SEMMELWEIS EGYETEM

DOKTORI ISKOLA

Ph.D. értekezések

3184.

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

PhD thesis

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Budapest

2025

Table of contents

Abbreviations

(ADHD)	Attention Deficit Hyperactivity Disorder
(CDR)	Cognitive Drug Research System
(CGI)	Clinical Global Impression
(CGI-A)	Clinical Global Impression Scale - Aggression
(CGI-BP)	Clinical Global Impression-Bipolar
(CGI-I)	Clinical Global Impression-Improvement
(CGI-SCH)	Clinical Global Impression-Schizophrenia
(CGI-S)	Clinical Global Impression-Severity
(C-SSRS)	Columbia-Suicide Severity Rating Scales,
(EMA)	European Medicinal Agency
(ES)	Effect Sizes
(EPS)	Extrapyramidal Symptoms
(FAST)	Functioning Assessment Short Test
(FDA)	Food and Drug Administration
(GAD)	Generalized Anxiety Disorder
(GABA)	Gamma-Aminobutyric Acid
(HAMA)	Hamilton Anxiety Rating Scale
(HAMD)	Hamilton Depression Rating Scale
(HiTOP)	Hierarchical Taxonomy of Psychopathology
(ITT)	Intention-to-treat
(ICD)	International Classification of Diseases
(LSMD)	Least Square Mean Difference
(MDD)	Major Depressive Disorder

(MMRM)	Mixed-effects Model for Repeated Measures
(MADRS)	Montgomery-Åsberg Depression Rating Scale
(PANSS)	Positive and Negative Syndrome Scale
(PANSS-FSPS)	PANSS Positive Factor Score
(PANSS-FSNS)	PANSS Negative Factor Score
(PSP)	Personal and Social Performance scale
(PTSD)	Post-traumatic Stress Disorder
(OCD)	Obsessive-compulsive Disorder
(RTC)	Randomized Clinical Trials
(RDoC)	Research Domain Criteria
(SSRIs)	Selective Serotonin Reuptake Inhibitors
(5-HT)	Serotonin 5-hydroxytryptamine
(SDS)	Sheehan Disability Scale
(DSM)	Statistical Manual of Mental Disorders
(TGI-P)	Transdiagnostic Global Impression - Psychopathology Scale
(YMRS)	Young Mania Rating Scale

1. Introduction

1.1 Transdiagnostic Approach in Psychiatry

Throughout history, distress and suffering have been integral to the human experience. However, our reflections on and descriptions of extreme mental duress have evolved significantly. For over a century, particularly in Western societies, mental health struggles have been conceptualized through formal taxonomic systems. These systems organize symptoms into distinct categories and compile comprehensive lists of psychiatric diagnoses. The leading taxonomies today—the Diagnostic and Statistical Manual of Mental Disorders (DSM, 5th edition) and the International Classification of Diseases (ICD, 11th edition)—have a global impact and profoundly shape our understanding, assessment, and management of mental health (1,2).

The origins of psychiatric diagnosis trace back to Europe in the late 17th century. Influenced by classification systems used in natural sciences for animals and plants, and later by Kraepelin's Compendium der Psychiatrie (1883) the DSM and ICD classifications emerged (2). The first edition of the DSM (DSM-I) was published in 1952. In 1980, the DSM-III introduced a comprehensive multiaxial diagnostic system with carefully defined criteria for a wide range of disorders. It was considered a 'paradigm shift' in diagnostic psychiatry, rescuing the profession from unreliability and irrelevance. The current version, the DSM-5, was published in 2013 (1). Both, the DSM and the ICD have evolved into manuals that profoundly shape our understanding of mental health. Today, these systems form the foundation for textbooks in psychiatry and clinical psychology. They guide mental health training across various professions and shape how we assess, manage, and treat mental health issues worldwide. They influence health insurance practices, pharmaceutical industry approaches, and are backed by government and legal policies, dominating social and public discussions about mental illness. However, these diagnostic systems have their limitations and have faced criticism from the start. Some of these limitations include that both classifications can oversimplify the complexity of mental health by categorizing conditions into discrete labels, which may not capture the nuances of individual experiences. People with the same diagnosis can exhibit very different symptoms, making it difficult to generalize the disorder. Additionally, many symptoms occur across multiple diagnoses, leading to overlapping conditions that can complicate treatment. Furthermore, these systems are largely based

on Western perspectives, which may not be fully applicable to other cultures. Additionally, assigning a specific diagnosis can lead to stigma and discrimination. As a result, newer approaches aim to move away from these traditional diagnostic systems and adopt a more holistic view of mental health (1).

The transdiagnostic approach tries to adopt a more holistic view of mental health. 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 (2). The concept originated within cognitive behavioral theories and treatments, initially focusing on eating disorders, and later extended to other areas of anxiety and depressive disorders. The first study on the subject was published by Norton et al. in 2004 (3). Subsequently, research in this area has continued to grow (2). However, to date, the development and validation of an alternative classification system, which has genuine clinical value has been negligible (4). Existing studies rarely account for general psychopathology and shared neuropsychological pathways (4). 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" (2).

1.2 Underlying Mechanisms

Overall, the underlying rationale for transdiagnostic thinking rests on the key points of shared genetical backgrounds and neurobiological pathways.

Genetic mutations and variations play a crucial role in the development and manifestation of psychiatric and neurological disorders. Research has highlighted that many psychiatric disorders share common genetic architecture, which suggests that these disorders may have overlapping biological pathways, which could explain the co-occurrence of multiple psychiatric conditions in individuals. A systematic review assessing the genetic and phenotypic similarity across major psychiatric disorders, including schizophrenia, bipolar disorder, major depressive disorder, autism spectrum disorder, and attention deficit hyperactivity disorder found that nearly 75% of significant genetic loci are shared by at least two disorders (5). Another article found that also alcoholism shared common genetic

components with the previous major psychiatric disorders (6). Further, a large study of genetic data from 494,162 healthy control subjects and 232,964 people diagnosed with at least one psychiatric disorder identified 109 gene variants that affect the risk for more than one psychiatric disorder (7). Genetic studies have further revealed that psychiatric disorders often share biological pathways related to brain development, neurotransmitter systems, and synaptic functioning and found that variations in genes involved in dopamine and serotonin signaling are relevant in several disorders (8). However, widespread genetic overlap is not only observed across psychiatric disorders but also between neurological and psychiatric disorders (9–11). For instance, a comprehensive analysis involving nearly one million cases across ten neurological diseases and ten psychiatric disorders identified common genetic risk factors and biological pathways for most (10).

Genetic mutations and variations can affect neurobiological pathways, e.g. how neurotransmitters are synthesized, released, and cleared from synaptic spaces (12,13). There are several neurotransmitters in the brain that are crucial for regulating psychiatric and motor symptoms across disorders (14,15), which are provided in Table 1.

Table 1: Neurotransmitters in the brain that regulate psychiatric and motor symptoms

Neurotransmitter	Action	Target for
Dopamine	Involved in reward, motivation, and motor control.	Dopamine receptors (D1, D2, D3, D4, D5): Targeted by antipsychotics, stimulants, and some antidepressants
Serotonin	Regulates mood, appetite, and sleep	Serotonin receptors (5-HT1A, 5-HT2A, 5-HT3, etc.): Targeted by antidepressants, antipsychotics, and anxiolytics.
Glutamate	The main excitatory neurotransmitter, crucial for synaptic plasticity and learning	Glutamate receptors (NMDA, AMPA, kainate): Targeted by certain anesthetics and neuroprotective agents
Gamma-Aminobutyric Acid (GABA)	The main inhibitory neurotransmitter, important for reducing neuronal excitability	GABA receptors (GABA_A, GABA_B): Targeted by anxiolytics, sedatives, and anticonvulsants
Acetylcholine	Involved in muscle activation, attention, and memory.	Acetylcholine receptors (nicotinic and muscarinic): Targeted by drugs for Alzheimer's disease and myasthenia gravis
Norepinephrine (Noradrenaline)	Active in arousal, alertness, and the stress response	Norepinephrine receptors (α1, α2, β1, β2): Targeted by antidepressants and some antihypertensives

Table 1: Neurotransmitters in the brain that regulate psychiatric and motor symptoms		
Neurotransmitter	Action	Target for
Epinephrine (Adrenaline)	Involved in the fight-or-flight response	Alpha and Beta-Receptors (α1, α2, β1, β2, β3). Targeted by anxiolytics and some antihypertensives
Histamine	Regulates sleep-wake cycles and immune responses	Histamine receptors (H1, H2, H3): Targeted by antihistamines and some antipsychotics
Endorphins	Act as natural painkillers and are involved in the feeling of pleasure.	Opioid receptors (μ, κ, δ): Targeted by analgesics and some antidiarrheals
Oxytocin	Plays a role in social bonding, sexual reproduction, and childbirth.	Oxytocin receptor (OXTR) Targeted for inducing labor and promoting lactation

Dopamine

Among these neurotransmitters, the two most investigated are dopamine and serotonin. Dopamine is a crucial neurotransmitter, involved in many brain functions, including reward, motivation, memory, attention, and motor control. Dysregulation of dopamine is implicated in a variety of psychiatric and neurological disorders as listed below. Within the brain, dopamine is primarily synthesized in the ventral tegmental area and the substantia nigra, both located in the midbrain. Dopamine for the tuberoinfundibular pathway is synthesized in the arcuate nucleus of the hypothalamus. From here, dopamine reaches wide areas of the brain through four major pathways (16).

- Mesolimbic Pathway: This pathway is primarily involved in the reward system and motivation. Dysregulation in the mesolimbic pathway is associated with addiction, schizophrenia, and depression. Overactivity in this pathway can lead to the positive symptoms of schizophrenia, such as hallucinations and delusions.
- Mesocortical Pathway: This pathway is involved in cognition, executive function, and emotional regulation. Dysfunction in the mesocortical pathway is linked to the negative and cognitive symptoms of schizophrenia.
- Nigrostriatal Pathway: This pathway plays a critical role in the coordination of movement. Degeneration of neurons in the nigrostriatal pathway is a hallmark of Parkinson's disease, leading to motor symptoms such as tremor, rigidity, and bradykinesia. This pathway is also implicated in Huntington's disease and dystonia.

- Tuberoinfundibular Pathway: This pathway regulates the secretion of prolactin from the pituitary gland. Dysregulation can lead to hyperprolactinemia, which can cause symptoms such as galactorrhea, amenorrhea, and sexual dysfunction.

Serotonin

Next to dopamine, serotonin (5-hydroxytryptamine, 5-HT) is also a crucial neurotransmitter that significantly influences various physiological and psychological processes. It is primarily found in the brain, intestines, and platelets (17). Serotonin pathways primarily originate from the raphe nuclei in the brainstem and project to various parts of the brain, including the cortex, hippocampus, and limbic system .(18) They are more diffuse than dopamine pathways, affecting a wide range of brain regions. Serotonin plays an important role in mood regulation, emotional well-being, anxiety, cognitive functions, sleep and appetite, which makes it a key player in the pathophysiology of several psychiatric and neurological disorders (18):

- Depression: Abnormalities in serotonin levels or its neural pathways are strongly associated with depression. Reduced serotonin activity is linked to depressive symptoms, and many antidepressants, such as selective serotonin reuptake inhibitors (SSRIs), work by increasing serotonin levels in the brain (19).
- Anxiety Disorders: Serotonin also plays a significant role in anxiety. Alterations in serotonergic neurotransmission can lead to heightened anxiety levels. SSRIs are commonly prescribed to manage anxiety disorders due to their ability to enhance serotonin signalling (19).
- Bipolar Disorder: Serotonin dysregulation is thought to contribute to the mood instability seen in bipolar disorder (19)
- Parkinson's Disease: Serotonin dysfunction is implicated in Parkinson's disease, particularly in non-motor symptoms such as depression, anxiety, and sleep disturbances (19).
- Alzheimer's Disease: In Alzheimer's disease, serotonin levels are often reduced, which may contribute to the cognitive decline and behavioral changes observed in patients. Enhancing serotonin function is being explored as a potential therapeutic strategy (19).
- Migraine: Serotonin is involved in the pathophysiology of migraine. Fluctuations in serotonin levels can trigger migraine attacks, and medications that modulate serotonin receptors are used to treat migraine .(19)

In summary, genes and genetic variations play a critical role in the functioning of neurotransmitter systems, which in turn can produce a wide range of neurological (motor) and psychiatric symptoms.

1.3 Transdiagnostic Symptoms

The newest addition to the transdiagnostic literature comes from 2024 and is a large-scale evaluation of artificial intelligence-based symptom profiling, employing conventional clustering and community detection methods (20). 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 (20) Concerning psychosis or better positive symptoms (defined as expressing delusions, hallucinations, disorganized thinking, disorganized speech according to DSM 5 and ICD 10), there are various other studies (21) supporting the notion that psychosis rather than schizophrenia accounts for the diverse manifestations seen in the general population and across mental disorders. Research indicates that weak expressions of positive psychotic symptoms can be measured also in the general population. These experiences are transdiagnostic in nature, and most individuals with these experiences have a diagnosis of a non-psychotic disorder (e.g. other mental disorder). Psychotic experiences, however, predict greater illness severity and poorer treatment response in these other illnesses (21).

Studying symptom profiles that span across different diagnoses, 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 (22). Among these, mood and self-perception were most closely linked to overall mental health in both individuals with psychiatric conditions and those without, with self-perception also being the most broadly applicable across different conditions (22).

In addition, sleep disturbances, impulsivity and negative symptoms are also considered transdiagnostic symptoms as they appear in various disorders (23,24). Sleep disturbances, such as insomnia, hypersomnia, and disrupted sleep patterns, are common in depression, anxiety disorders, and bipolar disorder (23,24). Impulsivity, defined as acting without

thinking, is found in attention deficit hyperactivity disorder (ADHD), borderline personality disorder, and substance use disorders (23,24).. Negative symptoms, defined as a reduction in emotional expression (blunted affect), lack of motivation (avolition), diminished interest in daily activities (anhedonia), poor speech output (alogia), and social withdrawal (asociality) are common in schizophrenia, autism, post-traumatic stress disorder (PTSD) and mood disorders (23,24).

In summary, various symptoms may be of transdiagnostic nature. Identifying underlying symptoms or symptom clusters that span across disorders is the way towards creating tools that apply to multiple disorders. The interest in this area is rapidly growing in the global scientific community, as evidenced by its increasing prominence at international meetings and scientific publications (25,26).

1.4 Transdiagnostic Measurement Tools

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), the Clinical Staging Model, and network models (25).

- The Research Domain Criteria (RDoC) (27) is a research framework developed by the National Institute of Mental Health. RDoC aims to understand mental disorders by examining fundamental dimensions of functioning across multiple levels of information, from genetic and neurobiological to behavioural and self-reported data. The RDoC matrix, which is subject to evolution with ongoing research, organizes these dimensions into major domains such as negative valence systems, positive valence systems, cognitive systems, systems for social

processes, arousal/regulatory systems, and sensorimotor systems. It has several limitations; it must be related to good hypothesis-driven research, it cannot operate with normative processes in dysfunctional contexts, meaning that if the data does not show a clear distinction between normal and dysfunctional states, it may be challenging to apply RDoC criteria effectively. Its biggest limitations however, that it is a research framework, not a diagnostic system.

- The Hierarchical Taxonomy of Psychopathology (HiTOP) (28) organizes symptoms into a hierarchical structure, rather than categorizing mental disorders into discrete, non-overlapping categories. This begins with specific symptoms and progresses to broader syndromes and general psychopathology dimensions. This model acknowledges the complexity and interrelatedness of mental health symptoms, which often do not fit neatly into singular diagnostic boxes. HiTOP's dimensional approach is grounded in empirical research and reflects the nuanced spectrum of psychopathology, ranging from mild to severe manifestations. The system identifies several main spectra, including internalizing, thought disorder, and externalizing behaviors, which are further subdivided into subfactors and components. This hierarchical organization facilitates a more precise and flexible understanding of mental health disorders, aligning with genetic, neurobiological, and behavioral data. However, its clinical utility is questionable.
- The clinical staging model (29), inspired by the staging systems used in general medicine, acknowledges the continuum of mental health disorders. It provides a framework for identifying an individual's current position on the continuum of mental health, ranging from stage 0, indicating potential risk, to stage IV, representing advanced stages of illness. Initially, symptoms are nonspecific and can either develop into different disorders, remain unchanged, or remit, but they cannot reverse. Treatment is tailored to the specific stage, with milder interventions typically used in the earlier stages (e.g., reducing illicit drug use in individuals at stage 0 who are at risk due to family history). This model offers a more dynamic and nuanced view of mental health than traditional diagnostic categories, but is designed to complement, rather than replace, the DSM or ICD.
- Network approaches (25) are compelling because they offer a multidimensional understanding of mental disorders, incorporating psychology, biology, sociology, and environmental factors. They conceptualize psychiatric disorders as intricate, causal interactions among symptoms. External factors (e.g., life events),

resilience, and the dynamic evolution of symptom networks over time can also be considered. A key concept is centrality, which refers to the interconnectedness of a symptom. However, the complexity of these approaches raises concerns about replicability and the validity of causal inferences from cross-sectional data.

While the above frameworks provide valuable insights, they are too abstract and obscure individual symptoms so much that they no longer reflect patients' actual problems. Hence, there is still a pressing need for uniform transdiagnostic tools that can consistently monitor the evolution of patients' symptoms over time in everyday clinical environments (25).

The Clinical Global Impression (CGI) scale is currently the most prevalent instrument to monitor the evolution of symptoms over time (30). Generally, the CGI rating scales are used to assess the intensity of symptoms, responses to treatments, and determining the effectiveness of interventions in individuals with mental health conditions. These concise scales, rated by observers, are versatile enough for use in both clinical and research settings. They offer an overarching evaluation of the severity of an illness and track clinical changes over periods (30). Building on this general scale, specialized scales such as the Clinical Global Impression-Schizophrenia (CGI-SCH), Clinical Global Impression Scale for Aggression (CGI-A), and Clinical Global Impression-Bipolar (CGI-BP) have been developed to address overall symptoms in different disorders. Lately, the CGI has also been explored in a broader, transdiagnostic context through the Transdiagnostic Global Impression - Psychopathology (TGI-P) scale (26)

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. Similar to the original CGI scale, the TGI-P uses a 7-point Likert scale ranging from 1 (normal) to 7 (extreme) to rate the severity of symptoms (26)

Positive symptoms in the context of the scale are defined as expressing delusions, hallucinations, disorganized thinking, disorganized speech, abnormal motor behavior (such as mannerism or catatonia). 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 (31). This is because negative symptoms are typically persistent and not influenced by mood; whereas depressive symptoms are often accompanied by feelings of sadness, guilt, and worthlessness and fluctuate over the course of the disorder (31). 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 (26).

The scale was developed with the help of clinicians for clinicians to help assess and monitor the severity of transdiagnostic symptoms in patients with complex psychiatric presentations independent of diagnosis (26). It may also guide treatment decisions by pointing out the most prevalent symptoms.

1.5 Transdiagnostic Pharmacological Treatment

In everyday clinical practice, treatment decisions often culminate in the prescription of medications, beyond other forms of intervention like psychotherapy (20). The selection of medication should ideally mirror the unique symptomatology of the patient, independent of their specific diagnosis. For example, antipsychotics target psychotic symptoms, anxiolytics are used for anxiety, sleeping medications address insomnia, and mood stabilizers are employed to regulate mood swings. Additionally, the choice of medication is dynamic, evolving with the patient’s condition as it may shift from unipolar depression to bipolar disorder, or from a substance use disorder to schizophrenia (20).

On one hand, there are existing treatments that target specific, well-defined symptoms across various disorders. On the other hand, it would be ideal to have a single drug that addresses multiple symptoms across multiple disorders. So far, no such "transdiagnostic drug" has been developed to treat neuro-psychiatric conditions, although some second-

generation antipsychotics are used for multiple psychiatric and some neurological conditions (see Table 2).

Table 2. Second generation antipsychotic medications and their approved indications

Drug	Schizophrenia	Bipolar Disorder Manic Episode	Bipolar Disorder Depressive Episode	Major Depression	Other
Cariprazine	Approved	Approved	Approved	Approved	-
Aripiprazole	Approved	Approved		Approved	Irritability associated with autistic disorder / Tourette's disorder
Amisulpride	Approved				-
Asenapine	Approved	Approved			-
Brexpiprazole	Approved			Approved	Agitation in Alzheimer's
Clozapine	Approved				Psychosis during the course of Parkinson's disease-
Lumateperone	Approved		Approved		Bipolar II depression
Lurasidone	Approved		Approved		-
Risperidone	Approved	Approved			Irritability associated with autistic disorder ; Persistent aggression in patients with moderate to severe Alzheimer's de mentia
Olanzapine	Approved	Approved	Approved only with flueoxetine	Approved only with flueoxetine	-
Quetiapine	Approved	Approved	Approved	Approved	
Ziprasidone	Approved	Approved			-

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 (32).

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 (33). In the European Union its sole indication is schizophrenia (32). Cariprazine is a D3 preferring, D3/D2 partial agonist antipsychotic (34). 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. Cariprazine has a low

affinity for serotonin 5-HT2C and adrenergic α1 receptors. It has no appreciable affinity for cholinergic muscarinic receptors (32).

Dopamine partial agonists (there are only three such antipsychotics: aripiprazole, brexpiprazole and cariprazine) are unique pharmacological agents that bind to dopamine receptors, exhibiting varying efficacy based on the surrounding dopaminergic environment (35). In conditions where dopamine levels are elevated, partial agonists act as antagonists, reducing excessive dopaminergic activity. Conversely, in low dopamine environments, they function as agonists, enhancing dopaminergic transmission. This dual functionality allows partial agonists to modulate both hyperdopaminergic and hypodopaminergic states, thereby maintaining a balanced dopaminergic system (35).

Among partial agonists and in fact all known antipsychotics, cariprazine is unique in having the highest affinity to the D3 receptors (36). 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. That is because cariprazine is the only antipsychotic which has an affinity for D_3 receptors about 3 orders of magnitude higher than dopamine. Hence, cariprazine may be the one agent to have clinically meaningful D3 receptor binding capability in vivo (36).

2. Objectives

2.1 Motivation and Contribution

As previously mentioned, cariprazine was initially discovered by the Hungarian company Gedeon Richter and developed for regulatory approval by Richter and its global partners. I have been employed at Gedeon Richter for the past 12 years and have been involved in the development of cariprazine since 2013. My roles have included project manager on clinical studies and later medical affairs manager, overseeing and coordinating the majority of clinical studies conducted with cariprazine. My responsibilities have encompassed study design, conducting post hoc analyses, identifying key messages, integrating these findings into further research, advancing research through disease area and unmet medical need knowledge in psychiatry, and interpreting clinical study results. I contributed to the submission of the regulatory approval dossier to the FDA and subsequently authored the regulatory approval dossier for the EMA, with whom I led the discussions of the integrated data in detail. This extensive responsibility has provided me with comprehensive knowledge about cariprazine, benefiting clinicians, regulatory bodies, and the industry. I have access to all raw data from the cariprazine clinical studies conducted since its inception.

I have also co-authored several publications. From my overall 32 peer-reviewed publications, 30 are about cariprazine in various disorders and clinical settings. One article was published in the Lancet, on two I am the first author and 9 publications were rated D1.

My work with cariprazine has been immensely rewarding, and my motivation for this thesis was to consolidate the data I have been working on with emerging trends in psychiatry. One such trend is the transdiagnostic concept, which aligns well with the fluid nature of clinical practice in psychiatry, as opposed to the rigid diagnostic criteria set by DSM and ICD. Given cariprazine's unique profile, particularly its high affinity for D3 receptors and its role as a dopamine partial agonist at both D3 and D2 receptors, I hypothesized that it could serve as an ideal transdiagnostic treatment for dopamine-related disorders. Therefore, this thesis aims to explore whether cariprazine can indeed be considered a transdiagnostic drug.

2.2 Aim of the present thesis

As outlined in the introduction section, 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.

This work aims to provide an integrated and consolidated presentation of cariprazine findings that formed the basis of my academic publications and of which this work is an integrated result.

3. Methods

3.1 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.

The data synthesis focused on summarizing the findings from these trials descriptively, highlighting key outcomes and trends observed across the studies (Result section 4.1).

3.2 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.

3.2.1 Included Studies

For potential new post-hoc analyses needed, data from 13 Gedeon Richter/Partners supported phase II/III, randomized, double-blind, placebo- or active controlled trials was used. These studies form the basis of the approval of cariprazine in different disorders by the Food and Drug Administration's (FDA (33)) and by the European Medicinal Agency (EMA (37)). A list of these so called "approval studies" is provided in Table 3.

Table 3. List of included approval studies

	Author, year, Internal code Reference	Design	Title	Indication	Transdiagnostic symptom
1	Durgam, 2014 (38)	Multicenter, randomized, double-blind, placebo-controlled, 6 week study	An evaluation of the safety and efficacy of cariprazine in patients with acute exacerbation of schizophrenia: A phase II, randomized clinical trial	Schizophrenia	positive, negative, cognitive, depressive, anxiety, hostility and self-harm
2	Kane, 2015 (39)	Multicenter, randomized, double-blind, placebo-controlled, 6 week study	Efficacy and safety of cariprazine in acute exacerbation of schizophrenia: Results from an international, phase III clinical trial	Schizophrenia	positive, negative, cognitive, depressive, anxiety, hostility and self-harm
3	Durgam, 2015 (40)	Multicenter, randomized, double-blind, placebo-controlled, 6 week study	Cariprazine in acute exacerbation of schizophrenia: A fixed-dose, phase 3, randomized, double-blind, placebo- and active-controlled trial	Schizophrenia	positive, negative, cognitive, depressive, anxiety, hostility and self-harm
4	Durgam, 2016 (41)	Multicenter, randomized, double-blind, placebo-controlled, up to 92 week study	Long-term cariprazine treatment for the prevention of relapse in patients with schizophrenia: A randomized, double-blind, placebo-controlled trial	Schizophrenia	positive, negative, cognitive, depressive, anxiety, hostility and self-harm
5	Németh, 2017 (42)	Multicenter, randomized, double-blind, active-controlled, 26 week study in negative symptoms	Cariprazine as monotherapy for the treatment of predominant negative symptoms in patients with schizophrenia: A randomized, double-blind, active-comparator controlled trial	Schizophrenia	positive, negative, cognitive, depressive, anxiety, hostility and self-harm
6	Durgam, 2015 (43)	Multicenter, randomized, double-blind,	The efficacy and tolerability of cariprazine in acute mania associated	Bipolar Mania	manic, positive, cognitive, hostility, sleep

Table 3. List of included approval studies					
	Author, year, Internal code Reference	Design	Title	Indication	Transdiagnostic symptom
		placebo-controlled, 3 week study	with bipolar I disorder: a phase II trial		
7	Sachs, 2015 (44)	Multicenter, randomized, double-blind, placebo-controlled, 3 week study	Cariprazine in the treatment of acute mania in bipolar I disorder: A double-blind, placebo controlled, phase III trial	Bipolar Mania	manic, positive, cognitive, hostility, sleep
8	Calabrese, 2015 (45)	Multicenter, randomized, double-blind, placebo-controlled, 3 week study	Efficacy and safety of low- and high-dose cariprazine in patients with acute and mixed mania associated with bipolar I disorder	Bipolar Mania	manic, positive, cognitive, hostility, sleep
9	Durgam, 2016 (46)	Multicenter, randomized, double-blind, placebo-controlled, 8 week study	An 8-week randomized, double-blind, placebo-controlled evaluation of the safety and efficacy of cariprazine in patients with bipolar I depression	Bipolar Depression	cognitive, depressive, anxiety, sleep, self-harm
10	Earley, 2019 (47)	Multicenter, randomized, double-blind, placebo-controlled, 6 week study	Cariprazine treatment of bipolar depression: A randomized, double blind, placebo-controlled phase 3 study	Bipolar Depression	cognitive, depressive, anxiety, sleep, self-harm
11	Earley, 2020 (48)	Multicenter, randomized, double-blind, placebo-controlled, 6 week study	Efficacy and safety of cariprazine in bipolar I depression: A double-blind, placebo-controlled phase 3 study	Bipolar Depression	cognitive, depressive, anxiety, sleep, self-harm
12	Durgam, 2016 (49)	Multicenter, randomized, double-blind, placebo-controlled, 8 week study	Efficacy and safety of adjunctive cariprazine in inadequate responders to antidepressants: A randomized, double-blind, placebo-controlled study in adult MDD patients	Major Depression	depression
13	Sachs, 2023 (50)	Multicenter, randomized, double-blind, placebo-controlled, 6 week study	Adjunctive Cariprazine for the Treatment of Patients With Major Depressive Disorder: A Randomized, Double-Blind, Placebo-Controlled Phase 3 Study	Major Depression	depressive anxiety

From the included studies, 5 were performed in the indication of schizophrenia incl. a study in a subpopulation with persistent, predominant, primary negative symptoms of

schizophrenia, 3 in bipolar I disorder manic episode (from now on short: bipolar mania), 3 in bipolar I disorder depressive episode (from now on short: bipolar depression), and 2 in major depressive disorder (MDD) add-on. These were all multicentre, multinational, randomized, double-blind, placebo- or active controlled, parallel-group studies.

In these studies, 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 MDD) 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 (37).

3.2.2 Study Patients

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 (43) and 273 in the major depressive disorder study (49). In most studies, patients were treated either with cariprazine or with placebo. In two schizophrenia studies an active comparator (risperidone 4 mg (38) and aripiprazole 10 mg (40)) was also used for assay sensitivity. In the MDD add-on studies, antidepressants were used as base treatment before cariprazine or placebo add-on (49,50). 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 (42). Treatment periods ranged from 3 weeks in the mania studies (43–45) to up to 92 weeks in schizophrenia relapse prevention study (41).

3.2.3 Efficacy evaluations

Efficacy on the 10 transdiagnostic symptoms was measured based on the primary and additional endpoints as used in the respective studies. Primary endpoints in the studies 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 (51). 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 (52). The aim was to refine the original PANSS structure into five distinct factors as shown in Table 4 below. This factor structure is widely accepted to better assess and target specific symptom domains (52). Therefore, wherever available, PANSS factor scores were used to describe the above symptoms domains instead of the PANSS total scores.

Table 4. PANSS factors scores by Marder

Factor score for negative symptoms (FSNS)		Factor score for positive symptoms (FSPS)		Factor score for Disorganised thought		Factor score for Uncontrolled hostility/excitement		Factor score for Anxiety/ depression	
N1	Blunted affect	P1	Delusions	N5	Difficulty in abstract thinking	G14	Poor impulse control	G2	Anxiety
N2	Emotional Withdrawal	P3	Hallucinatory behaviour	G5	Mannerisms and posturing	P4	Excitement	G3	Guilt feelings
N3	Poor rapport	P5	Grandiosity	G10	Disorientation	P7	Hostility	G4	Tension
N4	Passive social with drawal	P6	Suspiciousness	G11	Poor attention	G8	Uncooperative-ness	G6	Depression
N6	Lack of spontaneity	N7	Stereotyped thinking	G13	Disturbance of volition				
G7	Motor retardation	G1	Somatic concern	G15	Preoccupation				
G16	Active social avoidance	G9	Unusual thought content	P2	Conceptual disorientation				
		G12	Lack of judgement						

The Montgomery-Åsberg Depression Rating Scale (MADRS) is a clinical assessment tool used to measure the severity of depressive episodes in adults (53). It consists of 10 items (Table 5), each rated on a scale from 0 to 6, with higher scores indicating more severe depression. The MADRS is widely used in both clinical practice and research to evaluate treatment outcomes and monitor changes in depressive symptoms over time.

The Young Mania Rating Scale (YMRS) is a clinical assessment tool designed to evaluate the severity of manic symptoms (54). Developed by Robert Young and colleagues, the YMRS consists of 11 items that assess various aspects of mania, such as elevated mood, increased motor activity, sexual interest, sleep patterns, irritability, and speech (Table 5). Each item is rated on a scale, with some items ranging from 0 to 4 and others from 0 to 8, allowing for a nuanced measurement of symptoms. The total score can range from 0 to 60, with higher scores indicating more severe manic symptoms (54).

Table 5. Items of the MADRS and YMRS

MADRS		YMRS	
Item Number	**Item Description**	**Item Number**	**Item Description**
1	Apparent Sadness	1	Elevated Mood
2	Reported Sadness	2	Increased Motor Activity/Energy
3	Inner Tension	3	Sexual Interest
4	Reduced Sleep	4	Sleep
5	Reduced Appetite	5	Irritability
6	Concentration Difficulties	6	Speech (Rate and Amount)
7	Lassitude	7	Language/Thought Disorder
8	Inability to Feel	8	Content
9	Pessimistic Thoughts	9	Disruptive/Aggressive Behavior
10	Suicidal Thoughts	10	Appearance
		11	Insight

Secondary endpoints in the studies varied by either using the Clinical Global Impression (CGI) scale, the Sheehan Disability Scale (SDS), or a functionality scale such as the Personal and Social Performance (PSP) scale. The CGI scale includes two components: CGI-I (Improvement), which measures how much a patient's illness has improved or worsened over time, and CGI-S (Severity), which assesses the severity of a patient's illness at a specific point in time (30). The SDS evaluates the extent to which symptoms disrupt a patient's work, social life, and family responsibilities. Lastly, the PSP scale measures a patient's social and personal functioning in four areas: socially useful activities, personal and social relationships, self-care, and disturbing and aggressive

behaviors (55). These scales collectively provide a comprehensive picture of a patient's clinical status and the impact of treatment on their daily life.

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

The HAMA is one of the first rating scales developed to measure the severity of anxiety symptoms (56). Created by Max Hamilton in 1959, the HAMA 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 (57). 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 (58). 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 (CDR) is a computerized battery of cognitive tests designed to assess various aspects of cognitive function, including attention (59). 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 of above-mentioned scales were used to identify efficacy of cariprazine on transdiagnostic symptoms in the manner as outlined in Table 6.

Table 6: 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	HAMA	C-SSRS
Positive	PANSS FSPS	-	Item 8: Content	-	-
Negative	PANSS-FSNS	-	-	-	-
Cognitive	PANSS-disorganized factor score	Item 6: concentration difficulties	Item 7: Language-Thought Disorder	-	-
For cognition additionally: Cognitive Drug Research System Attention Battery from schizophrenia studies and FAST cognitive item from bipolar depression studies					
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

3.2.4 Statistical analysis

Studies in the same indications with similar designs were pooled. Singular studies with unique designs were evaluated separately.

Pooled studies

For schizophrenia, data was pooled from the 3 acute, randomized, placebo-controlled 6 week trials (38–40). 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 (38,40); 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 (43–45). 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 analysed using a mixed-effects model for repeated measures (MMRM), with treatment group, study, study centre 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 (46–48). 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.

Singular studies

An additional 2 schizophrenia (41,42), and 2 MDD add-on studies (49,50) 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.

4. Results

4.1 Cariprazine Efficacy Across Disorders

To review the clinical efficacy of cariprazine across disorders, a systematic literature review with a focus on randomized clinical trials (RCTs) was performed. 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.

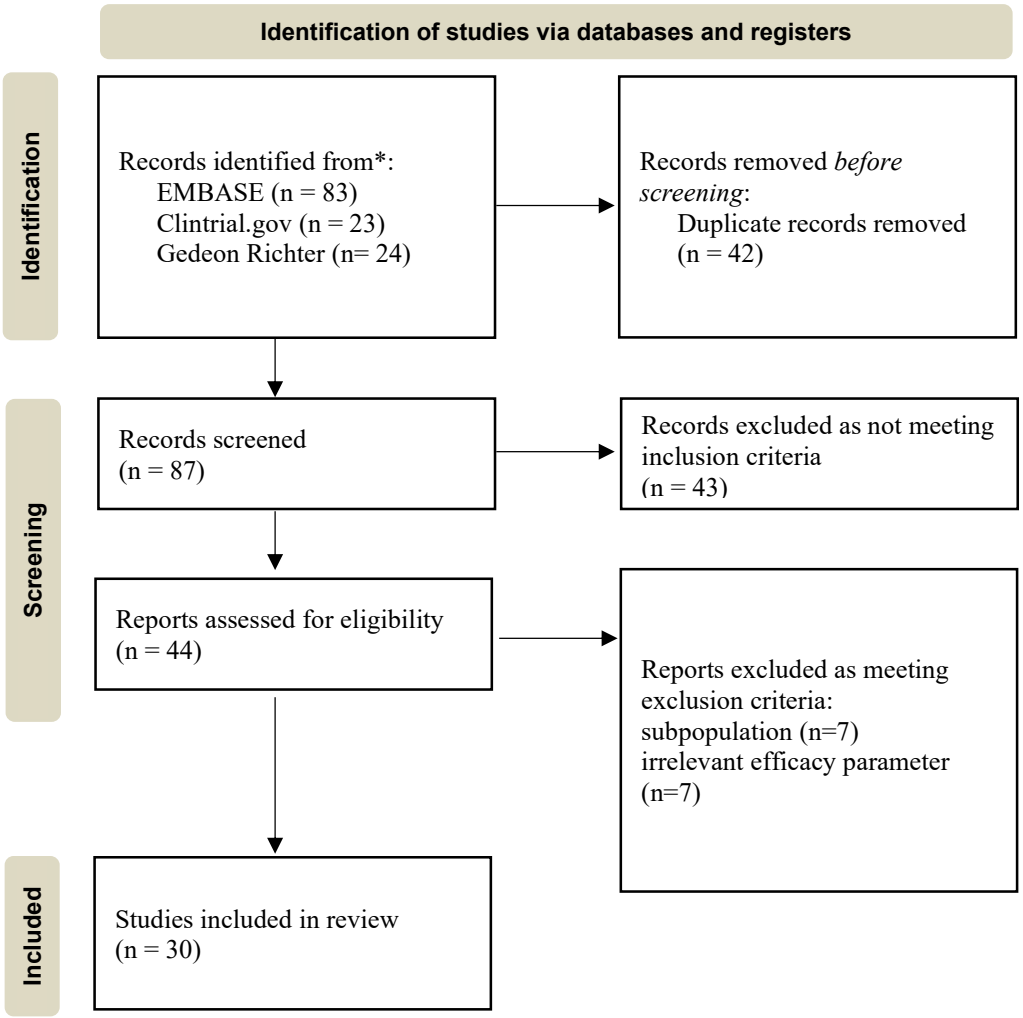

Figure 1. PRISMA flowchart of the systematic review

The 30 studies included into the review consisted of the 13 approval studies of Table 3 and an additional 17 studies as listed in Table 7 below.

Table 7. List of included studies in addition to the approval studies					
	Author, year Reference	Design Internal codes	Title	Indication/ Symptoms	Transdiagnostic symptom
14	Marder, 2019 (60)	Pooled post-hoc of 3RCT	Efficacy of cariprazine across symptom domains in patients with acute exacerbation of schizophrenia: Pooled analyses from 3 phase II/III studies	Schizophrenia	positive, negative, cognitive, depressive/ anxiety, hostility, self-harm
15	Citrome, 2016 (61)	Pooled post-hoc of 3RCT	The Effect of Cariprazine on Hostility Associated With Schizophrenia: Post Hoc Analyses From 3 Randomized Controlled Trials	Schizophrenia	hostility
16	Earley, 2019 (62)	Pooled post-hoc of 3RCT	Efficacy of cariprazine on negative symptoms in patients with acute schizophrenia: A post hoc analysis of pooled data	Schizophrenia	negative
17	Durgam, 2016 (63)	Multicenter, randomized, double-blind, placebo-controlled, 6 week study	Cariprazine in the treatment of schizophrenia: A proof-of-concept trial	Schizophrenia	-
18	Fleischhacker, 2019 (64)	Post-hoc of the 005 study	The efficacy of cariprazine in negative symptoms of schizophrenia: Post hoc analyses of PANSS individual items and PANSS-derived factors	Schizophrenia	negative
19	Citrome, 2024 (65)	Post-hoc of 3 RCT	Effects of cariprazine on reducing symptoms of irritability, hostility, and agitation in patients with manic or mixed episodes of bipolar I disorder	Bipolar mania	hostility
20	Vieta, 2015 (66)	Post-hoc of 3 RCT	Effect of cariprazine across the symptoms of mania in bipolar I disorder: Analyses of pooled data from phase II/III trials	Bipolar mania	positive cognitive sleep hostility
21	Yatham, 2020 (67)	Pooled post-hoc of 3RCT	Broad efficacy of cariprazine on depressive symptoms in bipolar disorder and the clinical implications	Bipolar Depression	depression cognition anxiety sleep suicide

Table 7. List of included studies in addition to the approval studies					
	Author, year Reference	Design Internal codes	Title	Indication/ Symptoms	Transdiagnostic symptom
22	Jain, 2024 (68)	Pooled post-hoc of 2 RCT	Efficacy of cariprazine in patients with bipolar depression and higher or lower levels of baseline anxiety: a pooled post hoc analysis	Bipolar Depression	anxiety
23	Yatham, 2020 (69)	Multicenter, randomized, double-blind, placebo-controlled, 8 week study	Evaluation of cariprazine in the treatment of bipolar I and II depression: A randomized, double-blind, placebo-controlled, phase 2 trial	Bipolar Depression	-
24	McIntyre, 2024 (70)	Multicenter, randomized, double-blind, placebo-controlled up to 39 weeks study	Cariprazine as a maintenance therapy in the prevention of mood episodes in adults with bipolar I disorder	Bipolar disorder both episodes	-
25	Vieta, 2024 (71)	Pooled post-hoc of 6 RCT	Full-spectrum efficacy of cariprazine across manic and depressive symptoms of bipolar I disorder in patients experiencing mood episodes: Post hoc analysis of pooled randomized controlled trial data	Bipolar disorder both episodes	-
26	Fava, 2018 (72)	Multicenter, randomized, double-blind, placebo-controlled, 8 week study	Efficacy of adjunctive low-dose cariprazine in major depressive disorder: a randomized, double-blind, placebo-controlled trial	Major Depression	-
27	Earley, 2018 (73)	Multicenter, randomized, double-blind, placebo-controlled, 8 week study	Cariprazine augmentation to antidepressant therapy in major depressive disorder: Results of a randomized, double-blind, placebo-controlled trial	Major Depression	-
28	Riesenberg, 2023 (74)	Multicenter, randomized, double-blind, placebo-controlled,	Cariprazine for the Adjunctive Treatment of Major Depressive Disorder in Patients With Inadequate Response to	Major Depression	-

Table 7. List of included studies in addition to the approval studies					
	Author, year Reference	Design Internal codes	Title	Indication/ Symptoms	Transdiagnostic symptom
		6 week study	Antidepressant Therapy: Results of a Randomized, Double-Blind, Placebo-Controlled Study		
29	Citrome, 2024 (75)	Pooled post-hoc of 5 RCT	Adjunctive cariprazine for the treatment of major depressive disorder: Number needed to treat, number needed to harm, and likelihood to be helped or harmed	Major Depression	-
30	McIntyre, 2023 (76)	Pooled post-hoc in all indications	The efficacy of cariprazine on cognition: a post hoc analysis from phase II/III clinical trials in bipolar mania, bipolar depression, and schizophrenia	-	cognition

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.

4.1.1 Schizophrenia

First, a phase II, dose finding study helped establish the correct dose-range in schizophrenia (63). In the acute schizophrenia studies, statistically significant results were seen in favor of cariprazine over placebo on the primary endpoint PANSS total score and the secondary endpoint CGI in all studies (38–40). All examined doses (1.5 mg - 3 mg - 4.5 mg - 6 mg and 9 mg) of cariprazine showed statistically significant effects in all 3 studies (38–40). After pooling the data from the 2 acute fixed dose, short term studies, the LSMD was −6.5 for the 1.5 mg cariprazine, the 95% confidence interval (CI) (−9.8, −3.2), P=0.0001, with an effect size (ES) of 0.37. For the 3 mg LSMD was −7.3 (CI −9.8, −4.8), P=<0.0001 and ES 0.38; for the 4.5 mg LSMD was −9.5 (CI −12.7, −6.2), P=<0.0001 and ES 0.53; for the 6 mg LSMD was −9.2 (CI −12.4, −6.0),−7.3 (CI −9.8, −4.8), P=<0.0001 and ES 0.45 (38,40).

The efficacy in schizophrenia was further supported by an up-to 92-week schizophrenia maintenance study, where patients stabilized on cariprazine for 20 weeks were

randomized to receive either placebo or cariprazine in the doses of 3 mg, 6 mg or 9 mg . Statistically significant results were seen in favor of cariprazine over placebo on relapse criteria. Time to relapse was significantly longer with cariprazine treatment versus placebo treatment (P=0.001, log-rank test). Relapse occurred in 24.8% of cariprazine- and 47.5% of placebo-treated patients (hazard ratio = 0.45; [95% CI: 0.28, 0.73) . This study underlined the efficacy of cariprazine also in a long-term setting. Additionally, based on PANSS total scores a significant reduction of symptoms for patients treated with cariprazine compared to those given a placebo was seen (41).

Additionally, statistically significant results were seen in favor of cariprazine over risperidone on the PANSS-FSNS in a specially designed study on primary negative symptoms of schizophrenia. Use of cariprazine led to greater least squares mean change in PANSS-FSNS from baseline to week 26 than did use of risperidone (LSDM: −1·46; 95% CI: −2·39 to −0·53; P=0·0022; ES 0·31) (42). Statistically significant effects were observed in favor of cariprazine over risperidone on the patient functionality as measured by the PSP from week 10 onward (14·30 points for cariprazine vs 9·66 for risperidone; LSMD 4·63, 2·71 to 6·56; p<0·0001; effect size=0·48) (42).

4.1.2 Bipolar Mania

In the mania studies, statistically significant results were seen in favor of cariprazine over placebo on the primary endpoint YMRS and the secondary endpoint CGI-S in all the 3-week acute mania studies (43–45). Only flexible dose studies were performed, examining the dose range of 3-12 mg/day.

After pooling the data, the LSMD for overall cariprazine versus placebo was −5.35; [95% CI −6.69, −4.01], P<0.0001; ES 0.54 (66). The difference in LS mean change from baseline in YMRS total score was statistically significant in favor of cariprazine over placebo from the first visit on day 4 until the last visit on day 21(66) .

4.1.3 Bipolar Depression

A phase II dose finding study helped establish the correct dose-range in bipolar depression (69). In the bipolar depression studies, statistically significant results were seen in favor of cariprazine over placebo on the primary endpoint MADRS for the 1.5 mg dose in all three approval studies (46–48). One study additionally confirmed the superiority of 3 mg

cariprazine over placebo (47). Statistically significant results were also seen in favor of cariprazine over placebo on the secondary endpoint CGI for the 1.5 mg dose in two studies (46,48).

After pooling the data, cariprazine showed significant results versus placebo on both doses: 1.5 mg/d: LSDM −2.8, 95% CI (-4.1 -1.6), P<0.001; 3 mg/d: LSDM −2.4, 95% CI (-3.7 -1.2), P<0.001 and pooled 1.5-3mg/d dose: LSMD -2.6, 95% CI (-3.7 -1.5), P<0.001 (67).

In a study examining the efficacy of cariprazine in treating both manic and depressive symptoms in patients with bipolar I disorder by pooling data from 3 mania (43–45) and 3 bipolar depression (46–48) studies revealed that cariprazine significantly reduces symptoms of both mania and depression (71). In patients experiencing a manic episode, cariprazine also significantly reduced depressive symptoms, and in patients with a depressive episode, there was no worsening of mania. The authors suggest that cariprazine has full-spectrum efficacy across the mood poles of bipolar I disorder and that its use is associated with a low risk of switching to the opposite mood pole (71).

Additionally, a maintenance study was also performed in bipolar disorder (70), where patients from either manic or depressive mood periods were first stabilized on cariprazine and then randomized to either receive cariprazine or placebo. Time to relapse and relapse rates to either mood period were observed. The assumed relapse rate for the placebo arm was 35%, however, the unexpectedly low actual crude rate of relapse was 19.7%. Hence, the study did not yield statistically significant differences between placebo and cariprazine. However, considering that all patients received cariprazine treatment in an open-label manner, before being randomized, and that the placebo relapse rates in similarly designed previous competitor trials with the same primary endpoint (time to relapse), in this patient population were 33.3%, 38%, 50%, 51%, 52%, and even 56%, the conclusion of the study may very well be that due to its long half-life, cariprazine offered early protection during the high-risk period of relapse in the early weeks after stabilization in bipolar disorder (70).

4.1.4 Major Depression add-on

A phase II, dose finding study helped establish the correct dose-range in major depression (72). Statistically significant results were seen in favor of cariprazine over placebo in the two approval studies (as add-on treatment to antidepressants) on the MADRS total score:

- In study 12 (49) patients taking cariprazine at doses of 2–4.5 mg/day, with a mean daily dose of close to 3 mg showed significantly greater mean reductions in the MADRS total score compared to placebo. By week 8, the LSMD for the cariprazine 2–4.5 mg/day group versus placebo was –2.2, 95% CI (–3.7 –0.6); P=0.0057). The LSMD for the cariprazine 1–2 mg/day group (mean 1.5 mg) was –0.9 95% CI (–2.4 0.6); P=0.2404).
- In the study 13 (50), adjunctive cariprazine 1.5 mg/day compared with placebo resulted in significantly greater mean reduction in MADRS total score from baseline to week 6 (LSDM:−2.5, 95% CI [−4.2, −0.9], P=0.0025). Cariprazine 3.0 mg/day vs placebo reached numerically greater reductions in MADRS total scores, however, this difference did not reach statistical significance (LSDM −1.5, 95% CI [−3.2, 0.1], P=0.0691).

Two additional studies in MDD supported the safety findings of previous studies, did however not prove an additional benefit of cariprazine over placebo (73,74). Nevertheless, after pooling data from all 5 MDD studies, adjunctive cariprazine proved to be a beneficial treatment option for patients with MDD as evidenced by the number needed to treat (NNT) and number needed to harm (NNH) (75). Statistically significant NNT values were observed for MADRS response (≥50% decrease in MADRS total score) and remission outcomes at week 6, with lower doses showing robust results. Additionally, the pooled safety analysis showed statistically significant NNH values for akathisia, constipation, fatigue, insomnia, nausea, restlessness, somnolence, and tremor, with all NNH values > 1015 (75).

4.2 Cariprazine Efficacy on Transdiagnostic Symptoms

To review the clinical efficacy of cariprazine on predefined transdiagnostic symptoms, both results of the systematic literature review and additional post-hoc analyses were performed.

4.2.1 Positive symptoms

In short, positive symptoms are experiences that add something unusual to a person's normal functioning. These include hallucinations, delusions, disorganized thinking, and abnormal motor behavior (23,24). These symptoms are most often associated with schizophrenia spectrum disorders, can however occur also in mania, in depression (here topics often revolve around themes of guilt, worthlessness, and hopelessness, such as believing they are responsible for terrible events or that they will drive their loved ones into poverty, etc), substance use and organic brain injuries (23,24).

For cariprazine, positive symptoms were measured in the schizophrenia and mania studies using the PANSS total score, PANSS-FSPS and the YMRS item 8 (content) score as assessment tools. In the bipolar depression and major depression add-on studies, psychotic patients were excluded, and psychotic symptoms were not tracked during the study.

In the framework of schizophrenia, in the acute schizophrenia studies, statistically significant results were seen in favor of cariprazine over placebo on the primary endpoint PANSS total score (38–40). Additionally, statistically significant differences of cariprazine (1.5–9.0 mg/d) versus placebo were seen on the PANSS-FSPS (ES = 0.37, $P < 0.0001$) and most of its subitems in the pooled studies (60)(Figure 2). Additionally, statistically significant differences of cariprazine versus placebo were seen in the 2 fixed-dose studies (38,40) for 3 mg/d LSMD −1.4, 95% CI (−2.2, −0.6), P=0.0011, ES 0.32; 4.5 mg/d −2.1 95% CI (−3.2, −1.1), P=0.0001, ES 0.52 and the 6 mg/d -2.2 95% CI (−3.3, −1.1), P<0.0001, ES 0.42. Numerical differences were also seen for the 1.5 mg which did not reach statistical significance (LSMD −0.7, 95% CI (−1.8, 0.4), P=0.2365, ES 0.25) (38,40).

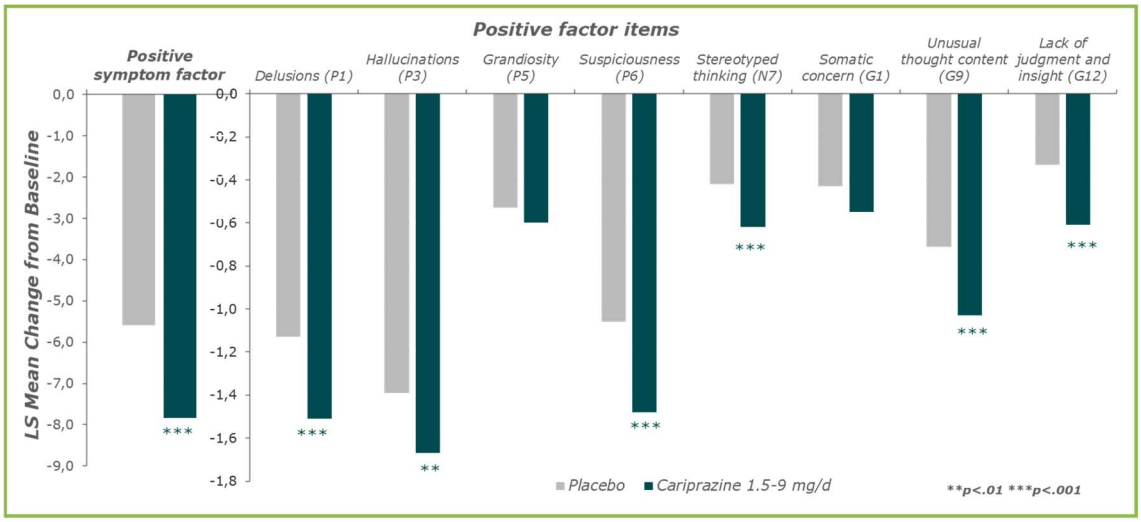

Figure 2. LS mean change from baseline to end on the PANSS-FSPS for pooled cariprazine and placebo - pooled schizophrenia studies, adapted based on the data from (60)

In the framework of mania, based on item 8 (content) of the YMRS, the difference in mean change from baseline to end (at 3 weeks) was statistically significant in favor of cariprazine over placebo (LSMD: -0.8, 95% CI (-1.0 -0.5), P<0.001 – see Figure 6) (66). Additionally, at week 3, the difference in mean change from baseline to end on the PANSS total score was statistically significant in favor of cariprazine over placebo in all mania studies (43–45).

4.2.2 Negative symptoms

In short, negative symptoms refer to a reduction or absence of normal behaviors and functions. These include avolition, anhedonia, asociality, blunted affect, and alogia (77). Negative symptoms can be primary (related to the disease and persistent of nature) and secondary (due to other reasons such as positive symptoms, depression, under-stimulation, side effects of antipsychotics – mimicking negative symptoms but really being something else) in nature (77).

For cariprazine, negative symptoms were measured in schizophrenia studies only, using the PANSS-FSNS. Cariprazine showed statistically significant effects on both primary and secondary negative symptoms of schizophrenia.

Measuring negative symptoms in the general/acute schizophrenia population (potentially with high secondary negative symptoms), at week 6, statistically significant differences versus placebo were seen for cariprazine on the PANSS-FSNS (with effect sizes for the different doses ranging between ES = 0.34 and 0.62 (P < 0.0001) (60)– Figure 3.

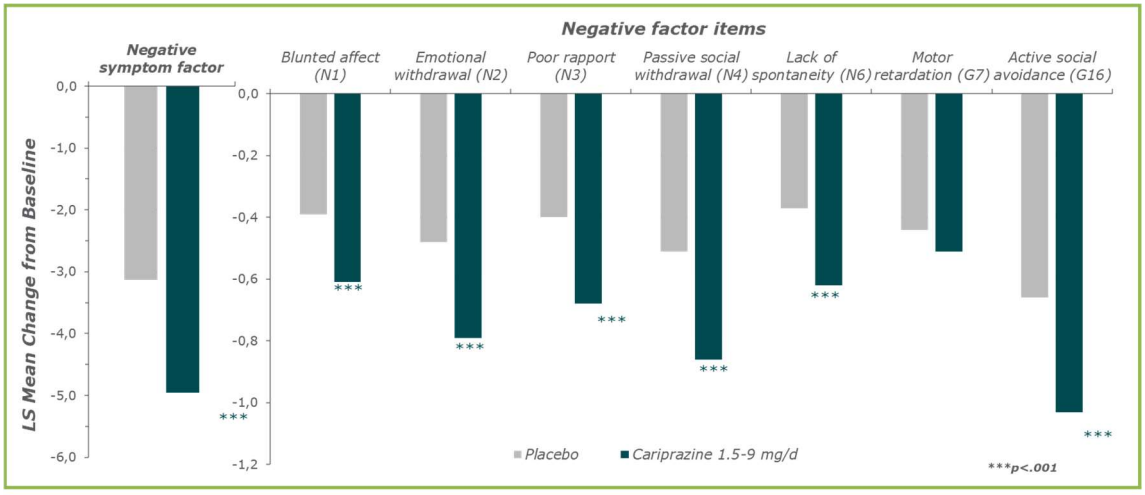

Figure 3. LS mean change from baseline to end on the PANSS-FSNS for pooled cariprazine and placebo - pooled schizophrenia studies, adapted based on the data from (60)

When looking at a subpopulation of patients from the same acute population, who predominantly experience negative symptoms, significant differences were found for cariprazine at doses of 1.5–3 mg/d (LSMD [95% CI] = −2.0 [−3.6, −0.3], P = 0.0179; ES = 0.41), cariprazine 4.5–6 mg/d (LSMD [95% CI] = −3.4 [−5.2, −1.7], P = 0.0002; ES = 0.71) as well as for risperidone (LSMD [95% CI] = −2.8 [−5.0, −0.5], P = 0.0149; ES = 0.57) over placebo in the treatment of these symptoms (62). However, no significant difference was observed for aripiprazole compared to placebo (LSMD [95% CI] = −1.0 [−3.0, 1.0], P = 0.3265). At week 6, the group receiving cariprazine at 4.5 mg/day showed a significantly greater reduction in PANSS-FSNS from baseline compared to the aripiprazole group (LSMD [95% CI] = −2.4 [−4.5, −0.4], P = 0.0197; ES = 0.50). No significant difference was found between cariprazine at 4.5–6 mg/day and risperidone (LSMD [95% CI] = −0.7 [−2.9, 1.6], P = 0.5464). (LSMD [95% CI] = −0.7 [−2.9, 1.6], P = 0.5464). After adjusting for changes in positive symptoms, cariprazine continued to show statistically significant differences vs placebo (1.5–3 mg/day: LSMD−1.4 [−2.7, −0.1], P = 0.0322; 4.5–6 mg/day: LSMD −2.1 [−3.5, −0.7], P = 0.0038), while risperidone (LSMD −1.1 [−2.8, 0.7], P = 0.2204) and aripiprazole (LSMD −0.2 [−1.8, 1.3], P = 0.7635) did not (62).

Further, in a specially designed study on primary negative symptoms of schizophrenia, cariprazine led to greater least squares mean changes in PANSS-FSNS from baseline to week 26 than did risperidone (LSDM: −1·46; 95% CI: −2·39 to −0·53; P=0·0022; ES 0·31) (42).

When analysing the data from this study, evaluating cariprazine's efficacy on different PANSS-derived factors that have been described in the literature previously (PANSS-Factor Score for Negative Symptoms, Liemburg factors, Khan factors, Pentagonal Structure Model Negative Symptom factor) along with single PANSS-FSNS items significant improvement was seen with cariprazine compared to risperidone on most single items (Figure 4) and across all PANSS-derived factors (64). Given that items representing various negative symptom dimensions may correspond to different underlying pathophysiological mechanisms, these results indicated cariprazine's broad-spectrum efficacy in treating the negative symptoms of schizophrenia (64).

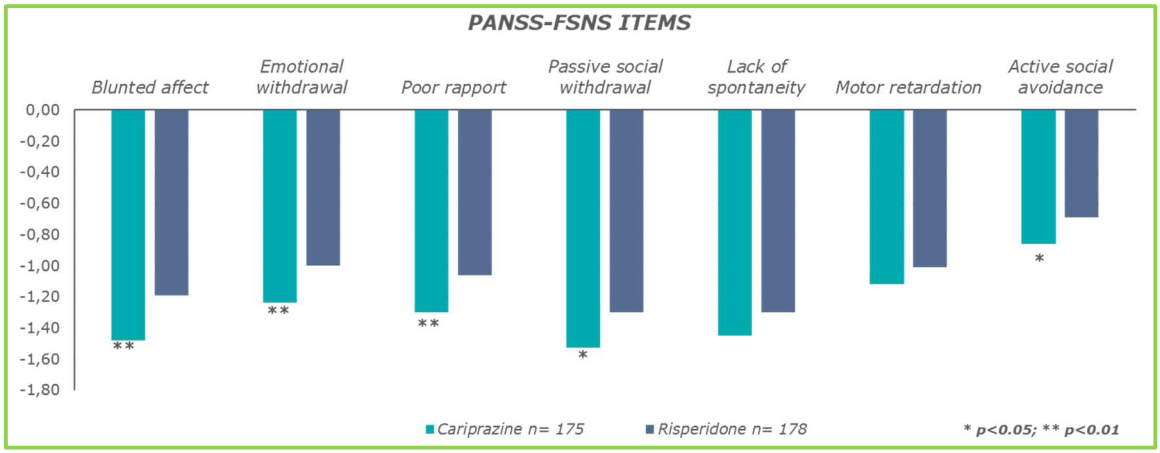

Figure 4. LS mean change from baseline to end on the PANSS-FSNS for cariprazine and risperidone – adapted based on the data from (64)

4.2.3 Cognitive symptoms

Cognitive symptoms refer to impairments in mental processes that affect how individuals think, learn, and remember. These symptoms can manifest in various ways, including difficulties with attention, memory, problem-solving, and processing speed. Cognitive symptoms are often associated with schizophrenia, depression, and ADHD, and they can persist even when other symptoms improve (23,24).

Cognitive symptoms were measured in all approval studies and cariprazine improved cognitive symptoms in schizophrenia, mania and depressed patients.

In the framework of schizophrenia, statistically significant differences of cariprazine (1.5–9.0 mg/d) versus placebo were seen on the PANSS disorganized thought factor (ES = 0.47, P < 0.0001 – Figure 5) (60). Additionally, statistically significant differences of cariprazine versus placebo were seen in the 2 fixed-dose studies (38,40) for all doses (1.5mg/d: LSMD −1.2 (95% CI: −2.0, −0.5), P=0.0009, ES 0.40; 3 mg/d: LSMD −1.2 (95% CI: −1.7, −0.6), P <0.0001, ES 0.38; 4.5 mg/d: LSMD−1.8 (95% CI: −2.5, −1.0), P <0.0001, ES 0.60 and the 6 mg/d: LSMD −1.7 (95% CI: −2.4, −1.0), P<0.0001, ES 0.49 (60).

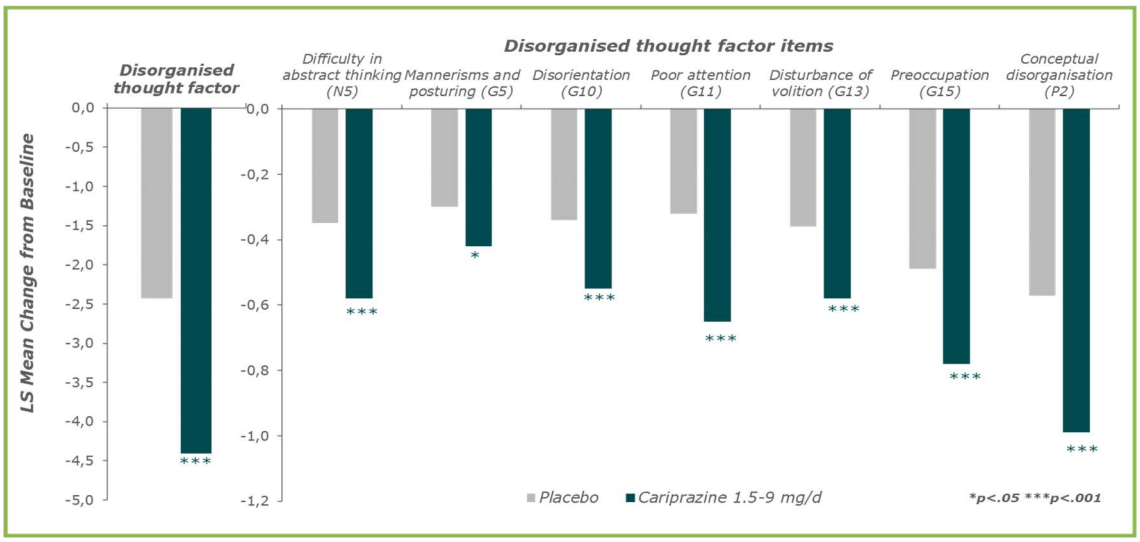

Figure 5. LS mean change from baseline to end on the PANSS- disorganized thought factor for pooled cariprazine and placebo – adapted based on the data from (60)**.**

In the pooled mania studies, at week 3, statistically significant differences versus placebo were seen on item 7 (Language-Thought Disorder: LSMD: -0,3 (CI 95% -0,5 -0,2), P <0.001, ES 0.36 – Figure 6) (66) and data on file.

In the bipolar depression studies, at week 6, statistically significant differences versus placebo were seen on item 6 (Concentration difficulties: LSMD: -0.3, 95% CI (-0,5 -0.1), P <0.001 – Figure 8) (67)and data on file.

Additionally, post hoc analyses were performed on bipolar I depression, mania and schizophrenia studies using the MADRS, FAST, PANSS and the Cognitive Drug Research System attention battery to measure cognition (76). LSMDs in changes from baseline to end were reported for specific patient subsets with varying levels of baseline cognitive symptoms. In patients with bipolar depression exhibiting at least mild cognitive symptoms, LSMDs showed significant differences for cariprazine compared to placebo on MADRS item 6 (across three studies: 1.5 mg = −0.5 [P < .001]; 3 mg/d = −0.2 [P <

.05]) and on the FAST Cognitive subscale (one study: 1.5 mg/d = −1.4; P=0.0039). For those with bipolar mania and mild cognitive symptoms, the LSMD in the PANSS disorganized thought factor score was also significant for cariprazine versus placebo (three studies: −2.1; P=0.001). In patients with schizophrenia experiencing high cognitive impairment, cariprazine 3 mg/d demonstrated improvements in attention power compared to placebo (P =0.0080), while no significant effect was noted for the 6 mg/d dosage. Additionally, enhancements in continuity of attention were observed for both cariprazine 3 mg/d (P = 0.0012) and 6 mg/d (P = 0.0073) on the Cognitive Drug Research System attention battery (76).

In the MDD add-on studies in study 13 (50), item 6 was not statistically significant for either dose (1.5 mg/d: LSMD -0.1, 95% CI (-0.33, 0.16), P=0.5084; 3 mg/d: LSMD 0.1, 95% CI (-0.19, 0.31), P=0.6180). In study 12 (49), item 6 was not statistically significant for either dose (1-2 mg/d: LSMD 0.2, 95% CI (-0.03, 0.43), P=0.0907; 2-4.5mg/d: LSMD 0.0, 95% CI (-0.25, 0.21), P=0.8718 – data on file).

4.2.4 Mania symptoms

Manic symptoms, often seen in conditions like bipolar disorder, include an elevated mood that can be euphoric or irritable, increased energy levels, and a decreased need for sleep. Individuals may experience racing thoughts and talkativeness, often speaking rapidly and engaging in multiple activities at once. There can also be an inflated sense of self-esteem and a tendency toward risky behaviors, such as impulsive spending or reckless driving (23,24).

Manic symptoms were measured in the 3 mania studies (43–45) and for safety reasons in the depression studies based on the YMRS total score. In the latter, little change was seen on the YMRS indicating that patients did not switch to mania during the study (71).

Cariprazine reduced manic symptoms in all mania studies (43–45). After pooling the data, all examined doses of cariprazine were statistically significant vs placebo: the LSMD for overall cariprazine versus placebo was −5.35; 95% CI [−6.69, −4.01], P<0.0001; ES 0.54 (66). Moreover, significant improvement in mean change from baseline to week 3 was seen on all 11 individual YMRS symptom items in favor of cariprazine versus placebo (Figure 6) (66) and data on file.

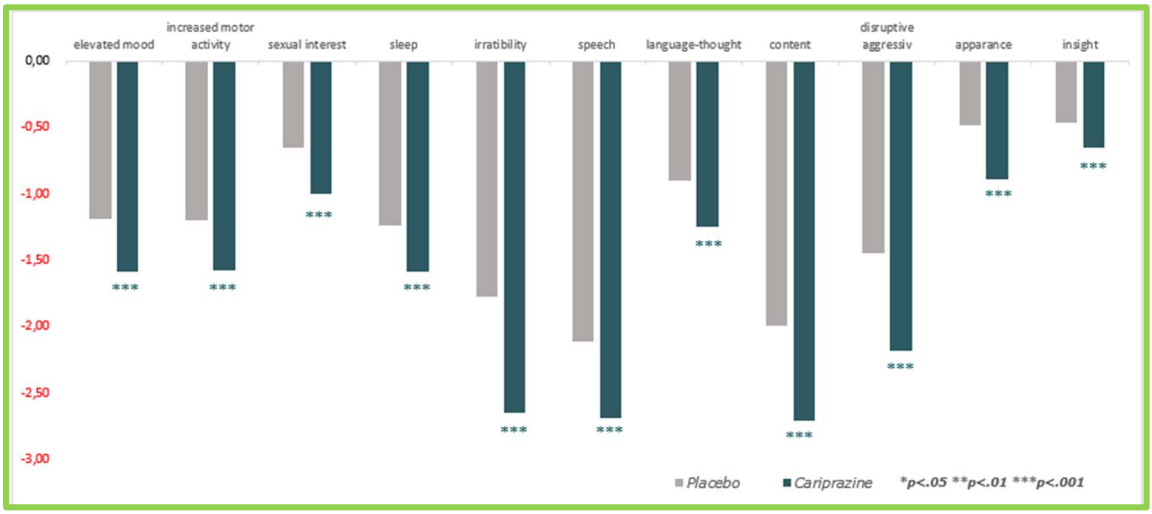

Figure 6. LS mean change from baseline to end on the YMRS single items for cariprazine and placebo (new re-ran pooled analyses, data on file)

4.2.5 Depressive symptoms

Common symptoms of depression include persistent feelings of sadness or emptiness, a loss of interest in activities once enjoyed, and fatigue. Individuals may also experience changes in appetite or sleep patterns, feelings of worthlessness or excessive guilt, and difficulty concentrating. In more severe cases, thoughts of self-harm or suicide may arise. Depressive symptoms can occur in a variety of mental health disorders and medical conditions, among them major depressive disorder and bipolar disorder (23,24).

Efficacy of cariprazine on depressive symptoms was measured in the schizophrenia studies (PANSS depression factor score/item)(38–40), bipolar depression studies (46–48) and MDD add-on studies (49,50) (MADRS total score/items). Additionally, to monitor switching to mania and mix states depressive symptoms were also monitored for safety reasons in the mania studies (MADRS total score/items) (43–45). Overall, cariprazine improved depressive symptoms across populations.

In the pooled schizophrenia studies, significant improvement was observed for cariprazine versus placebo on the anxiety/depression PANSS factor score (ES = 0.21, $P < 0.01$) and on the G6 item of depression ($P<0.5$ – Figure 7) (60).

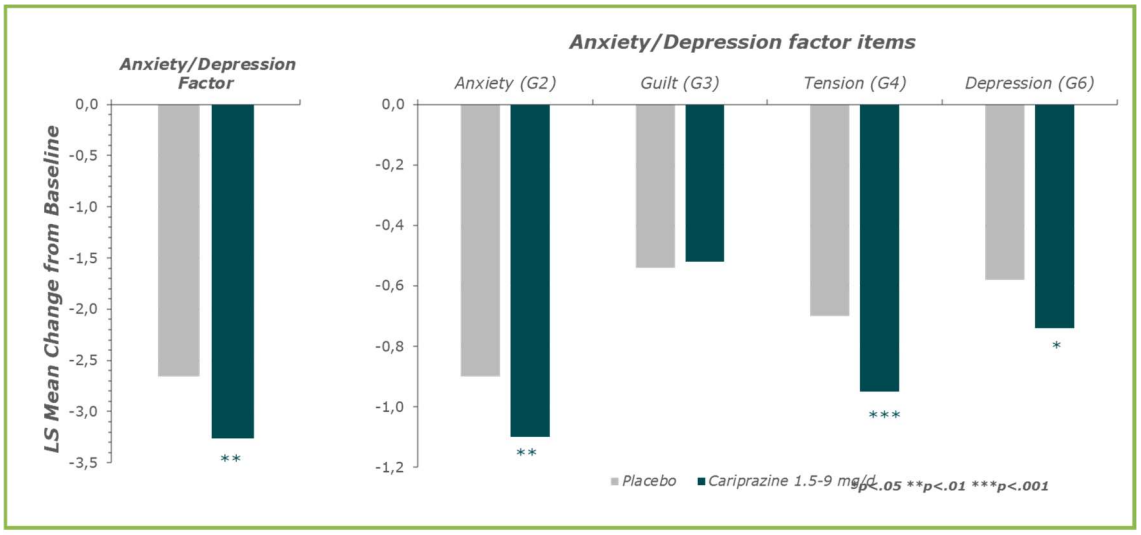

Figure 7. LS mean change from baseline to end on the PANSS-anxiety/depression factor score for pooled cariprazine and placebo – adapted based on the data from (60)**.**

In the bipolar depression studies, improvement in depressive symptoms was shown by statistically significant LSMDs versus placebo on MADRS total scores and all individual MADRS items (67). Cariprazine showed significant results versus placebo on the 1.5 mg/d: LSDM −2.8, 95% CI (-4.1 -1.6), P<0.001; 3 mg/d: LSDM −2.4, 95% CI (-3.7 -1.2), P<0.001 and pooled 1.5-3mg/d dose: LSMD -2.6, 95% CI (-3.7 -1.5), P<0.001 – Figure 8 (67) and data on file.

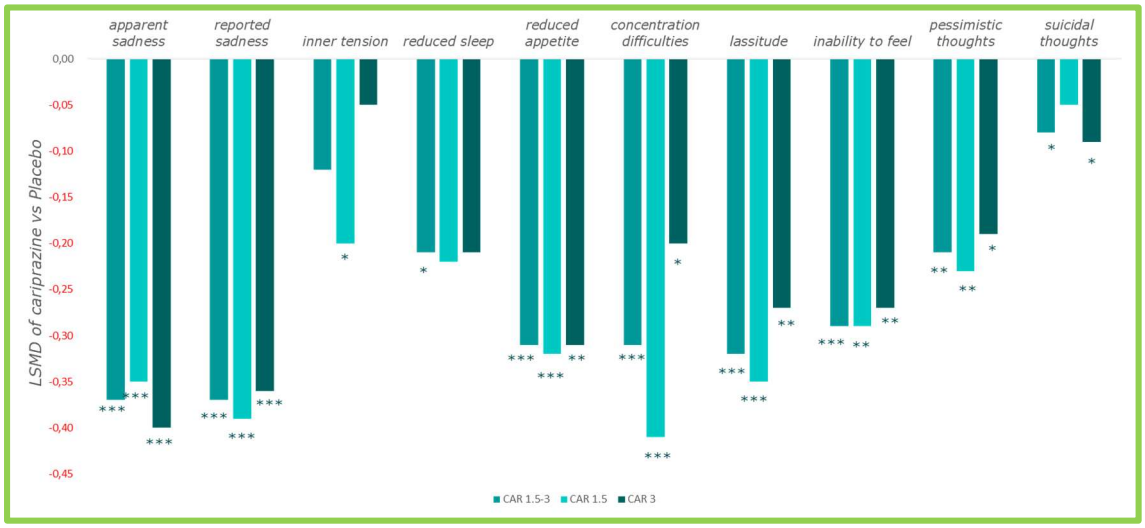

Figure 8. LS mean <u>difference</u> between cariprazine 1.5-3 mg, 1.5 mg and 3 mg vs placebo on the MADRS single item scores (new re-ran pooled analyses, data on file)

In the major depressive disorder add-on studies, adjunctive cariprazine 1.5 mg/day compared with placebo resulted in significantly greater mean reductions in MADRS total score from baseline to week 6 (LSDM:−2.5, 95% CI [−4.2, −0.9], P=0.0025) (50).

Cariprazine 3.0 mg/day vs placebo reached numerically greater reductions in MADRS total scores, however, this difference did not reach statistical significance (LSDM −1.5, 95% CI [−3.2, 0.1], P=0.0691) (50). In study 12 (49), patients taking cariprazine at doses of 2–4.5 mg/day showed significantly greater mean reductions in the MADRS total score compared to placebo by week 2 and at all subsequent visits. By week 8, the LSMD for the cariprazine 2–4.5 mg/day group versus placebo was –2.2, 95% CI (–3.7 –0.6), P = 0.0057. In contrast, the LSMD for the cariprazine 1–2 mg/day group at week 8 was –0.9 (95% CI (–2.4 0.6); P = 0.2404) (49).

4.2.6 Addiction symptoms

Symptoms of addiction include a loss of control over substance use or behavior, intense cravings, and neglect of responsibilities at work or home. Individuals may also withdraw from social activities and relationships, engage in risky behaviors, and develop a tolerance, requiring more of the substance to achieve the same effects. Additionally, withdrawal symptoms can occur when not using the substance, leading to physical and psychological distress (23,24).

Addiction symptoms were not assessed in the cariprazine clinical studies. In fact, known substance use disorder and/or positive urine drugs screens at baseline were exclusionary and were not repeated during the studies, so potential occasional use of illicit drugs was not reassessed.

4.2.7 Sleep symptoms

Symptoms of disturbed include difficulty falling asleep or staying asleep, waking up frequently during the night, and feeling unrested upon waking. Individuals may also experience excessive daytime sleepiness, irritability, and difficulty concentrating. Other symptoms can include unusual breathing patterns during sleep, such as snoring or gasping, and a strong urge to move while trying to sleep (23,24). Several common disorders can lead to disturbed sleep (23,24) among them mania, depression, and anxiety.

Cariprezine’s efficacy on sleep symptoms related to depression and mania were measured with item 4 of both the MADRS and the YMRS scales. In the mania studies (43–45), at week 3, statistically significant differences versus placebo were seen on item 4 (Sleep: LSMD -0,3, 95% CI (-0,5 -0,2), P <0.001 – Figure 6); (66) and data on file.

In the bipolar depression studies (46–48), at week 6, statistically significant differences versus placebo were seen on item 4 (Reduced sleep in the 1.5-3mg group: LSMD -0.2, 95% CI (-0.4 -0.0), P=0.04 – Figure 8); (67) and data on file.

In the MDD add-on study 13 (50), item 4 was not statistically significant (1.5mg/d: LSMD 0.0, 95% CI (-0.27, 0.27), P=0.9946; 3 mg/d: 0.2, 95% CI (-0.03, 0.50), P=0.0837). In study 12 (49), item 4 was also not statistically significant for either dose (1-2 mg/d: LSMD 0.1, 95% CI (-0.13, 0.36), P=0.3386; 2-4.5mg/d: LSMD 0.0, 95% CI (-0.21, 0.29), P=0.7432).

4.2.8 Anxiety symptoms

Anxiety signs include persistent feelings of nervousness, restlessness, or tension, often accompanied by a sense of impending doom. Individuals may experience physical symptoms such as an increased heart rate, rapid breathing, sweating, and trembling. Mental symptoms can include difficulty concentrating, irritability, and overwhelming worry that is hard to control. These symptoms can vary in intensity and may interfere with daily activities (23,24).

For cariprazine, anxiety symptoms were measured in the schizophrenia studies (38–40) using the PANSS and in the depression studies (46–50) with MADRS item 3 (inner tension). Additionally, and more specifically, in the depression studies (47,48,50) anxiety was assessed with the HAMA scale.

In the framework of schizophrenia, statistically significant differences of cariprazine (1.5–9.0 mg/d) versus placebo were seen on the PANSS Anxiety/depression factor (Anxiety (G2), Guilt feelings (G3), Tension (G4), Depression (G6) -- ES = 0.21, P < 0.01) (60). Statistically significant differences of cariprazine versus placebo were seen in the 2 fixed-dose studies (38,40) for 6 mg/d (LSMD −0.9 (−1.5, −0.3), P= 0.0032, ES 0.29) – Figure 7 (60).

In the pooled bipolar depression studies (46–48), at week 6, statistically significant differences versus placebo were seen on item 3 (Inner tension: for the 1.5mg/d: LSMD -0.2, 95% CI (-0.4 -0.0), P=0.03 – Figure 8 (67) and data on file). Moreover, depressive patients who also had higher levels of anxiety and were treated with cariprazine had greater reductions from baseline in HAMA total score than placebo-treated patients:

LSMDs versus placebo in HAM-A total score change at week 6 were statistically significant for cariprazine 1.5 mg/d in the higher anxiety subgroup (P = 0.0105) and cariprazine 3 mg/d in the lower anxiety subgroup (P = 0.0441) (68).

In the MDD add-on study 13 (50), item 3 was not statistically significant (1.5mg/d: LSMD -0.1 95% CI (-0.36, 0.08) P=0.2096; 3 mg/d: LSMD -0.1 95% CI (-0.28, 0.17) P=0.6170). However, depressive patients who also had higher levels of anxiety and were treated with 1.5 mg cariprazine had greater reductions from baseline in HAMA total score than placebo-treated patients, suggesting a potential anxiolytic benefit with cariprazine (LSMD -1.3, 95% CI (-2.47, -0.08), P=0.0370) – data on file.

In study 12 (49), item 3 was not statistically significant for either dose (1-2 mg/d: LSMD 0.0, 95% CI (-0.25, 0.16), P=0.6409; 2-4.5mg/d: LSMD -0.1, 95% CI (-0.33, 0.08), P=0.2267).

4.2.9 Hostility symptoms

Hostility is characterized by a range of symptoms that reflect negative emotions and aggressive behaviors. Individuals exhibiting hostility may display anger, resentment, and unfriendliness, often leading to confrontational interactions. Symptoms can include irritability, impatience, and a tendency to engage in arguments or fights. Hostile individuals may also experience feelings of alienation and mistrust, which can isolate them from others and negatively impact their social functioning. (23,24).

For cariprazine hostility symptoms were measured in the schizophrenia (38–40) and mania studies (43–45). Cariprazine reduced hostility symptoms in both indications.

In the framework of schizophrenia, statistically significant differences of pooled cariprazine (1.5–9.0 mg/d) versus placebo were seen on the PANSS Uncontrolled hostility/excitement factor ES = 0.34, P < 0.0001 (60). Additionally, statistically significant differences of cariprazine versus placebo were seen in the 2 fixed-dose studies (38,40) for all cariprazine doses (1.5 mg/d: LSMD −0.9 (−1.6, −0.2), P=0.0076, ES 0.39; 3 mg/d: LSMD −0.7 (−1.22, −0.2), P=0.0057, ES 0.33; 4.5 mg/d LSMD −0.6 (−1.2, 0.1), P=0.0716, ES 0.31 and the 6 mg/d −1.1 (−1.8, −0.5), P=0.0007, ES 0.36 – Figure 9) (60).

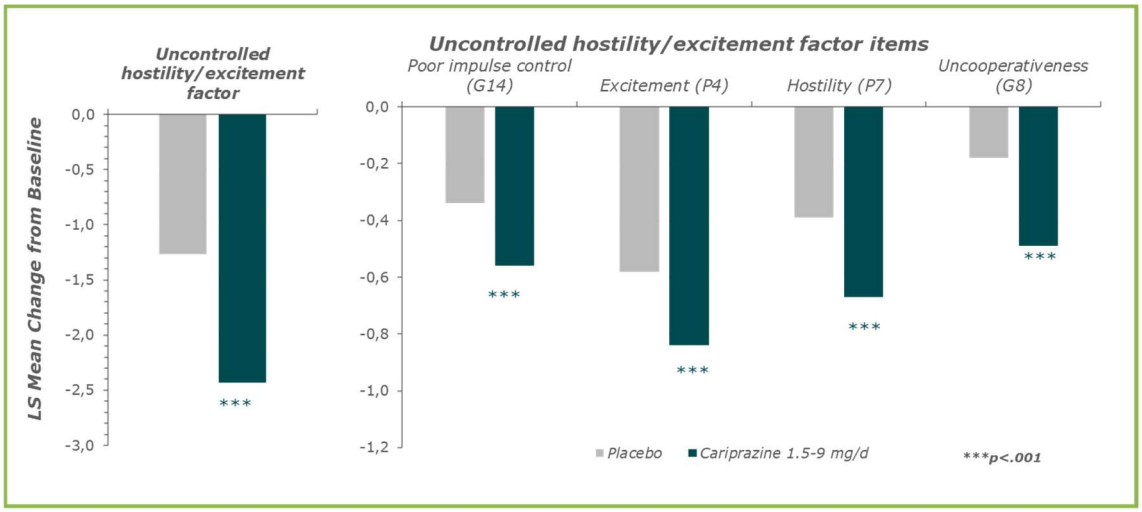

Figure 9. LS mean change from baseline to end on the PANSS uncontrolled hostility/ excitement factor score for pooled cariprazine and placebo - pooled schizophrenia studies, adapted based on the data from (60)

Furthermore, in a sub-analysis in patients exhibiting different levels of baseline hostility, the LSMD in the change from baseline to week 6 on the hostility item (P7) was statistically significant for cariprazine over placebo (LSMD –0.28 95% CI (-0.41 – 0.15); P < 0.0001) (61). Notably, the degree of change for cariprazine was greater among participants with higher baseline hostility, with LSMD values compared to placebo for subgroups of hostility item (P7) ≥ 2, ≥ 3, and ≥ 4 being –0.32, –0.37, and –0.51, respectively (all P < 0.01) (61).

In the framework of mania, based on the YMRS, both hostility items 5 (irritability) and 9 (disruptive-aggressive behaviors) were statistically significant in favor of cariprazine over placebo (Irritability: -0,8, 95% CI [-1,1 -0,6], P<0.001; Disruptive behavior: -0,7, 95% CI [-0,9 -0,5], P<0.001 – Figure 6). In fact, the largest effect sizes for cariprazine were noted on these two items (irritability [0.55] and disruptive–aggressive behavior [0.49] items) (66) and data on file. In a subgroup analysis in patients with baseline score ≥ 2 on both the YMRS irritability and disruptive-aggressive behavior items, LSMD in change from baseline to week 3 was statistically significant in favor of cariprazine versus placebo on both items (Irritability: LSMD –0.93, P<0.001; Disruptive behavior: LSMD -0.79, P<0.001) (65). In the same subgroup, patients were also examined on the change from baseline to end in their PANSS hostility item (P7) scores. Statistically significant results were attained compared to placebo for both cariprazine dosage groups (3–6 mg/d: LSMD –0.70; P < 0.0001; and 6–12 mg/d: LSMD –0.49; P = 0.0002) (65).

4.2.10 Self-harm symptoms

Self-harm, including both non-suicidal self-injury and suicidal self-injury, involves intentionally causing harm to oneself as a way to cope with emotional pain. Suicidal self-injury, in particular, indicates a more severe level of distress and a potential risk for suicide (23,24).

For cariprazine, individuals with suicidal tendencies were not included, which means that the impact of cariprazine on reducing suicidal symptoms could not be assessed. However, the C-SSRS was utilized in all studies to monitor suicidality across conditions such as schizophrenia, mania, bipolar depression, and MDD as a safety measure. This tracking ensured that any potential risks related to suicidality occurring in the course of the study either related to the disorder or due to side effects were carefully observed.

Analysing the data recorded on the C-SSRS in the single studies (39,40,43–50), no patient had suicidal behaviour and most had no suicidal ideations either. A low number of patients showed suicidal ideations, with most wishing to be dead but no plans to actively kill themselves. The most severe ideation recorded was “Active suicidal ideation with some intent to act, without specific plans” – data on file:

In the schizophrenia studies (38–40), ideation was reported in 2-2.6% of patients in Study 3, and 4.8-5.4% of patients in Study 2; no suicidal behavior was reported in either study. Study 1 did not assess the C-SSRS – data on file.

In the mania studies (43–45), ideation was reported in 2-2.5% of patients in Study 7, and 1.2-2.4% of patients in Study 8; no suicidal behavior was reported in either study. Study 6 did not assess the C-SSRS – data on file.

In the bipolar depression studies (46–48), ideation was reported in 3-6.5% of patients in Study 11, 7.9-10.8% of patients in Study 10 and 5.5-10.7% of patients in Study 9; no suicidal behavior was reported in either study – data on file. Additionally, at week 6, statistically significant differences versus placebo were seen on item 10 (suicidal thoughts: in the 1.5-3mg group: LSMD -0.1, 95% CI (-0.1 -0.0), P=0.04 – Figure 8 (67) and data on file.

In the major depression studies, ideation was reported in 7.7-8.1 % of patients in study 12 (49), and 6.7-10.4% of patients in study 13 (50); no suicidal behaviour was reported

in either study. Statistically significant differences versus placebo were seen for cariprazine 1.5 mg on item 10 in study 13 (50) (LSMD -0.1, 95% CI (-0.24, -0.04), P=0.009); but not in study 12 (49).

Based on the above, the conclusion is two-fold: 1. cariprazine did not cause suicidality as a side effect (data based on the C-SSRS), and 2. managed to keep patients stable (item 10). Despite their disorder, which often includes a risk of suicidality, the patients did not deteriorate.

5. Discussion

The objective of this thesis was to review the efficacy of cariprazine as a transdiagnostic drug, meaning across various disorders and across symptoms, including positive, negative, cognitive, manic, depressive, addiction, anxiety, sleep, hostility, and self-harm symptoms, irrespective of the underlying disorders.

Cariprazine has shown therapeutic benefits ***across disorders***, namely in the treatment of schizophrenia, bipolar disorder with both mood episodes (mania and depression), and MDD as add-on treatment. This efficacy as measured in randomized clinical trials and their post hoc analyses are further supported by real world effectiveness studies in schizophrenia (78–82) and bipolar disorder (83,84). Real world evidence studies also support the efficacy of cariprazine in other neuropsychiatric disorders; such as in OCD (85,86), substance use disorder (87–90), emotionally unstable personality disorder (EUPD) (91), autism (92), along with neurological disorders including Huntington's disease (93,94), Parkinson disease related psychosis (95), Wernicke-Korsakoff syndrome (96), Rett syndrome (97), organic brain injury (98,99) and Tourette syndrome (100).

Cariprazine has also shown therapeutic benefits ***across symptoms:*** A comprehensive analysis of cariprazine's efficacy on ten predefined transdiagnostic symptoms revealed statistically significant improvements (compared to placebo or comparator antipsychotics) on positive, negative, cognitive, manic, depressive, anxiety, hostility and sleep symptoms. Cariprazine did not cause suicidality as a side effect and kept patients stable. Addiction symptoms could not be assessed as they were exclusionary at baseline and not tracked during the studies.

This transdiagnostic efficacy (across disorders and symptoms alike) observed with cariprazine may be related to its mechanism of action and receptor binding profile. As presented above, cariprazine has 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. It has only a low affinity for serotonin 5-HT2C and adrenergic α1 receptors (34). In consequence, one would expect strong efficacy on positive and manic symptoms (D2 effect - (101,102)), along with strong effects on negative, cognitive and addiction symptoms (D3 effect (103–109), 5-HT1A (110)), improvement of mood (D3, 5-HT2C (111,112)) and anxiolytic effects based on 5-HT1A (Figure 10).

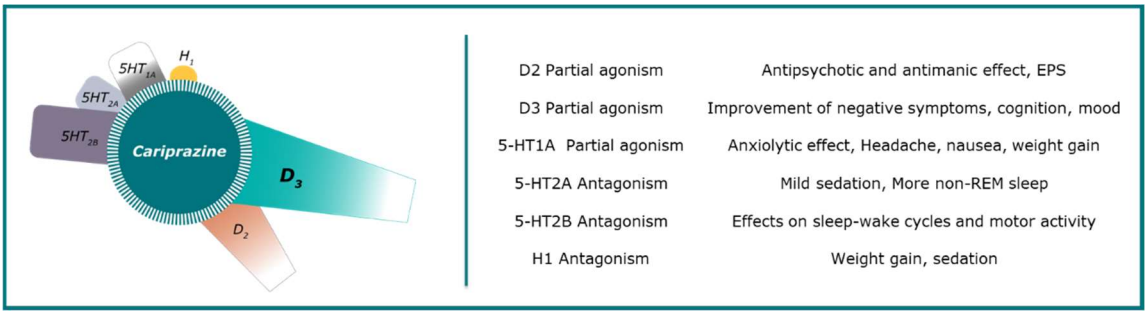

Figure 10. Cariprazine receptor profile and related effects and side effects -- adapted based on the data from (32,34)

Positive, hostility and manic symptoms are primarily associated with a dysregulation in the mesolimbic pathway where a hyperdopaminergic state leads to an overabundance of dopamine, which in turn exacerbates these symptoms. Although the pathology of positive symptoms also involves GABA and glutamate neuron dysfunction, antipsychotics today are mostly targeting D2 receptors (101). Traditionally, the action at D2 receptors was an antagonist one (first- and second-generation antipsychotics) (113), while newer drugs such as cariprazine, aripiprazole and brexpiprazole are dopamine partial agonists (114). This mechanism is particularly significant in the context of schizophrenia, where positive symptoms, such as hallucinations and delusions, are linked to hyperdopaminergic activity, while negative symptoms, including apathy and social withdrawal, are associated with hypodopaminergic functioning. By stabilizing dopamine levels, partial agonists offer a promising therapeutic approach for managing the complex symptomatology of schizophrenia (35).

All antipsychotic medications (first, second and newer generation antipsychotics) address positive symptoms of schizophrenia, hence the name antipsychotic (115). Current guidelines do not differentiate between antipsychotics for addressing positive symptoms. A large meta-analysis comparing the efficacy of oral antipsychotics found that “there are some efficacy differences between antipsychotics, but most of them are gradual rather than discrete” (115). Instead, treatment choices should consider other aspects such as safety, adherence, long-term functioning, as well as formulation, dosing, onset of effect, and half-life.

Cariprazine has proven to control positive, hostility and mania symptoms as well as overall schizophrenia and bipolar mania symptoms in the clinical studies. Real world effectiveness studies further support these findings (78,80,82,116)

Negative, cognitive and addiction symptoms are associated with a dysregulation in the prefrontal cortex, a region crucial for planning, decision-making, and social behavior (16,113). Additionally, dysregulation in the limbic system, which includes structures such as the hippocampus and amygdala also leads to disturbances in emotion and memory along with motivation and reward (16,113). These crucial aspects of human behavior are mediated by the D3 receptor. Dopamine D3 receptors are highly expressed in the ventral tegmental area, a region containing dopaminergic cells that project to limbic areas such as the nucleus accumbens (117). In the ventral tegmental area, somatic dopamine D3 receptors function as autoreceptors. Postsynaptic D3 receptors are found in glutamatergic synapses within the nucleus accumbens, part of the limbic system, and presynaptically on pyramidal cells in cortical layer 5, where they regulate axon initial segment activity (118–122). Cariprazine binds to dopamine (D3/D2) receptors in the substantia nigra, ventral tegmental area, and ventral striatum (part of the limbic system), as shown by positron emission tomography using a dopamine D3-preferring agonist radiotracer 11C-PHNO in chronic schizophrenic patients, with a 3-5-fold selectivity for dopamine D3 receptors (123). It has the highest affinity to the D3 receptors from all known antipsychotics (32,34).

A recent meta-analysis published in the Lancet, evaluated the effectiveness of various antipsychotic medications in treating negative symptoms of schizophrenia (124). The study, which analyzed 21 randomized controlled trials with 3,451 participants, found that amisulpride was effective compared to placebo and cariprazine compared to another antipsychotic for the treatment of primary negative symptoms (124). These were the only two drugs showing effects on predominant negative symptoms (little positive symptoms, high negative symptoms). Olanzapine and quetiapine were also noted to be more effective than risperidone for prominent negative symptoms (more negative than positive symptoms, but positive symptoms may very well be high), though these findings were based on single trials and did not control for secondary negative symptoms.

Cariprazine's efficacy on negative symptoms is also supported by several post-hoc analyses and real-world evidence: First, a study in Latvia investigated the effectiveness and safety of cariprazine in schizophrenia patients with negative symptoms who had not responded well to previous antipsychotic treatments (125). Conducted over 16 weeks with 116 patients, the study found significant improvement in negative symptoms and overall

clinical condition. Specifically, there was a notable reduction in negative symptom scores and over 70% of patients showed minimal to much improvement on the Clinical Global Impression-Improvement (CGI-I) scale. Further, a Slovakian study confirmed these findings. This was a 1-year longitudinal, prospective, multicentric cohort study, aimed to observe the treatment and psychosocial functioning of schizophrenia patients with predominant negative symptoms (126). The study showed significant improvement in negative symptoms and overall functionality with cariprazine as monotherapy but also combination. Most patients received polytherapy, with cariprazine being a common component. The study concluded that with appropriate treatment strategies, improvements in negative symptoms and daily functioning are achievable in schizophrenia outpatients. Additionally, a pilot study with a 6-month follow-up aimed to evaluate the efficacy of cariprazine in treating negative symptoms in patients with early psychosis (127). Conducted over six months, the case-series involved ten patients with prominent negative symptoms. Results showed a significant reduction in negative symptoms, with the mean PANSS negative score decreasing from 26.3 to 10.6. Additionally, there were notable reductions in total and positive PANSS scores also. Finally, an open-label observational study in 60 adult schizophrenia patients with predominantly negative symptoms (PANSS-FSNS ≥15, PANSS-FSPS <19) assessed the effectiveness of cariprazine on negative symptoms as measured by PANSS and other schizophrenia scales (128). Results suggest that cariprazine has an initial effect on negative symptoms as early as 1-2 weeks after treatment onset (128).

Real world evidence studies testing cariprazine on cognitive symptoms are ongoing, data are not yet available. In contrast, a real-world evidence study and various case reports are available to underscore cariprazine's efficacy on addiction symptoms (82,87–90,129). In a study by Szerman et al, authors examined the use of cariprazine for treating dual disorders, specifically comorbid substance use disorder (SUD) and schizophrenia (87). Cariprazine treatment led to significant improvements in schizophrenia symptoms, with a change of −47.88 points on the PANSS ($P < 0.0001$) and −8.26 points on the CGI-SCH Scale ($P<0.0001$). Additionally, cannabis use and dependence decreased, as evidenced by a −7.0 point change on the Cannabis Abuse Screening Test ($P < 0.0001$) and a −7.88 point change on the Severity of Dependence Scale ($P < 0.0001$). These findings suggest that cariprazine is effective for both schizophrenia and cannabis use disorder (CUD), although further research is needed to confirm these results (87). This is further supported by case

reports describing cariprazine's efficacy in reducing the craving and substance use in patients consuming methamphetamine, cocaine, cannabis, alcohol and tobacco (82,87–90,129). In consequence, current guidelines suggest cariprazine and other partial agonists as first line treatment in maintenance settings and as second line in acute settings of substance use disorder comorbidities (130–132). They emphasize, that cariprazine might have distinct benefits due to its high D3 activity.

The molecular basis of depression, anxiety, and suicidality involves complex interactions among various neurotransmitters and receptors (16). There are some overlapping mechanisms, that are involved in all three conditions. Serotonin receptors, particularly 5-HT1A and 5-HT2A, play a crucial role (112). Targeting these receptors with Selective Serotonin Reuptake Inhibitors (SSRIs) is a well-known treatment in depression and anxiety (113). Additionally, norepinephrine and its receptors (α1, α2, and β-adrenergic receptors) are involved in the stress response and mood regulation, contributing to depression and anxiety (16). These are targeted by Serotonin-Norepinephrine Reuptake Inhibitors (SNRI) that affect both serotonin and norepinephrine levels and may help with depression, anxiety and suicidality (113). Finally, dopamine and its receptors, especially D2 and D3, are implicated in the reward system and motivation, which are often disrupted in depression (133) and may also play a role in suicidality (134). GABAA receptors are critical for inhibitory neurotransmission, and their dysfunction can lead to increased anxiety (16). Benzodiazepines enhance GABAA receptor activity to produce a calming effect. Additionally, beta-blockers targeting β-adrenergic receptors reduce physical symptoms of anxiety (113). In suicidality, next to serotonin and dopamine pathways the most important player is the Hypothalamic-Pituitary-Adrenal Axis (134). Abnormalities in this stress response system are often found in individuals with suicidal behavior (134). Commonly used treatment strategies to manage underlying depression and anxiety, which can reduce suicidal thoughts are with SSRI and SNRI (113). Ketamine an NMDA receptor antagonist has also shown rapid antidepressant and anti-suicidal effects (135).

Cariprazine's antidepressant effects are primarily attributed to its partial agonism of dopamine D3, D2, and serotonin 5-HT1A receptors, as well as its antagonist activity at serotonin 5-HT2B and 5-HT2A receptors (16). At low doses, cariprazine provides anxiolytic effects by primarily targeting D3 receptors and maintaining balanced dopaminergic activity (68). However, at higher doses, anxiety becomes a more common

side effect (136). In fact, anxiety is frequently reported with higher doses of cariprazine, along with other side effects such as akathisia (a state of restlessness) and increased motor activity, which can further contribute to anxiety (136). The anti-suicidal effects of cariprazine are not well understood. Results of the above clinical studies suggest that cariprazine does not induce suicidality, but systematic examinations in this vulnerable suicidal populations are lacking. There is a case report of a suicidal adolescent patient who benefited from cariprazine, leading authors to suggest its potential usefulness in such cases (137).

Sleep is regulated by the interactions of homeostatic and circadian factors. Sleep disturbances are commonly associated with various mental disorders. Conditions such as anxiety disorders often lead to insomnia or restless sleep due to heightened worry and tension. Depressive disorders frequently result in changes to sleep patterns, including insomnia or hypersomnia, where individuals may sleep excessively yet still feel fatigued. Bipolar disorder can cause significant fluctuations in sleep, with manic episodes often leading to reduced need for sleep and depressive episodes resulting in increased sleep. Additionally, PTSD is linked to nightmares and difficulty falling asleep due to intrusive memories. ADHD can also contribute to sleep problems, as individuals may struggle with restlessness and difficulty winding down at night (23,24). Interestingly, while sleep issues can stem from the disorders themselves, they can also arise as side effects of antipsychotic treatments (15). Many antipsychotics can alter sleep patterns, leading to sedation or disrupted sleep cycles. This dual role of sleep disturbances highlights the complex interplay between mental health and treatment, emphasizing the need for careful management to ensure that both the symptoms of the disorder and the effects of medication are addressed effectively.

The molecular background of sleep involves a complex interplay of various neurotransmitters and receptors that regulate sleep-wake cycles. GABA is the primary inhibitory neurotransmitter in the brain, crucial for promoting sleep. GABA receptors, particularly GABA A receptors play a significant role in inducing sleep by reducing neuronal excitability (16). Orexin (Hypocretin) is a neuropeptide that promotes wakefulness and inhibits REM sleep, its receptors (OX1R and OX2R) are targets for certain sleep medications (138). Further, adenosine builds up in the brain during wakefulness and promotes sleep by inhibiting cholinergic wake-promoting neurons in the

basal forebrain via A1 receptors (139). Finally, melatonin, a hormone that regulates the sleep-wake cycle, serves as a target for sleep medications through its receptors (MT1 and MT2) . Based on these findings, sleep medications today, such as benzodiazepines and non-benzo sleep medications act by primarily targeting GABA receptors: Benzodiazepines primarily act on GABAA receptors. They bind to the GABAA receptors containing α1, α2, α3, and α5 subunits and while the α1-containing GABAA receptor is linked to sedative effects, the α2 and α3 are associated with anxiolytic effects (16). Binding enhances internal GABA's effect by increasing the frequency of chloride channel openings, leading to hyperpolarization and reduced neuronal excitability (140). Non-benzodiazepine sleep medications, often referred to as "Z-drugs" (e.g., zolpidem, zaleplon, eszopiclone), also target the GABAA receptors but are more selective for the α1 subunit, which is primarily responsible for their sedative effects (141).

Cariprazine has no meaningful affinity to any of these receptors, nevertheless it is described to be sedative in a therapeutic sense (for mania and depression where sleep is disturbed) but may also cause insomnia in patients (136). It is rather an activating drug than a sedative one, which might also underline its good efficacy in addressing negative symptoms specially amotivation (136). Its dual potential to cause insomnia or sedation is primarily attributed to its partial agonist activity at dopamine D2 and D3 receptors, combined with individual patient variability: In some patients, cariprazine’s partial agonist activity at D2 and D3 receptors can lead to increased dopaminergic activity, which may result in heightened alertness and difficulty in sleeping. Additionally, variations in individual sensitivity to dopamine receptor stimulation can also lead to insomnia in some patients. Conversely, in other patients, the partial agonist activity can lead to a net inhibitory effect on dopaminergic pathways, particularly if their baseline dopaminergic activity is high. This can result in sedation. Genetic differences in dopamine receptor expression and function can also influence how a patient responds to cariprazine, contributing to either insomnia or sedation.

In summary, cariprazine monotherapy has proven to be an effective treatment in patients suffering from schizophrenia, bipolar disorder (both mood periods) and MDD (combined with antidepressants). Secondly, 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.

The present work is of course not without limitations. These include the descriptive and post-hoc nature of results, as symptoms were not assessed by a transdiagnostic scale (such as the TGI scale) and followed prospectively but were rather measured on other scales and summarized for the purposes of this thesis. Further prospective, studies are needed to validate cariprazine's efficacy on the TGI at baseline and subsequent visits to be able to verify it as a transdiagnostic drug. Disorders of special interest should include patients with suicidality, anxiety disorder, substance use disorder and different sleep disorders, because these were less evaluated for cariprazine so far.

6. 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.

7. Summary

Introduction: Current diagnostic systems such as the DSM-5 and the ICD-11 are challenged in psychiatry due to their arbitrary nature. New trends are moving towards transdiagnostic approaches, as underlying genetic factors, and neurotransmitter systems are shared by most neuro-psychiatric disorders. A new tool emerged lately to assess transdiagnostic symptoms, called the TGI which measures 10 transdiagnostic symptoms (positive, negative, cognitive, manic, depressive, addiction, anxiety, sleep, hostility and self-harm symptoms) independent of underlying disorders.

Objective: The objective of this study was to examine cariprazine' s efficacy as a transdiagnostic drug across psychiatric disorders and the transdiagnostic symptoms.

Methods: A systematic literature review and post-hoc analyses of randomized clinical trials that form the basis of approval in the US and EU were performed. Primary efficacy endpoints such as PANSS, MADRS, YMRS along with additional endpoints such as the HAMA and C-SSRS were used to evaluate the efficacy of cariprazine in schizophrenia, bipolar mania, bipolar depression, major depressive disorder and on the 10 transdiagnostic symptoms.

Results: Cariprazine proved to be effective in schizophrenia, bipolar mania, bipolar depression and major depression as add-on treatment to antidepressants. Additionally, cariprazine has shown therapeutic benefits on positive, negative, cognitive, manic, depressive, anxiety, addiction, sleep and hostility symptoms throughout disorders. No increased suicidality was reported under cariprazine.

Conclusion: 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.

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10. Acknowledgements

I would like to thank my mentor Dr György Németh for his continued support, great ideas and thought inducing feedbacks. Additionally, I am thankful to be able to work at Gedeon Richter with cariprazine and I am thankful to my line-managers (Balázs Szatmári, Thomas Brevig) and my team (Zsófia Dombi, Réka Csehi, Darko Djuric) for their continued support.