THE ROLE OF THE DOPAMINERGIC SYSTEM IN NEGATIVE SYMPTOMS OF SCHIZOPHRENIA – AN INDUSTRY OUTLOOK INTO THE DEVELOPMENT OF A NEW-GENERATION ANTIPSYCHOTIC

Ph.D. thesis

Balázs Szatmári, MD

Semmelweis University Doctoral School
János Szentágothai Neurosciences Division

Supervisor: Dr György Németh

Official reviewers: Dr. Xenia Gonda
Dr. Róbert Herold

Head of the Complex Examination Committee:
Dr. Dániel Bereczki

Members of the Final Examination Committee:
Dr. Ildikó Vastagh
Dr. Péter Balicza

Budapest, 2025

1. Introduction

Schizophrenia is a lifelong mental disorder recognized as one of the most disabling illnesses globally, with a median lifetime prevalence of 0.749% and an incidence rate of 1.631 per 100 000 people. It typically begins in adolescence or early adulthood, with men being diagnosed slightly more often than women. The disorder is characterized by positive symptoms (e.g. hallucinations, delusions, disorganized thoughts), negative symptoms (e.g. alogia, blunted affect, avolition), and cognitive symptoms (e.g. impairments in memory, attention, and processing speed). This complex symptomatology fluctuates throughout the course of the disease.

The classification of schizophrenia has evolved, with the DSM-5-TR being the most recent and widely used system. Despite this, the thesis uses DSM-IV-TR nomenclature due to the timing of the studies discussed.

The dopamine hypothesis is the most widely accepted theory for the pathology of schizophrenia, underpinning the development of antipsychotic medications that target dopamine receptors. There are five major dopamine receptors, categorized into D1-like and D2-like receptors, and four major dopamine pathways in the brain. The mesolimbic pathway's hyperactivity is linked to psychosis, while the nigrostriatal pathway's blockage by antipsychotics can cause movement disorders (extrapyramidal symptoms, EPS). The tuberoinfundibular pathway's inhibition leads to hyperprolactinemia, and the mesocortical pathway's role in cognitive and negative symptoms is still under investigation.

Antipsychotic medications are classified into first-generation (typical), second-generation (atypical), and third-generation (atypical partial agonists). First-generation antipsychotics, like haloperidol, primarily target D2 receptors but cause significant side effects. Second-generation antipsychotics, such as risperidone and olanzapine, also target serotonin receptors to reduce motor side effects. Third-generation antipsychotics, like aripiprazole, aim to address positive, negative, and cognitive symptoms by targeting multiple dopamine receptors.

Cariprazine, developed by Gedeon Richter and Abbvie, is a third-generation antipsychotic with partial agonist activity on D3/D2 receptors and proven in vivo D3 receptor binding. It is approved for treating schizophrenia and bipolar disorder in adults, as well as adjunctive treatment in major depression. Clinical trials have demonstrated cariprazine's efficacy and safety in treating positive symptoms of schizophrenia, with a favorable side-effect profile compared to other antipsychotics.

Post-hoc analyses of cariprazine's clinical trials suggest its potential efficacy in treating negative symptoms, warranting further investigation in well-designed prospective studies.

2. Objectives

The objective of this research was to **assess the effectiveness** of a novel D3 preferring D3/D2 partial agonist cariprazine on the negative symptoms of schizophrenia.

Based on our post-hoc analysis there was a signal that cariprazine is effective in treating the negative symptoms of schizophrenia.

My objective was to validate or refute the hypothesis of cariprazine's efficacy through a well-designed clinical trial, in details:

- to identify the most suitable endpoint to assess efficacy on the primary negative symptoms of schizophrenia;
- to define the appropriate inclusion and exclusion criteria that ensure a patient population who is suffering from both primary and predominant negative symptoms;
- to define the appropriate efficacy and safety analyses from a medical perspective;
- to evaluate the results and define key messages for the clinical study report.

3. Methods

A randomized, double-blind, active-controlled Phase IIIb study was initiated specifically assessing the efficacy of cariprazine in patient with predominant negative symptoms (EudraCT 2012-005485-36).

3.1. Overall Study Design

This clinical study was a multinational, randomized, double-blind, active-controlled, parallel-group, fixed/flexible-dose study in adult patients with schizophrenia.

It consisted of three periods:

- 4-week prospective lead-in period;
- 26-week double-blind treatment period, including a 2-week up-titration (Part 1) and a 24-week treatment continuation (Part 2);
- 2-week safety follow-up period.

After a detailed screening visit (Visit 1) to assess inclusion and exclusion criteria, eligible patients entered the 4-week lead-in period. An intermediate visit (Visit 2) assessed ongoing eligibility, focusing on symptom stability. At the end of the lead-in period, a baseline visit (Visit 3) reassessed eligibility criteria before randomization. Eligible patients were then randomized to receive either cariprazine or risperidone (1:1). Initial doses were 1.5 mg/day cariprazine or 2.0 mg/day risperidone, increasing to 3.0 mg/day in the second week, and reaching target doses of 4.5 mg/day cariprazine or 4 mg/day risperidone by week 3.

Weekly visits were scheduled during the first month of double-blind treatment (Visits 4-7), followed by bi-weekly (Visit 8) and then monthly visits (Visits 9-13). Investigators were encouraged to maintain target doses but could adjust to 6 mg/day for impending relapse or 3 mg/day for tolerability, with a return to target doses as soon as possible. This dose flexibility was allowed once in each direction during the double-blind period.

3.2. Patient Selection

Eligible patients were 18-65 years old, diagnosed with schizophrenia based on DSM-IV-TR criteria via a structured clinical interview (SCID-CT), with onset at least 2 years before screening. Patients had to sign an informed consent form (ICF) and understand the patient information sheet before any study related procedures. They needed to be known to the investigator or referred with reliable documentation of their history for at least 1 year prior to screening.

Patients had to exhibit predominant negative symptoms for at least 6 months before screening, defined by the PANSS factor score for negative symptoms (PANSS-FSNS) and PANSS factor score for positive symptoms (PANSS-FSPS) scores. At screening and randomization, they needed a PANSS-FSNS score ≥24 and a score of ≥4 on at least 2 of the following PANSS items: N1 (Blunted affect), N4 (Passive/apathetic social withdrawal), N6 (Lack of spontaneity and flow of conversation). They also had to be stable in positive symptoms for at least 6 months, with a PANSS-FSPS score >19 and a score of ≥4 on more than 2 of the following PANSS items: P1 (Delusions), P3 (Hallucinatory behavior), P5 (Grandiosity), P6 (Suspiciousness), G9 (Unusual thought content) at screening and randomization.

Patients had to be on a stable dose of 1-2 antipsychotics for at least 30 days before screening. Other main exclusions included recent risperidone treatment, previous non-response to risperidone, clozapine treatment within the last 12 months, moderate to severe depressive symptoms, significant suicide risk, violent behavior, substance abuse, and significant parkinsonian symptoms.

Concomitant treatments had to be discontinued, except for current antipsychotics during down-titration, and specific and predefined medications for agitation, sleep, and EPS.

3.3. Study Variables

All scales were administered by experienced and certified raters, who underwent a predefined certification procedure involving live or online training and assessment by experts.

Structured Clinical Interview of the Positive and Negative Syndrome Scale (SCI-PANSS): This primary tool assesses positive symptoms, negative symptoms, and general psychopathology in schizophrenia. It consists of 30 items rated from 1 (not present) to 7 (extremely severe), with total scores ranging from 30 to 210. The primary endpoint, PANSS-FSNS, included the following 7 items N1 (Blunted affect), N2 (Emotional withdrawal), N3 (Poor rapport), N4 (Passive social withdrawal), N6 (Lack of spontaneity), G7 (Motor retardation), G16 (Active social avoidance) with a total score ranging from 7 to 49.

Personal and Social Performance Scale (PSP): This clinician-rated scale assesses overall functionality with a maximum score of 100, divided into four domains: social useful activities, personal and social relationships, self-care, and disturbing/aggressive behaviors. Higher scores indicate better functioning.

Clinical Global Impression Scales (CGI-S and CGI-I): CGI-S assesses the severity of the patient's condition on a scale from 1 (normal) to 7 (extremely ill). CGI-I measures improvement or worsening compared to baseline, with scores ranging from 1 (very much improved) to 7 (very much worse).

Calgary Depression Scale for Schizophrenia (CDSS): This 9-item scale assesses depressive symptoms in schizophrenic patients, with each item rated from 0 (absent) to 3 (severe).

3.4. Study Outcomes

The primary efficacy parameter of the study was the change from baseline (CfB) to week 26 (Visit 13) on the PANSS-FSNS.

The secondary efficacy parameter of the study was the CfB to week 26 (Visit 13) on the Personal and Social Performance Scale (PSP) total score.

Additional efficacy assessments included the changes on the PANSS negative subscale score, the PANSS total score, the PANSS general psychopathology subscale score, the CGI-S, the CGI-I and the responder rates based (≥20% improvement on the PANSS-FSNS).

Pseudospecificity was also assessed on the PANSS-FSPS, the CDSS total score, as well as the safety EPS scales (AIMS, BARS, SAS).

Safety was assessed using standard adverse event collection, vital signs, clinical laboratory, body weight, ECG parameters, physical examination, C-SSRS.

3.5. Statistical Methods

The study populations for statistical analyses were defined as follows:

- **Screened population:** All patients who attended screening (Visit 1), signed the ICF, and were assigned a patient number.
- **Randomized population:** All patients in the screened population who received a randomization number at baseline (Visit 3).
- **Safety population:** All patients in the randomized population who took at least one dose of double-blind treatment.
- **ITT population:** All patients in the safety population with at least one post-baseline PANSS-FSNS assessment.

Efficacy analyses were performed on the ITT population, with baseline values from Visit 3. Statistical tests were conducted at a two-sided 5% significance level. The sample size of 210 per arm was based on a 90% power to detect an effect size of 0.25, assuming a 2.25-point difference between cariprazine and risperidone arms, and a 10% drop-out rate.

The primary analysis used a mixed-effects model for repeated measures (MMRM), with fixed effects for treatment group, study center, visit, and their interactions, and covariates for baseline value and its interaction with visit. Sensitivity analyses included the pattern-mixture model and ANCOVA with the LOCF approach.

The same statistical methods were used for secondary and additional efficacy endpoints, including pseudospecificity. Responder rate analyses employed logistic regression with treatment group, study center, and baseline score as covariates. Safety endpoints were analyzed using descriptive statistics without hypothesis testing.

4. Results

4.1. Patient Disposition, Demographics and Schizophrenia History

A total of 533 patients were screened for the study, with 461 found eligible and randomized. Of these, 460 received at least one dose of double-blind treatment, and 456 were included in the ITT population. 356 patients (77.4%) completed the double-blind treatment period, and 355 completed the safety follow-up. The most common reason for early termination was adverse event (10.2%), with similar rates in both the cariprazine and risperidone groups.

The majority of patients were recruited from Ukraine (25.8%) and Russia (23.5%), with 40.9% from EU countries, including Bulgaria, Croatia, the Czech Republic, France, Hungary, Poland, Romania, and Spain. The median age of participants was 40 years, with a sex ratio of 57.4% male and 42.6% female. Most patients had paranoid schizophrenia (83.5%), with a median duration of 10.1 years. The majority had fewer than 5 exacerbations (59.6%), while a smaller proportion experienced 5-10 exacerbations (30.4%), 11-15 exacerbations (6.7%), and more than 15 acute episodes (3.3%).

4.2. Primary Efficacy Endpoint – PANSS Factor Score for Negative Symptoms

The primary efficacy parameter was the change from baseline to Week 26 in the PANSS-FSNS, analyzed using the MMRM approach. Total scores on the PANSS-FSNS ranged from 7 to 49, with lower scores being favorable. The least squares mean change from baseline at Week 26 was -8.9 for cariprazine and -7.4 for risperidone, with a pairwise difference of -1.5 (95% CI: -2.4, -0.5; P = 0.002). From Week 14 onwards, there was a statistically significant difference between the treatment arms, favoring cariprazine (Figure 1).

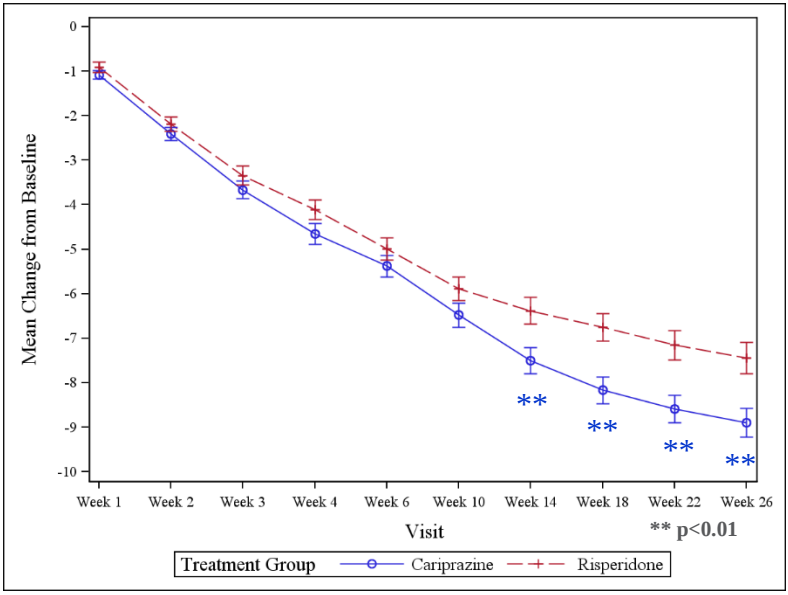

Figure 1 – Mean Treatment Profiles for the Change from Baseline (± SE) in PANSS Factor Score for Negative Symptoms (MMRM), ITT Population

Sensitivity analysis using an ANCOVA model with the LOCF approach also showed a statistically significant difference in favor of cariprazine. The LS mean CfB to Week 26/ET on the PANSS-FSNS were 8.1 and 6.8 for cariprazine and risperidone, respectively. The pairwise difference was 1.3 (95% CI: -2.2, 0.5; P = 0.003).

4.3. Secondary Efficacy Endpoint – Personal and Social Performance Scale

The secondary efficacy parameter was the change from baseline to endpoint (Week 26/ET) on the PSP total score, using the MMRM approach. The PSP score ranged from 1 to 100, with a higher score being favorable. The LS mean change from baseline at Week 26 was 14.3 for cariprazine and 9.7 for risperidone. The pairwise difference was 4.6 (95% CI: 2.7, 6.6), with a P value of 0.001. From Week 10 onwards, there was a statistically significant difference between the treatment arms, favoring cariprazine (Figure 2).

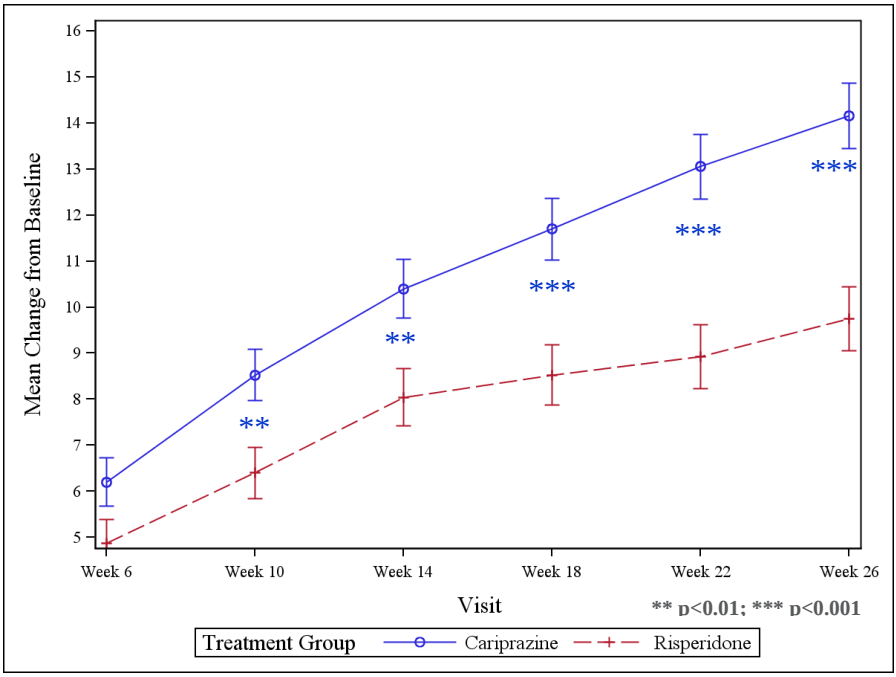

Figure 2 – Mean Treatment Profiles (± SE) for the Change from Baseline in the PSP Score (MMRM), ITT Population

The sensitivity analysis based on an ANCOVA model using the LOCF approach on the secondary endpoint also showed a statistically significant difference in favor of cariprazine over risperidone. The LS mean change from baseline to Week 26/ET on the PSP total score was 12.7 for cariprazine and 9.0 for risperidone. The pairwise difference was 3.7 (95% CI: 1.7, 5.6) with a P value of <0.001.

4.4. Additional Efficacy Endpoints of Interest

4.4.1. CGI-S and CGI-I

For the CGI-S and CGI-I analyses, the same MMRM approach was used to evaluate changes from baseline to the endpoint (Week 26/ET). At Week 26, the CGI-S LS mean change from baseline (CfB) was 0.9 for cariprazine and 0.7 for risperidone. The pairwise difference was -0.2 (95% CI: -0.4, -0.1), with a P value of 0.005. For the CGI-I, the LS mean CfB at Week 26 was 2.5 for cariprazine and 2.9 for risperidone. The

pairwise difference was -0.4 (95% CI: -0.6, -0.2), with a P value of <0.001.

4.4.2. PANSS Total Score

The PANSS total score was analyzed using the same MMRM methodology. At Week 26, the LS mean change from baseline (CfB) in PANSS total score was -16.9 for cariprazine and -14.8 for risperidone. The pairwise difference was -2.1 (95% CI: -4.3, 0.1), with a P value of 0.065.

4.4.3. PSP Subdomains

The PSP scale can be divided into four subdomains, each reflecting different aspects of patient functioning: socially useful activities, personal and social relationships, self-care, and disturbing/aggressive behavior. LS mean CfB scores and LS mean differences for these subdomains were also computed using the MMRM approach. At Week 26, cariprazine demonstrated more favorable CfB compared to risperidone in several areas.

In the socially useful activities area, the least squares mean CfB scores were -0.95 for cariprazine and -0.60 for risperidone, with a pairwise difference of -0.35. Cariprazine showed a more favorable CfB from Week 6 to Week 26, with statistically significant differences observed at Weeks 18 (P = 0.004), 22 (P = 0.003), and 26 (P < 0.001).

In the personal and social relationships area, the least squares mean CfB scores were -0.85 for cariprazine and -0.61 for risperidone, with a pairwise difference of -0.24 (P < 0.001). Cariprazine showed a more favorable CfB from Week 6 onward, with statistically significant differences at each follow-up visit where the scale was measured.

Lastly, in the self-care area, the least squares mean CfB scores at Week 26 were -0.70 for cariprazine and -0.50 for risperidone, with a pairwise difference of -0.20. The CfB favored cariprazine from Week 10 onward, with statistically significant differences at Weeks 22 (P = 0.023) and 26 (P = 0.004).

4.5. Pseudospecificity Analyses

The goal of the pseudospecificity analyses was to assess if the improvements seen on the primary endpoint can be attributed to improvement in primary negative symptoms or was influenced by other secondary factors, such as improvement in positive or depressive symptoms.

4.5.1. PANSS Factor Score for Positive Symptoms

The change from baseline to endpoint (Week 26/ET) on the PANSS-FSPS was assessed by utilizing the same MMRM approach as for the other parameters. The baseline mean PANSS-PSFS was low in both arms, 8.7 and 8.6 in the cariprazine and risperidone groups, respectively. The LS mean CfB at Week 26 were -1.1 for both treatment arms. The pairwise difference was therefore 0.0 (95% CI: -0.4, 0.5), with a P value of 0.963.

4.5.2. Calgary Depression Scale for Schizophrenia

The other pseudospecificity endpoint was the change from baseline to endpoint (Week 26/ET) on the CDSS, assessed using the MMRM approach. Due to the exclusion criteria, both arms had low baseline CDSS scores. The LS mean change from baseline at Week 26 was -0.3 for cariprazine and -0.2 for risperidone, with an LS mean difference of -0.1, showing no statistical difference (P = 0.658).

4.6. Safety Assessments

4.6.1. Overview of Adverse Events

Adverse events (AEs) were monitored throughout the study, but for analysis, only treatment-emergent adverse events (TEAEs) were considered. TEAEs are defined as any adverse events that began after the first dose of the investigational medicinal product (IMP) or worsened if already present. The analysis focused on the safety population.

The incidence of TEAEs during the double-blind period was similar between the cariprazine and risperidone groups, with 53.5% of patients in the cariprazine group and 57.0% in the risperidone group experiencing TEAEs.

Slightly fewer patients in the cariprazine group (36.5%) experienced TEAEs related to the study drug compared to the risperidone group (41.3%).

There was one death in the risperidone group, which was not related to the study drug or interventions. The cause of death was a brain tumor and pulmonary carcinoid tumor.

The most common adverse events (in ≥3% of patients) reported during the double-blind treatment period included:

- **Nervous System Disorders**: Akathisia (8.3% in cariprazine, 5.2% in risperidone), dizziness (1.7% in cariprazine, 4.8% in risperidone), headache (5.7% in cariprazine, 10.4% in risperidone), somnolence (3.9% in cariprazine, 5.7% in risperidone) and cogwheel rigidity (4.7% in cariprazine, 3.5% in risperidone).
- **Psychiatric Disorders**: Anxiety (5.7% in cariprazine, 4.8% in risperidone), insomnia (9.1% in cariprazine, 10.0% in risperidone), schizophrenia (6.5% in cariprazine, 4.3% in risperidone).
- **Gastrointestinal Disorders**: Nausea (3.9% in cariprazine, 2.6% in risperidone).
- **General Disorders**: Fatigue (2.2% in cariprazine, 4.3% in risperidone).
- **Infections**: Nasopharyngitis (1.3% in cariprazine, 3.0% in risperidone).

Adverse events leading to discontinuation were reported in 10.0% of patients in the cariprazine group and 11.7% in the risperidone group. The most common reasons for discontinuation were schizophrenia, insomnia, and akathisia.

The severity of adverse events was categorized as mild, moderate, or severe. The majority of adverse events were mild to moderate in both treatment groups. Severe adverse events were less common.

Non-Fatal Serious Adverse Events (SAEs) during the double-blind period were reported in 3.0% of patients in both treatment groups. Discontinuation due to serious adverse events was reported in 2.2% of patients in the cariprazine group and 3.0% in the risperidone group.

4.6.2. Scales Assessing the Extrapyramidal Symptoms

Three scales were utilized in the study to evaluate extrapyramidal symptoms, which are among the most significant adverse effects of antipsychotic drugs targeting the dopaminergic system.

Abnormal Involuntary Movement Scale (AIMS): this scale assesses involuntary movements related to antipsychotic treatment, including facial, oral, extremity, and trunk movements. It comprises 12 items, with 2 questions about dental status that are not rated for severity.

Barnes Akathisia Rating Scale (BARS): this 4-item scale measures drug-induced akathisia, including observation, self-awareness, distress associated with akathisia, and an overall severity question.

Simpson-Angus Scale (SAS): this 10-item scale evaluates parkinsonism associated with antipsychotic use, measuring gait, rigidity, glabella tap, tremor, and salivation.

All these scales were relevant both from a safety and a pseudospecificity perspective.

AIMS: at Week 26/ET, the mean total scores indicated no to mild symptoms, with means ranging between 0.1 and 0.2 in the cariprazine and risperidone groups, respectively. No clinically meaningful differences between treatment groups were observed throughout the study.

BARS: few patients reported distress related to akathisia (10 patients in both treatment arms, with mild to moderate intensity). The BARS total scores showed minimal changes throughout the study, with no differences between the groups.

SAS: this scale also showed no to mild symptoms of parkinsonism at Week 26/ET (0.4 and 0.6 in the cariprazine and risperidone arms, respectively), with virtually no change from baseline (-0.0 and 0.1 in the cariprazine and risperidone groups, respectively).

5. Conclusions

In conclusion, cariprazine has proven effective in treating primary, predominant negative symptoms. With the appropriately defined study's inclusion and exclusion criteria I was able to ensure the enrolment of an appropriate patient population, and the carefully selected primary efficacy endpoint (change from baseline to end on the PANSS-FSNS) made it possible to demonstrate a statistically significant advantage for cariprazine over risperidone. Patient functionality, measured as a secondary endpoint on the PSP, also improved significantly, indicating that symptom improvement led to meaningful functional gains.

With well-defined analyses, I was able to demonstrate consistent and robust data:

- improvement in negative symptoms was followed by enhanced functionality
- all relevant subdomains of functionality showed similar positive results
- overall patient condition improvements, measured by the Clinical Global Impressions scales, were consistent with symptom and functionality improvements
- positive and depressive symptoms, measured by the PANSS-FSPS and CDSS, respectively, did not improve, ruling out secondary improvement in negative symptoms
- this is also true for the extrapyramidal symptoms, measured by the BARS, AIMS, and SAS, as they did not show any concerning signals that would imply secondary, pseudospecific improvements in negative symptoms.

The study design and careful patient selection ensured the results are relevant and can be extrapolated to primary negative symptoms in patients with predominant negative symptoms.

Although the current study enrolled patient between 18 and 65 years, negative symptoms can be predominant at an earlier (adolescents, prodromal phase) or later stage (elderly, residual phase) of the disease as well. Overall data on antipsychotic efficacy and safety in adolescents and elderly are scarce. Cariprazine has safety data for both adolescents (13-

17 years) and elderly (≥65 years). A Phase I trial in adolescents showed it was safe and well-tolerated, with similar safety profiles to adults. Another study in conducted in Japan assessed the long-term safety and efficacy in the elderly, showing cariprazine is well-tolerated with fewer adverse events compared to risperidone.

In conclusion, although the exact pathophysiology of negative symptoms is still unknown, by this study I was able to provide first-time evidence in a clinical setting that D3 receptors might play an important role in negative symptomatology, offering the first effective treatment for patients suffering from negative symptoms.

6. Bibliography of the candidate's publications

Publications related to the thesis:

Culpepper L, Vieta E, Kelly DL, Patel MD, **Szatmári B**, Hankinson A, Earley WR. Minimal Effects of Cariprazine on Prolactin Levels in Bipolar Disorder and Schizophrenia. Neuropsychiatr Dis Treat. 2022 May 12;18:995-1011. doi: 10.2147/NDT.S348143. PMID: 35591886; PMCID: PMC9112044.

Szatmári B, Barabássy Á, Harsányi J, Laszlovszky I, Sebe B, Gál M, Shiragami K, Németh G. Cariprazine Safety in Adolescents and the Elderly: Analyses of Clinical Study Data. Front Psychiatry. 2020 Mar 3;11:61. doi: 10.3389/fpsyt.2020.00061. PMID: 32194443; PMCID: PMC7062963.

Earley W, Guo H, Daniel D, Nasrallah H, Durgam S, Zhong Y, Patel M, Barabássy Á, **Szatmári B**, Németh G. Efficacy of cariprazine on negative symptoms in patients with acute schizophrenia: A post hoc analysis of pooled data. Schizophr Res. 2019 Feb;204:282-288. doi: 10.1016/j.schres.2018.08.020. Epub 2018 Aug 29. PMID: 30172595.

Barabassy A, **Szatmári B**, Laszlovszky I, Németh G. Negative Symptoms of Schizophrenia: Constructs, Burden, and Management. IntechOpen, 2018; pp. 43-62, ISBN 978-953-51-5976-6.

Németh G, Laszlovszky I, Czobor P, Szalai E, **Szatmári B**, Harsányi J, Barabássy Á, Debelle M, Durgam S, Bitter I, Marder S, Fleischhacker WW. Cariprazine versus risperidone monotherapy for treatment of predominant negative symptoms in patients with schizophrenia: a randomised, double-blind, controlled trial. Lancet. 2017 Mar 18;389(10074):1103-1113. doi: 10.1016/S0140-6736(17)30060-0. Epub 2017 Feb 7. Erratum in: Lancet. 2017 Mar 18;389(10074):1102. doi: 10.1016/S0140-6736(17)30646-3. PMID: 28185672.

Publications not related to the thesis:

Rosa ME, Juhász Z, Pásztor Mészáros G, Magyar G, Harsányi J, **Szatmári B**, Hujber Z, Szabó M, Kapás M. Lack of Clinically Meaningful Effect of Cariprazine on the Pharmacokinetics of a Combined Oral Contraceptive. Neurol Ther. 2025 Feb;14(1):291-301. doi: 10.1007/s40120-024-00686-7. Epub 2024 Dec 19. PMID: 39699744; PMCID: PMC11762025.

Szabó M, Hujber Z, Harsányi J, **Szatmári B**, Dombi Zs B, Magyar G, Hegedűs Zs, Ratskó P, Pásztor Mészáros G, Barabássy Á. Coadministration of Cariprazine with a moderate CYP3A4 Inhibitor in patients with schizophrenia: Implications for Dose Adjustment and Safety Monitoring. Clin Pharmacokinet. 2024 Oct;63(10):1501-1510.

Meszár V, Magyar G, Pásztor GM, **Szatmári B**, Péter K, Marton L, Dombi ZB, Barabássy Á. Cariprazine Orodispersible Tablet: A New Formulation for Cariprazine. Pharmacopsychiatry. 2024 Jul;57(4):180-185. doi: 10.1055/a-2291-7130. Epub 2024 May 6. PMID: 38710207; PMCID: PMC11233223.

Barabássy Á, Sebe B, Acsai K, Laszlovszky I, **Szatmári B**, Earley WR, Németh G. Safety and Tolerability of Cariprazine in Patients with Schizophrenia: A Pooled Analysis of Eight Phase II/III Studies. Neuropsychiatr Dis Treat. 2021 Apr 7;17:957-970. doi: 10.2147/NDT.S301225. Erratum in: Neuropsychiatr Dis Treat. 2021 May 17;17:1481. doi: 10.2147/NDT.S316858. PMID: 33854317; PMCID: PMC8040316.

Demyttenaere K, Leenaerts N, Acsai K, Sebe B, Laszlovszky I, Barabássy Á, Fonticoli L, **Szatmári B**, Earley W, Németh G, Correll CU. Disentangling the symptoms of schizophrenia: Network analysis in acute phase patients and in patients with predominant negative symptoms. Eur Psychiatry, 2021; 1-27.

Leucht S, Barabássy Á, Laszlovszky I, **Szatmári B**, Acsai K, Szalai E, Harsányi J, Earley W, Németh G. Linking PANSS negative symptom scores with the Clinical Global Impressions Scale: understanding negative symptom scores in schizophrenia. Neuropsychopharmacology. 2019 Aug;44(9):1589-1596. doi: 10.1038/s41386-019-0363-2. Epub 2019 Mar 5. PMID: 30836381; PMCID: PMC6785000.

Earley W, Burgess MV, Rekeda L, Dickinson R, **Szatmári B**, Németh G, McIntyre RS, Sachs GS, Yatham LN. Cariprazine Treatment of Bipolar Depression: A Randomized Double-Blind Placebo-Controlled Phase 3 Study. Am J Psychiatry. 2019 Jun 1;176(6):439-448. doi: 10.1176/appi.ajp.2018.18070824. Epub 2019 Mar 8. PMID: 30845817.

Fleischhacker W, Galderisi S, Laszlovszky I, **Szatmári B**, Barabássy Á, Acsai K, Szalai E, Harsányi J, Earley W, Patel M, Németh G. The efficacy of cariprazine in negative symptoms of schizophrenia: Post hoc analyses of PANSS individual items and PANSS-derived factors. Eur Psychiatry. 2019 May;58:1-9. doi: 10.1016/j.eurpsy.2019.01.015. Epub 2019 Feb 7. PMID: 30738380.

Correll CU, Potkin SG, Zhong Y, Harsányi J, **Szatmári B**, Earley W. Long-Term Remission With Cariprazine Treatment in Patients With Schizophrenia: A Post Hoc Analysis of a Randomized, Double-Blind, Placebo-Controlled, Relapse Prevention Trial. J Clin Psychiatry. 2019 Jan 8;80(2):18m12495. doi: 10.4088/JCP.18m12495. PMID: 30695290.

Szatmari B, Balicza P, Nemeth G, Molnar MJ. The Panomics Approach in Neurodegenerative Disorders. Curr Med Chem. 2019;26(10):1712-1720. doi: 10.2174/0929867324666170705120038. PMID: 28685677.

∑IF: 121.081