A NOVEL TRANSDIAGNOSTIC APPROACH TO A DOPAMINE PARTIAL AGONIST ANTIPSYCHOTIC IN NEUROPSYCHIATRY

PhD thesis

Ágota Barabássy, MD
Semmelweis University Doctoral School
János Szentágothai Division

Supervisor: György Németh
Official reviewers: Lívia Balogh, Adrienn Máttyássy
Head of the Complex Examination Committee: Dániel Bereczki
Members of the Complex Examination Committee: Ildikó Vastagh, Péter Balicza

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Introduction

The transdiagnostic approach is a promising new approach in psychiatry. It draws its name from the Latin prefix ‘trans,’ which can signify both ‘across’ (as in ‘transatlantic’) and ‘beyond’ (as in ‘transcend’). In the context of mental health, a transdiagnostic approach aims to reach across disorders and surpass existing categorical diagnoses . There is still a lack of clarity and consistency in defining what “transdiagnostic” means, leading to varied interpretations and applications in research. Most commonly “transdiagnostic” is used to stress the aspect of “across physical and mental health diagnoses” or “overarching symptoms” .

Studying symptom profiles that span across different diagnoses is crucial for pinpointing factors that diminish mental health in people with psychiatric conditions. The newest addition to the transdiagnostic literature comes from 2024 and is a large-scale evaluation of AI based symptom profiling, employing conventional clustering and community detection methods . It discovered clusters that may act as endophenotypes, aiding in the search for genetic and other biomarkers. These clusters were depression, anxiety, psychosis, drug addiction, and self-harm. The work further proposed to refine and simplify existing questionnaires to account for these clusters . Other studies have pinpointed eight overarching symptom categories that include mood, self-perception (how individuals view and understand their own mental health symptoms and overall well-being), anxiety, agitation, empathy, non-social interest, hyperactivity and cognitive focus that have an impact on the well-being of individuals . In addition, sleep disturbances, impulsivity and negative symptoms are also considered transdiagnostic symptoms as they appear in various disorders .

Numerous specialized diagnostic assessment instruments have been crafted to quantify the intensity and nature of symptoms, aligning with the diagnostic criteria delineated in the ICD10 and DSM 5. Among these, the Positive and Negative Syndrome Scale (PANSS), the Montgomery-Åsberg Depression Rating Scale (MADRS), the Young Mania Rating Scale (YMRS), the Hamilton Anxiety Rating Scale (HAMA) and the Hamilton Depression Rating Scale (HAMD) are some of the most well-established tools. These tools are widely used in research and clinical practice alike.

To date, there is not an equally well-established tool to measure transdiagnostic processes, although there are frameworks that span across various mental disorders and adapt a transdiagnostic approach. The most established frameworks are the Research Domain Criteria (RDoC), the Hierarchical Taxonomy of Psychopathology (HiTOP), and the Clinical Staging Model, and network models . While these frameworks provide valuable insights, they are too abstract and obscure individual symptoms so much that they no longer reflect patients' actual problems. Hence, there's still a pressing need for uniform transdiagnostic tools that can consistently monitor the evolution of patients' symptoms over time in everyday clinical environments .

Recently a new tool has emerged in an aim to assess transdiagnostic symptoms: the transdiagnostic global impression psychopathy scale (TGI-P) . The TGI-P is a tool designed to assess the severity of 10 transdiagnostic symptoms across a wide range of psychiatric disorders. It covers positive symptoms, negative symptoms, manic symptoms, depressive symptoms, addiction symptoms, cognitive symptoms, anxiety symptoms, sleep symptoms, hostility symptoms and self-harm. Positive symptoms in the context of the scale are defined as

expressing delusions, hallucinations, disorganized thinking, disorganized speech, abnormal motor behavior. The presence of anger, tension, uncooperativeness, impulsivity, aggression, or irritability is rated as hostility. Expansive mood, grandiosity, racing thoughts, increased energy, excessive involvement in pleasurable activities are the criteria for manic symptoms; whereas low mood, anhedonia, persistent feeling of sadness, hopelessness and helplessness are the criteria for depressive symptoms. The latter are often hard to distinguish from negative symptoms which include blunted affect, alogia, asociality, avolition, anhedonia. If anhedonia is present without depressed mood, it is be rated as negative symptom . This is because negative symptoms are typically persistent and not influenced by mood; whereas depressive are often accompanied by feelings of sadness, guilt, and worthlessness and fluctuate over the course of the disorder . Impaired substance use control, craving, physical dependence are the symptoms of addiction. Cognitive symptoms are characterized by problems with concentration, attention, memory; sleep symptoms by hypersomnia or insomnia and self-harm by non-suicidal self-injury, suicidal ideation, intent, or attempt. Finally, anxiety is feeling nervous, restless, tense, or the fear of social interactions . Similar to the original CGI-S scale, the TGI-P uses a 7-point Likert scale ranging from 1 (normal) to 7 (extreme) to rate the severity of symptoms .

In everyday clinical practice, treatment decisions often culminate in the prescription of medications. The selection of medication should ideally mirror the unique symptomatology of the patient, independent of their specific diagnosis. So far, no such "transdiagnostic drug" has emerged, although some second-generation antipsychotics are used for multiple psychiatric and some neurological conditions. One of the

treatments that has approval across multiple disorders is cariprazine.

Cariprazine was originally discovered by the Hungarian company Gedeon Richter and developed for regulatory approval purposes by Richter and its global partners. Globally, cariprazine is approved for the treatment of schizophrenia and bipolar I disorder, including both manic and depressive episodes and as an adjunctive treatment for major depressive disorder. In the European Union its sole indication is schizophrenia.

Cariprazine is a D3 preferring, D3/D2 partial agonist antipsychotic. The therapeutic effect of cariprazine is mediated through a combination of partial agonist activity at dopamine D3, D2 and serotonin 5-HT1A receptors and antagonist activity at serotonin 5-HT2B, 5-HT2A and histamine H1 receptors. Among partial agonists and in fact all known antipsychotics, cariprazine is unique in having the highest affinity to the D3 receptors. The lower affinities of other antipsychotics for the D3 receptor relative to the very high affinity of dopamine itself for the D3 receptor means that in the living brain, the D3 receptor is not blocked by any antipsychotic other than cariprazine. Hence, cariprazine may be the one agent to have clinically meaningful D3 receptor binding capability in vivo.

Objectives

As outlined above, the most common definitions of "transdiagnostic" currently are "across disorders" and "across symptoms." Therefore, a "transdiagnostic treatment" must address both multiple disorders and transdiagnostic symptom clusters. Hence, the aim of this thesis was twofold:

1. To review cariprazine's efficacy in different psychiatric disorders.
2. To examine cariprazine's efficacy on transdiagnostic symptoms.

For defining transdiagnostic symptoms, I utilized the most recent definition published in the TGI-P, which I helped co-develop. My roles included concept development and item development based on clinical experience. According to this scale, transdiagnostic symptoms include positive, negative, cognitive, manic, depressive, addiction, anxiety, sleep, hostility, and self-harm symptoms, independent of underlying disorders.

Methods

Cariprazine Efficacy Across Disorders: To review the clinical efficacy of cariprazine across disorders, I conducted a systematic literature review focusing on randomized clinical trials (RCTs). Searches were performed on EMBASE using the keywords "cariprazine," "major topic," "randomized controlled trial," and "non-conference material," screening for cariprazine in the title or abstract. Additionally, the clinicaltrials.gov register was searched with the terms "cariprazine," "Phase: 2, 3, 4," "Interventional," and "Studies with results." Gedeon Richter's own database of clinical studies with cariprazine was also considered. The searches were limited to studies published until December 2024. Full-text articles were reviewed for eligibility based on predefined inclusion and exclusion criteria.

Inclusion criteria: Only RCTs specifically reporting on cariprazine's efficacy in adult population disorders were considered. Post-hoc analyses of these RCTs reporting new efficacy data were included if they addressed the research questions. Only English-language works were considered.

Exclusion criteria: Records focusing on other aspects of cariprazine treatment (e.g., safety, dosing, switching, pharmacokinetics, drug-drug interaction, formulations, health economics) were excluded. Records reporting the same efficacy data in different subpopulations (e.g., by race, age, sex, adolescents, elderly) were also excluded. Studies not providing sufficient data or not addressing the research questions (efficacy of cariprazine in treating different disorders and transdiagnostic symptom clusters) were excluded as well.

Cariprazine Efficacy on Transdiagnostic Symptoms: To review the clinical efficacy of cariprazine across symptoms, I used the studies of the systematic review as a starting point. For data that could not be retrieved from already published sources new post-hoc analyses were performed. For these, data from 13 phase II/III randomized, double-blind, placebo-controlled trials were included in the analyses that formed the basis of Food and Drug Administration's (FDA) and European Medicinal Agency's (EMA) approval of cariprazine in the indications of schizophrenia, bipolar mania, bipolar depression and major depression add-on treatment. Additionally, a phase III, randomized, double-blind, active-controlled trial performed in persistent primary negative symptoms of schizophrenia for the European approval was included. From the included studies, 4 were performed in the indications of schizophrenia incl. a study in a subpopulation with persistent, predominant, primary negative symptoms of schizophrenia, 3 in bipolar mania, 3 in bipolar depression, and 2 in major depression add-on.

These were multicenter, multinational, randomized, double-blind, placebo- or active controlled, parallel-group studies. Studies in the same indications with similar designs were pooled. Singular studies with unique designs were evaluated

separately. Pooled studies included a dataset of three 6-weeks schizophrenia studies; three 3-week mania studies, and three 6-8 week bipolar depression studies (with results at the end of 6 weeks).

Cariprazine was administered in the dose range of 0.1-12 mg either in a fixed or flexible dose design. Most commonly doses between 1.5 mg (in schizophrenia, bipolar depression and major depression) and 6 mg (schizophrenia and mania) were used. Doses above 6 mg (9 and 12 mg) showed additional efficacy, but also increased side effects; doses below 1.5 mg showed no efficacy; so the final approved dose range excludes these doses.

The diagnosis was established through the different editions of the DSM and was confirmed using validated assessment tools for the respective disorders. Inclusion criteria included cut-off values on these scales to recruit patients with a certain severity of their illness. Main exclusion criteria included other mental health disorders, acute risk for suicide or any other relevant disorders that could have interfered with the results of the study. Details about inclusion and exclusion criteria were outlined in the respective publications (Table 3). During the studies, patients were allowed to use their regular non-centrally active medications and centrally active rescue medications that included benzodiazepines, anti-extrapyramidal symptom medications and sleeping medications.

Patient numbers ranged between 118 per arm in a mania study and 273 in the major depressive disorder study . In most studies, patients were treated either with cariprazine or with placebo. In two schizophrenia studies an active comparator (risperidone 4 mg and aripiprazole 10 mg) was also used for assay sensitivity. In the major depressive add-on studies, antidepressants were

used as base treatment before cariprazine or placebo add-on . In schizophrenia, in the specific primary negative symptom study, cariprazine was compared to risperidone – this was an active controlled, superiority study that did not have a placebo arm . Treatment periods ranged from 3 weeks in the mania studies to up to 92 weeks in the schizophrenia maintenance study.

The primary and secondary endpoints were predefined in the respective studies and were meant to validate cariprazine' s efficacy in the respective disorders. Primary endpoints were assessed using the Montgomery-Åsberg Depression Rating Scale (MADRS), the Young Mania Rating Scale (YMRS), and the Positive and Negative Syndrome Scale (PANSS).

The Positive and Negative Syndrome Scale (PANSS) is a neuropsychometric tool used to measure the severity of symptoms in individuals with schizophrenia . Developed in 1987, it evaluates positive symptoms (like hallucinations and delusions), negative symptoms (such as emotional withdrawal and blunted affect) and general symptoms of schizophrenia. The scale consists of 30 items, each rated on a scale from 1 to 7. The PANSS factors scores by Marder were developed to provide a more nuanced understanding of the symptom dimensions assessed by the scale . The aim was to refine the original PANSS structure into five distinct factors: the positive factor score (PANSS-FSPS), the negative factor score (PANSS-FSNS), Disorganized Thinking, Hostility/Excitement factor, and Depression/Anxiety factor. This factor structure is widely accepted to better assess and target specific symptom domains . Therefore, wherever available, PANSS factor scores were used to describe the above symptoms domains instead of the PANSS total scores.

Additional psychometric tests used in the studies (such as the HAM-A: Hamilton Anxiety Rating Scale, C-SSRS: Columbia-Suicide Severity Rating Scales, FAST: Functioning Assessment Short Test or the Cognitive Drug Research System: Attention Battery) along with the primary endpoints serve as indicators of the efficacy of cariprazine on transdiagnostic symptoms.

The HAM-A is one of the first rating scales developed to measure the severity of anxiety symptoms . Created by Max Hamilton in 1959, the HAM-A consists of 14 items that assess both psychic anxiety (mental agitation and psychological distress) and somatic anxiety (physical complaints related to anxiety). Each item is rated on a scale from 0 (not present) to 4 (severe), with total scores ranging from 0 to 56.

The C-SSRS is a tool used to assess the severity and immediacy of suicide risk. Developed by researchers at Columbia University, the University of Pennsylvania, and the University of Pittsburgh, the C-SSRS evaluates both suicidal ideation and behavior through a series of structured questions . These questions cover aspects such as the presence and intensity of suicidal thoughts, the planning and preparation for suicide attempts, and the history of suicidal behavior.

The FAST is a widely used tool in psychiatry, particularly for assessing functional impairment in patients with bipolar disorder. This 24-item scale evaluates six areas of functioning: autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships, and leisure time.

The Cognitive Drug Research System is a computerized battery of cognitive tests designed to assess various aspects of cognitive function, including attention. Developed in the late 1970s, the

CDR System is widely used in clinical trials to measure the effects of drugs on cognitive performance.

Either total scores, factors scores or single item scores were used to identify efficacy on transdiagnostic symptoms in the manner outlined in Table 2.

Table 2: Predefined assessment of positive, negative, cognitive, manic, depressive, addiction, anxiety, sleep, hostility and self-harm symptoms based on the scales used in the clinical studies

	PANSS	MADRS	YMRS	HAM-A	C-SSRS
Positive	PANSS FSPS	-	Item 8: Content	-	-
Negative	PANSS-FSNS	-	-	-	-
Cognitive	PANSS-disorganized factor score Cognitive Drug Research System Attention Battery	Item 6: concentration difficulties FAST cognitive item	Item 7: Language-Thought Disorder	-	-
Depressive	Guilt feelings (G3) Depression (G6)	Total score	-	-	-
Manic	-	-	Total score	-	-
Addiction	-	-	-	-	-
Anxiety	Anxiety (G2) Tension (G4)	Item 3: inner tension	-	Total score	-
Sleep	-	Item 4: reduced sleep	Item 4: sleep	-	-
Hostility	PANSS hostility score	-	Item 5: Irritability item 9: Disruptive-Aggressive Behavior	-	-

Self-harm	-	Item 10: suicidal thoughts	-	-	Total score

Studies in the same indications with similar designs were pooled.

Pooled studies: For schizophrenia, data was pooled from the 3 acute, randomized, placebo-controlled 6-week trials. Post-hoc outcomes of interest were mean change from baseline to the end of the study on the PANSS factor scores and individual items of the PANSS. Analyses were based on the pooled intent-to-treat (ITT) population, which consisted of all patients who received study medication and had ≥1 postbaseline PANSS assessment. All cariprazine doses (1.5-9 mg/d) were pooled for these post-hoc analyses. To investigate the effects of cariprazine by dose, additionally efficacy on the PANSS factors was also evaluated using data from the ITT population of the 2 fixed-dose studies; data were pooled into placebo and cariprazine 1.5-, 3.0-, 4.5-, and 6.0-mg/d dose groups. Data were analyzed using a mixed-effects model for repeated measures (MMRM) approach with treatment, visit, and study as fixed factors, baseline as covariate, and treatment-by-visit and baseline-by-visit as interactions; an unstructured covariance matrix was used to model the covariance of within-patient scores.

For bipolar mania, data was pooled from the 3 acute, randomized, placebo-controlled 3-week trials. Outcomes of interest were mean change from baseline to the end of the study on the overall and individual items of the YMRS. Analyses were based on the pooled intent-to-treat (ITT) population, which consisted of all patients who received study medication and had ≥1 postbaseline YMRS assessment. All cariprazine doses (3–12

mg/d) were pooled for these post-hoc analyses. Data was analyzed using a mixed-effects model for repeated measures (MMRM), with treatment group, study, study center within study, visit, and treatment-group-by-visit interaction as fixed effects and baseline YMRS score and baseline-by-visit interaction as covariates; an unstructured covariance matrix was used to model the covariance of within-patient scores.

For bipolar depression, data was pooled from the 3 acute, randomized, placebo-controlled 6–8-week trials with cut-of at 6 weeks. Outcomes of interest were mean change from baseline to the end of the study on the overall and individual items of the MADRS. Analyses were based on the pooled intent-to-treat (ITT) population, which consisted of all patients who received study medication and had ≥1 postbaseline MADRS assessment. All cariprazine doses (1.5-3 mg/d) were pooled for these post-hoc analyses but were also analyzed in individual dose groups (1.5 mg/d or 3 mg/d). Data was analyzed using a mixed-effects model for repeated measures (MMRM) with study, treatment group, visit, and treatment group-by-visit as factors and baseline MADRS scores and baseline-by-visit interaction as covariates. All tests were 2-sided at the 5% significance level; P values were not adjusted for multiple comparisons.

An additional 2 schizophrenia and 2 MDD add-on studies were not pooled. Outcomes of interest were mean change from baseline to the end of the studies on their primary endpoint (time to relapse, PANSS factor score for negative symptoms respectively for schizophrenia and MADRS total score and individual item scores for MDD studies). Analyses were based on the pooled intent-to-treat (ITT) population, which consisted of all patients who received study medication and had ≥1 postbaseline assessment. Data was analyzed using a mixed-

effects model for repeated measures (MMRM) with study, treatment group, visit, and treatment group-by-visit as factors and baseline scores and baseline-by-visit interaction as covariates.

Results

Cariprazine Efficacy Across Disorders: The search identified 130 articles that were screened for eligibility after removing duplicates. Among the articles retrieved, 30 met the eligibility criteria. The PRISMA flowchart is shown in Figure 1.

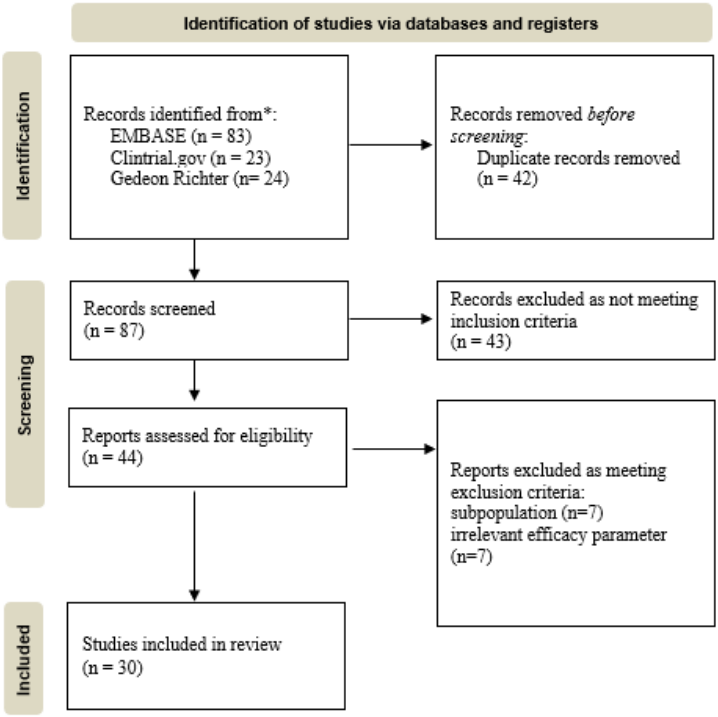

Figure 1. PRISMA flowchart of the systematic review

The 30 studies included into the review consisted of the 13 approval studies of Table 1 and an additional 17 studies. Based on these studies, cariprazine proved to be an effective treatment in schizophrenia (incl. persistent primary negative symptoms), bipolar I disorder with manic and depressive episodes, and in major depressive disorder as add-on treatment.

Cariprazine Efficacy on Transdiagnostic Symptoms: Cariprazine has shown therapeutic benefits on positive, negative, cognitive, manic, depressive, anxiety and hostility symptoms throughout disorders. Evidence for its anti-craving and anti-abuse effects come from real world evidence and underline that cariprazine might be a good therapeutic option in addiction. Its effects on sleep are two-fold: it effectively addressed sleep disorders related to mania and depression, while being rather activating in schizophrenia. Finally, the effects on suicidality can only be assessed in a non-suicidal population where no increased suicidality was reported under cariprazine. With this, cariprazine has proven efficacy as a transdiagnostic drug across disorders and various symptoms. Effects of cariprazine as a transdiagnostic drug may be attributed to its unique receptor profile.

DISORDERS / SYMPTOMS	**Bipolar depression**	**Bipolar mania**	**Major depression**	**Schizophrenia**
Positive	○	●	○	●
Negative	○	-	○	●
Cognitive	●	●	●	●
Depressive	●	○	●	○

Manic	○	●	-	○
Addiction	○	○	○	○
Anxiety	○	○	○	○
Sleep	●	●	●	○
Hostility	○	●	○	●
Self-harm	○	○	○	○

● – *core symptom;* ○ – *associated symptom;* - *unlikely to occur*
Efficacy based on clinical trials
Effectiveness based on real-world evidence

Conclusion

This thesis has provided a comprehensive exploration of cariprazine as a transdiagnostic drug, offering valuable insights into its effectiveness across multiple psychiatric disorders and a broad range of symptoms. As such, this is the first time the transdiagnostic approach has been examined in a real clinical setting, evaluating a drug as transdiagnostic treatment. Cariprazine monotherapy has proven to be an effective treatment in patients suffering from schizophrenia, bipolar disorder (both mood periods) and MDD (combined with antidepressants). Cariprazine has also shown therapeutic benefits on positive, negative, cognitive, manic, depressive, anxiety and hostility symptoms throughout disorders. Evidence for its anti-craving and anti-abuse effects come from real world evidence and underline that cariprazine might be a good therapeutic option in addiction. Its effects on sleep are two-fold: it effectively addressed sleep disorders related to mania and depression, while being rather activating in schizophrenia. Finally, the effects on suicidality can only be assessed in a non-suicidal population where no increased suicidality was reported under cariprazine.

Effects of cariprazine as a transdiagnostic drug may be attributed to its unique receptor profile.

The novelty of this work lies in its integrated approach to examining cariprazine as a transdiagnostic drug. For the first time, a drug has been assessed across multiple disorders and symptoms through a systematic literature review, post-hoc analyses, and enrichment with real-world evidence. This work consolidates and integrates the findings that formed the basis for my academic publications, serving as the ultimate result of my research on cariprazine. By advancing our understanding of this drug's broad applicability, this research contributes to a more nuanced understanding of psychiatric treatment, one that considers the full spectrum of patient symptoms rather than adhering strictly to categorical diagnoses.

In conclusion, this research has provided critical insights into the potential of cariprazine as a transdiagnostic treatment, offering a new perspective on how psychiatric disorders and their symptoms can be addressed more holistically. By considering the full spectrum of symptoms across various psychiatric conditions, this thesis challenges the traditional, categorical approach to psychiatric treatment and opens the door to more personalized, patient-centered care. The findings suggest that treating psychiatric disorders based on the individual's symptom profile—rather than a rigid diagnostic category—may be a more effective and nuanced approach to care, particularly for patients with complex, overlapping conditions.

The broader implications of this work extend beyond cariprazine itself. It serves as a model for how future drug development and clinical treatment strategies can benefit from a transdiagnostic perspective. By moving away from one-size-fits-all treatments

and acknowledging the fluid nature of psychiatric symptoms, this research lays the groundwork for further exploration into personalized medicine. Such approaches have the potential to improve treatment outcomes and enhance the quality of life for patients.

Furthermore, this thesis underscores the importance of integrating clinical data with research from the real world to bridge the gap between controlled trials and everyday practice. The inclusion of real-world evidence strengthens the case for cariprazine as a viable treatment option in various clinical settings, including those addressing addiction.

Ultimately, this research not only advances our understanding of cariprazine but also contributes to the growing body of knowledge that aims to reshape psychiatric treatment. As the field moves toward more integrative and personalized therapeutic approaches, this thesis highlights the importance of thinking beyond traditional diagnostic boundaries and embracing a more fluid and dynamic understanding of mental health treatment.

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