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Hormonal Effects of Cariprazine: Post Hoc Analysis of Pooled Data from Schizophrenia Studies for Sexual Dysfunction and Prolactin Changes

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INTRODUCTION

- Long-term treatment with antipsychotic agents is indicated for all patients with schizophrenia.
- Antipsychotic drugs can be of great benefit for a wide range of symptoms, but treatment is associated with unpleasant adverse effects including weight gain, metabolic and cardiac abnormalities, extrapyramidal symptoms (EPS), hyperprolactinaemia and sexual dysfunction.
- Hormonal changes (i.e. prolactin elevation) and sexual dysfunction are reported as some of the most distressing antipsychotic adverse effects and are directly related to treatment non-compliance. [1]
- Antipsychotics can cause sexual dysfunction through multiple mechanisms, among them hyperprolactinaemia and D2 antagonism. [2]
- Cariprazine, a potent dopamine D3/D2 receptor partial agonist with preferential binding to D3 receptors, is approved in the EU for the treatment of schizophrenia in adults and in the US for the treatment of schizophrenia and manic or mixed episodes associated with bipolar I disorder.

STUDY OBJECTIVE

Post hoc analysis of pooled data from schizophrenia studies investigated the hormonal effects of cariprazine, i.e. prolactin changes and sexual dysfunction in the approved therapeutic dose-range versus placebo and comparators in patients with schizophrenia.

METHODS

Study Design

- For prolactin, pooled data from
  - 4 short term schizophrenia efficacy studies - RGH-MD-03: NCT00404573, RGH-MD-16: NCT00694707, RGH-MD-04: NCT01104766 and RGH-MD-05: NCT01104779;
  - 2 long term schizophrenia safety studies - RGH-MD-17: NCT00839852 and RGH-MD-11: NCT01104792; and
  - 1 relapse prevention study RGH-MD-06: NCT01412060 were analyzed.
- For sexual dysfunction, pooled data from 2048 cariprazine, 683 placebo, 370 risperidone and 152 aripiprazole treated patients from eight Phase-2/3 schizophrenia studies were analyzed (the 7 above listed trials and the study RGH-188-005: EudraCT number 2012-005485-36).
- All studies included adult patients with DSM-IV TR diagnosis of schizophrenia.
- Safety measures included adverse events (AEs), clinical laboratory values, physical examinations, EPS scales, depression- and suicidality scales.
- Safety assessments were administered at baseline and at various treatment visits.

Data analyses

- Efficacy measures were analyzed using a mixed-effects model for repeated measures (MMRM) in the intent-to-treat (ITT) population
- Safety parameters were summarized using descriptive statistics.

RESULTS

Prolactin:

- Mean decreases from baseline were seen in all treatment groups with the exception of risperidone, for which a mean increase was observed.
- There was a gender difference: Changes were more pronounced in women than in man.
- Cariprazine did not cause hyperprolactinaemia: in fact cariprazine allowed decreases of previously high or high-normal levels of prolactin to reference range values.

Table 1 Change from Baseline to End in Prolactin Levels by Group and by Sex - Safety Population

Group	Male patients prolactin (ng/mL)	Female patients prolactin (ng/mL)	Overall prolactin (ng/mL)
Short term studies	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**
Placebo			
Baseline	13.86 ± 13.58	38.48 ± 41.65	20.94 ± 27.43
End of the study	9.07 ± 7.53	18.09 ± 24.53	11.66 ± 15.14
Change from baseline	***-4.79 ± 14.13***	***-20.39 ± 46.96***	***-9.28 ± 28.70***
Cariprazine 1.5-6 mg			
Baseline	15.53 ± 13.84	48.89 ± 61.29	24.99 ± 37.76
End of the study	7.71 ± 7.79	20.11 ± 20.14	11.22 ± 13.76
Change from baseline	***-7.83 ± 13.62***	***-28.78 ± 58.49***	***-13.77 ± 34.49***
Risperidone 4 mg			
Baseline	17.70 ± 20.83	37.08 ± 36.29	23.52 ± 27.75
End of the study	29.66 ± 19.11	92.31 ± 70.04	48.45 ± 50.31
Change from baseline	***11.95 ± 20.88***	***55.24 ± 76.85***	***24.94 ± 49.40***
Aripiprazole 10 mg			
Baseline	14.62 ± 12.23	51.47 ± 48.70	27.52 ± 35.03
End of the study	4.18 ± 5.06	12.06 ± 23.64	6.94 ± 14.96
Change from baseline	***-10.44 ± 12.61***	***-39.41 ± 46.36***	***-20.58 ± 32.21***
Long term studies			
Cariprazine 1.5-6 mg			
Baseline	15.19 ± 13.91	49.00 ± 70.65	25.97 ± 44.30
End of the study	6.88 ± 6.04	16.56 ± 14.04	9.96 ± 10.38
Change from baseline	***-8.32 ± 13.20***	***-32.44 ± 69.57***	***-16.00 ± 42.19***

CONCLUSIONS

- **Cariprazine did not cause hyperprolactinaemia in all investigated clinical trials despite of different treatment length. In fact it allowed previously high or high-normal levels of prolactin to normalize.**
- **Cariprazine caused less sexual dysfunction than investigated other active comparators risperidone and aripiprazole.**
- **Cariprazine can be a reliable treatment possibility for patients suffering from drug induced hormonal side effects.**

Table 2 Change From Baseline to End in Prolactin Levels by Group and by Sex - Safety Population

Group	Male patients prolactin (ng/mL)	Female patients prolactin (ng/mL)	Overall prolactin (ng/mL)
Relapse prevention study, open label	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**
Cariprazine 3-6 mg			
Baseline	20.59 ± 67.71	36.35 ± 39.53	25.78 ± 60.28
End of the study	9.89 ± 37.24	19.44 ± 16.39	13.04 ± 32.19
Change from baseline	***-10.70 ± 33.20***	***-16.90 ± 38,60***	***-12.70 ± 35.10***
Relapse prevention study, double blind			
Placebo			
Baseline	16.78 ± 15.59	30.93 ± 36.89	21.08 ± 24.76
End of the study	10.55 ± 10.15	24.28 ± 27.29	14.71 ± 18.21
Change from baseline	***-6.24 ± 13.43***	***-6.65 ± 37.63***	***-6.36 ± 23.31***
Cariprazine 3-6 mg			
Baseline	14.76 ± 13.95	40.85 ± 41.23	26.03 ± 31.48
End of the study	9.46 ± 8.86	42.57 ± 81.78	23.76 ± 55.84
Change from baseline	***-5.30 ± 14.68***	***1.72 ± 56.27***	***-2.27 ± 38.18***

Sexual dysfunction

- Mean decreases from baseline were seen in all treatment groups with the exception of risperidone, for which a mean increase was observed.
- Sexual dysfunction TAEs occurred in 0.3% of placebo treated patients versus 1% of cariprazine, 2,7% of risperidone and 2% of aripiprazole treated patients.
- Most common sexual dysfunction TAEs were libido decreased, erectile dysfunction and amenorrhoea.

Table 3 Incidence of Treatment Emergent Adverse Events Related to Sexual Dysfunction

	Placebo (N=683)	Cariprazine 1.5-6.0 mg (N=2048)	Risperidone (N=370)	Aripiprazole (N=152)
Any TEAE in this category (%)	**0.3**	**1.0**	**2.7**	**2.0**
Libido decreased	0.0	0.3	1.1	0.7
Libido increased	0.0	0.1	0.0	0.0
Anorgasmia	0.0	0.0	0.0	0.0
Female orgasmic disorder	0.0	0.2	0.0	0.0
Male orgasmic disorder	0.0	0.0	0.4	0.0
Orgasm abnormal	0.1	0.0	0.0	0.0
Erectile dysfunction	0.2	0.4	0.4	1.1
Ejaculation disorder	0.0	0.1	0.4	0.0
Ejaculation failure	0.0	0.1	0.0	0.0
Sexual dysfunction	0.0	0.0	0.0	0.7
Amenorrhoea	0.0	0.2	2.3	0.0

REFERENCES

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