

# OLANZAPINE – SCREENING AND MONITORING FOR METABOLIC ADVERSE EVENTS

Recent actions by regulatory bodies as well as published opinion papers have heightened awareness of the elevated risk of metabolic disorders in patients with serious mental illness and have again called into question the role that therapy with atypical antipsychotics may play in metabolic adverse events occurring in this patient population.

Given the possibility of an increased background risk of diabetes mellitus in patients with psychiatric illness, as well as the unclear relationship between atypical antipsychotic use and hyperglycemia-related adverse events, good clinical practice suggests that patients with mental illness should be evaluated for the development of diabetes, just as the general population, based on known risk factors. A summary of monitoring and management guidelines/recommendations recently published are summarized below.

## AMERICAN DIABETES ASSOCIATION

In November 2003, the American Diabetes Association (ADA) in cooperation with the American Psychiatric Association (APA), the American Association of Clinical Endocrinologists (AACE), and the North American Association for the Study of Obesity (NAASO) held a three-day consensus development conference on atypical, or second generation antipsychotics (SGAs) and diabetes[1].

The position paper published summarizing the expert panel’s opinions included the following conclusions: (1) SGAs are more effective and better tolerated than first generation antipsychotics (FGAs), (2) most data supports an increased prevalence of diabetes and obesity in patients with psychiatric illness, and (3) the role that antipsychotic therapy may play in glucose intolerance versus the illness itself is unknown. The panel made suggestions on monitoring patients taking SGAs for the development of diabetes (Table 1).

**Table 1: ADA Monitoring Recommendations for Patients on SGAs**

	Baseline	4 weeks	8 weeks	12 weeks	Quarterly	Annually	Every 5 years
Personal/Family History	X					X	
Weight (BMI)	X	X	X	X	X		
Waist Circumference	X					X	
Blood Pressure	X			X		X	
Fasting Plasma Glucose	X			X		X	
Fasting Lipid Profile	X			X			X

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The panel did not differentiate among available SGAs with respect to monitoring guidelines; however they did draw conclusions about differential risk among patients treated with these agents. The panel concluded that clozapine and olanzapine are associated with the greatest risk of diabetes, followed by quetiapine and risperidone, and lastly ziprasidone and aripiprazole being associated with little or no diabetes risk, although the panel acknowledged that these latter two agents have not been used as extensively as the other atypical antipsychotic agents.

It should be noted that the panel's conclusion of a differential diabetes risk among SGAs is in contrast to the results of several published large epidemiological trials. In a study of over 38,000 Veterans Administration (VA) patients, Sernyak and colleagues found that quetiapine, as well as olanzapine and clozapine, were associated with increased diabetes risk compared to FGA[2]. While diabetes risk in the risperidone group was not significantly different compared with the FGA group, confidence intervals around diabetes risk for individual SGAs overlapped. Among younger age groups, risperidone was associated with significantly increased diabetes risk compared with FGA. Similar results were found by Cunningham and colleagues in a second large VA study[3]. These authors found an increased risk for diabetes among patients treated with olanzapine, quetiapine, or risperidone compared with FGAs; however, the smaller quetiapine cohort did not achieve statistical significance. Lastly, in an analysis of over 50,000 patients taking either FGA or SGA, Buse and colleagues found that risperidone, but not olanzapine, had a significantly higher risk of diabetes compared with haloperidol[4].

While the panel recognized the limited data available for aripiprazole and ziprasidone, it nonetheless concluded that these agents have little or no diabetes risk. Although, large clinical trials sponsored by Pfizer, Bristol-Myers Squibb, and Eli Lilly and Company, found no significant differences in treatment-emergent hyperglycemia/diabetes between patients treated with olanzapine compared to aripiprazol[5], nor between patients treated with olanzapine versus ziprasidone[6, 7].

#### **FOOD AND DRUG ADMINISTRATION**

On the basis of an extensive review of data available for patients treated with atypical antipsychotics over a number of years, the FDA concluded: "epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with atypical antipsychotics"[8]. This resulted in the FDA requesting class-labeling for all atypical antipsychotics to include a warning about hyperglycemia-related adverse events. The FDA recognizes that the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. Since patients with schizophrenia may be at increased risk for developing diabetes, the FDA concluded that increased attention to the signs and symptoms of diabetes in all patients may lead to earlier detection and treatment, thus reducing the risk of serious outcomes.

Monitoring recommendations suggested by the FDA include the following:

- Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control.

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- Patients with risk factors for diabetes mellitus (e.g. obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment.
- Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness; and patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing.

## **OTHER CONSENSUS/OPINION RECOMMENDATIONS**

There have been several other opinion papers published in recent years by multi-disciplinary experts providing recommendations on monitoring for metabolic changes temporally associated with antipsychotics[9-14]. Most are similar to what has been suggested by the ADA. Common recommendations among all published guidelines include the following: (1) monitoring all patients, regardless of antipsychotic treatment, (2) baseline screening of patients' weight, fasting blood glucose and diabetes risk factors, and (3) follow-up every 3 to 12 months depending on the presence of risk factors.

### *Risk Factors*

Several factors have been associated with increasing the risk of diabetes including a family history, age  $\geq 45$  years, ethnicity (increased risk for non-Caucasians), and a previous history of glucose intolerance[15]. Other variable factors have included dyslipidemia, lack of exercise, hypertension, and obesity[16, 17]. Additionally, several consensus/opinion papers have recommended that the disease state of schizophrenia be included as a recognized risk factor for diabetes [9, 10, 12, 13].

In an analysis of the olanzapine integrated clinical trial database of over 5000 patients with schizophrenia, pre-treatment glucose levels and total number of diabetes risk factors were found to be significant predictors of subsequent treatment-emergent diabetes. Treatment-emergent weight gain, nor antipsychotic treatment assignment did not predict treatment-emergent diabetes in this trial[18].

## **MANAGEMENT RECOMMENDATIONS**

Common management recommendations include: referring high-risk patients, encouraging weight loss, exercise and smoking cessation where appropriate, and discontinuing or changing antipsychotic therapy, when appropriate.

## **CONCLUSIONS**

The increasing prevalence of diabetes mellitus in the general population worldwide is a significant public health issue. Most data available to date suggests patients with psychiatric illness may have an increased background risk of diabetes mellitus above and beyond the population at large. The potential relationship between atypical antipsychotic use and hyperglycemia-related adverse events continues to be unclear. Taking all available data into consideration, the possibility of differential rates of treatment-emergent diabetes among atypical antipsychotics is not supported.

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All treatment choices and their potential risks should be considered when a treatment decision is made. Good clinical practice suggests that patients with mental illness should be evaluated for the development of diabetes, just as the general population, based on known risk factors, regardless of therapy chosen.

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