Dyslipidemia and Atypical Antipsychotic Drugs

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Dyslipidemia is an increasing problem in most industrialized societies and is a risk factor for coronary heart disease (CHD). Imbalances in individual lipid components, including total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and serum triglycerides, have each been shown to contribute to this increased risk. Certain psychiatric patient populations, such as those afflicted with schizophrenia, are of particular concern. Psychiatric patients with schizophrenia are naturally at increased risk for dyslipidemia and obesity, in part due to poor diet and sedentary lifestyle, but these conditions can be exacerbated by some antipsychotic medications. Clozapine and olanzapine, for example, appear to be associated with hyperlipidemia, which may be associated with changes in body weight. Other, newer antipsychotic agents may exhibit less liability for weight gain and the development of dyslipidemia. This review is intended to briefly highlight the association between dyslipidemia and cardiovascular disease, the changes in serum lipids associated with some antipsychotic agents, and how these changes in serum lipids affect the monitoring of schizophrenia patients.
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In the past decade, the increased use of atypical antipsychotic drugs has provided a clear benefit for many patients with schizophrenia and similar disorders. The main advantage of atypical compared with conventional antipsychotics is their reduced association with the extrapyramidal side effects of akathisia, dystonia, parkinsonism, and tardive dyskinesia.

Although atypical antipsychotics are on the whole much better tolerated than conventional antipsychotics, some are now being associated with weight gain, increased risk of type 2 diabetes, and dyslipidemia, including increased levels of total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides. Weight gain can be an undesirable side effect, especially in patients who already have a higher than normal body mass index (BMI). Increased risk of diabetes is an obvious problem that can lead to significantly increased medical morbidity, decreased quality of life, and significant additional health care costs. The problems associated with dyslipidemia can result in cardiovascular disease (CVD), leading to significant long-term morbidity and mortality. Indeed, the consequences of dyslipidemias are likely to have a far more substantial public and individual health impact than diabetes, because the prevalence of dyslipidemia is much higher than disorders of glucose metabolism. This is particularly true for patients with psychotic diagnoses, as this group has significantly higher rates of death from cardiovascular and other medical diseases.[1]

There is some disagreement as to whether the metabolic adverse effects of atypical antipsychotics are a class pharmacologic effect or are linked more closely to individual drugs. This article will address this important question of differential drug risk by reviewing the evidence that is associated with each atypical antipsychotic for increased risk of hyperlipidemia or dyslipidemia.

CHOLESTEROL AND TRIGLYCERIDES AS RISK FACTORS FOR CARDIOVASCULAR DISEASE

Cardiovascular disease is truly a pandemic, with over 50 million deaths reported globally in a 1997 report.[2] Although some countries have witnessed recent declines in mortality due to CVD, other countries report that more than 50% of deaths in those older than 65 years are caused by CVD.[2]

Metabolic syndrome is a clustering of several metabolic risk factors for coronary heart disease (CHD), which includes insulin resistance, atherogenic dyslipidemia, abdominal obesity, and hypertension,[3–5] and was defined in part to emphasize that there are other risk factors for CVD than cholesterol dysregulation, as demonstrated by the Framingham Heart Study.[6]

The risk of CHD associated with LDL-cholesterol levels is very well established and is not covered again here in detail.[4,5,7–9] The Adult Treatment Panel III of the National Cholesterol Education Program[5] identifies specific fasting concentrations of LDL-cholesterol as optimal (< 100 mg/dL) and identifies LDL-cholesterol treatment goals based on risk factors, including whether a patient smokes cigarettes; has hypertension, low high-density lipoprotein (HDL) cholesterol, or a family history of coronary heart disease; and is of a certain age (≥ 45 years for men; ≥ 55 years for women). Based on recent clinical trial data,[10] further recommendations were recently described, among the more notable being that, in patients with the highest risks, an LDL-cholesterol goal of < 70 mg/dL is a reasonable clinical strategy, an option extending to patients at very high risk who have a baseline LDL-cholesterol level of < 100 mg/dL.

High HDL-cholesterol has been shown to be associated with reduced risk for CVD.[5] Several studies have demonstrated an inverse relationship between HDL-cholesterol levels and CHD.[9,11] Low HDL-cholesterol (< 40 mg/dL for men and < 50 mg/dL for women) has also been found to be a risk factor for CHD even if normal total cholesterol levels are found.[12]

Hypertriglyceridemia is also an independent risk factor for CHD.[7,13] This has been demonstrated in the Copenhagen Male Study[13] using fasting triglyceride levels and in the Physicians' Health Study[7,13] using nonfasting triglyceride levels. Even in patients treated with a statin, triglycerides remain a predictor of CHD risk.[8] Furthermore, elevated triglyceride levels appear to precipitate or exacerbate diabetes.[4] The exact mechanism through which triglycerides contribute to CHD is still under investigation, but changes in the number of small, triglyceride-rich lipoprotein particles are associated with angiographically confirmed coronary artery disease in some patients independent of LDL-cholesterol or HDL-cholesterol.[14]

Primary prevention of CHD is important as most myocardial infarctions occur as a result of coronary lesions that were previously not flow limiting.[15] In the United States for 2003, it has been estimated there will be 515,000 deaths due to CHD, of which 192,898 will be due to myocardial infarction.[16]

ASSOCIATION OF SECOND-GENERATION ATYPICAL ANTIPSYCHOTIC DRUGS AND DYSLIPIDEMIA

Many drugs affect serum lipid levels in a potentially harmful way and may increase the risk of cardiovascular disease. Diuretics, β-blocking agents, progestogens, some oral contraceptives, danazol, immunosuppressive agents, protease inhibitors, and enzyme-inducing anticonvulsants adversely affect the lipid profile. They can increase total cholesterol, LDL-cholesterol, and triglycerides and decrease HDL-cholesterol.[17] Many psychiatric drugs, including some mood stabilizers and tricyclic antidepressants, are associated with weight gain, which can contribute to or exacerbate dyslipidemia.[18] One notable exception is the observation of the cholesterol-lowering effect of the mood stabilizer divalproex sodium.[19,20] Serotonin reuptake inhibitors may induce weight loss during the first few weeks of treatment, but may be associated with weight gain during long-term treatment. Some of the second-generation antipsychotics are particularly notable for their association with both weight gain and dyslipidemia.

Clozapine

An analysis of medical and pharmacy data from the Iowa Medicaid program[21] compared the risk of hyperlipidemia in schizophrenia patients treated with clozapine and those receiving typical antipsychotics. Overall cumulative incidence rates for hyperlipidemia did not differ significantly between the groups, with 5.0% (26/518) of clozapine recipients developing hyperlipidemia compared with 3.9% (93/2373) of patients treated with typical antipsychotics.[21] However, when patients were stratified according to age, incidence rates for hyperlipidemia were significantly greater among patients 20–34 years old treated with clozapine therapy compared with typical agents (4.6% vs. 2.0%, relative risk = 2.4, 95% CI = 1.1 to 5.2).[21]

The effects of long-term clozapine treatment in 50 patients with schizophrenia or schizoaffective disorder were examined in a 12-month follow-up study of open-label clozapine therapy after a 10-week, double-blind study.[22] During clozapine treatment, mean serum triglyceride levels increased significantly (+41.8%, +54.7 mg/dL, p = .001), with 19 patients having elevated triglyceride levels at the end of study compared with 7 patients at baseline.[22] The change in triglyceride level was significantly associated with an increase in body weight (mean = +5.5 kg [12.1 lb]) seen during clozapine therapy (r = 0.43, p = .005).[22] Mean total cholesterol levels also increased significantly from baseline (+7.5%, +14.4 mg/dL, p < .001) and by the end of the study.[22]

Lipid levels were also examined in a prospective 14-week study[23] involving 157 inpatients with either schizophrenia or schizoaffective disorder randomized to treatment with clozapine, olanzapine, risperidone, or haloperidol. Patients receiving clozapine treatment showed a significant increase in mean cholesterol level from baseline during the initial 8 weeks of the study (14.7 mg/dL, p < .02); although the increase in cholesterol for the entire 14-week study period was similar, it was not statistically significant (16.3 mg/dL). Clozapine-treated patients also showed significant weight gain over the study period (mean = 4.8 kg [10.6 lb], p < .0003), and there was a significant correlation (r = 0.5, p = .0008) between weight gain and increased cholesterol, even after adjustment for initial cholesterol levels and baseline weight.[23]

An analysis of 39 clozapine-treated patients[24] showed significant increases from baseline in mean triglyceride levels (34%, p = .01), which were significantly higher than those for patients receiving haloperidol treatment (p = .008).

Several retrospective reviews[25–27] of patient records have found that clozapine significantly increases triglyceride levels. However, one retrospective chart review[28] did not find a significant increase with clozapine, but all antipsychotics raised triglyceride levels in this study. In the study by Ghaeli and Dufresne,[27] the relative risk of abnormally elevated triglyceride levels with clozapine versus typical antipsychotic therapy was 12.4 (95% CI = 3.1 to 48.7). Significant increases in cholesterol levels with clozapine were generally not found in these studies.[25,26,29]

In summary, results of clinical trials, chart reviews, and health care database analysis suggest that clozapine therapy is associated with increases in triglyceride levels. The effects of clozapine treatment on total cholesterol levels are less clear, with 2 studies observing increases in total cholesterol levels from baseline with clozapine,[22,23] while other studies observed no significant changes.[24–26,29] Correlations between increased body weight and raised triglyceride levels,[22] as well as changes in cholesterol levels,[23] have been observed, which is consistent with the frequently observed association between increases in body weight and lipid level changes.[30]

Risperidone

The risk of hyperlipidemia with risperidone therapy was evaluated using data from a large U.K.-based health care database (the U.K. General Practice Research Database [UK GPRD]).[31] A total of 18,309 patients with schizophrenia were identified using data from June 1997 to September 2000.[31] The incidence of hyperlipidemia was compared with these patients and matched case controls (N = 7598), using logistic regression analysis, adjusting for age, gender, and other medications and disease conditions affecting lipid levels (Figure 1).[31] There was no significant increase in the risk of hyperlipidemia with risperidone therapy compared with no antipsychotic medication (odds ratio [OR] = 1.12, 95% CI = 0.60 to 2.11) or typical antipsychotic treatment (OR = 0.81, 95% CI = 0.44 to 1.52).[31] In contrast, there was a significant increase in the risk of hyperlipidemia with olanzapine therapy compared with no antipsychotic therapy (OR = 4.65, 95% CI = 2.44 to 8.85) and typical antipsychotic treatment (OR = 3.36, 95% CI = 1.77 to 6.39).[31]

Meyer[32] evaluated the effects of 12 months of risperidone or olanzapine treatment on lipid parameters from a retrospective review of patient records. In the risperidone group, total cholesterol levels showed small, but not significant, increases from baseline for all 47 patients (7.2 mg/dL) and for those under 60 years old (N = 39; 7.2 mg/dL).[32] Fasting triglyceride levels increased sig-

Figure 1. Risk of Hyperlipidemia With Antipsychotic Therapy (N = 18,309)[a]
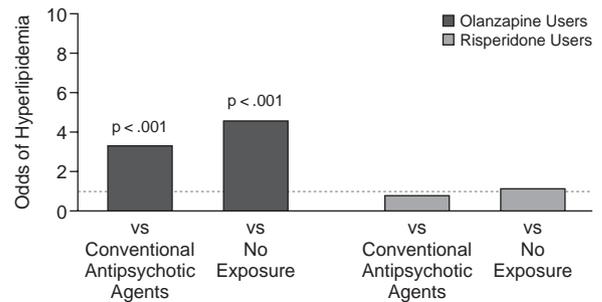
[a]Adapted with permission from Koro et al.[31] Adjusted for age, gender, duration of follow-up, and use of α-blocker, β-blocker, corticosteroid, thiazide diuretic, lithium, oral contraceptives containing norgesterol, or valproate.[31] Dotted line = rate in the general population.

nificantly from baseline for all patients (29.7 mg/dL, p = .028) and for the nonelderly (< 60 years) subgroup (31.7 mg/dL, p = .047).[32] These changes were, however, significantly smaller than the increases in total cholesterol and triglycerides seen with olanzapine therapy in both populations (p < .05).[32] Over the 12-month study period, risperidone-treated patients experienced a significant increase in mean body weight from baseline (all, 10.7 lb [4.9 kg]; < 60 years, 11.9 lb [5.4 kg], p ≤ .001), but with no significant correlation between weight gain and changes in triglyceride or cholesterol levels.[32]

In another retrospective review[24] of patient records, significant decreases in mean LDL-cholesterol levels (11%, p = .006) were observed from baseline with risperidone therapy—comparable to the changes observed with clozapine and olanzapine treatment. Mean triglyceride levels also showed a 19% increase from baseline.[24]

Risperidone treatment showed no significant effects on triglyceride or cholesterol levels in a retrospective analysis of 22 children and adolescents (mean age = 12.8 years) with behavioral, affective, or psychotic disorders.[33] In this chart review, mean triglyceride levels increased nonsignificantly by 8.6 mg/dL from pretreatment levels, while total cholesterol levels were largely unchanged.[33] Mean body weight increased significantly during the study (7.0 kg [15.4 lb], p < .001).[33]

Analysis of lipid levels in a prospective 14-week study[23] involving inpatients with either schizophrenia or schizoaffective disorder showed minimal mean changes in total cholesterol levels from baseline in patients treated with risperidone, but found significant increases in total cholesterol levels for those receiving either olanzapine or clozapine therapy.

Examination of lipid levels in an 8-week study[34] of risperidone and olanzapine therapy in 50 inpatients with schizophrenia, schizophreniform disorder, or schizoaffective disorder also showed no significant changes in

triglyceride and total cholesterol levels with risperidone treatment. In contrast, patients receiving olanzapine showed significant increases in triglyceride levels from baseline, but not total cholesterol.[34]

Changes in cholesterol and triglyceride levels were also reported in an 8-week randomized, double-blind study[35] of risperidone and olanzapine treatment in 377 patients with schizophrenia or schizoaffective disorder. The ratio of beneficial change to adverse change was presented for each parameter, when the change from an above-normal value at baseline to a normal value at study end was considered *beneficial* while the change from a normal baseline value to an above-normal value was *adverse*.[35] Overall, 21.9% and 20.1% of patients experienced a change (either beneficial or adverse) in cholesterol and triglyceride levels, respectively. Changes in triglycerides tended to be beneficial with risperidone treatment (ratio = 2.57) but adverse with olanzapine therapy (ratio = 0.45).[35] A beneficial change in triglyceride levels was significantly more likely with risperidone therapy than with olanzapine (risk ratio = 5.71, p = .003).[35] Similarly, changes in cholesterol levels tended to be beneficial with risperidone (ratio = 1.64) but not with olanzapine (ratio = 0.35), also suggesting a significantly greater likelihood of improvements in cholesterol levels with risperidone than with olanzapine (risk ratio = 4.70, p = .005).[35]

In summary, the evidence demonstrating associations between risperidone and hyperlipidemia is not firmly established. No increased risk of hyperlipidemia with risperidone therapy was observed in a case-control analysis of health care data from the United Kingdom.[31] This lack of a risk for hyperlipidemia is supported by studies that measured lipid levels. Minimal changes in total cholesterol levels were found in retrospective analyses of patient records[24,32,33] and clinical study reports.[23,34] One study analysis showed that beneficial changes in cholesterol levels with risperidone therapy outweighed adverse changes.[35] Statistically significant increases in triglyceride levels were reported in only a single study.[32] Furthermore, Conley and Mahmoud[35] reported that changes in triglyceride levels tended to be beneficial. However, the precaution remains that selected patients may experience significant changes in lipid levels with risperidone.

Olanzapine

As described in the previous section, data from the UK GPRD were analyzed to assess the risk of hyperlipidemia with risperidone, olanzapine, and typical antipsychotic therapy among patients with schizophrenia.[31] There was a significant increase in the risk of hyperlipidemia with olanzapine therapy compared with no antipsychotic therapy (OR = 4.65, 95% CI = 2.44 to 8.85) and typical antipsychotic treatment (OR = 3.36, 95% CI = 1.77 to 6.39), but in contrast, no increased risk was observed with risperidone (Figure 1).[31]

A second database analysis[36] used Medi-Cal data from 1997–2000 in which there were 4371 cases of schizophrenia and 8052 matched controls. Risk of hyperlipidemia was increased with exposure to both olanzapine (OR = 1.27, 95% CI = 1.15 to 1.39) and clozapine (OR = 1.17, 95% CI = 1.01 to 1.38) but not risperidone or quetiapine.[36] The risk of hyperlipidemia was greater with olanzapine than with risperidone (p = .002).[36]

A chart review[24] examined lipid levels in patients treated with different antipsychotics, including clozapine, risperidone, quetiapine, and olanzapine (N = 32). Mean triglyceride levels increased significantly from baseline with olanzapine therapy (38%, p = .02) and were significantly higher than those observed with haloperidol therapy (p = .02).[24] Overall, 39% of olanzapine-treated patients had elevated triglyceride levels.[24] A significant decrease in mean LDL-cholesterol levels (14%, p = .03), but not in total cholesterol levels, was observed with olanzapine.[24] However, mean HDL-cholesterol levels also decreased significantly from baseline (10%, p = .03), and minimum HDL-cholesterol levels were significantly lower than those observed with risperidone treatment.[24]

In his retrospective review of records, Meyer[32] found that patients in the olanzapine group experienced significant increases from baseline in fasting triglyceride (88.2 mg/dL, p ≤ .001) and fasting total cholesterol (23.6 mg/dL, p ≤ .001) levels. Increases in both triglyceride and total cholesterol levels with olanzapine were significantly greater than with risperidone for all patients (p < .05).[32] Mean body weight increased significantly from baseline with olanzapine therapy for all patients (17.5 lb [7.9 kg], p ≤ .001) and for those < 60 years old (20.4 lb [9.3 kg], p ≤ .001).[32] No significant correlation between weight gain and the change in triglyceride or cholesterol levels was observed in the nonelderly subgroup.[32] Meyer found similar results in an earlier retrospective review of patient records.[37] The mean time to peak triglyceride levels was 10.0 months, with peak triglyceride levels occurring within 12 months of starting treatment in 9 of the 12 cases.[37]

Significant changes in lipid levels have also been observed during clinical trials of olanzapine therapy. In a prospective, 14-week study,[23] inpatients with either schizophrenia or schizoaffective disorder were randomized to olanzapine, clozapine, risperidone, or haloperidol treatment. Data from the 26 patients randomized to olanzapine showed a significant increase in cholesterol level from baseline during the first 8 weeks of the study (12.3 mg/dL, p < .04) and throughout the 14-week study period (N = 22, 16.3 mg/dL, p < .002).[23] Body weight increased significantly from baseline with olanzapine therapy (mean = 7.3 kg [16.1 lb], p < .0001).[23] A significant association was found between weight gain and cholesterol increase (p = .035), although this was not significant after adjusting for baseline weight and cholesterol level.[23]

In other clinical trials, significant changes in several lipid parameters were observed with olanzapine treatment: increases in triglycerides,[34,35,38,39] increases in LDL-cholesterol,[40,41] increases in total cholesterol,[35,40] increases in weight,[34,38] reductions in HDL-cholesterol,[42] and a significant association between increases in triglycerides and weight was observed.[38]

In summary, evidence from database analysis, chart reviews, and prospective clinical trials suggests that olanzapine treatment is associated with an adverse effect on lipid levels. Analysis of health care data from the UK GPRD reports a significantly increased risk of hyperlipidemia with olanzapine compared with either typical or no antipsychotic therapy in patients with schizophrenia.[31] This finding is supported by the increases in triglyceride levels reported with olanzapine therapy in retrospective chart reviews[24,32,37] and 2 clinical trials.[38,39]

Increases in body weight are well documented with olanzapine therapy[43,44] and may impact on the increases in triglyceride levels seen with olanzapine therapy. Osser et al.[38] reported a significant association between weight gain and triglyceride increases. However, 2 studies by Meyer[32,37] found no significant correlation between weight gain and changes in triglyceride levels. These findings are consistent with other reports but may be confounded by the wide range of baseline weights and/or a large number of patients who are obese at baseline.

Findings from the analyses of total cholesterol levels were less clear. Two studies observed minimal changes in total cholesterol levels from baseline[24,38] and 2 other analyses revealed significant increases from baseline.[23,32] Meyer[32] found no significant correlation between weight gain and increased cholesterol levels, whereas with Lindenmayer et al.,[23] the correlation was not significant after adjusting for baseline weight and cholesterol levels. One published report[24] showed significant improvements in LDL-cholesterol levels from baseline with olanzapine therapy. However, these were accompanied by significant adverse changes in HDL-cholesterol levels.

Quetiapine

Wirshing et al.[24] reported changes in lipid levels associated with quetiapine treatment in their retrospective chart review. Beneficial changes in triglyceride levels (a 25% decrease from baseline) and LDL-cholesterol (a 13% decrease from baseline) were observed with quetiapine, although only the decrease in LDL-cholesterol represented a statistically significant change from baseline (p = .04). Mean total cholesterol (–4%) and HDL-cholesterol (+2%) levels showed minimal changes with quetiapine treatment. An 8-week, open-label study[45] of quetiapine treatment in 15 adolescents (mean age = 15.1 years; range, 13–17 years) with psychotic disorders also reported minimal changes in cholesterol levels from baseline.

In contrast, pooled laboratory data from the 3- to 6-week placebo-controlled quetiapine clinical trials[46] report a 17% increase in triglyceride levels and an 11% increase in total cholesterol with quetiapine therapy. In addition, Kurt and Oral[42] reported increases in total cholesterol, LDL-cholesterol, and triglyceride levels from baseline with quetiapine treatment, although these changes were not statistically significant. The undesirable decreases in HDL-cholesterol levels seen with quetiapine did, however, reach statistical significance (p < .05).[42]

Several cases of elevated lipid levels have also been reported with quetiapine therapy. Meyer[37] reported 14 cases of severe hypertriglyceridemia (fasting triglycerides > 600 mg/dL) in patients receiving olanzapine or quetiapine treatment, identified from a retrospective review of patient records. In addition, Domon and Cargile[47] reported hypertriglyceridemia and hyperglycemia associated with quetiapine therapy in a patient.

Overall, reports of changes in lipid levels with quetiapine therapy are limited and somewhat contradictory, as the decreases in triglyceride levels reported in the small study by Wirshing et al.[24] contrast with the increases in triglycerides reported for pooled data from the short-term clinical trials.[46]

However, these conflicting findings may be confounded by the drug therapy given to patients prior to starting quetiapine. If patients switched from a lipid-elevating drug, such as olanzapine, to quetiapine, as discussed by Wirshing et al.,[24] there is the possibility that quetiapine appears to be associated with a lipid-lowering profile when it may have only a less deleterious effect on lipids, as compared to the drug taken before quetiapine. Indeed, this concern about prior treatments and baseline lipid levels applies to all data sets reviewed in this article. Additionally, many of the reports with quetiapine are in patients who received relatively low doses. If there is a dose-related effect of quetiapine on lipids, it may not be apparent until a large number of patients are treated across a wide dose range.

Ziprasidone

A retrospective chart review[48] of 40 patients with mental retardation and behavioral disturbances receiving at least 6 months of ziprasidone treatment reported changes in lipid levels. Significant decreases in mean triglyceride (147.8 to 123.4 mg/dL, N = 29) and total cholesterol (200.5 to 176.4 mg/dL, N = 30) levels were observed during this period (p < .04).[48] Fasting HDL- and LDL-cholesterol levels, available for only 19 of the 40 patients, showed minimal changes during the first 6 months of ziprasidone therapy.[48] Additionally, no significant changes in fasting plasma lipid levels were reported with ziprasidone treatment in a 6-month blinded follow-up study[41] in patients with schizophrenia or schizoaffective disorder who were treated for an acute exacerbation of psychosis,

Figure 2. Effects of Aripiprazole and Placebo on Total Cholesterol, LDL-Cholesterol, HDL-Cholesterol, and Triglyceride Levels After 26 Weeks of Treatment in a Double-Blind Study[56]

A. Data Obtained From Mean Changes in Fasted Plasma Samples[a]
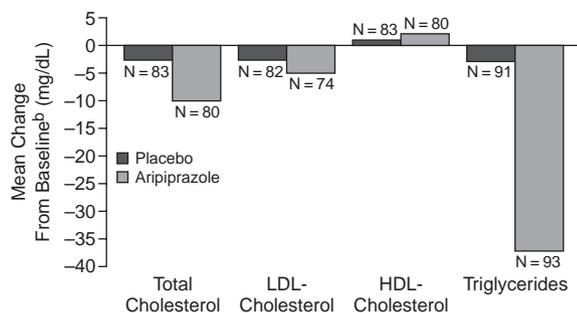
B. Incidence of Abnormal Lipid Values* in Patients Who Had Normal Levels at Baseline (placebo vs. aripiprazole)[c]
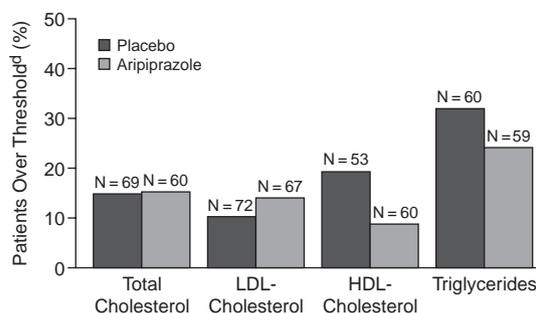
[a]Data from Pigott et al.[56] Last observation carried forward (LOCF) at endpoint.
[b]Baseline values—total cholesterol: placebo = 177 mg/dL, aripiprazole = 191 mg/dL; LDL-cholesterol: placebo = 102 mg/dL, aripiprazole = 113 mg/mL; HDL-cholesterol: placebo = 47 mg/dL, aripiprazole = 47 mg/dL; triglycerides: placebo = 143 mg/dL, aripiprazole = 161 mg/dL.
[c]Data from Pigott et al.[56] and Marder et al.[57]
[d]Abnormal lipid values: total cholesterol ≥ 200 mg/dL, LDL-cholesterol ≥ 130 mg/dL, HDL-cholesterol ≥ 40 mg/dL, triglycerides ≥ 150 mg/dL.
*p < .05.
Abbreviations: HDL = high-density lipoprotein, LDL = low-density lipoprotein.

and thus were not receiving effective doses of antipsychotics prior to ziprasidone therapy.

A review of fasting lipid levels from 5 short-term ziprasidone clinical trials[49] in patients with schizophrenia reported significant decreases in total cholesterol (p < .001) and triglyceride (p < .001) levels with ziprasidone therapy. Changes in total cholesterol, LDL-cholesterol, and triglyceride levels observed with ziprasidone were statistically significant compared to the elevations seen with olanzapine (p < .01).[49]

In a study[50] that switched 37 patients to ziprasidone from other antipsychotics, significant reductions in serum cholesterol (p < .001) and triglyceride (p = .018) levels from baseline were observed in the 6-week trial. These changes were independent of changes in BMI or previous antipsychotic usage, except for a significant correlation between BMI and triglyceride changes (r = 0.409, p =.018).[50]

The proportion of patients experiencing abnormal elevations in triglyceride and cholesterol levels was reported in a 6-week ziprasidone study[51] involving 302 patients with acute exacerbation of schizophrenia or schizoaffective disorder. More patients experienced abnormal elevations in cholesterol levels in the ziprasidone groups (80 mg/day, 25%; 160 mg/day, 17%) than with placebo (12%).[51] The percentage of patients experiencing abnormal elevations in triglyceride levels was similar in all 3 groups (ziprasidone 80 mg/day, 17%; ziprasidone 160 mg/day, 14%; placebo, 15%).[51]

The limited availability of data means that it is too early to draw any firm conclusions regarding the impact of ziprasidone treatment on the risk of developing dys-

lipidemia. Nevertheless, initial indications from available data suggest that ziprasidone does not have an adverse effect on lipid levels and may lead to beneficial changes in some lipid parameters, such as total cholesterol and triglycerides, if these elevated levels are due to the prior drug therapy.

THIRD-GENERATION ATYPICAL ANTIPSYCHOTIC DRUGS AND DYSLIPIDEMIA

Aripiprazole

A pooled analysis[52] of 5 short-term studies showed minimal changes in total cholesterol levels from baseline with aripiprazole treatment in patients treated for schizophrenia. The median increase in total cholesterol levels in the aripiprazole treatment group (1.0 mg/dL, N = 860) was similar to that in the placebo group (3.0 mg/dL, N = 392) and less than the observed increase with haloperidol treatment (8.0 mg/dL, N = 190), which differed significantly from placebo.[52] Other short-term clinical studies[53,54] have reported no clinically significant changes in lipid levels.

A longer-term 26-week trial of aripiprazole treatment in 310 patients with chronic stable schizophrenia evaluated changes in total, LDL-, and HDL-cholesterol and triglyceride levels.[55,56] In patients with chronic stable schizophrenia, there were comparable changes over the course of the study with aripiprazole and placebo in HDL-cholesterol (2.0 mg/dL vs. 0.89 mg/dL, respectively), triglycerides (–37.2 mg/dL vs. –2.9 mg/dL), and LDL-cholesterol (–5.1 mg/dL vs. –2.9 mg/dL) (Figure 2A).[56] The incidences of new-onset dyslipidemias, defined as ab-

normal lipid levels among patients with normal levels at baseline, were similar among patients treated with placebo and those treated with aripiprazole (Figure 2B).[56,57] Results from another 26-week trial (Stock et al.[58]), which compared weight gain liabilities of aripiprazole and olanzapine, are described elsewhere in this supplement. As expected, the rates of new-onset dyslipidemias in that trial were significantly lower with aripiprazole (which were similar to the findings with placebo in the Pigott et al.[56] study) than with olanzapine. In patients with lipid levels within normal range at baseline, treatment with olanzapine resulted in significantly more patients exhibiting clinically significant increases in total cholesterol (> 200 mg/dL, 47% with olanzapine and 17% with aripiprazole), LDL-cholesterol (> 130 mg/dL, 38% with olanzapine and 19% with aripiprazole), and triglyceride (> 150 mg/dL, 50% with olanzapine and 18% with aripiprazole) levels.[58] The results generally replicated those observed in the 26-week placebo-controlled trial.[56]

In summary, the data currently available for aripiprazole suggest that it has a desirable lipid profile. In patients who have lipid elevations due to prior antipsychotic treatment, lipid levels may come down to the patient's natural baseline levels. In patients who are not receiving prior treatment that is associated with lipid elevations, aripiprazole has a lipid-neutral profile.

DISCUSSION

The evidence reviewed here clearly indicates that there are differential effects of selected atypical antipsychotics on lipid dysregulation during treatment of schizophrenia and related psychoses. Thus, this is not a class effect of all atypical antipsychotic drugs. The lack of class effect is highly consistent with the recent joint consensus statement on antipsychotic drugs, obesity, and diabetes issued by the American Diabetes Association, the American Psychiatric Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity.[59] This consensus statement classified clozapine and olanzapine as being associated with an increased risk of worsening lipid profiles, whereas aripiprazole and ziprasidone were not associated with an increased risk for detrimental serum lipid changes. This group noted that there were conflicting data about the effect of quetiapine and risperidone on lipids.

Evidence reviewed here also indicates that adverse effects on triglyceride levels are relatively robust with olanzapine and clozapine, and several, but not all, studies found adverse effects on LDL-cholesterol. For risperidone and quetiapine, there are some data to suggest that these atypical antipsychotics are associated with adverse effects on multiple lipid measures, but the evidence is less strong than with olanzapine and clozapine. Finally, for the newer atypical antipsychotics, aripiprazole and ziprasidone, the

evidence indicates a lipid-neutral profile of no or minimal adverse effects on lipid levels.
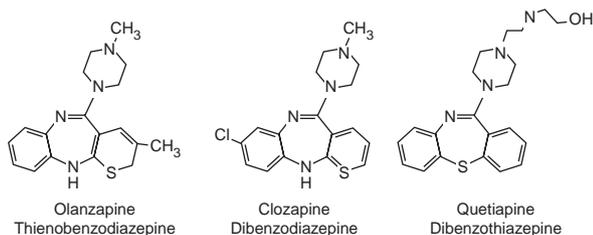
The results of studies reporting lipid changes with atypical antipsychotics need to be interpreted with caution, as observed changes depend on what antipsychotic drugs, if any, patients were taking prior to study commencement. For example, if patients had been treated with a drug that causes dyslipidemias prior to switching to another drug, the pattern of lipid changes is likely to be different than if patients were previously untreated.

Although some studies did find correlations between lipid changes and weight changes, other studies did not. This may be due to a number of possible explanations. Perhaps the effects of atypical antipsychotics on weight and lipids may occur through different mechanisms. For example, there may be a direct and early onset effect that is drug specific and an additional nonspecific drug effect that is associated with weight gain. Since weight gain may continue for many months with some atypical antipsychotics, the full effect of the dyslipidemias associated with weight gain may not be seen for an extended time frame. Additionally, many of the reports in the literature are of too short a duration to show the potential relationship between weight and lipid changes. Finally, the physiologic effect of the same amount of weight gain is likely to have different effects on patients who start at very different BMIs. Twenty pounds of weight gain may not have as much of a deleterious effect on a patient with a BMI of 22 compared to a patient with a BMI of 32.
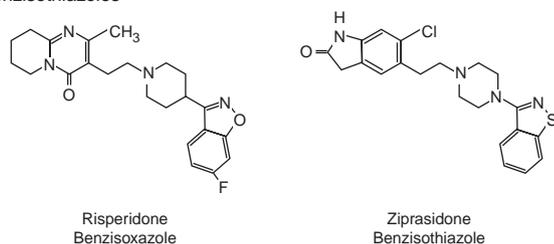
The exact mechanism of changes in lipid levels with atypical antipsychotics is unknown, and several putative mechanisms have been proposed.[37] Olanzapine, quetiapine, and clozapine are structurally related and are derived from dibenzodiazepine compounds. Ziprasidone and risperidone have somewhat similar structures that are distinct from the dibenzodiazepine-derived compounds, whereas aripiprazole is not structurally related to any of the other atypical antipsychotics (Figure 3).[37,60–62] It has been postulated that changes in lipid levels may be related to the 3-ring structure of the dibenzodiazepine-derived compounds that is conformationally similar to the phenothiazine nucleus, which has a known propensity to increase serum triglyceride levels, with a lesser effect on cholesterol levels.[63] These dibenzodiazepine-derived compounds are also potent antagonists of both serotonin 5-HT$_{2A}$ and 5-HT$_{2C}$ receptors.[63] Antagonism of the 5-HT$_{2C}$ receptor may be related to obesity, as mutant mice that lacked this receptor developed both obesity and insulin resistance and did not experience increases in triglyceride levels when fed standard or high-fat diets.[64] Against this hypothesis is the lack of correlation between drug effects at 5-HT$_{2C}$, weight gain, and dyslipidemias, as ziprasidone is potent at this receptor but is weight and lipid neutral.[65]

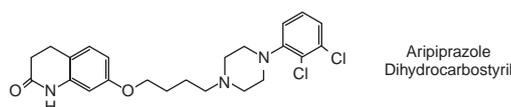Figure 3. Chemical Structures of Six Atypical Antipsychotics

Dibenzodiazepines

Olanzapine
Thienobenzodiazepine

Clozapine
Dibenzodiazepine

Quetiapine
Dibenzothiazepine

Benzisothiazoles

Risperidone
Benzisoxazole

Ziprasidone
Benzisothiazole

Dihydrocarbostyril

Aripiprazole
Dihydrocarbostyril

Periodic monitoring of medical health in addition to psychiatric status in patients taking atypical antipsychotics is important. Full lipid panel profiles (total cholesterol, low and high density lipids, and triglycerides) should be an integral part of these evaluations. Baseline levels should be determined at the beginning of treatment, or when changing drug therapy, and approximately 3 months later. Thereafter, monitoring should be determined by clinical indications. Annual reevaluations should be done in patients who have other cardiovascular disease risks or diabetes. If patients develop worsening dyslipidemia while on antipsychotic therapy, they should be considered as candidates for a switch to an agent that is not associated with significant weight gain or diabetes.[59] The lipid profiles can be conveniently obtained when monitoring other measures, such as weight, height, BMI, vital signs, and measures of glucose metabolism (e.g., fasting or random glucose, hemoglobin A_{1C}).

Clearly, data on the use of atypical antipsychotics indicate that some drugs in this class are associated with dyslipidemia, especially olanzapine and clozapine. Some newer atypical antipsychotics (i.e., ziprasidone and aripiprazole) do not appear to be associated with adverse effects on lipid levels. Psychiatrists and the rest of the medical community are now appropriately integrating plans for regularly monitoring their patients' lipid levels to avoid morbidity and mortality associated with chronic heart disease.

Drug names: aripiprazole (Abilify), clozapine (Clozaril, Fazaclo, and others), danazol (Danocrine and others), divalproex sodium (Depakote), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

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