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The effect of cariprazine on agitation and hostility in patients with schizophrenia: post-hoc analysis

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INTRODUCTION

Agitation and hostility are critical aspects in the treatment of schizophrenia. Psychotic patients characterized by agitation or hostile behavior are hospitalized more frequently and for longer durations and have poorer adherence to treatment. [1] Restraining and sedating these patients can be harmful both for the patient and to the therapeutic alliance. Noninvasive pharmacotherapy is recommended whenever possible. [2] Cariprazine (CAR) is an oral broad-spectrum antipsychotic, which was previously shown to be effective in hostility by Citrome et al. [3] The present analysis investigates additional outcomes in a broader sample with different subgroups and a constrained dose range.

STUDY OBJECTIVE

The aim of this post-hoc analysis was to investigate the efficacy of cariprazine (CAR) in the approved dose range versus placebo (PBO) for reducing agitation and hostility in adult patients with an acute exacerbation of schizophrenia.

METHODS

Pooled data from all four (NCT00404573, NCT01104766, NCT01104779, NCT00694707) phase 2/3, double-blind, randomized, placebo-controlled 6-week trials of acute schizophrenia were analyzed for CAR (1.5-6 mg/day) vs. PBO. Agitation and hostility were assessed as the individual items P4 excitement and P7 hostility along with the Marder Uncontrolled Hostility/Excitement Factor (P4, P7, G8 uncooperativeness, G14 poor impulse control) of the Positive and Negative Symptom Scale (PANSS). The score range of P4/P7 is 1–7, 1 indicating “absent” while 6 “severe” or 7 “extreme” may indicate impaired sleeping and eating functions, incoherence as well as physical aggression. The Marder Uncontrolled Hostility/Excitement Factor (H/E) is scored from 4 “absent” to 28 “extreme.” Cutoffs of 4 (for P4/P7) and 16 (for H/E) points were used to define patients with no to mild (<4; <16) and patients with moderate to extreme (≥4; ≥16) level of psychopathology. We followed the approach of Citrome et al. (2016), applying pooled analysis with the same MMRM model. Pooling was also necessary to ensure acceptable sample sizes and statistical power for the smaller subgroups. P values are nominal (not adjusted for multiple comparisons) and there is no overall control over Type I error.

RESULTS

A total number of 1643 patients (CAR=1075, PBO=568) had baseline and post-baseline PANSS assessments and were included in the post-hoc analyses. Baseline characteristics were similar between the placebo and cariprazine groups.

Table 1. Baseline measures by severity groups

		All patients		No to mild Baseline Severity		Moderate to extreme Baseline Severity	
		PBO	CAR	PBO	CAR	PBO	CAR
P4 / Excitement	n=	568	1075	394	727	174	348
	Baseline Mean (SD)	2.95 (1.08)	2.99 (1.03)	2.70 (0.78)	2.43 (0.73)	4.20 (0.44)	4.15 (0.38)
P7 / Hostility	n=	568	1075	475	890	174	348
	Baseline Mean (SD)	2.50 (1.05)	2.49 (1.09)	2.17 (0.80)	2.13 (0.80)	4.20 (0.44)	4.15 (0.38)
Marder H/E Factor	n=	568	1075	539	1010	29	65
	Baseline Mean (SD)	10.32 (3.20)	10.36 (3.20)	9.95 (2.82)	9.94 (2.80)	17.28 (1.33)	16.91 (1.04)

Cariprazine-treatment was significantly more effective than placebo in reducing excitement: LSMDs vs PBO (95% of CI) = -0.291 (-0.42, -0.16), p<.0001. Significant changes were seen from week 2 for all patients and for the subgroup of low baseline severity. Patients with high excitement levels at baseline showed significant improvement from week 3. (Figure 1)

Cariprazine significantly reduced hostility as well: LSMDs vs PBO (95% of CI) = -0.340 (-0.47, -0.21), p<.0001. Cariprazine’s anti-hostility effect was seen from week 1 onwards in all baseline severity groups. (Figure 2)

A statistically significant difference in change from baseline to week 6 was observed for Marder H/E Factor: LSMD (95% CI): -1.170 (-1.60, -0.74), p<.0001 in favor of cariprazine. Cariprazine was statistically significantly better than placebo from week 1, regardless of baseline severity. (Figure 3)

Following Cohen’s interpretation, 0.3 and 0.5 are clinically relevant ESs (medium and large, respectively). In subgroups with low baseline severity, however, even smaller ESs may also be clinically relevant, if statistically significant - since the room for average improvement is relatively small in these groups.

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CONCLUSIONS

Cariprazine treatment was efficacious for agitation and hostility in acute patients of schizophrenia. Higher levels of baseline severity were associated with a greater effect of cariprazine.

Figure 1. Mean change from baseline of excitement measured as the PANSS P4 excitement item

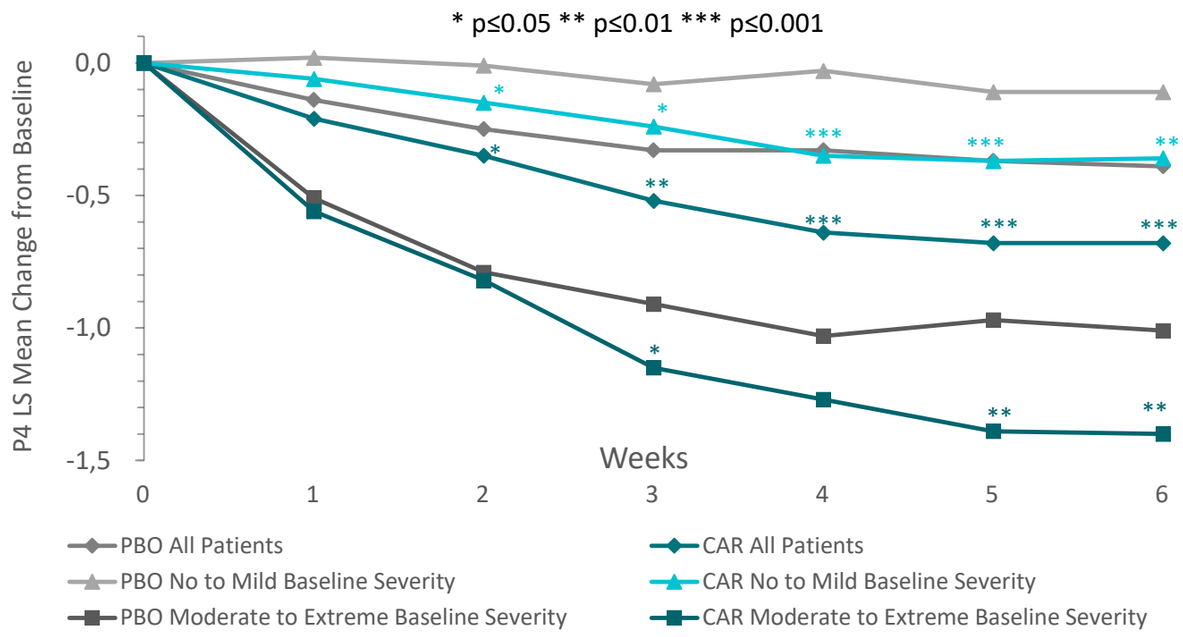

Figure 2. Mean change from baseline of hostility measured as the PANSS P7 hostility item

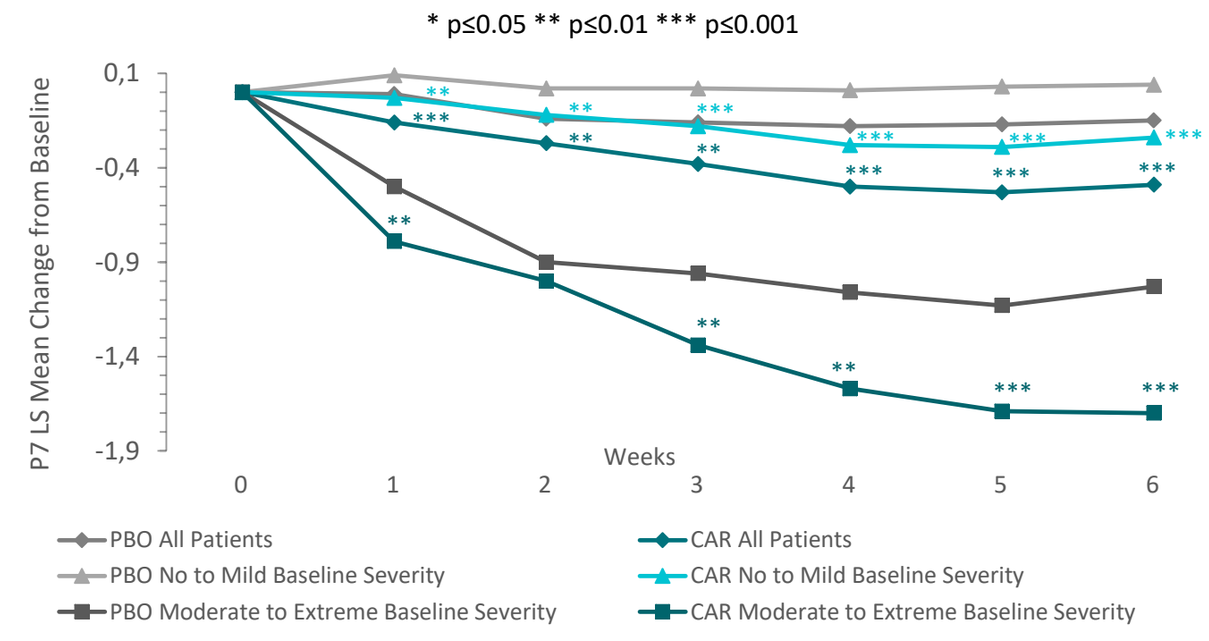

Figure 3. Mean change from baseline of the Marder Uncontrolled Hostility/Excitement Factor

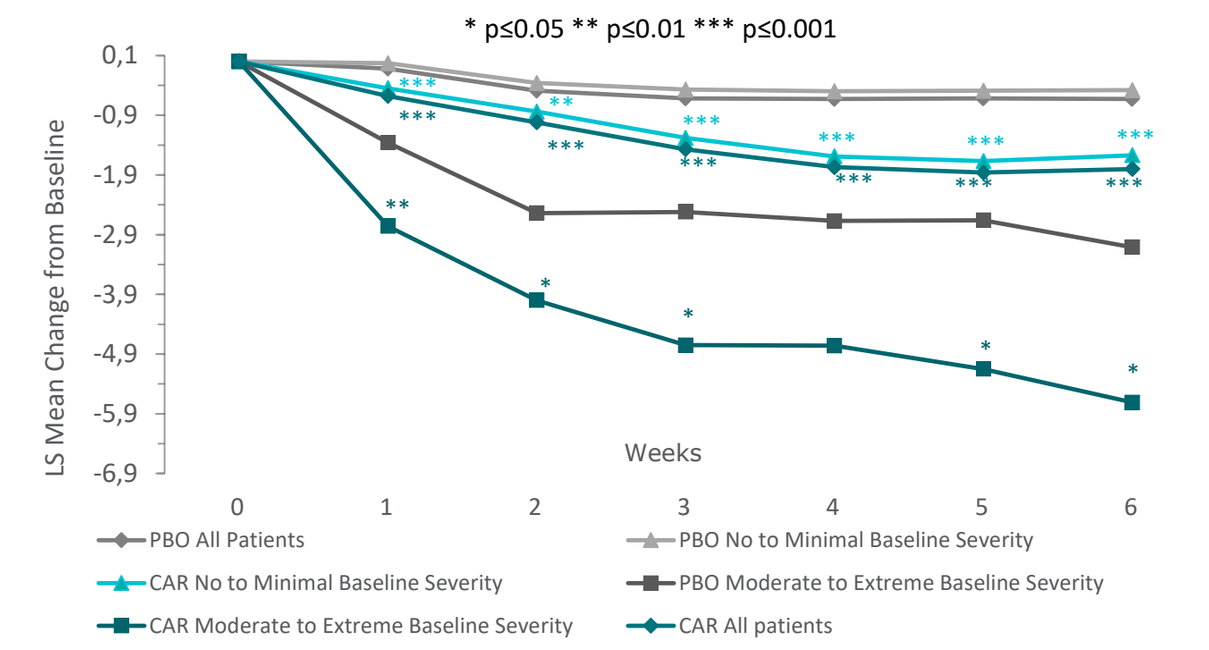

Table 2. Effect Sizes (ES) of cariprazine treatment on excitement and hostility by baseline severity at week 6

	All patients		No to mild Baseline Severity		Moderate to extreme Baseline Severity	
	LSMD (95% CI)	Effect Size	LSMD (95% CI)	Effect Size	LSMD (95% CI)	Effect Size
P4 / Excitement	-0.291 (-0.42, -0.16)	**0.26**	-0.248 (-0.40, -0.10)	**0.23**	-0.392 (-0.67, -0.12)	**0.30**
P7 / Hostility	-0.340 (-0.47, -0.21)	**0.30**	-0.281 (-0.42, -0.14)	**0.25**	-0.667 (-1.04, -0.29)	**0.53**
Marder H/E Factor	-1.170 (-1.60, -0.74)	**0.31**	-1.091 (-1.53, -0.65)	**0.29**	-2.605 -5.03, -0.18)	**0.59**

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