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The effectiveness and safety of cariprazine in schizophrenia patients with negative symptoms and insufficient effectiveness of previous antipsychotic therapy: an observational study

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The aim of the study 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 without sufficient success. This was an open-label, flexible-dose, 16-week, observational study in Latvia. The primary outcome measure was an array of anamnesis-based clinical questions on schizophrenia symptoms rated on a seven-point scale. Other outcome measurements were the clinical global impression improvement (CGI-I) and severity (CGI-S) scales. Safety parameters included spontaneous reports of adverse events and specific assessments of extrapyramidal side-effects. A mixed model for repeated measures was fit to the data to evaluate the mean change from baseline for all visits. A total of 116 patients enrolled in the study (completion: 83%). Change from baseline to termination in symptom control was statistically significant (−7.3; $P < 0.001$), with the most improvement in negative symptoms (−6.3; $P < 0.001$). Over 70% of patients improved minimally or much based on the CGI-I scores at the final visit, and the CGI-S scores indicated an overall improvement in severity from moderately to mildly ill. 40% of patients experienced treatment-emergent adverse events. Over 70% of doctors were satisfied with the effectiveness and tolerability of cariprazine. Cariprazine significantly improved negative symptoms in schizophrenia patients. *Int Clin Psychopharmacol* 36: 154–161 Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc.

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Introduction

Schizophrenia is a chronic psychotic disorder affecting about 20 million people worldwide (James *et al*., 2018). It is characterized by considerable distortions of thinking and perception driven by three symptom domains; positive, negative and cognitive (WHO, 2015, 2016). While the disorder is predominantly associated with and diagnosed by its positive symptoms (Feighner *et al*., 1972; APA, 2013; WHO, 2016), negative symptoms, such as anhedonia, avolition, asociality, alogia and blunted effect, are believed to be the core clinical dimension of schizophrenia (Bleuler, 1950; Bucci and Galderisi *et al*., 2017). As antipsychotics, the first line of treatment, target predominantly the positive symptom domain, managing negative symptoms represent a crucial and unmet medical need in achieving recovery (Erhart *et al*., 2006; Stahl and Buckley, 2007). Indeed, insufficient effectiveness of antipsychotic therapy due to the presence of negative symptoms has been repeatedly reported by several studies and meta-analyses (Leucht, Corves *et al*., 2009; Leucht, Komossa *et al*., 2009; Fusar-Poli *et al*., 2015; Iasevoli *et al*., 2018; Huhn *et al*., 2019).

Negative symptoms are a heterogeneous group with considerable differences in what causes them and to what treatment they respond (Galderisi *et al*., 2017; Galderisi *et al*., 2018). Secondary negative symptoms, for example, are driven by positive, depressive or movement symptoms and are not the primary manifestations of the core symptomatology (Galderisi *et al*., 2017; Kirschner *et al*., 2017; Galderisi *et al*., 2018). Similarly, cognitive symptoms are also strongly interlinked with negative symptoms and are worsening when present (Luther *et al*., 2020). This heterogeneity makes not only the treatment and management (Stahl and Buckley, 2007; Galderisi *et al*., 2018) but the assessment of negative symptoms difficult too (Marder *et al*., 2013; Galderisi *et al*., 2018). A review by Galderisi *et*

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al. (2018) has recently pointed out that although instruments for the measurement of negative symptoms are evolving (Daniel, 2013), such scales are predominantly used in the research context and assessment in routine clinical practice can be quite challenging. Indeed, in the case of schizophrenia, only 6.5% of the practitioners reported to use clinical scales routinely (Gilbody *et al.*, 2002). Among the reasons why, many believed that standardized measurements could be burdensome, clinically unhelpful and highly resource-dependent, especially in terms of administration (Gilbody *et al.*, 2002; Zimmerman and McGlinchey, 2008).

Cariprazine, a third-generation antipsychotic, has been recently introduced for the treatment of schizophrenia (Németh *et al.*, 2017; Krause *et al.*, 2018; Cerveri *et al.*, 2019). It is different from the other antipsychotic medications in the sense that it has 10 times greater affinity for D_3 than D_2 receptors *in vitro* (Kiss *et al.*, 2010), as well as exhibits high and balanced occupancy of both D_3 and D_2 receptors *in vivo* (Slifstein *et al.*, 2013). Evidence from short- and long-term double-blind, placebo-controlled trials provided support for the notion that cariprazine is a safe and effective treatment for schizophrenia patients (Durgam et al., 2014, 2015, 2016; Kane *et al.*, 2015). In contrast to the other available antipsychotics, cariprazine has also been found to be highly effective in treating patients with predominant negative symptoms (Németh *et al.*, 2017; Earley *et al.*, 2019). In a randomized, double-blind trial, Németh *et al.* (2017) reported greater change in the positive and negative syndrome scale factor score for negative symptoms (PANSS-FSNS) from baseline to week 26 than in risperidone (Németh *et al.*, 2017).

While randomized controlled trials (RCTs) are considered to be the gold standard in clinical research by providing high-quality data on efficacy, there is a considerable need for conducting studies that measure the effectiveness and the performance of compounds in everyday practice (Malm *et al.*, 2009). Observational and naturalistic studies can provide important information regarding the safety, effectiveness and appropriate usage of drugs in the real world (Van Vollenhoven and Severens, 2011). Although these types of studies are considered in general to be of lower quality due to their uncontrolled nature and selection bias, it is important to note that their primary goal is not to determine a drug's efficacy but rather to provide additional data on the real-life effectiveness after when the drug's efficacy has already been established (Dreyer *et al.*, 2010; Van Vollenhoven and Severens, 2011). Hence, the goal of the current study is to understand the effectiveness and safety of cariprazine outside the research context.

Methods

Study design and setting

This was an open-label, flexible-dose, 16-week, observational study of cariprazine conducted in nine psychiatric clinics involving 116 outpatients in Latvia.

Ethics

The study protocol was approved by the Research Ethics Committee of Riga Stradins University (27 September 2018; Nr. 6-2/2). The State Agency of Medicines of the Republic of Latvia published the permission on their official website (02 November 2018). All patients provided informed written consent to participate in the study.

Patients

Adult patients (18 or older) who have been diagnosed with schizophrenia according to the International Classification of Diseases 10th Revision (ICD-10), exhibited negative symptoms based on clinical judgment, were at least mildly ill according to the clinical global impression-severity (CGI-S) scale and have not previously received cariprazine were eligible to take part in the study. Additionally, only patients who did not have sufficient effectiveness of previous antipsychotic therapy on different symptoms, experienced side-effects and/or wanted to switch drugs could be included. Those patients who had known addiction to benzodiazepines or alcohol, used prolonged-release antipsychotics in the past 42 days, were diagnosed with a serious and unstable somatic disease, were pregnant women, or did not correspond to cariprazine's summary of product characteristics (SmPC) in any way were excluded.

Treatment

Patients received cariprazine according to the SmPC guidelines. The appropriate dosage (1.5, 3, 4.5 or 6 mg) during treatment was decided by the practitioners based on clinical judgment. Taking concomitant medications, including antipsychotic medication during cross-titration period, was allowed and recorded. Discontinuation of cariprazine was permitted any time the patient requested and in case of serious adverse reaction, noncompliance with the SmPC and/or based on clinical decision.

Outcomes

Given the observational nature of the study, the primary outcome measure was chosen to be an array of anamnesis-based clinical questions assigned with a seven-point rating scale, called the short assessment of negative domains (SAND), which was developed by one of the authors, E. Rancans, and based on similar principles as the clinical global impression-schizophrenia (CGI-SCH) outcome measure of one of the largest naturalistic SOHO study (Haro, Edgell *et al.*, 2003). The SAND is composed of seven-items; two positive (delusions and hallucinations) and five negative items (anhedonia, blunted affect, avolition, alogia and asociality), see Supplemental Table, Supplemental digital content 1, *http://links.lww.com/ICP/A81*. Each item is rated from 0 to 6 (not observed; minimal; mild; moderate; moderately severe; severe; extreme), similarly to the brief negative symptom scale (BNSS) (Kirkpatrick *et al.*, 2011). The SAND was primarily based on the five-factor structure of negative symptoms in schizophrenia (Ahmed *et al.*, 2019). In contrast

with the other validated assessment tools, which take about 15–40 min to complete (Daniel, 2013), the SAND is a short and simple way of evaluating negative symptoms, hence facilitating easier diagnoses and follow-up in everyday practice. Furthermore, it constitutes the two most deliberating positive symptoms, hallucinations and delusions, which are often the root of negative symptoms secondary to positive symptoms (Galderisi *et al.*, 2018). Although the SAND is not a validated measurement tool per se, it can be perceived as a modification and a combination of two validated assessment tools, the BNSS and the CGI-SCH (Haro, Kamath *et al.*, 2003). The latter, just as the SAND assesses the severity on a seven-point scale (Haro, Kamath *et al.*, 2003). Importantly, the CGI-SCH has been widely used in large-scale naturalistic studies and across different continents (Haro *et al.*, 2003; Suarez and Haro, 2008; Karagianis *et al.*, 2009).

Table 1 Patient disposition, baseline demographic, disease and treatment characteristics

Population	
Safety population, *n* (%)	116 (100)
Demographics	
Age, mean (SD), years	37.4 (11.3)
Men, *n* (%)	69 (59.5)
Weight, mean (SD), kg	84.6 (20.2)
BMI, mean (SD), kg/m^2	27.5 (6.2)
Schizophrenia characteristics	
Duration of illness, mean (SD), years	8.4 (7.0)
Schizophrenia diagnosis, *n* (%)	
Paranoid schizophrenia	82 (70.7)
Simple schizophrenia	15 (12.9)
Other schizophrenia	10 (8.6)
Previous antipsychotic therapy	
Inclusion reasons, *n* (%)[a]	
Insufficient effectiveness	94 (81.0)
Severe adverse effects	36 (31.0)
Patient desire	77 (66.4)
Signs of ineffectiveness, *n* (%)[a]	
Inadequate control of positive symptoms	35 (30.2)
Inadequate control of negative symptoms	103 (88.8)
Inadequate control of affective symptoms	46 (39.7)
Inadequate control of cognitive symptoms	58 (50.0)
Type of antipsychotic taken by >10% of patients within the last month before study entry, *n* (%)	
Quetiapine	38 (32.8)
Olanzapine	24 (20.7)
Haloperidol	23 (19.8)
Aripiprazole	22 (19.0)
Risperidone	19 (16.4)
Clozapine	14 (12.1)
Amisulpride	12 (10.3)
Non-antipsychotic therapy within the last month before study entry, *n* (%)	
Benzodiazepines	33 (28.5)
Antidepressants	46 (39.7)
Anti-EPS medication	57 (49.1)
Mood stabilizers	23 (19.8)
Sleeping agents	4 (3.5)
Cariprazine therapy	
Scheme of therapy change, *n* (%)	
Abrupt discontinuation	45 (38.8)
Cross-titration	71 (61.2)
Starting dose, *n* (%), mg/day	
1.5	101 (87.1)
3.0	9 (7.8)
4.5	2 (1.7)
6.0	4 (3.5)
Maintenance dose at termination of study, *n* (%), mg/day	
1.5	13 (11.2)
3.0	32 (27.6)
4.5	33 (28.5)
6.0	35 (30.2)
7.5[b]	3 (2.6)
Patient disposition	
Completed study, *n* (%)	96 (82.8)
Premature discontinuation, *n* (%)	20 (17.2)
Reasons for premature discontinuation, *n* (%)[a]	
Ineffective therapeutic response	4 (20.0)
Treatment-emergent adverse events	9 (45.0)
Withdrawal of consent	10 (50.0)
Other	6 (30.0)

[a]Categories are not mutually exclusive.
[b]Not according to summary of product characteristics (SmPC), protocol violation.

Additional outcome measurements were the clinical global impression improvement (CGI-I) and the CGI-S scales (Guy, 1976).

To assess safety, besides spontaneous adverse event reporting, special attention was attributed to extrapyramidal side-effects such as acute dystonia, parkinsonism, akathisia, tardive dyskinesia, as well as weight changes, all assessed prospectively on a 5-point Likert scale ranging from absent to severe via clinical interviews.

All the presented measurements were performed on weeks 0, 2, 6, 10 and 16 and/or on premature discontinuation day. The SAND, CGI-I and CGI-S was administered by the same certified psychiatrist who evaluated the patient's condition at the beginning of the study.

At the end of the study, psychiatrists were asked to provide their overall impression about effectiveness and tolerability on five-point Likert scale (very dissatisfied; satisfied; neutral; dissatisfied; very dissatisfied).

Statistical analyses

Analyses were based on the full analysis set, which includes all patients who took at least one dose of cariprazine during the study period. Patient baseline and demographic characteristics were summarized descriptively, in percentages, means and SD or standard errors.

A mixed model for repeated measures was fit to the data to evaluate the mean change from baseline for all visits in the effectiveness measures. The least squares means (LSM) were reported for the change from baseline to final visit. As a sensitivity analysis, the last observation carried forward (LOCF) imputed data were also analyzed to evaluate the change from baseline to final evaluation using an analysis of variance (ANOVA) model.

The reported adverse events were coded by MedDRA (version: 23.0) preferred terms before the analysis. The most common adverse events (>2%) were summarized for baseline visit (preexisting adverse events) and final visit. The most frequent (>2%) treatment-emergent adverse events (TEAEs not present at baseline visit but present at any postbaseline-visit or adverse events presented at baseline visit but worsened at any postbaseline visit) were also summarized.

Concomitant medications taken within 1 month prior and during the study were coded by WHO Drug

Dictionary (version: WHO Drug Global, 1 March 2020) and categorized as an antidepressant, antipsychotic, benzodiazepine, antiextrapyramidal symptom (anti-EPS) medication, mood stabilizer, sleeping agent or other medication.

Table 2 Effectiveness outcomes and overall effectiveness

Outcome measure	Baseline, mean (SE)	Final visit, mean (SE)	LSM change (SE)	
SAND, total score	18.1 (0.5)	11.9 (0.6)	MMRM	−7.3 (0.5)[a]
			LOCF	−6.2 (0.4)[a]
SAND, positive score	1.6 (0.2)	1.0 (0.2)	MMRM	−0.9 (0.2)[a]
			LOCF	−0.6 (0.1)[a]
Hallucinations	0.7 (0.1)	0.4 (0.1)	–	–
Delusions	0.9 (0.1)	0.6 (0.1)	–	–
SAND, negative score	16.5 (0.4)	10.9 (0.5)	MMRM	−6.3 (0.5)[a]
			LOCF	−5.6 (0.3)[a]
Anhedonia	3.2 (0.1)	2.1 (0.1)	–	–
Blunted affect	3.4 (0.1)	2.4 (0.1)	–	–
Avolition/apathy	3.5 (0.1)	2.2 (0.1)	–	–
Alogia	2.8 (0.1)	1.9 (0.1)	–	–
Asociality	3.5 (0.1)	2.3 (0.1)	–	–
CGI-I score	–	2.9 (0.1)	MMRM	2.6 (0.1)[a]
			LOCF	2.9 (0.1)[a]
CGI-S score	4.4 (0.1)	3.7 (0.1)	MMRM	−0.9 (0.1)[a]
			LOCF	−0.7 (0.1)[a]
Physicians' impression about overall effectiveness		Final visit, *n* (%)		
Very satisfied		37 (31.9)		
Satisfied		47 (40.5)		
Neutral		22 (19.0)		
Dissatisfied		10 (8.6)		
Very dissatisfied		–		

CGI-I, clinical global impressions-improvement; CGI-S, clinical global impressions-severity; LOCF, last observation carried forward; LSM, least squares mean; MMRM, mixed-effects model for repeated measures; SAND, short assessment of negative domains.
[a]<0.001.

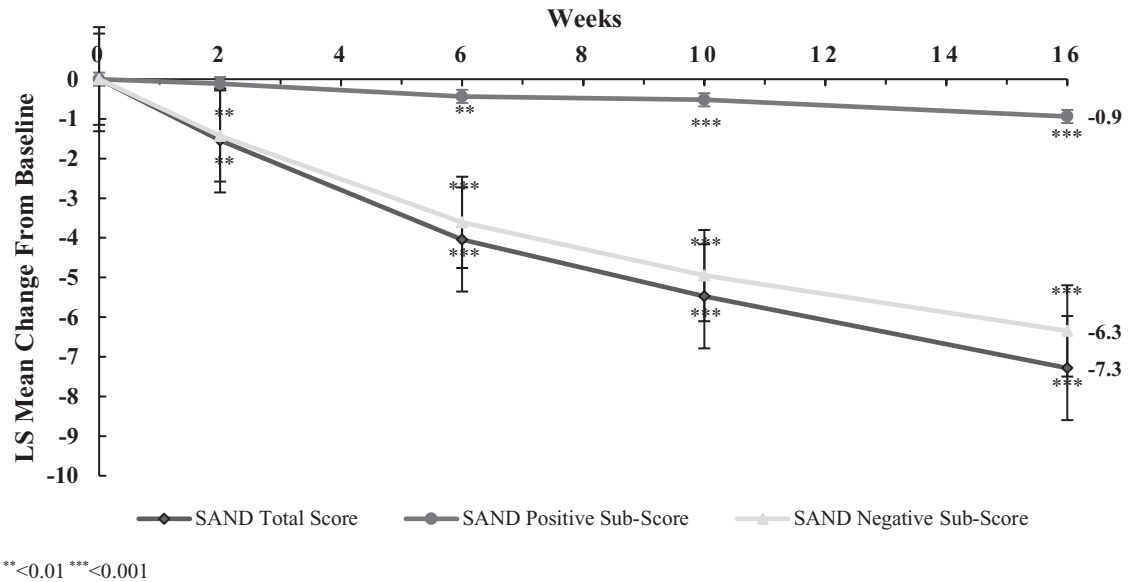
Results

Patient and treatment characteristics

Overall, 116 patients were included in the study, whose disposition, baseline demographic and disease characteristics are summarized in Table 1. The mean age of patients was around 37 years, of whom more than half (60%) was male. Seventy-one percent of patients were diagnosed with paranoid schizophrenia (ICD-10: F20.0), 13% with simple schizophrenia (ICD-10: F20.6) and 9% with other schizophrenia (ICD-10: F20.8). Approximately 83% of patients completed the study. The most frequent reasons for premature discontinuation were the withdrawal of consent (50%) and TEAEs (45%). Importantly, most of the dropouts happened in the early phase of the study, indicating that patients who had a good initial response to cariprazine treatment maintained to stay in the study.

Details of previous antipsychotic and cariprazine treatment are also summarized in Table 1. The most frequent reason for inclusion in the study was insufficient effectiveness of previous antipsychotic therapy, reported by 81% of patients. The main drivers of this were negative (89%), cognitive (50%) and effective (40%) symptoms. The most used antipsychotic medications, taken within a month before entering the study, were quetiapine (33%), olanzapine (21%), haloperidol (20%) and aripiprazole (19%). The scheme of therapy change was predominantly by cross-titration (61%) and most previous antipsychotics were discontinued by week 2. Besides antipsychotics, about half of the patients took anti-EPS medication (49%), antidepressants (40%) or benzodiazepines (28%) within a month before entering the study. Most patients

Fig. 1



<0.01 *<0.001

Change from baseline in SAND total score and in positive and negative subscores.

Table 3 CGI-I and CGI-S scores at baseline and final visit

CGI-I scores	Baseline	Final visit
Very much improved	–	7 (6.0)
Much improved	–	44 (37.9)
Minimally improved	–	40 (34.5)
No change	–	13 (11.2)
Minimally worse	–	4 (3.5)
Much worse	–	8 (6.9)
Very much worse	–	–
CGI-S score		
Normal	–	–
Borderline mentally ill	–	12 (10.3)
Mildly ill	13 (11.2)	41 (35.3)
Moderately ill	52 (44.8)	42 (36.2)
Markedly ill	42 (36.2)	12 (10.3)
Severely ill	9 (7.8)	9 (7.8)
Among the most extremely ill patients	–	–

CGI-I, clinical global impressions-improvement; CGI-S, clinical global impressions-severity.

Table 4 Treatment-emergent adverse events and overall tolerability

TEAEs throughout the study >2%, *n* (%)	
Total number of patients	46 (39.7)
Akathisia	15 (12.9)
Anxiety	12 (10.3)
Parkinsonism	7 (6.0)
Dizziness	4 (3.5)
Lethargy	4 (3.5)
Insomnia	3 (2.6)
Sleep disorder	3 (2.6)
Physicians' impression about overall tolerability, *n* (%)	
Very satisfied	52 (44.8)
Satisfied	45 (38.8)
Neutral	5 (4.3)
Dissatisfied	12 (10.3)
Very dissatisfied	2 (1.7)

TEAEs, treatment-emergent adverse events.

then started cariprazine treatment with 1.5 mg cariprazine/day (87%), although some started with 3.0, 4.5 or even 6.0 mg/day. The most used dose at the termination of the study was 6.0 (30%) and 4.5 mg (28%), followed by 3.0 mg (28%).

Effectiveness analyses

The average SAND baseline score was 18.1 (out of 42), with considerable differences between the positive (1.6 out of 12) and negative item scores (16.5 out of 30) (Table 2). The LSM change from baseline in SAND total score to final visit (week 16 or termination of study) was –7.3 (95% CI, –8.3 to –6.2; $P < 0.001$); statistical significance was detected from week 2 onward (Fig. 1). When looking at the subscores, significant changes were detected in both the negative item score (final visit: -–6.3; 95% CI, –7.3 to –5.4; $P < 0.001$) and the positive item score (final visit: –0.9; 95% CI, –1.2 to –0.6; $P < 0.001$); from week 2 and 6 onward. The robustness of the primary analyses was supported by LOCF sensitivity analyses for SAND total score (–6.2; $P < 0.001$), as well as for the negative (–5.6; $P < 0.001$) and positive (–0.6; $P < 0.001$) subscores.

Statistically significant improvement was observed in CGI-I, resulting in an LSM of 2.6 (95% CI, 2.4–2.8; $P < 0.001$) at the final visit, meaning patients had minimal/much improvement on the average (Table 2). At the final visit, 38% of the patients had much, 35% had minimal and 11% no improvement (Table 3).

The mean baseline score of CGI-S was 4.4, indicating that the study population was moderately ill. At the final visit, CGI-S scores changed statistically significantly by –0.9-point (95% CI, –1.0 to –0.7; $P < 0.001$) (Table 2), meaning an overall improvement in severity from markedly/moderately ill to moderately/mildly ill. At the final visit, 36% of the patients were moderately ill (vs. 45% at first visit), 35% were mildly ill (vs. 11% at first visit) and 10% were borderline mentally ill (vs. 0% at first visit) (Table 3).

The general impression regarding the effectiveness of cariprazine was 'satisfying' in 41% and 'very satisfying' in 32% of the psychiatrists (22 clinicians) (Table 2).

Safety analyses

A summary of adverse events alongside the psychiatrist's impression of cariprazine's tolerability is presented in Table 4. Forty-four percent of patients entered the study with preexisting adverse events due to previous antipsychotic medication [akathisia (23%), parkinsonism (16%) and hyperprolactinemia (8%)]. Forty percent of the patients experienced TEAEs during cariprazine treatment. Mean body weight at baseline was 84.6 kg (BMI, 27.5); while the mean difference from baseline to end of the study was –0.3 kg. Psychiatrists rated the overall tolerability mostly very satisfactory (45%) and satisfactory (39%).

Concomitant medication

Within the last month before entering the study, next to their antipsychotic treatment, 49% of patients were taking anti-EPS medication, 40% antidepressants, 28% benzodiazepines and 20% mood stabilizers (Table 1). In contrast, at the final visit, the number of patients taking concomitant medication decreased (41% of patients took anti-EPS medication, 36% antidepressants, 28% benzodiazepines and 14% mood stabilizers), indicating that fewer patients needed concomitant medication with cariprazine. Indeed, 14% of the patients stopped taking anti-EPS medication, 5% antidepressants and mood stabilizers and 3% benzodiazepines, while only 7% of the patients started anti-EPS medication, 5% antidepressants and benzodiazepines, and 2% sleeping agents. It is also important to note that about half of the patients continued to take the antipsychotic medication with cariprazine that was secondary to their previous antipsychotic.

Discussion

This was the first observational study examining the effectiveness and safety of cariprazine in routine psychiatric settings. The results demonstrated significant

improvement with cariprazine treatment in schizophrenia patients who have already been insufficiently treated with antipsychotics previously. Significant positive change was detected as early as the second week of the study in the SAND total score, as well as in the negative and positive subscores from weeks 2 and 6, respectively. This improvement was also supported by a 2.6 average in the CGI-I and a 1-point change in the CGI-S scores, meaning that patients improved minimally or much, and the severity of their disorder changed from moderately ill to mildly ill. Hence, it is not surprising that over 70% of the physicians were either 'satisfied' or 'very satisfied' with the effectiveness of cariprazine.

Pooled safety analyses of cariprazine based on short- and long-term randomized clinical trials have already been summarized in the literature (Earley *et al.*, 2017; Nasrallah *et al.*, 2017). Regarding the safety aspects of the drug in the present study, a similar safety profile emerged; over 80% of the physicians were 'satisfied' or 'very satisfied' with the tolerability of cariprazine. This can be explained by the fact that although there were some TEAEs throughout the study, their number and severity were still lower than those caused by previous antipsychotic medication. Finally, more patients stopped taking concomitant medication than started, indicating a decreased need for anti-EPS medication, mood stabilizers and benzodiazepines on cariprazine treatment.

The present findings provide further support for the notion that cariprazine is an effective and safe medication for treating schizophrenia patients with negative symptoms (Németh *et al.*, 2017; Fleischhacker *et al.*, 2019). Throughout the 16-week treatment period, not only negative symptoms decreased significantly, but hallucinations and delusions too, which are often the main drivers for secondary negative symptoms (Galderisi *et al.*, 2017; Kirschner *et al.*, 2017; Galderisi *et al.*, 2018). Besides effectiveness, cariprazine was also shown to be beneficial in safety, as about a third of the patients entered the study due to severe adverse effects caused by previous antipsychotic medication; however, only 8% discontinued cariprazine for the same reason. It is also important to note that these results were acquired in a real-life setting that may not be without bias, however, has higher external validity than those acquired from RCTs (Cohen *et al.*, 2015).

It is hard to link the present study to the literature as no previous observational study focusing on negative symptom patients has been conducted with cariprazine yet. Nonetheless, the results of this study are in line with many aspects with those obtained in a double-blind, randomized, cariprazine-comparative study (Németh *et al.*, 2017). Due to the similarity of the inclusion criteria of the two studies (18+ schizophrenia patients with predominant negative symptoms and low levels of positive symptoms) the baseline characteristics of the study populations are comparable. Unfortunately, as the primary outcome measure of the two studies is different, only results acquired from the CGI-S and CGI-I scales can be examined. Regarding the latter, an average CGI-I value of 2.5 was reported at the end of the treatment period (week 26) in the Németh study (Németh *et al.*, 2017). Similarly, a 2.5 value on the CGI-I at week 16 was indicated in the present study. Regarding CGI-S, the baselines were slightly different; however, the mean changes from baseline are again similar; –0.9-point at week 16 in the present study and –0.95 at week 26 in the study by Németh *et al.* (2017). Thus, it can be concluded that results acquired in real-life settings show a similar trend with those acquired in an RCT.

The present study is, however, not without limitations. First, given the nature of the study design—observational study—the results need to be interpreted with caution as the study has limited internal validity due to probable selection and information bias (Cohen *et al.*, 2015). Internal validity is important in determining efficacy or, in other words, that the observed effects are the result of the treatment and not the result of other factors (Cohen *et al.*, 2015). Nonetheless, the aim of this study was not to establish efficacy, which can be obtained from RCTs, but to determine the true benefit to patients in routine psychiatric settings (Cohen *et al.*, 2015). In fact, the present study was able to replicate part of the results of the Németh study and hence determine the translatability of the findings observed. Second, the primary outcome measure, SAND, is not a validated tool. Given the fact that there are limited objective measures in psychiatry (e.g., MRI) it is highly important to use reliable and valid questionnaires hence ensuring objectivity and comparability with other studies (Bolarinwa, 2015). Using standardized questionnaires in real-life settings, however, is often not feasible (Gilbody *et al.*, 2002; Zimmerman and McGlinchey, 2008). Thus, to mimic real-life settings while measuring the change in the negative symptoms, a short assessment (SAND) based on the five-factor structure of negative symptoms in schizophrenia (Kirkpatrick *et al.*, 2006) was developed, and despite not being validated, it shares high similarity with other standardized questionnaires, such as BNSS, CGI-SCH and PANSS-FSNS. The third limitation is the use of concomitant medication, such as antidepressants, throughout the study period that increases the risk of confounding (Viswanathan *et al.*, 2013). Nevertheless, taking other medications is highly common in real-life schizophrenia treatment (Correll *et al.*, 2017), and there were no significant changes in the concomitant medications, only in favor of stopping to taking them. Finally, in case of the positive symptoms, a floor effect is seen at baseline, meaning that the participants cluster toward the lower end of the scale, hence limiting the results.

Conclusion

Cariprazine, a novel antipsychotic with a unique D_3-D_2 receptor affinity profile, has been recently introduced for

the treatment of schizophrenia, with a special ability to alleviate predominant negative symptoms (Zimnisky *et al*., 2013; Németh *et al*., 2017). The present observational study aimed to investigate this feature in real-life settings in patients with negative symptoms who have already been treated with antipsychotics previously but without sufficient success. The results indicate that patients benefited from cariprazine treatment; their negative symptoms decreased significantly over the 16-week treatment period. Importantly, these findings also support a previous RCT (Németh *et al*., 2017) and show that those results are applicable to real-life settings too. Future research should focus on obtaining more data from routine psychiatric clinics using validated questionnaires as well as examining the effects of the drug on quality of life.

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Conflicts of interest

E.R. during the last 5 years has received research grants from Gedeon Richter and Lundbeck and speaker honoraria from, and is a member of advisory panels for, Abbvie, Gedeon Richter, Grindex, Janssen Cilag, Lundbeck, Servier and Zentiva. I.S., Z.B.D., P.M., Á.B., B.S. and G.N. acknowledge a potential conflict of interest as employees of Gedeon Richter Plc. G.N. has a patent issued for cariprazine.

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