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

PhD thesis

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1 Introduction

In neuropsychiatric disorders, symptom overlaps are common, often due to similar pathophysiological processes. One such overlap is the dysfunction of the dopamine system, which can present predominantly with motor symptoms, as seen in Parkinson's or Huntington's disease, or predominantly with psychiatric symptoms, such as in schizophrenia, bipolar disorder, or substance addiction. Mental symptoms are also present in disorders where motor symptoms dominate, but the focus is usually less on treating these psychological symptoms, despite their potential to equally diminish quality of life as extrapyramidal symptoms.

In schizophrenia, both hyper- and hypofunction of the dopamine system are observed in different areas, primarily involving dopamine D2 (positive symptoms) and D3 receptors (negative, affective, cognitive symptoms). Similarly, in bipolar disorder, D2 receptor dysfunction is linked to mania, and D3 receptor dysfunction to depression and cognition. In Huntington's disease, a biphasic change in dopamine levels is seen, with D1 and D2 receptors involved in motor symptoms and D3 receptors in cognitive and psychiatric (personality/behavioral) problems. In substance addiction, D3 receptors are notably important due to their anatomical location, with high expression in limbic areas, indicating their significant role in motivation and emotion regulation, and consequently, in addiction.

The pathophysiological and symptomatic overlaps allow a single drug to improve multiple conditions, simplifying treatment regimens and enhancing patient adherence. Effective treatments aim to improve as many symptom clusters as possible, especially those causing the most distress, such as negative, cognitive, or affective symptoms. Improvement in these areas enhances patients' quality of life, a currently unmet need in neuropsychiatric disorders.

Cariprazine is a dopamine D3 receptor-preferring D2/D3 partial agonist, approved by the European Medicines Agency for schizophrenia. Additionally, the US Food and Drug Administration has approved it for manic/mixed episodes and depressive episodes associated with bipolar I disorder as well as for the adjunctive treatment of major depressive disorder. Among antipsychotics, cariprazine uniquely binds to D3 receptors in vivo in the presence of dopamine, resulting in improvements in negative, cognitive, and affective symptoms associated with D3 activity. It also binds with high affinity to D2 receptors, exerting partial agonist effects, thus achieving improvements in mania, motor, and positive symptoms.

2 Aims and Objectives

2.1 The effectiveness of cariprazine in Huntington's Disease

Current treatments of HD are symptom-based with agents showing fairly good efficacy in controlling motor symptoms, but not non-motor symptoms. Yet, non-motor symptoms affect patient functioning and quality of life more adversely than motor symptoms, and compounds addressing all symptom domains are the most desired. Therefore, the aim of this study was to determine whether cariprazine has the potential to improve symptoms of HD, especially the non-motor symptoms.

2.2 Systematic review of cariprazine case reports

The efficacy and safety of cariprazine has 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. Therefore, the objective of this systematic review was to systematically 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.

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 huntingtin 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.

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. 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. Mixed model for repeated measures was used for statistical analysis.

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

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 Cognitive Examination (ACE) was performed, assessing five cognitive domains: attention, memory, fluency, language, and visuospatial abilities.

Motor symptoms were evaluated using the Motor Examination of the UHDRS. The Total Motor Score (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.

3.2 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

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 (Congress abstracts were excluded due to insufficient information), 4) written in English language.

3.2.3 Data Analysis

Necessary information was retrieved from all articles and 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. Descriptive analysis was 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

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. 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 3.79 (SD=2.89) 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 mg/day and another to 4.5 mg/day. Ten patients received a stable dose of TBZ during the treatment period.

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. 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, $p<0.0001$).

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).

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, $p=0.0009$).

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 on the majority of the UHDRS Motor Examination items: maximal chorea, maximal dystonia, eye movements, hand movements, balance, rigidity

and oropharyngeal symptoms. Regarding gait, there was no objective improvement, although patients reported a subjective improvement, and body bradykinesia stagnated.

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, while another patient 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. 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).

4.2.2 Overview of results/ demographics

Out of the 38 cases, 18 were male and 19 were female (one was not specified) with a mean age of 33.8 years (median=31). The majority of patients had schizophrenia diagnosis (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%). 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%).

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%). 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%).

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 substance use disorder (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.

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 substance use disorder 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. Patients experienced significant reductions in psychotic, cognitive and negative symptoms, as well as impulsivity, self-neglect and sleep-related issues (both insomnia and sedation).

4.2.5 Mood Disorders

Two patients were diagnosed with a mood disorder: one with bipolar I disorder and comorbid attention-deficit hyperactivity disorder and substance use disorder and one patient with major depressive disorder. The former patient experienced a significant reduction in agitation, restlessness, cognitive symptoms and became become substance free even after 27 months, while the latter experienced an improvement in sexual functioning (although no improvement in affective symptoms).

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 presented with a wide-range of residual symptoms: psychotic, cognitive and negative symptoms, as well as reduced psychosocial functioning and psychomotor retardation, in all which cariprazine yielded improvement. A male patient with a diagnosis of obsessive-compulsive disorder with paranoid schizophrenia, experienced obsessive-compulsive symptom reduction within a week. For the third patient with borderline personality disorder, cariprazine brought the complete resolution of impulsivity and hostility symptoms, and alleviated affective symptoms.

5 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 substance use disorder, reduced symptoms of obsessive-compulsive disorder 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.

6 Bibliography of the candidate's publications

6.1 Publications related to the dissertation

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