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CLINICAL POTENTIAL OF CARIPRAZINE IN THE TREATMENT OF ACUTE MANIA

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SUMMARY

Cariprazine (RGH-188, trans-4-{2-[4-(2,3-dichlorophenyl)-piperazine-1-yl]-ethyl}-N,N-dimethylcarbamoyl-cyclohexyl-amine hydrochloride), is a novel antipsychotic with dopamine D2 and D3 receptors antagonist–partial agonist properties. Cariprazine has also moderate affinity for serotonin 5-hydroxytryptophan (5-HT) 1A receptors, high affinity for 5-HT1B receptors with pure antagonism and low affinity for 5-HT2A receptors. Randomized, double blind, placebo controlled, flexible-dose (3–12 mg/day) studies have demonstrated cariprazine is effective in both schizophrenia and acute manic episodes associated with bipolar disorder. The incidence of serious adverse events in cariprazine arm was no different than in placebo arm in these studies. The most common adverse events were extrapyramidal symptoms, headache, akathisia, constipation, nausea, and dyspepsia which can be explained with cariprazine's partial dopamine agonism. Although cariprazine treatment was associated with a higher incidence of treatment-emergent adverse events, particularly akathisia and tremor, common side effects of marketed second generation antipsychotics such as weight gain, metabolic disturbances, prolactin increase or QTc prolongation were not associated with cariprazine, probably due to its moderate to low binding affinity for histamine H1 and 5-HT2C receptors. Animal studies show that cariprazine may have additional therapeutic benefit on impaired cognitive functioning with D3 receptor activity, however clinical data is still scarce. The aim of this article is to review the potential use of cariprazine for the treatment of acute manic episodes in the light of the preclinical and clinical trials reported to date.

Key words: *cariprazine – antipsychotic – psychopharmacology - bipolar disorder - mania*

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INTRODUCTION

The treatment of bipolar illness should be considered both in cross-sectional and longitudinal basis: the cross-sectional approach for the treatment of acute manic syndrome and the treatment of bipolar depression, the longitudinal approach for the maintenance treatment which is aimed at the prevention of the recurrence of both. Initially, lithium and anticonvulsants are considered as prophylactic treatment, while antidepressants and/or antipsychotics are reserved mainly for the treatment of acute episodes. As treatment of BD is as difficult and complex as the illness itself, different treatment needs have to be considered for manic, hypomanic, mixed and bipolar depression episodes, respectively (Fountoulakis & Vieta 2009). The complexity of treatment approaches can easily be followed through different reviews and treatment guidelines. Practice guidelines recommending treatment strategies are widely available in every country and there is a trend toward evidence-based medicine, as well. Thus, treatment guidelines should be both evidence-based and flexible enough to meet the needs of individual patients (Fountoulakis et al. 2007, Oral 2005).

Current treatment for mania aims to control the agitation, impulsivity, aggression, psychotic symptoms and to help patients regain their pre-morbid functioning (Tohen et al. 2000). From late 50s to 80s, lithium and chlorpromazine were the only medicines with regulatory approval for acute mania, although many others were used empirically (Baldessarini & Tarazi 2005). Recent treatment strategies mostly recommend mood stabilizers or second generation antipsychotics (SGAs) as the first-line monotherapy, and their combinations as second-line treatment. It has been a common practice to administer conventional antipsychotics to treat acute mania before 2000s (Zarate & Tohen 2000), despite well-known extrapyramidal side effects. It is estimated that more than 90% of patients with acute mania were prescribed antipsychotics, either in combination or as monotherapy (Chou et al. 1996, Tohen et al. 2001). Yet, SGAs have several advantages over the conventional ones and they were increasingly being used in bipolar mania because of their relatively benign side-effect profiles. Novel antipsychotics have been applied to treat mania in three aspects: 1) to treat psychotic symptoms 2) to control agitation (drugs like olanzapine and ziprasidone have intramuscular preparations which may increase their use for agitation) 3) they may have a specific antimanic effect (Breier et al. 2002). Double-blind monotherapy/ add-on studies have indicated the effectiveness of olanzapine, risperidone, quetiapine, ziprasidone, aripipra-

zole, asenapine and cariprazine in treating mania. A recent meta-analysis which reviews findings of randomized, placebo-controlled, short-term trials for acute mania including 38 studies involving 10800 patients, supported the efficacy of most clinically used antimanic treatments. It is stated that, of drugs tested in meta-analysis, 76% were founded more effective than placebo: aripiprazole, asenapine, carbamazepine, cariprazine, haloperidol, lithium, olanzapine, paliperdone, quetiapine, risperidone, tamoxifen, valproate, and ziprasidone (Yildiz et al. 2011).

The majority of these clinically effective SGAs have a broader pharmacological spectrum, ranging from high to modest affinity binding for dopamine D2 receptors and many other neurotransmitter receptors such as serotonergic, adrenergic and histaminergic (Markowitz et al. 1999). There is still a debate that the better side-effect profile of these SGAs is due to their serotonin 5-hydroxytryptophan (5-HT) 5-HT2A receptor antagonist activity (Meltzer et al. 2003) or to their higher dissociation rate constant at the D2 receptor (Kapur & Seeman 2001). More recently, a new pharmacological approach, partial dopamine agonism attracted clinicians' attention with a low risk of extrapyramidal symptoms, endocrine and metabolic disturbances separating it from other SGAs with unique mechanism of action. Aripiprazole is the only clinically used member of this novel concept with partial agonist activity at dopamine D2/D3 receptors, partial agonist activity at 5-HT1A receptors and antagonist activity at 5-HT2A receptors (Kane et al. 2012). Currently, it is thought that ideal candidate antipsychotic with a mixed D3/D2 receptor partial agonistic activity would have beneficial effects on cognition and negative symptoms and prevent the induction of extrapyramidal symptoms (EPS) or secondary negative symptoms by avoiding complete silencing of dopaminergic transmission (Agai-Csongor et al. 2012, DeLeon et al. 2004, Gyertyán et al. 2011). Herein, cariprazine a novel dopamine D2/D3 partial agonist antipsychotic that showed promising results in phase III studies, may be a new choice for the treatment of bipolar disorder with lower side effect profile and better effects on cognitive functions than commonly used SGAs (Starace 2012).

In this review, we aimed to evaluate cariprazine's pharmacological characteristics and potential clinical place in the treatment of acute bipolar mania considering the desperation of efficacy-side effect balance for current treatment choices in bipolar mania. PubMed, Medline and Google Scholar search was conducted by using the terms "cariprazine", "RGH-188" and/or "bipolar disorder", "mania", "treatment" with only English language restrictions on December 2012. The resulting manuscripts and their reference lists were reviewed carefully and then 9 articles that might be specifically related with the primary aim of the review were selected. A similar search method was also conducted for the ClinicalTrials.gov website on December 2012 and data of 3 completed studies about the treatment of bipolar mania was obtained. Additional information from abstract books of international annual meetings, news, updates and articles that are published on the internet were examined for cross-references.

CARIPRAZINE'S MODE OF ACTION & PHARMACOLOGICAL CHARACTERISTICS

Cariprazine (RGH-188, trans-4-{2-[4-(2,3-dichlorophenyl)-piperazine-1-yl]-ethyl}-N,N-dimethylcarbamoyl-cyclohexyl-amine hydrochloride), is a novel antipsychotic with antagonist–partial agonist properties at dopamine D2 and D3 receptors (Kiss et al. 2010). In multiple in-vitro/in-vivo assays, cariprazine exhibited high affinity for the dopamine D2/D3 receptors and moderate affinity for 5-HT1A receptors (Seneca et al. 2011). It also introduced high affinity for human 5HT2B receptors with pure antagonism and low affinity for human 5-HT2A receptors. Cariprazine has a moderate or low binding affinity for histamine H1 and 5-HT2C receptors which are associated with endocrine and metabolic side effects caused by most of the SGAs (Kiss et al. 2010).

The D3 receptor affinity of cariprazine is signifycantly higher than clinically used antipsychotics and may provide additional therapeutic benefits compared with more D2-selective agents (Seneca et al. 2011) considering the modulator role of D3 receptors on locomotor control, cognitive functions and drug abuse (Gyertyán & Sághy 2007, Joyce & Millan 2005). In animal studies, selective D3 receptor antagonists were reported to increase motor activity (Gyertyán & Sághy 2004, Gyertyán et al. 2008) and do not show cataleptogenic side effects in rodents (Gyertyán et al. 2011) by regulating motor functions in an opposite way compared with the D2 receptor (Accili et al. 1996). Additionally, cariprazine exhibited remedial effects on cognitive functions in scopolamine-treated rats with impaired learning performance in the water labyrinth test (Gyertyán et al. 2011) and diminished PCP-triggered cognitive deficits in an animal model via dopamine D3 receptors (Zimnisky et al. 2012). Additionally, in line with these findings, in a post mortem schizophrenia study, two fold increase in D3 receptors was found (Gurevich et al. 1997). Thus, all these studies provide a frame work for better understanding of the role of the dopamine D3 receptors and, declare a more effective antipsychotic with fewer side effects.

While most of the SGAs were thought to enhance cognitive functions via 5-HT2A receptors, cariprazine showed low affinity for this receptors but moderate affinity for another serotonin receptor, 5-HT1A (Kiss et al. 2010, Seneca et al. 2011). Interestingly, 5-HT2A receptor antagonism in frontal cortex indirectly results in the activation of 5-HT1A receptors. Besides, prototypical SGAs such as risperidone and olanzapine which are potent 5-HT2A receptor antagonists but do

not directly interact with 5-HT1A receptors, elicited dopamine release in frontal cortex by 5-HT1A antagonism (Ichikawa et al. 2001). On the other hand, the unique member of SGA class, clozapine, the gold standard for the treatment of resistant schizophrenia and bipolar patients, also exhibited 5-HT1A receptor agonism in various in vitro receptor models (Assié et al. 1997, Bruins Slot et al. 2005, Heusler et al. 2008, Newman-Tancredi & Kleven 2011). Additionally, cariprazine, like aripiprazole, also has binding affinity for 5-HT2B receptors which have a crucial role for regulating dopamine release in nucleus accumbens and hindering amphetamine-induced hyperlocomotion in rodents (Auclair et al. 2010, Doly et al. 2008, Newman-Tancredi & Kleven 2011). Taken together, all these results underline that 5-HT1A and 5-HT2B receptor affinity of a novel antipsychotic could improve negative symptoms, particularly cognitive functions in patients with both schizophrenia and bipolar disorders via activation of dopaminergic neurotransmission in frontocortical regions.

Taking a glimpse at the pharmacokinetics of cariprazine, one may realize some advantages of the drug. The plasma elimination half-life of cariprazine, ranging from 48 to 144 hours, suggests that once a daily dosage may improve treatment adherence (Caccia 2011). Otherwise, it can be interpreted that reaching to steady-state plasma concentration would take weeks due to longer elimination half-life. Cariprazine, as aripiprazole, is mainly eliminated by hepatic metabolism via CYP-3A4 enzyme system and has a moderate first-pass effect (Caccia 2011). In standard antipsychotic screening tests, cariprazine was efficacious between the dose range of 0.09–0.84 mg/kg (Gyertyán et al. 2011). Striatal D2/D3 dopamine receptor occupancy of cariprazine is reported to be 63–79% of 4 hour after repeated 0.5–1 mg doses for 2–12 days that led to marked drug accumulation compared to single doses in healthy subjects (Caccia 2011). Main active metabolites of cariprazine reported as desmethylcariprazine and di-desmethylcariprazine with 2–3 weeks of elimination half-life (Gründer et al. 2011). It was also shown that exposure to di-desmethylcariprazine exceeded that of cariprazine three to six fold after repeated treatment. Cariprazine and desmethylcariprazine reached steady-state within one week, while di-desmethylcariprazine did not even after three weeks due to slow elimination (Caccia 2011). In conlusion, in the light of these promising results from preclinical studies, cariprazine appears to be an encouraging novel antipsychotic model with unique pharmacological profile.

EFFICACY & TOLERABILITY OF CARIPRAZINE IN CLINICAL STUDIES

Recently, it was reported that antipsychotics, particularly SGAs and haloperidol, are more effective than mood stabilizers for the treatment of acute mania in three meta-analyses evaluating the efficacy and tolerability of antimanic agents in bipolar mania (Cipriani et al. 2011, Tarr et al. 2011, Yildiz et al. 2011). Despite the promising evidence of haloperidol and SGAs, their significant short- and long-term adverse effects such as EPS, tardive syndromes with haloperidol and metabolic-endocrine disturbances with SGAs, restrain clinical benefits of these drugs.

Table1. Completed trials of cariprazine in bipolar mania

Title	Phase	Study description	N	Outcome Measures	Study Dates	Status
A Double-Blind, Placebo-Controlled Evaluation of the Safety and Efficacy of RGH-188 in Patients With Acute Mania Associated With Bipolar I Disorder (NCT00488618)*	II	5 weeks; 3 weeks double-blind treatment and 2-weeks safety follow- up with 3-12 mg cariprazine oral per day	238	Primary YMRS, Secondary CGI-S	April 2007 - August 2008	Presented at the162nd Annual Meeting of the American Psychiatric Association, 2009 and the 49th Annual NCDEU Meeting, 2009
A Double-Blind, Placebo-Controlled, Evaluation of the Safety and Efficacy of Cariprazine in Patients With Acute Mania Associated With Bipolar I Disorder (NCT01058096)*	III	5 weeks; 3 weeks double-blind treatment and 2-weeks safety follow- up with once daily oral dose of cariprazine or placebo	323	Primary YMRS, Secondary CGI-S	January 2010 - September, 2011	Presented at the165th Annual Meeting of the American Psychiatric Association, 2012
A Double-Blind, Placebo-Controlled, Evaluation of the Safety and Efficacy of Cariprazine in Patients With Acute Mania Associated With Bipolar I Disorder (NCT01058668)*	III	5 weeks; 3 weeks double-blind treatment and 2-weeks safety follow- up with a once daily oral low or high dose of cariprazine or placebo	507	Primary YMRS, Secondary CGI-S	January 2010 - December 2011	Not published yet

*Clinical Trials. gov ID number; YMRS:Young Mania Rating Scale; CGI-S:Clinical Global Impression-Severity

Table 2. Side-effect profile of cariprazine compared to other second-generation antipsychotics

	RIS	PLP	OLZ	CLZ	QTP	ZIP	ASN	ARP	CRP
EPS	+++	+	+	+/-	+/-	++	+/-	-	-
Akathisia	+	+	+/-	+/-	-	++	+/-	++	++
Somnolence	++	+	+++	+++	+++	+	++	+/-	+/-
Hyperprolactinemia	+++	++	+	+	+/-	++	+	+/-	+/-
Weight gain	+	+	+++	+++	++	+	+	+	+/-
Hyperglicemia	+	+	+++	+++	++	+	+	+/-	-
QT prolongation	+	+	+	+	+	+++	+/-	-	-

EPS: Extrapyramidal syndrome; RIS: Risperidone; PLP: Paliperidone; OLZ: Olanzapine; CLZ: Clozapine; QTP: Quetiapine; ZIP: Ziprasidone; ASN: Asenapine; ARP: Aripiprazole; CRP: Cariprazine

Clinical efficacy of an antipsychotic requires 60–75% dopamine D2 receptor binding affinity that was reported in human neuroimaging studies (Kapur & Mamo 2003) and cariprazine 1.5 mg/day for 14 days in patients with schizophrenia resulted in >70% receptor occupancy (Laszlovszky et al. 2010). In line with this, cariprazine found to be more effective than placebo and well tolerated in a randomized double blind controlled phase III study among patients with schizophrenia (Bose et al. 2011).

Cariprazine was reported to be effective not only in schizophrenia, but also in bipolar mania (Knesevich et al. 2009). In a randomized, double-blind, placebo-controlled, flexible-dose (3–12 mg/day) phase II study among bipolar patients with mania indicated that cariprazine significantly reduced mania rating scores at week 3 compared to placebo. Beside the effectiveness of cariprazine, it was also well-tolerated in manic patients that serious adverse event rate was similar to placebo (4% with placebo, 3% with cariprazine) (Knesevich et al. 2009). The most common adverse events were extrapyramidal symptoms, headache, akathisia, constipation, nausea, and dyspepsia which can be explained with partial dopamine agonism (Knesevich et al. 2009). An unpublished study, presented in the 165th Annual Meeting of the American Psychiatric Association, revealed that cariprazine-treated patients (3–12mg) experienced significant improvements in manic symptoms comparing to placebo-treated patients (Table 1). In this randomized, double-blind, placebo-controlled, parallel-group, flexible dose multicenter phase III study, patients with bipolar mania were randomized to treatment with either cariprazine 3 to 12 mg daily, or placebo, for three weeks of double-blind treatment and separation from placebo was observed by day 4 and at every subsequent time point (Starace 2012). Although, cariprazine treatment was associated with a higher incidence of treatment-emergent adverse events, particularly akathisia and tremor, common side effects of marketed SGAs such as weight gain, metabolic disturbances, prolactin increase or QTc prolongation were not reported; while, discontinuation rates due to side effects were 10% with cariprazine and 7% with placebo, which are quite similar (Starace 2012).

As cariprazine did not exhibit the common long-term adverse effects of SGAs, this may increase the popularity of the drug. Yet, similar to aripiprazole, due to partial dopamine agonism, acute extrapyramidal symptoms like akathisia and tremor may limit its potential favour in terms of tolerability for manic patients. It may evoke the idea that, cariprazine is nothing but an improved form of aripiprazole, considering the similar mechanism of action. In in vivo neurochemical experiments, cariprazine, similar to aripiprazole, displayed D2-related partial agonistic activity and demonstrated higher D2 antagonist efficacy than aripiprazole (Kiss et al. 2010). Additionally, cariprazine has 10-fold preferential affinity to D3 receptors that distincts it from other potent antipsychotics, including risperidone and olanzapine (McCormick et al. 2010). The rat studies show that cariprazine has no significant effect in the learning tasks and it is 20-fold more potent than aripiprazole. Besides, risperidone and olanzapine with aripiprazole were less active and more cataleptogenic than cariprazine (Gyertyán et al. 2011). Interpreting phase II and III studies, as well as previous animal studies, cariprazine was found as effective as the other SGAs and may have additional beneficial effects on cognitive functions. Lack of metabolic-endocrine disturbance and low discontinuation rates due to its unique receptor profile make caripazine an encouraging candidate of choice for the treatment of bipolar mania (Table 2).

Table 2 was structured based on evidence derived from the mentioned articles (Almandil et al. 2013, Citrome 2013, Khanna et al. 2013, Komossa et al. 2011, Moteshafi & Stip 2012, Suzuki et al. 2013).

PATIENT FOCUSED PERSPECTIVE: CARIPRAZINE'S EFFECT ON QOL & FUNCTIONING

In clinical trials, both efficacy and tolerability are considered as the two major outcomes to evaluate a drug's future potential in clinical psychiatry practice. However, recent studies reflecting patients' perspective show that both quality of life (QoL) and overall functioning should also be considered as important domains of treatment, and require more attention. It has been demonstrated that both QoL and functioning are impaired in BD, even in euthymic periods (Michalak et

al. 2005, Robb et al. 1997, Sanchez-Moreno et al. 2009). Consequently, the desirable treatment should not only be efficacious and tolerable, but also improve QoL and functioning. Undoubtedly, these are all inter-related domains regarding the considerable improvement in functioning and QoL in both patients with BD and schizophrenia after the launching of SGAs, which are both efficacious and more tolerated than typical antipsychotics in terms of extrapyramidal side effects (Awad & Voruganti 2004a, Awad & Voruganti 2004b, Chue 2006, Jones et al 2006, Yen et al. 2008).

Moreover, SGAs are considered to be effective in improving cognitive functioning, a major factor contributing to both overall functioning and QoL (Keefe et al. 2007, Hori et al. 2006, Tomida et al. 2010). On the other hand, metabolic syndrome prevalence has dramatically increased with frequent use of SGAs, and related disorders like obesity, diabetes mellitus emerged as important health issues in patients treated with SGAs (Correll et al. 2008, Yumru et al. 2007). It should also be noted that, this metabolic and endocrine disturbance may have a negative impact on QoL, regarding lower scores in obese patients with schizophrenia or BD compared to non-obese group (Kolotkin et al. 2008).

Considering cariprazine receptor profile and clinical trials to date, it is plausible to say that it may have an improving effect on QoL and functioning. Besides being efficacious, cariprazine, probably, may have additional therapeutic benefit on impaired cognitive functioning with D3 receptor activity (Gyertyán et al. 2011, Kiss et al. 2010, Zimnisky et al. 2012). Additionally, cariprazine causes less metabolic disturbance owing to its receptor profile with moderate to low binding affinity for H1 and 5-HT2C receptors (Kiss et al. 2010, Knesevich et al. 2009, Newman-Tancredi & Kleven 2011, Starace 2012). However, on the down-side, studies demonstrate that adverse effects related with extrapyramidal system, particularly akathisia, are higher than the placebo (Knesevich et al. 2009, Starace 2012). Overall, we should state it is too early to reach a firm conclusion about cariprazine's effect on QoL and functioning. Well-designed, controlled, prospective studies are definitely needed in this area.

CONCLUSION

Evolution of the treatment guidelines underlined the importance of combination of mood stabilizers and SGAs in bipolar disorder. However, short- and long-term adverse effects of marketed SGAs have been stimulating the plausible concerns of clinicians in terms of efficacy and tolerability. At this point, findings from clinical trials of cariprazine do not permit any judgment about its therapeutic profile compared with other antipsychotic agents. Nevertheless, convincing evidence from phase II and III studies, indicates cariprazine may have an additional therapeutic effect on cognitive functioning with a comparable risk profile in the short and long term to the recently used antipsychotics. However, further clinical experience is still needed to confirm the benefit-risk profile and its impact on quality of life and functioning.

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