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DOPAMINERGIC DYSFUNCTION IN NEUROPSYCHIATRIC DISORDERS AND THE EFFECT OF CARIPRAZINE IN THEIR TREATMENT

PhD thesis

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List of Abbreviations

ACE = Addenbrooke's Cognitive Examination

AD = Alzheimer's disease

ADHD = attention-deficit hyperactivity disorder

BDI = Beck Depression Inventory

BL = baseline

CAG = cytosine-adenine-guanine

CAR = cariprazine

CNS = central nervous system

DA = dopamine

DSM = Diagnostic and Statistical Manual of Mental Disorders

ECG = electrocardiography

EPS = extrapyramidal symptoms

FDA = Food and Drug Administration

HD = Huntington's disease

HTT = huntingtin

ICD = International Classification of Diseases

LS = least square

MADRS = Montgomery-Åsberg Depression Rating Scale

MDD = major depressive disorder

mHTT = mutant huntingtin

MMRM = mixed model for repeated measures

MSN = medium spiny neuron

NAc = nucleus accumbens

OCD = obsessive-compulsive disorder

PD = Parkinson's disease

PET = Positron Emission Tomography

PFC = prefrontal cortex

SCH = schizophrenia

SGA = second-generation antipsychotic

SUD = substance use disorder

TFC = Total Functional Capacity

TMS = Total Motor Score

UHDRS = Unified Huntington’s Disease Rating Scale

VTA = ventral tegmental area

W = week

1 Introduction

Traditionally, nosological systems provide the basis for psychiatric practice and research. The main taxonomies include the Diagnostic and Statistical Manual of Mental Disorders (DSM, currently in the 5th edition) (1) and the International Classification of Diseases (ICD, currently in the 11th edition) (2), which were created to enable the conceptualisation, interpretation, assessment, research and the management of mental disorders (3). Despite their unequivocal benefits, they treat mental disorders and symptoms as separate entities and as all-or-none phenomena (3,4). Yet, evidence suggests that neuropsychiatric disorders and symptoms cannot simply be categorised as being either present or absent, they should rather be conceptualised along a continuum, ranging from 'being absent' to 'presenting with severe psychopathology' (3,5,6). Therefore, the current taxonomies do not accurately capture the intricate human experiences that manifest as mental disorders (7).

Indeed, one apparent epidemiological finding is that the rate of comorbidity (i.e., the individual meets the criteria for more than one diagnosis is met based on the presenting problems and symptoms) is considerably higher in psychiatric patients than it would be expected by chance - it is the rule rather than the exception (6,8,9).

Furthermore, the diagnostic criteria contain numerous symptoms, and diagnosis is made if the patient presents with just a subset of these symptoms (3). Such an approach allows different individuals to receive the same diagnosis despite having different symptoms - even no common symptoms at all (3) - and also having varying severity. This results in a substantial heterogeneity within diagnoses where thousands of different symptom profiles and severity levels can qualify for the same diagnosis (3,10). This further suggests that mental disorders have an underlying dimensionality and the complex constellation of clinical manifestations cannot be reduced to simple categorical diagnosis, as important information will be lost (11).

All these findings suggest the overlapping aetiology (common bio-psycho-social factors) and pathophysiology of disorders which have indeed been demonstrated by studies. It is important to note, however, that the biological and phenotypic overlap is not limited to psychiatric disorders only. Neurological and psychiatric disorders have shared symptomatology and pathophysiology, and their comorbidity is common (12). Motor symptoms primarily characterising neurological disorders often appear in psychiatric disorders, while it is common for neurological patients to experience psychiatric symptoms, especially affective and cognitive symptoms (13). These observations provide the basis for considering neuropsychiatry as a field in itself (14,15).

In summary, genetics - along with the environmental factors - have an immense impact on the development of neuropsychiatric disorders, both in polygenic (i.e. caused by a number of genes; like most psychiatric disorders) and monogenic (i.e. caused by a single genetic mutation; like Huntington's disease) disorders (16). In both subtypes, genes can alter the brain expression, which then causes the dysregulation of brain circuits (16). The consequently emerging symptom domains include cognitive impairment, positive and negative symptoms, affective disturbance or reward dysregulation - all of which can appear in various neuropsychiatric disorders, like schizophrenia, bipolar disorder, substance use disorder (SUD), major depressive disorder (MDD), Huntington's disease (HD) or Parkinson's disease (PD) (16).

1.1 Dopamine

One of these dysregulated circuits in neuropsychiatric disorders includes the dopaminergic system. Dopamine (DA) is a neurotransmitter that regulates numerous functions, like cognition, reward, feelings of pleasure or movement, among others (17,18). Having normal levels of DA is essential for optimal functioning - both high and low DA levels are associated with a variety of psychiatric and neurological symptoms (18).

1.1.1 Dopamine pathways

The dopaminergic system has four main pathways with differing functions and roles. The mesolimbic pathway stems from the ventral tegmental area (VTA) and innervates the striatum/nucleus accumbens (NAc) (19,20). It is involved in the regulation of the limbic system, which is involved in reward processing and therefore pleasure, but also in salience and threat evaluation (21). The dysfunction of this pathway has been associated with mental illness, especially psychotic disorders and SUD, where hyperactivation is observed (22). In psychosis, the salience part of the pathway is overstimulated, while drugs of abuse target the reward processing part, inducing feelings of pleasure and euphoria. Chronic substance use can also disrupt the salience part, resulting in drug-induced psychosis. However, although the mesolimbic theory has become the central dogma for psychosis, it is important to note that more updated views suggest that psychosis is rather associated with the dysfunction of the nigrostriatal pathway, more precisely, the associative striatum (23,24).

The mesocortical pathway connects the VTA and the prefrontal cortex (PFC) and the dysfunction of this pathway is implicated in many psychiatric disorders (19,20). As opposed to

the hyperactive mesolimbic pathway, this pathway is hypoactive, leading to the reduced stimulation of the PFC. Since the PFC is heavily involved in cognitive functioning, personality expression, moderating social behaviours, but also in motivation (25), this reduced stimulation leads to the emergence of affective and cognitive symptoms, as well as negative symptoms, like asociality, alogia (i.e. reduced speech), affective blunting (i.e. reduced facial expressions), anhedonia (lack of pleasure in previously enjoyed activities) or avolition (loss of motivation and ability to follow through with plans) (26).

The nigrostriatal pathway originates from the substantia nigra and connects to the caudate and putamen (18). It is essential in motor functioning, therefore disruptions to this pathway can severely impair motor control (18,27). Antipsychotics often interfere with this pathway, causing extrapyramidal symptoms (EPS), like akathisia, motor restlessness, tremors, parkinsonism or dyskinesia (28). Actually, more recent views suggest that there is a fifth pathway, in which the nigrostriatal pathway is divided into two, one innervating the associative striatum and the other the sensorimotor striatum (23,24). The latter is associated with the above mentioned motor functions, while the former is associated with salience stimuli assignment, and therefore, the emergence of psychotic symptoms (23,24).

The tuberoinfundibular pathway connects the hypothalamus and the brain stem. DA plays an inhibitory role in this pathway, inhibiting the release of prolactin, which is involved in lactation, metabolism, sexual functioning, and the immune system (29). The blockade of D2 receptors counters DA's inhibitory effect, inducing hyperprolactinemia, as seen with many antipsychotics (30). Increased prolactin levels disrupt the menstrual cycle, lowers libido, reduces fertility, and negatively affects bone health.

1.1.2 Dopamine receptors

Regarding DA receptors, there are five subtypes, categorised into two groups. The D1-like family contains the D1 and D5, while the D2-like family includes the D2, D3 and D4 receptor subtypes (18). Dopamine has a 10- to 100-fold greater affinity to the D2-like receptors than to the D1-like receptors (18). In the pathophysiology of neuropsychiatric disorders, the dopamine D1, D2 and D3 receptors are the most heavily involved among the five receptor subtypes. The D1 and D2 receptors are the most abundant in the central nervous system (31). Regarding receptor localisations, the D1 receptors are mostly expressed in the striatum (caudate, putamen, but also the nucleus accumbens) and the substantia nigra; D2 receptors are also abundant in the striatum (mostly the dorsal striatum) and the substantia nigra; while D3 receptors are mostly populated in the nucleus accumbens, the olfactory tubercle, and the islands of Calleja, but also

in the hippocampus (31).

1.2 The role of dopamine in neuropsychiatric disorders

Therefore, it is apparent that dopaminergic dysfunction is a well-established common underlying mechanism contributing to the development of various disorders, as it regulates many functions, and it is associated with many symptoms that are present in both predominantly psychiatric, and predominantly neurological disorders (32). Furthermore, such a circuit can be a promising target for therapeutic inventions - this would offer symptom-alleviation in most domains and could be utilised in various disorders (33). Therefore, this thesis will focus on the dopamine-related dysfunctions in neuropsychiatric disorders.

1.2.1 Schizophrenia

The dopaminergic system has received considerable attention in the research of the pathophysiology and the treatment of schizophrenia, and its dysfunction has long been established (34). According to the original view (mesolimbic hypothesis) (35), psychotic symptoms, that are the major characteristics of schizophrenia, emerge due to a hyperdopaminergic state in the mesolimbic pathway, while the other two main symptoms domains, negative and cognitive symptoms, are the result of hypodopaminergia in the mesocortical pathway. The mesolimbic hypothesis became the central dogma of schizophrenia due to the lack of robust evidence to refute it (36). Once neuroimaging methods advanced and it became possible to measure limbic dopamine function *in vivo*, findings revealed that the dysfunction of the dopaminergic system is the most prominent in the nigrostriatal, instead of the mesolimbic pathway (36,37). Therefore, the updated view suggests that the nigrostriatal pathway can actually be divided into two: the associative striatum, which is responsible for the psychotic symptoms, and the sensorimotor striatum that is associated with motor dysfunction (23,24). Indeed, studies have suggested that in psychosis, the associative striatum is one of the main regions where increased dopaminergic function is observed (38–40). In contrast to psychosis, the emergence of negative, cognitive and depressive symptoms has been linked to hypodopaminergic state in the mesocortical pathway (23,24). In summary, evidence points to the critical role of dopamine in the pathophysiology of schizophrenia, with a hyperdopaminergic state in the striatum, and a hypodopaminergic state in other areas (24). Among the dopamine receptors, the D2 and D3 are involved to the largest extent, with D2 having a crucial role in psychotic symptoms, and the D3 likely contributing to negative,

cognitive and depressive symptoms (41).

1.2.2 Bipolar disorders

Just like in schizophrenia, the dopaminergic system plays a central role in the development of both depressive and manic/hypomanic episodes associated with bipolar disorder – however, the exact mechanism of dysfunction is unclear. Nonetheless, it is believed that hyperdopaminergia in the ventral striatum is responsible for the emergence of manic/hypomanic symptoms, as evidenced by heightened D2 and D3 receptor availability and the hyper-responsivity of the reward system in the ventral striatum (42). In turn, reduced dopamine neurotransmission (as indicated by elevated striatal dopamine transporter availability) induces depressive episodes (42). It is hypothesised that the affective switches are produced by an excessive compensatory mechanism where these dysfunctional mechanisms precipitate each other (42). As the D2/D3 receptors levels increase and lead to dysfunctional reward processing (mania), a compensatory mechanism kicks off, whereby dopamine transporter levels increase to reduce neurotransmission. This normalises D2/D3 receptors levels, however, the compensatory increase in dopamine transporter levels do not normalise, precipitating a depressive switch. In turn, the compensatory process excessively upregulates the D2/D3 receptor levels, inducing a manic switch. As in the case of schizophrenia, among the dopamine receptors, D2 receptors are likely involved in mania, while the D3 receptors have an important role in cognition and depression (42).

1.2.3 Major depressive disorder

Traditionally, abnormalities in the serotonin and norepinephrine circuits were considered to be the cause of depressive symptoms (43,44). However, studies utilising neuroimaging, pharmacological, and electrophysiological techniques in both human subjects and animal models of depression have offered supporting evidence for the involvement of the DA system as well (43,45).

In particular, the involvement of the mesolimbic DA system has been suggested. These specific regions of the brain are responsible for processing the rewarding response to various pleasurable experiences, including activities like eating, engaging in sexual behaviour, and drug use. Studies have shown that both cardinal features of MDD, depression and anhedonia (i.e., diminished experience of pleasure) (1), have been associated with reduced striatal response to reward, implicating the disruption of the mesolimbic system in MDD.

Furthermore, Positron Emission Tomography (PET) studies suggest that MDD patients with anhedonia have lower DA transporter binding than healthy controls, which is suggestive of a downregulation due to low DA concentration (43,46,47).

1.2.4 Addiction

All substances of abuse elevate dopamine levels, either indirectly via blocking the inhibitory GABA control of dopamine (e.g. nicotine, alcohol, opiate) or directly by blocking dopamine reuptake (e.g. cocaine, amphetamine) (48,49). Dopamine is released from the VTA into the NAc (i.e. in the mesolimbic pathway), producing feelings of pleasure and reward (49). Dopamine is released as a response to neutral reinforcers as well, like food or sex, however, drugs of abuse increase dopamine levels more drastically in the brain's reward centre, thus creating a more efficient and intense effect than natural reinforcers do (49). However, repeated drug-administration and therefore increased dopamine levels result in the downregulation of receptors to counter the elevated neurotransmission (50). Receptors further become desensitised to neutral, weaker stimuli, this way facilitating further drug-seeking behaviour and drug consumption (49).

1.2.5 Parkinson's disease

The progressive loss of dopaminergic neurons located in the substantia nigra pars compacta in the midbrain is the pathological hallmark of PD, resulting in lowered DA neurotransmission (51,52). The nigrostriatal DA pathway connecting the substantia nigra pars compacta and the dorsal striatum are therefore the most heavily impacted in the disorder (52). The disturbance of this pathway contributes to the emergence of various motor symptoms, like bradykinesia, rigidity, tremor or postural control impairment (51).

1.3 Huntington's disease

One neuropsychiatric disorder in which dopamine plays a crucial role is Huntington's disease, which is a rare, inherited, autosomal dominant, progressive neurodegenerative disease (53). It develops due to a mutation in the huntingtin (HTT) gene on chromosome 4, which causes abnormally expanded trinucleotide (CAG) repeats (54). The number of repeats predicts disease development and progression. Individuals having 27-35 repeats are not considered to be at risk of developing symptoms, while those with 36-39 repeats have an increased risk - however, the unstable CAG repeats carry the risk of passing the disease onto future generations (55). Those

with at least 40 repeats are undoubtedly affected by the disease and will develop the associated symptoms, and those with at least 60 repeats will have juvenile onset HD before the age of 20, while the usual age of onset is around the ages of 40 to 50 (56). The number of repeats is inversely correlated with the age of onset, severity of the symptoms, and disease progression.

1.3.1 Symptoms

The most conspicuous clinical features of HD are motor symptoms, with chorea and dystonia being the most commonly appearing motor phenotype in patients (57). However, the emergence of bradykinesia, rigidity and oculomotor symptoms is also common along with problems of hand movement, gait, and balance (58). Since the symptoms that affect most patients are chorea and dystonia, HD is generally considered to be a predominantly hyperkinetic movement disorder (57), with chorea appearing in the earlier stages, and dystonia dominating the later stages (53).

Even though motor problems are the most noticeable signs of HD, patients present with other symptoms as well, like cognitive impairment (especially executive dysfunction) or neuropsychiatric manifestations, including depression, apathy (i.e. loss of motivation), anxiety, irritability or behavioural disinhibition (57). These non-motor symptoms often precede motor symptoms by years or even decades and they are associated with impaired patient functioning and overall worse quality of life not only for the patients, but their families and caregivers as well (57).

1.3.2 Neuropathology

Regarding the neuropathology of HD, the most prominently affected brain areas include the striatum and the cerebral cortex (53). Laminar thinning and the atrophy of the white matter is observed in the cerebral cortex (59), while the striatum undergoes atrophy due to the massive loss of medium-spiny neurons (60,61) which comprise 90-95% of striatal neurons (53,62).

Although the clinical manifestations of HD are attributed to neuronal loss in the striatum and the cortex, evidence suggests that neuronal dysfunction - and associated symptoms - often precede neuronal death (53,61,63).

1.3.3 The role of dopamine in HD

The idea of dopamine being involved in the pathophysiology of HD came from a predictive test in which one third of asymptomatic off-springs of HD patients developed dyskinesia - including chorea - following levodopa administration (64). Later, neurochemical studies have

shown that increased dopamine levels characterise the early stages of the disease (65), while post-mortem studies suggested that in later stages, dopamine levels are reduced (66,67). Such a biphasic alteration in dopamine levels could account for the observed motor symptoms across the course of HD - hyperkinetic symptoms are characteristic of the earlier, and hypokinetic symptoms are characteristic of the later stages (53,68,69).

Regarding motor movements, two striatal projection pathways - the direct and the indirect - are differentiated (70). The direct (excitatory or "go") pathway is associated with the initiation and the control of motor movement and consists of medium spiny neurons (MSNs) that express D1 receptors (53). In contrast, the MSNs of the indirect (inhibitory or "no-go") pathway express D2 receptors and this pathway is responsible for the suppression of motor movements (53). Studies suggest a preferential degeneration of MSNs in the indirect pathway early in the disease-course - the loss of these inhibitory neurons counters movement inhibition, and therefore produces hyperkinetic movements, mainly chorea (71). Nevertheless, more recent studies suggest the involvement of overactive MSNs in the direct pathway, which further contributes to the development of chorea (72–74).

Regarding DA receptors, post-mortem studies have found progressive D1 and D2 receptor loss in the striatum of HD patients (75–79), while imaging studies confirmed these findings in not only HD patients (80,81), but in asymptomatic HD mutation carriers as well (82,83).

Striatal and cortical loss of DA receptors and neurons has not only been linked to motor impairment, but to the emergence of non-motor symptoms as well, like cognitive decline and other psychiatric symptoms. The bidirectionally interconnected cortico-striatal circuitries play a crucial role in cognitive functioning and DA's modulation of these circuits allow it to regulate cognition (84). Abnormal levels of DA - both increased and decreased - especially in the PFC impair cognitive performance (85,86).

1.3.4 Treatment of HD

Regarding the treatment of HD, currently, there are no disease-modifying or causative therapies available, constituting a clear unmet need. Nonetheless, numerous treatment approaches have been designed to lessen mutant huntingtin (mHTT) concentrations in the central nervous system (87). Until a causal treatment is invented, the management of the disease lies on symptom alleviation.

The successful treatment of HD requires a multidisciplinary approach, meaning that both pharmacological and non-pharmacological therapies need to be offered to patients, starting from the early, even presymptomatic stages (57).

For the alleviation of motor symptoms, the only approved medications include tetrabenazine (TBZ) and deutetrabenazine (deuTBZ) which are indicated for the treatment of chorea, specifically. TBZ is a reverse inhibitor of the vesicular monoamine transporter 2, whose efficacy was demonstrated in a 12-week randomised controlled trial (TETRA-HD) (88). TBZ significantly outperformed placebo in the reduction of chorea, although no functional improvement was observed. The most common safety events included sleep disturbances (somnolence and insomnia), depressed mood, akathisia and parkinsonism. DeuTBZ is the deuterated form of TBZ, having a longer half-life and presumably a better tolerability profile than TBZ (89). To test this hypothesis, the FIRST-HD study showed greater reductions in chorea in the deuTBZ, than in the placebo arm, while the rate of emerging adverse events (depression, anxiety, akathisia) were comparable between the two groups (90). Although no head-to-head comparison of TBZ and deuTBZ is available, the two agents have similar efficacy in managing chorea, while the safety profile of deuTBZ is perceived to be more favourable, producing less neuropsychiatric symptoms and safety issues, like depression, somnolence, akathisia or parkinsonism (91,92). In addition to TBZ and deuTBZ, dopamine-blocking compounds are frequently used in clinical practice for chorea (87).

Despite the fact that the behavioural and cognitive symptoms often emerge earlier and cause greater functional impairment than motor symptoms, evidence for their treatment is scarce (87). The management of behavioural symptoms is largely based on expert consensus. Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors are often prescribed for depression and anxiety, and SSRIs could further reduce irritability (87). However, if irritability is more severe, sedating antidepressants, antipsychotics or mood stabilisers could be effective options (87). Regarding cognitive symptoms, acetylcholinesterase inhibitors for HD did not show a clear advantage and some compounds are being tested in randomised controlled trials (RCTs), like SAGE-718 (NMDA receptor modulator; NCT05107128) (87). Apathy remains to be a difficult symptom to treat - if present with depression, it is worth trying an antidepressant medication (87,93). Furthermore, although antipsychotics have shown promise in the management of chorea and other motor disturbances, they have failed to demonstrate adequate tolerability and effectiveness in the non-motor symptoms of HD (88,91,94). In fact, some medications potentially even worsen the non-motor symptoms, therefore it is important to find a medication that addresses all symptom domains.

Regarding antipsychotic treatment, they have rather shown some promise in the management of chorea and other motor symptoms, and to a lesser extent in non-motor symptoms (95). Aripiprazole showed similar efficacy as TBZ in improving chorea (96) and a case report

suggested a slight improvement in depressive symptoms (97). Haloperidol further improved chorea (98) and reduced mHTT aggregate formation in a rat model of HD (99), while clozapine is only efficacious in potentially higher doses (100), although results are mixed (101). Risperidone improved psychiatric symptoms and stabilised motor symptoms, which deteriorated in the placebo group (102). Olanzapine was shown to reduce chorea and improve some psychiatric symptoms, like depression, anxiety or irritability (103–105). Pridopidine, a dopamine stabilising drug, outperformed placebo on the UHDRS-modified Motor Score, while significant improvements on the Total Motor Score (TMS) were only observed with higher doses, although side-effects emerged (53).

1.4 Cariprazine

As established above, it is apparent that the dysregulation of the dopaminergic system contributes to the development of various disorders. In order to effectively target the associated symptoms, achieving differential effects on the different DA receptor subtypes is essential which can be accomplished with an appropriate pharmacological compound.

Cariprazine is a third-generation antipsychotic that exerts partial agonist activity at the DA D2/D3 receptors (106). It is approved for the treatment of schizophrenia in adults by the European Medicines Agency (107) and the Food and Drug Administration (FDA) (108). Cariprazine has further FDA-approval for the treatment of depressive and manic/mixed episodes associated with bipolar I disorder in adults (108), as well as for the treatment of MDD as adjunctive therapy to an antidepressant treatment (109).

1.4.1 Clinical development programme

The efficacy of cariprazine in schizophrenia was demonstrated by three short-term (6 weeks) acute studies (110–112) and one long-term (46-92 weeks) relapse-prevention study (113) compared to placebo. Furthermore, cariprazine showed efficacy in improving persistent, predominant negative symptoms compared to an active comparator, risperidone (114). The long-term safety and tolerability was further established in two 48-week open-label trials (115,116). Based on the findings, cariprazine was approved between the doses of 1.5 to 6.0 mg/day in schizophrenia.

In bipolar disorder, cariprazine achieved significant symptom-reductions in both depressive and manic/mixed episodes. The efficacy of cariprazine in bipolar depression was demonstrated by three positive studies. In an 8-week clinical trial, 1.5 mg/day cariprazine statistically

significantly outperformed placebo (117). The same dose group further outperformed placebo in a 6-week trial (118). The third bipolar depression trial demonstrated the superiority of both the 1.5 and 3.0 mg/day doses (119). Therefore, the doses of 1.5 and 3.0 mg/day were approved in bipolar depression.

In bipolar mania, three short-term (3 weeks) studies confirmed the efficacy of cariprazine. In all three studies, cariprazine 3.0-12.0 mg/day proved to be statistically significantly more effective in reducing manic/mixed symptoms than placebo (120–122). These results provided the basis for the approval of cariprazine between the doses of 3.0-12.0 mg/day in manic/mixed episodes. Furthermore, the safety and tolerability of cariprazine in bipolar mania/mixed episodes was established in a 16-week open-label study (123).

Lastly, cariprazine is approved by the FDA as an adjunctive therapy to an antidepressant treatment in MDD. The approval was supported by two positive clinical trials. In an 8-week trial, the add-on cariprazine 2.0-4.5 mg/day dose group (with an average dose of 2.6 mg/day) showed statistically significant separation from placebo (124). In a 6-week trial, add-on cariprazine 1.5 mg/day demonstrated superiority over placebo (125). Therefore, cariprazine is indicated for the adjunctive treatment of MDD in the doses of 1.5 and 3.0 mg/day.

1.4.2 Mechanism of action, receptor profile and pharmacodynamic properties

Dopamine, as a natural neurotransmitter, is present in high concentrations in different brain areas, but its affinity to the five DA receptor subtypes varies, having the highest affinity to D3 receptors (126). Consequently, due to dopamine's receptor-binding profile, it has been a challenge to create medication that has the ability to achieve the D3-receptor associated effects *in vivo*. A compound needs to have three characteristics in order to be able to achieve the desirable effects associated with the D3 receptors in the presence of dopamine *in vivo*: 1) having high affinity to D3 receptors, 2) showing preference towards D3 receptors, and 3) being able to achieve high concentrations in the brain (127).

Cariprazine satisfies all these criteria: it has the highest D3 affinity and its D3-selectivity is 6-8 times greater than that of other antipsychotics (106), making it the only approved antipsychotic that can occupy the D3 receptors in the presence of dopamine and achieve the D3-associated effects *in vivo* (128), as demonstrated by PET studies. These studies have explored the D2 and D3 receptor occupancy of cariprazine *in vivo* using [11C]-(+)-PHNO, a PET ligand (127,129). On day 15, cariprazine 12.0 mg/day produced a near 100% D2 and D3 receptor occupancy. For the lowest dose (1.0 mg/day), D3 and D2 occupancies were 75% and 45%, respectively, while the 3.0 mg/day group showed a 92% occupancy at the D3, and a 79%

occupancy at the D2 receptors (129). On the other hand, although showing some degree of D3 receptor occupancy *in vitro*, other antipsychotic drugs have failed to occupy the D3 receptors *in vivo* as demonstrated by their lack of effectiveness in inhibiting the PET ligand from binding to the D3 receptors (127,130–132).

With regards to its receptor profile (106), cariprazine binds to the D2 and D3 receptors with high affinity, while its D1, D4, and D5 receptor-affinity is negligible. Among serotonin receptors, cariprazine has a high affinity to 5-HT1A and 5-HT2B, and a weaker affinity to 5-HT2A and 5-HT2C receptors (106). Furthermore, cariprazine has a medium affinity to histamine H1, and a low affinity to alpha1-adrenergic receptors (106). Regarding intrinsic activity, cariprazine acts as a partial agonist at D2, D3 and 5-HT1A receptors, and as an antagonist at the rest of the mentioned receptors (106).

1.4.3 Pharmacokinetics

Cariprazine is metabolised by the CYP3A4 enzyme and to a lesser extent, the CYP2D6 (133). It has two pharmacologically active metabolites: desmethyl-cariprazine (DCAR) and didesmethyl-cariprazine (DDCAR) (133), both of which have a similar receptor profile as cariprazine. 90% of steady state is achieved within 1 week for CAR and DCAR, within 4 weeks for DDCAR, and within 3 weeks for Total CAR (i.e., CAR + DCAR + DDCAR) (134). The effective half-life is around 2 days for CAR and DCAR, while it is much longer, around 8 days, for DDCAR (134) and around 1 week for Total CAR. It takes around 3-4 weeks for the majority of CAR and its metabolites to be eliminated from the body (127,134). The long half-life means that even if the patients miss a dose, the chance of relapse or symptom-worsening is lower. However, this also means that side-effects may take more time to subside compared to a drug with shorter half-life.

2 Aims and Objectives

2.1 The effectiveness of cariprazine in Huntington's Disease (135,136)

The aim of this study was to determine whether cariprazine has the potential to improve symptoms of HD, especially the non-motor symptoms.

As outlined above, the current treatments of HD are symptom-based, with agents showing fairly good efficacy in the control of motor symptoms. Still, the non-motor symptoms, i.e. mood, behavioural and cognitive symptoms are not adequately addressed by current medications. Since these symptoms affect patient functioning and quality of life more adversely and detrimentally than motor symptoms, finding appropriate treatment options is of utmost importance. Moreover, compounds addressing all symptom domains are the most desired. Given these issues, cariprazine was trialled in this patient population to uncover whether it could effectively alleviate the non-motor, but also the motor symptoms associated with HD.

2.2 Systematic review of cariprazine case reports (137)

The objective of this systematic review was to gather and synthesise the available information from the separate case reports in which cariprazine was administered for patients, and to draw conclusions on the safety and effectiveness of cariprazine in real-world settings.

The efficacy and safety of cariprazine have been demonstrated in many clinical trials in various indications. However, it is important to investigate a compounds' real-life effectiveness and safety, in populations that are not controlled, but are highly heterogeneous. Many case reports have been published in the last years, providing important information on the safety and effectiveness of cariprazine. Hence, all available cariprazine case reports were systematically collected and reviewed.

3 Methods

3.1 The effectiveness of cariprazine in Huntington's Disease

3.1.1 Patients

Patients with an abnormal expansion of CAG (>36) in the HTT gene were included in the study. Clinical diagnosis was a motor diagnosis, using the Unified Huntington's Disease Rating Scale (UHDRS) diagnostic confidence level item, ranging from 0 (normal, no abnormalities) to 4 (motor abnormalities that are unequivocal signs of HD, > 99% confidence) (58).

The stage of the disease was determined using the Total Functional Capacity (TFC) of the UHDRS (Stage I: TFC scores 11-13 least severe; Stage II: scores 7-10; Stage III: scores 3-6; Stage IV: scores 1-2; and Stage V: score of 0, most severe) (138).

3.1.2 Study design

This was a 12-week, single-centre, open-label, single-arm, retrospective real-world study, evaluating the efficacy of cariprazine on cognitive, mood/behavioural and motor symptoms in HD. The use of cariprazine was indicated if patients presented with impairments in mood (e.g., depression, apathy) and cognition (e.g., executive and planning dysfunction, cognitive decline). The starting dose of cariprazine was 1.5 mg/day which was up-titrated to 3.0 mg/day if it was deemed necessary by the treating physician. The use of co-medications (e.g., TBZ, benzodiazepine, antidepressant, antipsychotic) was allowed, however, during the observational period, only procyclidine was initiated as a new medication.

3.1.3 Efficacy evaluations

All efficacy parameters were evaluated at three time points: baseline (BL), Week 8 (W8) and Week 12 (W12), and they examined motor, mood/behaviour and cognitive symptoms.

3.1.3.1 Mood and behavioural symptoms

Mood and behaviour were evaluated using two instruments: the Beck Depression Inventory (BDI) (139) and the Behavioural Examination of the UHDRS.

The BDI is a 21-item self-report measure in which the patient has to rate each statement from 0 to 3, where higher scores indicate more severe depression.

The UHDRS was developed by the Huntington Study Group in 1996, updated in 1999, while its Cognitive and Behavioural Sections were clarified in 2005.

The Behavioural Examination section has 11 items with each item being assessed separately based on frequency and severity from 0 to 4, with higher scores indicating greater frequency or severity, respectively. The evaluation is made based on the clinician's observations and the patient's and informant's report.

3.1.3.2 Cognition

Cognitive functions were evaluated with the Cognitive Examination of the UHDRS which consists of the three measures: the Verbal Fluency Task, the Symbol Digit Modalities Test and the computerised Stroop Interference Test (colour naming, word reading and interference). In addition, the Addenbrooke's Cognitive Examination (ACE) was performed, assessing five cognitive domains: attention, memory, fluency, language, and visuospatial abilities.

3.1.3.3 Motor symptoms

Motor symptoms were evaluated using the 15-item Motor Examination of the UHDRS, scored from 0 (normal) to 4 (severe). The TMS was calculated indicating the severity of motor symptoms. Furthermore, sub-analyses were conducted for 7 motor domains: chorea, dystonia, eye movements, hand movements, rigidity/bradykinesia, gait/balance and oropharyngeal symptoms.

3.1.4 Safety evaluations

Similarly to the efficacy parameters, safety assessments were conducted at BL, W8 and W12, consisting of routine laboratory testing, vital signs, body weight, neurological examination, electrocardiography (ECG), motor function assessment and adverse events.

3.1.5 Statistical analysis

Efficacy parameters were analysed using mixed model for repeated measures, with the terms of visit, baseline parameter values and their interaction, assuming unstructured covariance structure and using Kenward-Roger's approximation of the degrees of freedom. Least square (LS) mean changes were calculated and compared between visits. Because of the exploratory nature of the study, and since the changes might be correlated between the efficacy parameters, no adjustment for the possible increase of the type I error rate were applied, and differences were considered significant when $p<0.05$.

Improvements from baseline to Week 12 were calculated for mood/behavioural, cognitive, and motor measures. In addition, single items of the Motor Examination of the UHDRS were

grouped and improvements were calculated and expressed in percentages, comparing baseline to Week 8 and to Week 12.

3.1.6 Ethical approval and off-label use

The off-label use of cariprazine was granted by the Hungarian National Institute of Pharmacy and Nutrition for all participants. Ethical approval of the study was issued by the Regional, Institutional Scientific and Research Ethics Committee. The study was conducted in accordance with the Declaration of Helsinki and all participants provided written informed consent.

3.2 Systematic review of cariprazine case reports

3.2.1 Search Strategy

This systematic review was conducted in line with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement. Literature search was performed in two databases, Medline and Embase, aiming to identify English-language articles published between 2000 January and 2021 September. The search words included (cariprazin* OR "rgh-188" OR rgh188 OR vraylar OR reagila) AND ("case report*" OR "case report"/de OR "case stud*" OR "case study"/de OR "case seri*"). In addition, the bibliography of published case reports and review papers were checked, with the intention of discovering further relevant cases, this way complementing the findings of the database-search.

3.2.2 Inclusion and Exclusion Criteria

First, the title and abstract of the article were screened for eligibility by separate authors, followed by a joint discussion and agreement on whether to include the article in the systematic review. Articles were considered for inclusion if they satisfied all the following criteria: 1) case report, involving human subject(s), 2) the subject received cariprazine treatment, 3) sufficient information is available on cariprazine treatment, e.g., dosing and titration strategy, timeline, sufficient detail about the outcome, 4) written in English language. Articles were excluded if they did not satisfy these criteria, or if they were Congress abstracts (due to the lack of detail).

3.2.3 Data Analysis

Necessary information was retrieved from all articles, and then presented in tables in figures. It included gender; age; diagnosis; cariprazine starting dose; maintenance dose; titration

strategy; problem for which cariprazine was prescribed (not all problems that the patient experienced were listed, only the ones for which the author/doctor decided to prescribe cariprazine), concomitant medications, outcome attributed to cariprazine treatment by the authors/doctors. Descriptive analyses were performed on the following data: gender, age, diagnosis, starting dose, maintenance dose.

4 Results

4.1 The effectiveness of cariprazine in Huntington's Disease

4.1.1 Patients

Demographics data is summarised in Table 1. Sixteen patients were included in the study, however, the data of only 15 patients were analysed, as one patient had to be excluded due to non-compliance (P4, whose data is also excluded from the Tables and Figures).

The cohort comprised of 4 males and 11 females with a mean age of 48.13 (SD=10.6) years and a mean disease duration of 3.57 (SD=2.91) years. The CAG repeat expansion was 46 (SD=3.28) on average. One patient was pre-symptomatic, eight patients were in Stage I, five in Stage II and one in Stage III.

CAR was started at the dose of 1.5 mg/day in all patients, and this dose remained the maintenance dose in the majority of cases (n=13). Only one patient was up-titrated to 3.0 mg/day and another to 4.5 mg/day. Ten patients received a stable dose of TBZ during the treatment period.

Table 1. Patient demographics

Participant	Sex	Age	Disease duration	TFC	Stage	CAR dose (mg/d)	Concomitant medication dose (mg)
P1	M	42	4	10	I	1.5	TBZ 2x25
P2	F	48	1	10	I	1.5	TBZ 3x25
P3	F	51	4	10	I	1.5	TBZ 3x7.5 Paroxetin 1x20
P5	F	50	6	12	I	3	Glimepirid 1x4
P6	F	36	6	10	I	1.5	TBZ 4x25 Tiapridal 1x100

P7	F	40	0.5	15	P	4.5	-
P8	F	53	1	5	II	1.5	TBZ 2x12.5 Clonazepam 3x0.5 Chlorprothixen 3x12.5
P9	M	74	8	6	II	1.5	TBZ 3x25 Alprazolam 1x0.25
P10	F	43	1	6	II	1.5	Tiapridal 3.100 Escitalopram 1x5
P11	M	55	10	1	III	1.5	TBZ 4x25 Sertraline 1x50
P12	F	42	1	10	I	1.5	TBZ 3x12.5 Procyclidine 2x5
P13	F	66	4	8	II	1.5	TBZ 3x7.5 Paroxetin 1x20
P14	F	43	4	5	II	1.5	TBZ 3x50 Sertraline 1x50
P15	M	42	2	12	I	1.5	Tiapridal 3x100
P16	F	37	1	12	I	1.5	-
TFC=Total Functional Capacity; CAR=cariprazine; p=patient; M=male; F=female; TBZ=tetrabenazine							

4.1.2 Efficacy outcomes

4.1.2.1 Mood and behavioural symptoms

According to the Behavioural Examination of the UHDRS, at baseline, the most severe symptoms included irritable behaviour, anxiety, depressed mood, low self-esteem/guilt,

disruptive/aggressive behaviour, and apathy (Figure 1). By Week 12, the overall Behavioural Score showed statistically significant reduction compared to baseline (BL: 54.9 vs W12: 32.5, LS mean change -22.5, $p<0.0001$) (Figure 2). For individual baseline scores and changes from baseline to Week 8 and to Week 12 on the Behavioural Examination of the UHDRS, refer to Table 2.

The BDI measure also revealed statistically significant improvements in mood and apathy. The mean overall score was 17.7 at baseline which decreased to 10.0 by Week 12 (LS mean change: -7.7, $p<0.0097$) (Figure 3). For individual baseline scores and changes from baseline to Week 8 and to Week 12 on the BDI, refer to Table 2.

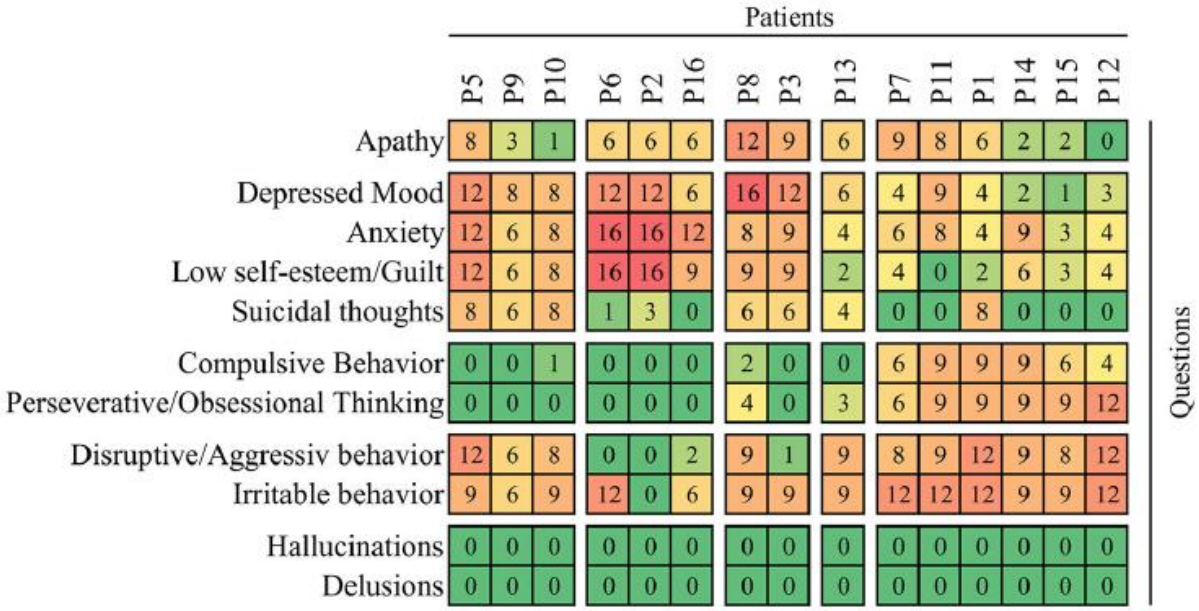


Figure 1. Individual profiles of behavioural impairment at BL

Individual profiles of behavioural impairment at baseline of observation before administration of cariprazine. The frequency x severity scores are shown on the heatmap with the maximum 16 points calculated as a product of 4 (which means very frequently, most all the time on a 0–4 scale) and 4 (severe, causing a restriction of activities). The rows (questions/items) and columns (patients) are clustered on the basis of average correlation and separated in blocks according to first-order branches of dendrograms.

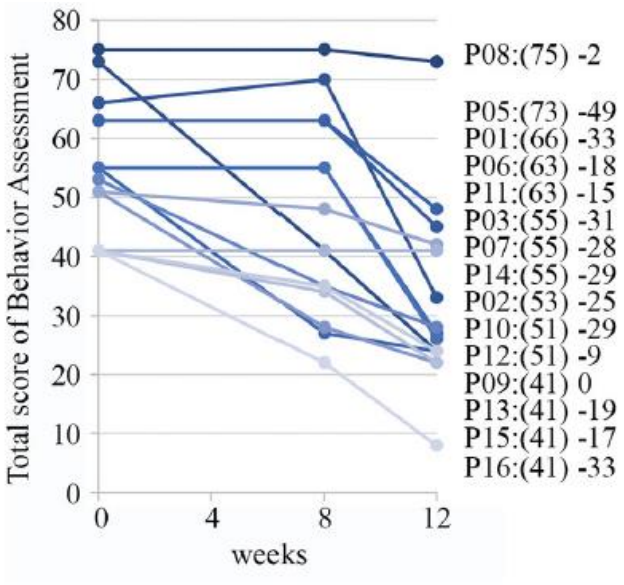


Figure 2. Individual changes in scores on the Behavioural Examination of the UHDRS

Individual patient profiles are shown with captions including baseline sum of frequency x severity scores in brackets and difference between baseline and assessed scores at week 12.

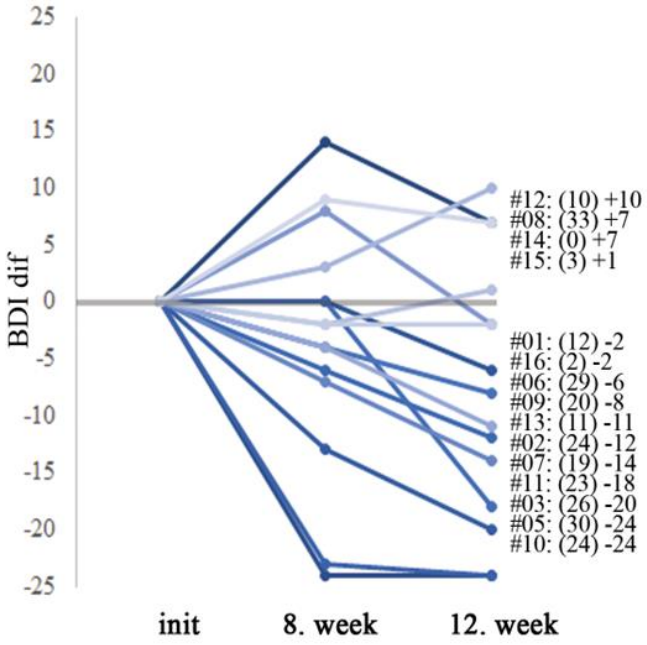


Figure 3. Individual changes in scores on the BDI

Line plot shows the difference between BL and Week 8 and between BL and Week 12 in individual scores, measured by the BDI (0–63). On the right hand side, patients are listed in order, from largest (bottom) to lowest (top) improvement. BL scores are shown in brackets, followed by the difference between BL and Week 12.

4.1.2.2 Cognition

Significant improvements were detected in cognitive functioning as measured by the ACE. The mean overall score was 75.1 at baseline, which then increased to 86.7 by Week 12 (LS mean change 11.5, p<0.0001) (Figure 4).

The Cognitive Examination of the UHDRS consisted of 3 sections. However, based on patients' performance on the computerised Stroop Interference Task at baseline, this measure was decided to be excluded from the analysis, as it proved to be highly challenging for patients to complete due to their cognitive and motor impairments. On both of the remaining two sections, patients showed statistically significant improvements: the Cognitive Verbal Fluency score increased from 6.2 (baseline) to 7.7 by Week 12 (LS mean change: +1.5, p=0.0103), while the Symbol Digit Test further detected improvement, as the score increased from 9.2 (baseline) to 12.3 by Week 12 (LS mean change: +3.1, p=0.0009) (Table 2).

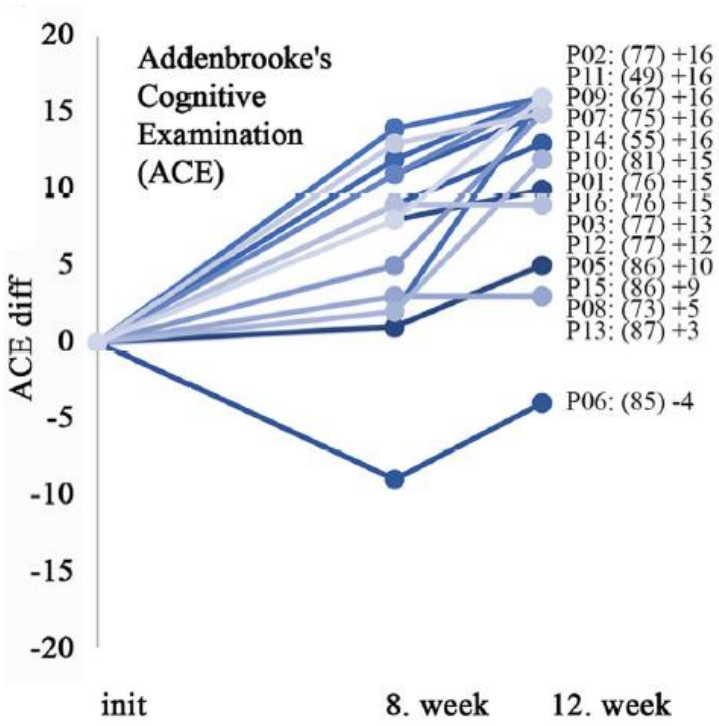


Figure 4. Individual changes in scores on the ACE

Line plot shows the difference between BL and Week 8 and between BL and Week 12 in individual scores, measured by the ACE (0–100). On the right hand side, patients are listed in order, from lowest (bottom) to largest (top) improvement. BL scores are shown in brackets, followed by the difference between BL and Week 12.

Table 2. Changes during the observation period in cognitive and behavioural symptoms

Individual's BL scores on the different measures are shown in bold, followed by the change from baseline to Week 8 (denoted in the W8 column) and from BL to Week 12 (denoted in the W12 column). Scores, and in case of Symbol Digit Test and Verbal Fluency, the correct answers within the specified time, are indicated.

	ACE			**Symbol Digit Test**			**Verbal Fluency**			**BDI**			**Behavioral Assessment**		
	BL	W8	W12	BL	W8	W12	BL	W8	W12	BL	W8	W12	BL	W8	W12
P1	**76**	5	15	**20**	0	1	**6**	1	2	**12**	8	-2	**66**	4	-33
P2	**77**	12	16	**6**	0	3	**5**	1	3	**24**	-6	-12	**53**	-18	-25
P3	**77**	9	13	**6**	4	4	**7**	2	1	**26**	-13	-20	**55**	-28	-31
P5	**86**	8	10	**18**	5	9	**10**	2	4	**30**	-24	-24	**73**	-32	-49
P6	**85**	-9	-4	**8**	0	0	**8**	-2	-1	**29**	0	-6	**63**	0	-18
P7	**75**	11	16	**8**	0	2	**8**	0	1	**19**	-7	-14	**55**	0	-28
P8	**73**	1	5	**8**	0	-2	**8**	0	-3	**33**	14	7	**75**	0	-2
P9	**67**	14	16	**3**	0	2	**2**	1	3	**20**	-4	-8	**41**	0	0
P10	**81**	11	15	**4**	3	4	**6**	3	4	**24**	-23	-24	**51**	-23	-29
P11	**49**	2	16	**0**	0	1	**2**	0	1	**23**	0	-18	**63**	0	-15
P12	**77**	2	12	**6**	0	3	**7**	-1	1	**10**	3	10	**51**	-3	-9
P13	**87**	3	3	**20**	5	10	**6**	1	1	**11**	-4	-11	**41**	-7	-19
P14	**55**	8	16	**0**	0	2	**2**	0	2	**0**	9	7	**55**	0	-29
P15	**86**	9	9	**15**	2	2	**9**	2	0	**3**	-2	1	**41**	-6	-17
P16	**76**	13	15	**16**	4	6	**7**	2	3	**2**	-2	-2	**41**	-19	-33

ACE=Addenbrooke's Cognitive Examination; BDI=Beck Depression Inventory; BL=baseline; W8=Week 8; W12=Week 12; P=patient

4.1.2.3 Motor symptoms

Motor symptom improvements were measured by the Motor Examination of the UHDRS. The mean TMS indicated statistically significant improvements not only at Week 12, but at Week 8 as well. The mean TMS was 36.8 at baseline, which decreased to 27.4 by Week 8, signifying a 26% improvement (LS mean change: -9.4, $p<0.0001$). The mean TMS at Week 12 further

reduced to 24.0, marking an additional 12% improvement (LS mean change: -12.8, p<0.0001) (Figure 5).

Significant improvement was observed in maximal chorea: compared to baseline, patients showed a 35% score reduction by Week 8 and a 52% reduction by Week 12. Similarly, the alleviation of dystonia was observed in patients, as indicated by the 58% improvement by Week 8 and a 85% improvement by Week 12 compared to baseline.

Eye movements showed a 35% improvement by Week 8 and a 47% improvement by Week 12 compared to BL.

Alleviation of motor symptoms affecting hand movements was further observed: 11% improvement at Week 8 and 19% at Week 12.

Patients' gait and balance improved by 22% at Week 8, and even though the improvement fell back to 16% by Week 12, it can still be considered significant.

Rigidity and bradykinesia first started to improve, achieving a 22% improvement by Week 8, but then it showed a slight worsening by Week 12.

Oropharyngeal symptoms improved 18% by Week 8 and 24% by Week 12.

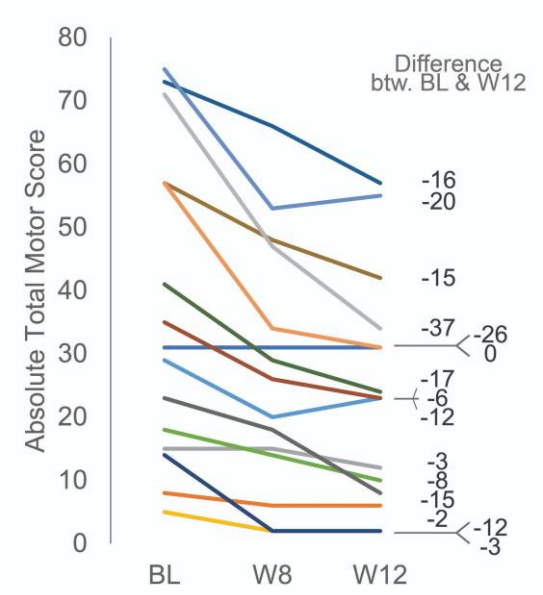


Figure 5. Individual changes in TMS scores, as measured by the Motor Examination of the UHDRS

4.1.3 Safety outcomes

The routine laboratory tests showed that all measures remained within the normal range throughout the treatment period. Only a slight glucose-level elevation was observed in 3

patients (6.3-7.1 mmol/l) at baseline, however, it remained stable. Vital signs, neurological examination and the ECG did not show any significant alterations that could be attributable to cariprazine treatment. Regarding adverse events, mild akathisia emerged in two patients (Patients 3 and 5), while another patient (Patient 12) experienced mild akathisia in addition to slight weight loss.

4.2 Systematic review of cariprazine case reports

4.2.1 Search Results

Altogether 65 articles were retrieved by the search: the Medline and Embase database-searches retrieved 60 articles, while an additional 5 articles were found via hand search. Next, duplicate findings were eliminated, after which 49 publications remained. Then, further articles (n=13) were excluded based on their titles and abstracts. The remaining 36 papers were read in full to assess their eligibility for inclusion in this systematic review, yielding the further exclusion of 14 articles. Reasons for elimination included that the text was a congress abstract (n=7), CAR treatment was not adequately described (n=4), the publication was not a case report (n=2) and that it was not an English-language paper (n=1). Finally, 22 publications describing 38 cases qualified to be included in this systematic review (PRISMA flowchart shown in Figure 6).

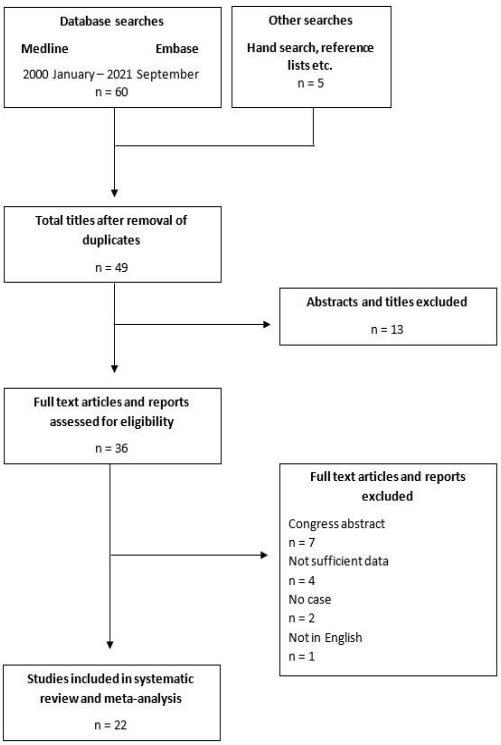


Figure 6. PRISMA chart

4.2.2 Overview of results/ demographics

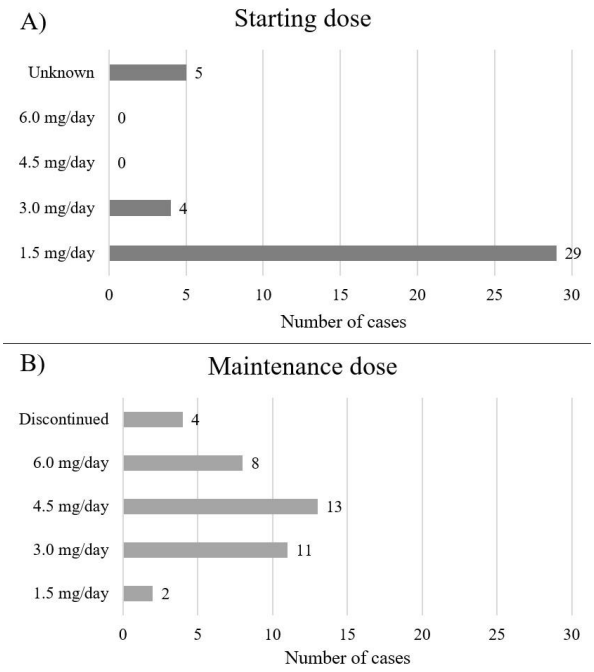
For a summary of demographics, refer to Table 3. Out of the 38 cases, 18 were male and 19 were female, while one was not specified and they had a mean age of 33.8 years (median=31). In terms of diagnosis, the majority of patients had schizophrenia (n=27, 71.1%), followed by other psychotic disorders (n=6, 15.8%), other disorders (n=3, 7.9%), and mood disorders (n=2, 5.3%).

Cariprazine was most commonly started at the dose of 1.5 mg/day (n=29, 76.3%), but there were instances where it was initiated at 3.0 mg/day (n=4, 10.5%), while it was not specified in some cases (n=5, 13.5%) (Figure 7A). For maintenance dose, 4.5 mg/day was most commonly chosen (n=13, 34.2%), followed by 3.0 mg/day (n=11, 28.9%), 6.0 mg/day (n=8, 21.1%) and 1.5 mg/day (n=2, 5.3%), while cariprazine was suspended in 4 cases (10.5%) (Figure 7B).

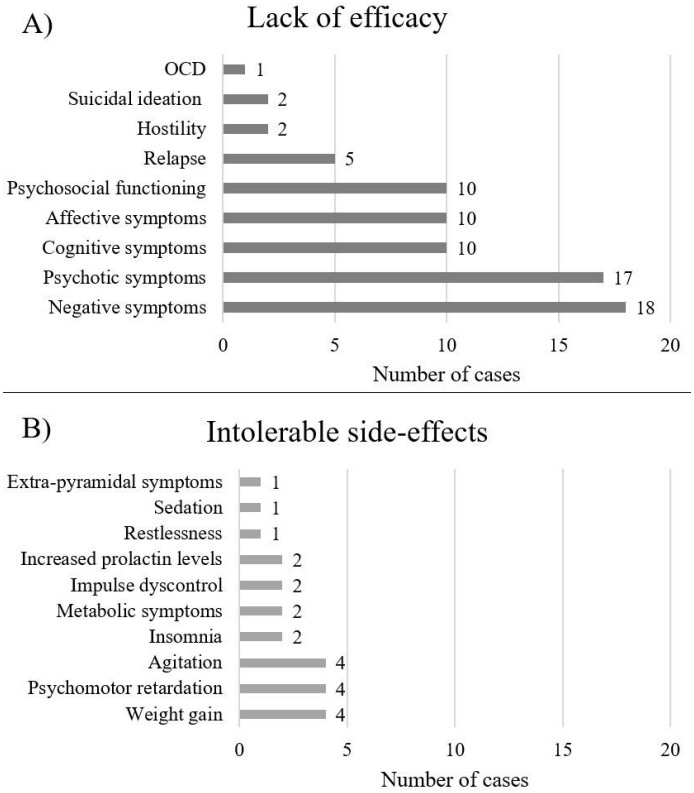
Cariprazine treatment was indicated and initiated for various efficacy- and safety-related concerns of previous treatments. Regarding efficacy issues, CAR was most commonly prescribed for negative symptoms (n=18, 47.4%) and psychotic symptoms (n=17, 44.7%), followed by cognitive (n=10, 26.3%) and affective symptoms (n=10, 26.3%), problems in psychosocial functioning (n=10, 26.3%) and relapse (n=5, 13.2%) (Figure 8A). Concerning tolerability problems of previous treatments, CAR initiation was primarily decided on due to weight gain, psychomotor retardation and agitation (all n=4, 10.5%) (Figure 8B). A detailed overview is given of each case in Table 4. Table 5 summarises the efficacy and safety outcomes of cariprazine treatment.

Table 3. Demographics

Number of cases	
Total, n	**38**
Diagnosis, n (%)	
Schizophrenia	**27 (71.1)**
Schizophrenia	13 (34.2)
Paranoid schizophrenia	8 (21.1)
Schizophrenia/schizoaffective with substance abuse	5 (13.2)
Disorganized schizophrenia	1 (2.6)
Other psychotic disorders	**6 (15.8)**
Early psychosis	3 (7.9)
Psychosis	2 (5.3)
Acute polymorphic psychotic disorder	1 (2.6)
Mood disorders	**2 (5.3)**
Bipolar I disorder	1 (2.6)
Major depression	1 (2.6)
Other	**3 (7.9)**
Wernicke-Korsakoff syndrome	1 (2.6)
Borderline personality disorder	1 (2.6)
Obsessive-compulsive disorder with paranoid schizophrenia	1 (2.6)
Sex, n (%)	
Male	18 (47.4)
Female	19 (50.0)
Not specified	1 (2.6)
Age	
Mean	33.8
Median	31



Figures 7A and 7B. Starting (A) and maintenance (B) doses of cariprazine



Figures 8A and 8B. Efficacy (A) and safety (B) reasons for initiating cariprazine treatment

Table 4. Detailed overview of cases

Author	No.	Sex	Age	Diagnosis	Problem	Starting dose	Titration strategy	Maintenance dose	Concomitant medication
Amore & Aguglia (2019) (140)	**Case 1**	Not specified	24	Schizophrenia	Negative, cognitive, and mild psychotic symptoms with risperidone treatment, reduced psychosocial functioning	1.5 mg/day	3.0 mg/day on day 15	3.0 mg/day	Risperidone gradually discontinued
Aubel (2021) (141)	**Case 2**	Female	59	Paranoid schizophrenia	Negative and psychotic symptoms, psychomotor retardation, reduced psychosocial functioning	1.5 mg/day	3.0 mg/day on day 4 and 4.5 mg on day 14	4.5 mg/day	Risperidone gradually discontinued
	Case 3	Male	31	Paranoid schizophrenia	Persistent negative symptoms, psychomotor retardation	1.5 mg/day	3.0 mg/day on day 4	4.5 mg/day	Amisulpride and then 2 months later clozapine gradually discontinued
	Case 4	Male	32	Paranoid schizophrenia	Desired switch to cariprazine due to psychotic symptoms and suicidal ideation	1.5 mg/day	3.0 mg/day on day 2 and 4.5 mg/day on day 3	4.5 mg/day	Aripiprazole and risperidone gradually discontinued
Carmassi et al. (2019) (142)	**Case 5**	Male	39	Schizophrenia with substance abuse (alcohol, cocaine, THC, MDMA)	Negative, cognitive, and psychotic symptoms, reduced psychosocial functioning	1.5 mg/day	3.0 mg/day on day 5, 4.5 mg/day on day 9, and 6.0 mg/day on day 13	6.0 mg/day	Aripiprazole gradually discontinued, benzodiazepine

	Case 6	Male	20	Schizophrenia with substance abuse (cocaine)	Psychotic and affective symptoms, restlessness, insomnia, suicide attempt, reduced psychosocial functioning	1.5 mg/day	3.0 mg/day on day 7	4.5 mg/day	Quetiapine gradually discontinued, biperiden 4mg/day
Cruz et al. (2021) (143)	**Case 7**	Male	30	Schizophrenia with substance abuse (amphetamine, cannabis)	Psychotic, negative, and cognitive symptoms, reduced psychosocial functioning	1.5 mg/day	6.0 mg/day on day 9	4.5 mg/day	Gradual down-titration of haloperidol over 2 weeks, quetiapine, add-on clonazepam, propranolol
De Berardis et al. (2021) (144)	**Case 8**	Female	29	Schizophrenia	Symptomatic despite clozapine 450mg/day and amisulpride 800mg/day treatment with weight gain	1.5 mg/day	3.0 mg/day after a week	3.0 mg/day	Clozapine 400mg/day
	Case 9	Male	35	Schizophrenia	Symptomatic despite clozapine, weight gain	1.5 mg/day	3.0 mg/day after three weeks	3.0 mg/day	Clozapine 350mg/day, then reduced to 300mg/day
De Berardis et al. (2019) (145)	**Case 10**	Female	21	Early psychosis	Psychotic, negative, and cognitive symptoms, increased sedation, and appetite despite olanzapine treatment	1.5 mg/day	3.0 mg/day on day 4, 4.5 mg/day around day 30	4.5 mg/day	-
	Case 11	Male	19	Early psychosis	Psychotic, negative, cognitive, and affective symptoms, insomnia, and impulse dyscontrol	1.5 mg/day	3.0 mg/day after a few days, 4.5 mg/day and then 6.0 mg/day after 14 days	6.0 mg/day	Alprazolam 1mg/day
De Berardis et al. (2020) (146)	**Case 12**	Male	26	Obsessive-compulsive disorder with paranoid schizophrenia	Persistent OCD symptoms despite paliperidone treatment	1.5 mg/day	3.0 mg/day on day 7	3.0 mg/day	Paliperidone oral suspended, add-on paliperidone long-acting injectable 100mg

Dieci et al. (2020) (147)	**Case 13**	Male	54	Major depression	Affective symptoms	1.5 mg/day	Not specified	1.5 mg/every second day	Citalopram 40mg/day
Di Sciascio & Palumbo (2019) (148)	**Case 14**	Male	26	Schizophrenia	Psychotic relapse, and negative and affective symptoms	1.5 mg/day	3.0 mg/day on day 2	3.0 mg/day	Risperidone discontinued in two days
	Case 15	Female	22	Disorganised schizophrenia	Relapse due to discontinuation of previous therapy (weight gain and metabolic syndrome), cognitive and psychotic symptoms, reduced psychosocial functioning	1.5 mg/day	6.0 mg/day	6.0 mg/day	Olanzapine gradually discontinued in 2 weeks
Grant & Chamberlain (2020) (149)	**Case 16**	Male	42	Borderline personality disorder	Affective symptoms, hostility, and impulsivity	3.0 mg/day	4.5 mg/day after 2 weeks, 6.0 mg/day after 3 weeks	6.0 mg/day	-
Halaris & Wuest (2019) (150)	**Case 17**	Male	37	Schizoaffective disorder with substance abuse (alcohol and tobacco)	Metabolic syndrome with olanzapine	Not specified	3.0 mg/day and then a year later 4.5 mg/day	4.5 mg/day	Olanzapine discontinued over 2 months
Heck et al. (2021) (151)	**Case 18**	Female	30	Paranoid schizophrenia with substance use disorder	Relapse followed by patient's request to discontinue quetiapine	1.5 mg/day	3.0 mg on day 6	Cariprazine was reduced to 1.5 mg/day 3 days after the onset of akathisia (day 16). Another 2 days later, cariprazine was stopped.	Quetiapine 300mg reinitiated on day 5

	Case 19	Male	22	Paranoid schizophrenia	Negative symptoms despite risperidone treatment	1.5 mg/day	3.0 mg/day after 2 weeks, then 10 days later reduced to 1.5 mg/day	1.5 mg/day	Risperidone 0.5mg/day to 3mg/day, biperiden 4mg/day (both discontinued)
	Case 20	Male	52	Paranoid schizophrenia	Psychotic symptoms due discontinuation of medication and history of severe negative symptoms	1.5 mg/day	3.0 mg/day 1 week later, 4.5 mg/day another 5 days later	4.5 mg/day	Pipamperone 40mg/day, then olanzapine 10mg/day added and pipamperone discontinued
	Case 21	Female	22	Paranoid schizophrenia	Hyperprolactinemia under aripiprazole 10 mg/d and amisulpride 250 mg/d.	1.5 mg/day	Increased to 3.0 mg/day, 4.5 mg/day, and 6.0 mg/day after 2, 4, and 12 weeks, respectively	6.0 mg/day	-
Jimoh et al. (2020) (152)	**Case 22**	Female	32	Wernicke-Korsakoff syndrome	Psychotic, cognitive, and negative symptoms, psychomotor retardation despite aripiprazole treatment, reduced psychosocial functioning	Not specified	Not specified	3.0 mg/day	Not specified
Kapulsky & Brody (2018) (153)	**Case 23**	Male	33	Schizophrenia	Psychotic and predominantly negative symptoms despite clozapine 225mg treatment	Not specified	Up to 6.0 mg/day in a week	Discontinued due to urinary retention	-
Mencacci et al. (2019) (154)	**Case 24**	Male	51	Schizophrenia	Negative symptoms despite ziprasidone, lurasidone and risperidone treatment, reduced psychosocial functioning	Not specified	Up to 4.5 mg/day	4.5 mg/day	Haloperidol and risperidone gradually discontinued

	Case 25	Female	49	Schizophrenia	Metabolic side-effects and negative symptoms despite olanzapine treatment	Not specified	Up to 4.5 mg/day until day 21	4.5 mg/day	Olanzapine gradually discontinued, and biperiden, lorazepam, antihistamine gradually reduced
Molnár et al. (2020) (155)	**Case 26**	Female	23	Early psychosis	Severe negative, cognitive and psychotic symptoms, agitation, reduced psychosocial functioning	1.5 mg/day	3.0 mg/day from day 4 to 12, 4.5mg/day from day 13	3.0 mg/day	-
Montes et al. (2021) (156)	**Case 27**	Male	31	Schizophrenia	Psychotic symptoms	3.0 mg/day	Not specified	3.0 mg/day	-
	Case 28	Female	54	Schizophrenia	Psychotic and affective symptoms, reduced psychosocial functioning	3.0 mg/day	6.0 mg/day on day 3	6.0 mg/day	Diazepam 10mg
	Case 29	Female	36	Schizophrenia	Psychotic symptoms, agitation, hostility despite aripiprazole treatment	3.0 mg/day	6.0 mg/day on day 3	6.0 mg/day	Quetiapine 50mg
Müller & Moeller (2021) (157)	**Case 30**	Female	38	Schizophrenia	Extrapyramidal and negative symptoms	1.5 mg/day	3.0 mg/day after 4 days, 4.5mg/day after another week	4.5 mg/day	-
	Case 31	Female	34	Psychosis	Psychotic relapse, negative and cognitive symptoms, and increased weight	1.5 mg/day	3.0 mg on day 3 for 3 weeks	4.5 mg/day	Risperidone until 4.5 mg cariprazine
Ricci et al. (2021) (158)	**Case 32**	Male	25	Methamphetamine-induced psychosis	Persistent psychotic, negative and affective symptoms	1.5 mg/day	3.0 mg/day on day 4, 4.5 mg/day on day 13	3.0 mg/day	Benzodiazepine

Riedesser & Gahr (2020) (159)	**Case 33**	Female	46	Paranoid schizophrenia	Psychotic, affective, and psychomotor symptoms and agitation	1.5 mg/day	1.5 mg/day	Discontinued after 5 days	Clozapine 12.5mg/day, escitalopram 10mg/day
	Case 34	Female	62	Paranoid schizophrenia	Haloperidol, then amisulpride without sufficient antipsychotic effect	1.5 mg/day	Up to 4.5 mg/day	3.0 mg/day	Amisulpride, biperiden (later phased out), hydro-chlorothiazide, amlodipine and ramipril
	Case 35	Female	19	Acute polymorphic psychotic disorder	Hyperprolactinaemia attributed to risperidone and olanzapine	1.5 mg/day	3.0 mg/day	Discontinued after 2 weeks	Olanzapine 5mg/day discontinued after 4 days; pantoprazole initiated
Sanders & Miller (2019) (160)	**Case 36**	Female	20	Bipolar I disorder, ADHD, substance use disorder (cannabis and alcohol)	Affective and cognitive symptoms and agitation	1.5 mg/day	3.0 mg/day after 3 weeks	3.0 mg/day	Quetiapine 25mg/day, clonazepam 2x0.5mg/day, methylphenidate XR 72mg/day
Vita et al. (2019) (161)	**Case 37**	Female	31	Schizophrenia	Negative symptoms despite risperidone treatment	1.5 mg/day	3.0 mg/day on day 4, 4.5 mg/day on day 7	4.5 mg/day	Risperidone dose decreased by 3 mg every 3 days until full discontinuation
	Case 38	Female	27	Schizophrenia	Psychotic relapse 2 weeks after the administration of paliperidone palmitate 1-monthly long-acting therapy	1.5 mg/day	3.0 mg/day on day 4, 4.5 mg/day on day 7, 6.0 mg/day on day 10	6.0 mg/day	Paliperidone discontinued

Table 5. Summary of the efficacy and safety outcomes of cariprazine treatment

AUTHOR	NO.	OUTCOME																		
		EFFICACY									SAFETY									
		Positive	Negative	Cognitive	Affective	Hostility	Substance abuse	OCD	Impulsivity	Psychosocial functioning	Psychomotor	Insomnia	Sedation	Weight gain	Metabolic syndrome	Increased prolactin levels	Agitation	EPS	Sexual dysfunction	Restlessness
Amore & Aguglia (2019) (162)	**Case 1**	↓	↓	↓	↓					↑						↓		↓	↓	
Aubel (2021) (163)	**Case 2**	X	↓							↑	X									
	Case 3	X	X		X					↑										
	Case 4	X		↓						↑										
Carmassi et al. (2019) (164)	**Case 5**	↓	↓	↓			X			↑	X		↓							
	Case 6		↓	↓	↓		X			↑								+		
Cruz et al. (2021) (165)	**Case 7**	↓	↓				X			↑								+		
De Berardis et al. (2021) (166)	**Case 8**	↓	↓							↑				↓						
	Case 9	↓	↓	↓						↑				↓						
De Berardis et al. (2019) (167)	**Case 10**	↓	↓	↓									↓							
	Case 11	↓	↓	↓	↓				X			↓								
De Berardis et al. (2020) (168)	**Case 12**							X												
Dieci et al. (2020) (169)	**Case 13**				↓													+	X	
Di Sciascio & Palumbo (2019) (170)	**Case 14**	↓	↓		↓					↑										
	Case 15	X	X	X	↓		X			↑			↓	↓						
Grant & Chamberlain (2020) (171)	**Case 16**				↓	X			X											
Halaris & Wuest (2019) (172)	**Case 17**	X	↓							↑				↓	↓					
Heck et al. (2021) (173)	**Case 18***	↓																+		+
	Case 19																	+		
	Case 20	↓	↓									↓								+
	Case 21															↑				
Jimoh et al. (2020) (152)	**Case 22**	↓	↓	↓						↑										
Kapulsky & Brody (2018) (174)	**Case 23***																			
Mencacci et al. (2019) (175)	**Case 24**		↓	↓						↑										
	Case 25	↓		↓										↓		↓				
Molnár et al. (2020) (176)	**Case 26**	↓	↓	X						↑							X	+		X

Montes et al. (2021) (177)	**Case 27**	↓			↓															
	Case 28	↓			↓	↓				↑										
	Case 29	↓			↓	↓														
Müller & Moeller (2021) (157)	**Case 30**		↓															X		
	Case 31	↓	↓	↓										↓						
Ricci et al. (2021) (158)	**Case 32**	↓	↓				X					+								
Riedesser & Gahr (2020) (178)	**Case 33***																+	+		
	Case 34	↓																+		
	Case 35															X		+		
Sanders & Miller (2019) (179)	**Case 36**			X			X			↑							X			X
Vita et al. (2019) (180)	**Case 37**	X	↓							↑										
	Case 38	X																		

↑ increase; ↓ decrease; X absent, + present

*discontinued due to akathisia (case 18, 33, 35) or urinary retention (case 23)

4.2.3 Schizophrenia

Among the cases, 27 had a diagnosis of schizophrenia (71.1%). Out of these 27 cases, eight was diagnosed with paranoid schizophrenia (29.6%), five with schizophrenia/schizoaffective disorder with concomitant SUD (18.5%), one with disorganised schizophrenia, while the rest of the cases (i.e., 13 patients, 48.1%) had a general diagnosis of schizophrenia, where the subtype was not determined.

For schizophrenia patients, cariprazine was prescribed for a variety of efficacy and safety issues. Regarding efficacy, cariprazine was most commonly initiated due to persisting psychotic symptoms (n=19, 70.4%), followed by negative symptoms (n=13, 48.1%), cognitive symptoms (n=4, 14.8%) and affective symptoms (n=4, 14.8%). Psychotic symptoms usually emerged due to medication non-adherence to previous medication and thus relapse. Negative symptoms were either not adequately addressed by prior antipsychotic agents or they developed as a result of these drugs. Most common negative symptoms included avolition, asociality and decline in everyday functioning, severely impairing patients' everyday functioning. Regarding safety and tolerability issues for which cariprazine was prescribed, patients presented with motor symptoms (n=4, 14.8%), mainly psychomotor retardation - one patient experienced such a severe psychomotor retardation that she became fully bedridden (case 2) (141). Cariprazine was further prescribed due to metabolic issues (n=3, 11.1%), and weight gain (n=3, 11.1%), where one patient gained over 30 kgs due to olanzapine treatment, causing metabolic disturbances as well (case 15) (148).

Regarding starting dose, 1.5 mg/d was the most commonly used dose (n=20, 74.1%), followed by 3.0 mg/d (n=3, 11.1%), while in 4 cases (14.8%), the dose was not specified. For maintenance dose, 11 patients were on 4.5 mg/d (40.7%), followed by 3.0 mg/d (n=6, 22.2%) and 6.0 mg/d (n=6, 22.2%). Only one patient (3.7%) received 1.5 mg/d for maintenance dose, and cariprazine was discontinued in 3 patients (11.1%).

Considering the outcomes of the treatment, cariprazine proved to be effective in a variety of symptom domains. It alleviated psychotic (n=20, 74.1%), negative (n=15, 55.6%), affective (n=8, 29.6%) and cognitive symptoms (n=8, 29.6%). It further reduced hostility (n=2, 7.4%) as well as yielded a significant improvement in psychosocial functioning (n=15, 55.6%). Strikingly, five patients (18.5%) (cases 5, 6, 7, 17, 18) (142,143,150,151) had comorbid SUD and even though cariprazine was not prescribed for this issue, 4 patients (14.8%) achieved complete abstinence. Additionally, patients experienced serious impairment in their functioning which cariprazine improved significantly.

In addition to the apparent effectiveness, cariprazine brought about desirable safety outcomes as well. It reversed five patients' (18.5%) weight gain that was caused by previous antipsychotics, it improved psychomotor functioning (n=2, 7.4%), alleviated sleep disturbances (sedation in two, and insomnia in 1 patient), normalised heightened prolactin levels (n=2, 7.4%; however, it increased prolactin in one patient) and improved one patient's sexual dysfunction (3.7%).

Looking at the side-effects and discontinuations, the most common adverse effect of cariprazine was the emergence of extrapyramidal symptoms (n=6, 22.2%), mainly akathisia, even though it alleviated such symptoms in 2 patients (7.4%). Furthermore, two patients (7.4%) presented with restlessness and one (3.7%) with agitation. Cariprazine treatment was terminated in 3 cases (11.1%), due to the emergence of akathisia (n=2, 7.4%) and urinary retention (n=1, 3.7%).

4.2.4 Other psychotic Disorders

Six patients were diagnosed with a psychotic disorder (other than schizophrenia). Three patients had early psychosis, one had acute polymorphic psychotic disorder, one had methamphetamine-induced psychosis and the sixth patient had psychosis.

In the case of the three early psychosis patients, psychotic, cognitive and negative symptoms dominated the clinical picture for which CAR was prescribed at the starting dose of 1.5 mg/d. Furthermore, impulsivity was observed with the male patient (case 11) (145), while self-neglect manifested in case of the female patients (cases 10 and 26) (145,155). All symptoms reduced after the initiation of CAR, and sleep-related issues - both insomnia and sedation - were well-controlled. Strikingly, one of the female patients (case 26) (155) was followed up for 52 weeks during which time she remained symptom-free.

For a female patient (case 35) (159) with acute polymorphic psychotic disorder, CAR was prescribed to overcome risperidone- and olanzapine-induced hyperprolactinemia. CAR was started at 1.5 mg/d and then increased to 3.0 mg/d, and although it successfully normalised prolactin levels, it was discontinued after 2 weeks of treatment due to the development of akathisia. In the case of the other two patients with psychosis (case 31) (157) and with methamphetamine-induced psychosis (case 32) (158), the most prominent symptoms included psychotic, negative, cognitive and affective symptoms - all of which were adequately addressed by CAR treatment. In addition, the patient with substance-induced psychosis remained abstinent as a result of CAR treatment (case 32) (158), and the other patient reported impressive weight loss (16 kgs) (case 31) (157).

4.2.5 Mood Disorders

Two patients were diagnosed with a mood disorder: one with bipolar I disorder and comorbid attention-deficit hyperactivity disorder (ADHD) and SUD (case 36) (160) and one with MDD (case 13) (147). The male patient with MDD had unresolved affective symptoms for which adjunctive CAR was prescribed in addition to an antidepressant (citalopram). The patient took CAR 1.5 mg/d which did not only yield reduction in affective symptoms, but also significantly improved the patient's sexual function within a month. As mild akathisia emerged, CAR was only administered every other day, which resulted in the disappearance of EPS. A female patient with a diagnosis of bipolar I disorder with ADHD and SUD (cannabis and alcohol), was decided to receive add-on cariprazine for her affective and cognitive symptoms, as well as agitation. After CAR 1.5 mg/d did not prove to sufficiently address her symptoms, it was up-titrated to 3.0 mg/d. According to the report, the patient's agitation, restlessness and cognitive symptoms were resolved, and more importantly, she managed to become substance free even after 27 months, adding greatly to her psychosocial functioning.

4.2.6 Other Disorders

Three patients had a diagnosis which had not been clinically investigated. A female patient with a diagnosis of Wernicke-Korsakoff syndrome (case 22) (152), presented with a wide-range of residual symptoms despite aripiprazole treatment: psychotic, cognitive and negative symptoms, as well as reduced psychosocial functioning and psychomotor retardation. Following CAR treatment (starting at 1.5 mg/day, then up-titrating to 3 mg/day), all symptoms showed improvement. A male patient (case 12) (146) received a diagnosis of obsessive compulsive disorder with paranoid schizophrenia, who was prescribed cariprazine after obsessive-compulsive disorder (OCD) symptoms resisted despite paliperidone treatment. CAR treatment was started and increased from 1.5 to 3.0 mg/d, which resulted in the OCD symptom reduction within a week. The third patient with borderline personality disorder (case 16) (149) was given CAR monotherapy due to affective symptoms, hostility and impulsivity. CAR was initiated at 3 mg/day, then up-titrated to 4.5 mg/d and then to 6mg/d. Seven months of treatment brought the complete resolution of impulsivity and hostility symptoms, and alleviated affective symptoms.

5 Discussion

The systematic review of case reports was the first one to collect, synthesise and analyse the findings of individual case reports on cariprazine, while the HD study was the first to investigate the effectiveness of cariprazine in this disease, reporting on treatment-outcomes in the main symptom domains of HD.

The study and the case reports included in this thesis all qualify as real-world evidence which is becoming increasingly sought for in virtually all medical fields, including neuropsychiatry. While randomized controlled trials (RCTs) are considered to be the gold standard for establishing treatment efficacy, they often have strict inclusion and exclusion criteria, which may limit their generalisability (181,182). Real-world data complements the knowledge gained from clinical trials, offering a broader perspective by including patients with comorbidities, concomitant medications, diverse demographics, and varying levels of adherence to treatment (181,182). It helps bridge the gap between controlled research settings and everyday clinical practice. Furthermore, real-world data aids the detection of safety concerns and adverse events associated with psychiatric treatments (182). By analysing data from large, heterogenous patient populations, researchers and clinicians can identify rare but significant long-term side-effects that may not have been captured during clinical trials (183).

Therefore, in order to learn about the real-world effectiveness, safety and clinical use of a drug, the collection of real-world evidence is recommended, which in fact was the aim of the systematic review of cariprazine case reports. Furthermore, the fact that case reports were collected in the frame of a systematic review - which sits at the top of the hierarchy of evidence along with meta-analysis (184) - makes the quality of evidence more robust.

5.1 Cognitive symptoms

Cognitive impairment is a prominent feature of numerous central nervous system (CNS) disorders, like schizophrenia, bipolar disorder, MDD, Alzheimer's disease (AD), PD, HD, SUD and many more (135). Although it is not considered to be the main, distinguishing clinical manifestation of these disorders, cognitive deficit causes severe impairments in the functioning of affected individuals, negatively impacting quality of life (84,185). They often emerge in pre-manifest/prodromal stages, years before the onset of motor/psychotic/depressive symptoms and get worse with illness progression (186,187). Yet, available treatments options for neuropsychiatric disorders, like antipsychotics, mood stabilisers, antidepressant or TBZ, do not adequately address these impairments - in fact, sometimes some agents even affect cognition

rather adversely (188–191). Therefore, finding appropriate agents with pro-cognitive effects is of high priority.

In the HD study, cariprazine effectively improved patients' cognitive functioning, as shown by the statistically significant increases in cognitive scores, measured by the ACE and the Cognitive Examination of the UHDRS (Symbol Digit Test and Verbal Fluency Task).

Furthermore, the systematic review of case reports provided further support for the effectiveness of cariprazine in enhancing cognition. At least 14 patients have demonstrated increased cognitive functioning in various domains, like concentration, mental alertness, thinking, memory, learning skills, as well as orientation in time, place and self.

The positive effects of cariprazine on cognition are in line with the findings of clinical trials in schizophrenia, bipolar mania and bipolar depression (192). In schizophrenia, the post-hoc analyses of pooled data from acute schizophrenia trials have shown statistically significant improvements for cariprazine (1.5-9 mg/day) versus placebo on the PANSS-derived Meltzer Cognitive Subscale as well as on the PANSS-derived Marder Disorganised Through Factor (193) - on both of these measures, the observed effect was driven by the significant difference on all single items. In a long-term schizophrenia trial in patients with primary, predominant negative symptoms, cariprazine 4.5 mg/day statistically significantly outperformed risperidone 4.0 mg/day on both the Meltzer Cognitive Subscale and the Marder Disorganised Thought Factor measures. In the pooled bipolar depression trials, cariprazine showed statistically greater reduction on the Montgomery-Åsberg Depression Rating Scale (MADRS) concentration item (item 6) than placebo (192). On the FAST Cognitive subscale, cariprazine 1.5 mg/day statistically significantly outperformed placebo. In the pooled bipolar mania trials, the observed improvement on the PANSS Cognitive Subscale demonstrated the superiority of cariprazine over placebo with the effect driven by 4 out of 5 items (192).

The role of dopamine in cognition has long been acknowledged, although the exact mechanisms are yet to be determined. Cortical dopamine has been most widely studied in relation to cognition due to the heavy involvement of the PFC in the higher executive functioning (189). Nevertheless, the role of subcortical regions, especially the basal ganglia, in complex cognitive processes have been further proven (189,194). Hence, it has become accepted that the bidirectionally interconnected cortico-striatal circuitries play a crucial role in cognitive functioning and dopamine's modulation of these circuits allow it to regulate cognition (84). Studies suggest that the relationship between dopamine levels and cognition follow an inverted U-shaped curve, especially in the PFC, illustrating how both too low and too high dopamine levels evoke cognitive impairment (41,84,85). Since striatal neuronal

dysfunction and then neurodegeneration is the hallmark feature of HD (53), and it is further linked to cognition, it partially explains the cognitive decline in patients.

D3 receptors have been identified as targets for the treatment of cognitive symptoms due to their anatomical localisation in areas associated with cognitive functioning, especially in PFC-related processes (195). Studies have further provided support for this notion, whereby both pharmacological, including cariprazine, and genetic manipulations of prefrontal D3 receptors had the potential to affect cognition (84,196–199). Moreover, cariprazine shows higher D3 occupancy than D2 occupancy at low doses, and low dose cariprazine treatment produced greater improvements in cognition than higher CAR doses, implying the involvement of D3 receptors in cognition (192).

Despite these promising findings, however, it must be noted that cognitive symptoms show a correlation with other symptoms, like loss of motivation (i.e., apathy in HD). Since no statistical analysis, e.g. path analysis, was conducted to establish causality in the HD study or in the other indications mentioned above, it makes it difficult to clearly distinguish actual, subjective improvement in cognitive functioning from overall symptom improvement (192).

5.2 Loss of motivation: apathy and negative symptoms

In HD, apathy, i.e. loss of motivation, can be present in 11-64% of pre-manifest patients, and in 47-76% symptomatic patients and has been associated with worse patient and caregiver quality of life (200–202). Loss of motivation is a characteristic symptom of other disorders as well, such as schizophrenia, MDD, PD or AD (203). However, there is a discrepancy in terminology despite overlapping aetiology (203): in neurological disorders, loss of motivation is referred to as apathy (meaning loss of motivation in three domains: physical, cognitive and/or emotional) (204), while in psychiatric disorders, loss of motivation corresponds to negative symptoms, like avolition (defined as a lack of motivation, sense of purpose) or anhedonia (denoting a lack of pleasure in previously enjoyed activities) (26).

Of note, several studies have shown that - unlike depression (205) - apathy becomes more prevalent and worsens with disease progression in HD and other neurological disorders, and it correlates with cognitive and motor decline, as well as the number of CAG repeats in HD (202,205). In fact, the correlation between apathy and other markers of disease progression, like cognitive impairment, has been suggested in other disorders as well, like AD, progressive supranuclear palsy (205,206) and PD (207–209), where patients with apathy showed greater cognitive deficits compared to non-apathetic patients (210).

Although the exact mechanisms underlying apathy are unknown, research has shed light on some brain areas that are likely involved in its development. Studies have suggested that apathy is linked to the dysfunction of circuits that connect the PFC, the basal ganglia/striatum and the limbic system (211). Evidence supporting this hypothesis includes the observation that apathy often emerges following the direct lesions of the PFC (211,212); that it is also a frequent clinical manifestation of basal ganglia diseases (211); and that apathy becomes apparent after focal lesions of specific basal ganglia structures, like the caudate nuclei (211,213). Furthermore, the striatum is the major site of early pathology with progressive worsening - such an early emergence and progressive worsening is evident in apathy as well, suggesting a link between the two (202). One study investigating this relationship found that pre-manifest HD patients scoring high on the apathy subscale of the Frontal System Behavioral Scale showed smaller striatal volumes (186). Furthermore, emotions and affect are crucial elements in the process of assigning motivational value to a given behaviour, implying the role of the limbic system as well (211). Since the corticostriatal circuit is implicated in cognitive impairment, as discussed in the previous section, it could explain the apparent correlation between cognition and apathy.

The involvement of the dopaminergic system has been implicated in many component processes of reward and motivation (214,215), suggesting dopamine's role in apathy (202). PD, AD and lesion studies showed that dopamine agonists alleviated apathy symptoms, proposing that these findings can be explained by the improved dopaminergic input to the PFC and the basal ganglia (202,216,217). Moreover, in PD and in patients with prefrontal and basal ganglia lesions, studies have shown that the administration of a dopaminergic medication alleviated apathy (216), while the following withdrawal of the drug after deep brain stimulation worsened apathy, warranting the need for restarting such medications. These findings therefore suggest that hypodopaminergic state underlies apathy. One study supporting this notion used functional imaging and found dopaminergic hypofunction especially in the PFC (218).

Among DA receptors, D3 has been implicated in motivation and reward-related behaviour due to their distribution in such brain areas (219). For instance, D3 receptors were shown to regulate the excitability of layer V pyramidal cells in the PFC (195). These pyramidal cells degenerate in HD, contributing to the worsening symptomatology (220). Therefore, drugs with partial agonist action at the D3 receptors, like cariprazine, can normalise dopamine levels in the PFC, and therefore enhance motivation.

In the HD study, apathy was measured as part of the Behavioural Examination of the UHDRS where patients showed statistically significant improvements by Week 12. However,

unfortunately, only one item evaluated apathy. Yet, given the neurobiological mechanisms underlying apathy, as well as the findings about the effectiveness of cariprazine in improving behavioural symptoms, it is possible that cariprazine can be an effective treatment option for apathy.

Although the efficacy of cariprazine in apathy, or loss of motivation, has not been investigated specifically, it has been evaluated in the treatment of primary, predominant negative symptoms (114) and anhedonia. As mentioned above, apathy corresponds most likely to anhedonia and avolition (which are part of the negative symptom domain), therefore, evidence from cariprazine trials in negative symptoms can have implications for apathy as well. Our systematic review of case reports has revealed that cariprazine was specifically initiated for the treatment of negative symptoms in many cases which were all resolved.

The positive effects cariprazine had on apathy and negative symptoms are further supported by clinical trial data. In a 26-week trial, cariprazine (4.5 mg/day) demonstrated superiority over an active comparator, risperidone, suggesting its efficacy in the treatment of primary, predominant negative symptoms (114). Furthermore, the impact of cariprazine on anhedonia symptoms (measured by the MADRS anhedonia factor score, which equals the sum of apparent sadness, reported sadness, concentration, lassitude, and inability to feel items) in patients with bipolar I depression was examined using pooled data of 3 pivotal clinical studies (221). In the subgroup of patients presenting with higher anhedonia, cariprazine 1.5 and 3.0 mg/day statistically significantly reduced anhedonia compared to placebo, while in the subgroup of patients with lower anhedonia, cariprazine 1.5 mg/day yielded statistically significantly greater reductions than placebo.

Therefore, findings from these trials support the notion that cariprazine has the potential to reduce negative symptoms and anhedonia, and therefore might be effective in the treatment of apathy in HD. However, future studies with appropriate apathy measures are warranted in order to properly evaluate the efficacy of cariprazine in apathy.

5.3 Depressive symptoms

Depressive symptoms are prominent features of many neuropsychiatric disorders, like schizophrenia, HD or PD, and are hallmark features of MDD and BD (222). They have been associated with reduced patient and caregiver quality of life and increased risk of suicide, making their effective treatment crucial (223).

The HD study revealed that cariprazine effectively reduced depressive symptoms as measured by the BDI and the Behavioural Examination of the UHDRS. In the systematic review, many cases (n=11) reported a reduction of affective symptoms.

The efficacy of cariprazine was confirmed by clinical trial data as well in various indications. In a post-hoc analysis of pooled acute schizophrenia trials, cariprazine (1.5-9.0 mg/day) statistically significantly outperformed placebo in the PANSS-derived Marder Anxiety/Depression Factor, with the effect being driven by 3 out of 4 items (193). In a post-hoc analysis of pooled bipolar depression data, cariprazine (1.5-3 mg/day) showed statistically significant reductions compared to placebo in the MADRS Total Score, with the effect being driven by 9 out of 10 items (224). In MDD, adjunctive cariprazine to an antidepressant (1.5 mg/day (125) 2.0-4.5 mg/d (124)) has shown statistically significant superiority over placebo plus antidepressant. In another clinical trial, 1.5 mg/day cariprazine as add-on to an antidepressant statistically significantly outperformed placebo plus an antidepressant (125).

Emerging evidence suggests the pivotal role of the D3 receptors in depression (219). D3 receptor availability and function is reduced in stress and depression which appear to be reversed by antidepressants (219,225). This implies that increased DA neurotransmission mediated by the D3 receptors contributes to the adaptive changes associated with antidepressant activity (219,226). Therefore, the partial agonist activity of cariprazine at D3 receptors to which it binds with high affinity likely contributes to its antidepressant activity in addition to its effects on serotonin receptors, especially the 5-HT1A.

Although some aspects of depression and apathy could be perceived as overlapping, in HD, studies have shown that apathy and depression are distinct behavioural dimensions (205). While apathy is associated with hypofunction in the PFC, depression is associated with hypofunction in the parietal-temporal regions (218). Their separation in clinical practice can often be challenging, even though it would be crucial, as treatment differs for the two, especially in terms of pharmacotherapy (227). While antidepressants, like selective serotonin reuptake inhibitors (SSRIs), can presumably alleviate depressive symptoms, their success is limited in apathy (205,227). However, the efficacy of cariprazine was shown in depression and negative symptoms. If future studies with more appropriate measures confirm its effectiveness in apathy, then cariprazine could be a good pharmacological treatment option for the behavioural symptoms associated with HD.

5.4 Motor symptoms

Motor symptoms are the hallmark features of HD and official diagnosis is based on their emergence (53). There are pharmacological treatment options that address motor symptoms fairly well, however, they often have detrimental side effects, impacting on the other symptom domains (like behavioural symptoms) negatively (53).

This was the first study to investigate the effectiveness of cariprazine in motor symptoms associated with HD, revealing positive effects on a wide range of motor symptoms, as measured by the Motor Examination of the UHDRS. The TMS showed statistically significant reductions at Week 8 and Week 12 as well. Significant improvements were observed in chorea, dystonia, hand and eye movements, oropharyngeal symptoms, rigidity, postural stability and tandem gait. The only two symptoms that failed to show improvements were bradykinesia and gait, although a subjective change was reported by patients in gait, while bradykinesia was not severe at the start of cariprazine treatment either.

Although cariprazine effectively reduced motor symptoms without causing serious adverse events, a notable finding warrants attention: upon individual data analysis, a minor decline in the improvement of UHDRS motor score was evident in a few cases (see Figure 5): three patients showed no further progress from Week 8 to Week 12 (Patients 5, 7, and 16), while a slight increase in the motor score at Week 12 compared to Week 8 was observed in two cases (Patients 6 and 12). A few potential reasons could lie behind these observations. First, the demographic data indicates that these patients – unlike others – were in the early stages of the disease and had high TFC scores, indicating high functionality. They also had relatively low motor scores at baseline (except for Patient 6), suggesting less severe motor symptoms at the start of cariprazine treatment. Consequently, at the time of the study, these patients were less impacted by the disease, so smaller improvements or even stagnation after the initial improvement could be anticipated. This was corroborated by the regression plot generated, which indicated that patients with more severe symptoms at baseline experienced greater improvements throughout the treatment period. Second, motor symptoms can naturally exhibit slight, spontaneous fluctuations. Assessing such symptoms at specific time points can lead to occasionally "unexpected" observations. Lastly, medication non-compliance could further hinder improvement – although the examiners monitored for non-compliance and excluded patients from the analysis in such cases (like Patient 4), it cannot be completely ruled out.

Although the exact mechanism via which cariprazine could have achieved the normalisation of motor functions is unknown, there are some potential explanations. For example, early stage

HD is associated with neuronal loss in the indirect pathway containing D2 receptors, inducing hyperkinetic movements, like chorea (73). D2 partial agonist compounds, like aripiprazole (96) or brexpiprazole (228), and other antipsychotics with D2 antagonism have been shown to reduce symptoms of chorea in HD patients, like haloperidol, risperidone or clozapine (98,101,102). Since cariprazine has high affinity to D2 receptors and due to its partial agonist activity, it is possible that its activity at the D2 receptors is responsible for the alleviation of chorea and other hyperkinetic symptoms.

Another potential mechanism is autophagy. Autophagy is a lysosomal degradation process that ensures the preservation of cellular homeostasis. Studies (229) have shown that autophagy has a key role in preventing the development of aggregate-prone proteins that are responsible for the neuronal death in several neurodegenerative diseases, like HD, as well as in psychiatric disorders, including schizophrenia and depression. In HD, the accumulation of the soluble mHTT protein is responsible for neurodegeneration, mainly affecting the MSNs in the striatum. Autophagy comes into play in degrading these mHTT proteins, therefore exerting neuroprotective effects – in HD, autophagy is dysfunctional, requiring autophagy-inducer interventions (229).

Novel autophagy inducers include molecules with affinity to dopamine D2 and D3 receptors (229,230). For instance, pramipexole is a D2-D3 receptor agonist which is used as first-line treatment in PD (231). The autophagy-inducer effect of pramipexole was first shown in mice studies, where the autophagic vacuoles increased after pramipexole administration (232) with following studies then attributing this to D2-D3 receptor activity (233). However, studies found that pramipexole induced autophagy in mice, however, this effect was D3-, but not D2-dependent (232). More specific studies have shown that pramipexole reduced soluble mHTT in mice and therefore exerted striatal neuroprotective effects, and this was attributed to D3 receptor-mediated mechanism (229). In fact, administering an autophagy inducer molecule early on in the illness could hypothetically slow down the neurodegeneration process. Therefore, given the involvement of D3 receptors in autophagy induction, cariprazine could potentially induce autophagy and reduce mHTT proteins and consequently improve the symptoms, or at least reduce the progression of the disease via its D3 activity.

Furthermore, growing evidence suggests that D3 stimulation has neurotrophic, neuroprotective and neurorestorative effects on dopamine neurons. Therefore, D3 receptors might have an essential role in preventing pathological alterations underlying neurodegeneration (234). The activation of the D3 receptors has been shown to promote neurogenesis (235) mainly in the substantia nigra pars compacta and the subventricular zone. Since these areas provide the

striatum with neurons that were formed here, they can counter neurodegeneration affecting HD patients (MSNs) and therefore improve motor symptoms (236).

Another piece of evidence presumably linking D3 receptors to motor symptoms concerns that in PD, levodopa-induced dyskinesia (LID) was alleviated following the administration of a preferential D3 receptor antagonist or partial agonist (234,237). This was supported by other findings where LID was reduced via the knock-down of striatal D3 receptor expression (234,238) or in other studies where the overexpression of D3 receptors in the dorsal striatum (i.e. caudate and putamen that are the major sites of neurodegeneration in HD) exacerbated dyskinetic behaviour (234,239). D3 receptors are co-localised with D1 receptors in the striatum and they form heteromers that enable their functional integration (234). Indeed, the anti-dyskinetic properties of D3 partial agonists and antagonists might be attributable to their effect on the normalisation of the D1-D3 heteromers (234).

Despite the positive findings, it must be noted that 10 patients were taking TBZ during the treatment phase. Nonetheless, they had already been taking a stable dose of TBZ prior to the start of cariprazine treatment. Therefore, the observed improvements in motor symptoms during the treatment period is likely attributable to cariprazine. However, potential synergistic effects of TBZ and cariprazine needs to be considered too. Despite the outlined mechanisms that could account for the observed effect in motor symptom alleviation due to cariprazine administration, the nature of the study, i.e., observational, does not allow causality to be drawn.

5.5 Addiction

The systematic review included some case reports where cariprazine effectively addressed substance use, including cocaine, alcohol, cannabis, methamphetamine, even yielding complete abstinence in many patients. Some investigator-initiated trials were started to investigate the efficacy of cariprazine in SUD, however, only one is still ongoing (NCT05063201), the rest had to be halted. Therefore, evidence mainly comes from case reports, animal studies and an observational study. In one animal study, cariprazine effectively lessened the rewarding effects of cocaine and prevented relapse in a rat model – the potency of cariprazine was 20 times higher than that of aripiprazole, which is another partial agonist (240). In a 6-month observational study (241), the antipsychotic and anti-addiction effects of cariprazine in 58 patients with both schizophrenia and cannabis use disorder were evaluated in a real-world setting. In addition to cariprazine's antipsychotic effects and its positive impact

on patient functioning, cannabis use and dependence also decreased (most common doses were 4.5 and 3.0 mg/day).

Since the conduction of the systematic review of case reports, five further case reports have been published about cariprazine's effects on addiction, with four reporting on the effectiveness of cariprazine. Regarding effects on addiction, in one report, a patient with a psychotic disorder stopped cannabis use completely (242); a patient with post-traumatic stress disorder, MDD and methamphetamine-induced psychotic disorder reported no cravings of methamphetamine and eventually achieved abstinence (243); another patient with post-traumatic stress-disorder, bulimia nervosa and methamphetamine-induced psychosis reported no cravings and had negative urinary drug tests (243); and another patient with bipolar disorder stopped cocaine consumption (244) – all attributed to cariprazine treatment.

A narrative review has investigated the role of the dopaminergic system - especially the D2 and D3 receptor - in SUD (245). The involvement of the D3 receptors have especially sparked interest in addiction research due to two reasons. The first is their anatomical localisation, as they are mainly expressed in areas that form the reward circuit. This implies that D3 receptors are key players in mediating motivation, emotions and reward - all of which are involved in addiction (245,246). Second, endogenous dopamine has the highest affinity to D3 receptors (Ki= 30nM) compared to other receptor subtypes (247,248). This suggests that elevation in dopamine by drugs of abuse will lead to the greater occupancy of D3 receptors (249). PET studies have confirmed the pivotal role of the D2 and D3 receptors in addiction: blunted dopamine release at D2 receptors were shown (250), as well as a heightened D3 receptor expression (251,252).

Therefore, D2/D3 partial agonists, like cariprazine, could have a beneficial role in managing addiction, however, evidence is needed from trials with more rigorous design, like the one ongoing mentioned above, in order to be able to draw any conclusions.

5.6 Safety evaluations

When assessing a medication, it is indispensable to evaluate its safety and tolerability in addition to its efficacy - both aspects are equally important. Tolerability issues do not only affect quality of life and treatment-adherence detrimentally, but they also negatively impact efficacy (253). Therefore, it is crucial to find safe and tolerable pharmacological treatments for patients with neuropsychiatric disorders.

In the HD study, akathisia was the only reported side-effect of cariprazine, in addition to one incidence of weight loss. In the systematic review, the emergence of akathisia was also observed and as a result, it was discontinued in three cases (151,159). These outcomes are in line with the findings of clinical trials, where akathisia was the most commonly reported adverse effect of cariprazine (254). However, in the event of akathisia-emergence, there are some methods that can help ease the symptoms: via the reduction of cariprazine dose or the administration of an anti-akathisia medication, like propranolol (254). During clinical trials, the median time to resolution was 17 days when anti-akathisia medication was given, which led to the resolution of 85% of events (254). In case of cariprazine down-titration, the median time to resolution was 15 days and over 95% of events resolved (254). Therefore, it is recommended to try either down-titration or an anti-akathisia medication first before withdrawing cariprazine completely. In addition, prevention is key: the introduction of cariprazine should be slow and the dose should be kept at the lowest dose that effectively addresses the symptoms, as dose-response relationship was suggested for akathisia (254).

It is well-known that second-generation antipsychotics (SGAs) have the propensity to cause significant weight gain and metabolic syndrome (255). Their prevention, as well as the appropriate and effective management should be a top priority, as weight gain and metabolic syndrome were shown to reduce patients' quality of life and satisfaction with care. Furthermore, they contribute to the premature death of patients, compared to the general population (256). The cases included in the systematic review have confirmed these findings, whereby many patients experienced weight gain and other metabolic issues. Cariprazine effectively reversed these adverse effects of previous antipsychotics, inducing weight reduction in six patients and improving metabolic syndrome in one. Clinical trials demonstrated that cariprazine is a metabolically-neutral medication, causing only slight changes in metabolic parameters, like weight, lipid levels, blood glucose levels and diabetes mellitus (254,257). Importantly, no dose-response relationship was suggested in metabolic parameters (254,257).

Hyperprolactinaemia is another common side-effect of SGAs, contributing to sexual dysfunction and therefore a reduction in patients' quality of life (258). The case reports of the systematic review have shown that these symptoms were present in some cases which were all addressed effectively by cariprazine. The neutral effect of cariprazine on prolactin level and sexual dysfunction is confirmed by the findings of clinical trials as well (254).

Finally, another common adverse effect of SGAs includes sedation (259). Clinical trials have revealed that in addition to akathisia, insomnia is one the most common adverse effects of

cariprazine, making it an activating, rather than a sedating agent (254). Therefore, it is not surprising that cariprazine improved sedation in some of the cases.

The potential explanation for the gentle safety profile of cariprazine lies in its advantageous receptor profile. Cariprazine exerts partial agonist activity at serotonin 5-HT1A receptors and antagonist activity at 5-HT2B receptors (106). Furthermore, it has lower affinity for 5-HT2A, 5-HT2C, histamine H1 and alpha1 receptors, while its affinity for other receptors is negligible (106). Therefore, such a receptor profile could account for the lower risk of cardiovascular, metabolic, sedative and hyperprolactinaemia-related side-effects with cariprazine treatment (254).

5.7 Limitations and suggestions for future studies

One limitation of the systematic review concerns publication bias (260,261). It is a common phenomenon that individuals are hesitant to write up the findings as a publication if the results/outcomes are not what was expected/are neutral. This is especially true for case reports (261,262) about medication, where authors tend to submit a paper if the findings are either positive or if a serious adverse effect emerges. This bias can potentially be observed in our review as well: only a few studies (n=4, 10.5%) reported on negative findings about cariprazine, and all these negative findings related to serious adverse effects.

Regarding the HD study, the design of the study holds some limitations. For instance, due to the observational nature of the study, causality cannot be drawn, therefore it is not possible to determine with certainty whether cariprazine is in fact efficacious in both the motor and non-motor symptoms of HD. Furthermore, there was no control group, thus it is not possible to compare the effects of cariprazine on symptoms versus no treatment on symptoms, further complicating causality to be drawn. However, this was the first study to investigate the potential of cariprazine, a D3 partial agonist, in the treatment of HD. Before conducting more rigorous, cost- and time-consuming studies, such an observational study can serve as a good starting point in determining whether this direction is useful to follow up on.

In addition to the design, it has to be noted that the sample size is relatively small, making extrapolation of the findings difficult. However, it is important to note that HD is a rare disease, making patient recruitment difficult. Yet, future studies should aim for a larger sample size in order to confirm the validity of these findings, as well as follow up on patients for a longer time.

Furthermore, the choice of scales used in the study could be improved to make the evaluation of different symptoms more robust. Apathy was evaluated with a single item of the UHDRS Behavioural Examination subscale, therefore it is not possible to determine whether cariprazine truly alleviated apathy. However, literature shows that this is a commonly used scale for the evaluation of apathy (202) - yet, a separate scale is recommended. Therefore, one of the most important adaptations future studies should make is the administration of an appropriate apathy evaluation scale, like the Apathy Evaluation Scale in order to properly detect potential improvements in apathy. Additionally, BDI has received some criticism stating that it is not the most optimal choice for evaluating changes in depressive symptoms as it is not sensitive enough for detecting changes (263). Nevertheless, we did not experience this problem, as statistically significant changes were observed from baseline to Week 12. Yet, in the future, the use of an alternative (or additional) depression scale should be considered, like the MADRS which is widely used in both clinical practice and research and is rated by the clinician. It has to be further noted that the BDI is a self-report measure, relying on the patient's own perception of their symptoms, which can be distorted. Therefore, it would be important to include an additional clinical- or informant-reported measure.

6 Conclusions

The first-ever study of cariprazine in HD showed that cariprazine effectively reduced the motor, cognitive, and behavioural/mood symptoms associated with HD.

Cariprazine might have the potential to address one of the major unmet needs in HD, which is to adequately address and improve apathy (i.e., loss of motivation), based on the following observations:

- Previous findings showed that some parts of the PFC and the striatum play a crucial role in apathy;
- Since the D3 receptors are expressed in these areas, their role is implicated in apathy;
- Some aspects of the negative symptom cluster (i.e., avolition and anhedonia) in psychiatric disorders correspond to apathy in neurological disorders;
- Cariprazine was demonstrated to improve primary, predominant negative symptoms in schizophrenia, outperforming an active comparator, risperidone;
- Further evidence is available from other indications; this thesis showed that cariprazine can improve negative symptoms in Wernicke-Korsakoff syndrome and methamphetamine-induced psychosis as well;
- This thesis provided the first-ever evidence for the effectiveness of cariprazine in the improvement of behavioural symptoms in HD;
- Cariprazine is a D3-preferring partial agonist, which is the only approved antipsychotic that can occupy the D3 receptors in the presence of dopamine *in vivo* and can therefore alleviate the D3-associated symptoms, including negative symptoms.

However, further studies are warranted with more rigorous design to confirm the findings of this study.

Furthermore, cariprazine appeared to address motor dysfunction in HD. Although the exact mechanism underlying this improvement is unknown, it is likely attributable to the high affinity of cariprazine to D2 and D3 receptors where it exerts partial agonist activity.

In addition, this systematic review was the first one ever to collect, synthesise, and evaluate the available case reports of cariprazine. It confirmed the effectiveness and safety of cariprazine in real-world settings, in heterogeneous patient populations with varying diagnosis, age, illness-severity and comorbid conditions. This confirms and complements the knowledge gained from clinical trials.

Of note, cariprazine effectively addressed the neuropsychiatric symptoms in various indications other than the classic, approved ones. For instance, it aided the complete abstinence

of patients with SUD, reduced symptoms of OCD and improved neuropsychiatric symptoms in Wernicke-Korsakoff syndrome. These findings support the transdiagnostic approach that suggests that disorders have shared underlying mechanisms and therefore a compound could be effective in many different indications and symptoms. Hence, cariprazine could be a good pharmacotherapeutic option for patients with different disorders, as it can likely improve neuropsychiatric symptoms independent of the diagnosis.

7 Summary

The HD study was the first one ever to investigate the effectiveness of cariprazine in this patient population. It was a 12-week, open-label, single arm, retrospective, observational study with 15 enrolled patients. Cognitive symptoms were evaluated using the ACE and the Cognitive Examination of the UHDRS, both of which revealed the effectiveness of cariprazine. Behavioural/mood symptoms were examined using the BDI and the Behavioural Examination of the UHDRS - again, cariprazine proved to be efficacious in the alleviation of these symptoms as well. Strikingly, cariprazine did not only improve cognitive and behavioural/mood symptoms, but also the motor symptoms, as measured by the Motor Examination of the UHDRS, with the positive effect being driven by the vast majority of the single items.

In addition to the HD study, a systematic review of the available cariprazine case reports was conducted, which was the first one to do so. In fact, generally, there are not many systematic reviews of case reports investigating the real-world effectiveness and safety of psychiatric compounds. The systematic review synthesised, analysed and evaluated information from 38 cases. In addition to the approved indications (i.e., schizophrenia, depressive and manic/episodes associated with bipolar disorder and MDD as adjunctive therapy), it included patients with disorders that have not been investigated before in relation to cariprazine, especially not in clinical trials. These included SUD (yielding abstinence in most cases), Wernicke-Korsakoff syndrome (reducing psychotic, cognitive and negative symptoms and improving psychosocial functioning), OCD (reducing OCD symptoms completely) and borderline personality disorder (reduction in affective symptoms, and completely resolving hostility and impulsivity).

Taken together, cariprazine seems to be a promising treatment option for the treatment of various disorders, including HD and SUD. The uniqueness of cariprazine lies in its partial agonist activity at D3 receptors to which it binds with high affinity - even higher than endogenous dopamine, making it the only approved antipsychotic to occupy the D3 receptors in the presence of dopamine *in vivo*. Therefore, cariprazine can achieve the effects associated with D3 receptors (i.e., cognitive, negative, and affective symptom-reduction). In summary, the findings imply that cariprazine could alleviate the most troublesome symptoms from patient functioning point-of-view, which are cognitive, negative, and affective symptoms. However, the efficacy cariprazine needs to be established in these indications as well, by conducting studies with more rigorous design to be able to draw causality.

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9 Bibliography of the candidate' publications

9.1 Publications related to the dissertation

Csehi, R., Molnár V., Fedor, M., Zsumbera, V., Palásti, Á., Acsai, K., Grosz, Z., Németh, G. & Molnár, M. J. Improving motor symptoms in Huntington's disease during cariprazine treatment. Orphanet J. Rare Dis. 2023;18:1-10.

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9.2 Publications not related to this dissertation

Németh G, Csehi R. Editorial: Novel antipsychotics within and beyond clinical trials: The treatment of overlapping psychiatric disorders with D3-D2 partial agonists. Front Psychiatry. 2022;13:1–4.

Grunze H, Csehi R, Born C, Barabássy Á. Reducing addiction in bipolar disorder via hacking the dopaminergic system. Front Psychiatry. 2021;12:1–7.

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Riches S, Azevedo L, Steer N, Nicholson S, Vasile R, Lyles S, Csehi R, Fialho C, Waheed S, Lokhande M. Brief videoconference-based Dialectical Behaviour Therapy skills training for Covid-19-related stress in acute and crisis psychiatric staff. Clin Psychol Forum. 2021;337.

Riches S, Csehi R, Steer N, Azevedo L, Vasile R, Lokhande M. Video call-based psychological therapy for inpatients during the COVID-19 lockdown. Cyberpsychology Bull. 2020;3.

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NYILATKOZAT EREDETISÉGRŐL ÉS SZERZŐI JOGRÓL

a PhD disszertáció elkészítésére vonatkozó szabályok betartásáról

Alulírott Csehi Réka jelen nyilatkozat aláírásával kijelentem, hogy a ’Dopaminergic dysfunction in neuropsychiatric disorders and the effect of cariprazine in their treatment’ című PhD értekezésem önálló munkám, a dolgozat készítése során betartottam a szerzői jogról szóló 1999. évi LXXVI tv. vonatkozó rendelkezéseit, a már megjelent vagy közlés alatt álló közlemény(ek)ből felhasznált ábra/szöveg nem sérti a kiadó vagy más jogi vagy természetes személy jogait.

Jelen nyilatkozat aláírásával tudomásul veszem, hogy amennyiben igazolható, hogy a dolgozatban nem saját eredményeimet használtam fel vagy a dolgozattal kapcsolatban szerzői jog megsértése merül fel, a Semmelweis Egyetem megtagadja PhD dolgozatom befogadását, velem szemben fegyelmi eljárást indít, illetve visszavonja a már odaítélt PhD fokozatot.

A dolgozat befogadásának megtagadása és a fegyelmi eljárás indítása nem érinti a szerzői jogsértés miatti egyéb (polgári jogi, szabálysértési jogi, büntetőjogi) jogkövetkezményeket.

Tudomásul veszem, hogy a PhD értekezés nyilvánosan elérhető formában feltöltésre kerül az Országos Doktori Tanács honlapjára.

Budapest, 2024.05.25.

aláírás