SAFETY OF CARIPRAZINE IN THE LIGHT OF ITS RECEPTOR PROFILE

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INTRODUCTION

Antipsychotic treatment is indicated for all patients with schizophrenia; however different receptor-related side effects may arise, from which movement disorders (D2)[1], hyperprolactinemia (D2)[2], cognitive impairment (M1)[3], cardiovascular effects (M1, α1)[4], sedation (H1, 5-HT2A)[5,6] and weight gain (5-HT2C, H1)[7] are the most typical. Cariprazine (CAR) is a dopamine D3/D2 and serotonin 5HT1A partial agonist approved for schizophrenia and manic, depressive, or mixed episodes of bipolar disorder.

STUDY OBJECTIVES

The aim is to characterize the safety profile of cariprazine by describing its receptor profile and the related adverse safety observations in patients with schizophrenia.

METHODS

The *in vitro* receptor binding profile of cariprazine was determined. Pooled data from eight Phase 2/3 schizophrenia trials (NCT00404573, NCT00694707, NCT01104766, NCT01104779, EudraCT2012-005485-36, NCT01412060, NCT01104792, NCT01104792, NCT00839852) with 2.048 cariprazine (1.5-6 mg) and 683 placebo (PBO)- treated patients were analyzed. Safety measures are shown with descriptive statistics.

RESULTS

Cariprazine's receptor affinities are shown in **Figure 1**. It has high affinities to human dopamine D3 and D2 receptors (Ki= Ki=0.085 and 0.49 nM), as well as to 5-HT2B and 5-HT1A receptors (Ki=0.58-1.1 and 1.4-2.6 nM); moderate to low affinities to 5-HT2A, H1, 5-HT2C, and α1 (Ki= 18.8 nM, 23, 134 and 155 nM) receptors; and a negligible affinity to human M1, α2, D1 and D3 receptors (Ki>1,000nM) receptors. Related treatment-emergent adverse events are shown in **Table 1.**

CONCLUSION

The receptor profile of cariprazine may lead to favourable safety properties. Cariprazine treatment was associated with no hyperprolactinemia and only minimal weight gain, or increased heart rate. Sedation, cognitive impairment occurred with low incidences, while the most common adverse events were akathisia and extrapyramidal disorder.

Figure 1. Cariprazine's *in vitro* receptor affinities (Ki values, nM)

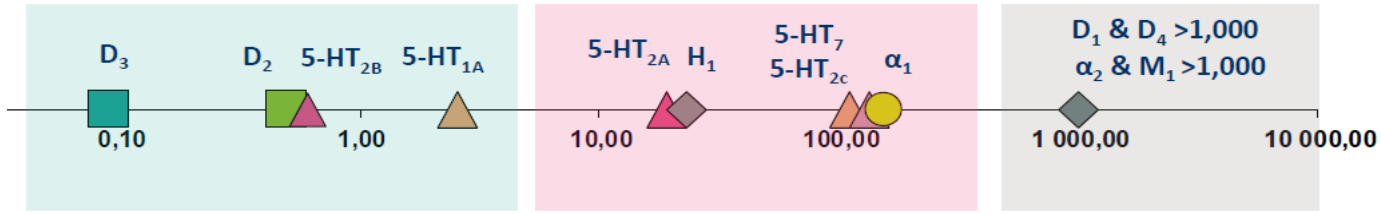

Table 1 Treatment emergent adverse events (%)

Adverse events	CAR	PBO	Potentially related receptor effects
Akathisia/Extrapyramidal disorder	14.6% / 7.0%	0% / 3.2%	D2 functional antagonism
Hyperprolactinemia	0%	0%	D2 functional antagonism
Sedation	3.7%	3.1%	H1 antagonism
Cognitive imapirment	0.5%	0.3%	M1 antagonism*
Weight gain	1.0kg	0.9kg	5-HT2C*, H1 antagonism
Change from baseline in heart rate	2.0 bpm,	0.7 bpm	Indirect effect of α1 antagonism*, M1 antagonism*

* The affinities of cariprazine to these receptors are low; thus, other mechanisms may underlie the corresponding adverse effects.

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DISCLOSURE

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