



## Original article

# The efficacy of cariprazine in negative symptoms of schizophrenia: Post hoc analyses of PANSS individual items and PANSS-derived factors

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## ARTICLE INFO

## Article history:

Received 19 September 2018

Received in revised form 9 January 2019

Accepted 12 January 2019

Available online 7 February 2019

## Keywords:

Cariprazine  
Risperidone  
Schizophrenia  
Negative symptoms  
PANSS  
Cognition

## ABSTRACT

**Background:** Negative symptoms in schizophrenia are heterogeneous and multidimensional; effective treatments are lacking. Cariprazine, a dopamine D<sub>3</sub>-preferring D<sub>3</sub>/D<sub>2</sub> receptor partial agonist and serotonin 5-HT<sub>1A</sub> receptor partial agonist, was significantly more effective than risperidone in treating negative symptoms in a prospectively designed trial in patients with schizophrenia and persistent, predominant negative symptoms.

**Methods:** Using post hoc analyses, we evaluated change from baseline at week 26 in individual items of the Positive and Negative Syndrome Scale (PANSS) and PANSS-derived factor models using a mixed-effects model for repeated measures (MMRM) in the intent-to-treat (ITT) population (cariprazine = 227; risperidone = 227).

**Results:** Change from baseline was significantly different in favor of cariprazine versus risperidone on PANSS items N1–N5 (blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, difficulty in abstract thinking) ( $P < .05$ ), but not on N6 (lack of spontaneity/flow of conversation) or N7 (stereotyped thinking). On all PANSS-derived negative symptom factor models evaluated (PANSS-Factor Score for Negative Symptoms, Liemburg factors, Khan factors, Pentagonal Structure Model Negative Symptom factor), statistically significant improvement was demonstrated for cariprazine versus risperidone ( $P < .01$ ). Small and similar changes in positive/depressive/EPS symptoms suggested that negative symptom improvement was not pseudospecific. Change from baseline was significantly different for cariprazine versus risperidone on PANSS-based factors evaluating other relevant symptom domains (disorganized thoughts, prosocial function, cognition;  $P < .05$ ).

**Conclusions:** Since items representing different negative symptom dimensions may represent different fundamental pathophysiological mechanisms, significant improvement versus risperidone on most PANSS Negative Subscale items and across all PANSS-derived factors suggests broad-spectrum efficacy for cariprazine in treating negative symptoms of schizophrenia.

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## 1. Introduction

Schizophrenia, an often chronic and debilitating psychiatric disorder, is characterized by a constellation of clinical signs and symptoms that are categorized into distinct positive, negative, disorganization and cognitive symptom domains. Although

positive symptoms (eg, delusions, hallucinations) must be present for a diagnosis of schizophrenia to be made, negative symptoms, typified by the absence of normal function and loss of behaviors and motivation, are highly detrimental to patient functioning and quality of life [1–7]. While antipsychotic treatment is effective against positive schizophrenia symptoms, effective treatment for negative symptoms is lacking and most improvement occurs secondarily to improvement in positive symptoms [1]. Research suggests that negative symptoms are heterogeneous, with potentially different pathophysiological mechanisms and psychopathological outcomes [8,9]. As such, understanding how an

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<http://dx.doi.org/10.1016/j.eurpsy.2019.01.015>

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antipsychotic performs across the range of negative symptoms may help improve clinical management of this fundamental dimension of schizophrenia.

Through efforts to consolidate the negative symptom concept [10–13], broad consensus has emerged that the most prominent constructs are the 5 A's of negative symptoms: affective flattening, alogia, anhedonia, asociality, and avolition [12,14]. Briefly, blunted affect is a decrease in observed expression of emotion; alogia is reduced quantity of speech/spontaneous information; anhedonia is the diminished capacity to experience pleasure during an event (consummatory anhedonia) or in anticipation of one (anticipatory anhedonia); asociality is reduced social initiative due to decreased interest in forming and maintaining relationships; and avolition is reduced initiation/persistence of goal-directed activity. The Positive and Negative Syndrome Scale (PANSS) [15] is a frequently used clinical rating scale, which generally includes items to evaluate the 5 A's. Although newer scales have been developed to more specifically assess negative symptoms [13,16] and the PANSS has limitations, no consensus has been reached regarding the best rating scale for assessing negative symptoms in schizophrenia.

The negative symptom structure is multidimensional, with evidence emerging in support of models generally consisting of 2–5 factors [10]. The most stable and replicated models include 2 factors clustering into the potentially related but distinct subdomains of diminished expression (ie, blunted affect, alogia) and avolition/apathy (ie, avolition, asociality, anhedonia) [8]; this model is supported in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) [2]. Interestingly, just as it is proposed that negative and positive symptoms have different pathophysiological mechanisms, evidence suggests similar underlying differences within the negative symptom subdomains [12].

Cariprazine, an orally active and potent dopamine D<sub>3</sub>-preferring D<sub>3</sub>/D<sub>2</sub> receptor partial agonist and serotonin 5-HT<sub>1A</sub> receptor partial agonist [17,18], is approved for the treatment of adult patients with schizophrenia (Europe and US) and for acute treatment of manic/mixed episodes of bipolar I disorder (US). Unlike other atypical antipsychotics, cariprazine shows high and balanced in vivo occupancy at dopamine D<sub>2</sub> and D<sub>3</sub> receptors at clinically relevant doses [17,19]. In animal models, cariprazine has demonstrated dopamine D<sub>3</sub> receptor-dependent procognitive and anti-anhedonic effects, suggesting that it may be useful in treating negative symptoms of schizophrenia [20,21].

In a 26-week randomized, double-blind, active-comparator controlled study, cariprazine and risperidone were compared in stable patients with schizophrenia and persistent, predominant negative symptoms (PPNS) (EudraCT Number 2012-005485-36) [22]. Cariprazine was significantly more effective than risperidone in improving negative symptoms as shown by change from baseline to week 26 on the primary efficacy parameter, the PANSS Factor Score for Negative Symptoms (PANSS-FSNS) [23], which is also known as the Marder factor for Negative Symptoms [24]. A significant between-group difference for cariprazine versus risperidone was also seen on the secondary efficacy parameter, the Personal and Social Performance Scale (PSP) [25], demonstrating that negative symptom improvement was accompanied by improvement in day-to-day functioning for cariprazine-treated patients.

This well-designed large-scale study in patients with schizophrenia and PPNS provided important evidence of the clinically significant superiority of cariprazine over another second-generation antipsychotic in treating negative symptoms. To further evaluate negative symptom improvement with cariprazine in prospectively defined patients with schizophrenia and PPNS, we assessed changes in PANSS individual subscale items and PANSS-derived factors using post hoc analyses. Given the results of the original trial, we expect that our more detailed investigations will

show that cariprazine has greater efficacy than risperidone on negative symptoms and related constructs when change from baseline to week 26 is assessed using PANSS individual items and PANSS-derived factors.

## 2. Materials and methods

### 2.1. Primary study design

Detailed methods of the prospective cariprazine versus risperidone study (RGH-188-005) have been published [22]. Briefly, the study consisted of a 4-week lead-in period, 26-week double-blind treatment (2-week up-titration and 24-week continuation treatment), and a 2-week safety follow-up. Patients were randomized (1:1) to once-daily oral cariprazine or risperidone; after up-titration, patients received the target dose of cariprazine (4.5 mg/d) or risperidone (4 mg/d). The target dose could be decreased or increased (once time each) in case of poor tolerability or impending psychotic deterioration during the double-blind continuation phase. The accepted fixed doses of cariprazine (3, 4.5, or 6 mg/d) and risperidone (3, 4, or 6 mg/d) were chosen in accordance with the respective product labels.

### 2.2. Patients

Male and female patients (18–65 years old, inclusive) who participated in the study had a DSM-IV-TR [26] diagnosis of schizophrenia and an available psychiatric history to ensure the presence of PPNS and low levels of positive symptoms. Patients had an illness duration  $\geq 2$  years and a stable condition for at least 6 months (ie, no acute exacerbations, psychiatric hospitalizations, or imprisonments). Clinical inclusion criteria required PPNS for  $\geq 6$  months, PANSS-FSNS score  $\geq 24$ , and a score  $\geq 4$  on at least 2 of 3 PANSS negative symptom items (blunted affect, passive/apathetic social withdrawal, lack of spontaneity/flow of conversation).

Patients were excluded from the primary study for various reasons, including a current DSM-IV-TR axis I disorder other than schizophrenia or unstable clinical condition. Most importantly, clinical criteria excluded patients with moderate-to-severe positive, depressive, and extrapyramidal symptoms (EPS) to ensure that negative symptom changes could be genuinely attributed to improved negative symptoms and not to secondary improvements in these other psychopathological domains (ie, pseudospecific improvement). Specifically, patients were excluded for: score  $\geq 4$  on more than 2 specific PANSS items (P1 [delusions], P3 [hallucinatory behavior], P5 [grandiosity], P6 [suspiciousness], G9 [unusual thought content]); PANSS factor score for Positive Symptoms (PANSS-FSPS)  $> 19$  [27]; total score  $> 6$  (moderate/severe symptoms) on the Calgary Depression Scale for Schizophrenia (CDSS) [28]; or clinically relevant parkinsonian symptoms as judged by an investigator and/or defined as a sum  $> 3$  on the first 8 items of the Simpson Angus Scale (SAS) [29].

### 2.3. Post hoc analyses

Changes from baseline to week 26 on the single items of the PANSS Negative Symptom and General Psychopathology subscales (Table 1) were analyzed to investigate the efficacy of cariprazine on individual symptoms that contribute to heterogeneity in schizophrenia pathology. To assess the multidimensional aspect of negative symptoms, changes from baseline to week 26 on the individual items of the PANSS-FSNS were evaluated. Additional PANSS-derived factors for negative symptoms [30–33] were located through an extensive search of the literature and our data were further analyzed using these models (Table 1). Factors of interest in other domains (supplementary Table 1), including

**Table 1**  
PANSS-derived negative symptoms factors.

PANSS Items	Liemburg		Khan <sup>c</sup>		PSM Negative Factor
	FSNS <sup>a</sup>	Avolition/ Asociality <sup>b</sup>	Expressive Deficit	Expressive Deficit	
<b>Negative Symptom Subscale</b>					
N1: Blunted affect	✓		✓	✓	✓
N2: Emotional withdrawal	✓	✓			✓
N3: Poor rapport	✓		✓	✓	✓
N4: Passive/ apathetic social withdrawal	✓	✓			✓
N5: Difficulty in abstract thinking					
N6: Lack of spontaneity/ flow of conversation	✓		✓	✓	✓
N7: Stereotyped thinking					
<b>General Psychopathology Subscale</b>					
G1: Somatic concern					
G2: Anxiety					
G3: Guilt feelings					
G4: Tension					
G5: Mannerisms/ posturing			✓		✓
G6: Depression					
G7: Motor retardation	✓		✓	✓	✓
G8: Uncooperativeness					✓
G9: Unusual thought content					
G10: Disorientation					
G11: Poor attention					
G12: Lack of judgement/insight					
G13: Disturbance of volition			✓		✓
G14: Poor impulse control					✓
G15: Preoccupation					
G16: Active social avoidance	✓	✓			✓

FSNS, Factor Score for Negative Symptoms; PANSS, Positive and Negative Syndrome Scale; PSM, Pentagonal Structure Model.

<sup>a</sup> Also known as the Marder Factor for Negative Symptoms.

<sup>b</sup> The same items comprise the Liemburg Avolition/Asociality factor and the Khan Experiential Deficit factor.

<sup>c</sup> Also known as the Fervaha 2-factor model: the Fervaha Amotivation factor and Khan Experiential Deficit factor are identical, and the Fervaha Diminished Expression factor and Khan Expressive Deficit factor are identical.

disorganized thoughts (items N5, P2, G5, G10–11, G13, G15) [24], prosocial function (items N2, N4, N7, P3, P6, G16) [34], and cognition (items N5, N7, P2, G10–11) [35], were also evaluated. Furthermore, the possibility that negative symptom improvement was related to improvement in positive symptoms was investigated via changes on the individual items of the PANSS Positive subscale (items P1–7) and PANSS-FSPS (items P1, P3, P5–6, G9); Marder factors for Depression/Anxiety (items G2–4, G6), Uncontrolled Hostility/Excitement (items P4, P7, G8, G14), and Positive Symptoms (N7, P1, P3, P5–6, G1, G9, G12) were also analyzed as controls for pseudospecificity [24] (supplementary Table 1).

Analyses of PANSS single items and factors were based on all postbaseline scores using observed cases without imputing missing values; the final assessment was omitted if the study drug had been stopped for more than 5 days. Change from baseline to week 26/endpoint in individual PANSS items and PANSS factors was analyzed using a mixed-effects model for repeated measures (MMRM) with treatment group, visit, study center, and treatment group-by-visit interaction as fixed effects, and the baseline value and baseline value-by-visit interaction as the covariates in the intent-to-treat (ITT) population. Analyses were performed in SAS (PROC MIXED) (Version 9.2. Cary, NC: SAS Institute Inc. 2012), using an unstructured covariance matrix to model the covariance of within-patient scores; the resultant F-tests were based on Kenward–Roger's adjusted denominator degrees of freedom [36].

### 3. Results

In the primary, prospective study (RGH-188-005), a total of 461 patients were randomized to double-blind treatment (cariprazine = 230; risperidone = 231); 456 patients were included in the ITT

population (cariprazine = 227; risperidone = 229) [22]. The least squares mean difference with 95% confidence interval (LSMD [95% CI]) was statistically significant in favor of cariprazine versus risperidone on the PANSS-FSNS (-1.46 [-2.39, -0.53];  $P = .0022$ ; effect size = 0.31) and the PSP (4.63 [2.71, 6.56];  $P < .0001$ ; effect size = 0.48).

#### 3.1. Post hoc analyses

##### 3.1.1. Baseline values

Mean baseline values for individual PANSS Negative and Positive subscale items were similar between groups (Table 2) and supported that inclusion criteria succeeded in selecting a patient population with at least moderate negative symptoms and mild positive symptoms. Although general items are inconsistently related to the negative symptom subdomain, items from the General Psychopathology subscale often map to negative symptom factors. Of interest, several general items that map to negative symptom factors or to the Disorganized Thought/Cognition factor (ie, G5, G7, G11, G13, G15, G16) were among the general items with higher baseline scores. As expected given the study's inclusion criteria, scores for general items that map to the Marder Depression factor (G2, G3, G4, G6) were generally low.

Mean baseline values on the first 8 items of the SAS (gait, arm dropping, shoulder shaking, elbow rigidity, wrist rigidity, leg pendulousness, head dropping, glabella tap) ranged from 0 to 0.4, indicating a population without clinically significant parkinsonism (score range per item = 0–4; lower scores indicate less severe symptoms). Baseline CDSS total score values (score range = 0–27; lower score is favorable) indicated a population without substantial depressive symptoms (cariprazine = 0.7; risperidone = 0.9).

**Table 2**  
Baseline values for PANSS Negative and Positive Symptom subscales single items (ITT population).

PANSS	Mean Baseline Value	
	Cariprazine n = 227	Risperidone n = 229
<b>Negative Symptom Subscale</b>		
N1: Blunted affect	4.5	4.4
N2: Emotional withdrawal	4.3	4.3
N3: Poor rapport	3.9	3.8
N4: Passive/apathetic social withdrawal	4.6	4.6
N5: Difficulty in abstract thinking	3.7	3.7
N6: Lack of spontaneity and flow of conversation	4.1	4.1
N7: Stereotyped thinking	3.4	3.4
<b>Positive Symptom Subscale</b>		
P1: Delusions	1.9	1.9
P2: Conceptual disorganization	2.6	2.6
P3: Hallucinatory behavior	1.4	1.4
P4: Excitement	1.5	1.4
P5: Grandiosity	1.2	1.3
P6: Suspiciousness/persecution	2.2	2.1
P7: Hostility	1.2	1.2
<b>General Psychopathology Subscale</b>		
G1: Somatic concern	1.7	1.6
G2: Anxiety	1.9	2.1
G3: Guilt feelings	1.3	1.3
G4: Tension	1.8	2.0
G5: Mannerisms/posturing	2.6	2.5
G6: Depression	1.5	1.5
G7: Motor retardation	3.2	3.1
G8: Uncooperativeness	1.5	1.5
G9: Unusual thought content	2.0	2.0
G10: Disorientation	1.8	1.8
G11: Poor attention	3.1	3.0
G12: Lack of judgement/insight	3.1	3.1
G13: Disturbance of volition	3.5	3.4
G14: Poor impulse control	1.4	1.4
G15: Preoccupation	2.6	2.8
G16: Active social avoidance	3.1	3.1

PANSS item scores range from 1–7. Lower scores indicate less severe symptoms.  
PANSS, Positive and Negative Syndrome Scale.

### 3.1.2. Individual items of the negative symptom and general psychopathology subscales

On individual items from the PANSS Negative Symptom subscale, LSMDs in change from baseline were statistically significant in favor of cariprazine versus risperidone on most items (Fig. 1A). Mean change by week in the individual items of the PANSS Negative Symptom subscale is presented in online supplementary material (Fig. 1A–G). Differences in mean change on several items evaluating the 5 A's of negative symptoms were statistically significant in favor of cariprazine versus risperidone (ie, affect blunted: N1; avolition: N2 [emotional withdrawal]; asociality: N3 [poor rapport] and N4 [passive/apathetic social withdrawal]). Because there is no specific PANSS item for anhedonia, this construct must be evaluated indirectly through negative symptom items that may be descriptive of the concept. For example, change was greater for cariprazine than risperidone on items N2 and N4 evaluating lack of interest in life events and diminished interest/involvement in social interactions leading to reduced personal involvement and neglect of daily activities, respectively [11]. On the key construct of alogia, measured by item N6, a greater than 1-point improvement was seen in both the cariprazine- and risperidone-treatment groups, but the between-group difference was not statistically significant.

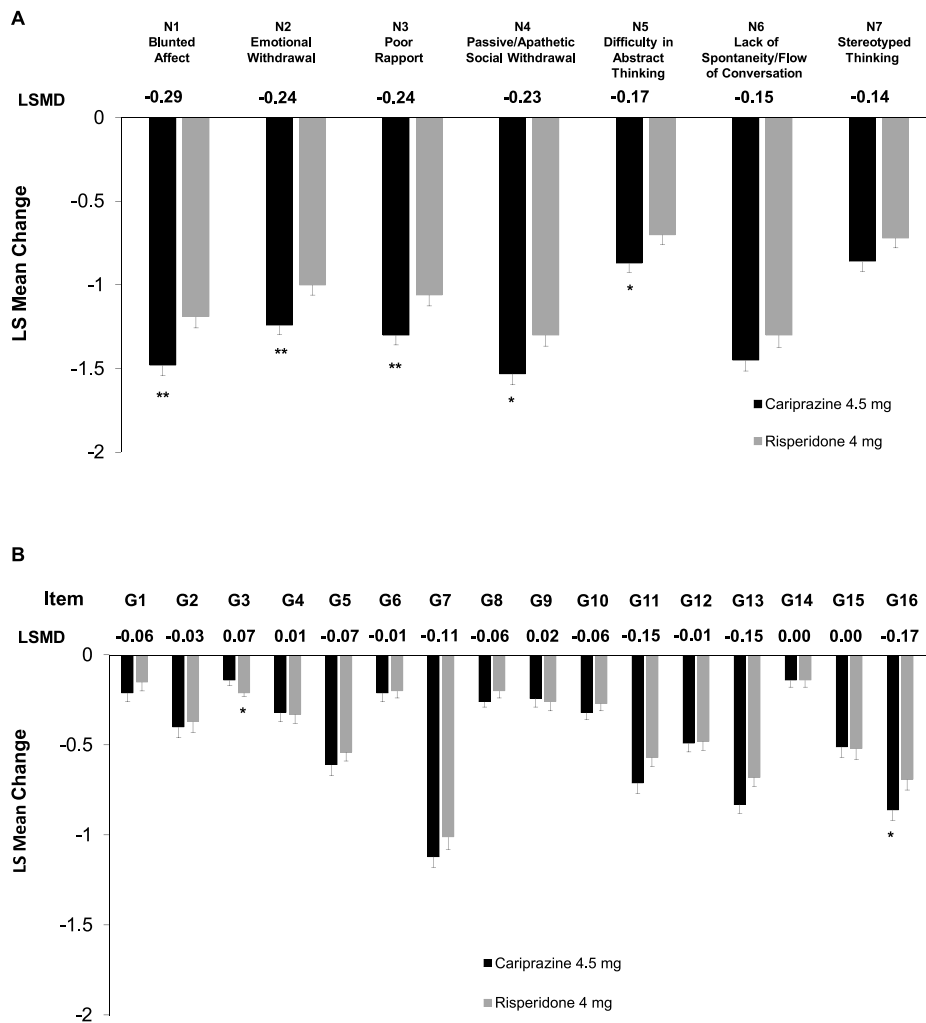
Changes from baseline to week 26 on the individual items of the General Psychopathology subscale were small (range, -0.14 to -1.12) and generally similar between groups; significant differences were seen on only 2 items, active social avoidance (G16) in favor of cariprazine over risperidone ( $P = .042$ ), and guilt feelings (G3) in favor risperidone over cariprazine ( $P = .048$ ) (Fig. 1B).

### 3.1.3. PANSS-derived factors supporting a treatment effect for cariprazine

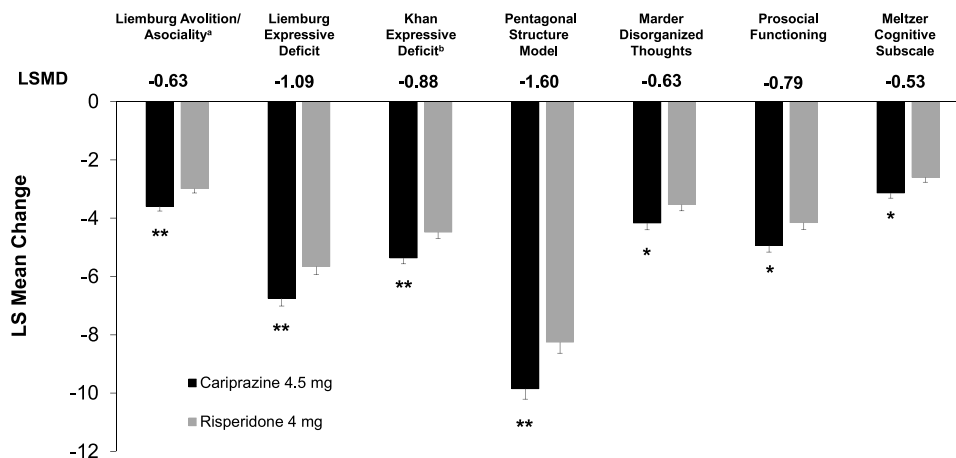
On the individual items of the PANSS-FSNS, significant differences in change from baseline at week 26 were seen in favor of cariprazine over risperidone on 4 of the 5 negative symptom items included in the factor (N1, N2, N3, N4); no between-group difference was noted for N6 (Fig. 1A). For items included from the General Psychopathology subscale, a significant difference in favor of cariprazine was seen on item G16, but not on item G7 (Fig. 1B).

In this PPNS population, prospective PANSS-FSNS results were supported by significant differences in favor of cariprazine over risperidone in change from baseline on other PANSS-derived factors evaluating negative symptoms (Fig. 2). On the 2-factor model utilized by Liemburg et al, mean changes from baseline were significantly greater for cariprazine versus risperidone on the Avolition/Social Amotivation (-3.60 vs -2.98;  $P = .004$ ) and Expressive Deficit (-6.75 vs -5.66;  $P = .004$ ) factors. Similarly, in the 2-factor model utilized by Khan et al and Fervaha et al, the difference in mean change from baseline on the Khan Expressive Deficit factor (also known as the Fervaha Diminished Expression factor) was statistically significant for cariprazine (-5.36) versus risperidone (-4.48;  $P = .003$ ); the same items are included in the Liemburg Avolition/Asociality factor, the Khan Experiential Deficit factor, and the Fervaha Amotivation factor. Finally, mean change from baseline was again significantly different in favor of cariprazine (-9.85) versus risperidone (-8.25;  $P = .003$ ) on the Pentagonal Structure Model (PSM) Negative Symptom factor score.

On factors assessing changes in domains relevant to negative symptoms, differences in mean change from baseline at week 26

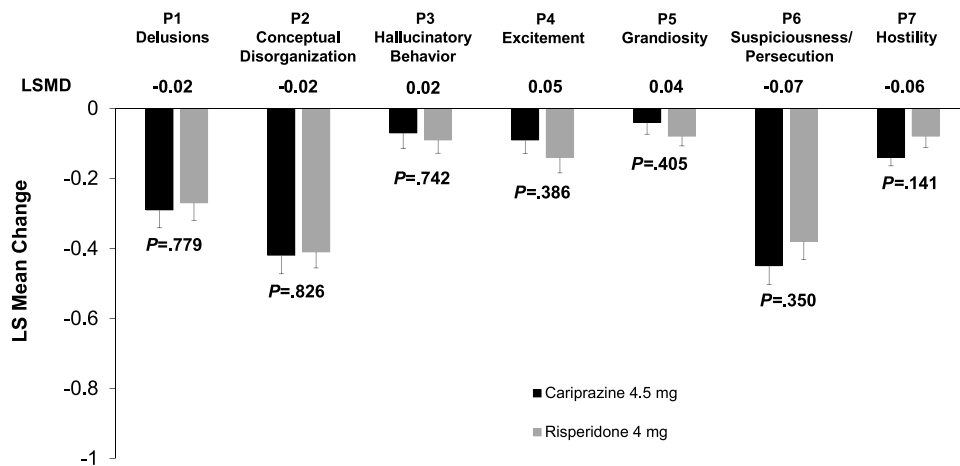


**Fig. 1.** Mean change from baseline in individual items of the PANSS Negative Symptom (A) and General Psychopathology subscales (B) at week 26 (ITT, MMRM). *P* value vs risperidone: \**P* < .05; \*\**P* < .01. Items: somatic concern (G1), anxiety (G2), guilt feelings (G3), tension (G4), mannerisms/posturing (G5), depression (G6), motor retardation (G7), uncooperativeness (G8), unusual thought content (G9), disorientation (G10), poor attention (G11), lack of judgement/insight (G12), disturbance of volition (G13), poor impulse control (G14), preoccupation (G15), active social avoidance (G16). Baseline values ranged from 1.3 (guilt feelings) to 3.5 (disturbance of volition). ITT, intent to treat; LS, least squares; LSMD, least squares mean difference; MMRM, mixed-effects model for repeated measures; PANSS, Positive and Negative Syndrome Scale.



**Fig. 2.** Mean change from baseline at week 26 in PANSS-derived factors for negative and cognitive symptoms (MMRM, ITT). *P* value vs risperidone: \**P* < .05; \*\**P* < .01. <sup>a</sup>The same items are included in the Liemburg Avolition/Asociality factor, the Khan Experiential Deficit factor, and the Fervaha Amotivation factor; <sup>b</sup>the same items are included in the Khan Expressive Deficit factor and the Fervaha Diminished Expression factor. PANSS-derived factors (lower score is favorable): Liemburg factor for Avolition/Asociality and Khan Experiential Deficit factor = items N2, N4, G16; Liemburg factor for Expressive Deficit = items N1, N3, N6, G5, G7, G13; Khan Expressive Deficit factor = N1, N3, N6, G7; negative symptom factor of the Pentagonal Structural Model = items N1-N4, N6, G5, G7-8, G13-14; Marder factor for Disorganized Thoughts = items N5, P2, G5, G10, G11, G13, and G15; Prosocial functioning factor = N2, N4, N7, P3, P6, G16; Meltzer cognitive subscale = items N5, N7, P2, G10, G11. ITT, intent to treat; LS, least squares; LSMD, least squares mean difference; MMRM; mixed-effects model for repeated measures; PANSS, Positive and Negative Syndrome Scale.





**Fig. 3.** Mean change from baseline in PANSS positive symptoms at week 26 (ITT, MMRM). ITT, intent to treat; LS, least squares; LSMD, least squares mean difference; MMRM, mixed-effects model for repeated measures; PANSS, Positive and Negative Syndrome Scale.

were statistically significant in favor of cariprazine versus risperidone on the Marder factor for Disorganized Thoughts (-4.16 vs -3.53;  $P=.05$ ), the Prosocial Functioning factor (-4.94 vs -4.15;  $P=.014$ ), and the Meltzer Cognitive subscale (-3.13 vs -2.60;  $P=.028$ ) (Fig. 2).

### 3.1.4. Demonstrating that negative symptom change is genuine: pseudospecificity analyses

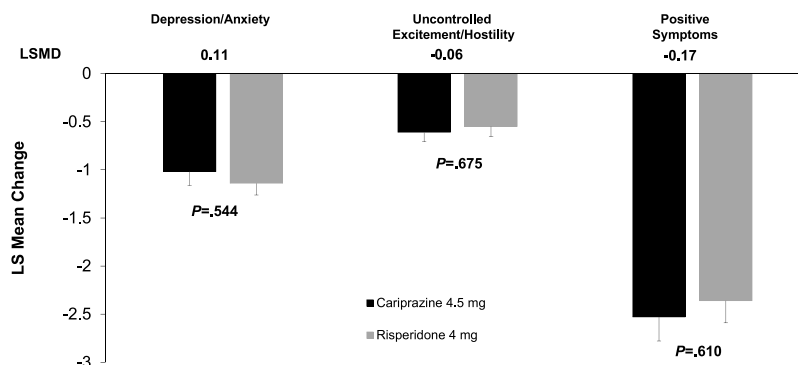
In prospective analysis of the PANSS-FSPS, mean change from baseline at week 26 was the same for cariprazine and risperidone (-1.1;  $P=.963$ ), providing primary evidence for the lack of pseudospecific change in negative symptoms related to positive symptom improvement. In post hoc analyses, these results were supported by small and similar between-group mean changes on the individual positive items included in the PANSS-FSPS (P1, P3, P5, P6) (Fig. 3); mean change in unusual thought content, a general item included in the PANSS-FSPS (G9), was -0.24 for cariprazine and -0.26 for risperidone, with no significant between-group difference noted.

Post hoc analyses of additional factors related to pseudospecificity also supported primary evidence that changes in negative symptoms were not secondary to changes in symptoms from other domains. Namely, changes were small and similar for cariprazine and risperidone on the PANSS-derived Marder factors for Depression/Anxiety, Uncontrolled Excitement/Hostility, and Positive Symptoms (Fig. 4).

Additionally, small mean changes (range, -0.02 to 0.03) on each of the first 8 items of the SAS were not statistically different for cariprazine and risperidone, showing that improvement in negative symptoms was not an artifact of treatment-related differences in EPS liability. Of note, mean changes from baseline in CDSS total score were also small and not significantly different for cariprazine (-0.28) and risperidone (-0.22;  $P=.66$ ), providing prospective evidence that improvement in negative symptoms was not pseudospecific to improvement in depressive symptoms [22].

## 4. Discussion

Heterogeneity in schizophrenia pathology contributes to the challenges associated with understanding and treating negative symptoms. To further explore the effectiveness of cariprazine versus risperidone in patients with schizophrenia and PPNS, we conducted post hoc analyses of PANSS individual items and PANSS-derived factors using data from the prospective negative symptom study. Differences on most individual items and all factors relevant to negative symptoms, cognitive symptoms, and social functioning were statistically significant in favor of cariprazine versus risperidone. Collectively, no significant differences were seen on pseudospecificity measures (ie, positive symptoms, depression, EPS) that would suggest that negative symptom improvement was due to changes in other symptom domains, supporting a genuine treatment effect for cariprazine in negative symptom improvement.



**Fig. 4.** Mean change from baseline at week 26 in Marder factors assessing pseudospecificity. Marder factors to assess pseudospecificity (lower score is favorable): Depression/Anxiety = items G2, G3, G4, G6; Uncontrolled Excitement/Hostility = items P4, P7, G8, G14, Positive Symptoms = items N7, P1, P3, P5, P6, G1, G9, G12. LS, least squares; LSMD, least squares mean difference.

Despite some overlap among the 5 A's, affective flattening, avolition, anhedonia, asociality, and avolition have been identified as key constructs of negative symptoms, with evidence suggesting separate neurobiological underpinnings that may represent different therapeutic targets [8,12]. Hypotheses regarding the pathogenesis of blunted affect include abnormalities in identifying emotion, perception of nonverbal cues, and deficits in motor activity; interestingly, since decreased emotional expression is observed in medicated and nonmedicated patients alike, blunted affect cannot just be attributed to antipsychotic-related effect [37–40]. In our post hoc analysis, a significant between-group difference in change from baseline on PANSS item N1 (blunted affect) was noted, suggesting improvement in this fundamental construct for cariprazine- versus risperidone-treated patients.

Several mechanisms, including working memory deficit, general fluency disturbance, and word finding difficulties [41], have been proposed to explain avolition. On the PANSS, avolition is assessed by item N6 (lack of spontaneity/flow of conversation) through observed reduction in the normal flow of conversation associated with apathy, avolition, defensiveness, or cognitive deficit. In our analysis, although a greater than 1-point improvement from baseline was observed in both treatment groups, no significant between-group difference was seen on the avolition item, suggesting that risperidone may have also had some efficacy in this domain.

Anhedonia has traditionally been a key feature of both depression and schizophrenia [14]. Neurobehavioral models differentiate between consummatory and anticipatory pleasure [11], with research suggesting that schizophrenia may be characterized by intact consummatory pleasure, but impaired anticipatory pleasure [11]. This distinction may be important when evaluating functional outcomes in patients with schizophrenia since inability to anticipate a rewarding experience may underlie impaired initiative or incapacity to seek pleasant activities. Unlike some psychometric scales that directly measure anhedonia in schizophrenia [13,16,42], no specific PANSS item evaluates anhedonia, which limits the ability of this scale to assess change in this key construct.

Asociality, which may predate the onset of schizophrenia [43], is generally regarded as social amotivation according to supportive evidence from factor analyses where it loads on the same factor as avolition [10,44,45]. Since people with schizophrenia compared with healthy individuals may have fewer opportunities to participate in social interaction because of external factors (eg, fewer intact relationships, stigma) [12,45], assessment of asociality should include both reduction in social activity and decreased interest in forming relationships [14]. In our analysis, changes from baseline were significantly different for cariprazine versus risperidone on PANSS items that measure asociality (poor rapport and passive/apathetic social withdrawal), with results contributing to significant improvement for cariprazine on the PANSS-FSNS and the PSM Negative Symptom factor.

Finally, studies suggest a key role for avolition in the relationship between negative symptoms and impaired functional outcomes [7,46,47]. The PANSS emotional withdrawal item (N2) assesses avolition through reports and observation of a patient's interest in their surroundings, which may make it challenging to assess reduced initiation and persistence of goal-directed activity that is not socially oriented. Change from baseline in emotional withdrawal was significantly different in favor of cariprazine versus risperidone, with results again contributing to improvement for cariprazine on several negative symptom factors.

Several studies support a stable 2-factor model [48–54], with key negative symptoms grouping into avolition/apathy and diminished expression domains that may be associated with

different neurobiological abnormalities and psychosocial outcomes [8]. Namely, diminished expression may have a stronger association with nonsocial and neuropsychological function [30], while avolition/apathy is theorized to have a direct impact on functional outcomes in schizophrenia [46]. Of interest, our post hoc analyses found significant differences at week 26 in favor of cariprazine versus risperidone on PANSS-derived Expressive Deficits and Avolition/Asociality factors, which both supports prospective PANSS-FSNS and PSP results, and suggests that cariprazine has broad-spectrum pharmacological properties that improve symptomatic and functional aspects of negative symptoms. Given that functional impairment is an enormous burden for patients with negative symptoms [55], effective treatment can only be considered clinically relevant if symptom improvement translates into improved patient functioning.

In our analyses, significant differences in favor of cariprazine were also seen on factors assessing domains other than negative symptoms (disorganized thought, cognition, prosocial functioning), suggesting that improvements for cariprazine-treated patients were not limited to one domain. Small changes and no statistical differences between cariprazine and risperidone on factors for Depression/Anxiety, Uncontrolled Excitement/Hostility, and Positive Symptoms support a genuine treatment effect for cariprazine and the lack of pseudospecific change to explain negative symptom improvement.

Although post hoc analyses have inherent limitations, they allowed for single item and dimensional evaluation of PPNS in patients with stable schizophrenia who were treated with cariprazine or risperidone. Interpretation of our results are limited by the lack of placebo control. As is typical in post hoc evaluations, *P* values were not adjusted for multiple comparisons, which could allow random chance to play a role in determining statistically significant differences. Since patients included in the prospective study had stable schizophrenia and PPNS, results may not be generalizable to other patient populations. Interpretation of factor analyses for negative symptoms may be limited by the inclusion of items that map inconsistently or may no longer be considered part of the negative symptom domain (ie, stereotyped thinking, difficulty in abstract thinking). This may help explain the lack of effect for cariprazine on item N7 (stereotyped thinking) in the individual item analysis. Additionally, item G5 (mannerisms and posturing) is included in the Liemburg Expressive Deficits factor and the PSM negative symptom factor although it is not generally regarded as a negative symptom. Although the PANSS is widely used in clinical trials, it is subject to psychometric limitations, including the lack of an anhedonia item. Further, since avolition is also poorly assessed by the PANSS, the differential effect of cariprazine and risperidone in this domain cannot be proven or excluded by our analysis. The PANSS-FSNS is a fully validated measure of negative symptom change [24], and although it was the only scale used to assess negative symptom improvement in the prospective trial, this study served regulatory purposes and use of a PANSS negative symptom outcome measure was specifically requested by authorities. Finally, although significant improvement was observed for cariprazine versus risperidone on most outcomes, this does not negate the possibility that risperidone also had some treatment effect.

The 5 A's provide an important framework for conceptualizing the multidimensional aspects of negative symptoms in schizophrenia. Post hoc analysis of data from patients with schizophrenia and PPNS demonstrated significant improvement for cariprazine over risperidone on PANSS negative symptom items and PANSS-derived factors related to some of these key constructs. Research suggesting that clusters of individual items may represent different fundamental pathophysiological mechanisms of negative symptoms indicates that improvement across symptoms and

factors may imply broad-spectrum efficacy for cariprazine. Small changes in positive symptoms, depressive symptoms, and EPS support our assertion that negative symptom improvement was a genuine cariprazine treatment effect that did not occur secondary to improvement in other symptom domains. Given the lack of negative symptom treatment options, these results are clinically interesting and may be another step toward addressing a considerable unmet need in schizophrenia.

## 5. Contributors

I. Laszlovszky, B. Szatmári, Á. Barabácssy, K. Acsai, E. Szalai, J. Harsányi, and G. Németh contributed to the study design, analysis, and interpretation of data. W. Fleischhacker, S. Galderisi, W. Earley, and M. Patel contributed to the analysis and interpretation of the data. All authors revised and approved the final version of the manuscript.

## Declaration of interest

W. Wolfgang Fleischhacker received grants and personal fees from Janssen-Cilag, grants and personal fees from Otsuka, grants and personal fees from Lundbeck, personal fees from Roche, personal fees from Takeda, personal fees from Amgen, personal fees from Teva, personal fees from Targacept, personal fees from Richter, grants and personal fees from Boehringer Ingelheim, outside the submitted work.

Silvana Galderisi received honoraria and advisory board or consulting fees from Angelini Acraf, Gedeon Richter, F Hoffman-La Roche, Janssen Pharmaceuticals, Lundbeck, Otsuka, and Pierre Fabre.

István Laszlovszky, Ágota Barabácssy, Balázs Szatmári, Judit Harsányi, Erzsébet Szalai, and György Németh report personal fees from Gedeon Richter Plc., outside the submitted work. Dr. Németh and Dr. Laszlovszky have issued patents for cariprazine; Dr. Szatmári has a patent pending for cariprazine.

Mehul Patel and Willie Earley are employees of Allergan.

## Funding

This study was funded by Gedeon Richter Plc..

## Acknowledgements

The authors would like to thank Carol Brown, MS, of Prescott Medical Communications Group, a contractor of Gedeon Richter Plc, for providing writing and editorial assistance.

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