Author’s response to reviews

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

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Author’s response to reviews:

Dear Dr. Manchia, dear reviewers,

Thank you very much for the attention you have paid to our case report entitled “Cholinergic rebound syndrome following abrupt low-dose clozapine discontinuation in a patient with bipolar affective disorder. A case report” and for the insightful comments that you have made.

Please find below the specific answers to the reviewers. The corresponding changes in the text are highlighted in yellow.

Reviewer 1: Dr. Nicolas Nunez

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.

The diagnosis has been added (Title, line 2, page 1)

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."
The sentence has been rephrased. (Background, lines 18-19, page 1)

Case presentation:

Line 21: Please change phrase to: "A 66 year old male of Spanish origin.. It has been done. (Case Presentation, line 23, page 2)

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

Terminology has been applied throughout all the text as required.

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

“the” has been removed throughout the manuscript, when appropriated.

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).

The diagnosis has been specified. Patient was considered resistant which is now specified in the manuscript. (Case Presentation, line 23, line 29, page 2)

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?

Unfortunately we do not have more information. On admission, the patient wife was not aware of the reason, the patient was not able to answer the question when he gave consent and the private psychiatrist did not respond to our solicitation. The patient did not have lymphopenia and agranulocytosis on admission.

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).

The sentence has been rephrased and the Crohn condition added (Case Presentation, lines 24 and 26, page 2)

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).
The precision has been made. (Case Presentation, lines 102-103, page 5)

Keywords:

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

Keyword has been included (Keywords, lines 42-43, page 2)

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: et al 1996: Clozapine withdrawal effects and receptor profiles of typical and atypical neuroleptic.

The reference has been added (References, line 228, page 10)

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.)

The references has been added (References, line 224, page 10)

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

The sentence was restructured and expanded (Background, lines 72-74, page 4)

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

The sentence has been rephrased (Background, lines 80-81, page 4)

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.

There was a record that has been added (Case Presentation, lines 87-89, page 4)

Line 73: improve flow.

Efforts have been made to improve the 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 \(9.44 \times 10^9/L\)) and levels of CK (CK) (up to 5870 U/L).

The biochemistry results are now given in details with normal ranges when appropriated. (Case Presentation, lines 92-94, pages 4-5)

Line 81: "gazometry" typo error. switch for gasometry.

It has been corrected (Case Presentation, line 95, page 5)

Discussion and conclusions


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

Treatments have been briefly discussed and references added (Discussion and Conclusion, lines 185-189, page 8)

Line 103: state differential diagnoses and what neurological conditions.

Differential diagnoses have been stated (Discussion and Conclusion, line 120, page 6)

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

It has been done (line 130, page 6)

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

It has been done (line 137, page 6)

Line 130: spell correction: reports…

It has been done (line 159, page 7)

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…

It has been done (line 178, page 8)

Line 146: typo error: pharmacodynamics

Corrected (line 175, page 8)

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

It has been done in the discussion (lines 186-187, page 8)

Care checklist:

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

The 2016 version of the CARE checklist was added to the submission and The CARE guidelines were cited (line 205, page 9; References, line 283, page 11)

Reviewer 2: Dr Richard Musil

Abstract:

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

The timing of the withdrawal manifestations (“three days after”) is now added in the abstract (Abstract, line 20, page 1)

Background:

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

The muscarinic receptor subtypes blocked by clozapine are now specified (line 62, page 3)

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.

This is now stated and differences of anticholinergic activity are discussed. (lines 72-77, page 4)
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.

The information has been cleared out (Case presentation, line 87, page 4)

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. NA

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.

The timing or the recovering of the ability to speak is now stated as well as the evolution of the other symptoms. (Case Presentation, lines 112-116, page 5)

Discussion and Conclusion:

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

Clozapine reintroduction is now specified. (Discussion, line 125, page 6)

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

The correction has been done. (see above)

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.

This point is now discussed. (Discussion, lines 140-145, pages 6-7)

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…).

The manuscript has been revised by an English native speaker and the inconsistencies have been systematically checked.
Reviewer 3: Dr Nicholas Ara Mischel

This is a very interesting case of an unfortunate patient who seemed to develop clozapine withdrawal cholinergic plus neuromuscular signs consistent with catatonia. I have some questions that may help clarify the complex pharmacologic presentation.

Were clozapine blood levels determined in this patient before discontinuing clozapine? It would be very interesting to see if, in this particular patient, there were blood levels in excess of what one would expect with a dose of 50mg.

Clozapine blood level was unfortunately not determined on admission. This is now stated in the manuscript. (Case Presentation, lines 97-98, page 5)

Was the patient taking any other medication or nutritional supplement that would inhibit the metabolism of clozapine through cytochrome P450 inhibition?

Potential drug-drug interactions are now discussed, as well as the theoretical potential increase of clozapine blood concentration. (Discussion, lines 140-145, pages 6-7)

I appreciated how the authors separated the issue of withdrawal catatonia mediated by dopaminergic systems versus withdrawal symptoms mediated by cholinergic systems. The manuscript may benefit from some exploration of the interactions of these two systems. For example, a common treatment of acute dystonia from dopamine blockade is to give an anticholinergic medicine like diphenhydramine or benztropine.

The interaction between these two systems is a key issue supporting this case report considering clozapine unique anticholinergic properties compared to its dopamine blockade activity.

The discussion on dopamine blockade catatonia and withdrawal catatonia has been expanded and a referenced mention of the interaction between the dopamine and cholinergic systems and the way they are counterbalancing each other has been added (reference 21). (Discussion, lines 150-163, page 7)

In the case presentation I think it may help to separate presenting symptoms of rebound cholinergia versus catatonia rather than just stating that the patient presented as catatonic. It would help to specify which particular symptoms of catatonia were present using an objective scale such as the Bush-Francis or Fink-Taylor.

The symptoms has been separated and catatonic symptoms specified. (Case Presentation, lines 85-89, page 4)

There seems to be scant literature on this, but I wonder if it can be determined whether sudden anti-adrenergic withdrawal contributed to the significant hypertension and tachycardia seen in this case. In vitro, the binding affinity of clozapine to alpha adrenergic receptors seems to actually be a bit higher than the binding affinity to muscarinic receptors based on data from this database:
Anti-adrenergic withdrawal may have contributed to the observed hypertension and tachycardia, even though they are typical features of cholinergic rebound syndrome. As mentioned, the literature on clinical manifestations of anti-adrenergic withdrawal is scarce and the classical clinically relevant antipsychotic withdrawal syndromes are dopamine and cholinergic rebound (Correl. European Psychiatry 25 (2010) S12-S21). Besides a search on the suggested data base, restricted on human recombinant receptors, showed that clozapine affinity for muscarinic receptors was higher than for alpha 1-adrenergic receptor (see Richelson E and Shoulder T Life Sci. 2000 Nov 24;68(1):29-39, for example). Hence we allowed ourselves not to add this alpha 1 adrenergic withdrawal theory to this already rather complex discussion on receptors.

Finally, I think the authors are underemphasizing the role of risperidone overdose and full dopamine receptor blockade in the emergence of the neuromuscular symptoms of this case. In my experience and based on the database cited above the equivalent dose of risperidone to 50mg of clozapine is closer to 0.5-1mg rather than 2mg. I think it is very likely the reason why neuromuscular symptoms were evoked in this patient after discontinuation of only 50mg whereas other cases in the literature report withdrawal catatonia with neuromuscular signs only after discontinuation of much higher doses.

Our equivalence calculation came from the reference used in our institution (reference 24). We have implemented the proposed range of antipsychotic equivalence.

The role of risperidone overdose has been clearly discussed in the abstract as well as in the discussion and is definitely part of the differential diagnosis. We are not sure of what this comment is requiring to add.

The improvement in neuromuscular symptoms with biperiden argues against this but also consider the comment above related to the interaction between dopaminergic and cholinergic systems in treatment of neuroleptic-induced dystonias.

The timing of the improvement after biperiden administration pointed to a cholinergic supersensitivity even though in the case of dopamine blockade manifestation due to risperidone overdose, anticholinergic administration may also have helped. Beside the patient was not acutely dystonic but catatonic.