Adverse Effects of Atypical Antipsychotics

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Atypical antipsychotics have the potential to cause weight gain and derangement of glucose metabolism. These side effects can lead to obesity, diabetes mellitus, and dyslipidemia and should be considered in the management of the behavioral and psychological symptoms of dementia.
(J Clin Psychiatry 2001;62[suppl 21]:7–10)

A number of new atypical antipsychotics have emerged over the past decade. While these all appear to have good efficacy in psychotic disorders, each has a different side effect profile.[1–3] Tardive dyskinesia is one of the major problems with the conventional neuroleptics, such as thioridazine and fluphenazine. In contrast, most of the atypical antipsychotics are associated with a much lower incidence of tardive dyskinesia, but they may have other adverse properties. In particular, some of the novel antipsychotics have a tendency to cause weight gain and its usual sequelae, such as glucose intolerance and dyslipidemia.

This review presents data on the relative impact of the new compounds on changes in weight, glucose tolerance, and lipid profile. It also outlines my clinical approach to tracking and ameliorating these worrying risk factors. It is likely and reasonable that the prescribing physician will be responsible for the management of the "somatic fallout" of his or her antipsychotic regimen. We will all have to be as vigilant and responsive to this toxic domain as we have been to tardive dyskinesia in the past. Weight gain, diabetes mellitus, and dyslipidemia may come to assume the importance of tardive dyskinesia when choosing pharmacotherapy for the behavioral and psychological symptoms of dementia.

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Presented at the symposium "Restoring Harmony—Adding Life to Years," which was held June 16–17, 2000, in Seville, Spain, and supported by an unrestricted educational grant by Janssen Cilag and Organon.

Financial disclosure: Dr. Wirshing is a consultant for Janssen; has received grant/research support from Janssen, Pfizer, Lilly, Bristol-Myers, Zeneca, and Novartis; has received honoraria from Janssen, Pfizer, and Organon; and is a member of the speaker/advisory boards of Janssen and Pfizer.

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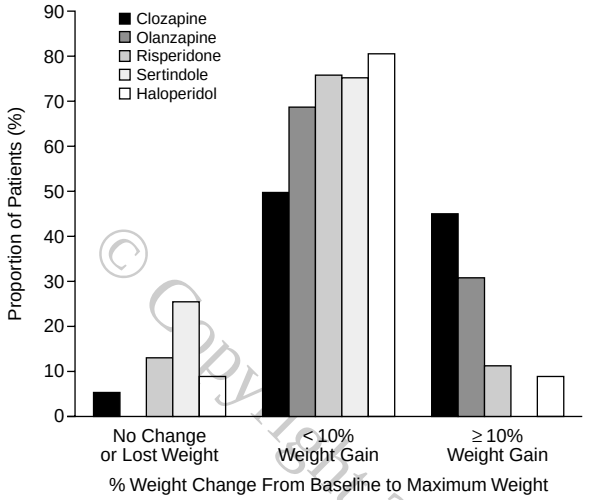
WEIGHT GAIN

Weight gain in developed countries such as the United States can be described as an epidemic. In 1995, for example, America spent over $50 billion on health care related to obesity.[4] A large proportion of this expenditure was on diabetes mellitus and its associated complications. Coronary artery disease, hypertension, gallbladder disease, osteoarthritis, and some forms of cancer are other notable sequelae of obesity.[5] Given the increase in morbidity and mortality associated with weight gain, it is important that medication does not increase this risk. Weight gain is a known problem with the conventional neuroleptics, but it has become more of a focus with the newer antipsychotic agents because of their otherwise relatively benign side effect profiles.

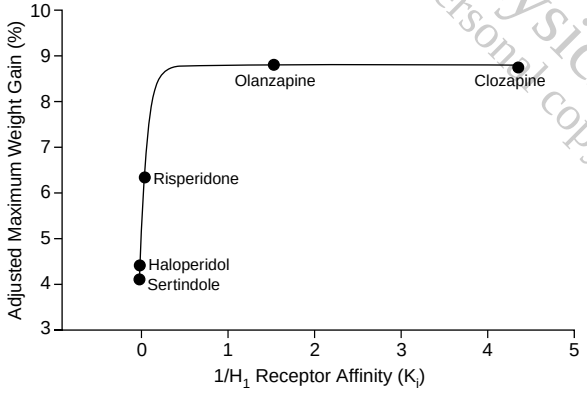
We recently reported data from our laboratory on the relative weight gain liabilities of the atypical antipsychotics.[6] The results can be seen in Figure 1. It was notable that all the patients who were receiving olanzapine gained weight. Furthermore, patients treated with clozapine or olanzapine appeared to gain weight for a longer period. The underlying mechanism was initially thought to be serotonergic. The data, however, did not support this. Instead, what emerged was a correlation between weight gain and relative histaminergic receptor affinity. Clozapine has the most histaminergic activity, followed by olanzapine; risperidone has relatively little in comparison (Figure 2). Quetiapine, however, has a lower H_1 receptor affinity than risperidone but appears to be associated with a higher incidence of weight gain. Similarly, the conventional neuroleptics associated with weight gain (e.g., thioridazine and chlorpromazine) have significant histamine receptor affinity. It is likely, however, that a single-receptor explanation of weight gain is too simplistic—other receptor systems are likely to be involved, including serotonin ($5\text{-}HT_{2C}$) receptors.[7–9] The U.S. Food and Drug Administration (FDA) regards a weight gain of more than 7% as an adverse event. Figure 3 shows the relative pro-

Figure 1. Relative Weight Gain Liabilities of Atypical Antipsychotic Drugs[a]



[a]Reproduced from Wirshing et al.,[6] with permission.

Figure 2. Weight Gain as a Function of Histaminergic H_1 Affinity[a]

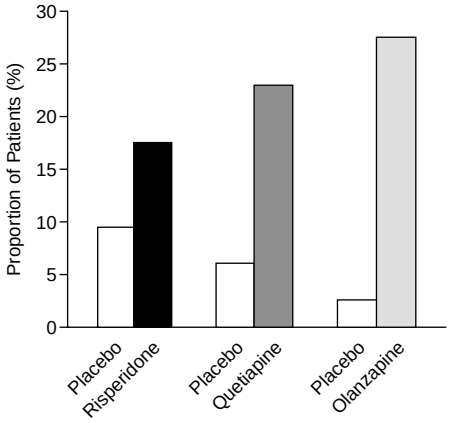


[a]Reproduced from Wirshing et al.,[6] with permission. $y = 4.7(1 - e^{-12.5x}) + 4.1$, where y = adjusted maximum weight gain (%) and x = $1/H_1$ receptor affinity (K_i).

portions of patients receiving risperidone, quetiapine, or olanzapine who gained more than 7% in weight.[10–12] It should be noted, however, that weight gain, and indeed other metabolic effects associated with atypical antipsychotics, may be less severe in elderly patients compared with nongeriatric patients.

As mentioned previously, weight gain is often associated with the development of type 2 diabetes mellitus, particularly if patients are already overweight.[13] At present, however, it is unclear whether weight gain among patients receiving atypical antipsychotic therapy is directly responsible for the increased risk of type 2 diabetes mellitus observed within this population. In a study of 82 patients with schizophrenia who were prescribed clozapine, 36.6% were

Figure 3. Relative Proportions of Patients Receiving Risperidone, Quetiapine, or Olanzapine Who Gained More Than 7% in Weight[a]



[a]Data from package inserts.[10–12]

diagnosed with diabetes mellitus during 5 years of follow-up.[14] Weight gain was significant for the first 4 years of therapy, but was not identified as a significant risk factor for the development of diabetes mellitus. Popli et al.[15] reached the same conclusion after assessing 4 patients who experienced new-onset or severe exacerbation of diabetes mellitus while receiving clozapine. As I will discuss later, new-onset diabetes mellitus can present with or without concurrent weight gain.

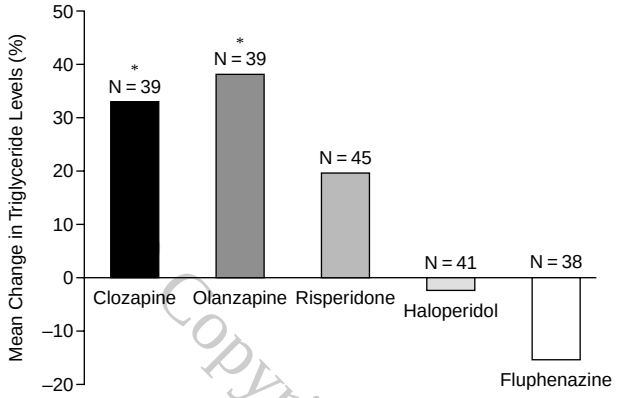
LIPID PROFILE

One consequence of weight gain is an increase in triglycerides. This is an important understanding because an elevated level of triglycerides leads to increased risk of coronary artery disease, cerebrovascular accident, and other serious sequelae. My colleagues and I (D.A.W.; J. A. Boyd, Pharm.D.; L. R. Meng, Pharm.D., et al., unpublished data, 2001) examined patients before and after they were treated with various antipsychotic agents. We found that patients treated with clozapine and olanzapine had significantly ($p < .05$) increased levels of triglycerides compared to patients treated with risperidone and the conventional neuroleptics that were tested (Figure 4). Our results were confirmed by a recent retrospective analysis comparing the metabolic effects of olanzapine with those of risperidone.[16] Again, after 1 year of therapy, olanzapine was associated with significantly greater increases in fasting triglyceride ($p = .042$) and cholesterol ($p = .029$) levels than risperidone.

DIABETES MELLITUS

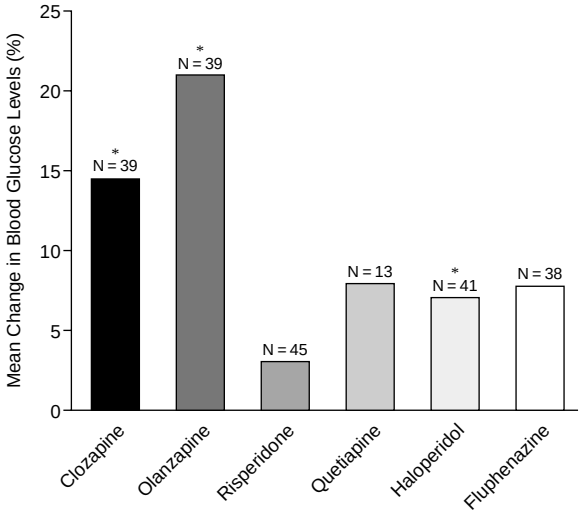
A further side effect that has emerged as being associated with certain of the atypical antipsychotics, notably

Figure 4. Change in Triglyceride Levels Following Treatment With an Antipsychotic Drug[a]



[a]Data are unpublished (D.A.W.; J. A. Boyd, Pharm.D.; L. R. Meng, Pharm.D., et al., 2001).
*p < .05.

Figure 5. Change in Blood Glucose Levels Following Treatment With an Antipsychotic Drug[a]



[a]Data are unpublished (D.A.W.; J. A. Boyd, Pharm.D.; L. R. Meng, Pharm.D., et al., 2001).
*p < .05.

clozapine and olanzapine, is new-onset diabetes mellitus.[3] The FDA has received over 140 reports of new-onset diabetes mellitus in patients receiving clozapine.[17] Of these, about 36 cases were new-onset diabetic ketoacidosis, a very serious and potentially fatal side effect.[17] Since November 1998, 19 cases of olanzapine-associated diabetes mellitus have been published[18–24] and 2 cases have been linked with quetiapine use.[25,26] There have been 3 published cases of risperidone-associated new-onset diabetes mellitus.[27,28] Recently presented data confirm that risperidone is associated with a low risk of developing diabetes mellitus. According to Mahmoud et al.,[29] the odds of a risperidone-treated patient presenting with type II diabetes mellitus during the first 12 months of treatment are 0.79 ± 2.39, a risk not significantly different from that of healthy controls. In contrast, other antipsychotics were associated with a significantly greater risk of diabetes mellitus, e.g., olanzapine 2.44 ± 2.10 and clozapine 6.72 ± 4.71 ($p < .05$ vs. control). After a retrospective analysis of 33,945 patients, Caro et al.[30] also associated olanzapine with a higher risk of diabetes mellitus than risperidone, particularly in women. Furthermore, in a small study of 126 patients, Wilson et al.[31] observed that new-onset diabetes mellitus was associated with clozapine, olanzapine, or quetiapine therapy. Patients receiving clozapine or olanzapine should be monitored closely, as diabetic ketoacidosis may be difficult to differentiate from the underlying psychiatric disease.

My colleagues and I measured the blood glucose levels of patients before and after they were treated with various antipsychotics (D.A.W.; J. A. Boyd, Pharm.D.; L. R. Meng, Pharm.D., et al., unpublished data, 2001). A statistically significant ($p < .05$) increase in levels of blood glucose was observed in those patients treated with olanzapine, clozapine, and haloperidol. Risperidone and fluphenazine, however, did not produce a significant change in blood glucose levels (Figure 5). Meyer[16] also observed greater elevation of blood glucose levels among patients receiving olanzapine when compared with risperidone-treated patients ($p = .03$).

In 1998, we added 6 new cases of diabetes mellitus associated with either clozapine or olanzapine to the literature, which at that time consisted of 9 cases of clozapine-associated diabetes.[3] Of the reports published up to 1998, the majority of patients were of African-American ethnicity, suggesting nutritional factors and perhaps impaired access to health care.[15] This demographic characteristic has not held true among the cases reported since our 1998 publication. For example, there has recently been a preponderance of white patients who have developed diabetes while receiving olanzapine.[18–24] In most cases, the onset of diabetes occurred within 6 months of new-treatment initiation.[18–24] Most patients developing diabetes were male, indicating a potential hormonal effect on glucose metabolism,[32] and most were obese. Puzzlingly, some of the patients were not obese. It may be that drugs such as clozapine and its chemical analogues, olanzapine and quetiapine, have a direct toxic effect on the pancreas, and some data support this hypothesis.[3,33,34] The mechanism for this potential effect has still to be elucidated, but it is likely to involve the serotonergic system for several reasons[35–37]: antagonism of 5-HT_{1A} sites can cause decreases in insulin output by reducing pancreatic β-cell responsiveness, agonism of $5\text{-HT}_{2A/C}$ receptors can cause hyperglycemia, and simultaneous blockade of 5-HT_{1A} and $5\text{-HT}_{2A/C}$ receptors has unpredictable effects.

The issue of diabetes mellitus has potentially serious implications for older patients, in whom type II diabetes

mellitus is already more common. For example, derangement of glucose homeostasis may lead to an alteration in mental status. As data relating to antipsychotic-induced diabetes mellitus in the elderly are scarce, it is reasonable to recommend that those patients receiving clozapine, olanzapine, and, possibly, quetiapine, should be monitored regularly for changes in levels of blood glucose and hemoglobin Hb A_{1c}.

All patients should also be monitored for changes in weight, as a 5% increase in weight is associated with a doubling of risk for development of glucose intolerance. Physicians should therefore routinely ask patients if they are having symptoms of diabetes such as increased thirst or frequent urination. Furthermore, patients should also be asked if they have noted any change in pant or belt sizes.

CONCLUSION

Weight gain and derangements in glucose metabolism and triglyceride levels are important side effects of some of the atypical antipsychotics and of the conventional neuroleptics. I recommend that patients receiving atypical antipsychotic medications should therefore be monitored for changes in weight, glucose metabolism, and lipid profiles every 3 months.

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

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