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: 1 Date: 26 Dec 2018

Reviewer: Nicholas Mischel

Reviewer’s report:

I appreciate how thoroughly the numerous comments were addressed. This case report provides a clear and concise narrative of an unfortunate case of psychopharmacology gone awry. Some minor points:

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 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.

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:

Acceptable

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