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Akathisia during cariprazine treatment: Post-hoc analyses of pooled schizophrenia studies

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INTRODUCTION

Long-term treatment with antipsychotic agents is indicated for all patients with schizophrenia. [1] Antipsychotic drugs can be of great benefit for a wide range of symptoms, but some treatments are associated with unpleasant adverse effects including weight gain, cardiac abnormalities, hyperprolactinaemia, and extrapyramidal symptoms (EPS). [2] Akathisia, a feeling of muscle quivering, internal restlessness, or an inability to sit still, is an EPS side effect of antipsychotic agents and some antidepressants. [3] This side effect can range from mild symptoms to debilitating restlessness, which when severe may increase the risk of poor compliance, suicidal ideation and treatment discontinuation. [4] Treatment of this common side effect is complex but can be managed effectively with available pharmacology. [5]

STUDY OBJECTIVE

The aim of the current post-hoc analyses was to present the incidence rates and management of akathisia during treatment with cariprazine (CAR) and placebo (PBO) in patients with schizophrenia.

METHODS

Pooled data from 2048 cariprazine (approved dose-range: 1.5-6 mg daily) and 683 placebo treated patients from eight Phase 3, schizophrenia studies was analyzed, including: 4 short-term, 6-week studies (RGH-MD-03: NCT00404573, RGH-MD-16: NCT00694707, RGH-MD-04: NCT01104766 and RGH-MD-05: NCT01104779), 1 long-term, 26-week study in patients with negative symptoms of schizophrenia (RGH-188-005: EudraCT 2012-005485-36), 2 long-term, 48-week safety studies (RGH-MD-17: NCT00839852, RGH-MD-11: NCT01104792), 1 long-term, up to 92-week maintenance of effect study (RGH-MD-06: NCT01412060). Safety measures included adverse events (AEs), clinical laboratory values, physical examinations, EPS-, depression- and suicidality scales. Assessments were administered at baseline and at various treatment visits. Akathisia adverse events (AEs), severity of these AEs, concomitant medications, study drug down-titrations and discontinuation rates during treatment were examined. The potential relationship between akathisia and suicidality was also assessed. Safety parameters were summarized using descriptive statistics. All studies included adult patients with DSM-IV TR diagnosis of schizophrenia. Cariprazine data is presented within the approved dose range.

RESULTS

Incidence of akathisia

Akathisia was reported by 14.6% CAR and 3.4% PBO treated patients. Most cases were mild to moderate in intensity (CAR 97.5%, PBO 95.8%).

Table 1 Incidence of akathisia in the pooled schizophrenia studies

Parameter	Placebo N=683 n (%)	Cariprazine N=2048 n (%)
Patients with Akathisia (n)	23 (3.4)	299 (14.6)
Akathisia events (n)[1]	23	334
Mild	14 (60.8)	180 (53.9)
Moderate	8 (34.8)	145 (43.5)
Severe	1 (4.4)	9 (2.6)

[1]One patient might have experienced more than one akathisia event. Events were counted separately if there were 3 or more days between them.

Anti-EPS medication

The most often used treatment intervention to address akathisia was anti-EPS medication. The most often used anti-EPS medication in both groups was propranolol.

Table 2 Incidence of akathisia treated with anti-EPS medication

Parameter	Placebo n (%)	Cariprazine n (%)
Akathisia events treated with anti-EPS medication	12 (52.1)	188 (56.3)
Median time of anti-EPS medication administration (days)	7	18
Median time to resolution of akathisia with anti-EPS medication (days)	16	17
Number of unresolved events after anti-EPS treatment	7 (58.3)	28 (14.9)

CONCLUSIONS

- **In the approved dose range of cariprazine 1.5-6 mg, the incidence of akathisia in schizophrenia was 14.6%.**
- **Most cases were mild to moderate in intensity (>95%). Symptoms were managed with anti-EPS treatment or down-titration.**
- **Akathisia was not associated with an increased risk of suicidality. Overall, with the right steps taken, akathisia can be manageable.**

Table 3 Administered anti-EPS medications for akathisia

	Placebo n (%)	Cariprazine n (%)
Propranolol	7 (43.8)	107 (53.0)
Benzatropine	5 (31.3)	40 (19.8)
Trihexyphenidyl	3 (18.8)	35 (17.3)
Diphenhydramine	-	8 (3.9)
Biperiden	-	6 (3.0)
Procyclidine	-	2 (1.0)
Lorazepam	-	2 (1.0)
Oxazepam	-	1 (0.5)
Hydroxyzine	-	1 (0.5)
Clonidine	1 (6.3)	-

One akathisia event might have been treated with more than one medication. Percentage was calculated as the number of administered anti-EPS medication/ total number of administered anti-EPS medications in the given group.

Study drug down-titration

Study drug down-titration was also applied. Median time to resolution of akathisia in the cariprazine group was 15 days.

Table 4 Incidence of akathisia treated with study drug down-titration

Parameter	Placebo n (%)	Cariprazine n (%)
Akathisia events resulting in study drug down-titration	-	61 (18.3)
Median (days) time to resolution of akathisia in patients with study drug down titration	-	15
Number of unresolved events in patients with study drug down titration	-	4 (6.6)

Discontinuation

Discontinuation rate due to akathisia was similar (6.3% of CAR and 4.4% of PBO). The median time of akathisia resolution after drug discontinuation was 26.5 days for CAR, while akathisia did not resolve within 30 days in the PBO group.

Table 5 Incidence of akathisia that led to study discontinuation

Parameter	Placebo n (%)	Cariprazine n (%)
Akathisia events resulting in discontinuation	1/23 (4.4)	21/334 (6.3)
Time (days) to resolution of akathisia in patients with discontinuation	did not resolve	27

Tolerance

In 28.2% (CAR) and 47.8% (PBO) of akathisia events no action was taken to resolve akathisia; nevertheless akathisia resolved in 87.2% and 63.6% of the PBO and CAR cases with a median time of 14 days for CAR and 8 days for PBO on its own despite ongoing treatment. This potentially indicates that a tolerance develops after 2 weeks.

Suicidality and akathisia

A relationship between akathisia and suicidal tendency was not observed in the CAR schizophrenia program: In the short term studies more patients experienced concurrent akathisia and suicidality on placebo and aripiprazole treatments than on cariprazine treatment (PBO 3.8%, ARI 13%, CAR 2.7%); while in the overall, pooled schizophrenia studies, rates of any suicidality was comparable between placebo (3.6%) and cariprazine (5.2%).

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DISCLOSURES & FUNDING STATEMENT

Studies were funded by Gedeon Richter Plc. and Allergan Plc.
Dr. Barabássy, Dr. Sebe, Dr. Szatmári, Dr. Laszlovszky, Dr Harsányi, Acsai, Seregi and Dr. Németh are employees of Gedeon Richter Plc., Dr. Earley and Dr. Patel are employees of Allergan.

Presented at the 32nd Congress of the European College of Neuropsychopharmacology, September 7-10, 2019, Copenhagen, Denmark