Safety During Polypharmacy: A Post-hoc Analysis Examining The Safety Profile Of Cariprazine With Other Antipsychotics In The Cross-Titration Phase

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INTRODUCTION

Although recommendations by leading guidelines favour antipsychotic monotherapy for schizophrenia[1], the combination of antipsychotics (polypharmacy) is common in everyday clinical practice[2,3]. This especially true in the case of switching medications, where during the cross-titration phase the patient receives two or even more drugs for a certain amount of time[4]. The administration of more than one pharmacological agent, however, increases the chance of experiencing side effects[5].

Cariprazine, a dopamine D3 receptor preferring D3/D2 receptor partial agonist was found to be generally well-tolerated in patients with schizophrenia experiencing predominant negative symptoms[6], however the safety profile of the drug has not been analysed in combination with other antipsychotics yet.

STUDY OBJECTIVES

The aim of the present poster is to examine the treatment emergent adverse events (TEAEs) during the co-administration of cariprazine with other antipsychotics throughout the cross-titration period of a randomized trial.

METHODS

TEAE data from a randomized, double-blind, parallel-group, active-controlled study (EudraCT Number: 2012-005485-36) in adult patients with schizophrenia having predominant negative symptoms was analysed in the first two weeks of the double-blind treatment period, where gradual cross-titration occurred between cariprazine (3-6 mg/day) and other antipsychotics (including amisulpride, aripiprazole, fluphenazine, haloperidol, olanzapine, paliperidone, quetiapine, and risperidone).

After the cross-titration period ended, 24 weeks of cariprazine monotherapy followed.

RESULTS

Overall, 230 patients were included in the analysis (Table 1). About half of the patients were male (54%) and the mean of the group was 40 years. The mean duration of schizophrenia from diagnosis to enrolment was 12 years. More than half of the patients took antipsychotic medication prior enrolment (56%). Most of them were treated with olanzapine (16%), risperidone (13%) and aripiprazole (6%).

Table 1: Baseline demographics

Demographics	
Number of patients, n	230
Male, n (%)	124 (53.9%)
Mean age, n (SD)	40.2 (10.5)
Mean duration of schizophrenia, n (SD)	12.0 (8.1)
Prior antipsychotic medication, n (%)	129 (56.1)
Amisulpride	9 (3.9)
Aripiprazole	13 (5.7)
Fluphenazine	5 (2.2)
Haloperidol	7 (3.0)
Olanzapine	36 (15.7)
Paliperidone	9 (3.9)
Quetiapine	12 (5.2)
Risperidone	30 (13.0)
Other antipsychotics	8 (3.5)

Overall, during the two-week cross-titration period, 17.8% of patients experienced at least one TEAE (Table 2). After the two-week cross-titration period (24 weeks) 45.6% of patients experienced at least one TEAE (including patients who did not take any prior antipsychotic medication). The most commonly experienced TEAEs during the cross-titration period were nausea (2.6%), insomnia (2.2%), headache (2.2%), akathisia (1.7%) and restlessness (1.3%). After the cross-titration period most patients had insomnia (7.4%), akathisia (7.0%) and headache (6.5%).

Table 2: TEAEs during and after* the cross-titration period, affecting more than 1% of patients

TEAE, n (%)	During cross-titration	After* cross-titration
All	41 (17.8)	105 (45.6)
Nausea	6 (2.6)	3 (1.3)
Insomnia	5 (2.2)	17 (7.4)
Headache	5 (2.2)	15 (6.5)
Akathisia	4 (1.7)	16 (7.0)
Restlessness	3 (1.3)	2 (0.9)

** TEAEs of patients who had not taken any prior antipsychotic medication calculated into the After Cross-titration column*

CONCLUSION

- **Based on the results of the post-hoc analysis, the co-administration of cariprazine with other antipsychotic medications did not show an unexpected safety profile nor overlapping toxicities, suggesting that it is unlikely that safety will be compromised if polypharmacy with cariprazine is unavoidable.**
- **Nonetheless, it is worth to note that the results are limited by small sample size and short cross-titration period.**

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DISCLOSURE

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ABSTRACT

Introduction

Although monotherapy is preferable, in every day clinical practice polypharmacy is often unavoidable due to the need of treatment enhancement or cross-titration phases with shorter or longer overlaps of two or more drugs. However, administration of more than one drug treatment is often associated with more side effects.

Objectives

The aim of the present post-hoc analysis was to examine treatment emergent adverse events (TEAEs) during co-administration of cariprazine with other antipsychotics.

Methods

Treatment emergent adverse event data (TEAE) from a randomized, double-blind, parallel-group, active-controlled study (EudraCT Number: 2012-005485-36) in adult patients with schizophrenia having predominant negative symptoms was examined in the first two weeks of the double-blind treatment period, where gradual cross-titration occurred between cariprazine (3-6 mg/day) and other antipsychotics (including amisulpride, aripiprazole, fluphenazine, haloperidol, olanzapine, paliperidone, quetiapine, and sertindole). Thereafter, 24 weeks of cariprazine monotherapy followed.

Results

During the cross-titration period, 17.83% of patients experienced at least one TEAE. The TEAEs were in line with the well-established safety data: nausea (2.61%), insomnia (2.17%), headache (2.17%), akathisia (1.74%) and restlessness (1.3%) were the most common. Most events were mild in severity (66.1% mild, 32.2% moderate, 1.7% severe (insomnia)).

Conclusions

While not definitive, and limited by small sample size, the co-administration of cariprazine with other antipsychotics did not show an unexpected safety profile or overlapping toxicities. This is an important finding, if intermittent or longer co-administration of other antipsychotics are unavoidable with cariprazine treatment.