Adverse Events Related to Olanzapine

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Olanzapine, a serotonin-dopamine receptor antagonist, is one of the novel atypical antipsychotics that is effective against the positive and negative symptoms of schizophrenia with significantly fewer treatment-emergent extrapyramidal symptoms and less akathisia associated with traditional antipsychotics. Compared with traditional agents, olanzapine shows only a few adverse events such as dry mouth, sedation, and increase in appetite. Compared with risperidone, olanzapine causes greater increases in weight gain and body mass index but less hyperprolactinemia. Transient, non–dose-dependent, asymptomatic elevations in liver enzymes have also been noted in olanzapine-treated patients. Because of the comparative efficacy and improved side effect profiles of the atypical antipsychotics, consideration should be given to using the newer agents as preferred treatment for schizophrenia and related psychoses. *(J Clin Psychiatry 2000;61[suppl 8]:26–29)*

Olanzapine was approved for the treatment of schizophrenia in 1996. It has structural and pharmacologic properties similar to clozapine, the prototype atypical antipsychotic, and has been found to be effective in the treatment of both positive and negative symptoms in treatment-responsive schizophrenic patients. As with clozapine, the effectiveness of olanzapine is most likely linked to its combined serotonin-dopamine receptor antagonistic properties. Olanzapine treatment is associated with adverse events such as an increase in appetite, weight gain, hyperglycemia, the onset of diabetes, and dry mouth. Like with other atypical antipsychotics, fewer treatment-emergent extrapyramidal symptoms (EPS) occur with olanzapine than with traditional antipsychotics. The safety profile of olanzapine, based on the primary clinical trial safety database, is derived from data obtained from 4 clinical trials: the United States Clinical Trial (Study 1),[1] the North American Study (Study 2),[2] the Eastern Hemisphere Study (Study 3),[3] and the International Study (Study 4).[4] In view of the improved side effect profile of the newer atypical antipsychotics, clinicians are becoming more aware of the limitations of traditional antipsychotics, and consideration should be given to using the newer agents as preferred treatment for schizophrenia and related psychoses.

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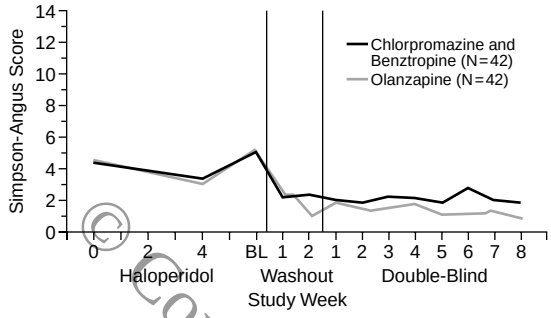
SAFETY IN CLINICAL TRIALS

In the large multicenter international olanzapine trial,[4] there were highly significant differences between olanzapine and haloperidol, especially in the area of treatment-emergent EPS. Data on EPS were gathered by spontaneous reporting and by scores on 2 EPS severity rating scales, the Simpson-Angus Rating Scale and the Barnes Akathisia Scale. Dystonia, parkinsonian symptoms, akathisia, and other residual events (i.e., movement disorder, myoclonus, and itching) were reported significantly less often in olanzapine- than in haloperidol-treated patients, and any extrapyramidal event was reported less often in olanzapine-treated patients (19.2%) than in haloperidol-treated patients (45.2%). This difference also reflected a greater need for anticholinergic medications in patients taking haloperidol. Additionally, the Abnormal Involuntary Movement Scale total scores indicated that significantly fewer olanzapine- than haloperidol-treated schizophrenic patients developed long-term treatment-emergent tardive dyskinesia.

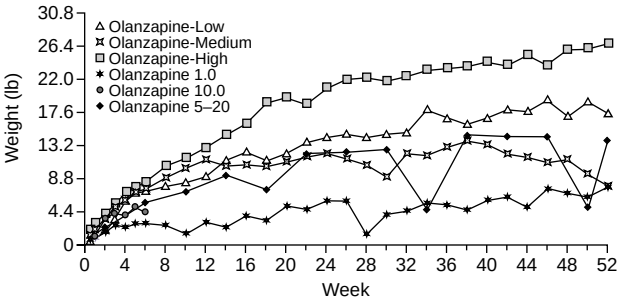
A recent fixed-dose study[5] compared efficacy and adverse events among 84 treatment-resistant schizophrenic patients treated with 25 mg/day of olanzapine versus 1200 mg/day of chlorpromazine plus 4 mg/day of benztropine. The purposefully high dose of olanzapine (25 mg/day) was used as a safeguard against negative findings that can result from inadequate dosage and also to examine possible olanzapine-induced motor side effects. Among the observed side effects, the chlorpromazine-treated patients exhibited significantly more dry mouth, orthostatic changes, unsteady gait, and EPS than the olanzapine-treated patients. Olanzapine and chlorpromazine showed similar efficacy, but the olanzapine-treated patients had fewer motor and cardiovascular side effects than the chlorpromazine-treated patients. EPS and akathisia were simi-

Figure 1. Simpson-Angus Rating Scale Scores[a] Among 84 Schizophrenic Patients Treated With Olanzapine or Chlorpromazine Plus Benztropine[b]



[a]Minus salivation.
[b]Data from reference 5.

Figure 2. Mean Change in Weight During Clinical Studies of Olanzapine[a]



[a]Reprinted from reference 9, with permission.

lar in the 2 groups, although no antiparkinsonian drugs were used in the olanzapine group. The findings on the Simpson-Angus Rating Scale (minus salivation) and the Barnes Akathisia Scale during lead-in, washout, and randomization pointed to a decrease in EPS and akathisia in both treatment groups (Figure 1). Because clinicians and their patients occasionally have differing perceptions of side effects,[6] the estimated prevalence of akathisia may vary depending on the form of assessment used. Akathisia is sometimes misinterpreted by clinicians as a side effect of atypical antipsychotics in patients who are feeling more active, alert, and awake from treatment with the newer antipsychotics. In the olanzapine/chlorpromazine study,[5] the Barnes Akathisia Scale, which rates both observed movements and the subjective experience of restlessness, showed a decrease in akathisia in both patient groups. In a meta-analysis[7] of EPS associated with the atypical drugs olanzapine, quetiapine, risperidone, and sertindole compared with traditional antipsychotics, all the newer antipsychotics were associated with less frequent use of antiparkinsonian medication than haloperidol.

WEIGHT GAIN

Weight gain is potentially the most significant side effect associated with some of the newer atypical antipsychotics because it is a life-altering complication of treatment that may have serious sequelae over time. Recent studies raise the question of whether clinicians should alert patients to the potential for early weight gain when antipsychotic treatment is started. Other questions to ponder are whether weight gain is simply associated with improvement of the patient's overall sense of well-being, whether underweight schizophrenic patients are just reestablishing their mean body weight, and what happens to the patient's weight over time. Allison et al.[8] recently estimated and compared the distribution of body mass index (BMI) values among individuals with and without schizophrenia in order to place the weight gain–inducing effects of antipsychotic drugs into context. The authors concluded that while a small subpopulation of schizophrenic individuals may be underweight, individuals with schizophrenia were generally as obese or more obese than individuals without schizophrenia.

In the overall expression of side effects in the 4 clinical trials of olanzapine,[1–4] only increased appetite and dry mouth were more common in olanzapine- than haloperidol-treated patients. Weight gain in the amount of 4.4 to 6.6 lb (2–3 kg) was seen in patients taking olanzapine in comparison with both placebo and haloperidol during the 6-week acute phases of the clinical trials, and the most significant weight increases occurred in patients who were the most underweight prior to beginning treatment with olanzapine (Figure 2).[9] Patients receiving 15 ± 2.5 mg/day of olanzapine experienced a mean 26-lb (11.8 kg) weight gain at the end of 1 year of treatment during the clinical trials.[9] Premarketing data[10] also showed that during long-term trials, 56% of olanzapine-treated patients reported a weight gain of greater than or equal to 7% of their body weight, the commonly accepted starting point for clinically significant weight-related problems.

Changes in weight between patients treated with risperidone and those treated with olanzapine have been assessed in several studies. Martinez et al.[11] conducted a retrospective review of 60 charts from an outpatient community mental health center of patients prescribed olanzapine or risperidone for at least 6 months with a compliance rate of 80%. On average, patients were treated with 18.6 mg/day of olanzapine and 5.5 mg/day of risperidone. The mean ± SD change in BMI values was 6.4% ± 11.4% for olanzapine-treated patients and 4.1% ± 10.0% for risperidone-treated patients. In a recent large (N = 377) 8-week comparison of olanzapine and risperidone,[12] olanzapine-treated patients had significantly greater increases in mean body weight and BMI than risperidone-treated patients. At week 8, the olanzapine-treated patients had gained a mean of 8.6 lb (3.9 kg) and had a mean increase in BMI

of 1.3 kg/m^2, as opposed to the risperidone-treated patients who gained a mean of 4.4 lb (2.0 kg) and had a mean increase in BMI of 0.7 kg/m^2. The greater mean increase in weight gain from baseline was seen in the olanzapine-treated patients from each BMI strata at study entry (low weight, normal weight, overweight). When weight gain between olanzapine and risperidone was compared in a group of patients with bipolar disorder,[13] the average increase at week 12 was 23.5 lb (10.7 kg) for the olanzapine-treated patients and 3.7 lb (1.7 kg) for the risperidone-treated patients. Ganguli[14] reported a retrospective study of weight gain in 100 patients with schizophrenia who were treated with risperidone or olanzapine for 4 months. At the end of the follow-up period, the olanzapine-treated patients had gained a mean of 5 lb (2.3 kg), while the risperidone-treated patients had lost about 2 lb (0.9 kg). A statistically significant increase in BMI was seen in the olanzapine group, but not the risperidone group.

A meta-analysis by Allison et al.[15] of mean change in body weight among patients taking traditional and atypical antipsychotics included data on weight change during antipsychotic treatment. Data showed a mean weight gain after 10 weeks of treatment of 9.8 lb (4.5 kg) with clozapine, 9.1 lb (4.2 kg) with olanzapine, 4.6 lb (2.1 kg) with risperidone, and 1.9 lb (0.9 kg) with ziprasidone. Wirshing et al.[16] conducted a retrospective analysis of 122 clinical records of 92 male schizophrenic patients that examined the relative weight gain liabilities of clozapine, risperidone, olanzapine, and sertindole compared with haloperidol. The authors concluded that clozapine and olanzapine caused the most weight gain, risperidone was intermediate, and sertindole had less associated weight gain than haloperidol. These findings generally strengthen the notion that antipsychotic-induced weight gain is an important concern for many individuals.

Diabetes and Hyperglycemia

Olanzapine has been linked to hyperglycemia,[17,18] the onset of diabetes,[19,20] and diabetic ketoacidosis.[19,21,22] Weight gain after the initiation of clozapine or olanzapine treatment may exacerbate subclinical diabetes or promote glucose metabolic abnormalities. Goldstein et al.[19] reported on 7 patients who developed new-onset diabetes between 5 weeks and 17 months after starting olanzapine treatment. Five of these patients required hospitalization to manage hyperglycemia, 3 had a definite family history of diabetes, and 4 continued to require medical treatment for diabetes.

Increased plasma triglyceride levels, which have been reported in patients treated with olanzapine, may precipitate or exacerbate diabetes.[23] Sheitman et al.[24] reported on 9 chronically institutionalized patients whose fasting plasma lipid levels and weight were measured before starting treatment with olanzapine. After 6 months of treatment with a mean dose of 19 mg/day of olanzapine, mean triglyceride levels increased from 170 to 240 mg/dL (normal range = 25–200 mg/dL). After 12 weeks of treatment with a mean ± SD dose of 13.8 ± 4.4 mg/day of olanzapine, fasting triglycerides increased a mean of 60 mg/dL (from 162 ± 121 mg/dL to 222 ± 135 mg/dL) in 25 inpatients.[25]

Since the medical consequences of overweight and obesity include both diabetes and cardiovascular disease,[26] weight, blood glucose levels, and triglyceride levels should be routinely monitored in patients treated with olanzapine, and particularly in those with other risk factors such as a family history of diabetes, preexisting obesity, smoking, or hypertension. For patients who develop large triglyceride elevations, it would seem advisable to consider the use of lipid-lowering agents. A change in antipsychotics may be necessary for patients who continue to experience weight gain, episodes of hyperglycemia, or very high triglyceride levels.

OTHER SIDE EFFECTS

Transient, non–dose-dependent, asymptomatic elevations in liver enzymes have also been noted in olanzapine-treated patients.[9] Patients included in the olanzapine clinical trials and the olanzapine/chlorpromazine trial[5] were stringently screened for abnormal liver function prior to starting medications. Thus, questions remain about the effect of olanzapine on hepatic function in patients with preexisting liver disease—a frequent finding among Asian patients—or in patients who have hepatic transaminase elevations secondary to comorbid substance abuse or hepatotoxic drugs.

CONCLUSION

Olanzapine, a serotonin-dopamine receptor antagonist, is one of the new atypical antipsychotics that is effective against the positive and negative symptoms of schizophrenia without causing the treatment-emergent EPS and akathisia often encountered with traditional antipsychotics. Since weight gain and new-onset diabetes are the most serious adverse effects of olanzapine, weight, blood glucose levels, and triglyceride levels should be routinely monitored in olanzapine-treated patients, particularly those with risk factors such as a family history of diabetes, preexisting obesity, smoking, and hypertension.

In view of the improved side effect profile of the newer atypical antipsychotics, clinicians are becoming more aware of the limitations of the traditional antipsychotics. Thus, consideration should be given to using the newer agents as preferred treatment for schizophrenia and related psychoses.

Drug names: benztropine (Cogentin and others), chlorpromazine (Thorazine and others), clozapine (Clozaril and others), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

Disclosure of off-label usage: The authors of this article have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents has been presented herein that is outside U.S. Food and Drug Administration–approved labeling.

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