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Evan A. Reaume
Philadelphia College of Osteopathic Medicine

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Is Cariprazine Effective and Safe in Treating Acute Mania in Bipolar I Disorder?

Evan A. Reaume, PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

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Abstract

Objective: The objective of this selective EBM review is to determine whether or not "Is cariprazine effective and safe in treating acute mania in bipolar I disorder?"

Study Design: This review is based on three double-blind, randomized controlled trials (RCTs) published in English, in 2015. These studies compared both the efficacy, safety, and tolerability of cariprazine in the treatment of acute mania in bipolar I disorder.

Data sources: Three double-blind, placebo-controlled, RCTs published in English, in peer-reviewed journals, and found using Medline, Pubmed, and Cochrane Review databases.

Outcomes Measured: The primary efficacy scale used in all studies was the Young Mania Rating Scale (YMRS) which is a screening tool that objectively and subjectively measures acute mania items including: irritability, speech, content, disruptive behavior, elevated mood, increased motor activity, sexual interest, sleep, language-though disorder, appearance, and insight. Safety was measured through the occurrence of one or more of the following during treatment as experienced by the patient: extrapyramidal disorder, headache, akathisia, constipation, nausea, dyspepsia, dizziness, insomnia, vomiting, diarrhea, restlessness, sedation, vision blurred, mania, pain in extremity, pyrexia, tremor, agitation, or toothache.

Results: All three studies found cariprazine demonstrated efficacy and general tolerability in the treatment of mania in acute bipolar I disorder compared to placebo ($p<0.05$). The YMRS baseline scores compared to week 3 after treatment with carpirazine low dose (3 mg/day) and high dose (12 mg/day) were significantly lower than the placebo group ($p<0.05$) in all three studies. According to all three studies the most common treatment related adverse events were: akathisia, extrapyramidal symptoms, nausea, and constipation.

Conclusions: The results based on these three studies is the cariprazine is effective and generally well-tolerated for patients experiencing acute mania in bipolar I disorder. Future study is warranted to determine the remission rate of manic episodes after treatment with cariprazine for bipolar I disorder.

Key Words: Cariprazine, bipolar disorder

Introduction

Bipolar I disorder is a mood disorder causing shifts in mood, energy levels, and ability to function in daily living that is characterized by both manic and depressive episodes.[4,5] These manic episodes are characterized by decreased need for sleep, flight of ideas, increase in psychomotor agitation, or excessive involvement of pleasurable activities that have high risk of consequence for at least 1 week.[4,8] Following these manic episodes cycles depressive states of decreased pleasure, diminished interest, apathy, and decreased appetite.[8] Patients diagnosed with bipolar I disorder have may have continued difficulty in psychosocial functioning with daily living.[5,8] This paper evaluates three randomized controlled studies exploring the efficacy and safety of cariprazine, a partial dopamine receptor agonist in treating acute mania in bipolar I disorder.

Bipolar disorder affects 5.7 million American adults, or 2.6% of adults over 18 every year.[6] The typical age of onset is between 20 and 30 years old, although premorbid symptoms are commonly reported in early adolescence.[4,8] The prevalence is equal between men and women, however men are more prone to manic episodes, while women are susceptible to more depressive episodes over respective lifetimes.[8] The estimated total healthcare cost of bipolar disorder was $45 billion per year in 1991 (the most recent data). Most of the cost was attributed to decreased functional capacity and lost work days.[7] There is no exact estimate of total hospitalizations, but in 2002-2003, the diagnosis of bipolar disorder of youth 19 and younger in office visits was 1,003 for every 100,000.[5]

The cause of bipolar disorder in currently being studied and is ill-defined. It is believed to be multifactorial including: hormone alterations of serotonin and dopamine in the brain, hyperexcitability of neuron potentials, genetic, and environmental.[4,5] Genetic predispositions

play a large role in bipolar I disorder carrying a risk of 80% for monozygotic twins.[8] Genome studies have identified diacylglycerol kinase (DGKH), ankryin G (ANK3), L-type voltage-gated calcium channel (CACNA1C), and a region on chromosome 16p12 as being pertinent to bipolar 1 disorder.[4,8] Environmental factors such as stress, social-behavioral patterns, and increasing sympathetic nervous activity have been shown to affect the disease process.[4] Elevation of cortisol (through stress) impairing hippocampal events decreased limbic activation and neurogenesis. In addition, regulation of dopamine in the nucleus accumbens has been associated with depressive episodes, while over expression of glycogen synthase kinase in glutamate receptors have been associated with manic episodes.[8]

The diagnosis of bipolar I disorder is made on the history and physical exam of the patient with one or more manic episodes (lasting at least 1 week) which cycle with depressive episodes.[4] There is no definitive cure for bipolar I disorder and treatment includes a multi-modality approach including medication, cognitive-behavioral therapy, and electroconvulsive therapy. Acute treatment of manic episodes in bipolar I disorder include: lithium, valproic acid, and possibly benzodiazepines (with psychotic symptoms).[5,8] Second generation anti-psychotics such as olanzapine, risperidone, and quitepaine have also been shown to be effective.[4,8] Current treatments such as lithium are continually being evaluated because of adverse side effects including tremor, hypothyroidism, arrhythmias, seizures and blood monitoring every 4-8 weeks.[8]

Bipolar disorder is a complex, multifactorial disease that involves recurrence and variable severity of symptoms even with current treatment regimens as listed above. Cariprazine is being proposed to safely treat acute mania in bipolar I disorder with positive long term effects on quality life.

Objective

The objective of this selective EBM review is to determine whether or not carpirazine is effective and safe in treating acute mania in bipolar I disorder.

Methods

Three double-blind, placebo-controlled, randomized controlled studies were included in this systematic review. In all three studies the patient population included male and female adults ages 18 to 65 years old with a diagnosis of bipolar I disorder, mixed or manic type, with or without psychotic symptoms. These studies used oral cariprazine 3 mg -12 mg per day as the intervention. Calabrese et al.[1] randomly assigned patients to either cariprazine 3-6 mg per day which was considered low dose or 6-12 mg per day which was considered high dose. Durgam et al.[2] and Sachs et al.[3] both initiated patients in the randomized treatment group on cariprazine 1.5 mg per day and doubled the dosing after day 2, continuing up to a maximum dose of 12 mg per day if tolerability and patient response met safety criteria.

All three studies included a no-drug washout period up to 7 days, a 3-week treatment phase, and a 2-week safety follow-up. Patients were randomized to either the cariprazine treatment group or the placebo experimental group. The cariprazine group was compared to the placebo group in terms of YMRS scores to determine the outcomes of efficacy in treating acute mania in bipolar I disorder.[1,2,3] The adverse events and safety of cariprazine was also measured using subjective symptoms reported by the patient, vital signs, liver function, metabolic laboratory data and extrapyramidal symptoms.[1,2,3]

Data sources include three peer-reviewed journal articles, published in English in 2015. All articles were researched through Medline, Pubmed, and Cochrane Review databases. These

articles were chosen based on their clinical relevance to my question and inclusion of POEMS. Key words searched in Pubmed included "cariprazine" and "bipolar disorder".

Inclusion criteria for all three studies included male and female patients ages 18-65 years old with a diagnosis of bipolar I disorder, manic or mixed type, with or without psychotic symptoms. Additional inclusion criteria included a YMRS score of ≥ 20, a score of ≥ 4 on at least two items: irritability, speech, content, or aggressive behavior, a Montgomery-Asberg Depression Rating Scale < 18, and a BMI of 18-40 mg/kg. Exclusion criteria varied slightly between studies but generally included pregnant women, positive pregnancy test at screening, substance abuse, additional axis I diagnosis, suicide risk, significant medical conditions (malignancy, hematologic, endocrine, cardiovascular, respiratory, renal, or hepatic disorders), current use of psychotropic medication, patients treated with cariprazine within 90 days of screening, patients who received electroconvulsive therapy within 3 months of screening, or a history of neuroleptic malignant syndrome.

Statistics reported in all three studies included relative risk reduction (RRR), absolute risk reduction (ARR), numbers needed to treat (NNT), and p-values. Primary statistical analyses were performed using mixed-effects model with repeated measures (MMRM), analysis of covariance model (ANCOVA), and 2-sded 95% confidence intervals (CI).[1,2,3] Table 1 below displays the demographics and characteristics of the three studies.

Table 1: Demographics & Characteristics of Included Studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Calabrese[1] (2015)	Double blind RCT	497	18-65 years	Age 18-65 years with a diagnosis of bipolar I disorder	First manic episode, additional psychiatric disorder, risk of suicide, or ECT within 3 months	127	Cariprazine low dose 3-6mg/d or high dose 6-12mg/d orally
Durgam[2] (2015)	Double blind RCT	236	18-65 years	Age 18-65 years with a diagnosis of bipolar I disorder	First manic episode, additional psych disorder, previous treatment within 90 days with depot neuroleptic	88	Cariprazine 3-12mg/d orally
Sachs[3] (2015)	Double blind RCT	312	18-65 years	Age 18-65 years with a diagnosis of bipolar I disorder	Axis I diagnosis other than bipolar I, substance abuse within 3 months, ECT within 3 months or cariprazine within 10 years	98	Cariprazine 3-12mg/d orally

Outcomes Measured

The three studies measured acute mania signs and symptom improvement using the Young Mania Rating Scale (YMRS). The YMRS measures irritability, speech, content, disruptive-aggressive behavior, elevated mood, increased motor activity, sexual interest, sleep, language-thought process, appearance, and insight through patient report as well as investigator observation.[1,2,3] These YMRS scores were administered at the beginning of the study (baseline), days 3, 5, 7, 10, 14, and 21.[1,2,3] The YMRS scores on day 21 were then compared to baseline scores in both the placebo and treatment group for efficacy.[1,2,3]

Treatment adverse events were also measured using patient subjective reports, vital signs, laboratory parameters, and extrapyramidal symptoms.[1,2,3] The treatment adverse events (AE's) measured included headache, akathisia, constipation, nausea, dyspepsia, dizziness, insomnia, vomiting, diarrhea, mania, tremor, and agitation.[1,2,3] The vital signs measured in Durgam et al.[2] included systolic blood pressure (mm Hg), diastolic blood pressure (mm Hg), pulse (bpm), and body weight (kg). Calabrese et al.[1] and Sachs et al.[3] included these vital signs as well as waist circumference (cm). The laboratory values measured at baseline as well as week 3 included total cholesterol (mg/dL), LDL (mg/dL), HDL (mg/dL), triglycerides (mg/dL), and glucose (mg/dL) in Durgam et al.[2] Calabrese et al.[1] and Sachs et al.[3] also included alanine aminotransferase (U/L), aspartate aminotransferase (U/L), total bilirubin (mg/dL), prolactin (ng/dL), and creatine kinase (U/L).

Results

All three studies reviewed patients ages 18-65 with a diagnosis of bipolar I disorder treatment with oral cariprazine 3mg-12mg per day compared to that receiving a placebo. In

Calabrese et al.[1] there was a total of 497 patients enrolled in the study with the studies being performed at 65 different study centers. A total of 48 patients discontinued the study (9%) due to adverse events, 25 being the highest in the high dose cariprazine group.[1] Patients who were experiencing their first manic episode, significant suicidal risk, pregnant, diagnosed with an additional axis I disorder, had a substance disorder, significant medical illness, treated with ECT within the previous 3 months, or treated with depot neuroleptics within 3 months were excluded from this study.[1] The patients were enrolled in a 6-week study that included a no-drug washout period for up to 7 days, 3 weeks of double-blind treatment, and 2-week safety follow up.[1] Patients were randomly assigned to low dose cariprazine 3-6 mg/day group, high dose cariprazine 6-12 mg/day group, or a placebo.[1] The control event rate (CER) was calculated to be 37.5% in the control group and the experimental event rate (EER) was calculated to be 60.6% in the treatment group.[1] This indicates that 60.6% of the patients receiving cariprazine for treatment of acute mania in bipolar I disorder had a $\geq 50\%$ reduction in YMRS scores at week 3 of the study compared to the 37.5% in the control group (placebo). The study revealed a relative risk reduction (RRR) of 61.6% and an absolute risk reduction (ARR) of 23.1%.[1] This indicates that patients taking cariprazine had a 61.6% lower risk of developing acute mania and an absolute 23.1% decrease in acute mania rates compared to the placebo. The number needed to treat (NNT) was calculated to be 5 (CI 95%), so for every 5 patients taking cariprazine, 1 patient will have a >50% reduction in acute mania in bipolar I disorder.[1]

In Sachs et al.[2] there was a total of 312 patients enrolled with the studies being performed at 38 approved study centers. A total of 98 patients discontinued the study, the majority being withdrawal of consent (16.5%) and patients in the placebo group with an insufficient therapeutic response (10.4%).[2] Patients who were pregnant, had substance abuse disorder, additional axis I

diagnosis, had suicide risk, had another significant medical condition, had been treated with

clozapine within the last 10 years, or received ECT/depot neuroleptic drugs within the last 3

months were excluded from the study.[2] The study included a 3-week, double-blind evaluation of

patients randomized to either cariprazine 3-12 mg/day (based on tolerability) or placebo to treat

acute mania.[2] The CER was calculated to be 44.1% for the control group and the EER was

calculated to be 58.9% in the treatment group.[2] This indicates that 58.9% of the patients

receiving cariprazine for treatment of acute mania in bipolar I disorder had a $\geq$ 50% reduction in

YMRS scores at week 3 of the study compared to the 44.1% in the control group (placebo). The

study revealed an RRR of 33.5% and an ARR of 14.8%.[2] This indicates that patients taking

cariprazine had a 33.5% lower risk of developing acute mania and an absolute 14.8% decrease in

acute mania rates compared to the placebo. The NNT was calculated to be 7 (CI 95%), so for

every 7 patients taking cariprazine, 1 patient will have a >50% reduction in acute mania in

bipolar I disorder.[2]

In Durgam et al.[3] there was a total of 238 patients enrolled in 29 study centers according

with the Good Clinical Practice guidelines. A total of 88 patients discontinued the study, the

majority being patients in the placebo group with insufficient therapeutic response (18) and those

in the treatment group with adverse events (17).[3] Patients who were pregnant, had an additional

axis I disorder, had substance abuse, having their first manic episode, diagnosed with serious

medical condition (example cardiovascular), had a history of tardive dyskinesia, had neuroleptic

malignant syndrome, or were treated with a depot neuroleptic/ECT within the last 3 months were

excluded from the study.[3] The study included a 3-week, double-blind evaluation of patients

randomized to either cariprazine 3-12 mg/day (based on tolerability) or placebo to treat acute

mania.[3] The CER was calculated to be 29.5% for the control group and the EER was calculated

to be 49% in the treatment group.[3] This indicates that 49% of the patients receiving cariprazine

for treatment of acute mania in bipolar I disorder had a greater reduction in YMRS scores at

week 3 of the study compared to the 29.5% in the control group (placebo). The study revealed an

RRR of 66.1% and an ARR of 19.5%.[3] This indicates that patients taking cariprazine had a

66.1% lower risk of developing acute mania and an absolute 19.5% decrease in acute mania rates

compared to the placebo. The NNT was calculated to be 5 (CI 95%), so for every 5 patients

taking cariprazine, 1 patient will have a greater reduction in acute mania in bipolar I disorder.[3]

Table 2: Treatment effects of cariprazine for acute mania in bipolar I disorder

Study	P-value/CI	CER	EER	RRR	ARR	NNT
Calabrese et al.[1]	p<0.001/95%	37.5%	60.6%	61.6%	23.1%	5
Sachs et al.[2]	p<0.01/95%	44.1%	58.9%	33.5%	14.8%	7
Durgam et al.[3]	p<0.001/95%	29.5%	49.0%	66.1%	19.5%	5

In all three studies, cariprazine was generally safe and well-tolerated. In Calabrese et al.[1]

there were a total of 10 serious adverse events (SAEs), 3 being in the placebo group and 7 being

in the low dose cariprazine group. 7 of the 10 SAEs were associated with worsening mania and

there were no SAEs in the high dose cariprazine group.[1] The most common ($\geq$5% in any group)

treatment-emergent adverse events (TEAEs) in Calabrese et al.[1] were akathisia, nausea,

constipation, and tremor (high dose cariprazine group only). There were no statistically

significant differences in change from baseline metabolic laboratory parameters or vital signs

between the treatment and placebo group.[1]

In Sachs et al.[2] there were a total of 8 patients with SAEs, 3 being in the placebo group

and 5 being in the treatment group. The only SAE reported in more than one patient was

worsening of mania (1 in placebo and 2 in the treatment group).[2] The only TEAEs that led to

discontinuation were worsening of mania, akathisia, and rash (5/2, 0/5, and 2/0 for placebo/treatment groups respectively).[2] In Sachs et al.[2] the mean changes in vital signs and metabolic laboratory parameters were small and similar between groups.

In Durgam et al.[3] there were a total of 10 SAEs, 6 being in the placebo group and 4 being in the treatment group. The most common SAE was worsening of mania, which occurred in 6 patients (4 placebo and 2 treatment).[3] The most common TEAEs ($\geq$10% of treatment group) were extrapyramidal disorder, headache, akathisia, constipation, nausea, and dyspepsia.[3] Mean changes in vital signs and metabolic laboratory parameters were small and similar between groups with the exception of fasting glucose (increase with treatment group, $p = 0.04$).[3] A summary of calculated safety and tolerability for all three studies is demonstrated in Table 3.

Table 3: Safety and tolerability of oral cariprazine for acute mania in bipolar I disorder

Study	Control event rate (CER)	Experimental event rate (EER)	Relative risk reduction (RRR)	Absolute risk increase (ARI)	Number needed to harm (NNH)
Calabrese et al.[1]	1.9%	4.2%	121.1%	2.3%	44
Sachs et al.[2]	1.3%	0.60%	-53.8%	-.70%	-142.9%
Durgam et al.[3]	4.2%	3.4%	-19.0%	-.80%	-125.0%

Discussion

Cariprazine is a second generation antipsychotic medication that is a D2, D3, 5-HT$_{1A}$ receptor partial agonist and a 5-HT$_{2B}$ receptor partial antagonist.[2] It is mainly used to treat acute mania in bipolar I disorder and schizophrenia, but has been used off-label to treat psychosis associated with dementia.[9] There is a black box warning however, that states cariprazine is not approved for dementia related psychosis due to increased mortality with cardiovascular events.[9] The only documented contraindication to cariprazine is hypersensitivity, although multiple

cautions are issued including neuroleptic malignant syndrome history, seizure history, cerebrovascular disease, cardiovascular disease, hypovolemia, dehydration, diabetes mellitus, and leukopenia.[9]

These studies were limited by the lack of a competitive medication, short study duration, and adequate measurement of remission rates for acute mania. Although there was significant discontinuation among patients in all 3 studies, most were due to insufficient therapeutic response or withdrawal of consent in the placebo group. Overall, TEAEs were generally mild and similar side effects have been demonstrated in the second generation antipsychotic drug class.

Conclusion

This review demonstrated that cariprazine is effective and safe in treating acute mania in bipolar I disorder. Cariprazine was associated with a significantly greater reduction in acute mania scores compared to placebo after three weeks of treatment in all studies reviewed. TEAEs in all three studies were considered mild to moderate in intensity. The tolerability of cariprazine was similar with minimal difference in laboratory parameters and vital signs between placebo and treatment groups. Future studies are warranted to evaluate the long term outcomes of treatment, competitive medication such as another antipsychotic, and accurate measurement of remission rates. Studies conducted in the future should consider using a fixed dosing schedule to improve efficacy and tolerability interpretations at specific doses of cariprazine. Cariprazine as a second generation antipsychotic may continue to improve quality of life as a treatment option for bipolar I disorder

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