – 7.844; – 5.622, high dosage – 6.888, – 7.965; – 5.811; $I^2 = 7.5\%$, $\text{tau}^2 = < 0.001$; number of pairwise comparisons = 14; Fig. 2 panel b). Cariprazine was also observed as effective in improving positive (low dosage – 2.218, 95% CI – 2.895; – 1.541, medium dosage – 1.906, 95% CI – 2.491; – 1.320, high dosage – 1.957, 95% CI – 2.555; – 1.358; $I^2 = 26.9\%$, $\text{tau}^2 = 0.018$; number of pairwise comparisons = 9; Fig. 2c) and negative symptoms (low dosage – 1.938, 95% CI – 2.748; – 1.129], medium dosage – 1.711, 95% CI – 2.297; – 1.125, high dosage – 1.699, 95% CI – 2.318; – 1.080; $I^2 = 41.0\%$, $\text{tau}^2 = 0.131$; number of pairwise comparisons = 9; Fig. 2d).

3.3 Depressive Symptoms

Cariprazine was observed as effective in improving depressive symptoms, as evaluated by MADRS scores (low dosage −2.396, 95% CI −3.432; −1.360, medium dosage −2.438, 95% CI −3.712; −1.165, high dosage −1.228, 95% CI −1.859; −0.596; $I^2 = 0\%$, $\text{tau}^2 = < 0.001$; number of pairwise comparisons = 12; Fig. 2e).

3.4 Manic Symptoms

Cariprazine was observed as effective in improving manic symptoms across the psychosis spectrum, as evaluated by YMRS scores (mean difference: −5.722, 95% CI −6.951; −4.494; $I^2 = 0\%$, $\text{tau}^2 < 0.001$). As less than one observation per dosage was retrieved for this outcome, it was not possible to estimate a ranking of efficacy by treatment dosage.

3.5 Anxiety Symptoms

Cariprazine was observed as effective in improving anxiety symptoms across the psychosis spectrum, as evaluated by HAMA scores (mean difference: −1.243, 95% CI −1.922; −0.564; $I^2 = 0\%$, $\text{tau}^2 < 0.001$). As less than one observation per dosage was retrieved for this outcome, it was not possible to estimate a ranking of efficacy by treatment dosage.

3.6 Sensitivity Analyses

First, studies conducted in an open-label fashion or not in a non-double-blind manner (i.e. MP-241, Nakamura et al. [46]) were excluded. Cariprazine was significantly associated with an improvement for all outcomes even excluding this single study (see Supplementary Materials—Results S2). Secondly, as some RCTs excluded patients with bipolar disorders exhibiting psychotic symptoms, only RCTs enrolling patients with psychotic symptoms were included in secondary control analyses. Cariprazine was significantly associated with an improvement for all outcomes also when including only studies enrolling patients with psychotic symptoms (see Supplementary Materials—Results S2). However, no study assessing HAM-A in patients with psychotic features was retrieved, and this secondary control analysis could not be conducted for this outcome.

4 Discussion

The current work proposed an updated systematic review of the existing literature on the efficacy of cariprazine across the psychosis spectrum, examining core symptoms (clinical severity, psychotic symptoms and manic symptoms) as well as mood (depressive) and anxiety symptoms. Current results suggest that cariprazine may offer clinicians a valid tool to target affective and anxiety symptoms along with overall psychotic symptoms [47, 48]. Second, a dose-response effect can also be observed, with different degrees of response on clinical severity by different dosages of cariprazine.

As previously mentioned, two meta-analyses assessed the efficacy of cariprazine across acute schizophrenia, namely Corponi and colleagues, 2017 [4]; and Zhao and colleagues,

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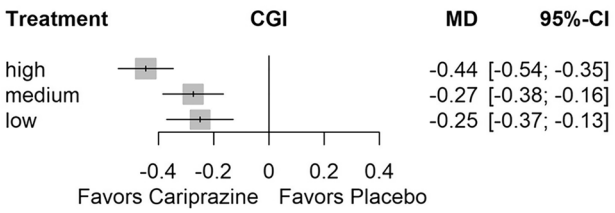

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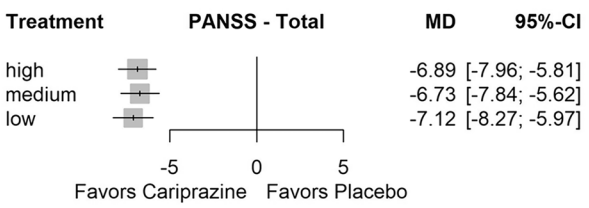

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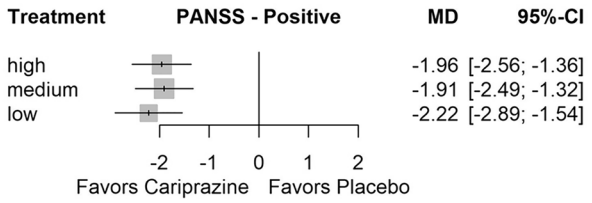

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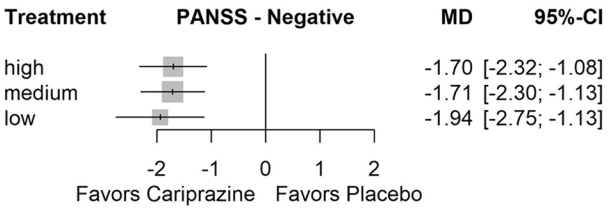

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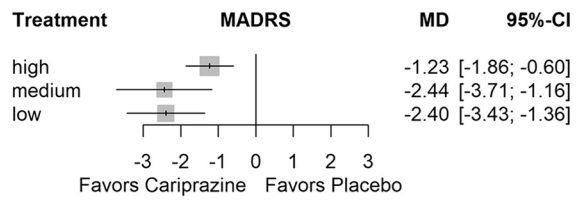

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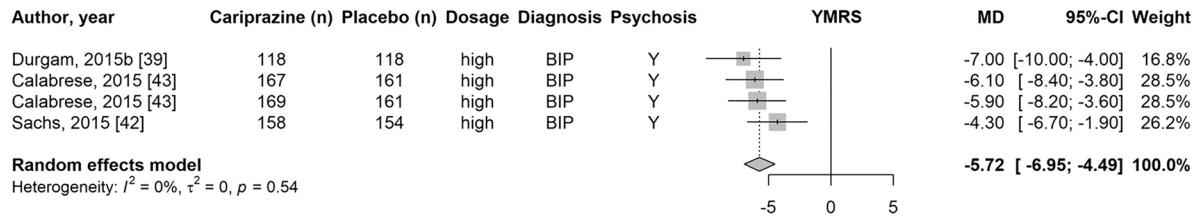

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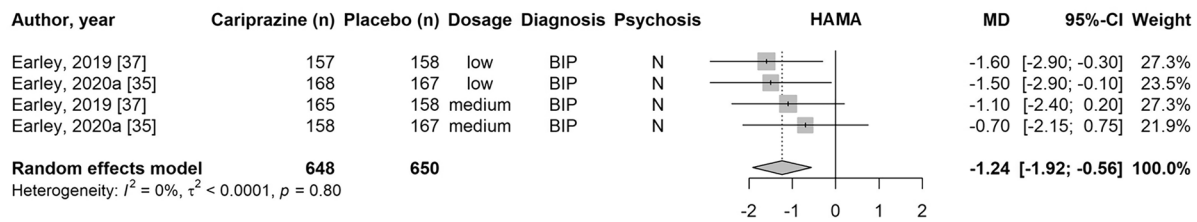

2018 [5]. The first assessed efficacy by dose adopting a network meta-analysis, similarly to the current work. Nonetheless, it was conducted before the results of NCT00404573 were available, and only assessed cariprazine dosages as 'high' (higher than 6 mg/day) versus 'low' (less than 6 mg/day). This division may not fully reflect the design of

◂**Fig. 2** Treatment effect [mean difference (MD)] of cariprazine across the psychosis spectrum. Above solid line: comparing cariprazine versus placebo, as well as different dosages of cariprazine against each other. Below solid line: comparing cariprazine versus placebo. **A** Clinical Global Impression scale. **B** Positive and Negative Symptom Scale, total score. **C** Positive and Negative Symptom Scale, positive symptoms subscale. **D** Positive and Negative Symptom Scale, negative symptoms subscale. **E** Montgomery–Asberg Depression Rating Scale. **F** Young Mania Rating Scale. **G** Hamilton Anxiety Rating Scale. *CGI* Clinical Global Impression Scale, *HAMA* Hamilton Anxiety Rating Scale, *MADRS* Montgomery–Asberg Depression Rating Scale, *PANSS* Positive and Negative Symptom Scale, *YMRS* Young Mania Rating Scale

included RCTs, which commonly employ dosages lower than 1.5 mg/day or 3 mg/day (see Table 1 for a summary of dosages used across RCTs). This low dose threshold may also explain why a dose/response gradient was not observed across any evaluated dimension by Corponi and colleagues [4].

The second meta-analysis, conducted by Zhao and colleagues, instead assessed the available evidence at the time (thus, also not retrieving NCT00404573) through standard meta-analytical methods. The use of standard meta-analytical methods did not allow for inclusion of a second RCT available at the time, which however did not have a control group treated with placebo (MP-214). An assessment of the influence of dosage on observed effects was not conducted. Moreover, cariprazine was evaluated only for its efficacy on psychotic symptoms (PANSS scores), and for the risk of premature discontinuation. Regarding psychotic symptoms, the results of Zhao and colleagues suggested that cariprazine interventions reduce psychotic symptoms in patients with schizophrenia, while also being safe and tolerable at the individual level.

Regarding the only other review that adopted a transdiagnostic approach to evaluate cariprazine efficacy [9], the current review observed a higher mean difference between placebo and cariprazine in both depression (MD: − 1.43 in Cooper et al., 2020; versus − 1.78 in current results), and manic symptoms (MD: − 5.64 in Cooper et al., 2020; versus − 5.72 in current results). The authors suggest that this divergence may be explained by the inclusion of three RCT studies in Cooper et al., 2020 which enrolled patients with major depression treated with cariprazine as antidepressant augmentation therapy rather than as an antipsychotic agent.

A transdiagnostic and dimensional approach to psychiatry and pharmacology is timely, as recent research suggests that schizophrenia, schizoaffective disorders and bipolar disorder may exist on a spectrum of continuity, rather than being distinct disorders [11, 12]. This transdiagnostic, dimensional approach to the spectrum of psychosis is supported not only by overlapping symptoms, as described by diagnostic criteria [49], but also by genetic risk factors, and neural mechanisms that have been found between these conditions [50, 51]. For instance, the genetic correlation between schizophrenia and bipolar disorder is the highest across most psychiatric disorders [52].

In summary, the current work found that cariprazine is efficacious in treating patients across the psychosis spectrum, along all of symptomatic domains evaluated (psychotic symptoms—positive and negative, affective symptoms—depressive or manic and anxiety).

4.1 Limitations

A number of limitations may hinder the generalizability of current results. First, the number of pairwise comparisons for each outcome ranged between 14 and 3. No comparison was retrieved for schizoaffective disorders. For this reason, less extensively studied outcomes, such as mania and anxiety, and less extensively studied diagnostic categories (schizoaffective disorder) may warrant further research on the topic.

Second, the quality of the reported data influences subsequent meta/analytic efforts. However, the overall risk of bias for included studies was low (see Fig. S1) and no significant publication bias was observed when excluding the single study employing an open-label design (see Fig. S2). Nonetheless, sample and intervention characteristics were not uniform across studies (e.g. phase study ranged from phase 2 to phase 3, with different durations of treatment). Although sensitivity analyses confirmed that controlling for these sources of heterogeneity did not change the direction of observed effects, future studies might explore how real-world applications might differ from RCT settings.

Finally, the safety and tolerability of cariprazine were previously assessed, and were not within scope of the current work. Nonetheless, especially when considering treatment ranking by dosage, the incidence of side effects may influence the choice of intervention at the individual level, considering cost/benefit ratios.

5 Conclusions

The current meta-analysis reinforces the evidence in support of the efficacy of cariprazine in schizophrenia or bipolar disorder, also when adopting a transdiagnostic perspective. Moreover, the current work highlighted how cariprazine may be effective in addressing psychotic, affective and anxiety symptoms across this clinical continuum. Previous evidence showed how cariprazine exhibits a similar profile of side effects in comparison to other atypical antipsychotics. For this reason, future research is warranted on the safety and tolerability of cariprazine, to carefully assess clinical risk/benefit ratios in these populations. Finally, future

socio-economic perspectives might inform the adoption of cariprazine in specific clinical guidelines across different countries.

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Declarations

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Availability of data and material The database of the studies, with the extracted data items, can be shared upon reasonable request to the corresponding author.

Code availability The code supporting the present work can be shared upon reasonable request to the corresponding author.

Authors contributions L.T.: Conceptualization, methodology, software, formal analysis, investigation, data curation, writing—original draft, writing—review and editing and visualization. S.B.: Conceptualization, methodology, investigation, data curation, writing—original draft preparation and writing—review and editing. C.D.: Conceptualization, methodology, investigation, data curation, writing—original draft preparation and writing—review and editing. E.C.: Conceptualization, methodology, investigation, writing—original draft preparation, writing—review and editing and supervision. E.R.: Conceptualization, methodology, investigation, writing—original draft preparation, writing—review and editing and supervision. S.L.: Conceptualization, investigation, writing—review and editing and supervision. V.R.: Conceptualization, investigation, writing—review and editing, supervision and project administration. S.C.: Conceptualization, methodology, data curation, investigation, writing—original draft preparation, writing—review and editing and supervision. G.C.: Conceptualization, methodology, investigation, writing—original draft preparation, writing—review and editing, supervision and project administration. All authors have read and approved the final submitted manuscript and agree to be accountable for the work.

References

1. Vraylar (cariprazine). Silver Spring; 2015 Sep. Report No.: 3821760. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/204370Orig1Orig2s000Approv.pdf. Accessed 22 Aug 2024.
2. European Medical Agency. Reagila: EPAR—Summary for the public. 2017. Report No.: EMA/339882/2017. https://www.ema.europa.eu/en/documents/overview/reagila-epar-summary-public_en.pdf. Accessed 22 Aug 2024.
3. Vraylar (cariprazine). Silver Spring; 2022 Dec. Report No.: 5095981. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/204370s009lbl.pdf. Accessed 22 Aug 2024.
4. Corponi F, Serretti A, Montgomery S, Fabbri C. Cariprazine specificity profile in the treatment of acute schizophrenia: a meta-analysis and meta-regression of randomized-controlled trials. Int Clin Psychopharmacol. 2017;32:309–18.
5. Zhao M-J, Qin B, Wang J-B, Zhang Y-P, Zhao J-T, Mao Y-G, et al. Efficacy and acceptability of Cariprazine in acute exacerbation of schizophrenia: meta-analysis of randomized placebo-controlled trials. J Clin Psychopharmacol. 2018;38:55–9.
6. Wang Y, Xu Y, Wu P, Zhou Y, Zhang H, Li Z, et al. Exploring the interplay between core and mood symptoms in schizophrenia: a network analysis. Schizophr Res. 2024;269:28–35.
7. Pavlova B, Perlis RH, Alda M, Uher R. Lifetime prevalence of anxiety disorders in people with bipolar disorder: a systematic review and meta-analysis. Lancet Psychiatry. 2015;2:710–7.
8. 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 Disord. 2020;22:360–71.
9. Cooper H, Mishriky R, Reyad AA. Efficacy and safety of cariprazine in acute management of psychiatric disorders: a meta-analysis of randomized controlled trials. Psychiatr Danub. 2020;32:36–45.
10. Stanghellini G, Broome M, Fernandez AV, Fusar-Poli P, Raballo A, Rosfort R, et al editors. The oxford handbook of phenomenological psychopathology. Oxford: Oxford University Press; 2019.
11. DeRosse P, Karlsgodt KH. Examining the psychosis continuum. Curr Behav Neurosci Rep. 2015;2:80–9.
12. Merola GP, Tarchi L, Saccaro LF, Delavari F, Piguet C, Van De Ville D, et al. Transdiagnostic markers across the psychosis continuum: a systematic review and meta-analysis of resting state fMRI studies. Front Psychiatry. 2024. https://doi.org/10.3389/fpsyt.2024.1378439.
13. Consoli A, Brunelle J, Bodeau N, Louët E, Deniau E, Perisse D, et al. Diagnostic transition towards schizophrenia in adolescents with severe bipolar disorder type I: an 8-year follow-up study. Schizophr Res. 2014;159:284–91.
14. Cardno AG, Owen MJ. Genetic relationships between schizophrenia, bipolar disorder, and schizoaffective disorder. Schizophr Bull. 2014;40:504–15.
15. Ihler HM, Lyngstad SH, Mørch-Johnsen LE, Lagerberg TV, Melle I, Romm KL. A transdiagnostic approach to negative symptoms: exploring factor structure and negative symptoms in bipolar disorders. Front Psychiatry. 2023. https://doi.org/10.3389/fpsyt.2023.1136097.

16. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372: n71.
17. Higgins JP, Li T, Deeks JJ. Choosing effect measures and computing estimates of effect. Cochrane Handb Syst Rev Interv. New York: Wiley; 2019. p. 143–76.
18. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366: l4898.
19. Fernández-Castilla B, Jamshidi L, Declercq L, Beretvas SN, Onghena P, Van den Noortgate W. The application of meta-analytic (multi-level) models with multiple random effects: a systematic review. Behav Res Methods. 2020;52:2031–52.
20. Gooty J, Banks GC, Loignon AC, Tonidandel S, Williams CE. Meta-analyses as a multi-level model. Organ Res Methods. 2021;24:389–411.
21. Van den Noortgate W, López-López JA, Marín-Martínez F, Sánchez-Meca J. Three-level meta-analysis of dependent effect sizes. Behav Res Methods. 2013;45:576–94.
22. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327:557–60.
23. Riley RD, Gates S, Neilson J, Alfirevic Z. Statistical methods can be improved within Cochrane pregnancy and childbirth reviews. J Clin Epidemiol. 2011;64:608–18.
24. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315:629–34.
25. Chaimani A, Caldwell DM, Li T, Higgins JP, Salanti G. Undertaking network meta-analyses. Cochrane Handb Syst Rev Interv. New York: Wiley; 2019. p. 285–320.
26. Rücker G, Schwarzer G. Resolve conflicting rankings of outcomes in network meta-analysis: partial ordering of treatments. Res Synth Methods. 2017;8:526–36.
27. Salanti G, Ades AE, Ioannidis JPA. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. J Clin Epidemiol. 2011;64:163–71.
28. R Core Team. R: A language and environment for statistical computing. Vienna, Austria; 2024. https://www.R-project.org.
29. RStudio Team. RStudio: Integrated Development for R. Boston, MA: RStudio, PBC; 2024. http://www.rstudio.com/.
30. Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. Evid Based Ment Health. 2019;22:153–60.
31. Balduzzi S, Rücker G, Nikolakopoulou A, Papakonstantinou T, Salanti G, Efthimiou O, et al. netmeta: an R package for network meta-analysis using frequentist methods. J Stat Softw. 2023. https://doi.org/10.18637/jss.v106.i02.
32. Viechtbauer W. Conducting meta-analyses in R with the metafor package. J Stat Softw. 2010. https://doi.org/10.18637/jss.v036.i03.
33. Haddaway NR, Page MJ, Pritchard CC, McGuinness LA. PRISMA2020: an R package and Shiny app for producing PRISMA 2020-compliant flow diagrams, with interactivity for optimised digital transparency and Open Synthesis. Campbell Syst Rev. 2022;18: e1230.
34. Wickham H, Averick M, Bryan J, Chang W, McGowan LD, François R, et al. Welcome to the tidyverse. J Open Sour Softw. 2019;4:1686.
35. Earley WR, Burgess MV, Khan B, Rekeda L, Suppes T, Tohen M, et al. Efficacy and safety of cariprazine in bipolar I depression: a double-blind, placebo-controlled phase 3 study. Bipolar Disord. 2020;22:372–84.
36. Earley WR, Burgess M, Rekeda L, Hankinson A, McIntyre RS, Suppes T, et al. A pooled post hoc analysis evaluating the safety and tolerability of cariprazine in bipolar depression. J Affect Disord. 2020;263:386–95.
37. Earley W, Burgess MV, Rekeda L, Dickinson R, Szatmári B, Németh G, et al. Cariprazine treatment of bipolar depression: a randomized double-blind placebo-controlled phase 3 study. Am J Psychiatry. 2019;176:439–48.
38. Durgam S, Cutler AJ, Lu K, Migliore R, Ruth A, Laszlovszky I, et al. Cariprazine in acute exacerbation of schizophrenia: a fixed-dose, phase 3, randomized, double-blind, placebo- and active-controlled trial. J Clin Psychiatry. 2015;76:e1574-1582.
39. Durgam S, Starace A, Li D, Migliore R, Ruth A, Németh G, et al. The efficacy and tolerability of cariprazine in acute mania associated with bipolar I disorder: a phase II trial. Bipolar Disord. 2015;17:63–75.
40. Kane JM, Zukin S, Wang Y, Lu K, Ruth A, Nagy K, et al. Efficacy and safety of cariprazine in acute exacerbation of schizophrenia: results from an international, phase III clinical trial. J Clin Psychopharmacol. 2015;35:367.
41. Durgam S, Starace A, Li D, Migliore R, Ruth A, Németh G, et al. An evaluation of the safety and efficacy of cariprazine in patients with acute exacerbation of schizophrenia: a phase II, randomized clinical trial. Schizophr Res. 2014;152:450–7.
42. Sachs GS, Greenberg WM, Starace A, Lu K, Ruth A, Laszlovszky I, et al. Cariprazine in the treatment of acute mania in bipolar I disorder: a double-blind, placebo-controlled, Phase III trial. J Affect Disord. 2015;174:296–302.
43. Calabrese JR, Keck PE, Starace A, Lu K, Ruth A, Laszlovszky I, et al. Efficacy and safety of low- and high-dose cariprazine in acute and mixed mania associated with bipolar I disorder: a double-blind, placebo-controlled study. J Clin Psychiatry. 2015;76:284–92.
44. Durgam S, Earley W, Lipschitz A, Guo H, Laszlovszky I, Németh G, et al. An 8-week randomized, double-blind, placebo-controlled evaluation of the safety and efficacy of cariprazine in patients with bipolar I depression. Am J Psychiatry. 2016;173:271–81.
45. Earley W, Durgam S, Lu K, Laszlovszky I, Debelle M, Kane JM. Safety and tolerability of cariprazine in patients with acute exacerbation of schizophrenia: a pooled analysis of four phase II/III randomized, double-blind, placebo-controlled studies. Int Clin Psychopharmacol. 2017;32:319–28.
46. Nakamura T, Kubota T, Iwakaji A, Imada M, Kapás M, Morio Y. Clinical pharmacology study of cariprazine (MP-214) in patients with schizophrenia (12-week treatment). Drug Des Dev Ther. 2016;10:327–38.
47. Stahl SM. Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications. 5° edizione. Cambridge: Cambridge University Press; 2021.
48. Huhn M, Nikolakopoulou A, Schneider-Thoma J, Krause M, Samara M, Peter N, et al. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. Lancet. 2019;394:939–51.
49. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders: Fifth Edition Text Revision DSM-5-TR™. American Psychiatric Association Publishing; 2022.
50. van Dellen E, Börner C, Schutte M, van Montfort S, Abramovic L, Boks MP, et al. Functional brain networks in the schizophrenia spectrum and bipolar disorder with psychosis. NPJ Schizophr. 2020;6:22.
51. Wingo TS, Liu Y, Gerasimov ES, Vattathil SM, Wynne ME, Liu J, et al. Shared mechanisms across the major psychiatric and neurodegenerative diseases. Nat Commun. 2022;13:4314.
52. Cross-Disorder Group of the Psychiatric Genomics Consortium. Genomic relationships, novel loci, and pleiotropic mechanisms across eight psychiatric disorders. Cell. 2019;179:1469–82 (**e11**).