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# Olanzapine in Schizophrenia and Affective Disorders

In a recently published meta-analysis by Moteshafi et al.,[1] the authors concluded that "schizophrenia patients may be more vulnerable to olanzapine-induced weight gain". In addition, they stated that schizophrenia patients have a higher incidence of treatment-emergent parkinsonism.

These results are at odds with previous reports with other similar drugs and with clinical experience. This led us to carefully review the methodology of the meta-analysis, to avoid potentially misleading clinical conclusions. In the mentioned meta-analysis, even though mean daily doses of olanzapine were comparable between groups (14.2 mg/day vs 13.2 mg/day), differences in total drug exposure (mean daily dose × duration of treatment) were quite different. In the schizophrenia group, drug exposure was 2.29 (2.7 g vs 1.18 g) and 2.88 (3.83 g vs 1.33 g) times higher when considering the randomized controlled trials used for estimating weight change and parkinsonism incidence, respectively.

Moreover, the report indicates that the authors were aware that trial duration was different between groups; hence, they stratified analyses by treatment duration and found out that weight gain was no longer significant, but did not consider this in their conclusions.

Besides drug exposure which is highly relevant for a drug-tolerability analysis, a higher incidence of parkinsonism could be explained by a carry-over effect (i.e. schizophrenic patients included in trials are more likely than bipolar patients to have been previously exposed to other antipsychotics for a longer time).[2] In addition, the authors cite the Cavazzoni et al.[3] trial as having the same results as their own. However, Cavazzoni et al.[3] concluded that olanzapine therapy does not increase the risk of treatment-emergent extrapyramidal symptoms (EPS) for patients with bipolar disorder. Specifically, they found that bipolar patients had more EPS when exposed to haloperidol than patients suffering from schizophrenia, even after adjusting by drug exposure, and found no differences between groups when treated with olanzapine. They only found higher rates of treatment-emergent parkinsonism in schizophrenia patients when analysing the Simpson Angus Scale data in the haloperidol controlled database.

The authors make a good point in considering tolerability as an important issue when defining subgroups of patients to whom tailored treatment should be given; however, drug exposure is a crucial issue to consider when analysing drug-emergent adverse effects. This meta-analysis has, therefore, substantial limitations and, in our view, may lead to unwarranted conclusions.

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# The Authors' Reply

We thank Dr Undurraga et al.[1] for their comments, which actually are very similar to those expressed by Dr Baldessarini,[2] and we encourage them to read our previous reaction.[3] We think the two groups' comments are valuable. Generally, in both meta-analyses conducted by our group,[4,5] olanzapine seems to induce significantly more weight gain in schizophrenia patients compared with the bipolar disorder group, while with aripiprazole treatment, bipolar disorder patients gained weight and schizophrenia patients lost weight. Olanzapine treatment increased blood glucose, cholesterol and triglyceride levels more in schizophrenic patients compared with bipolar disorder patients. However, these changes were not significant between the two groups. By examining the lipid profile of five second-generation antipsychotics (SGAs) between schizophrenia and bipolar disorder patients, quetiapine treatment was associated with significant elevation in mean level of total blood cholesterol and low-density lipoprotein in the schizophrenia group compared with bipolar disorder patients. In quetiapine treatment, schizophrenia patients gained more weight and showed more changes in triglyceride levels; however, these differences were not significant. It is to some extent astonishing that the daily doses of these five SGAs did not differ between our diagnostic groups. This may be a consequence of fixed trial protocols used in phase III studies.

The results on extrapyramidal symptoms (EPS) defined that, in general, affective disorder patients tend to be more susceptible for movement disorders compared with schizophrenia patients with SGA treatment, except for olanzapine treatment.[5] On the one hand, previous studies have shown that patients with bipolar disorder are particularly sensitive to the development of EPS compared with the same treatment in the schizophrenia group.[6,7] On the other hand, the results of Cavazzoni et al.[8] showed that this increased vulnerability in the bipolar disorder group is just presented with first-generation antipsychotic treatment and not for olanzapine treatment, which agrees with the potential findings of our work in regard to olanzapine. Furthermore, based on the results of the review by Gao et al.[7] different tolerability in different psychiatric conditions is more likely due to the nature of illness of each individual psychiatric disorder. The exact reasons for different tolerability profiles for SGA treatments among various psychiatric conditions are unclear. A reduced risk of EPS, especially akathisia, is important and can be expected to improve acceptability of treatment for patients with mental disorders. All these results confirmed certain heterogeneity, and we agree with the letters that this lack of consistency might also be due to the difficulty to well recognize the crucial role of different measures of drug exposure.

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