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: 28 Oct 2018

Reviewer: Nicolas Nunez

Reviewer’s report:

This manuscript represents an important and clinical concern which pertains to the cholinergic rebound syndrome after discontinuation of clozapine. The authors summarize its main clinical presentation, mention previous case reports supporting the diagnosis as well as its differential diagnoses and potential implications. Finally ends with brief clinical recommendations suggesting the importance of progressive tapering in any case (eg. even in low to high doses). Finally, this is the first report of a cholinergic rebound syndrome with low doses of clozapine in a patient with bipolar disorder.

Minor revisions

Title: considering that this is the first case report of a cholinergic syndrome in a patient with bipolar disorder it should be important to add the diagnosis in the title.

- Abstract:

* Line 17-20 : rephrase to improve flow. Suggestion: ...However, in all the previous case reports, patients were taking high doses of clozapine for schizophrenia.."

- Case presentation:

*Line 21: Please change phrase to : "A 66 year old male of Spanish origin.."

* Be consistent with the terminology: "apply cholinergic rebound syndrome throughout all the text."

Please revise and modify in the manuscript the use of "the" bipolar affective disorder for "bipolar affective disorder" accordingly.

-Case presentation:

* it will be important to clarify patients diagnosis: BDI or BDII and if the patient could be classified as treatment resistant (by the use of clozapine as mood stabilizer).
* could it be possible to gather more information on why the patient was discontinued from clozapine? Did he manifest neutrofilia or any other side effects?

*Line 23: Rephrase sentence. Include perhaps the following: "Overall, patients clinical parameters were unremarkable". Should be important to include here his medical condition (Crohn disease).

*Line 25: Should be important to mention if this was his first clozapine trial and if not how many trials and at what dosages. It is not totally clear to me if the patient can be considered treatment resistant or not (considering failure to previous mood stabilizers).

-Keywords:

Please include in the keywords section the word: "case report" as per CARE checklist.

-Background

* if possible authors could support claim with a previous case series by Durst et al 1999 supporting a rebound cholinergic phenomenon and the following reference: Verghese et al 1996: Clozapine withdrawal effects and receptor profiles of typical and atypical neuroleptic.

*Line 55: It should be important to add a reference from a psychoparmacology based text book such as Stahl's Essential Psychopharmacology or The American Psychiatric Association Publishing Textbook of Psychopharmacology, Fifth Edition( Schatzberg & Nemeroff) or the seminal article of Dr. Meltzer (Meltzer, H. Y. (1994). An overview of the mechanism of action of clozapine. The journal of clinical psychiatry.)

*Line 65: Restructure sentence, not totally clear. Expand.

*Line 69: Rephrase: "may be impaired by the polymorphic clinical presentation". Suggestion: "may be difficult due to a heterogeneous clinical presentation".

-Case presentation:

* are there any records of this patient on a standardized scale for catatonia (eg. Bush Francis Catatonia Scale)? It would be important to add if possible.

*Line 73: improve flow.

*Line 80: .."the blood biochemistry showed no significant abnormalities". Should be important to reference the normal values against patients values (renal and liver tests). Also, it should be important to include if the patient had or not neutrophilia (up to 9.44∗109/L) and levels of CK (CK) (up to 5870 U/L).

*Line 81: "gazometry" typo error. switch for gasometry.
-Discussion and conclusions

*Authors could expand briefly on suggested treatments for cholinergic and serotonergic reboud syndromes (e.g. Benzotropine) such as adding the following reference: Shields M. K., Bastiampillai T., Mohan T. Managing clozapine discontinuation - Acute and chronic maintenance strategies. Australian & New Zealand Journal of Psychiatry. 2012;46(11):1104-1105.

* it should be important to add also other treatment modalities such as ECT mentioned in a case series by Modak et al 2017.

*Line 103: state differential diagnoses and what neurological conditions.

*Line 112: I would directly modify the term" old study" for a "previous study".

*Line 119: "that is more" could be rephrased to Moreover.

*Line 130: spell correction : reports...

*Line 136: It is important how the authors point out the equivalence when switching to or from anti psychotics.

*Line 143: I would rephrase: " the pharmacological thinking.." for: clinicians should consider drugs pharmacodynamic properties when switching...

*Line 146: typo error: pharmacodynamics

* authors should expand briefly on why they included biperiden and not for example benzotropine? See comment above.

-Care checklist:

*Authors should add the latest version (eg. 2016) and cite "The CARE guidelines: consensus-based clinical case reporting guideline development"

**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.

Unable to assess

**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

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Please indicate the quality of language in the manuscript:

Needs some language corrections before being published

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