The Effects of Novel Antipsychotics on Glucose and Lipid Levels

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Background: The novel antipsychotics are extensively used based on their favorable extrapyramidal side effect profiles. However, accumulating evidence suggests that these agents, particularly clozapine and olanzapine, have serious side effects of their own, including weight gain and elevated glucose and triglyceride levels. The goal of this study is to compare the effects of novel antipsychotics clozapine, olanzapine, risperidone, and quetiapine and typical antipsychotics haloperidol and fluphenazine on glucose and lipid levels.

Method: The charts of 590 patients were retrospectively reviewed. Of those, 215 patients had adequate laboratory data for inclusion. Glucose and lipid level data from $2^1/_2$ years before and after initiation of the target antipsychotic were included. Covariates, including patients' age, the duration of antipsychotic treatment, other medications that may affect glucose or lipid levels, and the initial laboratory values, were controlled for in the analyses.

Results: Glucose levels were increased from baseline for patients treated with clozapine, olanzapine, and haloperidol. There were statistically and clinically significant differences among the medications' effects on lipid profiles ($p < .05$). Those receiving clozapine and olanzapine demonstrated statistically significant increases in triglyceride levels compared with the other groups. Over one third of patients treated with any of the novel antipsychotics had clinically meaningful triglyceride elevations.

Conclusion: It has been shown that novel antipsychotics are associated with weight gain. This risk factor along with others, such as elevated glucose and triglyceride levels, compounds the risk for coronary artery disease. Routine monitoring of glucose and lipid levels during treatment with novel antipsychotics should be advocated.

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Several key studies have been published recently that address weight gain associated with the novel antipsychotics.[1,2] In addition, more recently, there have been numerous case reports suggesting that novel antipsychotics may result in other adverse effects, including elevated glucose levels and possibly drug-induced diabetes, as well as elevations in triglyceride levels.[3–24] Taken together, these factors further compound a patient's risk for developing coronary artery disease and thus deserve attention.

Over the last decade, we have observed that drug-induced weight gain can be a substantial problem for patients taking novel antipsychotic drugs, particularly because it appears to be associated with a number of other health problems including diabetes, dyslipidemia, coronary artery disease, and various types of cancer.[25] In a retrospective study[1] of 122 clinical records of 92 patients in our outpatient clinic **(**none of which were included in our current study**)**, we found that weight gain was a significant problem for the majority of our patients taking novel antipsychotic drugs. Clozapine was associated with the most weight gain (6.9 ± 0.8 kg) (controlling for age, baseline body mass index [BMI], and treatment duration) of the antipsychotic drugs, followed by olanzapine (6.8 ± 1.0 kg), risperidone (5.0 ± 0.6 kg), haloperidol

(3.7 ± 0.6 kg), and then sertindole (3.1 ± 1.2 kg). We also found that weight gain in our patients was related to the relative histamine (H_1) receptor affinity of these medications.[1] The results of this study were limited somewhat by a small sample size for certain agents.

Other studies have confirmed our findings on weight gain. Allison and colleagues[2] performed a comprehensive meta-analysis on antipsychotic-induced weight gain and identified over 80 articles that included data on weight gain in antipsychotic-treated populations. Placebo was associated with weight loss of 0.74 kg, while among the conventional antipsychotics, the mean weight change ranged from a decrease of 0.39 kg with molindone to an increase of 3.19 kg with thioridazine. Among the novel antipsychotic drugs, they found the following: clozapine was associated with a 4.45-kg weight gain, olanzapine with a 4.15-kg weight gain, sertindole with a 2.92-kg weight gain, risperidone with a 2.1-kg weight gain, and ziprasidone with a 0.04-kg weight gain. At the time of their study, there were too few data to analyze the effect of quetiapine on weight changes.

In addition to our group's report of the weight gain associated with novel antipsychotic drugs,[1] we reported in late 1998 on a possible association between new-onset diabetes and these medications.[3] At the time of our report, there were 9 published cases of clozapine-associated diabetes.[4–9] We presented 6 additional cases of novel antipsychotic drug–associated diabetes, 2 involving olanzapine and 4 involving clozapine. Since the publication of our article in November 1998,[3] there have been 12 additional case reports of olanzapine-associated diabetes.[26–29] One case was a clear exacerbation of diabetes during treatment with olanzapine.[16] Henderson and colleagues[30] published a 5-year naturalistic study that showed that 36.6% of patients started on clozapine therapy in their clinic were diagnosed with diabetes. Mohan et al.[12] reported on a case of diabetes associated with clozapine that did not resolve when the patient was switched to risperidone. Additionally, the U.S. Food and Drug Administration (FDA) recently published a report summarizing data collected via their MedWatch program, a program where physicians voluntarily reported 384 cases of diabetes associated with clozapine. Two hundred forty-two cases were new onset, 54 were diabetic exacerbations, and 80 were cases of diabetic ketoacidosis, a potentially life-threatening condition.[31] The average age of the patients in the report was 40 ± 12 years and the male:female ratio was 2:1. The onset of diabetes usually occurred within 6 months of starting clozapine treatment. Quetiapine has been associated with diabetes and ketoacidosis.[32,33] At the time of this writing, there have been 3 published reports of possible risperidone-associated diabetes.[34,35]

Hägg and colleagues[10] examined blood glucose tests and glucose tolerance tests to assess the prevalence of diabetes mellitus or impaired glucose tolerance (IGT) in 63 patients treated with clozapine compared with 67 patients treated with conventional depot neuroleptics. Of the subjects treated with clozapine, 12% had type 2 diabetes and 10% had IGT. These rates were higher than those for the conventionally treated patients (6% had type 2 diabetes and 3% had IGT) but were not statistically significant ($p = .06$). Because of the relatively small sample size in this study, it is likely that type II error accounts for this negative result.

In addition to weight gain and diabetes, the novel antipsychotic medications may cause elevations of triglyceride levels. Studies have demonstrated that elevated triglyceride levels represent an independent risk factor contributing to the extent of coronary atherosclerosis.[36,37] The National Institutes of Health has advocated that although mild elevations in triglyceride levels do not pose a risk for the development of cardiovascular disease, triglyceride levels over 250 mg/dL may increase the risk for cardiovascular disease by up to 2-fold.[38] The majority of published reports on elevated triglyceride levels focus on clozapine and olanzapine; however, many are limited by a design in which confounding factors were uncontrolled. Many studies, for example, were unable to assess weight gain as a covariate to determine whether increases in triglyceride levels are related to changes in weight. Nevertheless, results from numerous studies suggest that triglyceride levels do significantly increase in patients being treated with either clozapine or olanzapine.[18–25]

Very little published information exists regarding elevated triglyceride levels among patients receiving risperidone or quetiapine. Most of the available information arises from premarketing clinical drug trials or package insert information. In the package insert for risperidone,[39] Janssen Pharmaceutica reports hypertriglyceridemia as a "rare" side effect, with an incidence of fewer than 1/1000 patients. The Zeneca Pharmaceuticals' package insert reports a 17% increase in triglyceride levels in patients being treated with quetiapine[40] (from a pool of 3- to 6-week placebo-controlled trials). In addition, they report an 11% increase in total cholesterol. They note that these changes are "weakly related" to increases in weight. Overall, they consider hyperlipidemia to be an "infrequent" adverse event occurring in 1/100 to 1/1000 patients.

To our knowledge, there have been no studies comparing the effects of all available novel antipsychotics on glucose or lipid levels. In addition, there has been very little information available relating to the effects of novel antipsychotics on other lipid measurements such as total cholesterol, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) levels. The purpose of this study is to determine the relative liability of an individual novel antipsychotic to affect glucose and lipid levels.

Table 1. Drugs That May Affect Lipid or Glucose Levels[a]

Glucose Level		Total Cholesterol, LDL, or Triglyceride Level	
Increase	Decrease	Increase	Decrease
Acetazolamide	Acarbose	Antipsychotics (other)	Cholestyramine
Antipsychotics (other)	Glitazones	Asparaginase	Clofibrate
Asparaginase	Insulin	β-Blockers	Colestipol
β-Blockers	Metformin	Cyclosporine	Gemfibrozil
Clonidine	Sulfonylureas	Estrogens	HMG-CoA reductase inhibitors
Corticosteroids		Interferons	
Estrogens		Isotretinoin	
Glycerin		Loop diuretics	
Indapamide		Oral contraceptives	
Lithium		Protease inhibitors	
Loop diuretics		Thiazide diuretics	
Metolazone			
Minoxidil			
Niacin			
Oral contraceptives			
Pentamidine			
Phenytoin			
Protease inhibitors			
Thiazide diuretics			
Thyroid supplements			

[a]Abbreviations: HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A, LDL = low-density lipoprotein.

METHOD

Pharmacy records were used to generate a list of patients who were receiving any one of the antipsychotics of interest (clozapine, olanzapine, risperidone, quetiapine, haloperidol, or fluphenazine). Patients were not required to give informed consent, as determined by the hospital's Institutional Review Board, because this was a review of preexisting data. No patients were contacted, and patients' identities were kept confidential. Data were coded to protect privacy, and each patient was assigned a unique identification number. In order to be included in the study, patients must have had at least 1 laboratory value (glucose, total cholesterol, triglycerides, LDL, or HDL) before initiation of the antipsychotic and 1 laboratory value or more at least 1 week after initiation. BMI (calculated as weight in kilograms divided by height in meters squared) measurements were also recorded. Only those laboratory values that were measured in the morning were included in the analysis, as these were presumed to be fasting measurements. Patients with adequate laboratory data were selected to be included. Those patients who demonstrated a lack of compliance (based on a poor refill history or chart documentation of poor compliance) were excluded from the study. Using Statistical Analysis System (SAS; version 6.12),[41] 2-tailed t tests were performed ($p < .05$ considered significant) to determine whether a particular antipsychotic was associated with a significant increase or decrease in glucose or lipid levels. All laboratory values within $2^1/_2$ years before or after initiation were included. Of these, both the mean and the maximum laboratory values (or minimum value in the case of HDL) were compared within and between drug groups. The changes in mean and maximum values were also compared. Analyses of covariance were conducted to determine the effects of each individual antipsychotic on glucose and lipid levels. Patients' age, the duration of time on antipsychotic treatment, the glucose or lipid value at time of drug initiation, and other medications that may affect glucose or lipid levels (e.g., β-blockers, diuretics, estrogens) were controlled for in the statistical analyses using an analysis of covariance. Refer to Table 1 for a list of medications that may affect glucose or lipid levels.

Lastly, we determined the percentage of patients who had clinically significant changes in glucose or lipid measurements, excluding those patients who met clinically significant laboratory cutoff values prior to initiation of the target medication and/or those patients who were taking glucose- or lipid-lowering agents prior to initiation. Based on the standard guidelines set forth by the American Diabetes Association[42] and the National Cholesterol Education Program,[43] we defined clinical significance as fasting glucose ≥ 126 mg/dL, total cholesterol ≥ 200 mg/dL, triglyceride levels ≥ 200, LDL ≥ 160 mg/dL, and HDL < 35 mg/dL. In order to compensate for the fact that glucose data gathered may not have necessarily been fasting measurements, a second glucose cutoff point of 200 mg/dL was also used (random glucose level).[42] Although random blood sugar measurements are by no means specific to the diagnosis of diabetes, they are often used in clinical practice to detect possible glucose intolerance. We utilized chi-square analyses to determine the relative clinical significance of our findings. Patients taking quetiapine were excluded from the analyses of covariance due to the small sample size.

RESULTS

Subjects

A total of 590 charts of patients taking the selected antipsychotics were reviewed. Of these, 375 patients were excluded based on lack of adequate data. Thus, 215 patients were included in the study and antipsychotic use was noted as follows: clozapine (N = 39), olanzapine (N = 32), risperidone (N = 49), quetiapine (N = 13), haloperidol (N = 41), and fluphenazine (N = 41). Patient demographics are detailed in Table 2. The majority of patients in this study were male, and there were no significant differences in gender between the groups. There were statistically significant differences in age between the groups; thus, this was controlled for in the analyses. Patients on haloperidol therapy were significantly older than those on treatment with olanzapine, risperidone, and

Table 2. Patient Demographics[a]

Drug	N	Male N	Male %	Age, y[b] Mean	Age, y[b] SD	White[c] N	White[c] %	African American[c] N	African American[c] %	BMI (kg/m^2)[d]	Treatment Duration, mo Mean	Treatment Duration, mo SD	Time Until Weight Measured, y Mean	Time Until Weight Measured, y SD
Clozapine	39	34	87.2	51.2	8.9	28	71.8	9	23.1	29.8	43.3	21.3	2.5	3.6
Olanzapine	32	30	93.8	45.5	7.4	14	43.8	13	40.6	31.9	13.5	10.8	1.3	1.1[e,f,g]
Risperidone	49	47	95.9	50.7	10.2	17	34.7	18	36.7	28.6	19.2	13.0	0.9	1.6[e,f,g]
Quetiapine	13	12	92.3	49.8	8.0	9	69.2	2	15.4	33.0	7.3	4.6	0.5	0.6[e,f,g]
Haloperidol	41	40	97.6	56.5	11.8	13	31.7	21	51.2	29.6	37.1	28.3	3.0	3.1[f]
Fluphenazine	41	41	100.0	54.6	12.5	15	36.6	22	53.7	25.2	47.9	24.1	4.8	4.0[e]

[a]Abbreviation: BMI = body mass index.
[b]Haloperidol is significantly different from olanzapine, risperidone, and quetiapine. Clozapine is significantly different from olanzapine (F = 5.0, df = 5,209; p = .0003).
[c]Clozapine and quetiapine are significantly different from the other groups (χ^2 = 35.3, df = 15, p = .002).
[d]Fluphenazine is significantly different from olanzapine and quetiapine (F = 2.5, df = 5,131; p = .04).
[e]Significantly different from clozapine (F = 22.71, df = 5,143; p < .0001).
[f]Significantly different from fluphenazine (F = 22.71, df = 5,143; p < .0001).
[g]Significantly different from haloperidol (F = 22.71, df = 5,143; p < .0001).

quetiapine (F = 5.0, df = 5,209; p = .0003). Patients on clozapine therapy were significantly older on average than those patients on olanzapine therapy (F = 5.0, df = 5,209; p = .0003). Ethnic composition varied somewhat between groups. Clozapine- and quetiapine-treated subjects were predominantly white compared with the other groups (χ^2 = 35.3, df = 15, p = .002). Due to the lack of available data on patients' weight over time, only 1 weight was recorded on each patient during treatment with the particular antipsychotic of interest. However, we did find statistically significant differences in BMIs between groups. Patients on fluphenazine therapy weighed significantly less than those on treatment with olanzapine and quetiapine (F = 2.5, df = 5,131; p = .04). There were also differences in treatment duration between drug groups; however, this was controlled for in the analysis.

The following results summarize the principal findings from the data listed in Table 3 and Figure 1.

Glucose

Patients on treatment with clozapine, olanzapine, and haloperidol showed a significant increase in glucose level from baseline (+14%, t = –2.0, df = 34, p = .05 for clozapine; +21%, t = –2.3, df = 31, p = .03 for olanzapine; +7%, t = –2.2, df = 32, p = .04 for haloperidol). Patients on clozapine and olanzapine therapy also showed significant increases in maximum glucose levels (+31%, t = –2.3, df = 34, p = .03 for clozapine; +37%, t = –2.1, df = 31, p = .04 for olanzapine). Analysis of covariance revealed no significant difference in mean (F = 0.4, df = 4,148; p = .8) or maximum glucose level (F = 1.3, df = 4,148; p = .3) between groups or a significant difference in change of mean (F = 0.2, df = 4,148; p = .9) or change of maximum (F = 1.3, df = 4,148; p = .3). Following the initiation of clozapine, 5 patients (13%) in the clozapine group required initiation of a glucose-lowering agent. No patients in the olanzapine group required initiation of a glucose-lowering agent; however, 2 patients (6%) in this group were previously controlled on glucose-lowering agents and required an increased dose to control their glucose level following initiation of olanzapine. In contrast, no patients from the risperidone, quetiapine, haloperidol, or fluphenazine groups required an intervention. Table 4 displays the mean number of glucose levels measured prior to initiation of the drug and during drug therapy.

Total Cholesterol

There were statistically significant differences among the groups in both mean total cholesterol (F = 2.9, df = 4,137; p = .03) and maximum total cholesterol (F = 3.3, df = 4,137; p = .01) levels. There were also statistically significant differences among the groups in changes in mean (F = 2.5, df = 4,137; p = .04) and changes in maximum cholesterol level (F = 2.6, df = 4,137; p = .04) levels. Patients receiving risperidone demonstrated a statistically significant decrease from baseline in maximum total cholesterol level (–6%, t = 2.2, df = 29, p = .04). Those receiving fluphenazine demonstrated a significant decrease from baseline in mean total cholesterol (–6%, t = 2.2, df = 31, p = .04) and maximum total cholesterol (–6%, t = 2.4, df = 31, p = .03) levels. Post hoc comparisons demonstrated that clozapine resulted in significantly higher mean total cholesterol levels than fluphenazine (F = 2.9, df = 4,137; p = .03) and significantly higher maximum total cholesterol levels (F = 3.3, df = 4,137; p = .02) compared with risperidone. Six patients (15%) in the clozapine group required initiation of a cholesterol-lowering agent after beginning treatment with clozapine. Four patients (13%) in the olanzapine group required increases in doses in their lipid-lowering agents to bring their lipid levels back to normal following the initiation of olanzapine.

Triglyceride Levels

There were statistically significant differences among the groups in both mean triglyceride (F = 6.6, df = 4,115;

Table 3. Mean Laboratory Values and Mean of the Maximum Laboratory Values (minimums are reported in the case of HDL)[a]

	Mean Value					Maximum Value (minimum for HDL)				
	Baseline		After		Change	Baseline		After		Change
Value	Mean	SD	Mean	SD	(%)	Mean	SD	Mean	SD	(%)
Glucose (mg/dL)	(F = 0.4, df = 4,148; p = .8)					(F = 1.3, df = 4,148; p = .3)				
Clozapine	102.3	18.5	116.9	44.7[b]	+14	111.2	25.1	145.8	96.0[b]	+31
Olanzapine	105.8	22.9	128.0	65.0[b]	+21	116.6	30.3	160.3	126.5[b]	+37
Risperidone	118.3	65.0	122.3	44.6	+3	133.4	74.6	144.6	63.2	+8
Quetiapine	106.6	18.9	115.7	50.1	+9	133.4	68.9	133.3	100.2	0
Haloperidol	98.9	17.5	106.2	15.7[b]	+7	107.5	25.2	114.9	21.5	+7
Fluphenazine	103.5	29.1	111.9	39.3	+8	123.7	55.1	118.6	44.3	–4
Total cholesterol (mg/dL)[c,d]	(F = 2.9, df = 4,137; p = .03)					(F = 3.3, df = 4,137; p = .01)				
Clozapine	200.8	38.5	210.7	39.2	+5	210.6	42.8	220.7	40.9	+5
Olanzapine	219.8	46.3	207.5	29.2	–6	233.6	49.1	223.0	33.5	–5
Risperidone	195.6	41.5	188.2	36.6	–4	209.7	49.6	197.5	43.1[b]	–6
Quetiapine	206.3	67.4	204.8	40.3	–1	216.2	65.9	220.6	48.2	+2
Haloperidol	205.0	53.0	205.8	49.1	0	217.2	55.6	218.4	58.6	+1
Fluphenazine	215.7	55.9	203.3	43.0[b]	–6	228.1	54.7	214.7	47.8[b]	–6
Triglycerides (mg/dL)[c,d]	(F = 6.6, df = 4,115; p = .0001)					(F = 4.7, df = 4,115; p = .002)				
Clozapine	164.4	126.6	219.9	137.7[b]	+34	190.6	134.1	270.2	187.9[b]	+42
Olanzapine	185.3	113.8	255.0	177.2[b]	+38	238.8	194.1	338.3	312.8	+42
Risperidone	133.0	108.1	157.8	133.5	+19	175.6	171.2	197.9	250.1	+13
Quetiapine	272.4	227.4	204.2	117.3	–25	285.3	224.9	216.3	134.6	–24
Haloperidol	115.6	59.4	112.8	50.6	–2	139.4	83.3	126.2	57.1	–9
Fluphenazine	136.5	73.2	118.0	80.0	–14	163.4	99.4	141.1	104.4	–14
LDL (mg/dL)[d]	(F = 2.3, df = 4,116; p = .06)					(F = 4.8, df = 4,116; p = .001)				
Clozapine	129.2	33.0	123.6	38.7	–4	139.5	37.0	132.0	38.5	–5
Olanzapine	129.7	42.2	111.3	28.1[b]	–14	138.0	45.5	122.4	33.7[b]	–11
Risperidone	122.8	31.8	109.2	31.8[b]	–11	136.7	41.9	116.5	35.8[b]	–15
Quetiapine	138.7	50.5	120.9	39.4[b]	–13	143.3	51.6	125.1	38.1[b]	–13
Haloperidol	134.9	48.1	136.6	47.0	+1	141.7	51.4	147.3	53.6	+4
Fluphenazine	138.8	40.0	134.0	37.2	–3	151.6	40.6	143.6	39.2	–5
HDL (mg/dL)[c,d]	(F = 2.4, df = 4,126; p = .05)					(F = 5.2, df = 4,126; p = .0005)				
Clozapine	41.6	12.5	38.9	10.2	–6	39.8	12.6	34.8	8.4[b]	–13
Olanzapine	43.1	12.9	38.8	9.1[b]	–10	41.6	14.5	36.6	8.4	–12
Risperidone	45.4	18.4	47.7	17.8	+5	41.4	17.2	45.9	18.3	+11
Quetiapine	43.4	12.6	44.2	8.5	+2	41.8	11.6	41.7	8.0	0
Haloperidol	48.7	16.3	45.5	14.3	–7	45.9	16.6	43.6	14.2	–5
Fluphenazine	48.2	10.0	48.1	14.9	0	43.8	10.4	44.1	14.3	+1

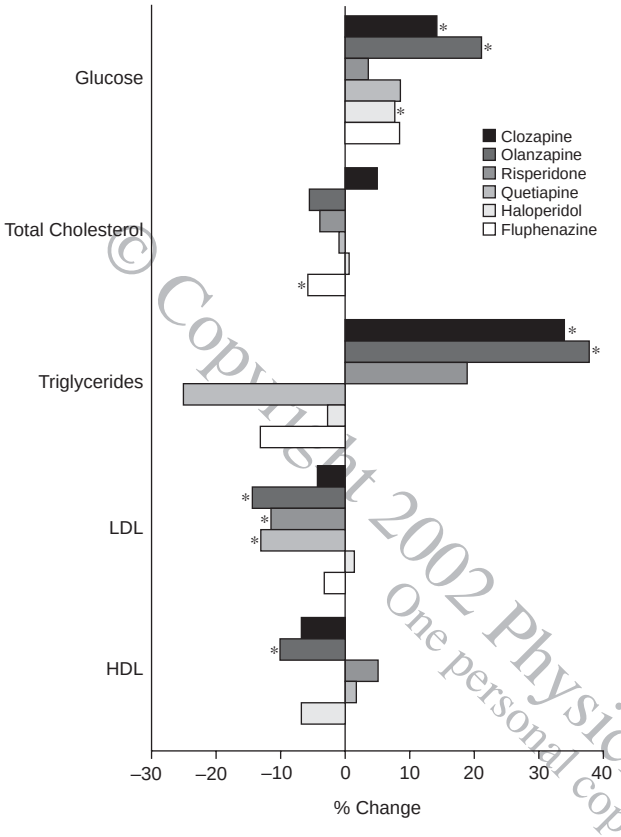
[a]Abbreviations: HDL = high-density lipoprotein, LDL = low-density lipoprotein.
[b]Significant difference from baseline ($p < .05$).
[c]Significant difference between mean laboratory values among different groups.
[d]Significant difference between mean of the maximum values (minimum for HDL) among different groups.

p = .0001) and maximum triglyceride (F = 4.7, df = 4,115; p = .002**)** levels. There were also statistically significant changes among the groups in mean (F = 4.1, df = 4,115; p = .004) and maximum triglyceride (F = 4.1, df = 4,115; p = .004) levels. Patients on treatment with clozapine and olanzapine demonstrated significant increases in mean triglyceride levels from baseline (+34%, t = –2.5, df = 26, p = .01 for clozapine; +38%, t = –2.7, df = 26, p = .02 for olanzapine). Clozapine-treated patients also experienced a statistically significant increase in maximum triglyceride levels (+42%, t = –2.6, df = 26, p = .02). Post hoc comparisons demonstrated that clozapine and olanzapine resulted in significantly higher mean triglyceride levels than haloperidol (clozapine vs. haloperidol [F = 6.6, df = 4,115; p = .008]; olanzapine vs. haloperidol [F = 6.6, df = 4,115; p = .02]) and fluphenazine (clozapine vs. fluphenazine [F = 6.6, df = 4,115; p = .0003]; olanzapine vs. fluphenazine [F = 6.6, df = 4,115; p = .002]). In addition, clozapine (F = 4.7, df = 4,115; p = .004) and olanzapine (F = 4.7, df = 4,115; p = .02) both resulted in significantly higher maximum triglyceride levels compared with fluphenazine.

LDL

There was a statistically significant difference among the groups on maximum LDL levels (F = 4.8, df = 4,116; p = .001) and a trend that nearly reached statistical significance among the groups on mean LDL levels (F = 2.3, df = 4,116; p = .06). No difference was found in changes in mean LDL levels (F = 2.3, df = 4,116; p = .06). However, a significant difference was found in changes to maximum LDL values (F = 3.79, df = 4,116; p = .006). Patients receiving olanzapine, risperidone, and quetiapine, interestingly, all showed significant decreases in mean LDL levels from baseline (–14%, t = 2.4, df = 19, p = .03 for olanzapine; –11%, t = 3.1, df = 24, p = .006 for risperidone; and –13%, t = 2.6, df = 6, p = .04 for quetiapine) as well as significant decreases in maximum

Figure 1. Percentage of Change in Mean Glucose and Lipid Values[a]



[a]Abbreviation: HDL = high-density lipoprotein, LDL = low-density lipoprotein.
*p < .05.

LDL levels (–11%, t = 2.3, df = 19, p = .04 for olanzapine; –15%, t = 3.0, df = 24, p = .006 for risperidone; –13%, t = 2.8, df = 6, p = .03 for quetiapine). Post hoc comparisons demonstrated that risperidone resulted in significantly lower maximum LDL levels than clozapine and haloperidol (F = 4.8, df = 4,116; p = .0001). In addition, olanzapine resulted in significantly lower maximum LDL levels than haloperidol (F = 4.8, df = 4,116; p = .001).

HDL

There were statistically significant differences among the groups on both mean (F = 2.4, df = 4,126; p = .05) and minimum HDL levels (F = 5.2, df = 4,126; p = .0005). Patients on clozapine treatment demonstrated significantly lower minimum HDL values compared with baseline (–13%, t = 2.5, df = 28, p = .02). Patients on olanzapine treatment developed significantly lower mean HDL levels compared with pretreatment (–10%, t = 2.3, df = 23, p = .03). Post hoc analysis revealed that clozapine (F = 5.2, df = 4,126; p = .0005) and olanzapine (F = 5.2, df = 4,126; p = .02) resulted in significantly lower minimum HDL levels compared with risperidone, which actually resulted in an increase in mean HDL levels by 5% and minimum HDL levels by 11%. Clozapine also resulted in a significantly lower minimum HDL than fluphenazine (F = 5.2, df = 4,126; p = .04). No differences were found between groups in changes in mean HDL values (F = 1.71, df = 4,126; p = .2); however, there were statistically significant differences in changes in minimum HDL levels (F = 3.9, df = 4,126; p = .005).

Table 4. Mean (SD) Number of Glucose Values Measured Before and During Therapy

	No. of Glucose Measurements			
	Before		During	
Drug	Mean	SD	Mean	SD
Clozapine	3.0	2.3	4.5	2.1
Olanzapine	5.0	4.0	2.9	2.0
Risperidone	4.7	3.1	3.2	1.9
Quetiapine	6.3	7.1	2.0	1.1
Haloperidol	3.7	3.2	4.3	3.3
Fluphenazine	4.8	3.8	5.1	3.2

Clinical Significance

Using a cutoff of 126 mg/dL for fasting blood glucose, 44% of patients receiving clozapine, 27% of patients receiving olanzapine, 36% of patients receiving risperidone, and 13% of patients receiving quetiapine developed clinically significant elevations in fasting glucose levels compared with 33% of patients in the haloperidol group and 19% of patients in the fluphenazine group ($\chi^2 = 3.7$, df = 4, p = .5). Using a cutoff of 200 mg/dL for random blood glucose, 4% of patients receiving clozapine, 5% of patients receiving olanzapine, 8% of patients receiving risperidone, and 0% of those receiving quetiapine developed clinically significant elevations in random glucose levels compared with 0% for haloperidol and 5% for fluphenazine ($\chi^2 = 1.8$, df = 4, p = .8). No statistical differences were found for the percentage of patients with clinically significant changes in glucose levels between groups. Overall, 48% of patients receiving clozapine, 25% of patients receiving olanzapine, 21% of patients receiving risperidone, and 25% of those receiving quetiapine developed clinically significant elevations in total cholesterol level (defined as total cholesterol ≥ 200 mg/dL) compared with 26% of patients receiving haloperidol and 28% of patients receiving fluphenazine ($\chi^2 = 4.3$, df = 4, p = .4). Fifty-six percent of patients receiving clozapine, 39% of patients receiving olanzapine, 31% of patients receiving risperidone, and 40% of patients receiving quetiapine developed clinically significant elevations in triglyceride levels (defined as triglycerides ≥ 200 mg/dL) compared with 0% of patients receiving haloperidol and 8% of patients receiving fluphenazine ($\chi^2 = 21.7$, df = 4, p = .0002). Though not statistically significant, 18% of patients receiving clozapine, 8% of patients receiving olanzapine, 0% of patients

Table 5. Percentage of Patients With Clinically Significant Changes in Glucose and Lipid Values[a,b]

	Clozapine		Olanzapine		Risperidone		Quetiapine		Haloperidol		Fluphenazine				
Value (mg/dL)	N	%	N	%	N	%	N	%	N	%	N	%	χ^2	df	p Value
Glucose ≥ 126	11/25	44.0	6/22	27.3	9/25	36.0	1/8	12.5	7/21	33.3	4/21	19.1	3.7	4	.5
Glucose ≥ 200	1/25	4.0	1/22	4.6	2/25	8.0	0/18	0	0/21	0	1/21	4.8	1.8	4	.8
Cholesterol ≥ 200	10/21	47.6	5/20	25.0	4/19	21.1	2/8	25.0	6/23	26.1	7/25	28.0	4.3	4	.4
Triglycerides ≥ 200	10/18	55.6	5/13	38.5	5/16	31.3	2/5	40.0	0/21	0	2/24	8.3	21.7	4	.0002
LDL ≥ 160	3/17	17.7	1/13	7.7	0/16	0	0/6	0	5/22	22.7	4/22	18.2	4.8	4	.3
HDL < 35	9/25	36.0	5/22	22.7	1/22	4.6	1/8	12.5	5/23	21.7	6/25	24.0	6.8	4	.1

[a]Clinically significant changes defined as glucose ≥ 126 or 200 mg/dL, total cholesterol ≥ 200 mg/dL, triglycerides ≥ 200 mg/dL, LDL ≥ 160 mg/dL, or HDL < 35 mg/dL.[40,41] Abbreviations: HDL = high-density lipoprotein, LDL = low-density lipoprotein.
[b]Quetiapine was not included in the statistical analysis due to the small number of patients in this group.

receiving risperidone, and 0% of patients receiving quetiapine developed clinically significant elevations in LDL levels (defined as LDL ≥ 160 mg/dL) compared with 23% of patients receiving haloperidol and 18% of patients receiving fluphenazine ($\chi^2 = 4.8$, df = 4, p = .3). Thirty-six percent of patients receiving clozapine, 23% of patients receiving olanzapine, 5% of patients receiving risperidone, and 13% of patients receiving quetiapine developed clinically significant decreases in HDL levels (defined as HDL < 35 mg/dL) compared with 22% of patients in the haloperidol group and 24% of patients in the fluphenazine group ($\chi^2 = 6.8$, df = 4, p = .1) (Table 5).

DISCUSSION

This retrospective study demonstrates that novel antipsychotics have different patterns of effects on glucose, triglyceride, and cholesterol levels. Also, interestingly, we found that the conventional antipsychotics carried some liability in terms of these parameters as well. Both clozapine and olanzapine were associated with the greatest increases in glucose levels. Patients on clozapine and olanzapine treatment also showed the most significant increases in triglyceride levels compared with the other groups. Our work also shows curious effects on LDL and HDL levels. The decrease in LDL level among patients on clozapine, olanzapine, risperidone, and quetiapine treatment is actually salutary; however, patients on treatment with clozapine and olanzapine also experience a decrease in HDL level, which may offset these positive effects and increase a patient's risk for coronary artery disease.

On average, the patients included across all the groups were overweight, with a mean BMI > 25 kg/m^2. Antipsychotics have been shown to result in weight gain and elevated glucose levels, as well as drug-induced diabetes and elevated triglyceride levels.[25,26,44] Thus, these patients have compounding risk factors for coronary artery disease. In addition, it has been shown that weight gain is a cause of treatment nonadherence with antipsychotics, which could result in rehospitalization and increased costs.[45,46] These potential adverse effects should influence the clinician's drug therapy decision in all patients, particularly those with preexisting risk factors for coronary artery disease prior to antipsychotic initiation. It is yet to be determined whether changes in glucose and lipid levels occur independent of weight gain.[43,47–50]

The effects of quetiapine on lipid measurements that we found are not consistent with the information reported by the package insert for quetiapine.[40] AstraZeneca Pharmaceuticals reports a 17% increase in triglyceride levels in patients being treated with quetiapine based on a pool of data from 3- to 6-week placebo-controlled trials and an 11% increase in total cholesterol. They found these changes in lipid levels to be "weakly related" to increases in weight. Our findings may, in part, be explained by any one of the following reasons: (1) the recent titration off of olanzapine in 3 of the 13 patients on quetiapine therapy may have resulted in an elevation of triglyceride levels prior to the initiation of quetiapine; (2) only a small number of patients were included in the quetiapine groups (N = 13); and (3) patients in the quetiapine groups took this medication for a much shorter duration of time compared with the other groups (see Table 2).

Several limitations in this study deserve attention. First, due to the retrospective nature of this study, it was unknown whether the laboratory measurements obtained through medical records were fasting measurements. Although only those laboratory results measured in the morning were included in the analysis, we have no way of knowing if patients were indeed fasting. The lack of fasting glucose levels may account for the alarmingly high rates of clinically significant glucose elevations seen with the 126 mg/dL cutoff. However, this inability to confirm a fasting state is true for both baseline laboratory measurements (those drawn before initiation) and laboratory values taken during treatment with the antipsychotic of interest. Thus, these effects were assumed to cancel each other out. Secondly, many patients were excluded from the study because they had inadequate laboratory data. The failure to measure appropriate laboratory data was due, primarily, to the fact that people were unaware of these untoward effects on lipid and glucose parameters in the years prior to this study. Third, patients who were

receiving clozapine were more likely to have cholesterol and glucose measurements simply because they were having their blood drawn on a regular basis (every 1–2 weeks) for a complete blood count. Thus, it was more likely that any changes in glucose or lipid levels would be captured for those patients on clozapine treatment.

On the basis of the data presented here and those that have been previously published, it appears as if some of the novel antipsychotics, particularly clozapine and olanzapine, have greater adverse effects on glucose and triglyceride levels than others, such as risperidone. Risperidone appears to be associated with some liability in terms of triglyceride elevations, but it may actually have a positive benefit on other cholesterol subfractions (possibly decreasing LDL). It is not surprising that the patients taking medications associated with the highest weight gain, clozapine and olanzapine, also were linked with the greatest increases in triglyceride levels.[1]

Possible explanations for weight gain with these agents include the pharmacodynamic effects of 5-HT_{2C} antagonism and H_1 antagonism.[1,49,51] Fenfluramine is thought to suppress appetite by way of 5-HT_{2C} agonism.[52] Because most of the novel antipsychotic drugs are powerful 5-HT_{2C} antagonists, they may increase food intake.[51] Furthermore, it is thought that H_1-receptor antagonism can cause overeating by peripherally interfering with normal satiety signals from the gut.[45,53] Since some of the novel antipsychotic drugs have substantial affinity for this receptor, it is possible that this characteristic contributes to this toxicity.[54] Our previous research has demonstrated that the receptor affinity characteristic that most closely correlated with weight gain among novel antipsychotic drugs was, in fact, histamine (H_1).[1] Another possible mechanism that may help to explain increases in body weight in relation to antipsychotic treatment is an insensitivity to elevated leptin levels.[55]

One potential mechanism of antipsychotic-induced diabetes is an increase in adiposity, which in turn leads to insulin insensitivity, glucose intolerance, and diabetes. This notion is supported by a study by Yazici et al.,[56] who demonstrated that clozapine resulted in an increase in blood glucose, insulin, and C-peptide levels, suggesting that glucose intolerance was due to increased insulin resistance. Serotonin is also known to play a complex role in glucose metabolism; however, the literature on this phenomenon is often contradictory.[57–59] It is generally believed, for example, that agonism of 5-HT_{1A} receptors lowers blood glucose levels, while antagonism leads to a decrease in insulin, and thus hyperglycemia.[57–59] One of the other possible mechanisms causing diabetes is elevation of free fatty acids.[60] Thus, it is interesting to note that over one third of those patients taking clozapine, olanzapine, risperidone, or quetiapine experienced clinically significant increases in their triglyceride levels, whereas less than 10% of those patients taking haloperidol or fluphenazine experienced these changes. We will need to see in the prospective work whether or not patients experiencing increases in triglyceride levels will go on to develop glucose abnormalities in the future.

Clinicians managing patients with mental illness may overlook important factors that affect a patient's general state of health. This study indicates that it is important to monitor body weight, glucose levels, and lipid panels in these patients and to ask questions to assess glucose tolerance (e.g., "Have you been experiencing increased thirst? hunger? urinary frequency?").

Our previous research demonstrated that simple behavioral measures to lose weight were effective in patients treated with risperidone and olanzapine.[1] Clinicians may also need to consider weight loss agents as adjuncts to treatment. Reinstein and colleagues[61] demonstrated in a retrospective review that the addition of quetiapine (and reduction of clozapine) in clozapine-treated patients resulted in weight loss and improved glucose parameters. Ziprasidone may be a good alternative, as premarketing studies show that it has little effect on weight.[2]

Little is known about the mechanism by which antipsychotics cause dyslipidemia. Ghaeli and Dufresne[22] report a case series of 4 clozapine-treated patients whose triglyceride levels decreased upon changing from clozapine to risperidone (a decrease in triglyceride levels occurred over a period ranging from 12 days to 4 months). In addition, in 2 of the patients, triglyceride levels increased to their previous levels within 4 months of rechallenge with clozapine.

This study demonstrates not only that both novel and conventional antipsychotics may be associated with changes in glucose levels and dyslipidemias, but also that patients are infrequently monitored for these parameters. The fact that we could find such data in only one third of our patients' records is of concern. This study adds to the growing body of literature that supports the notion that novel antipsychotic medications may increase the risks of diabetes and hyperlipidemia. Physicians need to be more aggressive in monitoring glucose and lipid levels in patients treated with these agents. Monitoring these parameters may aid in preventing the untoward consequences of diabetes and coronary artery disease in the future.

Drug names: acarbose (Precose), acetazolamide (Diamox and others), cholestyramine (Questran, Locholest, and others), clofibrate (Atromid-S and others), clonidine (Catapres, Duraclon, and others), clozapine (Clozaril and others), colestipol (Colestid), cyclosporine (Sandimmune, Neoral, and others), fluphenazine (Prolixin, Permitil, and others), gemfibrozil (Lopid and others), haloperidol (Haldol and others), indapamide (Lozol and others), insulin (Novolog, Lantus, and others), isotretinoin (Accutane), metformin (Glucophage, Glucovance, and others), metolazone (Mykrox, Zaroxolyn), minoxidil (Loniten and others), molindone (Moban), niacin (Niaspan, Niacor, and others), olanzapine (Zyprexa), pentamidine (Nebupent, Pentam, and others), phenytoin (Dilantin and others), quetiapine (Seroquel), risperidone (Risperdal), thioridazine (Mellaril and others), ziprasidone (Geodon).

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