Monitoring Lipids in Patients Treated With Ziprasidone or Aripiprazole

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Despite a consensus that lipids should be monitored in all patients treated with a second-generation antipsychotic, lipid monitoring is inconsistent for patients receiving ziprasidone or aripiprazole. Here's why, and how an investigation at one VA medical center prompted practice recommendations.

Antipsychotic medications are the mainstay of therapy for schizophrenia and bipolar disorder. Introduced more than 50 years ago, antipsychotic medications can make tremendous differences in patients' lives. Like many other medications, however, they may cause complicated and debilitating adverse effects. While first-generation antipsychotics (FGAs) can cause dystonia, drug-induced parkinsonism, akathisia, and tardive dyskinesia, second-generation antipsychotics (SGAs), also known as atypical antipsychotics, can cause metabolic abnormalities.[1,2]

To gain a better understanding of the relationship between SGAs and obesity, diabetes, dyslipidemia, and cardiovascular disease, members of the American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, and North American Association for the Study of Obesity met in November 2003 and developed consensus guidelines on the appropriate use of these drugs.[1,2] The consensus conference determined that, based on available evidence, clozapine and olanzapine had the greatest association with hyperlipidemia, while ziprasidone and aripiprazole had no effect on lipids (Table 1). Epidemiologic data on ziprasidone and aripiprazole, however, were limited because the drugs had been approved for only 2 years and 1 year, respectively, before the conference. For this reason, conference recommendations called for a fasting lipid profile (FLP) to be obtained at baseline and after 12 weeks of therapy for patients using any SGA (Table 2).[1,2]

In light of these recommendations, the VA Pharmacy Benefits Management Strategic Healthcare Group and Medical Advisory Panel conducted a MEDLINE review to evaluate the evidence associating antipsychotic drugs and adverse metabolic effects.[3] The panel concluded that both FGAs and SGAs are associated with weight gain and metabolic changes, particularly hyperglycemia. Among the antipsychotic drugs, clozapine and olanzapine are associated with a greater risk of weight gain than are risperidone and quetiapine. Due to insufficient data, no conclusions could be drawn about the effects of ziprasidone or aripiprazole on weight, lipids, or glucose. An addendum to the panel report recommended that all patients prescribed SGAs receive baseline and periodic monitoring of weight, body mass index, fasting blood glucose, lipids, and blood pressure, as well as patient teaching about the signs and symptoms of related potential adverse effects. A second addendum referenced the Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes, underscoring that their findings and monitoring recommendations were similar to those of the VA.[3]

BACKGROUND

Many studies have compared the effects of ziprasidone and aripiprazole with those of other antipsychotic agents. In an open-label, multicentered, double-blind, randomized, placebo-controlled trial, Chrzanowski and colleagues compared the long-term efficacy and safety of aripiprazole with olanzapine in patients with either acute relapsing or chronic stable schizophrenia.[4] Patients received either aripiprazole 15 to 30 mg/day or olanzapine 10 to 20 mg/day for 52 weeks. Between the 2 groups, lipid panels differed significantly. Olanzapine-treated patients experienced significantly

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Table 1. Metabolic changes associated with SGAs[1,2]

Agent	Weight gain	Diabetes risk	Worsening lipid profile
Clozapine	+++	+	+
Olanzapine	+++	+	+
Risperidone	++	D	D
Quetiapine	++	D	D
Aripiprazole	+/–	–	–
Ziprasidone	+/–	–	–

D = discrepant results; SGAs = second-generation antipsychotics; + = increased effect; – = no effect.

greater increases in both total cholesterol (TC) and low-density lipoprotein (LDL) cholesterol at weeks 8, 16, 28, and 52. By week 52, there were small increases in high-density lipoprotein (HDL) cholesterol in aripiprazole-treated patients, while olanzapine-treated patients demonstrated worsening HDL ($P < .05$) and triglycerides (TG), though the latter was nonsignificant. Aripiprazole proved to have a significantly superior safety and tolerability profile for TC (52% vs 24%; $P = .002$) and LDL (38% vs 16%; $P = .007$).[4]

Similarly, Brown and colleagues found olanzapine treatment resulted in significantly greater adverse effects on patients' lipid panels than did ziprasidone treatment, which produced favorable effects with regard to TC, LDL, and HDL. The study was a retrospective cohort chart review of 191 patients, randomly assigned treatment with either ziprasidone (88) or olanzapine (103) for schizophrenia or other psychoses. It was conducted at the Portland VA Medical Center in Oregon. Patients treated with olanzapine had an 8% increase in TC ($P = .01$), an 11% increase in LDL ($P = .06$), a 4% decrease in HDL ($P > .05$), and a 27% increase in TG ($P = .05$). In contrast, ziprasidone-treated patients improved in all measures, including a 7% reduction in TC ($P < .01$), a 14% reduction in LDL ($P = .001$), an 8% increase in HDL ($P < .05$), and a 7% decrease in TG ($P > .05$).[5]

Table 2. Monitoring protocol for patients taking SGAs[1,2,a]

Parameter	Baseline	4 weeks	8 weeks	12 weeks	Quarterly	Annually	Every 5 years
BMI	X	X	X	X	X		
Waist circumference	X					X	
BP	X			X		X	
FPG	X			X		X	
FLP	X			X			X

BMI = body mass index; BP = blood pressure; FLP = fasting lipid profile; FPG = fasting plasma glucose; SGAs = second-generation antipsychotics.
[a]Assessment frequency should be based on individual patient status.

METHODS

This retrospective study, performed at the North Chicago VA Medical Center (NCVAMC) in Illinois sought to evaluate adherence to guidelines for FLP monitoring of patients using the SGAs aripiprazole or ziprasidone, in light of their apparent superior safety profile. Adherence to guidelines was defined as drawing an FLP at baseline (no more than 6 months before the start of medication) and again 12 weeks after initiation. Data were collected once approval was obtained from the Hines VA Medical Center Institutional Review Board in Illinois. A secondary objective was to identify any changes in FLP associated with the use of these 2 SGAs.

Inclusion and exclusion criteria

Individuals were included in this study if they were veteran inpatients at NCVAMC who had a diagnosis of schizophrenia, schizoaffective disorder, or bipolar disorder and were treated with either aripiprazole or ziprasidone, but not both, between January 2005 and December 2005. Patients receiving nonantipsychotic psychotropics or lipid-lowering agents were included in the study, but patients were excluded if they were using any other antipsychotic agent in addition to the SGA or if they did not have a documented FLP within 6 months prior to the start of the SGA therapy.

The NCVAMC's computerized patient record system (CPRS) provided the following information: demographics, name and dose of the prescribed SGA, and dates and results of baseline and follow-up FLP.

Statistical analysis

Researchers used χ^2 tests to analyze FLP data and paired *t* tests to assess changes in TC, LDL, HDL, and TG from baseline.

RESULTS

The CPRS showed 79 patients were treated with 1 of the 2 study drugs within the study period, of whom 50 remained after inclusion and exclusion criteria were applied: 34 treated with ziprasidone and 16 treated with aripiprazole. Most patients were white males (Table 3), though sex bias is anticipated in a VA setting.

Complete adherence, defined as obtaining FLP at baseline and 12 weeks after initiating SGA therapy, was 30% (Table 4). Only 15 of the 50 patients were monitored in accordance with the guidelines. Providers were more consistent in measuring baseline FLP and less consistent in obtaining FLPs 12 weeks after drug initiation.

FLP data for the 15 patients monitored in accordance with guidelines show mean changes in TC, TG, LDL, and HDL (Table 5). Although none of the mean changes in the lipid parameters was statistically significant, TG dipped an average of 57.3 mg/dL with SGA treatment. There was also a trend showing a reduction in TC. Decreases in TC and TG may show clinical significance in certain patient populations for whom lowering non-HDL cholesterol is a goal. Eight patients were taking ziprasidone and 7 were taking aripiprazole; no differences were observed in the effects of each drug on FLP. Due to the minimal adherence to guidelines, no statistical analyses were performed on the secondary endpoints.

DISCUSSION

The use of SGAs in the VA setting has been expanding. Treatment with these agents is associated with adverse metabolic effects, including dyslipidemia. In 2004, the Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes developed an evidence-based schedule for monitoring FLPs in patients receiving SGA treatment.[1,2] It is essential to follow consensus guidelines for such monitoring because increased TC, LDL, and TG can lead to cardiovascular disease.

The current study investigated the practice of FLP monitoring of NCVAMC patients taking ziprasidone and aripiprazole because, of the available SGAs, these have been shown to have least negative effect on lipids[1,2] and might be assumed to require no monitoring. The findings showed that appropriate lipid monitoring, as defined by the consensus conference,[1,2] is not practiced consistently among providers at the NCVAMC who treat patients with either of these drugs. Only 30% of patients receiving either drug were being monitored in accordance with consensus guidelines.

Table 3. Patient demographics (n = 50)

Characteristic	Study sample, No. (%)
Sex	
Male	41 (82)
Female	9 (18)
Ethnicity	
White	30 (60)
Black	15 (30)
Asian	2 (4)
Other	3 (6)
Diagnosis	
Schizophrenia	13 (26)
Schizoaffective disorder	16 (32)
Bipolar disorder	21 (42)

Table 4. Primary endpoints: Provider adherence to FLP recommendations in patients treated with SGAs (n = 50)

Time point for FLP monitoring	Patients receiving FLP per recommendations, No. (%)
Baseline	33 (66)
12 weeks	19 (38)
Complete adherence	15 (30)

FLP = fasting lipid profile; SGAs = second-generation antipsychotics.

Limitations

The greatest limitations of this study apply to its secondary objective: to identify any changes in FLP associated with the use of these 2 SGAs. Chief among them is the study's retrospective design, which made it impossible to account for such confounding variables as inpatient diet regimens; patient adherence to dietary restrictions and medication usage; and concomitant medications or diseases, such as hypothyroidism or renal or hepatic impairment that increase cholesterol levels. In addition, patients

Table 5. Secondary endpoints: Effect of SGA treatment on lipids in patients monitored per recommendations (n = 15)

Lipid parameter	Mean change in mg/dL	95% CI	*P* value
TC	–12.1	–1.140–25.43	.070
LDL	+0.133	–15.37–15.10	.985
TG	–57.3	–6.617–120.7	.073
HDL	+1.7	–5.574–1.707	.274

CI = confidence interval; HDL = high-density lipoprotein; LDL = low-density lipoprotein; SGA = second-generation antipsychotic; TC = total cholesterol; TG = triglycerides.

previously diagnosed with dyslipidemia and those taking lipid-lowering agents were not excluded from the study, and patients with diabetes, who have stricter FLP goals, were not identified. These limitations, in conjunction with the small size of the group that was appropriately monitored, made it impossible to draw any conclusions about the respective potential effects of ziprasidone and aripiprazole on serum lipids.

Although the 57.3-mg/dL drop shown in TG levels within this group may be clinically significant in specific patient populations, no expectation can be extrapolated from a sample this small. Even if the sample had been larger, the VA setting limited the patient population to one that was primarily elderly, male, and white, making it difficult to generalize from this population to others with more demographic diversity.

RECOMMENDATIONS

Upon the completion of this study, researchers recommended taking action to align FLP monitoring of patients treated with SGAs at the NCVAMC with consensus guidelines. The administration is currently considering a proposal to insert clinical reminder prompts in the charts of all patients who have an active antipsychotic prescription. Many mental health care providers may be unaware of the consensus guidelines, and adding a quick clinical reminder is an inexpensive, simple option for improved adherence with recommended practice. Physician and pharmacist in-services on adverse effects of antipsychotic medications and the importance of appropriate monitoring are scheduled for the near future. These provide an ideal opportunity for pharmacists to offer assistance and support in monitoring the serum lipids of patients who are treated with SGAs. In the future, investigations are expected to evaluate the implementation and execution of a monitoring system that tracks and reports all interventions related to SGA administration. Trials controlling for the confounding factors identified in this study are under discussion.

Author disclosures

The authors report no actual or potential conflicts of interest with regard to this article.

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