A Retrospective Comparison of Weight, Lipid, and Glucose Changes Between Risperidone- and Olanzapine-Treated Inpatients: Metabolic Outcomes After 1 Year

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Background: Metabolic side effects have been increasingly noted during therapy with novel antipsychotics, but there is a dearth of comprehensive comparative data in this area. The goal of this retrospective study was to examine the changes in weight parameters, fasting glucose, and fasting lipids in long-term inpatients treated with either risperidone or olanzapine.

Method: A retrospective study was performed by reviewing charts of patients at Oregon State Hospital, Salem, who were treated during July and August 1999, comparing metabolic outcomes during the first year of therapy with either risperidone or olanzapine. Data were analyzed also by age, sex, and concurrent use of lithium or valproate. Included for analysis were patients at least 18 years old with baseline weights obtained within 3 weeks of drug initiation, and baseline fasting triglycerides, cholesterol, and glucose obtained within 3 months prior to drug initiation and at 1 year of treatment (± 4 weeks). The patients meeting these criteria in each drug cohort (risperidone, N = 47; olanzapine, N = 47) included 1 patient with diagnosed diabetes mellitus prior to onset of treatment.

Results: Among those patients under 60 years old, olanzapine patients (N = 37) experienced significantly greater increases at 1 year in all metabolic parameters than the risperidone group (N = 39), except for weight variables: triglycerides +104.8 mg/dL (olanzapine) versus +31.7 mg/dL (risperidone) (p = .037); cholesterol +30.7 mg/dL (olanzapine) versus +7.2 mg/dL (risperidone) (p = .004); glucose +10.8 mg/dL (olanzapine) versus +0.74 mg/dL (risperidone) (p = .030). Patients under 60 years of age with concurrent use of lithium or valproate were associated with greater weight gain in both drug groups, but this difference was statistically significant only for the olanzapine cohort. Neither weight change nor use of lithium or valproate was associated with increases in glucose or lipids among those under 60 years old for either drug.

Conclusion: Olanzapine therapy is associated with significantly greater increases in fasting glucose and lipid levels for nongeriatric adult patients than risperidone, and the increases are not correlated with changes in weight parameters. Appropriate monitoring of fasting glucose and serum lipid levels should be considered during extended treatment with atypical antipsychotics.

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The effectiveness of clozapine in refractory schizophrenia with minimal extrapyramidal side effects (EPS) led to the synthesis of newer agents designed to harness clozapine's unique psychopharmacologic properties, but without the risk of agranulocytosis.[1,2] Like clozapine, the newer atypical antipsychotics are antagonists at serotonin 5-HT_{2A} receptors, but less potent antagonists than typical antipsychotics at dopamine D_2 receptors.[3] These agents have a reduced propensity for EPS compared with typical antipsychotics and are associated with more favorable cognitive and psychiatric outcomes than achieved during therapy with typical agents.[4–10] Increasingly, however, a number of studies and case reports have emerged that document statistically significant weight gain with all of the atypical agents available in the United States through 2000: clozapine, risperidone, olanzapine, and quetiapine. Even with the recently available ziprasidone, whose effects on weight are comparable to those of haloperidol, 21.8% will experience clinically significant weight increases after 28 weeks.[11] Adverse effects on serum lipids and glucose tolerance have also been described during atypical antipsychotic therapy, particularly with the dibenzodiazepine-derived atypical antipsychotics clozapine and olanzapine and with quetiapine (a dibenzothiazepine).[12–23] Prospective data in this area are sorely lacking, but the evolving picture gleaned from retrospective studies is one of differential effects of the various atypical agents on metabolic outcomes, such

as weight gain and changes in fasting serum lipids and glucose.

One of the first health issues to be raised surrounding treatment with certain atypical antipsychotics was excessive weight gain. Weight gain plays a decided role in the health status of individuals, with the prevalence of comorbid conditions such as coronary artery disease (CAD), hypertension, and type 2 diabetes mellitus increasing significantly in those with body mass indices (BMI) in the overweight range (BMI 25.0–29.9 kg/m^2) and even more so for obese individuals (BMI ≥ 30 kg/m^2).[24] Issues of weight gain related to antipsychotic medication have been present for decades and were notable even in the pre–atypical antipsychotic era.[25–34] Moreover, compliance may be adversely affected by weight gain.[35] One interview study demonstrated that obese psychiatric patients are 13 times more likely than nonobese patients to request discontinuation of their antipsychotic medications due to weight gain and 3 times more likely to be noncompliant with their prescribed medication regimen.[36]

The issue of diabetes and glucose intolerance among patients with schizophrenia is singularly interesting, with research implicating weight gain, the use of certain antipsychotic agents, and perhaps the diagnosis of schizophrenia itself as risk factors. That the diagnosis of schizophrenia may carry an inherent risk of glucose intolerance is not well established but is suggested by 2 types of data: (1) prevalence data from the United States and other countries document 2- to 3-fold higher rates of diabetes mellitus among patients with schizophrenia[37–39] and (2) results of glucose tolerance testing reveal abnormalities among patients with schizophrenia compared with controls even when matched for age and adiposity.[40,41] Obesity itself is known to increase the relative risk of diabetes by 28-fold and certainly plays a role in the development of diabetes among patients with schizophrenia, but this issue has become complicated by the multiple clinical reports of new-onset insulin-resistant diabetes, occasionally with ketoacidosis, among individuals treated with the dibenzodiazepine-derived compounds clozapine and olanzapine and the dibenzothiazepine quetiapine who experienced minimal or no weight gain.[12,15,21,22,42–57] These data, combined with the results of glucose tolerance testing in schizophrenic patients receiving typical and atypical antipsychotics, have led investigators to conclude that there may be a direct adverse effect of certain agents such as clozapine and olanzapine on glucose tolerance independent of the contribution of weight gain.[37,41] Although there are many possible etiologies for the induction of insulin resistance by any agent, the mechanism underlying this phenomenon associated with atypical antipsychotic therapy is unclear.

Use of certain classes of antipsychotic agents also has an impact on serum lipids, with elevations in fasting triglycerides most commonly reported. This fact assumes significant importance among patients with schizophrenia, since these individuals typically possess multiple risk factors for CAD, in particular smoking.[58] Butyrophenones have minimal effects on lipid profiles, but phenothiazine therapy is associated with modest increases in fasting triglycerides and mild decreases in high-density lipoproteins, with a concomitant increase in low-density lipoproteins.[59–61] One-year clozapine data show a 35% increase in fasting triglycerides for females and a 48% increase for males,[62] whereas short-term (84-day) olanzapine treatment shows a 37% increase, again without significant effects on serum cholesterol for either drug.[13] Longer term data are not available for olanzapine. Ziprasidone appears to be relatively neutral in its effects on serum lipids, with short-term improvements noted among individuals switched from olanzapine or risperidone.[63] Of particular concern are recent reports of severe hypertriglyceridemia (> 500 mg/dL) occurring in patients treated with all of the dibenzodiazepine-derived drugs (clozapine, olanzapine, quetiapine), with fasting triglyceride levels exceeding 7500 mg/dL noted in 1 individual.[22]

This study arose in part as an attempt to better understand the comparative health outcomes with newer antipsychotic agents. Since the availability of risperidone in 1994 and olanzapine in 1996, these have become the most widely used atypical antipsychotics in the United States.[64] With weight gain and serum prolactin levels the only commonly reported health outcomes measures in comparative clinical trials, there is a gap in the existing literature examining changes in serum lipid and fasting glucose levels during extended treatment with these drugs. Moreover, the influence of factors such as concomitant lithium or valproate use, or advanced age, on metabolic outcomes with either risperidone or olanzapine is not well documented.

METHOD

This retrospective investigation was performed by reviewing the charts of patients at Oregon State Hospital, Salem, who had received treatment with olanzapine (N = 175) or risperidone (N = 155) during July and August 1999. Institutional Review Board (IRB) approval was obtained for this study. Included for analysis were patients at least 18 years old with baseline weights obtained within 3 weeks of drug initiation and baseline fasting triglyceride, cholesterol, and glucose levels obtained within 3 months prior to drug initiation and at 1 year of treatment (± 4 weeks). Each drug cohort (risperidone, N = 47; olanzapine, N = 47) included 1 patient with diagnosed diabetes mellitus prior to onset of treatment. Excluded were those with incomplete data at baseline or at 1-year endpoint. Also excluded were those who received a second atypical antipsychotic for more than 4 weeks at any time during the first year of treatment with olanzapine or risperidone, thus allowing for a limited period of cross-titration at the onset

Table 1. Baseline Demographic Data in Patients Treated With Risperidone and Olanzapine[a]

Groups[b]	Sex	Mean Age (y)	Lithium or Valproate	Weight (lb)	BMI (kg/m^2)	Triglycerides (mg/dL)	Cholesterol (mg/dL)	Glucose (mg/dL)
All patients								
Risperidone (N = 47)	40M/7F	44.0	32%	192.5	28.4	156.7	184.0	95.0
Olanzapine (N = 47)	42M/5F	45.1	43%	180.7	27.2	151.6	187.4	91.4
p Value	.542	.748	.291	.087	.268	.769	.672	.269
Patients under 60 y								
Risperidone (N = 39)	35M/4F	38.6	36%	197.6	28.8	166.3	186.3	94.1
Olanzapine (N = 37)	34M/3F	37.9	51%	184.3	27.5	165.9	186.0	89.3
p Value	.749	.786	.179	.089	.302	.984	.974	.170
Patients 60 y and older								
Risperidone (N = 8)	5M/3F	70.6	12%	167.7	26.5	110.0	172.9	99.1
Olanzapine (N = 10)	8M/2F	71.8	10%	167.7	26.2	98.8	192.4	99.1
p Value	.440	.813	.876	1.00	.852	.571	.091	.998

[a]Abbreviation: BMI = body mass index.
[b]Each group had 1 patient under 60 years of age with diabetes mellitus at baseline.

Table 2. Mean Group and Between-Drug Outcomes Comparison at 1 Year[a]

Group[b]	Weight (lb)	BMI (kg/m^2)	Triglycerides (mg/dL)	Cholesterol (mg/dL)	Glucose (mg/dL)
All patients					
Risperidone (N = 47)	+10.7[1]	+1.55[2]	+29.7[3]	+7.2[4]	+0.68[5]
Olanzapine (N = 47)	+17.5[6]	+2.55[7]	+88.2[8]	+23.6[9]	+7.26[10]
p Value	.133	.129	.042	.029	.100
Patients under 60 y					
Risperidone (N = 39)	+11.9[11]	+1.73[12]	+31.7[13]	+7.2[14]	+0.74[15]
Olanzapine (N = 37)	+20.4[16]	+2.98[17]	+104.8[18]	+30.7[19]	+10.8[20]
p Value	.091	.083	.037	.004	.030

[a]Abbreviation: BMI = body mass index.
[b]Compared with predrug baseline: [1]p ≤ .001. [2]p ≤ .001. [3]p = .028. [4]p = .131. [5]p = .762. [6]p ≤ .001. [7]p ≤ .001. [8]p ≤ .001. [9]p ≤ .001. [10]p = .031. [11]p ≤ .001. [12]p ≤ .001. [13]p = .047. [14]p = .198. [15]p = .758. [16]p ≤ .001. [17]p ≤ .001. [18]p = .002. [19]p ≤ .001. [20]p = .009.

of therapy. (No patients in the risperidone cohort were titrated off another atypical antipsychotic, but 5 in the olanzapine group were titrated from risperidone.) Demographic variables employed in the analyses include age and sex but not race, as both samples were predominantly white (> 95%), non-Hispanic. Concurrent use of lithium or valproate, drugs known to be associated with significant weight gain, was noted if either mood stabilizer was prescribed for at least 2 months during the first year of treatment with risperidone or olanzapine. Fifteen risperidone-treated patients and 20 olanzapine-treated patients used lithium or valproate for 2 months or longer during the first year of therapy with these atypical agents.

Statistics

Individual drug outcomes were performed using Student t test for paired samples, and comparative drug outcomes were assessed by t test for independent samples. Since Kolmogorov-Smirnov testing revealed a trend toward non-normality of distribution for some outcome variables, nonparametric (Spearman) correlation coefficients were calculated to examine associations between outcome parameters. All statistical calculations were performed utilizing SPSS version 9.0.[65]

RESULTS

Forty-seven patients had complete data for all parameters in each drug group. No significant differences in age, gender, weight, BMI, or fasting serum triglyceride, fasting glucose, or fasting cholesterol levels existed at baseline between the 2 groups (Table 1). The mean risperidone dose at 1 year for this group was 4.5 mg/day, and the mean olanzapine dose, 16.7 mg/day. Among the nonelderly cohort (those patients less than 60 years old), there were no significant demographic differences between the risperidone and olanzapine groups. At baseline, the elderly subgroups (N = 8 for risperidone, N = 10 for olanzapine) had BMI similar to the BMI of younger patients for both the risperidone (26.5 kg/m^2, p = .272) and olanzapine cohorts (26.2 kg/m^2, p = .314).

Both risperidone- and olanzapine-treated patients had statistically significant increases in weight parameters during the first year of treatment compared with baseline, but there was no significant difference between the 2 drugs when compared for all patients or those under 60 years old (Table 2). Overall the olanzapine patients gained more weight from baseline (+17.5 lb, p ≤ .001) than the risperidone patients (+10.7 lb, p ≤ .001), and this difference was greater when examined among those under 60 years old: +20.4 lb, p ≤ .001 for the olanzapine cohort and +11.9 lb, p ≤ .001 for the risperidone cohort. However, these differences between drugs were not significant at the .05 level.

Risperidone-treated patients did have a statistically significant increase in fasting triglyceride concentration from baseline, but the olanzapine-treated patients had markedly greater increases in fasting triglyceride levels at 1 year compared with baseline and with the risperidone

Table 3. Effect of Concurrent Lithium or Valproate Usage and Age on Individual Drug Outcomes[a]

	Effect of Age			Effect of Lithium or Valproate Use		
Drug/Variable[b]	< 60 y	≥ 60 y	Between-Group p Value	Lithium or Valproate Use	No Lithium or Valproate Use	Between-Group p Value
Risperidone	N = 39	N = 8		N = 15	N = 32	
Weight (lb)	+11.9[1]	+4.6[2]	.461	+16.1[3]	+8.1[4]	.249
BMI (kg/m^2)	+1.73[5]	+0.671[6]	.489	+2.27[7]	+1.21[8]	.285
Triglycerides (mg/dL)	+31.7[9]	+20.0[10]	.624	+50.1[11]	+20.1[12]	.227
Cholesterol (mg/dL)	+7.2[13]	+7.3[14]	.994	+6.7[15]	+7.4[16]	.942
Glucose (mg/dL)	+0.74[17]	+0.38[18]	.951	+2.3[19]	–0.09[20]	.632
Olanzapine	N = 37	N = 10		N = 20	N = 27	
Weight (lb)	+20.4[21]	+6.6[22]	.046	+27.4[23]	+10.1[24]	.009
BMI (kg/m^2)	+2.98[25]	+0.940[26]	.047	+4.06[27]	+1.43[28]	.006
Triglycerides (mg/dL)	+104.8[29]	+26.9[30]	.021	+92.9[31]	+84.8[32]	.861
Cholesterol (mg/dL)	+30.7[33]	–2.8[34]	.036	+28.8[35]	+19.7[36]	.419
Glucose (mg/dL)	+10.8[37]	–5.8[38]	.001	+15.3[39]	+1.3[40]	.032

[a]Abbreviation: BMI = body mass index.
[b]Compared with predrug baseline: [1]p ≤ .001. [2]p ≤ .621. [3]p = .015. [4]p = .023. [5]p ≤ .001. [6]p = .645. [7]p = .016. [8]p = .024. [9]p = .047. [10]p = .296. [11]p = .011. [12]p = .257. [13]p = .198. [14]p = .343. [15]p = .462. [16]p = .192. [17]p = .758. [18]p = .955. [19]p = .592. [20]p = .972. [21]p ≤ .001. [22]p = .232. [23]p ≤ .001. [24]p = .015. [25]p ≤ .001. [26]p = .259. [27]p ≤ .001. [28]p = .018. [29]p = .002. [30]p = .011. [31]p ≤ .001. [32]p = .050. [33]p ≤ .001. [34]p = .837. [35]p ≤ .001. [36]p = .024. [37]p = .009. [38]p = .008. [39]p = .024. [40]p = .659.

groups. The risperidone group had a mean increase of 29.7 mg/dL (p = .028) for the group as a whole and 31.7 mg/dL (p = .047) for those under 60 years old, generating a mean total triglyceride concentration at 1 year of 186.4 mg/dL for the entire sample and 198.0 mg/dL for the nonelderly subsample. The olanzapine cohort had mean increases of 88.2 mg/dL (p ≤ .001) for the aggregate sample and 104.8 mg/dL (p = .002) for the nonelderly, with a mean total triglyceride concentration at 1 year of 239.8 mg/dL for the group as a whole and 270.7 mg/dL among those under 60 years old. Compared with the risperidone cohort, olanzapine-treated patients had significantly greater increases in triglycerides for the entire sample (p = .042) and those under 60 years old (p = .037).

There was no significant increase in fasting total cholesterol for the risperidone-treated patients or the subsample under 60 years old, but the olanzapine group experienced significant increases compared both to baseline and to the risperidone cohorts. Nonsignificant increases of 7.2 mg/dL were found for the entire risperidone group (p = .131) and the nonelderly subsample (p = .198), while the olanzapine cohort experienced increases in fasting cholesterol from baseline of 23.6 mg/dL (p ≤ .001) for the entire sample and 30.7 mg/dL (p ≤ .001) in the nonelderly. Total cholesterol at 1 year was 191.2 mg/dL for all risperidone patients and 193.5 mg/dL in the nonelderly subsample, but was 211.0 mg/dL for the entire olanzapine group and 216.7 mg/dL in the nonelderly. At 1 year, the increases in total cholesterol levels were significantly greater for the olanzapine group compared with the risperidone group as a whole (p = .029) and for comparison between the nonelderly subsamples (p = .004).

No significant increases in fasting glucose from baseline were experienced by the risperidone-treated patients (+0.68 mg/dL, p = .762) or the nonelderly risperidone group (+0.74 mg/dL, p = .758). The olanzapine cohort as a whole (+7.3 mg/dL, p = .031) and the nonelderly (+10.8 mg/dL, p = .009) did have increases that were significant compared with baseline. The difference in fasting glucose levels between the 2 drugs was not significant for the groups as a whole (p = .10), but was for the nonelderly subpopulation (p = .03). One case of new onset diabetes mellitus occurred in an olanzapine-treated patient. The dosage at 12 months did not correlate with changes in fasting glucose or any of the other metabolic outcome parameters for either atypical agent.

To examine whether metabolic effects were significant among the elderly, the data were stratified by age into 2 groups comprising patients under 60 years old and patients aged 60 and over. Age 60 was chosen as the cutoff as this represents the typical age at entrance into the geriatric wards of the hospital (Table 3). Patients aged 60 and over did not manifest significant increases in any metabolic parameter at 1 year for either drug. The younger olanzapine patients experienced significantly greater increases from baseline in all metabolic parameters at 1 year compared with those aged 60 and over, but the younger risperidone patients had no significant differences compared with the older risperidone cohort. Although the nonelderly experienced greater weight gain than those aged 60 and over, there was no significant correlation between weight gain and changes in fasting glucose or lipids in the former subpopulation for either drug (Table 4).

Both risperidone- and olanzapine-treated patients without concurrent use of lithium or valproate experienced statistically significant increases in weight and BMI during the first year of therapy, but the risperidone group did not have significant changes in fasting lipid or glucose levels, while the olanzapine group had significant increases in fasting triglyceride concentrations (+84.8 mg/dL, p = .05), and total cholesterol (+19.7 mg/dL, p = .024), but not fasting glucose levels (Table 3). The addition of lithium or

Table 4. Spearman Correlations Between Weight Gain and Change in Triglycerides, Cholesterol, and Glucose (Age < 60 y)[a]

	Olanzapine (N = 37)		Risperidone (N = 39)	
Variable	R_S	p Value	R_S	p Value
Triglycerides	.113	.506	.046	.781
Cholesterol	–.164	.333	.055	.738
Glucose	–.080	.636	.013	.938

[a]Abbreviation: R_s = Spearman rank correlation coefficient.

Table 5. Spearman Correlations Between Lithium and Valproate Use and Outcome Variables (Age < 60 y)[a]

	Olanzapine (N = 37)		Risperidone (N = 39)	
Variable	R_S	p Value	R_S	p Value
Weight	.385	.019	.126	.445
BMI	.408	.012	.131	.428
Triglycerides	.137	.420	.223	.171
Cholesterol	–.041	.812	.135	.411
Glucose	.281	.092	–.045	.785

[a]Abbreviations: BMI = body mass index, R_s = Spearman rank correlation coefficient.

valproate doubled the weight gain (+16.1 lb vs. +8.1 lb) and BMI increases (+2.27 kg/m^2 vs. +1.21 kg/m^2) in the risperidone patients, but this was not statistically significant. Among the olanzapine cohort, the use of these mood stabilizers nearly tripled the increases in both weight gain (+27.4 lb vs. +10.1 lb) and BMI (+4.06 kg/m^2 vs. + 1.43 kg/m^2), and these differences were significant (p = .009 and p = .006, respectively). For the risperidone group, the use of concurrent lithium or valproate was associated with a significant increase in fasting triglycerides (+50.1 mg/dL, p = .011), but not cholesterol or glucose compared with baseline, while the comparable olanzapine cohort experienced significant increases in all of these parameters, particularly fasting glucose (+15.3 mg/dL, p = .024). Among the nonelderly, the use of these 2 mood stabilizers correlated only with increases in weight and BMI for olanzapine-treated patients, but not other variables, and did not correlate with changes in any metabolic parameter for the risperidone cohort (Table 5).

DISCUSSION

Concerns about the overall health care of patients with schizophrenia fit neatly into the broadening scope of treatment of this disorder during the recent decade. In the past, treatment of schizophrenia was focused primarily on the alleviation of both positive and negative symptoms, but recently clinics and institutions have devised plans of care that include measures to address deficits in cognitive and social functioning.[66,67] While these additional neurocognitive and functional domains of illness are important, patients with schizophrenia also suffer increased medical morbidity and mortality compared with the general population, with a large body of literature documenting both increased prevalence and severity of medical disorders and undertreatment of common medical conditions such as hyperlipidemia and CAD.[68–73] The resurgence of interest in this area over the last half decade coincides with the realization that atypical antipsychotics may be contributors to the medical morbidity of schizophrenia. It has also been recognized that there are differential effects among these agents on metabolic outcomes, with the dibenzodiazepine-derived atypicals (clozapine, olanzapine) and the dibenzothiazepine quetiapine associated with greater adverse effects on weight, glucose, and serum lipids than risperidone (benzisoxazole) or ziprasidone (benzisothiazolyl), an atypical antipsychotic released in the United States in March 2001 that has low propensity for weight gain or adverse effects on glucose tolerance or serum lipids.[11,34,63]

There is a gradient of weight increases seen during extended treatment with atypical agents, with published studies showing relatively less gain with risperidone, ziprasidone, and quetiapine and substantial gains with clozapine and olanzapine. Mean increases during the first year of therapy are 5.3–6.3 kg (11.7–13.9 lb) for clozapine, and 6.8–11.8 kg (15.0–26.0 lb) for olanzapine, with substantial fractions in each group gaining more than 20% of their initial body weight in this time frame.[16,74–76] Risperidone and quetiapine studies report mean gains of 2.0–2.3 kg (4.4–5.1 lb) and 2.8–5.6 kg (6.1–12.3 lb), respectively, over 12 months, which compare favorably with low potency typical antipsychotics.[7,17,18,77–80] Ziprasidone appears to have the most favorable weight gain profile among the currently available atypicals, with a mean gain of 0.23 kg (0.5 lb) at 6 months of treatment.[11] The synergistic effects of histamine H_1 and serotonin 5-HT_{2C} antagonism have been postulated as a pharmacologic mechanism underlying generally greater weight gain experienced with atypical antipsychotics, with effects on leptin homeostasis possibly playing a role.[19,78,81]

As expected from the literature, both risperidone and olanzapine groups in this study had statistically significant increases in weight from baseline, and these effects were magnified by concurrent use of lithium or valproate. Administration of lithium or valproate alone is clearly associated with significant weight gain and the concurrent use of either mood stabilizer with risperidone or olanzapine increased the amount of weight gain. The difference in weight gain between those who did or did not receive these mood stabilizers, however, was statistically significant only for the olanzapine cohort.[82] Smaller sample size for the risperidone cohort receiving a mood stabilizer (N = 15) may explain the lack of statistical significance, despite nearly double the weight gain compared with those on risperidone alone. Although those who received lithium

or valproate experienced greater weight gain, the use of these agents was not correlated with changes in fasting glucose or lipid values. Valproate treatment is not known to have any impact on glucose handling, but there is a small body of literature from epilepsy studies documenting minimal, or possibly favorable, effects on triglycerides and high-density lipoproteins.[83–85] Lithium therapy is not associated with changes in serum lipids, and long-term studies in lithium-treated bipolar patients demonstrate no greater prevalence of diabetes mellitus.[86,87] Further studies may help to clarify the role of mood stabilizers in metabolic outcomes and also the role of an underlying mood disorder (e.g., bipolar, schizoaffective) as an independent covariate.

Weight gain is generally associated with increases in fasting glucose and lipids, but in this study weight changes did not correlate with increases in fasting glucose or lipids for those patients under 60 years old receiving either atypical antipsychotic.[24,88] The published literature is largely retrospective and demonstrates a variable correlation between the role of weight gain and metabolic outcomes with atypical antipsychotic therapy. Long-term clozapine data from Henderson et al.[16] do not demonstrate a correlation between weight parameters and the development of diabetes, and the information gleaned from multiple case reports[12,22,45] also indicates that in some individuals on olanzapine or clozapine therapy the onset of type 2 diabetes is independent of significant weight gain. Henderson et al.[16] did show a significant correlation between weight gain and increases in fasting cholesterol and triglyceride levels when controlled for time of exposure, and Osser et al.[13] showed a relationship between increases in fasting triglycerides and weight gain for a group of olanzapine-treated patients; however, in one study,[22] there was no correlation with serum triglycerides for a series of patients treated with olanzapine or quetiapine who developed severe hyperlipidemia.[13,22] Moreover, a recent study[89] comparing cardiovascular risk between olanzapine and risperidone found that 32% of the olanzapine group manifested the atherogenic metabolic triad of hyperinsulinemia, elevated apolipoprotein B concentrations, and small dense low-density lipoprotein, but only 5% of the risperidone group had these manifestations despite similar BMI values for the 2 drugs (olanzapine 26.9 ± 5.6 kg/m^2; risperidone 26.7 ± 4.7 kg/m^2).

The results of the current study generally support the hypothesis that the dibenzodiazepine-derived atypical antipsychotic agents may have direct effects on serum lipids and fasting glucose independent of their effects on weight and BMI. While patients in both drug categories who did not use mood stabilizers experienced similar amounts of weight gain, olanzapine therapy was associated with a much greater impact on fasting lipids, with significant increases from baseline for both triglycerides and cholesterol. This result would argue for drug exposure, independent of effects on weight, as the driving mechanism. Nevertheless, without the use of a mood stabilizer, the risperidone group did not experience significant increases in fasting glucose or lipids at 1 year, but the addition of lithium or valproate resulted in an increase in serum triglycerides that was significant when compared with baseline. As mentioned previously, the additional weight gain from lithium or valproate use was not statistically significant for risperidone-treated patients, yet one might reasonably suggest that this larger elevation of serum triglycerides may be physiologically related to the greater weight gain from concurrent mood stabilizers. The correlation between changes in weight and other metabolic parameters is thus not a consistent finding and underscores the need for prospective studies in this area.

The metabolic effects of both drugs were attenuated among those aged 60 and older, with neither group having statistically significant differences in any metabolic parameter at 1 year compared with baseline. Old age is typically associated with minimal weight gain or weight loss from psychotropic agents, but the limited published data have shown that weight gain may occur during therapy with some atypical antipsychotics among older populations.[90–93] In this study, the elderly subgroups had comparable BMI at baseline compared with the younger patients for both the risperidone (26.5 kg/m^2, p = .272) and olanzapine cohorts (26.2 kg/m^2, p = .314). Greater dietary restrictions placed upon the geriatric population within the state hospital setting may explain the modest weight gain seen in those 60 years and older. Again, replication with larger sample sizes is indicated.

Despite the uncertainty over the role of weight gain and metabolic changes with atypicals, the medical implications of this study bear noting. The increases in BMI for patients under 60 receiving either agent placed these groups on average in the obese category, thereby increasing their risk for comorbid disorders. The change in fasting triglycerides after 1 year was statistically significant for the nonelderly risperidone cohort, but placed the mean fasting triglycerides at 198.0 mg/dL, in the borderline-high range; however, the comparable olanzapine group experienced mean increases in fasting triglycerides that were more clinically significant. Among patients less than 60 years old, a mean triglyceride at 1 year of 270.7 mg/dL was found for olanzapine-treated patients. Elevated triglycerides represent an independent risk factor for CAD, and patients with schizophrenia typically possess other risk factors for CAD including smoking, overweight, or obesity, thus making abnormalities in serum triglycerides an important clinical concern.[70,73,94,95]

This study has several limitations, including the retrospective nature of the data collected; the absence of a control group receiving typical antipsychotic agents; the predominantly male, white, non-Hispanic demographic; and the fact that the population of interest comprised long-term

state hospital patients. The small sample sizes also limit the power to detect significant differences, especially among clinically important subgroups such as those 60 years and older, and those receiving lithium or valproate. Dose correlations calculated for this study may not be as useful as those performed in a more stable outpatient cohort due to the significant and frequent dosage adjustments performed during the first year of treatment with both agents in this severely ill state hospital population. Despite these limitations, the data presented here help fill a void in the existing literature, which heretofore has documented comparative psychiatric outcomes with risperidone and olanzapine, but paid sparse attention to other aspects of overall patient health.

CONCLUSION

As clinical experience accrues with atypical antipsychotics, the strengths and limitations of each agent are becoming clearer. Risperidone is a more potent dopamine D_2 antagonist than other atypicals and may cause extrapyramidal side effects or hyperprolactinemia in a dose-dependent manner, yet appears to have a lower propensity for metabolic side effects than clozapine, olanzapine, and quetiapine. The results of further studies will help determine the extent to which any atypical antipsychotic may contribute directly to impaired glucose tolerance and hyperlipidemia independent of its effects on weight. For the present, the current study, combined with other emerging literature on this subject, argues for a reasoned approach in the monitoring of metabolic outcomes for patients receiving antipsychotic therapy, particularly with agents associated with higher risk for adverse outcomes. A proposed metabolic monitoring protocol for patients receiving maintenance atypical antipsychotics, especially dibenzodiazepine, appears in Appendix 1. Psychiatrists and mental health workers are often the only medical professionals who interact with many individuals with schizophrenia. The failure to appropriately monitor metabolic variables may result in significant undetected short and long-term morbidity in a patient population that is typically medically underserved. The recently reported death of 1 patient from complications of ketoacidosis associated with olanzapine therapy reinforces the need for vigilance in this area.[96]

Drug names: clozapine (Clozaril and others), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

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Appendix 1. Monitoring Recommendations

There is presently a lack of consensus among psychiatrists on the issue of metabolic monitoring during atypical antipsychotic therapy, but the concern over severe adverse metabolic outcomes (diabetic ketoacidosis and severe hypertriglyceridemia) necessitates some initiatives in this area. The following suggested program is derived from consultation with psychiatrists in multiple treatment settings and input from endocrinologists. These recommendations can be applied to all adults aged 18 and over, particularly glucose monitoring, as new-onset type 2 diabetes associated with antipsychotic therapy has been seen at Oregon State Hospital, Salem, in individuals as young as 18 years old. This protocol should be considered a first approximation, which hopefully will be refined as the literature in this area continues to grow:

1. **Weight:** Baseline and monthly weights for all patients should be taken, and nutritional and behavioral intervention for obese individuals (BMI ≥ 30) or those who experience significant weight gain (≥ 7%) during treatment should be provided.

2. **Lipids:** Given the updated recommendations for hyperlipidemia teatment and the fact that patients with schizophrenia typically possess multiple cardiovascular risk factors, a full lipid panel with fractionation of cholesterol should be performed annually as part of routine health monitoring for inpatients and outpatients.[97] Quarterly fasting total triglycerides and cholesterol should be considered during the first year of atypical antipsychotic therapy. This frequency may be decreased depending on the results obtained and the agent used.

3. **Glucose:** Screening for family and personal history of diabetes should be considered for all patients with schizophrenia, particularly those with high risk due to obesity or ethnicity. Education about the symptoms of diabetes (fatigue, thirst, polyuria) should be performed for those who will be started on higher risk agents or who possess risk factors, particularly those in high risk ethnic groups.

   The American Diabetes Association[98] has established the following values for fasting glucose:

Normal	< 110 mg/dL
Impaired	110–125 mg/dL
Diabetic range	≥ 126 mg/dL or > 200 mg/dL (random glucose)

   Cases of provisional diabetes should have values confirmed on a subsequent day and must also manifest clinical symptoms if only the random glucose threshold is used.

   A baseline and quarterly fasting glucose during the first year of therapy for patients with schizophrenia should be obtained in those receiving atypical antipsychotics and may be decreased to semiannually if no changes in fasting glucose are noted and if the individual lacks other risk factors (e.g., obesity, ethnicity). In general, symptoms of diabetes should be inquired about at each clinical visit. Monthly examination for the first 3 months and a consideration of glucose tolerance testing or postprandial glucose testing may be indicated in those who are at high risk for the development of diabetes due to ethnicity, agent used, family history, or obesity or who manifest abnormal fasting glucose measurements. A high index of suspicion for ketoacidosis should be maintained in these individuals.

   Glycosylated hemoglobin values reflect changes in glycemic control over a period of 120 days and thus will lag several months behind abnormalities in fasting and postprandial glucose. It is best used as a monitoring tool for those with established impairments in glucose control, but not as a routine method of screening for diabetes.

[NB: The total cost for a fasting glucose, fasting total triglyceride, and total cholesterol is $6.50.]