

9. Discussion and Conclusions

The results of the analyses of databases of 78 controlled clinical trials suggest that the incidences and rates of development of hyperglycemia with olanzapine and other antipsychotics are comparable to those observed in the population not treated with antipsychotics. When hyperglycemia did develop in temporal association with olanzapine use, it generally emerged at less than 200 days of therapy in both clinical trials and spontaneous reports. This finding supports the utility of the pooled prospective studies with long-term extensions directly comparing olanzapine with placebo for ascertaining whether or not olanzapine is associated with any increased risk of development of diabetes, beyond risk factors present in the psychiatric population under study. No excess risk was observed with olanzapine. The incidence and rate of development of hyperglycemia were relatively high in both olanzapine and placebo-treated patients.

In addition, the spontaneous reports of hyperglycemia or diabetes with antipsychotic use represent only a small percentage of patients treated with these agents. The Clintrace search identified 431 case reports of possible hyperglycemia or diabetes with olanzapine treatment, of which 419 were determined to be actual cases of hyperglycemia. To date, approximately 4.5 million patients, predominantly patients with schizophrenia, have been treated with commercially-marketed olanzapine. There were 28 cases of positive dechallenge and 6 cases of negative dechallenge. Among these reports, there were few attempts to evaluate causality by rechallenge. Six rechallenges meeting the inclusion criteria for assessment were reported with 2 positives, 2 negatives, and 2 unknown responses.

If some causal association between olanzapine and hyperglycemia does exist, as possibly suggested (although not proven), by the 2 positive rechallenge cases, the incidence over and above the background incidence, is extremely low. The implication of substantial frequency reflected in reports of uncontrolled case series and retrospective chart analyses is driven by the background incidence of hyperglycemia that is not insignificant (suggested by historical literature and confirmed by experience with prospective placebo treatment) and selective attention to open-label data for atypical antipsychotics, now being used with increasing frequency in clinical practice.

The predisposing factors for the development of diabetes with olanzapine (all treatments in the clinical trial analysis) in both analyses were African American or Hispanic ethnicity, obesity at baseline, and weight gain during treatment. In the clinical trials, increase in obesity and increased age were also risk factors. In the spontaneous reports, male gender may have also conveyed increased risk. These predisposing risk factors are known risk factors for the development of diabetes in the both the schizophrenic and general populations.

The results of these analyses suggest that the incidence and rates of hyperglycemia with olanzapine (as well as clozapine, risperidone, and haloperidol) are comparable to those

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reported for the general schizophrenic population represented by patients treated with placebo in the clinical trials. In contrast to the implications of current case report literature, olanzapine does not appear to be associated with an increased risk of hyperglycemia. In summary, the results from this review of olanzapine data with respect to the development of hyperglycemia are sufficiently conveyed in the labeling change submitted to FDA on May 9, 2000 and no additional labeling changes are warranted at this time.

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