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 Editor-in-Chief, dear reviewers,

Many thanks for considering our case report for publication and for this second set of comments.

The required changes have been made and you will find below the point by point answers.

Kind regards

Response to Dr N. Nunez (Reviewer 1):

• « His » was switched to : « He was described catatoni and presented hypertension... »
  (Abstract/Case Presentation, lines 25-26, page 2)

Response to Dr Richard Musil (Reviewer 2):

• « His » was replaced (see the previous comment) (Abstract/Case Presentation, lines 25-26, page 2)
• « for the presentation » was changed to « at presentation » (Abstract/Case Presentation, lines 26-27, page 2)
• «less pronounced that the… » was changed to « less pronounced than the… » (Background, line 75, page 4)

• «γG) » was changed to « γGT » and its normal range was added (Case Presentation, line 96, page 5)

• « 24-EEG » was changed to « 24h-EEG » (Discussion and Conclusion, line 123, page 6)

Response to Dr Nicholas Ara Mischel, Ph.D. (Reviewer 3):

• The use of the descriptor or diagnosis of "catatonia" is not well-defined or used consistently throughout the report. If a reasonable assessment of a Bush-Francis score can be made retroactively by a psychiatrist who evaluated the patient in person, please state it was made retroactively. A bush-francis score cannot be done appropriately based on a clinical description alone. The score listed of 4 may be a typo, but if not then a 4 hardly qualifies as catatonic by most sources and the DSM-5. Please define the diagnosis or description of catatonia based on an objective score cut-off or a set of symptoms that is generally used in your practice to assess for the presence of this syndrome. I'll acknowledge that catatonia as a syndrome is not well-defined or discussed consistently among psychiatrists in general, but please give some brief description of how it is defined in your practice.

The patient was described to have catatonic features on admission, mutism, stupor, staring, immobility and rigidity and this set of symptoms, used as traditional descriptors of catatonia, suggested the syndrome. The Buchs-Francis score was established retroactively by the psychiatrist in charge of the patient on admission, as suggested in the first review of this paper. The score was 8 (4 was a typo). However, a formal diagnosis of catatonia, using an objective cut-off on a questionnaire was not made. The fact that the patient was « described as catatonic » is now clarified in the case-report (Abstract, Case report and Discussion sections, Lines 25, 86-87, 148).

• The fact that the patient improved with biperidin does not exclude the hypothesis that risperidone overdosing contributed significantly to this presentation. Good examples of this are cases of risperidone overdosing that improve dramatically with anti-cholinergic treatments, including biperiden.


Please note that these cases relate to the author's case not in the relative dose of risperidone involved or the clinical manifestations described, but rather to illustrate that symptoms of risperidone overdosing are treated by biperiden and medications similar to it. The discussion of a
possible effect of clozapine on GABA systems is not relevant given that this effect is not well-established and that benzodiazepines were not included in the treatment. Rather, please briefly discuss the relevant underlying physiology of the clinical manifestations of classic cholinergic rebound, produced plausibly by low-dose clozapine withdrawal in this case, compared to and contrasted with the clinical manifestations of risperidone overdosing, also a plausible contributor to some of the described symptoms. For example, the GI symptoms described can be attributed moreso to cholinergic rebound effects via the dense vagal/parasympathetic innervation of the GI tract whereas neuromuscular signs and autonomic instability can be features of either, plausibly in this case both, cholinergic rebound and acute dopamine receptor full blockade.

Since clinical manifestations of exaggerated dopamine blockade and cholinergic rebound are overlapping, (except the GI manifestations), the exact contribution of both phenomenon is undeterminable and remains subject to interpretation. Given the balance between these two pathways, anticholinergic drug administration to counteract the effect of dopamine blockade is well described, and does not allow to fully answer the question. The discussion was developed in that sense and the two suggested references were added. Our interpretation was that a cholinergic rebound was involved here (at least partly) and therefore was worth to report but we agree that there may be another interpretation putting emphasis on risperidone overdose (Discussion section, Lines 159, 164-167).

Since the discussion of clozapine withdrawal catatonia mechanism implicating the GABAergic system was deemed irrelevant, we removed it as required.