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Dr Xiu-Xia Song,

Vice Director,

Editorial Office

**Baishideng Publishing Group Inc**

Dear Dr Xiu-Xia Song

We would like to thank the reviewers for their comments on our manuscript entitled “**Pharmacological modulation of cholinergic system: Potential approach to treating cognitive deficits of schizophrenia**“ which is an approved invited Review. We will address the comments by the reviewer in a systematic fashion:

The section in which the cholinergic system is explained is too long. Too many details that are well known (or could easily be referred to) can be removed. Also, there is much information that is not relevant for this review. Similarly, the section on the RECEPTOR ALLOSTERISM is too detailed and too much basic information is given.

*We have taken these comments into account in shortening portions of our revised manuscript (see sections OVERVIEW OF THE CHOLINERGIC SYSTEM and RECEPTOR ALLOSTERISM).*

In the section where the authors describe the Neuropsychopharmacology of the cholinergic system the authors refer to studies in which cholinergic drugs were used. Most of these studies have been used to show that the cholinergic deficit is related to Alzheimer’s Disease.

*Whilst we appreciate this comment our Invited Review was to focus on schizophrenia but we feel the data on the use of muscarinic receptor antagonists in healthy subjects as well as heir effects on cognition and psychosis is a valid focus of our Review. However we have edited some of our revised manuscript to try an acknowledge the issue raised here (See section Neuropsychopharmacology).*

The authors should the at least should provide more experimental evidence (based on previous studies).

*Additional evidence has been supplied to support the role of cholinergic drugs producing cognitive deficits (see section Neuropsychopharmacology).*

There is an overlap between cognitive deficits in AD and schizo, but there are also some differences. The authors would at least need to make the case that the effects of cholinergic drugs are related moreto Schizo.

*Whilst there are overlap and differences in the cognitive deficits experienced by patients with Alzheimer’s disease and schizophrenia, we are arguing that improvement of cognitive impairment by targeting the muscarinic M1 receptor will be beneficial irrespective of diagnosis. The is evidenced by the small scale Xanomeline trial in treatment resistant schizophrenia patients demonstrating that cholinergic agonism improve s both positive and cognitive outcomes for these patients.*

Of note, a study with an M1 antagonist did not find a cognitive effect in a learning task that shows deficits in schizo patients (Int J Neuropsychopharmacol. 2012 Nov;15(10):1375-85). So, this would not be in favor of a specific involvement of the cholinergic system in Schizo.

*The experiment referred to used a single dose of Biperiden without first doing a dose response study; it is not clear if they conducted the testing during peak plasma concentrations; and the authors refer to several studies which report impairment of cognitive function after Biperiden (J Clin Psychopharmacol. 2000 Feb;20(1):77-83; Psychopharmacology 2005 Sept;181(3): 582-594). The authors consider the test used to relate to attention and whilst they did not find an effect of Biperiden, another report found deficits in a task related to both working memory and attention using a higher dose of Biperiden (J Clin Psychopharmacol. 2000 Feb;20(1):77-83).*

There have some recent reviews on the same topic. I am not convinced that this review adds further information to the existing literature: - Neurosci Biobehav Rev. 2015 Aug;55:393-402 - Handb Exp Pharmacol. 2012;(213):233-65 - Drug News Perspect. 2010 May;23(4):229-40 Other points:

*Any Reviewer can have an opinion as to the value of any Review however we were approached to provide a Review to the Journal and the title of the Review was submitted and approve by the Editorial Team. Therefore a decision as to whether a Review on the topic is of value should have been made before the Review topic had been made.*

Biperiden is considered to be a preferential M1 antagonist (section Neuroleptic drug treatment).

*Text updated to reflect M1 preference (see section Neuroleptic drug treatment)*

There are some papers that should be included in the review: Neuropharmacology. 2012 Mar;62(3):1544-53. Schizophr Bull. 2005 Jan;31(1):117-38.

*Thank you for bringing these reviews to our attention, we have added them in as appropriate (See INTRODUCTION).*

Typos: gulatmateric > glutamatergic spacial > spatial proof of principal > proof of Principle

*Typos amended (See sections Neuropsychopharmacology, The glutamate hypothesis, and Xanomeline: A proof of principale drug trial in schizophrenia).*

Our original manuscript has been revised to address the comments raised by the one out of three reviewers (*italics*) and therefore we hope that the version of the manuscript we now submit is suitable for publication in The World Journal of Pharmacology.

We look forward to hearing from you.

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Shaun Hopper Brian Dean

(On Behalf of the Authors)