



PEER-REVIEW REPORT

Name of journal: *World Journal of Psychiatry*

Manuscript NO: 89955

Title: Relationship between plasma risperidone concentrations and clinical features in chronic schizophrenic patients in China

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 02445242

Position: Editorial Board

Academic degree: MAMS, MBBS, MD

Professional title: Professor

Reviewer's Country/Territory: India

Author's Country/Territory: China

Manuscript submission date: 2023-11-21

Reviewer chosen by: Lin Zhang

Reviewer accepted review: 2024-01-16 16:30

Reviewer performed review: 2024-01-19 16:14

Review time: 2 Days and 23 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Novelty of this manuscript	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Good <input checked="" type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No novelty
Creativity or innovation of this manuscript	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Good <input checked="" type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No creativity or innovation



Scientific significance of the conclusion in this manuscript	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Good <input checked="" type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No scientific significance
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input checked="" type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous
	Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

ABSTRACT “The present study assessed physical situation, psychopathology and functionality of the patients and explored the associations and correlations between clinical variables and plasma levels.” 1. It is not clear what the term “physical situation” means. 2. In the Methods section of the main manuscript (Study Variables and Questionnaire), there is no mention of a scale to measure functioning (functionality) 3. On the other hand, severity of depression was rated on the PHQ-9. This is not mentioned here. “Significantly the men received higher doses of risperidone than the women, risperidon+9-hydroxyrisperidone (active moiety)/dose 、 risperidon+9-hydroxyrisperidone / (dose × kg) were higher in the women.” 4. Doses and plasma concentrations in men and women should be included. INTRODUCTION 5. The authors fail to mention a significant fact about the receptor binding profile of risperidone, which might have influenced their results. Risperidone has a high 5-HT2A/D2 ratio, which should protect against extrapyramidal symptoms. However, at higher doses, risperidone produces significant EPS, indicating that 5-HT2A antagonism alone cannot eliminate EPS associated with substantial D2 receptor blockade (Marder SR,



Meibach RC. Risperidone in the treatment of schizophrenia. The American Journal of Psychiatry. 1994;151(6):825-35). 6. Although therapeutic drug monitoring is recommended for all psychotropics, one wonders if it is practical to measure plasma risperidone and its metabolites in routine clinical practice. METHOD 7. The PHQ-9 might not be an appropriate instrument to rate the severity of depression in schizophrenia. 8. It is not clear why concentrations risperidone+9-hydroxyrisperidone in plasma had to be estimated. 9. Taking trihexyphenidyl is not a suitable proxy measure for the presence of EPS because it is often prescribed indiscriminately. The authors should have used a standard scale or at least an unstructured rating of EPS on examination. 10. Similarly, it is not clear why the authors chose to examine only EPS and constipation as side effects, when other side effects such as sedation, weight gain, and others are far more common. RESULTS 11. Some of the findings are not new or unusual. Men received higher doses but this could be a function of the predominance of men in a relatively small sample. 12. Women had significantly higher levels of risperidone and risperidon+9-hydroxyrisperidone, whereas men had non-significantly higher levels of 9-hydroxyrisperidone. I think apart from age, the sex difference is the only notable finding of this study. However, the other gender difference, that is a significant association between risperidone+9-hydroxyrisperidone levels and PANSS scores only in men has not been highlighted properly. 13. Similarly, the lack of association between EPS and risperidone levels has not been explained adequately. DISCUSSION “The characteristics of the sample are those which could be expected based on previous studies of groups of patients with resistant schizophrenia..” 14. This comes as a surprise because there is no mention of patients meeting criteria for treatment-resistant schizophrenia. 15. The authors must realize that their sample size is small and methodology not quite perfect. Therefore, conclusions such as “risperidone at therapeutically effective plasma concentration does not seem to predispose patients to



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QTc interval lengthening" may be quite misleading. 16. This study has serious methodological limitations, but these have hardly been mentioned. LANGUAGE 17. The text needs to be edited by a professional.



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Professional title: Professor

Reviewer’s Country/Territory: Mexico

Author’s Country/Territory: China

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Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Novelty of this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No novelty
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Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous
	Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

The manuscript by Xu et al. entitled "Relationship between plasma risperidone concentrations and clinical features in chronic schizophrenic patients in China" presents an interesting report showing that risperidone and 9-hydroxy risperidone have a significant effect in women and older patients and recommends considering this finding to adjust doses in patients to achieve a more substantial benefit from the therapeutic capabilities of risperidone. The manuscript is very well elaborated and presented; I only recommend abounding on the systemic effects that induce the consumption of this antipsychotic, for which I recommend the following review doi: 10.3389/fend.2020.00195