The efficacy and safety of cariprazine in schizophrenia patients with insufficient effectiveness of previous antipsychotic therapy: A Latvian observational study

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INTRODUCTION

Schizophrenia is a chronic and severe psychotic disorder characterized by distortions of thinking driven by three symptom domains; positive, negative and cognitive[1]. While the disorder is mainly associated with its positive symptoms[1], negative symptoms are believed to be a core clinical dimension of schizophrenia[2]. As currently available antipsychotics target predominantly the positive symptom domain, managing negative symptoms represent an unmet medical need[3]. Cariprazine, a novel antipsychotic was reported to be a safe and effective treatment for not only broad-spectrum schizophrenia, but also for treating predominant negative symptoms, based on evidence from double-blind trials[4,5]. While such trials are considered to be the gold standard in clinical research, there is a considerable need for conducting studies that measure effectiveness, the performance of compounds in everyday practice, too[6].

STUDY OBJECTIVE

The aim was to examine the effectiveness and safety of cariprazine in routine psychiatric settings on schizophrenia patients with negative symptoms who have been treated with antipsychotics previously but with insufficient effectiveness.

METHODS

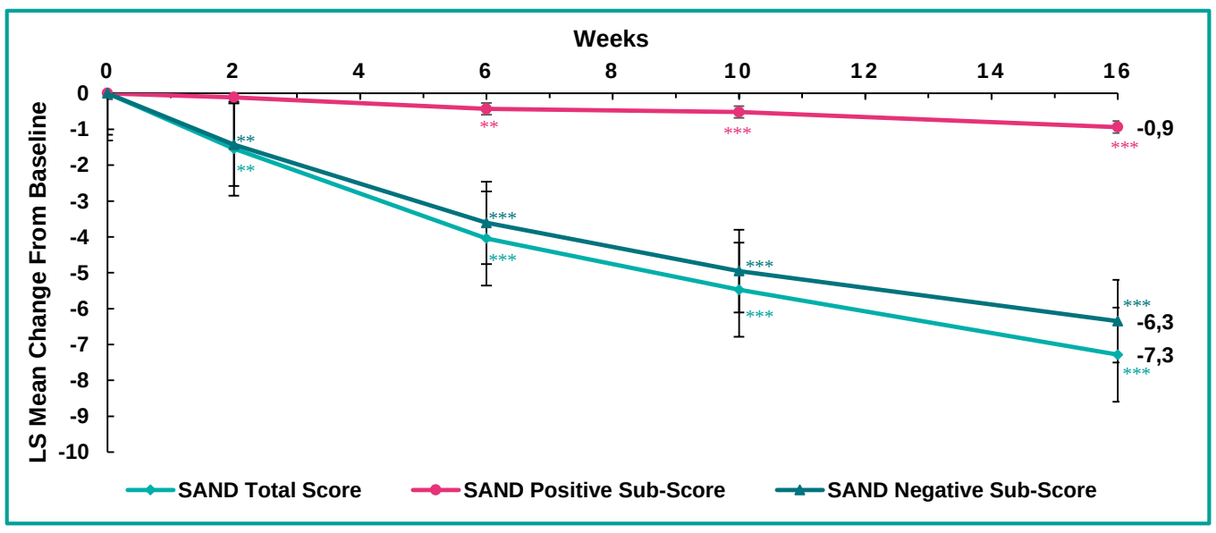
This was an open-label, flexible-dose, 16-week, observational study conducted in outpatient psychiatric clinics in Latvia. Adult schizophrenia patients (diagnosis based on the International Classification of Diseases 10th Revision) who exhibited negative symptoms based on clinical judgement, were at least mildly ill according to the Clinical Global Impression - Severity scale (CGI-S) and did not receive cariprazine 30 days before the inclusion were eligible to take part in the study. Psychiatrists were instructed to prescribe cariprazine (1.5, 3.0, 4.5 or 6.0 mg/day) to any patients meeting the inclusion criteria and receiving a non-effective antipsychotic treatment, experiencing side effects and/or wishing to switch drugs. The primary outcome measure was chosen to be an array of targeted clinical statements assigned with a 7-point rating scale, simply called the Short Assessment of Negative Domains (SAND). The SAND was composed of 7-items; 2 positive (delusions and hallucinations) and 5 negative symptom items (anhedonia, affective flattening, avolition/apathy, alogia, and emotional- and social withdrawal)[7,8]. Each item was rated from 0 to 6 (not observed, minimal, mild, moderate, severe and extreme), similarly to the Brief Negative Symptom Scale and the Clinical Global Impression – Schizophrenia scale[9]. Other outcome measurements were the CGI-Improvement (CGI-I) and the CGI-Severity (CGI-S) scales. Safety parameters included spontaneous reports of adverse events, as well as specific assessments of acute dystonia, parkinsonism, akathisia, dyskinesia, and weight changes; all measured with a 5-point Likert-scale (0 – absent, 4 – severe). Both effectiveness and safety measurements were performed on weeks 0, 2, 6, 10 and 16 and/or at premature discontinuation from the study. A mixed model for repeated measures (MMRM) was fit to the data to evaluate the mean change from baseline for all visits using an autoregressive covariance structure.

RESULTS

Effectiveness

Overall 116 patients participated in the study. Statistically significant improvement was detected as early as week 2 in the SAND total score from baseline (18.1) to week 16 (Least square mean [LSM] change: -7.3; p<0.001) as well as in the negative (LSM change: -6.3; p<0.001) and positive (LSM change: -0.9; p<0.001) sub-scores from week 2 and 6, respectively.

Figure 1 Change from Baseline in SAND Total and in Positive and Negative Sub-Scores

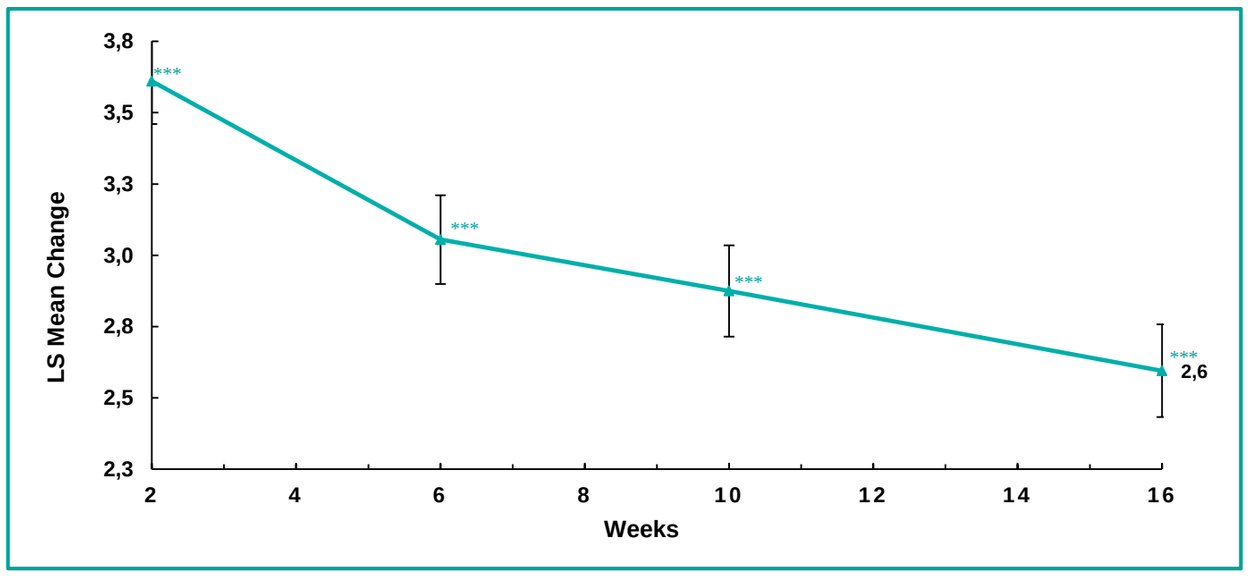


CONCLUSIONS

- **Cariprazine significantly improved the negative symptom domain of schizophrenia in previously insufficiently treated patients, as indicated by the primary (SAND total score), secondary (CGI-I) and additional (CGI-S) outcome measures.**
- **The number of patients experiencing adverse events and the severity of EPS-related side effects declined from baseline to last visit, indicating that indeed cariprazine has a good safety profile.**

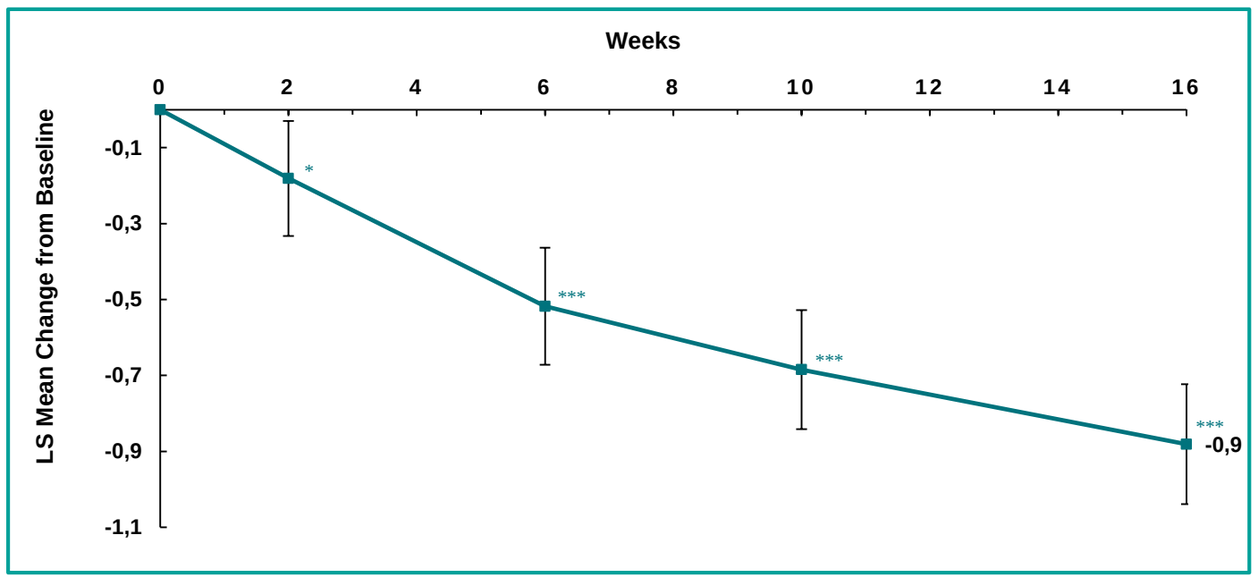
Statistically significant improvement was also observed from week 2 onwards in the secondary endpoint, the CGI-I, resulting in a LS mean score of 2.6 (p<0.001) at week 16; meaning that patients showed minimally to much improvement.

Figure 2 CGI-Improvement Scores throughout the study



By week 16, CGI-S scores were statistically significantly decreased (LSM change: -0.9; p<0.001) from baseline (4.4), meaning an overall improvement in severity from moderately ill to mildly ill.

Figure 3 Change from Baseline in CGI-Severity Score



Safety analyses

44% of patients entered the study with pre-existing adverse drug reaction due to previous antipsychotic medication. Most of them suffered from akathisia (23%), parkinsonism (16%) and hyperprolactinemia (8%). Throughout the study 41% of the patients experienced newly emerged adverse drug reaction, meaning having an adverse drug reaction that they have not experienced before or a worsening in the severity of any pre-existing adverse drug reaction. Most of the newly emerged drug reactions were akathisia (13%), anxiety (10%) and parkinsonism (6%). Importantly, most of these newly emerged adverse drug reactions were of mild severity and the severity of the pre-existing adverse events also decreased to mild. In terms of body weight, the mean difference from baseline (64.6 kg; BMI 27.5) to termination of study was -0.3 kilograms.

Table 1 Pre-existing and newly-emerged adverse events occurring in more than 5% of patients

Pre-existing adverse events, n (%)	
Number of patients	51 (44.0)
Akathisia	27 (23.3)
Parkinsonism	19 (16.4)
Prolactin related	9 (7.8)
Acute dystonia	7 (6.0)
Newly-emerged events, n (%)	
Number of patients	48 (41.4)
Akathisia	15 (12.9)
Anxiety	12 (10.3)
Parkinsonism	7 (6.0)

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