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Comparing Tolerability of Olanzapine in Schizophrenia and Affective Disorders: A Meta-Analysis

This is to comment in response to a report on relative risks of adverse effects associated with olanzapine among patients diagnosed with schizophrenia vs bipolar disorder.[1]

Based on meta-analyses of a total of 33 reports involving 4547 patients treated with the second-generation antipsychotic drug olanzapine, the report found major differences in risks for several general medical and neurological measures, with consistently higher rates among schizophrenia patients. The report concludes that the differences are not accounted for by differences in the 'dose of olanzapine' and suggests that differences in vulnerabilities between the diagnostic groups may be involved.

This conclusion is intriguing and of potential interest. However, the drug exposures involved are far from matched. Whereas mg/day dosages were only 8% higher in schizophrenia subjects, the duration of exposure (weeks) was 2.2-times greater, and their product (gram-weeks) was 2.3-times greater: 2.48 (95% CI 1.77, 3.20) in schizophrenia patients vs 1.07 (95% CI 0.65, 1.50) in bipolar disorder patients. This highly significant difference could readily account for the observed differences in risk, particularly for weight-gain and metabolic effects that are especially likely to be exposure time-dependent.

Ross J. Baldessarini
Harvard Medical School, McLean Hospital,
Belmont, MA, USA

Reference

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The Authors' Reply

We thank Dr Baldessarini[1] for his comments on our results showing differences in risks for metabolic syndrome and neurological measures, with higher rates among schizophrenia patients compared with bipolar disorder. Our study[2] suggests that the effect of olanzapine dose is minimal and proposes that differences in vulnerabilities between the phenotype groups may be involved. Baldessarini[1] mentioned that the duration of exposure (2.2-times greater), and gram-weeks measures (2.3-times greater) in schizophrenia vs bipolar disorder patients may be responsible, particularly for weight gain and metabolic effects that are especially likely to be exposure time-dependent. This is possible, and, using stratification between short-term and longer-term studies, we failed to explain the treatment duration effect on these differences.

Recently, we also conducted another meta-analysis[3] with other antipsychotics (N = 14 319). By stratification based on treatment duration, the results of short-term studies (between 3 and 12 weeks) for quetiapine treatment remained the same as the main analysis. It means that increases in cholesterol and low-density lipoprotein levels stayed significantly higher for schizophrenia patients compared with bipolar disorder patients in short-term studies. In addition, among all the studies with olanzapine, only a few demonstrated a dose-dependent effect on weight gain.[4] Furthermore, as mentioned by Sengupta et al.,[5] olanzapine effect on lipid levels happens early in treatment: triglyceride levels increase even in the first 3 weeks for first-episode patients. A functional magnetic resonance imaging study found that olanzapine treatment in schizophrenia patients has not only an effect on lipid levels *per se* but also on appetite information processing, which has not been studied in affective disorders to date.[6] It seems that the olanzapine effects in neural network related to food information processing are visible in healthy subjects within 1 week.[7] In conclusion, the effects of olanzapine on metabolic side effects are not limited to the cumulative dosage or the time duration.

Emmanuel Stip and *Hoda Moteshafi*
University of Montreal, Montreal, QC, Canada

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