



Efficacy of cariprazine on negative symptoms in patients with acute schizophrenia: A post hoc analysis of pooled data

Willie Earley ^{a,*}, Hua Guo ^a, David Daniel ^b, Henry Nasrallah ^c, Suresh Durgam ^a, Yan Zhong ^a, Mehul Patel ^a, Ágota Barabácssy ^d, Balázs Szatmári ^d, György Németh ^d

^a Allergan plc, Madison, NJ, USA

^b George Washington University/Bracket Global, LLC, Washington, DC, USA

^c Saint Louis University, St. Louis, MO, USA

^d Gedeon Richter Plc, Budapest, Hungary

ARTICLE INFO

Article history:

Received 31 January 2018

Received in revised form 5 July 2018

Accepted 13 August 2018

Available online 29 August 2018

Keywords:

Cariprazine

Schizophrenia

Negative symptoms

Aripiprazole

Risperidone

ABSTRACT

Although currently approved antipsychotics exert efficacy on positive symptoms of schizophrenia, treatments for negative symptoms remain a major unmet need. Post hoc analyses were used to investigate the possible efficacy of cariprazine in patients with moderate/severe negative symptoms of schizophrenia and no predominance of positive symptoms. Data were pooled from 2 randomized, double-blind, placebo- and active-controlled cariprazine studies in patients with acute schizophrenia (NCT00694707, NCT01104766). Analyses included data from a subset of patients with a Positive and Negative Syndrome Scale factor score for negative symptoms (PANSS-FSNS) ≥ 24 , PANSS factor score for positive symptoms (PANSS-FSPS) ≤ 19 , and scores of ≥ 4 on ≥ 2 of 3 PANSS items (blunted affect [N1], passive/apathetic social withdrawal [N4], lack of spontaneity/flow of conversation [N6]). Changes from baseline to week 6 in PANSS-FSNS were evaluated in the following treatment groups: placebo ($n = 79$), cariprazine 1.5–3 ($n = 94$) and 4.5–6 mg/d ($n = 66$), risperidone 4 mg/d ($n = 34$), or aripiprazole 10 mg/d ($n = 44$). Significant differences were observed versus placebo for cariprazine (1.5–3 mg/d, $P = .0179$; 4.5–6 mg/d, $P = .0002$) and risperidone ($P = .0149$), but not aripiprazole ($P = .3265$), and versus aripiprazole for cariprazine 4.5–6 mg/d ($P = .0197$). After adjusting for positive symptom changes, differences versus placebo remained statistically significant for cariprazine (1.5–3 mg/d, $P = .0322$; 4.5–6 mg/d, $P = .0038$) but not for risperidone ($P = .2204$). PANSS-FSNS response ($\geq 20\%$ reduction from baseline) rates were significantly higher with cariprazine (1.5–3 mg/d = 54.3%, $P = .0194$; 4.5–6 mg/d = 69.7%, $P = .0001$) than placebo (35.4%). In patients with acute schizophrenia and moderate/severe negative symptoms, cariprazine was associated with significantly greater improvement in negative symptoms compared with placebo and aripiprazole, warranting further exploration of the efficacy of cariprazine on negative symptoms.

© 2018 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

Schizophrenia is a complex neuropsychiatric brain syndrome characterized by 3 core symptom domains: positive symptoms (e.g., hallucinations, delusions), negative symptoms (e.g., blunted affect, alogia, anhedonia, avolition, asociality), and cognitive impairment. Negative symptoms can be categorized as primary negative symptoms, which are a core feature of the disease, or secondary negative symptoms, which are associated with or caused by psychotic symptoms, depression, or neurologic side effects due to excessive dopamine antagonism from antipsychotic treatment. Although atypical antipsychotics were initially expected to exert efficacy on primary negative

symptoms, they have demonstrated minimal efficacy on this domain (Keefe et al., 2007; Nasrallah et al., 2011). The only approved treatment for negative symptoms in schizophrenia is amisulpride, which is available in several European countries; no treatment is approved for negative symptoms in the United States (US). Negative symptoms contribute greatly to disease burden and can persist despite remission of positive symptoms. They have been linked to poor social and occupational functioning, profoundly impacting daily life and contributing to high levels of unemployment experienced by patients with schizophrenia (Hunter and Barry, 2012; Marder and Galderisi, 2017; Milev et al., 2005; Rabinowitz et al., 2013a; Rabinowitz et al., 2013b; Suttajit and Pilakanta, 2015). Drugs that treat primary negative symptoms remain a major unmet need in the management of schizophrenia.

Due to preferential expression in the mesolimbic circuit, the dopamine D₃ receptor has been identified as a potential target for treating

* Corresponding author at: 5 Giralda Farms, 3.316C, Madison, NJ 07940, USA
E-mail address: Willie.Earley@Allergan.com (W. Earley).

the negative, cognitive, and mood symptoms associated with schizophrenia (Gyertyán et al., 2008; Joyce and Millan, 2005; Kiss et al., 2008; Laszly et al., 2005; Leggio et al., 2013). Moreover, dopamine D₃ autoreceptor activity has been linked to regulation of dopamine synthesis and release (Aretha et al., 1995; Levant, 1997; Millan et al., 2008; Pugsley et al., 1995). Antagonism of D₃ receptors has been hypothesized to enhance dopaminergic and cholinergic neurotransmission in certain areas of the brain, such as the prefrontal cortex (Lacroix et al., 2003; Stahl, 2017), which may help alleviate negative and cognitive symptoms of schizophrenia. Cariprazine is an orally active and potent dopamine D₃-preferring D₃/D₂ receptor partial agonist and 5-HT_{1A} receptor partial agonist (Gyertyán et al., 2011; Kiss et al., 2010). Cariprazine is approved in the US and Europe for the treatment of schizophrenia and in the US for the treatment of manic or mixed episodes associated with bipolar I disorder. Unlike other atypical antipsychotics, cariprazine shows high in vivo occupancy at both dopamine D₂ and D₃ receptors at clinically relevant doses (Girgis et al., 2016; Gyertyán et al., 2011). In animal models, cariprazine has demonstrated dopamine D₃ receptor-dependent procognitive and anti-anhedonic effects, suggesting potential for treating negative symptoms (Duric et al., 2017; Zimnisky et al., 2013). In support of this hypothesis, a 26-week, randomized, double-blind, active-controlled, phase IIIb study in 461 stable patients with predominant negative symptoms of schizophrenia demonstrated the superior efficacy of cariprazine versus risperidone in improving negative symptoms (Németh et al., 2017).

This prospective study demonstrated the ability of cariprazine to treat stable patients with schizophrenia and persistent, predominant negative symptoms. However, since patients with an acute exacerbation of schizophrenia frequently have both prominent positive and negative symptoms, we were interested in investigating the efficacy of cariprazine on negative symptoms in this population as well. Given the unique pharmacology of cariprazine, it may be possible for clinicians to reasonably anticipate improvement in symptoms from both positive and negative domains during short-term treatment. To evaluate this possibility, we performed a post hoc analysis of 2 Phase II/III short-term studies in patients with acute schizophrenia to see if an efficacy signal for negative symptoms could be detected in a subpopulation of patients with moderate-to-severe negative symptoms and no predominance of positive symptoms.

2. Materials and methods

2.1. Study design

For post hoc analyses, data were pooled from 2 similarly designed, positive, 6-week, randomized, double-blind, placebo- and active-controlled, fixed-dose, international, phase II/III studies of cariprazine in adult patients with acute exacerbation of schizophrenia (NCT00694707, NCT01104766). Detailed methods for the studies have been previously published (Durgam et al., 2015; Durgam et al., 2014). The trials consisted of a 1-week washout period, 6 weeks of double-blind treatment, and 2 weeks of safety follow-up. Patients were randomized 1:1:1 to fixed doses of cariprazine, placebo, or an active comparator, which was included for assay sensitivity. In the phase II study (RGH-MD-16), patients received placebo, cariprazine 1.5, 3.0 or 4.5 mg/d, or risperidone 4.0 mg/d; in the phase III study (RGH-MD-04), patients received placebo, cariprazine 3.0 or 6.0 mg/d, or aripiprazole 10 mg/d.

2.2. Patients

Component studies enrolled male and female patients aged 18–60 years, inclusive, with a diagnosis of schizophrenia per DSM-IV-TR (APA, 2000) criteria for a minimum of 1 year and current acute exacerbation of schizophrenia (<2 weeks in duration). Clinical inclusion criteria included Clinical Global Impressions-Severity of Illness (CGI-S)

(Guy, 1976) score ≥ 4 , Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) total score ≥ 80 and ≤ 120 , and a score ≥ 4 on at least 2 of the PANSS positive symptoms of delusions, hallucinatory behavior, conceptual disorganization, or suspiciousness/persecution. Patients with other DSM-IV-TR psychiatric disorders (e.g., schizoaffective disorder, bipolar disorder, severe axis II disorders), treatment resistance (i.e., poor response to ≥ 2 antipsychotics of adequate dose and duration during the past 2 years), substance abuse within 3 months of the study, or suicide risk (based on the psychiatric interview or the Columbia-Suicide Severity Rating Scale [C-SSRS]) (Posner et al., 2011) were excluded.

Post hoc analyses were conducted using data from a subset of acutely exacerbated patients in the intent-to-treat (ITT) population (i.e., patients who received investigational product and had a post-baseline PANSS assessment). A subset of patients with moderate/severe negative symptoms was identified using PANSS-based criteria at baseline that approximated the inclusion criteria from the prospective study of cariprazine efficacy on predominant negative symptoms of schizophrenia (Németh et al., 2017). Negative and positive symptom severity were assessed using 2 PANSS-based factor scores, the PANSS factor score for negative symptoms (PANSS-FSNS) and the PANSS factor score for positive symptoms (PANSS-FSPS). The PANSS-FSNS is a clinically validated factor developed by Marder et al. (Marder et al., 1997) to identify core negative symptoms; it consists of 7 of the 30 PANSS items: blunted affect (N1), emotional withdrawal (N2), poor rapport (N3), passive social withdrawal (N4), lack of spontaneity (N6), motor retardation (G7), and active social avoidance (G16). The PANSS-FSPS was developed by Mohr et al. (Mohr et al., 2004) to characterize core positive symptoms and consists of the following PANSS items: delusions (P1), hallucinatory behavior (P3), grandiosity (P5), suspiciousness/persecution (P6), and unusual thought content (G9). For post hoc analyses, data were pooled from patients with baseline PANSS-FSNS ≥ 24 and PANSS-FSPS ≤ 19 , as well as scores ≥ 4 on at least 2 of the following PANSS items: blunted affect (N1), passive/apathetic social withdrawal (N4), or lack of spontaneity and flow of conversation (N6).

2.3. Post hoc analyses

Placebo, pooled cariprazine 1.5–3 mg/d, pooled cariprazine 4.5–6 mg/d, risperidone 4 mg/d, and aripiprazole 10 mg/d treatment groups were analyzed. Treatment-group data from each component study were also analyzed. Post hoc efficacy measures evaluated least squares (LS) mean change from baseline to week 6 in PANSS-FSNS, PANSS-FSPS, and PANSS total scores; LS mean differences (LSMD) between treatment arms were calculated.

Analyses used a mixed-effects model for repeated measures (MMRM) approach with treatment group, study, region (US or non-US), visit, region-by-visit interaction, and treatment group-by-visit interaction as fixed effects and baseline value and baseline-by-visit interaction as covariates. An unstructured covariance matrix was used to model the covariance of within-patient scores. *P* values were from the test of no difference between the cariprazine dose group and placebo or active controls at a given visit; effect sizes (ES) were calculated using Cohen's *d*. To assess whether changes in negative symptoms were related to changes in positive symptoms, change from baseline in PANSS-FSPS was also included as a covariate in the MMRM model. To assess whether changes in negative symptoms were related to changes in extrapyramidal symptoms (EPS), mean changes from baseline to week 6 in Abnormal Involuntary Movement Scale (AIMS) (Guy et al., 1976) total score, Barnes Akathisia Rating Scale (BARS) (Barnes, 1989) total score, and Simpson-Angus Scale (SAS) (Simpson and Angus, 1970) total score were evaluated.

PANSS-FSNS response rates ($\geq 20\%$ reduction from baseline in PANSS-FSNS at week 6) were evaluated using a last observation carried forward (LOCF) approach and were based on a logistic regression model for the probability of response; the model included treatment group,

study, region, and corresponding baseline value as explanatory variables. Odds ratios (OR) versus placebo, 95% confidence intervals (CIs), P values, and numbers needed to treat (NNTs) were calculated.

3. Results

3.1. Patient demographics and disposition

At baseline, moderate/severe negative symptom criteria were met by at least 20% of patients in each treatment group in the pooled ITT population (placebo = 26.6% [79/297], cariprazine 1.5–3 mg/d = 21.8% [94/431], cariprazine 4.5–6 mg/d = 22.1% [66/299], risperidone 4 mg/d = 24.6% [34/138], aripiprazole 10 mg/d = 29.3% [44/150]). The majority of patients in the negative symptom subgroup were men and the mean age was 36 to 39 years across dose groups (Table 1). Baseline PANSS total (range, 97–100) and CGI-S (range, 4.7–4.8) scores indicated that patients were moderately to markedly ill (Leucht et al., 2005). Study completion rates were generally similar among active-treatment groups, although a lower percentage of placebo-treated patients completed the component studies. Most discontinuations were due to adverse events, insufficient therapeutic response, and withdrawal of consent, with the highest percentage of discontinuations due to adverse events seen in the cariprazine high-dose group and the highest percentage of discontinuations due to insufficient therapeutic response seen in the placebo group (Table 1).

3.2. Efficacy parameters

Compared with placebo, mean reductions in PANSS-FSNS from baseline to week 6 were significantly greater in the cariprazine 1.5–3 mg/d (LSMD [95% CI] = -2.0 [-3.6, -0.3], *P* = .0179; ES = 0.41), cariprazine 4.5–6 mg/d (LSMD [95% CI] = -3.4 [-5.2, -1.7], *P* = .0002; ES = 0.71), and risperidone (LSMD [95% CI] = -2.8 [-5.0, -0.5], *P* = .0149; ES = 0.57) treatment groups. However, LS mean change in PANSS-FSNS score was not significantly different between aripiprazole and placebo (LSMD [95% CI] = -1.0 [-3.0, 1.0], *P* = .3265) (Fig. 1A). For both cariprazine dose groups, significant differences versus placebo in PANSS-FSNS change occurred at week 2 and remained significant at all subsequent visits. For the risperidone group, a significant difference versus placebo in PANSS-FSNS change was observed at week 3 and all

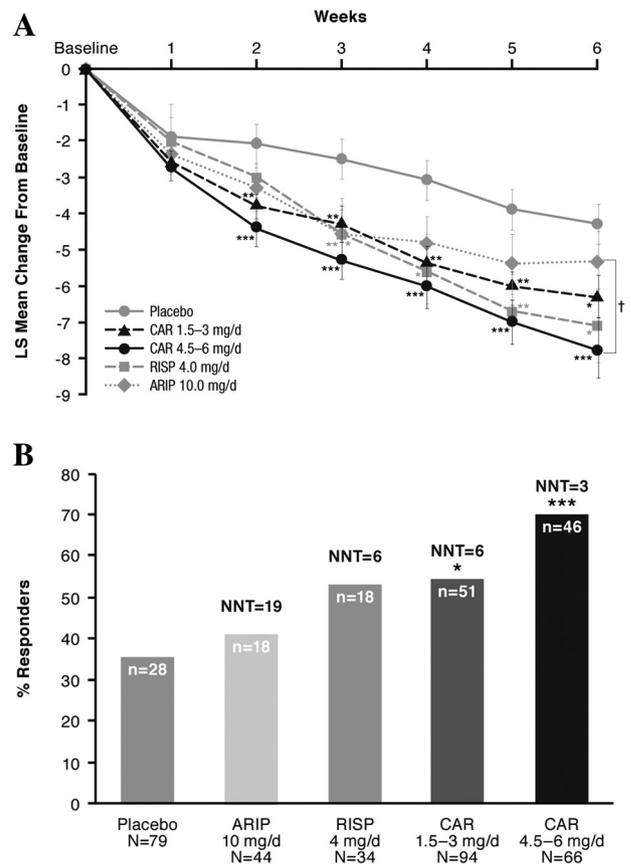


Fig. 1. Efficacy on PANSS-FSNS outcomes. A.) Plotted values represent by-visit LS mean change from baseline in PANSS-FSNS score. B.) PANSS-FSNS response rates ($\geq 20\%$ reduction from baseline) at week 6. ARIP, aripiprazole; CAR, cariprazine; LS, least squares; NNT, number needed to treat; PANSS-FSNS, Positive and Negative Syndrome Scale factor score for negative symptoms; RISP, risperidone. **P* < .05, ***P* < .01, ****P* < .001 versus placebo; †*P* < .05 versus aripiprazole.

Table 1
Patient disposition, baseline demographics, and baseline disease characteristics.

	Placebo (n = 79)	Cariprazine 1.5–3 mg/d (n = 94)	Cariprazine 4.5–6 mg/d (n = 66)	Risperidone 4.0 mg/d (n = 34)	Aripiprazole 10.0 mg/d (n = 44)
Completed study, n (%)	49 (62.0)	71 (75.5)	47 (71.2)	26 (76.5)	34 (77.3)
Reason for premature discontinuation, n (%)					
Adverse event	10 (12.7)	8 (8.5)	10 (15.2)	1 (2.9)	4 (9.1)
Insufficient therapeutic response	14 (17.7)	5 (5.3)	4 (6.1)	3 (8.8)	5 (11.4)
Withdrawal of consent	5 (6.3)	8 (8.5)	4 (6.1)	3 (8.8)	1 (2.3)
Other	1 (1.3)	2 (2.1)	1 (1.5)	1 (2.9)	0
Age, mean (SD), y	39.3 (11.3)	37.6 (10.9)	37.5 (11.2)	35.6 (10.7)	39.1 (10.4)
Men, n (%)	46 (58.2)	58 (61.7)	41 (62.1)	24 (70.6)	30 (68.2)
Race, n (%)					
White	53 (67.1)	66 (70.2)	51 (77.3)	23 (67.6)	30 (68.2)
All other races	23 (29.1)	27 (28.7)	14 (21.2)	11 (32.4)	11 (25.0)
Weight, mean (SD), kg	76.3 (18.2)	71.8 (14.7)	74.0 (18.0)	71.4 (14.5)	77.3 (16.4)
BMI, mean (SD), kg/m²	26.3 (5.1)	24.6 (4.8)	24.8 (5.0)	24.6 (3.9)	25.7 (4.4)
Baseline efficacy score, mean (SD)					
PANSS total	98.0 (8.1)	99.0 (8.9)	98.6 (8.5)	99.6 (8.1)	96.9 (7.9)
PANSS-FSNS	27.4 (2.8)	27.7 (3.4)	27.7 (3.0)	27.6 (3.6)	27.9 (3.1)
PANSS-FSPS	16.6 (2.1)	16.9 (2.0)	16.9 (2.0)	17.2 (1.8)	16.5 (1.6)
CGI-S	4.7 (0.6)	4.8 (0.6)	4.8 (0.6)	4.7 (0.7)	4.7 (0.5)

Baseline summary statistics were based on patients with baseline and at least 1 postbaseline measurement; summary statistics for other timepoints are based on subjects with both baseline assessment and post-baseline measurement at that timepoint. BMI, body mass index; CGI-S, Clinical Global Impressions-Severity; PANSS, Positive and Negative Syndrome Scale; PANSS-FSNS, PANSS factor score for negative symptoms; PANSS-FSPS, PANSS factor score for positive symptoms; SD, standard deviation.

subsequent visits; a significant difference between aripiprazole and placebo occurred at week 3 only (LSMD [95% CI] = -2.1 [-3.7, -0.5]; $P = .0084$) (Fig. 1A).

Compared with the aripiprazole group at week 6, the cariprazine 4.5 mg/d group had a significantly greater reduction from baseline in PANSS-FSNS (LSMD [95% CI] = -2.4 [-4.5, -0.4], $P = .0197$; ES = 0.50); no significant difference was noted for cariprazine 4.5–6 mg/d versus risperidone (LSMD [95% CI] = -0.7 [-2.9, 1.6], $P = .5464$). The LSMDs were not significantly different between cariprazine 1.5–3 mg/d and either risperidone (0.8 [-1.3, 2.9], $P = .4721$) or aripiprazole (-1.0 [-2.9, 1.0], $P = .3191$).

After adjusting for changes in positive symptoms, between-group differences at week 6 remained statistically significant for both cariprazine doses versus placebo (1.5–3 mg/d: -1.4 [-2.7, -0.1], $P = .0322$; 4.5–6 mg/d: -2.1 [-3.5, -0.7], $P = .0038$); conversely, risperidone (-1.1 [-2.8, 0.7], $P = .2204$) and aripiprazole (-0.2 [-1.8, 1.3], $P = .7635$) did not statistically separate from placebo after adjustment for changes in positive symptoms. Additionally, the difference between cariprazine 4.5–6 mg/d and aripiprazole at week 6 remained statistically significant in favor of cariprazine after adjusting for changes in positive symptoms (-1.9 [-3.47, -0.24]; $P = .0244$); no significant differences were observed between cariprazine 1.5–3 mg/d versus aripiprazole, or for either cariprazine dose versus risperidone after positive symptom adjustment. Changes from baseline to week 6 in AIMS, SAS, or BARS total scores were minimal in all treatment groups (Supplementary Fig. 1).

At week 6, the percentage of patients who met PANSS-FSNS response criteria ($\geq 20\%$ reduction from baseline in PANSS-FSNS) was significantly higher for both cariprazine dose groups compared with placebo (cariprazine 1.5–3 mg/d: OR [95% CI] = 2.12 [1.13, 3.99], $P = .0194$, NNT = 6; cariprazine 4.5–6 mg/d: 4.25 [2.10, 8.60], $P = .0001$, NNT = 3) (Fig. 1B). The percentage of patients who achieved PANSS-FSNS response with risperidone (OR [95% CI] = 2.02 [0.83, 4.89], $P = .1199$, NNT = 6) and aripiprazole (OR [95% CI] = 1.29 [0.58, 2.85], $P = .5320$, NNT = 19) was numerically higher than with placebo, although differences were not statistically significant.

Analysis of individual study data demonstrated a similar trend to the pooled analyses with respect to cariprazine improvements in negative

symptoms (Fig. 2). Compared with placebo, cariprazine treatment was associated with significantly greater LS mean changes from baseline to week 6 in the PANSS-FSNS in the cariprazine 4.5 mg/d group in RGH-MD-16 and the 6 mg/d group in RGH-MD-04. Neither risperidone nor aripiprazole significantly differed from placebo in PANSS-FSNS change in the individual component studies.

LS mean changes from baseline to week 6 in PANSS total score were significantly greater for all 4 treatment groups versus placebo (cariprazine 1.5–3 mg/d: LSMD [95% CI] = -7.2 [-13.1, -1.3], $P = .0177$; cariprazine 4.5–6 mg/d: -10.9 [-17.4, -4.5], $P = .0010$; risperidone: -12.7 [-20.6, -4.7], $P = .0020$; aripiprazole: -7.5 [-14.7, -0.3], $P = .0416$) (Fig. 3). Compared with placebo, significantly greater changes from baseline to week 6 in PANSS-FSNS were observed with cariprazine 4.5–6 mg/d (-2.1 [-3.5, -0.7], $P = .0044$) and risperidone (-2.6 [-4.4, -0.8], $P = .0039$); the cariprazine 1.5–3 mg/d (-0.8 [-2.2, 0.5], $P = .2029$) and aripiprazole (-1.5 [-3.1, 0.1], $P = .0715$) groups did not significantly differ from placebo on this scale (Fig. 4).

4. Discussion

In this subset of patients with acutely exacerbated schizophrenia and concurrent negative symptoms, cariprazine and risperidone were associated with significantly greater improvement in negative symptoms than placebo. In addition, higher cariprazine doses (4.5–6 mg/d) were significantly more effective than aripiprazole in improving negative symptoms in this population. The effects of cariprazine on negative symptoms appeared to be at least partially independent of improvements in positive symptoms and EPS, which is important since negative symptom improvement is often secondary to improvements in other domains, making it difficult to identify treatment effects on primary negative symptoms. The percentage of patients who met PANSS-FSNS response criteria at week 6 was significantly greater for both cariprazine doses versus placebo, while differences for risperidone and aripiprazole versus placebo did not meet statistical significance. These results suggest that cariprazine was effective in treating negative symptoms in acutely exacerbated patients with moderate/severe negative symptoms of schizophrenia and no predominance of positive symptoms.

In a previous pooled post hoc analysis of 5 studies, aripiprazole 5–30 mg/d demonstrated efficacy against multiple symptom domains, including negative symptoms, in patients with acutely exacerbated schizophrenia (Janicak et al., 2009). Similar to our analysis, the aripiprazole analysis did not specifically select for patients with negative symptoms, so it is unknown whether effects were direct effects or secondary to improvements in positive symptoms. Contrary to the aripiprazole pooled analysis, aripiprazole 10 mg/d was not effective

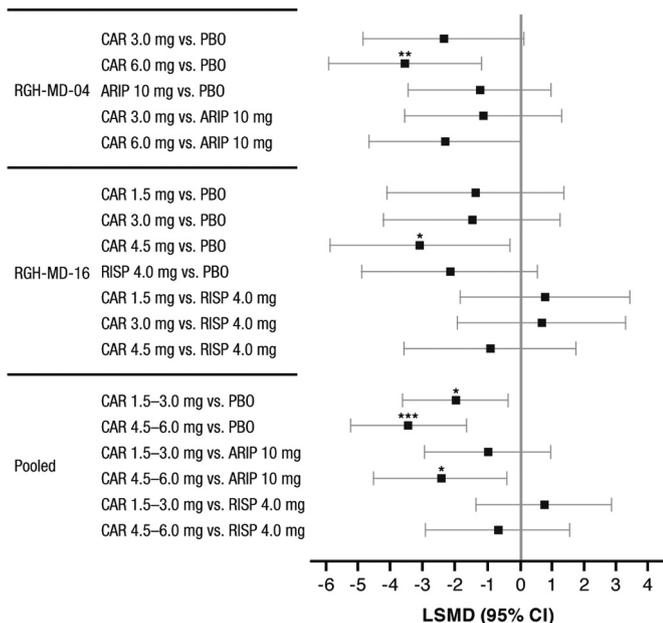


Fig. 2. PANSS-FSNS efficacy in the component studies. Plotted values represent LSMD (95% CI) values for each treatment group in the component studies. ARIP, aripiprazole; CAR, cariprazine; CI, confidence interval; LSMD, least squares mean difference; PBO, placebo; RISP, risperidone. * $P < .05$, ** $P < .01$, *** $P < .001$ versus comparator.

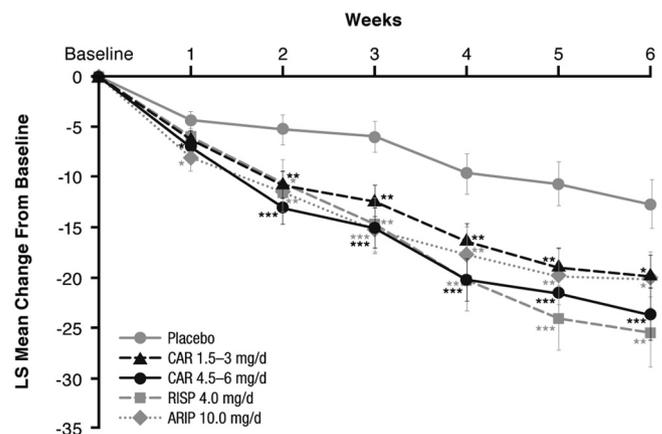


Fig. 3. Efficacy on PANSS total score. Plotted values represent by-visit LS mean change from baseline in PANSS total score. ARIP, aripiprazole; CAR, cariprazine; LS, least squares; PANSS, Positive and Negative Syndrome Scale; RISP, risperidone. * $P < .05$, ** $P < .01$, *** $P < .001$ versus placebo.

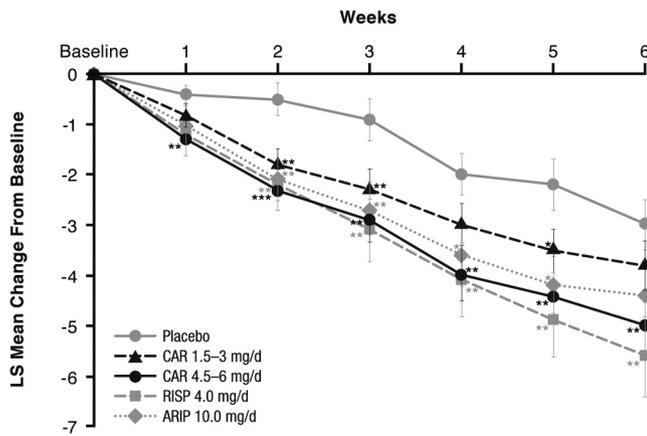


Fig. 4. Efficacy on PANSS-FSPS. Plotted values represent by-visit LS mean change from baseline in PANSS-FSPS. ARIP, aripiprazole; CAR, cariprazine; LS, least squares; PANSS, Positive and Negative Syndrome Scale; PANSS-FSPS, PANSS factor score for positive symptoms; RISP, risperidone. * $P < .05$, ** $P < .01$, *** $P < .001$ versus placebo.

against negative symptoms in a subpopulation of patients with moderate/severe negative symptoms in our analysis and the cariprazine 4.5–6 mg/d group demonstrated significantly greater improvement in negative symptoms compared with the aripiprazole group after 6 weeks of treatment. However, only one aripiprazole dose that was at the low end of the approved dose range was evaluated in our analysis, which could have influenced the drug's performance. While aripiprazole and cariprazine share some pharmacological similarities, including both acting as partial agonists at dopamine D₂ and D₃ receptors, cariprazine is more selective for the D₃ versus D₂ receptor, while aripiprazole has greater selectivity for D₂ receptors (Kiss et al., 2010). Additionally, in a recent PET study of cariprazine and aripiprazole in healthy adults, cariprazine showed substantial dopamine D₃ receptor occupancy (>60%) at a dose of 1 mg/d while aripiprazole showed negligible occupancy at 4 mg/d (Girgis et al., 2017). As the dopamine D₃ receptor has been hypothesized to modulate negative symptoms, the higher affinity of cariprazine for the dopamine D₃ receptor may contribute to its efficacy against negative symptoms. In support of this hypothesis, cariprazine, but not aripiprazole, exhibited dopamine D₃ receptor-dependent antidepressant-like effects in a rodent model of anhedonia (Duric et al., 2017).

The improvements in negative symptoms observed with cariprazine in the present analysis support results from a previous, prospectively designed study of cariprazine in clinically stable patients with schizophrenia and predominant negative symptoms. In that 26-week, double-blind, active-controlled trial, cariprazine treatment resulted in significantly greater improvement than risperidone on negative symptoms and social functioning (Németh et al., 2017). Although differences between cariprazine and risperidone did not reach statistical significance on any symptom domain in our post hoc analysis, the treatment effects on negative symptoms were higher for cariprazine (ES = 0.706) than for risperidone (ES = 0.565). The high-dose cariprazine treatment group also had a smaller NNT for PANSS-FSNS response than did the risperidone group, suggesting that fewer patients may need to be treated with this dose of cariprazine than with risperidone to achieve an additional positive result. Of note, significant differences between cariprazine and risperidone in the Németh study were not observed until after 14 weeks of treatment and treatment differences continued to increase until the end of the study (Németh et al., 2017). In contrast, the studies used in this post hoc analysis were only of 6 weeks in duration. Enduring negative symptoms may require longer treatment duration than positive symptoms to see full improvement.

To put our results in the context of the literature, a meta-analysis comparing first- and second-generation antipsychotics found that only 4 second-generation agents (amisulpride, clozapine, olanzapine,

risperidone [effect sizes = -0.13 to -0.32]) were more effective on negative symptoms than first-generation agents and 5 second-generation antipsychotic drugs (i.e., aripiprazole, quetiapine, sertindole, ziprasidone, and zotepine) were not (Leucht et al., 2009b). The authors concluded that efficacy on negative symptoms cannot therefore be considered a core component of atypicality. In a second meta-analysis comparing second-generation antipsychotics with placebo, antipsychotics had greater efficacy in treating negative symptoms than did placebo, but the effect size for negative symptoms (-0.39) was smaller than the effect sizes for overall symptoms (-0.51) or positive symptoms (-0.48) (Leucht et al., 2009a). It should be noted that most of the studies included in these meta-analyses investigated patients with predominantly positive symptoms, so some improvement was possibly attributable to changes in symptoms from other symptom domains (e.g., positive, depressive, EPS).

While the post hoc analyses attempted to minimize pseudospecific effects by selecting patients with low positive symptom scores, baseline positive symptom scores were higher in the acute studies than in the Németh study due to the different inclusion criteria (Durgam et al., 2015; Durgam et al., 2014; Németh et al., 2017). In our analyses, both cariprazine and risperidone treatment led to statistically significant improvements versus placebo on both positive and negative symptoms. After controlling for improvement in positive symptoms, significant improvement in negative symptoms was still demonstrated for cariprazine versus placebo, as well as for cariprazine 4.5–6 mg/d versus aripiprazole, suggesting that at least part of its efficacy may be due to differential effects on negative symptoms. In contrast, the significant improvement in negative symptoms for risperidone versus placebo was lost after controlling for changes in positive symptoms, suggesting that its efficacy may be primarily driven by improvements in positive symptoms. Changes in EPS were minimal in this patient population, as reflected by consistent SAS, BARS, and AIMS scores over time; therefore, treatment effects of cariprazine on negative symptoms in these patients are not likely related to changes in EPS.

Limitations of this post hoc analysis include the short duration of the component studies, which may be insufficient for complete evaluation of negative symptom improvement. Moreover, the sample size of patients with negative symptoms was small in some treatment groups, especially in the active comparator arms. These findings may not be generalizable to all patients with negative symptoms because of the inclusion/exclusion criteria in the primary studies, including the requirement that patients were experiencing an acute exacerbation of schizophrenia. As is common in investigations of negative symptoms in schizophrenia, patients included in these analyses met the criteria for acute exacerbation of schizophrenia with moderate-to-severe negative symptoms, but they were not prospectively selected for the presence of predominant negative symptoms. As such, some improvements in negative symptoms may have been secondary to improvements in positive symptoms, depression, or extrapyramidal symptoms. *P* values were not adjusted for multiple comparisons in this post hoc analysis, increasing the risk of type I errors. All dosages analyzed were within the FDA-recommended dose range for adults with schizophrenia; the recommended dose range is 1.5–6 mg/d for cariprazine (Vraylar, 2017), 4–8 mg/d for risperidone (Risperidone, 2009), and 10–15 mg/d for aripiprazole (Abilify, 2016). The cariprazine dosages used in the component studies were pooled into high- (4.5 and 6 mg/d) and low-dose (1.5 and 3 mg/d) groups for post hoc analysis, while only one dose each of risperidone (4 mg/d) and aripiprazole (10 mg/d) were analyzed. Efficacy and tolerability in schizophrenia have been established at these doses for risperidone and aripiprazole, although it is unknown if higher doses of these compounds would have been more effective in these analyses. Finally, since risperidone and aripiprazole were each used in only one of the component studies, the number of patients in these treatment groups was smaller than the number in the pooled cariprazine groups; fewer patients per group may have limited the ability to detect a significant difference versus placebo.

In conclusion, cariprazine compared with placebo was an effective treatment against negative symptoms of schizophrenia. These improvements were at least in part due to direct effects on primary negative symptoms, as cariprazine resulted in significant improvement versus placebo in negative symptoms after controlling for positive symptoms. These results support those of the previous study in stable patients with persistent, predominant negative symptoms, suggesting that cariprazine is efficacious in treating primary negative symptoms of schizophrenia. The efficacy of cariprazine in primary negative symptoms of schizophrenia represents a treatment breakthrough in a symptom domain that has limited treatment options.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.schres.2018.08.020>.

Author disclosures

Role of funding source

This study was sponsored by Forest Research Institute, Inc., an Allergan affiliate (USA), and Gedeon Richter Plc (Hungary). All authors met ICMJE authorship criteria. Neither honoraria nor payments were made for authorship.

Contributors

W. Earley, S. Durgam, Á. Barabácssy, B. Szatmári, and G. Németh were involved with the study design, analysis, and interpretation of data. M. Patel, D. Daniel and H. Nasrallah contributed to the analysis and interpretation of the data. H. Guo and Y. Zhong performed statistical analyses. All authors contributed to and have approved the final manuscript.

Conflict of interest

D. Daniel is an employee of Bracket Global, LLC. H. Nasrallah has been a consultant for Acadia, Alkermes, Allergan, Boehringer Ingelheim, Grünenthal USA, Inc., Janssen Pharmaceuticals, Inc., Lundbeck, Merck Sharp & Dohme Corp., Novartis Corporation, Otsuka Pharmaceutical Co., Ltd., Roche/Genentech, Sunovion Pharmaceuticals, Inc., and Vanda Pharmaceuticals; has served on speakers' bureaus for Acadia, Alkermes, Allergan, Janssen Pharmaceuticals, Inc., Otsuka Pharmaceuticals, Sunovion Pharmaceuticals, Inc. and Vanda; and has received grant/research support from Forest Pharmaceuticals, Inc., Otsuka Pharmaceutical Co., Ltd., and Roche/Genentech. W. Earley, S. Durgam, H. Guo, M. Patel and Y. Zhong are employees of Allergan. Á. Barabácssy, B. Szatmári and G. Németh are employees of Gedeon Richter Plc.

Acknowledgements

Writing and editorial assistance were provided by Jennifer Fetting, PhD, of Prescott Medical Communications Group (Chicago, IL), a contractor of Allergan.

References

Abilify, 2016. Package Insert. Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan.
 APA, 2000. Diagnostic and Statistical Manual of Mental Disorders. 4th ed. American Psychiatric Association, Washington, DC, p. 2000 text revised.
 Aretha, C.W., Sinha, A., Galloway, M.P., 1995. Dopamine D3-preferring ligands act at synthesis modulating autoreceptors. *J. Pharmacol. Exp. Ther.* 274 (2), 609–613.
 Barnes, T.R., 1989. A rating scale for drug-induced akathisia. *Br. J. Psychiatry* 154, 672–676.
 Durgam, S., Starace, A., Li, D., Migliore, R., Ruth, A., Németh, G., Laszlovszky, I., 2014. An evaluation of the safety and efficacy of cariprazine in patients with acute exacerbation of schizophrenia: a phase II, randomized clinical trial. *Schizophr. Res.* 152 (2–3), 450–457.
 Durgam, S., Cutler, A.J., Lu, K., Migliore, R., Ruth, A., Laszlovszky, I., Németh, G., Meltzer, H.Y., 2015. Cariprazine in acute exacerbation of schizophrenia: a fixed-dose, phase 3, randomized, double-blind, placebo- and active-controlled trial. *J. Clin. Psychiatry* 76 (12), e1574–e1582.
 Duric, V., Banasr, M., Franklin, T., Lepack, A., Adham, N., Kiss, B., Gyertyan, I., Duman, R.S., 2017. Cariprazine exhibits anxiolytic and dopamine D3 receptor-dependent

antidepressant effects in the chronic stress model. *Int. J. Neuropsychopharmacol.* 20 (10), 788–796.
 Girgis, R.R., Slifstein, M., D'Souza, D., Lee, Y., Periclou, A., Ghahramani, P., Laszlovszky, I., Durgam, S., Adham, N., Nabulsi, N., Huang, Y., Carson, R.E., Kiss, B., Kapas, M., Abi-Dargham, A., Rakhit, A., 2016. Preferential binding to dopamine D3 over D2 receptors by cariprazine in patients with schizophrenia using PET with the D3/D2 receptor ligand [(11)C]-(+)-PHNO. *Psychopharmacology* 233 (19–20), 3503–3512.
 Girgis, R.R., Abi-Dargham, A., Slifstein, M., Chen, L., Periclou, A., Adham, N., Earley, W., 2017. In vivo dopamine D3 and D2 receptor occupancy profile of cariprazine versus aripiprazole: a PET study. 56th Annual Meeting of the American College of Neuropsychopharmacology. Palm Springs, CA.
 Guy, W., 1976. The clinician global severity and impression scales. ECDEU Assessment Manual for Psychopharmacology. Rockville, MD: National Institute of Mental Health; 218–222. DHEW Publication No. 76-338.
 Guy, W., National Institute of Mental, H. Psychopharmacology Research, B. Early Clinical Drug Evaluation, P., 1976. ECDEU Assessment Manual for Psychopharmacology. U.S. Dept. of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, National Institute of Mental Health, Psychopharmacology Research Branch, Division of Extramural Research Programs, Rockville, Md.
 Gyertyán, I., Sághy, K., Laszy, J., Elekes, O., Kedves, R., Gémesi, L.I., Pásztor, G., Zájér-Balázs, M., Kapás, M., Ágai Csongor, E., Domány, G., Kiss, B., Szombathelyi, Z., 2008. Subnanomolar dopamine D3 receptor antagonism coupled to moderate D2 affinity results in favourable antipsychotic-like activity in rodent models: II. Behavioural characterisation of RG-15. *Naunyn Schmiedeberg's Arch. Pharmacol.* 378 (5), 529–539.
 Gyertyán, I., Kiss, B., Sághy, K., Laszy, J., Szabó, G., Szabados, T., Gémesi, L.I., Pásztor, G., Zájér-Balázs, M., Kapás, M., Csongor, E., Domány, G., Tihanyi, K., Szombathelyi, Z., 2011. Cariprazine (RGH-188), a potent D3/D2 dopamine receptor partial agonist, binds to dopamine D3 receptors in vivo and shows antipsychotic-like and procognitive effects in rodents. *Neurochem. Int.* 59 (6), 925–935.
 Hunter, R., Barry, S., 2012. Negative symptoms and psychosocial functioning in schizophrenia: neglected but important targets for treatment. *Eur. Psychiatry* 27 (6), 432–436.
 Janicak, P.G., Glick, I.D., Marder, S.R., Crandall, D.T., McQuade, R.D., Marcus, R.N., Eudicone, J.M., Assuncao-Talbot, S., 2009. The acute efficacy of aripiprazole across the symptom spectrum of schizophrenia: a pooled post hoc analysis from 5 short-term studies. *J. Clin. Psychiatry* 70 (1), 25–35.
 Joyce, J.N., Millan, M.J., 2005. Dopamine D3 receptor antagonists as therapeutic agents. *Drug Discov. Today* 10 (13), 917–925.
 Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophr. Bull.* 13 (2), 261–276.
 Keefe, R.S., Bilder, R.M., Davis, S.M., Harvey, P.D., Palmer, B.W., Gold, J.M., Meltzer, H.Y., Green, M.F., Capuano, G., Stroup, T.S., McEvoy, J.P., Swartz, M.S., Rosenheck, R.A., Perkins, D.O., Davis, C.E., Hsiao, J.K., Lieberman, J.A., 2007. Neurocognitive effects of antipsychotic medications in patients with chronic schizophrenia in the CATIE trial. *Arch. Gen. Psychiatry* 64 (6), 633–647.
 Kiss, B., Laszlovszky, I., Horváth, A., Némethy, Z., Schmidt, E., Bugovics, G., Fazekas, K., Gyertyán, I., Ágai-Csongor, E., Domány, G., Szombathelyi, Z., 2008. Subnanomolar dopamine D3 receptor antagonism coupled to moderate D2 affinity results in favourable antipsychotic-like activity in rodent models: I. Neurochemical characterisation of RG-15. *Naunyn Schmiedeberg's Arch. Pharmacol.* 378 (5), 515–528.
 Kiss, B., Horváth, A., Némethy, Z., Schmidt, E., Laszlovszky, I., Bugovics, G., Fazekas, K., Hornok, K., Orosz, S., Gyertyán, I., Ágai-Csongor, E., Domány, G., Tihanyi, K., Adham, N., Szombathelyi, Z., 2010. Cariprazine (RGH-188), a dopamine D(3) receptor-preferring, D(3)/D(2) dopamine receptor antagonist-partial agonist antipsychotic candidate: in vitro and neurochemical profile. *J. Pharmacol. Exp. Ther.* 333 (1), 328–340.
 Lacroix, L.P., Hows, M.E., Shah, A.J., Hagan, J.J., Heidbreder, C.A., 2003. Selective antagonism at dopamine D3 receptors enhances monoaminergic and cholinergic neurotransmission in the rat anterior cingulate cortex. *Neuropsychopharmacology* 28 (5), 839–849.
 Laszy, J., Laszlovszky, I., Gyertyán, I., 2005. Dopamine D3 receptor antagonists improve the learning performance in memory-impaired rats. *Psychopharmacology* 179 (3), 567–575.
 Leggio, G.M., Salomone, S., Bucolo, C., Platania, C., Micalè, V., Caraci, F., Drago, F., 2013. Dopamine D(3) receptor as a new pharmacological target for the treatment of depression. *Eur. J. Pharmacol.* 719 (1–3), 25–33.
 Leucht, S., Kane, J.M., Kissling, W., Hamann, J., Etschel, E., Engel, R.R., 2005. What does the PANSS mean? *Schizophr. Res.* 79 (2–3), 231–238.
 Leucht, S., Arbtter, D., Engel, R.R., Kissling, W., Davis, J.M., 2009a. How effective are second-generation antipsychotic drugs? A meta-analysis of placebo-controlled trials. *Mol. Psychiatry* 14 (4), 429–447.
 Leucht, S., Corves, C., Arbtter, D., Engel, R.R., Li, C., Davis, J.M., 2009b. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. *Lancet* 373 (9657), 31–41.
 Levant, B., 1997. The D3 dopamine receptor: neurobiology and potential clinical relevance. *Pharmacol. Rev.* 49 (3), 231–252.
 Marder, S.R., Galderisi, S., 2017. The current conceptualization of negative symptoms in schizophrenia. *World Psychiatry* 16 (1), 14–24.
 Marder, S.R., Davis, J.M., Chouinard, G., 1997. The effects of risperidone on the five dimensions of schizophrenia derived by factor analysis: combined results of the North American trials. *J. Clin. Psychiatry* 58 (12), 538–546.
 Milev, P., Ho, B.C., Arndt, S., Andreasen, N.C., 2005. Predictive values of neurocognition and negative symptoms on functional outcome in schizophrenia: a longitudinal first-episode study with 7-year follow-up. *Am. J. Psychiatry* 162 (3), 495–506.

- Millan, M.J., Svenningsson, P., Ashby Jr., C.R., Hill, M., Egeland, M., Dekeyne, A., Brocco, M., Di Cara, B., Lejeune, F., Thomasson, N., Munoz, C., Mocaer, E., Crossman, A., Cistarelli, L., Girardon, S., Iob, L., Veiga, S., Gobert, A., 2008. S33138 [N-[4-[2-[(3aS,9bR)-8-cyano-1,3a,4,9b-tetrahydro[1]-benzopyrano[3,4-c]pyrrol-2((3H)-yl)-ethyl]phenylacetamide]]], a preferential dopamine D3 versus D2 receptor antagonist and potential antipsychotic agent. II. A neurochemical, electrophysiological and behavioral characterization in vivo. *J. Pharmacol. Exp. Ther.* 324 (2), 600–611.
- Mohr, P.E., Cheng, C.M., Claxton, K., Conley, R.R., Feldman, J.J., Hargreaves, W.A., Lehman, A.F., Lenert, L.A., Mahmoud, R., Marder, S.R., Neumann, P.J., 2004. The heterogeneity of schizophrenia in disease states. *Schizophr. Res.* 71 (1), 83–95.
- Nasrallah, H., Tandon, R., Keshavan, M., 2011. Beyond the facts in schizophrenia: closing the gaps in diagnosis, pathophysiology, and treatment. *Epidemiol. Psychiatr. Sci.* 20 (4), 317–327.
- Németh, G., Laszlovszky, I., Czobor, P., Szalai, E., Szatmári, B., Harsányi, J., Barabácssy, A., Debelle, M., Durgam, S., Bitter, I., Marder, S., Fleischhacker, W.W., 2017. Cariprazine versus risperidone monotherapy for treatment of predominant negative symptoms in patients with schizophrenia: a randomised, double-blind, controlled trial. *Lancet* 389 (10074), 1103–1113.
- Posner, K., Brown, G.K., Stanley, B., Brent, D.A., Yershova, K.V., Oquendo, M.A., Currier, G.W., Melvin, G.A., Greenhill, L., Shen, S., Mann, J.J., 2011. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. *Am. J. Psychiatry* 168 (12), 1266–1277.
- Pugsley, T.A., Davis, M.D., Akunne, H.C., MacKenzie, R.G., Shih, Y.H., Damsma, G., Wikstrom, H., Whetzel, S.Z., Georgic, L.M., Cooke, L.W., et al., 1995. Neurochemical and functional characterization of the preferentially selective dopamine D3 agonist PD 128907. *J. Pharmacol. Exp. Ther.* 275 (3), 1355–1366.
- Rabinowitz, J., Berardo, C.G., Bugarski-Kirolo, D., Marder, S., 2013a. Association of prominent positive and prominent negative symptoms and functional health, well-being, healthcare-related quality of life and family burden: a CATIE analysis. *Schizophr. Res.* 150 (2–3), 339–342.
- Rabinowitz, J., Werbeloff, N., Caers, I., Mandel, F.S., Stauffer, V., Menard, F., Kinon, B.J., Kapur, S., 2013b. Negative symptoms in schizophrenia—the remarkable impact of inclusion definitions in clinical trials and their consequences. *Schizophr. Res.* 150 (2–3), 334–338.
- Risperidone, 2009. Package Insert. Janssen Pharmaceutical Ltd., Wallingstown, Little Island, County Cork, Ireland.
- Simpson, G.M., Angus, J.W., 1970. A rating scale for extrapyramidal side effects. *Acta Psychiatr. Scand. Suppl.* 212, 11–19.
- Stahl, S.M., 2017. Drugs for psychosis and mood: unique actions at D3, D2, and D1 dopamine receptor subtypes. *CNS Spectr.* 22 (5), 375–384.
- Suttajit, S., Pilakanta, S., 2015. Predictors of quality of life among individuals with schizophrenia. *Neuropsychiatr. Dis. Treat.* 11, 1371–1379.
- Vraylar, 2017. Package Insert. Allergan, Irvine, CA.
- Zimnisky, R., Chang, G., Gyertyán, I., Kiss, B., Adham, N., Schmauss, C., 2013. Cariprazine, a dopamine D(3)-receptor-preferring partial agonist, blocks phencyclidine-induced impairments of working memory, attention set-shifting, and recognition memory in the mouse. *Psychopharmacology* 226 (1), 91–100.