3/5/02

CHANGES IN GLUCOSE AND CHOLESTEROL LEVELS IN PATIENTS WITH SCHIZOPHRENIA TREATED WITH TYPICAL AND ATYPICAL ANTIPSYCHOTICS

Jean-Pierre Lindenmayer, MD 2,5; Pal Czobor, PhD; Jan Volavka, MD, PhD 1,2; Leslie Citrome, MD, MPH 1,2; Brian Sheitman, MD 3,4; Joseph McEvoy, MD 6 ; Thomas B. Cooper, MA 1,2,7 ; Miranda Chakos, MD3,4 ; Jeffrey A. Lieberman, MD 3.

1 Nathan Kline Institute; 2 New York University; 3 University of North Carolina; 4 Dorothea Dix Hospital; 5 Manhattan Psychiatric Center; 6 Duke University and John Umstead Hospital; 7 Psychiatric Institute and Columbia University.

Corresponding author: J.P. Lindenmayer, MD; Psychopharmacology Research Unit-Nathan Kline Institute for Psychiatric Research, Wards Island, New York, NY 10035; email:

lindenmayer@nki.rfmh.org

Acknowledgements:

NIMH grant (R10 MH53550) provided the principal support for this project. Additional support was provided by the UNC-Mental Health and Neuroscience Clinical Research Center (MH MH33127) and the Foundation of Hope, Raleigh North Carolina. We thank Janssen Pharmaceutica Research Foundation, Eli Lilly and Company, Novartis Pharmaceuticals Corporation, and Merck and Co., Inc. for their generous gifts of medications. Redacted Redacted However, overall experimental design, data acquisition, statistical analyses, and interpretation of the results were implemented without any input from any of the pharmaceutical companies. Linda Kline, RN, MS, CS was the chief coordinator of the entire project.

ABSTRACT

Hyperglycemia and hypercholesterolemia associated with atypical antipsychotics have been documented in case reports and uncontrolled studies. The effects of typical and atypical antipsychotics on glucose and cholesterol levels were measured during a randomized double blind 14-week trial comparing clozapine, olanzapine, risperidone and haloperidol in hospitalized patients with schizophrenia or schizoaffective disorder. Methods: The trial consisted of Periods 1 (fixed dose, 8 weeks) and 2 (variable dose, 6 weeks). Planned assessments included fasting glucose and cholesterol, collected at baseline, at endpoints of Period 1 and of Period 2. Results: Of 157 subjects, 108 provided blood samples at baseline and at least at one point after randomization during the treatment trial. Seven of these patients were diabetics with glucose levels > 125 mg/dL at baseline resulting in 101 patients for statistical analysis. During Period 1 there was an overall significant increase in mean glucose levels (F=4.4; df=3,99; p=0.006). There were significant increases in glucose at Period 1 endpoint for clozapine (17.1 mg/dL, SD=30.5;t=2.92; p<0.01) and for haloperidol (8.4 mg/dL, SD=17.7;t=2.37; p=0.03). The olanzapine group showed a significant increase of glucose levels for Period 2 (14.3 mg/dL, SD=25.5; t= 2.62; p<0.02). Fourteen of the 101 subjects developed abnormal glucose levels (>125mg/dL) during the trial (6 on clozapine, 4 on olanzapine, 3 on risperidone, and 1 on haloperidol). Cholesterol levels were increased in Period 1 for clozapine (14.7 mg/dL, SD=30.5; t=2.50; p<0.02) and olanzapine (12.3 mg/dL, SD=28.1; t=2.22; p<0.04) and in Period 2 for olanzapine (20.1 mg/dL, SD=26.8; t=3.52; p<0.002). Conclusion: To our knowledge this is the first study comparing plasma glucose and cholesterol levels during randomized treatment with three atypical antipsychotic medications. Clozapine, olanzapine, and haloperidol were associated with an increase of plasma glucose, while cholesterol levels were increased for the clozapine and olanzapine groups. These mean changes remained within clinically normal ranges, but approximately 14% of patients developed abnormally high glucose levels (> 125 mg/dL) during the course of their participation in the study

INTRODUCTION

Abnormalities in glucose regulation have been reported in schizophrenia prior to and after the introduction of antipsychotic medications[1-6]. More recently, hyperglycemia in the context of treatment with atypical antipsychotic medications has been documented in several series of uncontrolled case reports, with clozapine and olanzapine being implicated more frequently than risperidone[7-35]. Complicating this issue is the observation that patients with schizophrenia are more likely to develop diabetes mellitus than the general population[4] regardless of antipsychotic use. In addition, there is a trend towards an increase in the prevalence of diabetes mellitus in the general population[36]. Moreover, large epidemiological studies have provided conflicting information regarding the relative risk of diabetes and exposure to different antipsychotics[33,37-40].

Similarly, significant elevations in triglyceride and cholesterol levels have been reported in the context of treatment with atypical antipsychotics[26,32,41]. However, the true incidence of both hyperglycemia and hypercholesterolemia induced by different typical or atypical medications is not known at this time. We had the opportunity to study the effects of both typical and atypical antipsychotic medications on glucose and cholesterol levels during a randomized controlled, prospective trial in patients with suboptimal response to prior antipsychotic medication.

MATERIALS AND METHODS

The data for this investigation were collected during a randomized, double-blind 14-week clinical trial of clozapine, olanzapine, risperidone, and haloperidol in patients with schizophrenia or schizoaffective disorder. The primary purpose of the trial was to

investigate the comparative efficacy of atypical antipsychotics in a sample of inpatients with suboptimal therapeutic response to previous antipsychotic treatments. A brief description of relevant details of the parent study is provided here; the complete report of the trial is available elsewhere[42].

Study design

The prospective, double-blind trial consisted of two periods, Period 1 (fixed dose, 8 weeks) and Period 2 (variable dose, 6 weeks). In Period 1, the planned duration of dose escalation (and gradual discontinuation of previous treatments) was 7 days for olanzapine, risperidone, and haloperidol, and 24 days for clozapine. The fixed dose target levels were 500, 20, 8, and 20 mg/day, for clozapine, olanzapine, risperidone and haloperidol, respectively. For subjects who were included into the main sample for statistical analyses (N=101; main sample defined below), the actual, average dose levels (mg/day; mean+SD) at the end of Period 1 were 443.7+120.17 for clozapine, 20.1+1.2 for olanzapine, 8.5+2.2 for risperidone, and 20.0+0.0 for haloperidol. In Period 2, the dose levels were adjusted on the basis of the patients' clinical status (e.g., lack of adequate improvement, side effects). Blind psychiatrists made the adjustments and the allowed dose range was 200-800 mg/day for clozapine; 10-40 mg/day for olanzapine; 4-16 mg/day for risperidone; and 10-30 mg/day haloperidol. The average observed daily doses (mg/day; mean+SD) at the end of Period 2 were 477.2+157.2, 31.4+6.0, 11.6+3.7, and 25.8+5.1, for the clozapine, olanzapine, risperidone and haloperidol group, respectively. Benztropine (4 mg/day) was administered prophylactically to all patients receiving haloperidol. Patients assigned to atypical antipsychotics were initially receiving only benztropine placebo, but if the patient's psychiatrist (who was unaware of the patient's antipsychotic assignment) determined clinically that the patient should be treated for extrapyramidal side effects, prescriptions for "benztropine supplements" could be written that would result in real benztropine gradually replacing benztropine placebo

(up to 6 mg/day). An analogous arrangement for "supplements" was available to raise the dose of benztropine from 4 to 6 mg/day in patients assigned to haloperidol for emerging extrapyramidal symptoms. Propranolol was allowed for the treatment of akathisia. Lorazepam, diphenhydramine hydrochloride or chloral hydrate were permitted as needed for agitation and insomnia. No other adjunctive psychotropic medication was allowed in the study.

Subjects

Patients were enrolled at 4 participating hospitals, 2 in New York State and 2 in North Carolina. Patients included in the parent study were required to meet the DSM-IV criteria for schizophrenia or schizoaffective disorder and were inpatients throughout the entire period of the trial. All subjects met both of the following criteria for suboptimal treatment response: (1) presence of persistent positive symptoms (hallucinations, delusions, or marked thought disorder) after at least 6 contiguous weeks of treatment with one or more typical antipsychotics at dosages equivalent or greater than 600 mg/day of chlorpromazine, and (2) a poor level of functioning over the past two years (i.e., lack of competitive employment; no enrollment in an academic or vocational program; lack of age-expected interpersonal relations with someone outside the biological family of origin with whom they maintain ongoing regular contacts). In addition, patients had to display sufficient initial overall symptom severity, as defined by a total score of $\geq$60 on the Positive and Negative Syndrome Scale (PANSS)[43]. Patients were excluded from the trial, if they had (a) history of failure to respond to clozapine, risperidone, or olanzapine; (b) history of clozapine, olanzapine, risperidone, or haloperidol intolerance; (c) depot antipsychotic treatment within 30 days before randomization and (d) significant medical illness. After complete description of the study to the subjects, written informed consent was obtained.

Assessments

Assessments for the present analysis included blood samples for glucose and cholesterol at three time points: baseline (before the first dose of study medication), at end of Period 1 and of Period 2. The inclusion criteria for the present analysis were the availability of glucose levels both at baseline and at some time during the study period. Only the results of blood samples collected at AM fasting times were included in the analyses. Plasma glucose and cholesterol levels were determined by enzymatic procedures using the Boehringer Mannheim/Hitachi 714 automated chemistry analyzer utilizing the standard analytical system packs Glucose/HK and Cholesterol/HP. Patients' weight was determined at baseline and endpoint. Patient's height was measured at the time of the enrollment in the study. Weight gain was computed as the absolute and relative (%) change of body weight (kg) between baseline and study end point. Body Mass Index (BMI) was computed as the quotient of body weight (kg) divided by the square of height (m).

Measures of medication effects not considered in the present analysis, including PANSS ratings and assessments for the Nurses' Observation Scale (NOSIE)[44], were performed at baseline at each week during the first month of the study and at every other week thereafter.

STATISTICAL ANALYSIS

The principal objective of the analyses described in this report was to examine change in glucose levels during treatment with typical and atypical antipsychotics and to determine the incidence of hyperglycemia during such treatment in subjects who had no known

history of diabetes at the time of the enrollment in the study. Accordingly, patients whose glucose blood levels at baseline were within normal laboratory limits constituted the main sample for the statistical analyses.

Relationship between change in glucose and cholesterol levels and antipsychotic medication was investigated by ANCOVA. Change in glucose and cholesterol level between baseline and end of Period 1 and between baseline and end of Period 2 were used as the dependent variable; a separate analysis was performed for each of the two measures in each of the two study periods. Last observation carried forward was used within the respective study periods. Type of medication (treatment group) was used as independent variable. Glucose and cholesterol level at baseline were used as covariates. In order to investigate change over time in terms of transitions from normal to abnormal metabolic ranges, we constructed shift tables for each of the two study periods (Period 1, Period 2) by using each of the two laboratory indices (glucose, cholesterol). Abnormal glucose level was defined in our study as > 125 mg/dL; abnormal cholesterol level was defined as >200 mg/dL.

Since the main sample comprised patients whose baseline glucose blood levels were within normal range, the shift tables for glucose change (in each group) contained only two cells (normal to abnormal, normal to normal), as each patient in the main sample could exhibit one of two potential transition sequences between baseline and the end of a study period (i.e., normal to abnormal or normal to normal). The proportion of subjects who shifted from normal to abnormal glucose levels within each treatment group was compared by chi-square analysis.

For cholesterol changes, the shift tables for each study group comprised four cells (since elevated cholesterol values could occur in the main sample at baseline). Specifically, each of the four cells in a 2 x 2 shift table represented one of four potential transition

sequences for each subject: normal to abnormal, abnormal to normal, normal to normal, abnormal to abnormal. Since the observations in a 2x2 shift table are not independent of each other, the analysis of the shift tables was based on McNemar's test.

Relationship between weight gain and change in blood levels of glucose and cholesterol was investigated by ANCOVA. Weight gain was used as the dependent variable. Change in blood levels and medication group were used as independent variables; baseline weight and blood level at baseline were used as covariates. An interaction between blood level change and medication group was included in the model. A separate ANCOVA analysis was performed for glucose and cholesterol.

RESULTS

Demographic and Basic Descriptive Data

Altogether, 157 subjects entered the double-blind trial[42]. 133 subjects provided fasting glucose levels at some point during the study. Of these, 7 subjects were excluded due to lack of baseline glucose level, and 18 due to lack of glucose levels at points during the study. This resulted in 108 subjects who were included in the present report. Seven of these subjects were diabetics who had elevated glucose levels (>125 mg/dL) at baseline and were therefore not included into the main sample; their results are presented separately in this report. The remaining 101 patients constitute the main sample for statistical analyses. Demographic characteristics of the main sample (N=101) are displayed in Table 1, which also shows the treatment assignments. Analysis of variance revealed a statistically significant difference among the four groups in glucose baseline levels ($F=4.0$; $df=3,100$; $p<0.01$). Post-hoc analyses (Tukey's studentized range test for pair-wise comparisons) for glucose levels showed that subjects in the clozapine and risperidone groups showed significantly ($p<0.05$) higher levels at baseline as compared to those in the haloperidol group. No other group baseline differences relevant for the

present analysis, including ethnic distribution among the four medication groups, showed statistical significance in the analyses.

Patient Attrition

The completion rate for the full 14-week trial was 70.3% (N=71) among the 101 subjects who were included in the main sample. There was no significant difference in the proportion of subjects who completed the entire 14 week trial in terms of the four medication groups: 64.3% (n=18 of 28) for clozapine, 68.0% (n=17 of 25) for haloperidol, 84.6% (n=22 of 26) for olanzapine and 63.6% (n=14 of 22) for risperidone.

Change in Glucose Levels over Time

Descriptive information for change in glucose in Period 1 and Period 2 is displayed in Table 2. ANCOVA analyses were conducted to examine whether there was a statistically significant difference in change over time among the 4 treatment groups. Results of these analyses indicated that differences among treatment groups reached significance in Period 1 ($F=4.4$; $df=3, 99$; $p=0.006$), but not in Period 2 ($F=1.14$; $df=3, 72$; $p=0.34$ [n.s.]). As the table shows, the increase in mean glucose blood levels over time reached statistical significance in the clozapine group after 8 weeks (Period 1: mean change =17.1 mg/dL; SD=30.5; paired-t=2.92; p=0.01), whereas the increase reached statistical significance in the olanzapine group after 14 weeks (Period 2: mean change =14.3 mg/dL, SD=25.5; paired-t=2.62; p=0.02). Significant increase in mean glucose level was also seen with haloperidol (Period 1: mean change = 8.4 mg/dL, SD=17.7; paired- t=2.37; $p<0.03$), while no significant change over time in glucose was detected in the risperidone group. All mean glucose level increases remained within the normal clinical range. Fourteen of the 101 subjects developed abnormal glucose levels (>125mg/dL) during randomized treatment (see Table 3). As the table shows, in the sample that displayed glucose elevation at some point in the trial African-American patients were represented at a higher proportion (18.6%) than White patients (10.3%) or Hispanic patients (0%).

However, these differences between the three ethnic groups failed to reach statistical significance.

The treatment group difference in the proportion of subjects with a shift of normal to abnormally elevated glucose levels in Periods 1 and 2 was not statistically significant, although there was a numerical trend for clozapine to show a higher number of shifts than for the other three groups during Period 1.

Subjects with elevated baseline glucose levels (N=7) had identified diabetes mellitus and were treated with antihyperglycemic agents during the study. As indicated by data in Table 4, glucose levels decreased in 5 of the seven subjects during the study.

Change in Cholesterol Levels over Time

Table 5 displays descriptive data for mean changes in cholesterol levels in Period 1 and Period 2. Differences among treatment groups reached significance in Period 1 ($F=10.4$; $df=3,99$; $p=0.037$) and marginal significance in Period 2 ($F=2.65$; $df=3,72$; $p=0.06$). Post-hoc pair-wise analyses (Tukey's studentized range tests) for Period 1 revealed that the difference between the clozapine and haloperidol groups reached statistical significance ($p<0.05$). Analogous analyses for Period 2 indicated no significant differences between the four treatment groups.

As shown in Table 5, there was an increase in cholesterol blood level in the clozapine group in Period 1 (mean change =14.7 mg/dL; SD=30.5; paired-t=2.50; p=0.02) and in the olanzapine group in Period 1 (mean change=12.3 mg/dL; SD=28.1; paired-t=2.22; p=0.04). Cholesterol blood level elevation in the clozapine group in Period 2 was of a similar magnitude to that seen in Period 1, however it failed to reach statistical significance. The cholesterol increase in the olanzapine group reached statistical significance in Period 2 (mean change =20.1 mg/dL; SD=26.8; paired-t=3.52; p=0.002).

No significant change over time in cholesterol was detected in the haloperidol or risperidone groups. All mean cholesterol increases remained within normal clinical range (see Table 5). The analysis of shift tables for cholesterol revealed no significant change over time in terms of transitions from normal to abnormal level in any of the four treatment groups.

Relationship between weight increase and metabolic changes:

[redacted] The largest weight gain was seen with olanzapine (mean change=7.3 kg; SD=7.6; paired-t=4.94; df=27; p<0.0001), followed by clozapine (mean change=4.8 kg; SD=6.1; paired- t=4.1; df=26; p<0.0003) and by risperidone (mean change=2.4 kg; SD=6.3; paired- t=1.79; df=21; p=0.09). There was minimal weight gain with haloperidol. ANCOVA analysis indicated no main effect or treatment interaction for the relationship between glucose change and weight gain in any of the two treatment periods.

A significant main effect for cholesterol change and weight gain was found for each of the two treatment periods (Period 1: F=9.16; df=1,98; p=0.003; Period 2: F=9.28; df=1,72; p=0.003). Exploring the effect in each individual group, we found a significant association between cholesterol increase and weight increase in Period 1 in the clozapine group (r-square=0.34; t=2.24; df=25; p=0.036). For Period 2, the association failed to reach statistical significance in any of the four treatment groups.

DISCUSSION

We believe that this is the first report comparing the simultaneous effects of four antipsychotic medications on two important metabolic measures indexing glucose and

lipid metabolism in patients with chronic schizophrenia and past suboptimal antipsychotic treatment response assigned in a randomized and blind fashion to one of four treatments. The effects of antipsychotic drugs on glucose and cholesterol metabolism is important because weight gain and metabolic effects have been reported to be classwide properties of the atypical drugs and potentially the most serious adverse effects of these drugs ([redacted]). Regarding glucose levels, we found that clozapine and haloperidol showed significantly elevated mean levels after 8 weeks of treatment, while olanzapine significantly increased glucose levels after 14 weeks of treatment. Risperidone did not increase these levels. These mean increases were modest and remained within clinically normal ranges, but approximately 14% of patients (6 on clozapine, 4 on olanzapine, 3 on risperidone, and 1 on haloperidol) developed abnormally high glucose levels (> 125 mg/dL) during the course of their participation in the study. Clozapine showed a nonsignificant trend towards a higher number of patients shifting glucose levels from normal baseline levels to clinically abnormal levels after 14 weeks of treatment. Changes in glucose levels were independent from weight increase in all four treatment groups, despite significant weight gains, which were highest for olanzapine, followed by clozapine and risperidone. In the small subset of patients with pre-existing treated diabetes, the antipsychotics we tested did not appear to have a deleterious effect on glucose metabolism.

In a nonrandomized study that compared the same three atypical and typical antipsychotics as in our study, similar results were found for clozapine and olanzapine (Personal communication with JW Newcomer). When challenged with a modified glucose tolerance test, the olanzapine and clozapine treated patient groups had significant elevations in post-load glucose levels at all time points compared with untreated controls and haloperidol-treated subjects. With regard to risperidone, mean glucose levels were significantly elevated but only compared with the control group [redacted].

We reviewed reports of hyperglycemia and diabetes mellitus (DM) during treatment with atypical antipsychotics since 1994, and found that the majority of cases implicated clozapine (20 reports), followed by olanzapine (13 reports). Case reports of quetiapine (3 reports) were reported less frequently, and of risperidone only recently (4 reports).[7-35] There is not enough data on the occurrence of DM with ziprasidone at this time. However, the frequency of case reports suffers from many limitations and reporting biases and is neither a true indication of incidence normeasure of the relative risk of developing hyperglycemia. Our present rate of 14 % is about double the incidence rates of hyperglycemia of diabetes reported in a large survey of the US population (6-8%)[45], and somewhat higher than the current prevalence rate of 10 % found by Dixon et al.[4] in a recent and extensive study of three US national schizophrenia samples. In the reviewed case reports, diabetic ketoacidosis had been the presenting symptom[8-11]. In most instances, hyperglycemia was not dose-dependent, was reversible upon cessation of the atypical antipsychotic medication, and reappeared upon the reintroduction of the precipitating agent. As in our study weight gain was not clearly associated with hyperglycemia. The time to occurrence ranged from 10 days to 18 months with an average of 3 months. Our observation of the occurrence of mean elevation of glucose levels in the first 8 weeks of treatment with clozapine as compared to olanzapine, where it occurred only after 14 weeks of treatment, was also seen by Mir and Taylor[46]. They found a clear difference between clozapine patients and olanzapine patients in the time for hyperglycemia or ketoacidosis to emerge. It appears that with olanzapine, these adverse effects may take longer to manifest than with clozapine. Paradoxically, we observed for the clozapine group that glucose levels were lower in Period 2. In part, this may have been due to a selective attrition rate in Period 2 resulting in the drop out of patients with elevated glucose levels. However, this drop was shown by the completer group, which may suggest an improvement in glycemic control in a subgroup of patients.

Johnson et al.[47] have reported on a patient who developed hyperglycemia and ketoacidosis while being treated with olanzapine. Although this patient was kept on olanzapine while receiving adjunctive insulin, requirements in insulin decreased as treatment with the atypical continued indicating an improved glycemic control.

Among the traditional neuroleptics, we have observed from prevailing literature that chlorpromazine[48] and thioridazine[49,50] are the agents most closely associated with DM, although the associations are not in a comparable range as with olanzapine or clozapine. In our study, the typical antipsychotic haloperidol was associated with an elevation of mean glucose levels within clinically normal range. However, the glucose baseline level in this group was low, and we cannot exclude a regression to the mean underlying this observation.

I THINK YOU CAN OMIT THE DISCUSSION OF MOA TO SAVE SPACE

We also found significant increases in mean cholesterol levels. They were elevated during the first 8 weeks of treatment with clozapine, while they were elevated at the end of 14 weeks of treatment with clozapine and olanzapine, but remained overall within normal clinical range. There was no elevation with risperidone and haloperidol. Weight gain significantly interacted with cholesterol elevations for olanzapine and marginally for clozapine in the first 8 weeks of treatment. Our findings are consistent with open label and retrospective data demonstrating a greater association of olanzapine and clozapine treatment with increases in cholesterol and triglycerides as compared to risperidone treatment[32,55]. Henderson found in a group of 81 patients treated with clozapine significant increases in both fasting cholesterol and triglycerides[54]. It appears that the more pronounced effect of antipsychotic treatments on lipid metabolism may be on triglycerides, which were not measured in the present study[56-59]. Meyer[32] postulates that antipsychotics with a dibenzodiazepine-derived structure may be associated with significant elevating effects on fasting triglyceride levels and with lesser effects on

cholesterol levels. Clozapine, olanzapine, quetiapine and the typical antipsychotic chlorpromazine all possess a 3-ring structure and have been reported to be associated with such changes.

Limitations of our study include the attrition rate of our sample during Period 2. While this rate was governed by clinical factors, it was comparable among the four treatment groups. Given that the attrition rate was smaller for Period 1, we feel that the data for this first period of treatment is more robust. In addition, Period 2 allowed for a variable dose of the antipsychotic medication in contrast to the fixed dose design of Period 1. This may have been an additional factor influencing our results. Finally, the duration of 8 weeks for Period 1 was relatively short and may not have been sufficient to allow for more changes in glucose and cholesterol levels to emerge.

Given the concerns regarding endocrine dysregulation in the context of treatment with atypical medication, we recommend that baseline and 6-month monitoring of fasting plasma glucose levels, Hb1Ac, fasting cholesterol and triglycerides with all antipsychotics be obtained in routine clinical practice in order to monitor the risk for development of hyperglycemia and hypercholesterolemia. Baseline weight and regular follow up weight measurements are further recommended. Given the serious implications for increased morbidity and mortality due to diabetes and elevated cholesterol, clinicians need to be aware of these risk factors when treating patients with chronic schizophrenia.

TABLE 1. BASIC CHARACTERISTICS OF STUDY SAMPLE

	Clozapine (N=28)	Haloperidol (N=25)*	Olanzapine (N=26)	Risperidone (N=22)	
MEAN AGE and SD (yrs.)	42.3 (± 8.3)	37.4 (± 12.1)	40.9 (± 7.3)	40.7 (± 9.9)	
GENDER					
Male	25	20	22	18	85
Female	3	5	4	4	16

DIAGNOSIS					
Schizophrenia	26	19	24	20	89
Schizoaffective	2	6	2	2	12
ETHNICITY					
White	11	7	4	7	29
African American	15	16	17	11	59
Hispanic	2	2	3	4	11
Asian Pacific	0	0	2	0	2
PREVIOUS HOSPITALIZATIONS					
One	2	2	3	5	12
Two	11	9	10	6	36
Three	3	7	4	4	18
Four	12	6	9	7	34

* One subject had missing data for Previous Hospitalizations

TABLE 2. CHANGE IN GLUCOSE LEVELS±SD (MG/DL)

	N	Baseline	N	8 Weeks	Δ	t, p	N	14 Weeks	Δ	t, p

Clozapine	28	93.1 (10.5)	27	110.6 (29.6)	17.1 (30.5)	2.92, 0.01	17	98.6 (19.5)	4.4 (17.1)	1.06, n.s.
Haloperidol	25	82.6 (14.8)	25	91.0 (11.1)	8.4 (17.7)	2.37, 0.03	20	92.6 (17.7)	10.6 (25.2)	1.9, n.s.
Olanzapine	26	91.7 (14.0)	26	93.6 (19.2)	1.9 (16.9)	0.57, n.s.	22	105.5 (30.4)	14.3 (25.5)	2.62, 0.02
Risperidone	22	94.0 (13.0)	22	92.6 (17.3)	-1.3 (14.9)	0.41, n.s.	14	97.2 (19.8)	2.7 (12.2)	0.84, n.s.

TABLE 3. GLUCOSE LEVELS IN PATIENTS WHO DEVELOPED HYERGLYCEMIA (125mg/dL)

Treatment	Pt ID#	Ethnicity	Gender	Baseline Weight (kg)	Age	Glucose Levels (mg/dL)		
						Baseline	Period 1	Period 2
Clozapine	6007	African American	M	82.0	54	102	193	95
Clozapine	6016	White	M	55.3	65	84	145	--
Clozapine	6017	African American	M	95.4	44	80	177	--
Clozapine	9011	African American	M	51.8	40	93	144	87
Clozapine	9021	African American	M	57.4	51	110	149	158
Clozapine	7016	African American	M	76.8	52	108	120	131
Haloperidol	9020	White	M	81.6	43	100	107	132

Olanzapine	7020	African American	M	98.2	48	107	135	202
Olanzapine	8035	African American	M	102.0	59	112	128	150
Olanzapine	9033	African American	F	73.5	43	123	97	147
Olanzapine	9039	African American	M	83.8	41	95	126	113
Risperidone	6006	White	M	81.5	43	108	155	--
Risperidone	8022	African American	M	88.5	55	108	97	135
Risperidone	9022	African American	M	105.7	34	113	101	132

TABLE 4. PATIENTS WITH ELEVATED BASELINE GLUCOSE LEVEL (>125mg/dL)

Treatment	Pt ID#	Ethnicity	Gender	Baseline Weight (kg)	Age	Glucose Levels (mg/dL)		
						Baseline	Period 1	Period 2
Haloperidol	9017	African American	Male	79.2	46	190	127	120
Olanzapine	6005	White	Male	82.8	54	436	360	---
Olanzapine	8030	Hispanic	Male	80.0	47	297	49	253
Olanzapine	9028	African American	Male	72.2	56	127	214	---
Risperidone	7030	African American	Male	82.7	56	255	147	169
Risperidone	9016	African American	Male	62.2	48	303	217	254
Risperidone	9026	African American	Male	73.9	54	135	242	---

TABLE 5. CHANGE IN CHOLESTEROL LEVELS ±SD (MG/DL)

	N	Baseline	N	8 Weeks	Δ	t, p	N	14 Weeks	Δ	t, p
Clozapine	28	174.2 (31.7)	27	189.0 (31.7)	14.7 (30.5)	2.50, 0.02	17	196.5 (35.1)	16.3 (39.6)	1.7, n.s.
Haloperidol	25	176.5 (32.2)	25	171.7 (27.7)	4.9 (17.7)	1.37, n.s.	20	171.7 (36.2)	4.4 (25.2)	0.77, n.s.
Olanzapine	26	179.8 (37.4)	26	192.1 (33.9)	12.3 (28.1)	2.22, 0.04	22	197.6 (36.2)	20.1 (26.8)	3.52, 0.002
Risperidone	22	184.2 (30.4)	22	188.4 (48.2)	4.2 (29.7)	0.66, n.s	14	188.8 (49.2)	9.2 (36.7)	0.94, n.s.

REFERENCES:

1. Kasanin J. The blood sugar curve in Mental Disease.II.The schizophrenic (dementia praecox) groups. Archives on Neurology and Psychiatry 1926;16:414-19.

2. Thonnard-Neumann E. Phenothiazines and diabetes in hospitalized women. Am J Psychiatry 1968;124:978-82.

3. Braceland FJ, Meduna LJ, Vaichulis JA. Delayed action of insulin in schizophrenia. Am J Psychiatry 1945;102:108-10.

4. Dixon L, Weiden P, Delahanty J, et al. Prevalence and correlates of diabetes in national schizophrenia samples. Schizophr Bull 2000;26,4:903-12.

5. Tabata H, Kikuoka M, Kikuoka H et al. Characteristics of diabetes mellitus in schizophrenic patients. J Med Assoc Thai 1987;70, 2 Suppl:90-3.

6. Mukherjee S, Decina P, Bocola V et al. DM in schizophrenic patients. Compr Psychiatry 1996;37:68-73.

7. Ai D, Roper TA, Riley JA. Diabetic ketoacidosis and clozapine. Postgraduate Medical Journal 1998;74(874):493-4.

8. Colli A, Cociolo M, Franconbaniera G et al. Diabetic ketoacidosis associated with clozapine treatment. Diabetes Care 1999;22,1:176-7.

9. Kamran A, Doraiswamy PM, Jane JL, et al. Severe hyperglycemia associated with high does of clozapine. Am J Psychiatry 1994;151:1395.

10. Koval MS, Rames LJ, Christie S. Diabetic ketoacidosis associated with clozapine treatment. Am J Psychiatry 1994;151:1520-21.

11. Maule S, Giannela R, Lanzio M et al. Diabetic ketoacidosis with clozapine treatment. Diabetes Nutr Metab 1999;12:187-8.

12. Melkersson KI, Hulting AL, Brismar KE. Different influences of classical antipsychotics and clozapine on glucose-insulin homeostasis in patients with schizophrenia or related psychoses. J Clin Psychiatry 1999;60,11:783-91.

13. Mohan D, Gordon H, Hindley N et al. Schizophrenia and DM. Br J Psychiatry 1999; 180-81.

14. Peterson GA, Byrd SL. Diabetic ketoacidosis from clozapine and lithium cotreatment. Am J Psychiatry 1996;153:1520-21.

15. Pierides. Clozapine monotherapy and ketoacidosis. Br J Psychiatry 1997;171:90-1..

16. Popli A, Konicka PE, Jurjus GS, et al. Clozapine and associated diabetes mellitus. J Clin Psychiatry 1997;58,3:108-11.

17. Smith H, Kenney-Herbert J, Knowles L. Clozapine induced diabetic ketoacidosis. Aust N Z J Psychiatry 1999;33:120-21.

18. Thompson J, Chengappa KNR, Good CB, et al. Hepatitis, hyperglycemia, pleural effusion, eosinophilia, hematuria and proteinuria occurring early in clozapine treatment. Int Clin Psychopharmacol 1998;13:95-8.

19. Wirshing DA, Spellberg BJ, Erhart SM et al. Novel antipsychotics and new onset diabetes. Biol Psychiatry 1988;44:778-83.

20. Yazici KM, Erbas T, Yazici AH. The effect of clozapine on glucose metabolism. Exp Clin Endocrinol Diabetes 1998;106:475-77.

21. Bettinger TL, Mendelson SC, Dorson PG, et al. Olanzapine-induced glucose dysregulation. Ann Pharmacother 2000;34, 7-8:865-7.

22. Fertig MK, Brooks VG, Shelton PS. Hyperglycemia associated with olanzapine. J Clin Psychiatry 1998;59,12:687-9.

23. Gatta B, Rigalleau V, Gin H. Diabetic ketoacidosis with olanzapine treatment. Diabetes Care 1999;22,6:1002-3.

24. Goldstein LE, Sporn J, Brown S et al. New-onset DM and diabetic ketoacidosis associated with olanzapine treatment. Psychosomatics 1999;40,5:438-43.

25. Hayek DV, Hutll V, Reiss J, et al. Hyperglycemia and ketoacidosis on olanzapine. Nervenarzt 1999;70:836-7.

26. Melkersson KI, Hulting AL, Brismar KE. Elevated levels of insulin, leptin, and blood lipids in olazapine-treated patients with schizophrenia or related psychoses. J Clin Psychiatry 2000;61,10:742-9.

27. Ober SK, Hudak R, Rusterholtz A. Hyperglycemia and olanzapine. Am J Psychiatry 1999;156:969-70.

28. Procyshyn RM, Pane S, Tse G. New onset diabetes mellitus associated with quetiapine. Can J Psychiatry 2000;45,7:668-9.

29. Sobel M, Jaggers ED, Franz M. New onset diabetes mellitus associated with initiation of quetiapine treatment. J Clin Psychiatry 1999;60,8:556-7.

30. Croarkin PE, Jacobs DM, Bain B. Diabetic ketoacidosis associated with risperidone treatment. Psychosomatics 2000;41,4:369-70.

31. Kostakoglu AE, Yazici KM, Erbas T, et al. Ketoacidosis as a side effect of clozapine: a case report. Acta Psychiatr Scand 1996; 93,3:217-18.

32. Meyer JM. A retrospective comparison of lipid, glucose, and weight changes at one year between olanzapine and risperidone treated inpatients. In: Proceedings of the 39th Annual Meeting of the American College of Neuropsychopharmacology, Dec 10-14, 2000; San Juan, Puerto Rico, 184.

33. Wilson DR, D'souza L, Sarkar N, et al. New-onset diabetes and ketoacidosis with atypical antipsychotics. In: Proceedings of the 39th Annual Meeting of the American College of Neuropsychopharmacology, Dec 10-14, 2000; San Juan, Puerto Rico.

34. Iqbal N, Oldan RL, Baird G, et al. Diabetes Mellitus induced by atypical antipsychotics. In: Proceedings of the 153rd Annual Meeting of the American Psychiatric Association, May 16, 2000; Chicago, Illinois.

35. Lindenmayer JP, Nathan A, Smith, RC. Hyperglycemia associated with the use of atypical antipsychotics. J Clin Psychiatry 2001;62 (suppl. 23): 30-8.

36. Burke JP, Williams K, Gaskill SP et al. Rapid rise in the incidence of type 2 diabetes from 1987 to 1996: results from the San Antonio Heart Study. Arch Intern Med 1999;159:1450-6.

37. Lund BC, Perry PJ, Brooks JM, Arndt S. Clozapine use in patients with schizophrenia and the risk of diabetes, hyperlipidemia, and hypertension. Arch Gen Psychiatry 2001;58:1172-6.

38. Cavazzoni P, Baker RW, Kwong K et al. A pharmacoeidemiological study of diabetes mellitus and antipsychotic treatment in the United States. Poster presented at 41st New Clinical Drug Evaluation Unit meeting, Phoenix, AZ, May 28-31, 2001.

39. Gianfrancesco F, Grogg A, Mahmaoud R, Markowitz J, Nasrallah HA. Association of new-onset diabetes and antipsychotics: findings from a large health plan database. Poster presented at 41st New Clinical Drug Evaluation Unit Meeting, Phoenix, AZ, May 28-31, 2001.

40. Breier A, Kwong K, Hornbuckle K, et al. A retrospective cohort study of diabetes mellitus and antipsychotic treatment in the United Kingdom. Poster presented atss 40th Annual Meeting of the ACNP, Hawaii, December 9-13, 2001.

41. Smith RC, Lindenmayer JP, Khandat A, et al. A prospective study of glucose and lipid metabolism with atypical and conventional antipsychotics. In: Proceedings of New York State Office of Mental Health 14th Annual Research Conference, Dec 3-5, 2001, Albany, NY.

42. Volavka J, Czobor P, Sheitman B, et al. Clozapine, Olanzapine, Risperidone, and Haloperidol in Patients with Chronic Schizophrenia and Schizoaffective Disorder. Am J Psychiatry 2002;159(2):255-62.

43. Kay SR, Opler LA, Lindenmayer JP. Reliability and validity of the Positive and Negative Syndrome Scale for schizophrenia. Psychiatry Res 1988;23:99-110.

44. Honigfeld G. Nosie-30: history and current status of its use in pharmacopsychiatric research. Mod Probl Pharmacopsychiatry 1974;7:238-63.

45. Harris MI, Flegal KM, Cowie CC et al. Prevalence of diabetes, impaired fasting glucose and impaired glucose tolerance in US adults, Diabetes Care, 1998, 21, 518-24.

46. Mir S, Taylor D. Atypicals antipsychotics and hyperglycemia. Int Clin Psychopharmacol 2001;16:63-74.

47. Johnson RP, Al-Taher MT, Madlock LE, et al: Decreasing Insulin Dose for Olanzapine-Related Diabetes. Am J Psychiatry 159(1):150-1.

48. Karenyi C, Lowenstein B. Chlorpromazine induced diabetes. Diseases of the Nervous System 1968;29,12:827-8.

49. Baldessarini RJ, Lipinski JF. Toxicity and side effects of antipsychotic, antimanic, and antidepressant medications. Psychiatric Annals 1976; 6,10:484-93).

50. Bourcharlat J, Chatelain R. An exceptional neuroleptic accident: insipid diabetes induced by thioridazine. Annales Medico-Psychologiques 1968;1(2) :306.

51. Wirshing DA, Spellberg BJ, Erhart SM, et al. Novel antipsychotics and new onset diabetes. Biol Psychiatry 1998;44:777-83.

52. Melkersson KI, Hulting AL. Insulin and leptin levels in patients with schizophrenia or related psychoses—a comparison between different antipsychotic agents. Psychopharmacology 2001;154:205-12.

53. Goldstein L, Henderson D. Atypical antipsychotic agents and diabetes mellitus. Primary Psychiatry 2000; 7:65-8.

54. Wozniak KM, Linnoila M. Hyperglycemic properties of serotonin receptor antagonists. Life Sciences 1991;49:101-9.

55. Henderson DC, Cagliero E, Gray C, Nasrallah RA, Hayden DL, Schoenfeld DA, Goff DC. Clozapine, diabetes mellitus, weight gain, and lipid abnormalities. Am J Psychiatry 2000;157 (6):975-81.

56. Ghaeli P, Dufresne RL. Serum triglyceride levels in patients treated with clozapine. Am J Health System Pharm 1996;53:2079-81.

57. Sheitman BB, Bird PM, Binz W, et al. Olanzapine-induced elevation of plasma triglyceride levels [letter]. Am J Psychiatry 1999;156:1471-2.

58. Osser DN, Najarian DM, Dufresne RL. Olanzapine increases weight and serum triglyceride levels. J Clin Psychiatry 1999;60:767-70.

59. Clark ML, Ray TS, Paredes A, et al. Chlorpromazine in women with chronic schizophrenia: the effect on cholesterol levels and cholesterol-behavior relationships. Psychosom Med 1967;29:634-42.