Effects of Cariprazine on Prolactin Levels in Patients With Bipolar I Disorder

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CONCLUSIONS

1. In post hoc analyses of patients with bipolar I disorder and a current depressive or manic/mixed episode, mean prolactin changes were small and generally similar for cariprazine and placebo in both male and female subgroups in short-term treatment
2. Decreases in prolactin levels were seen with acute cariprazine and placebo treatment, and with longer-term open-label cariprazine treatment in patients with manic/mixed episodes associated with bipolar I disorder
3. Prolactin-related sexual and reproductive AEs occurred infrequently for cariprazine-treated patients
4. These results suggest that cariprazine is not a prolactin-elevating agent in male or female patients with bipolar I disorder and that it is associated with minimal hormonal adverse effects
5. Cariprazine may be a useful treatment choice for patients with manic or depressive episodes of bipolar I disorder who are concerned about sexual or reproductive side effects

RESULTS

- In the bipolar depression studies, 1265 patients were included in the analyses; 485 were male (placebo=173, cariprazine 1.5 mg=151, cariprazine 3 mg=161) and 780 were female (placebo=250, cariprazine 1.5 mg=277, cariprazine 3 mg=253)
- In the bipolar mania studies, 1065 patients were included in the analyses; 633 were male (placebo=268, cariprazine 3-6 mg=148, cariprazine 9-12 mg=217) and 432 were female (placebo=174; cariprazine 3-6 mg=115, cariprazine 9-12 mg=143)
- In most laboratories, the upper limit for prolactin serum concentrations is 20 ng/mL for men and 24-25 ng/mL for women[3]
- As may be expected, baseline values were generally higher for women than for men, and some female treatment groups had mean baseline values that were outside the normal range (**Table 1**)
  - Some values may have been affected by previous treatment with a dopamine antagonist

Table 1. Baseline Prolactin Values

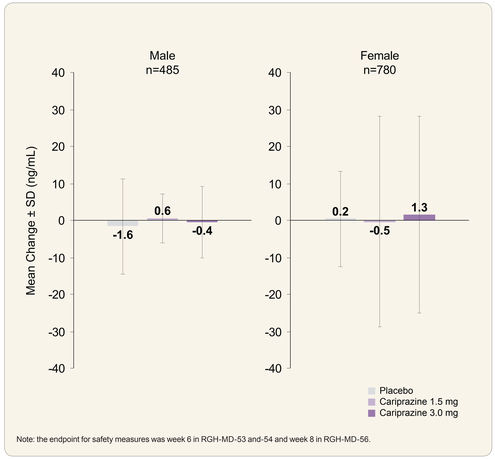
Study	Dose Groups	Baseline Prolactin Values, ng/mL	
		Male	Female
Bipolar depression (6 or 8 week)	Placebo	13.3	13.4
	CAR 1.5 mg/d	10.2	18.2
	CAR 3 mg/d	10.7	15.2
Bipolar mania (3 week)	Placebo	14.3	25.2
	CAR 3-6 mg/d	12.2	26.7
	CAR 9-12 mg/d	13.8	28.3
	CAR overall	13.2	27.6
Bipolar mania (open-label, 16 week)	CAR 3-6 mg/d	11.4	14.4
	CAR 9-12 mg/d	11.7	21.8
	CAR overall	11.5	17.2

CAR, cariprazine.

Pooled Bipolar Depression Studies

- In male and female subgroups of patients, mean changes in prolactin values from baseline to the end of the study were small in all treatment groups (**Figure 1**)

Figure 1. Pooled 6- or 8-Week Bipolar Depression Studies: Mean Change From Baseline in Prolactin Levels

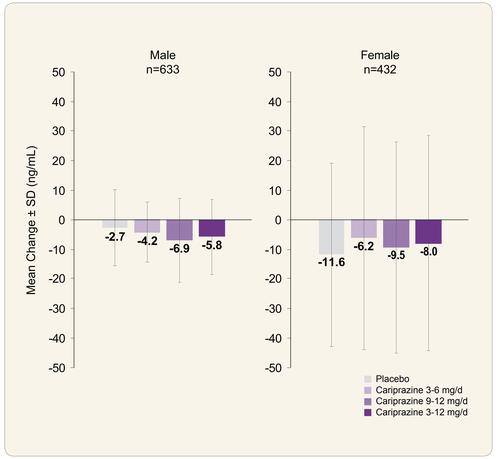


Note: the endpoint for safety measures was week 6 in RGH-MD-53 and-54 and week 8 in RGH-MD-56.

Pooled Bipolar Mania Studies

- In patients with bipolar mania, prolactin levels decreased in all dose groups for male and female patients (**Figure 2**)

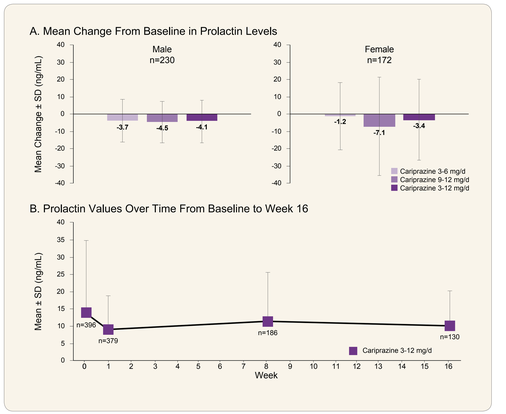
Figure 2. Pooled 3-Week Acute Bipolar Mania Studies: Mean Change From Baseline in Prolactin Levels



Longer-Term Bipolar Mania Study

- In the longer-term bipolar mania study, mean prolactin levels decreased from baseline to the end of the study in the male and female subgroups (**Figure 3A**)
  - For cariprazine 3-12 mg/d in the combined group of male and female patients, the mean (SD) change in prolactin level from baseline to study endpoint was -3.8 (17.8) ng/mL (**Figure 3B**)

Figure 3. Open-Label 16-Week Bipolar Mania Study



Prolactin-Related Adverse Events

- Prolactin-related AEs in the acute studies occurred infrequently for cariprazine- and placebo-treated patients with bipolar I disorder and a current depressive or manic/mixed episode (**Table 2**)

Table 2. Cariprazine Acute Studies: Prolactin-Related Treatment-Emergent Adverse Events[a]

Adverse Event	Bipolar I Mania, n (%)				Bipolar I Depression, n (%)		
	Placebo n=422	CAR 3-6 mg n=263	CAR 9-12 mg n=360	CAR 3-12 mg n=623	Placebo n=468	CAR 1.5 mg n=470	CAR 3 mg n=469
Amenorrhea	0	0	0	0	0	0	0
Anorgasmia	0	0	0	0	0	0	0
Orgasm abnormal	0	0	0	0	0	0	2 (0.4)
Libido decrease	0	0	1 (0.3)	1 (0.2)	0	1 (0.2)	0
Libido increase	0	0	0	0	0	0	0
Ejaculation failure	0	0	0	0	0	0	0
Erectile dysfunction	3 (1.1)	0	4 (1.8)	4 (1.1)	0	2 (1.2)	3 (1.6)
Ejaculation disorder	0	0	1 (0.5)	1 (0.3)	0	0	0
Sexual dysfunction	0	0	0	0	0	0	0
Oligomenorrhea	0	0	0	0	0	0	0
Gynecomastia	0	0	0	0	0	0	0
Galactorrhea	1 (0.2)	0	0	0	0	0	0

[a] For sex-specific AEs, percentages are relative to the number of patients of the appropriate sex.

INTRODUCTION

Background

- Hyperprolactinemia frequently occurs with full dopamine antagonists that are used to treat bipolar disorder due to nonselective dopamine D_2 receptor blockade[1]
- Prolactin elevation has important implications because of its association with sexual and reproductive adverse events (AEs) and medical complications (eg, osteoporosis)[2]
- Hyperprolactinemia can affect quality of life and wellness due to serious consequences including infertility, oligomenorrhea, amenorrhea, galactorrhea, and vaginal dryness in women, and decreased libido, impotence, infertility, gynecomastia, and erectile dysfunction in men[1]
- Sexual AEs can cause negative attitudes toward treatment, which can contribute to low adherence in patients with bipolar disorder[2]
- Cariprazine, a dopamine D_3/D_2 and serotonin 5-HT_{1A} receptor partial agonist, is approved for the treatment of manic/mixed (3-6 mg/d) and depressive (1.5-3 mg/d) episodes associated with bipolar I disorder

Objective

- To evaluate the effect of cariprazine treatment on prolactin levels in male and female patients with a current manic/mixed or depressive episode associated with bipolar I disorder

METHODS

- Post hoc analyses were conducted on pooled data from acute randomized, double-blind, placebo-controlled trials of cariprazine in patients with bipolar mania (3-week endpoint) and bipolar depression (6- or 8-week endpoint)
  - Bipolar mania studies: RGH-MD-31 (NCT00488618), -32 (NCT01058096), -33 (NCT01058668)
  - Bipolar depression studies: RGH-MD-56 (NCT01396447), -53 (NCT02670538), -54 (NCT02670551)
- Longer-term prolactin changes in bipolar mania were also evaluated in a 16-week open-label cariprazine 3-12 mg flex-dose study (RGH-MD-36 [NCT01059539])
- In the bipolar depression studies, placebo and cariprazine 1.5 mg/d and 3 mg/d were evaluated
  - A 0.75 mg/d dose group was also analyzed in RGH-MD-56 only; it was not included in these analyses because it is below the approved dose range
- In the bipolar mania studies, placebo, modal daily cariprazine doses (3-6 mg/d and 9-12 mg/d), and cariprazine 3-12 mg/d were evaluated
  - Modal daily dose is the most frequent dose taken during the study
- Mean change from baseline to study endpoint in prolactin levels was analyzed using descriptive statistics in male and female subgroups of patients
- Prolactin-related treatment-emergent AEs in the acute studies were also investigated
- Although these studies included a drug wash-out period prior to baseline, patients could have been treated with dopamine blocking agents before entering the cariprazine studies, and these prior medications could have affected baseline and change from baseline values for prolactin

DISCLOSURES

Support for these analyses was provided by Allergan plc. Writing and editorial assistance was provided by Prescott Medical Communications Group (Chicago, IL), a contractor of Allergan. Statistical analysis support was provided by Qing Dong and Lei Luo, of Allergan (Madison, NJ). All authors met the ICMJE authorship criteria. Neither honoraria nor payments were made for authorship.

L. Culpepper has served as an advisor or consultant for Acadia Pharmaceuticals, Allergan Pharmaceuticals, Eisai Pharmaceuticals, Merck & Co., Takeda, Supernus Pharmaceuticals; owns stock in M-3 Information, LLC, and has received royalties from UpToDate and Oxford University Press in addition to receiving payment from Physicians Postgraduate Press as Editor in Chief of the Primary Care Companion for CNS Diseases. E. Vieta has received grants and served as consultant, advisor, or speaker for: AB Biotics, Abbott, Alexza, Almirall, Allergan, Angelini, AstraZeneca, Bristol Myers Squibb, Casen Recordati, Cephalon, Dainippon Sumitomo Pharma, Elan, Eli Lilly, Ferrer, Forest Research Institute, Gedeon Richter, GlaxoSmithKline, Janssen Cilag, Jazz, Johnson and Johnson, Lundbeck, Merck, Novartis, Organon, Otsuka, Pfizer, Roche, SAGE, Sanofi Aventis, Servier, Schering Plough, Shire, the Spanish Ministry of Science and Innovation, the Seventh European Framework Programme, the Stanley Medical Research Institute, Sunovion, Takeda, Teva, United BioSource Corporation, and Wyeth. D. Kelly serves as an advisor to Lundbeck and HLS Therapeutics. M. Patel, T. Moreira, and W. Earley are employees of Allergan; M. Patel is shareholder of Allergan. W. Earley is a shareholder of Allergan, AstraZeneca, and Eli Lilly.

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Poster presented at the Psych Congress
San Diego, California | October 3-6, 2019

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