Reviewer’s report

Title: Cholinergic rebound syndrome following abrupt low-dose clozapine discontinuation in a patient with type I bipolar affective disorder. A case report.

Version: 0 Date: 31 Oct 2018

Reviewer: Richard Musil

Reviewer’s report:

In this case report the authors present a 66-year old male who is diagnosed and treated for bipolar affective disorder. After abrupt switching the drug regime from clozapine 50 mg / day and valproic acid 1000 mg / day to risperidone 5 mg / day, quetiapine 200 mg / day and valproic acid 300 mg / day, he developed symptoms of a cholinergic rebound syndrome as well as catatonia and aphasia. The symptoms partly improved after the patient was being treated with biperiden 2.5 mg. The authors discuss the occurrence of a cholinergic rebound syndrome after ending a low-dose clozapine treatment abruptly. They also discuss the possibility of a risperidone overdose to explain further symptoms of the patient presented and point out the importance of the clinician being aware of withdrawal symptoms, pharmacodynamic properties of drugs and use adequate switching strategies.

Abstract:

The Time of withdrawal of clozapine („3 days ago”) should already be mentioned in the abstract, as this is a crucial information.

Background:

Line 57: Please present the muscarinic receptor subtypes blocked by clozapine.

Line 64/65: The fact that olanzapine has clear anticholinergic properties should be explicitly stated in this paragraph which adds to the strangeness described herein.

Case presentation:

Line 76: The authors describe the clinical impression of the patient seeming "…nauseated, without vomiting". In the sentence before they mention the patient suffering from trismus. I would suggest clearing out the formulation of being nauseated as it seems to be difficult not to look nauseated when suffering from trismus and stick instead to the fact of the lack of vomiting.
Beside the improvement of the ability to speak please describe the improvement of further symptoms associated with a cholinergic rebound syndrome such as sweating or nausea and if the patient was asked retrospectively concerning anxiety or psychotic symptoms.

Line 97: please specify the term "dramatic recovery of the patient's ability to speak" and give at least time units to get a more detailed impression of the recovery.

Discussion and Conclusion:

Line 107: Please specify the point of time when clozapine was reintroduced after the male being treated in the emergency unit.

Line 130: spelling: "reports" instead of "rapports"

Please mention that there are possible pharmacological interaction between clozapine and valproic acid, even when a strong increase of the plasma level of clozapine shouldn't be expected.

The Language should be edited by a native speaker as there are quite a few sentences with odd grammar and typos. Authors should further look out for inconsistencies (e.g. „cholinergic rebound syndrome" (correct towards the end of the manuscript and „rebound cholinergic syndrome" - inkorrekt at the beginning, or format of 5HT receptors…).

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

Yes

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

Yes

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

Not relevant to this manuscript
Quality of written English
Please indicate the quality of language in the manuscript:

Needs some language corrections before being published

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