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Efficacy of cariprazine in the treatment of acute and primary negative symptoms of schizophrenia: posthoc analyses versus risperidone

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INTRODUCTION

Functional outcome of schizophrenia is highly related to the presence and severity of negative symptoms. Nevertheless sufficient treatment of primary negative symptoms is still an unmet need.[1,2]

Although four atypical antipsychotics, including risperidone, showed better efficacy than typical antipsychotics in a large meta-analysis, specific studies failed to verify their effect on primary negative symptoms.[3,4]

Cariprazine is a dopamine D3/D2 partial agonist, which, on top of being effective in acute and long-term management of overall symptomatology, has proven to be efficacious in the treatment of persistent, predominant negative symptoms (PNS) of schizophrenia.[5–7]

STUDY OBJECTIVE

The objective of the present analyses is to evaluate the effects of cariprazine (CAR) versus risperidone (RISP) in the treatment of overall, prominent and predominant negative symptoms.

METHODS

Short-term analyses are based on a 6 week, phase 3, randomized, placebo and risperidone-controlled study in patients with acute symptoms of schizophrenia[5], and are performed in two groups: in the full analysis sample, called the intention to treat (ITT) population having a Positive and Negative Syndrome Scale (PANSS) total score of ≥ 80 and ≤120 at baseline and a subgroup of patients with predominant negative symptoms (PNS) having PANSS-factor score for negative symptoms (PANSS-FSNS) ≥24 and PANSS-factor score for positive symptoms (PANSS-FSPS) ≤19 at baseline. Long-term analyses are based on a 26 week, phase 3, risperidone-controlled study in patients with persistent (for at least 6 months) predominant negative symptoms and stable condition in terms of psychotic symptoms.[7] Pseudospecific factors were controlled for treatment groups in the long-term study.

Patients prior stabilized on risperidone were excluded from the risperidone groups. Efficacy measures were analyzed using mixed-effects model for repeated measures (MMRM). Results are presented in equivalent doses of cariprazine (4.5 mg/day) and risperidone (4 mg/day).

RESULTS

Efficacy in acute patients

Table 1. Change from baseline in PANSS total and PANSS-FSNS score – acute ITT population

PANSS total score			
	Placebo N = 148	CAR 4.5 mg N = 145	RISP 4.0 mg N = 67
Baseline, mean ± SD	96.6 ± 9.77	96.9 ± 8.64	97.3 ± 9.84
Change from baseline, LS Mean (SE)	-13.14 (1.85)	-23.71 (1.76)	-26.31 (2.60)
LSMD vs Placebo (95% CI)	-	-10.57 (-15.57, -5.57)	-13.17 (-19.41, -6.92)
p-value	-	**<0.0001**	**<0.0001**
		CAR 4.5 mg vs RISP 4 mg p=0.4071	

SD= standard deviation, LSMD= Least squares mean difference, CI= confidencia interval

Table 2. Change from baseline in PANSS-FSNS score – acute PNS subgroup

PANSS-FSNS Score			
	Placebo N = 35	CAR 4.5 mg N = 35	RISP 4.0 mg N = 16
Baseline, mean ± SD	26.9 ± 2.88	27.4 ± 3.27	26.0 ± 2.61
Change from baseline, LS Mean (SE)	-5.56 (0.95)	-8.30 (0.90)	-7.13 (1.40)
LSMD vs Placebo (95% CI)	-	-2.73 (-5.31, -0.16)	-1.56 (-4.95, 1.82)
p-value	-	**0.038**	0.361

SD= standard deviation, LSMD= Least squares mean difference

CONCLUSIONS

- **While cariprazine and risperidone were equally effective in controlling acute overall symptoms, only cariprazine improved negative symptoms in acute patients.**
- **Cariprazine treatment was better than risperidone for predominant negative symptoms of schizophrenia.**
- **Cariprazine is able to improve primary negative symptoms, as results in pseudospecific parameters exclude indirect effects related to positive, depressive, or extrapyramidal symptom improvement.**

In the full analysis sample of acute patients both cariprazine and risperidone reduced significantly the overall symptoms of schizophrenia, as measured by the PANSS total score. Cariprazine and risperidone were equally effective.

In the subset of acute patients with PNS, changes in negative symptoms were significant for cariprazine, but not for risperidone treatment.

Efficacy in patients with persistent, predominant negative symptoms

In the long term study, designed specifically for persistent predominant negative symptoms cariprazine outperformed risperidone in controlling negative symptoms.

Table 3. Change from baseline in PANSS-FSNS score - patients with persistent PNS

PANSS-FSNS Score		
	CAR 4.5 mg N = 227	RISP 4.0 mg N = 229
Baseline, mean ± SD	27.70 (2.50)	27.50 (2.39)
Week 26 change from baseline, LS Mean	–8·90	–7·44
LSMD vs risperidone	–1.46	-
p-value	**0.0022**	

SD= standard deviation, LSMD= Least squares mean difference

Pseudospecificity

No significant difference was obsereved in positive symptoms, depression, or movement scores between CAR and RISP.

Table 4. Pseudospecificity measures (repeated measures ANCOVA mixed effects model)

	CAR 4.5 mg vs RISP 4 mg	
	LSMD (95% CI)	p-value
PANSS-FSPS	0.010 (-0.43, 0.45)	0.963
CDSS total score	-0.06 (0.33, 0.21)	0.658
SAS items 1–8	-0.07 (-0.23, 0.09)	0.389
SAS total score	-0.12 (-0.31, 0.06)	0.196
BARS	-0.07 (-0.23, 0.09)	0.384
AIMS total score	0.04 (-0.07, 0.08)	0.913

CDSS=Calgary Depression Scale for Schizophrenia. SAS=Simpson-Angus Scale. PANSS-FSNS=PANSS factor score for negative symptoms; BARS=Barnes Akathisia Rating Scale; AIMS=Abnormal Involuntary Movement Scale, LSMD= Least squares mean difference, CI= confidencia interval

REFERENCES

[1] Foussias, G., *et al. Eur. Neuropsychopharmacol.* **24**, 693–709 (2014).
[2] Remington, G. *et al. Curr. Treat. Options Psychiatry* 133–150 (2016).
[3] Leucht, S. *et al*. *Lancet* **373**, 31–41 (2009).
[4] Krause, M. *et al. Eur. Arch. Psychiatry Clin. Neurosci.* **268**, 625–639 (2018).
[5] Durgam, S. *et al. Schizophr. Res.* **152**, 450–457 (2014).
[6] Durgam, S. *et al. J. Clin. Psychiatry* **76**, e1574-82 (2015).
[7] Németh, G. *et al*. *Lancet* **389**, 1103–1113 (2017).

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