

2021/03/13

Subject: Revision and resubmission of manuscript 63408

Dear Professor Rajesh R Tampi,

Thank you for your letter and the opportunity to revise our paper. The suggestions offered by the reviewer have been immensely helpful, and we also appreciate your insightful comments on revising the abstract and other aspects of the paper.

I have included the reviewer comments immediately after this letter and responded to them individually, indicating exactly how we addressed each concern or problem and describing the changes we have made. The revisions have been approved by all authors. The changes are marked in red in the paper.

Most of the revisions prompted by the reviewers' comments are minor and require no further explanation than what appears in my responses below.

We hope the revised manuscript will better suit the *World Journal of Psychiatry*, and we thank you for your continued interest in our paper.

Sincerely,

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Reviewer Comments, Author Responses and Manuscript Changes

Comment 1: In Abstract, "Emerging evidence indicates the role of genetic polymorphisms associated with antipsychotic-induced AIWG and metabolic disturbances." You have already abbreviated AIWG, so shift antipsychotic-induced before metabolic disturbances.

Response: Thank you! We found your comment helpful and have revised accordingly.

Comment 2: "Although antipsychotic medications are essential for schizophrenia treatment, clinicians should monitor and manage the resulting weight gain and metabolic disturbances" should be "Antipsychotic medications are essential for schizophrenia treatment, hence clinicians should monitor and manage the resulting weight gain and metabolic disturbances".

Response: Thanks for your comment. We have revised accordingly.

Comment 3: In ANTIPSYCHOTIC DRUGS AND WEIGHT GAIN, "increased risk of overweightness and obesity" should be "increased risk of being overweight and with obesity".

Response: Thanks for your suggestion. We have revised accordingly.

Comment 4: Further on, "Low-potency FGAs", specify you refer to their D2 blocking ability.

Response: Thank you for your comment. We have added the following description about FGAs. "*FGAs act on the dopaminergic system by blocking the dopamine type 2 (D2) receptors.*"

Comment 5: In the next paragraph, "the incidence of weight gain is nonsignificant", change to "the incidence of weight gain is not significant".

Response: Thanks for your comment. We have revised accordingly.

Comment 6: In MECHANISM UNDERLYING WEIGHT GAIN AND METABOLIC DISTURBANCES DUE TO ANTIPSYCHOTIC DRUGS, Hormones, "Acylated ghrelin (AG) and desacylated ghrelin (DAG)" contains two abbreviations that may be confusing; DAG is commonly associated with diacylglycerol. I suggest that you change to AGh and DAGh and their ratio to AGh/DAGh.

Response: Thanks for your suggestion. The abbreviations for acylated ghrelin (AG) and desacylated ghrelin (DAG) are not commonly used. Therefore, we choose to use the full

name in the content. *“Acylated ghrelin and desacylated ghrelin are the two main forms of ghrelin play opposing roles in energy homeostasis. Lower acylated ghrelin/desacylated ghrelin ratios are associated with better metabolic profiles in patients with schizophrenia treated with olanzapine.”*

Comment 7: In this section, there is no mention of cholecystokinin (CCK); there is evidence of its implication in metabolic syndrome (Zwirnska-Korczala K, Konturek SJ, Sadowski M, Wylezol M, Kuka D, Sowa P, Adamczyk-Sowa M, Kukla M, Berdowska A, Rehfeld JF, Bielanski W, Brzozowski T. Basal and postprandial plasma levels of PYY, ghrelin, cholecystokinin, gastrin and insulin in women with moderate and morbid obesity and metabolic syndrome. *J Physiol Pharmacol.* 2007;58 Suppl 1:13-35; Mesgari-Abbasi M, Abbasalizad Farhangi M. Serum concentrations of cholecystokinin, peptide YY, ghrelin and high sensitive C-reactive protein in association with metabolic syndrome ingredients in obese individuals. *Acta Endocrinol (Buchar).* 2020;16(1):37-42. doi: 10.4183/aeb.2020.37).

Response: Thank you for this excellent suggestion. We have added a paragraph to discuss the potential role of cholecystokinin in obesity and metabolic syndrome.” *Cholecystokinin (CCK) plays an important role in induction of gallbladder contraction, stimulation of pancreatic secretion, regulation of gastrointestinal motility and induction of satiety. Studies found that CCK is related to obesity and metabolic syndrome in general population. Animal studies reported that olanzapine could counteract the satiating effect of CCK and clozapine could reduce hypothalamic mRNA of CCK-2 receptor. But human studies found that CCK level did not change significantly after olanzapine treatment. The role of CCK in the antipsychotic-induced metabolic disturbances warrants further investigations.”*

Comment 8: Same section, Neurotransmitters, "The support for α 1- and α 2- adrenergic receptors' involvement in the AIWG etiology" change to "The support for α 1- and α 2- adrenergic receptor involvement in the etiology of AIWG".

Response: Thanks for your suggestion. We have revised accordingly.

Comment 9: In Potential predictors, you conclude "Lan et al applied artificial intelligence to develop a neurofuzzy model with a 93% prediction rate for weight changes among patients with schizophrenia treated with antipsychotics; variables included physical factors (baseline weight, height, and waist and hip circumferences), lifestyle factors (smoking, dietary patterns, and exercise levels), genetic factors (ADRA1A, ADRB3, ADRA2A, HTR2A, and HTR2C), and psychopathology severity[84]." You should discuss what were their conclusions.

Response: Thanks for your comment. We have revised this sentence accordingly. *“Lan et al applied artificial intelligence to develop a neurofuzzy model, including physical factors (baseline weight, height, and waist and hip circumferences), lifestyle factors (smoking, dietary patterns, and exercise levels), genetic factors (ADRA1A, ADRB3, ADRA2A, 5-HTR_{2A}, and 5-HTR_{2C}), and psychopathology severity as predictor variables, with a 93% prediction rate for weight gains among patients with schizophrenia treated with antipsychotics”*

Comment 10: At the end of INTERVENTIONS, add that all interventions should be adequately monitored, as individual patients may respond unpredictably to any of these pharmacological and natural agents.

Response: Thanks for your suggestion. We have added the sentence.

Comment 11: REFERENCES. Add 11 to Misiak et al.

Response: Thanks for your comment. We have corrected it.