An Archival, Follow-Forward Exploration of the Metabolic Syndrome in Randomly Selected, Clozapine-Treated Patients

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Abstract

Objectives: Cross-sectional studies indicate that clozapine is associated with unusually high rates of the metabolic syndrome (MetS) in schizophrenia. These studies cannot address the extent to which schizophrenia or other factors are major risks for the MetS, independent of clozapine exposure. The objectives of this study were to longitudinally examine metabolic risk factors before and after clozapine initiation: 1) to determine MetS prevalence rates during first-generation antipsychotic (FGA) and clozapine treatment; 2) to identify metabolic changes contributing to the MetS; and, 3) to evaluate the extent to which prior treatment and subject variables contributed to increased MetS prevalence rates. **Methods:** Using an archival, follow-forward design, metabolic risk factors were sampled on a quarterly basis from medical records of twenty-five randomly selected inpatients. The sampling period was six years (three years of FGA and three years of clozapine). All subjects had been treated *only* with FGAs prior to clozapine exposure. **Results:** During clozapine treatment 16 of 25 (64%) subjects met MetS criteria; however, half (8 of 16) of the subjects already met MetS criteria during FGA treatment. Increased MetS prevalence with clozapine resulted from increases in fasting glucose and triglyceride levels and increased systolic BP. BMI was stable over time. Gender, age of clozapine initiation, and clozapine dose and duration may have contributed to long-term MetS risk. **Conclusions:** Clozapine-treated patients are at increased risk for the MetS. When observed longitudinally, however, it is clear that a significant proportion of the metabolic risk involves factors other than clozapine exposure alone.

Key Words: Schizophrenia, Clozapine, Metabolic Side Effects

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Introduction

Awareness of metabolic disturbance in schizophrenia dates back at least to 1879 when Sir Henry Maudsley (1) wrote: *"Diabetes is a disease which often shows itself in families in which insanity prevails."* Subsequent studies (2-11), all predating antipsychotic medications, showed that weight gain, insulin dysregulation, and impaired glucose tolerance were associated with schizophrenia. Interestingly, when insulin coma was used to treat mental illness in the 1920s, it was well known that more insulin was needed for patients with schizophrenia, indicating some degree of insulin resistance (12). Unfortunately, these early observations failed to generate a deeper understanding of the pathogenesis or treatment of diabetes or any theoretical linkages between diabetes and schizophrenia, and interest faded. Even when clinically significant weight gain was observed with the first FDA-approved antipsychotic medication, chlorpromazine, little concern was raised (13).

Clinical Implications

The high prevalence of metabolic dysregulation observed in clozapine-treated individuals is real and has serious long-term health implications. These afflicted individuals have a significant increase in risk for cardiovascular disease and all-cause mortality. But, unfortunately, even with regular metabolic monitoring there is little evidence to guide the "real-life" next steps when faced with these emergent concerns. In the past, clozapine was often simply replaced with a lower risk antipsychotic agent. This is a common sense approach—clozapine is presumed to be the causal risk factor. And, in fact, this "switching" strategy has gained empirical support as a method for managing metabolic problems arising with other atypical antipsychotic agents (47). However, clozapine is a special case. These individuals usually have not responded meaningfully to numerous prior antipsychotic agents and, therefore, the risk/benefit considerations of "switching" are vexing. Thankfully, clinical practice is beginning to include metabolic screening for metabolic dysregulation; with "baseline" metabolic information available, research should be stimulated that will lead to a better understanding of the complex interactions among the effects of schizophrenia, medications, lifestyle, and individual pharmacogenetics. Many important questions remain unanswered, including appropriate and feasible screening approaches, prevention, and forms of optimal metabolic treatment. These answers will not come easily. Yet, progress has already accelerated and the developing insights will begin to unlock fundamental questions to eventually bring relief from metabolic burden.

This lack of concern changed considerably when the concept of the metabolic syndrome (MetS) was introduced into psychiatry (14). Weight gain and new-onset diabetes had been recognized as a treatment concern, but when the MetS (15) was introduced, attention became focused on a constellation of symptoms that significantly increase risk for coronary heart disease, a leading natural cause of death in schizophrenia (16). Metabolic side effects began to be reported with the newer, atypical antipsychotic medications, particularly clozapine and olanzapine. The initial concern was weight gain. A meta-analysis of published results (17) found a mean weight gain of 9.8 pounds after ten weeks of clozapine treatment. Glucose abnormalities were reported (18). Further papers linked clozapine with hypertriglyceridemia (19), increased total cholesterol levels (20), hypertension (21), and insulin resistance (22). Soon an expert consensus report stated that olanzapine and clozapine were the antipsychotic agents with the highest risk for the metabolic syndrome (23).

The first controlled prevalence study (24) of the MetS among clozapine-treated patients found a 53.8% prevalence rate. To date, this is the highest prevalence rate reported in the schizophrenia literature. Other large population studies (25-28) reported overall MetS prevalence rates of 44.7%, 40.9%, 35% and 28.4%. Two of these studies (240 and 689 subjects) (25, 26) contained no clozapine-treated patients, and another (430 subjects) did not examine their clozapine patients separately (27). One study (269 subjects) (28) that did contain clozapine-treated patients reported a prevalence rate of 35% overall, with the clozapine subsample having a 48% prevalence rate. Another very recent report (29) found that 46.4% of its clozapine sample (N=84 subjects) fulfilled criteria for the MetS.

These studies document an increased risk for the MetS among clozapine-treated patients, and shine a light on a growing crisis in mental healthcare. But, unfortunately, these studies cannot indicate the degree to which clozapine was the major contributing risk factor, independent of schizophrenia or developmental variables (e.g., aging). There are several reasons for this lack of clarity. First, the MetS etiology is multifactorial in nature (30). When it emerges within the context of schizophrenia, untangling the etiology becomes far more challenging. People with schizophrenia often have a family history of diabetes (31, 32). Low birth weight, which predisposes to the development of the MetS, is thought to be more prevalent in those with schizophrenia (33). Some investigators (34) have speculated that schizophrenia involves shared genetic vulnerabilities for both psychosis and metabolic disease. To add to the complexity, those with schizophrenia tend to be less physically active and have poor dietary habits. Their meals are often sporadic, low in fiber content, and rich in fat, refined sugars and carbohydrates. Such a lifestyle increases their risk of the MetS (35). Second, the literature predating antipsychotic drugs suggests that schizophrenia itself (or the secondary consequences of the illness) is a major risk factor for the MetS. Recent small-scale studies seem to suggest that increased visceral adiposity and glycemic dysfunction (36, 37) occur at higher-than-normal rates among neuroleptic-naive patients, although these findings have not been

replicated (38). Third, the study designs are cross-sectional. Such designs may generate important hypotheses, but they can only provide suggestive evidence of causal relationships. To date, these "snapshots" have provided no historical metabolic information—thus, it is possible that the samples already had the MetS before starting clozapine. The results do not stem from randomly-selected clozapine subjects, drawn from large populations; as a result, unknown sources of sampling bias cannot be ruled out. To date, the published study samples are from Scandinavia, Belgium, and Ireland, raising questions of generalizability. These critiques are not meant to suggest that quasi-experimental and/or observational, epidemiologic studies are without merit. But the underlying basis of the MetS is not simple, and more sophisticated approaches will be needed to elucidate the underlying etiology and to specify the proportional magnitude of each key metabolic risk factor to the overall clinical picture.

This study moves from cross-sectional designs toward a longitudinal approach. Metabolic measurements were extracted from hospital records for a group of subjects, both before and after the initiation of clozapine treatment. Using an "archival–follow forward" design, subjects were randomly selected from a much larger pool of potential subjects who were historically treated only with first-generation antipsychotic (FGA) medications and then "switched" to clozapine by their treating psychiatrists. Detailed metabolic measures and related information were systematically abstracted from their hospital records to span both FGA- and clozapine-treatment periods. The specific aims were: 1) to longitudinally examine the MetS prevalence rates across FGA- and clozapine-treatment periods; 2) to identify which specific measures within the constellation of metabolic risk factors contributed to the development of the MetS diagnosis with clozapine treatment; and, 3) to evaluate the extent to which prior treatment (dose and class) and selected subject variables (i.e., race, gender) contributed to MetS prevalence rates over time.

Methods

Sampling and Subjects

The study began with an examination of the electronic pharmacy database of approximately 3,000 patient records maintained as a comprehensive and up-to-date pharmaceutical treatment record at Norristown State Hospital (NSH). This electronic record was initiated in 1989, prior to FDA approval of clozapine. Using a custom-designed program, the entire electronic pharmacy record from 01-Jan-1990 to 16-Jan-2005 was screened for any evidence of clozapine treatment (brand and generic). A total of 378 individuals were identified as having been exposed to clozapine. Of these, 84 pharmacy records indicated that clozapine treatment had been preceded by FGA treatment only, and that records were present for at least 9 months before and after the initiation of clozapine treatment. Using a computer-generated random numbers table, these patients were placed in random order by which the hospital charts were then examined. As this was a preliminary study, only the first 25 subjects meeting inclusion criteria became the study population; 28 cases were evaluated to ascertain 25 cases meeting criteria. The project was considered a zero-risk quality assurance project with no direct patient contact, and was authorized by the local Institutional Review Board, the local HIPAA officer, and NSH administration.

The *a priori* inclusion criteria were:

1) a *minimum* of 9 months of continuous hospitalization prior to clozapine treatment and 9 months of continuous hospitalization after the initiation of clozapine therapy. The *maximum* time period was 36 months prior to clozapine treatment and 36 months after the initiation of clozapine therapy. Thus, the data collected ranged from a minimum time period of 18 months to a maximum of 72 months (6 years).
2) continuous FGA treatment prior to clozapine treatment.
3) continuous clozapine monotherapy for a minimum of six months before any switching to, or augmentation with, another antipsychotic medication.
4) continuous inpatient treatment—any patient discharged and readmitted during the study period was not included.

When data gathering was complete, 21 of 25 (84%) subjects had acceptable data for the full 72-month time period. Thus, this 6-year period became the recognized duration of the study.

Training and Metabolic Data Acquisition

All team members took part in extensive training that included an introduction to, and overview of, hospital chart structure, common diagnostic and medication nomenclature, location of pertinent data within the chart, and using the computer application designed specifically for the data acquisition of this study. Several "training" charts were abstracted, and the team reviewed the results for common data collection problems and/or questions.

With training complete, the first step was to directly examine the medication administration record (MAR) for each potential subject to certify the exact date of clozapine initiation. The MAR was considered the best evidence for determining the exact "switch date" to clozapine treatment and whether the subject met the minimum time period for inclusion into the study. With the "switch date" confirmed,

two-member teams developed quarterly "target dates" for each subject specifying 12 quarters (36 months) prior to clozapine initiation and 12 quarters following clozapine initiation. Using these quarterly "target dates," metabolic measures were extracted from paper hospital records including: psychiatric medication (drug and total daily dosage), concomitant medications, clinical laboratory values (standard clinical panels, hematology, and urine analysis), weight, vital signs, significant medical events, and pertinent demographic information. (Note: Norristown State Hospital maintained a comprehensive clinical laboratory service on the hospital grounds until 1990. Hospital policy mandated a comprehensive annual physical examination and monthly follow-up for each patient. Because a complete laboratory service was available on site, at no additional cost, a high rate of laboratory testing was ordered by the medical staff and maintained for each patient. These clinical laboratory services were contracted to outside vendors beginning in 1990, but the high level of laboratory utilization persisted due to the increased medical vigilance associated with clozapine treatment.)

The database was designed to mitigate data entry errors by providing the abstractors immediate visual feedback by highlighting values that were out of the expected preloaded range of clinical laboratory values. Not all metabolic measures took place on the exact "target date;" therefore, a "target date" window (± two weeks) was accepted as representative of that quarter. With data acquisition complete, individual subject records were merged into a single master dataset that was screened for errors both visually and with electronic edit checks. As needed, hospital charts were reexamined to correct aberrant values or to search for missing data.

Data Handling and Analytical Plan

The **observed cases** served as our primary data. An additional data set was developed using the method of last observation carried forward (LOCF) to create a full 36-month set of values only for the 12 subjects who were either discharged from the hospital due to a good treatment response to clozapine (N=4) or who were switched to risperidone (N=8) before the full 3-year time span of clozapine treatment was completed. The LOCF method was not applied to data prior to clozapine treatment.

Determining Metabolic Prevalence Rates

The MetS criteria for this study were based on those provided by the National Cholesterol Education Program (NCEP) (39). There were three modifications: 1) the new lower threshold for impaired fasting glucose of 100 mg/dl (40) was incorporated; 2) body mass index (BMI) was used as a proxy for visceral adiposity; and, 3) high density lipoprotein (HDL) values were seldom available, particularly during the FGA period. HDL measures were used when available, but total cholesterol was more commonly used.

To determine MetS prevalence rates, observed data values for each subject were evaluated to identify abnormalities in each metabolic risk factor for each quarter. To be categorized as abnormal, a risk factor had to meet one of the following criteria:

1) the value had to exceed the modified NCEP criteria.
2) the subject had to be receiving medication for a specific metabolic disorder. (Note: Medications that were initiated for the treatment of a metabolic condition were, in most cases, continued over time. Doses tended to be increased, and in some cases the patients were switched to a different class of medications. It is important to understand that fluctuations in metabolic values over time were not the result of starting and stopping treatment.); or,
3) the subject had received a medical diagnosis from his treating internist for the metabolic condition.

At every quarter, each risk factor was designated as either "abnormal" or "normal" for each subject. In cases where an abnormal laboratory value was medically treated and subsequently brought back into the normal range, the risk factor was still tagged as "abnormal" since medication was being administered for the condition. A previously "abnormal" risk factor was considered "normal" if this status was achieved without pharmacologic intervention (i.e., slightly elevated glucose, modified through exercise and diet). Next, the five metabolic factors were combined into a single MetS diagnosis (per quarter) using the following method: those with 0-2 "abnormal" risk factors were designated as "normal" (no MetS), while those with 3 or more "abnormal" risk factors were designated as "abnormal" (having MetS). This resulted in each subject receiving a quarterly metabolic diagnosis across FGA- and clozapine-treatment periods.

Statistical Procedures

A series of statistical procedures was conducted. The MetS prevalence rates were computed each quarter as a simple percentage using **observed data only**. If any metabolic measures were missing for a given subject, but the subject still fulfilled MetS diagnostic criteria, he or she was designated "abnormal." If metabolic measures were missing, and the subject *did not* fulfill MetS diagnostic criteria, that subject was not included in the computation for that quarter. As a result, the reported prevalence rates are conservative, particularly during the early FGA period, when smaller groups were more common due to missing metabolic data. MetS prevalence rates were computed for each quarter, then for each year, and then separately for the three-year FGA and clozapine periods. A matched-pair t-test was used to compare prevalence rates.

Next, each subject was classified into one of four groups:

Group 1 subjects who were MetS "normal" during both FGA and clozapine periods; Group 2 subjects who were MetS "normal" during FGA but became "abnormal" with clozapine treatment; Group 3 subjects who were MetS "abnormal" during FGA treatment and became "normal" with clozapine; and, Group 4 subjects who were MetS "abnormal" during both FGA and clozapine periods. Change scores were computed as the mean of the first two clozapine periods minus the mean of the last two FGA periods for each MetS risk factor (Δ score=mean [+1CLOZ & +2CLOZ] - mean [-2FGA & -1FGA]). Then, univariate ANOVAs were performed using the change score for each metabolic risk factor as a dependent variable to determine whether any statistically significant differences existed among subject groups.

Finally, using the LOCF dataset, a series of exploratory analyses of variance (ANOVA) was performed. Each ANOVA involved a between-subject repeated measures model (2 x 2) using the actual number of metabolic risk factor abnormalities as the dependent variable. The within-subject independent variable of "time" included two levels: -1FGA and +12CLOZ quarter. (Note: In the +12CLOZ quarter, 21 of 25 subjects had complete observed data. LOCF data were used for the remaining 4 subjects. The -1FGA was considered the "baseline" for clozapine comparisons.)

The between-subject independent variables were: *gender, age of clozapine initiation, race, mean cumulative clozapine dose* (median split: high versus low dosage), *class of FGA prior to clozapine treatment* (high versus low potency), *mean dose of FGA prior to clozapine treatment* (chlorpromazine equivalent median split: high versus low dose), and *-1FGA (baseline) values of BMI, fasting glucose, fasting triglyceride, systolic and diastolic BPs* (median splits: high versus low). Although a single model would be the most efficient manner of analyzing these data, the series of repeated-measures models with two factors and their interactions was used for simplicity and power considerations. All significance tests were performed using 2-tailed comparisons with alpha level of 0.05.

Results

Demographic, Dosing and Descriptive Information

Pertinent subject information is summarized in Table 1. Mean age of clozapine initiation was 45.8 years (standard deviation [SD]=10.38). Sixteen (64%) of 25 subjects were males. For subject race/ethnicity, 21 (84%) were Caucasian and 4 (16%) were African American. Psychiatric diagnoses were taken from the hospital chart: schizophrenia (N=21) or schizoaffective disorder (N=4). Twenty-one (84%) of the sample remained in the hospital for the full three years following the initiation of clozapine treatment; 4 of the subjects were discharged based on a positive response to clozapine. The FGAs used varied across the sample, but dosages remained relatively stable over time, with a cumulative average daily chlorpromazine equivalence (41) of 1,358 mg (SD=837.52, range 200–3,800 mg/day). The cross-titration strategy from FGA to clozapine varied, but in no case did FGA treatment extend beyond two weeks after clozapine initiation. Starting dose of clozapine was usually 12.5 mg once daily, although a few subjects started at 12.5 mg twice daily. The pattern of dosage increases varied, with the cumulative average daily dose of clozapine being 472 mg (SD=222.24, range 50–800 mg/day). Three (12%) individuals included in this sample are known to have since died, as a result of cancer, pulmonary disease, and an automobile accident.

Table 1 Demographic and other Pertinent Characteristics of the Clozapine Sample (N=25)

Demographic Variables		
Mean Age *at time of switch to clozapine* (in years, SD)		45.8 (10.38)
# Male		16 (64%)
# Female		9 (36%)
Duration of Clozapine Treatment		
Clozapine Exposure *	(N=25 total)	
12 Quarters	13	all remained on CLZ for 3 years
9 Quarters	2	2 switched to risperidone after 2¼ years of CLZ exposure
8 Quarters	3	3 switched to risperidone after 2 years of CLZ exposure
6 Quarters	6	3 discharged with good CLZ response, 3 switched to risperidone after 1½ years of CLZ exposure
3 Quarters	1	discharged with good CLZ response

*Duration of clozapine exposure for all 25 subjects, regardless of whether they were discharged or switched to risperidone.
CLZ=clozapine

Using observed data only, annual group mean values and standard deviations for all metabolic measures are summarized in Table 2. While the annual group mean values were relatively stable over time, the initiation of clozapine (see Year +1) was associated with elevations in fasting glucose and fasting triglyceride values.

MetS Prevalence Rates

Eight of 25 (32%) subjects met MetS criteria during the FGA-treatment period as compared to 16 of 25 (64%) during clozapine treatment (matched-pairs *t-test, t=-3.36, df=24, p<0.003*). Females had higher cumulative prevalence rates during both FGA and clozapine treatments (44% and 78%, respectively) as compared to males (25% and 56%, respectively). All 8 subjects meeting MetS criteria during the FGA period continued to meet MetS criteria throughout clozapine treatment.

Table 2 Annual Metabolic Measures—Means (SD)

Measure	Study Years					
	-3	-2	-1	+1	+2	+3
BMI (morning)	26.9 (4.9)	27.6 (5.3)	27.5 (5.4)	27.3 (5.2)	26.6 (5.3)	27.3 (5.0)
Glucose (fasting)	88.8 (16.7)	87.5 (19.6)	89.0 (21.6)	102.6 (37.9)	88.4 (20.6)	85.4 (15.9)
Triglyceride (fasting)	131.3 (75.9)	123.6 (51.9)	133.9 (81.3)	163.2 (93.9)	140.9 (69.6)	161.2 (93.2)
Cholesterol (fasting)	173.7 (63.7)	171.1 (49.2)	184.8 (35.2)	184.1 (34.4)	176.2 (38.7)	185.3 (40.4)
Blood Pressure (morning)						
Systolic	117.4 (13.1)	117.5 (13.7)	118.1 (13.6)	118.6 (12.4)	118.9 (11.6)	119.0 (14.3)
Diastolic	76.5 (9.9)	75.7 (10.4)	75.5 (9.9)	79.0 (10.0)	76.2 (8.7)	78.4 (8.7)

Metabolic Changes Contributing to MetS Diagnosis

For the purposes of this study, the most interesting subjects are the 8 of 25 (32%) who were categorized as "normal" during FGA treatment, and then developed the MetS during clozapine treatment. Another 8 of 25 (32%) subjects met diagnostic criteria for MetS during both the FGA- and clozapine-treatment periods. Nine of 25 (36%) were diagnosed as "normal" across both FGA- and clozapine-treatment periods. None of the subjects diagnosed with the MetS during FGA treatment became "normal" with clozapine treatment.

Which metabolic measures shifted from "normal" to "abnormal" with clozapine leading to the MetS diagnosis? Table 3 displays univariate ANOVA results of MetS *"change scores"* for the three groups. The primary contributors leading to a MetS diagnosis with clozapine treatment were: ΔGlucose, ΔTriglyceride, and ΔSystolic Blood Pressure. Statistically significant results were achieved for ΔGlucose and ΔSystolic Blood Pressure (both $p<0.03$). The ΔTriglyceride measure did not achieve statistical significance. All three groups had elevated ΔTriglyceride measures with large standard deviations; however, those who did develop the MetS with clozapine had a much greater increase in triglyceride levels. The ΔBMI, ΔCholesterol, and ΔDiastolic Blood Pressure comparisons did not yield statistically significant results.

Table 3 ANOVA Comparisons of MetS Risk Factor Shift—Mean (SD) Change Scores

Variable	"Both Normal" (N=9)	"CLZ Only Abnormal" (N=8)	"Both Abnormal" (N=8)
ΔBMI	0.83 (1.8)	-0.87 (1.8)	-0.1 (1.7)^{ns}
ΔGlucose	6.9 (16.6)	29.9 (57.1)	4.38 (24.1)*
ΔTriglycerides	120.3 (32.4)	207.6 (34.4)	176.7 (34.9)^{ns}
ΔCholesterol	3.1 (7.8)	-2.4 (8.3)	-4.3 (8.4)^{ns}
ΔBlood Pressure			
ΔSystolic	-6.6 (8.9)	7.8 (9.5)	0.25 (11.2)†
ΔDiastolic	6.8 (7.6)	3.9 (6.6)	-0.19 (10.5)^{ns}

ns=not significant
*Main Effect for Group: F=3.57; df=2,24; $p<0.03$
†Main Effect for Group: F=4.49; df=2,24; $p<0.02$
CLZ=clozapine; MetS=metabolic syndrome

Exploratory ANOVAs of Subject Variable Effects on Individual MetS Risk

Table 4 provides a summary of results from the between-group, repeated-measures ANOVAs performed to explore long-term influence of selected subject variables on MetS abnormalities. All main effects for *"time"* (-1FGA *versus* +12CLOZ) reached statistical significance with the exception of *duration of clozapine treatment*, which yielded a trend toward significance; in each case, the number of MetS abnormalities was elevated after three years compared to FGA baseline values.

The more informative findings are the between-group effects and interaction terms. The between-group effects and interaction terms for "*race*," "*prior CPZ class*," "*prior CPZ dose*," and "*BP*" did not achieve statistical significance and will not be considered further.

The between-group effects for "*gender*" (males< females), "*age at clozapine initiation*" (younger<older), "*baseline BMI*" (low<high), and "*baseline glucose*" (low< high) were all statistically significant. The between-group effect for "*baseline triglyceride*" revealed a trend toward statistical significance.

The only ANOVA interaction achieving statistical significant was the "*clozapine duration x time*" term ($p<0.01$). Longer treatment with clozapine was associated with more metabolic abnormalities. The "*dose x time*" interaction term

Table 4 ANOVA Summary Table—Factors Associated with Increased MetS Risk after Three Years

ANOVA Terms[a]	TIME Within Group	Subject Variable Between-Group	Interaction
GENDER *(m vs. f)*	F=7.7§	F=4.9†	*ns*
AGE[b]	F=9.49§	F=3.2*	*ns*
CLOZDOSE[c]	F=10.35§	*ns*	F=2.88*
CLOZDURATION[d]	F=3.97*	*ns*	F=5.97‡
RACE *(white vs. black)*	F=11.78§	*ns*	*ns*
CPZ Class (potency)[e]	F=4.85†	*ns*	*ns*
CPZ Dose[f]	F=10.35§	*ns*	*ns*
Baseline BMI[g]	F=9.55§	F=16.12§	*ns*
Baseline GLU[g]	F=8.55‡	F=4.1†	*ns*
Baseline TRI[g]	F=10.91§	F=2.8*	*ns*
Baseline BP (systolic)[f]	F=10.02§	*ns*	*ns*
Baseline BP (diastolic)[f]	F=10.48§	*ns*	*ns*

Levels of significance: *=statistical trend; †=p<0.05; ‡=p<0.01; §=p<0.005

[a] The ANOVA models used degrees of freedom (1,23).

[b] Age when started on clozapine; mean split.

[c] Mean dose of clozapine across study; median split.

[d] Mean duration of clozapine across study; those treated full 3 years versus the other subjects.

[e] High- versus low-potency antipsychotic during period prior to clozapine treatment.

[f] Mean CPZ equivalent dosage prior to clozapine treatment; median split.

[g] Median split of biological measure values.

MetS=metabolic syndrome; CPZ=clozapine; BMI=body mass index; GLU=glucose; TRI=triglycerides; BP=blood pressure.

approached statistical significance with higher clozapine doses being associated with more metabolic abnormalities at the end of three years.

Discussion

Clozapine is a very effective medication in the treatment of schizophrenia and schizoaffective disorders (42). It has been associated with numerous side effects, some minor and others very serious and potentially life-threatening; as a result, clozapine has been relegated to third-line use. Undoubtedly, the MetS is one of the concerns that has led to the under utilization of clozapine, which is still the only proven effective medication for treatment-resistant psychotic disorders.

But, what is the magnitude of MetS risk with clozapine treatment? One observation from this longitudinal study stands out immediately. While more than half (64%) of this cohort met MetS criteria during the clozapine-treatment period, half (32%) of them had developed the MetS prior to any clozapine exposure. In other words, when considering potential sources of risk for the MetS during clozapine treatment, at least 50% of this cumulative risk had nothing to do with clozapine exposure. This may appear to be nothing more than statistical rhetoric, but the implications are actually important. Clozapine no doubt plays some etiologic role(s) in the MetS. But, when seen in the historical context of this sample, it becomes clear that other metabolic risks were at play, and, moreover, that an uncritical attribution of risk to clozapine alone is not the best way to understand this situation. The development of treatment strategies that are targeted to mechanisms that underlie the MetS will require that the proportional contributions of all key risk factors will need to be clearly elucidated—including the role of clozapine itself—or undue attention may be directed toward factors of lesser importance instead of the factors that matter.

After switching to clozapine the source of metabolic risk is still ambiguous. Other developmental factors are ongoing and uncontrolled during clozapine treatment, such as the effects of aging or total lifetime exposure to neuroleptic drugs and, to an unknown degree, these factors (and others) undoubtedly contributed to metabolic dysregulation. A comparison with subjects treated with FGAs only would help to clarify the contribution of developmental factors. Of course, the ideal comparison would be never-medicated subjects, but such subjects are nearly impossible to find. Nevertheless, if other developmental risk factors did play a role in this sample, then the proportional risk attributable to clozapine is even less than 50% of the total cumulative risk. Admittedly this sample is small, and it would be easy to over interpret the meaning of these results. But within this longitudinal design, even with a small sample, it is clear that the underlying metabolic risks are multifactorial, the disease pathway is complex, and attributing the major proportion of metabolic risk to clozapine exposure alone is overly simplistic.

When looking more closely at specific metabolic changes leading to the MetS, there are some surprising observations. One surprise was body weight. Prior to clozapine, 13 of 25 (52%) subjects had BMI values over 30. Why were more than half of the subjects obese prior to clozapine treatment? Perhaps it reflects a selection bias toward choosing overweight individuals for clozapine treatment. Or, maybe it was simply the age of our sample. In the United States, clozapine is not considered a first-line antipsychotic treatment—it is reserved for patients with treatment-refractory psychotic symptoms who are relatively older and, as a result, usually heavier. Not only was the sample disproportionately obese, but the group mean weight did not appreciably change over time. This observation runs counter to ubiquitous findings

of clozapine-associated weight gain, and the reasons for this divergence are unclear. In general, the factors influencing weight are threefold: food intake, metabolic activity, and energy output. As was previously noted (35), psychotic patients living in the community often have poor dietary habits. That being the case, one could speculate that the lack of weight gain in our sample was a result of all the subjects being hospitalized for the entire duration of the study, where they received three nutritionally balanced meals daily. (Note: At Norristown State Hospital, each patient has a prescribed diet. Most receive the standard diet that is rich in fiber and low in fat, refined sugars and carbohydrates. Others receive meals that are specifically ordered by their internists in cooperation with the hospital dietary department.) Organized physical activities at the hospital may also have contributed to the absence of weight gain. These nutritional and exercise conditions are not the standard of care in community living situations, and may have worked in favor of weight maintenance.

Fasting glucose measures were also interesting. Abnormal glucose elevation was observed in 6 of 25 (24%) of the subjects during FGA treatment, and this rate rose to 14 of 25 (56%) during clozapine treatment. Interestingly, the short-term glucose elevation returned to "baseline" after nine months, a pattern previously reported by others (43, 44). A reexamination of subject charts suggested that dietary and pharmaceutical interventions may have contributed to glucose declination in four subjects.

With the longitudinal design, it was also possible to explore whether certain subject or treatment variables were associated with the number of metabolic abnormalities after three years of clozapine treatment. These exploratory results are summarized in Table 4. The significant main effect for "*time*" simply indicates that metabolic abnormalities increased over the three-year period; the effect was an amalgam of "switching" to clozapine, along with the effects of aging, lifetime exposure to neuroleptic treatment, dosing increases of clozapine, and probably other developmental factors. Thus, an unambiguous interpretation of the "*time*" effect is not possible. As for the between-group findings, the interpretation is more straightforward. The effects for "*gender*," "*age of clozapine initiation*," "*baseline BMI*," and "*baseline GLU*" all achieved statistical significance. Across the study, females had more metabolic abnormalities than males, and older individuals had more metabolic abnormalities than younger individuals. Those with higher BMI or fasting glucose measure at baseline remained elevated or slightly increased over time. The "*group x time*" interaction terms involving "*dose of clozapine*" and "*duration of clozapine*" were the only ANOVA observations directly implicating clozapine risk; those individuals on higher doses of clozapine and longer duration of clozapine exposure were associated with more metabolic abnormalities over time. Again, these observations require replication in larger samples.

Obviously, these preliminary results need to be interpreted within the study limitations. The longitudinal design using randomly selected hospitalized patients, who were naive to clozapine, is important. However, the sample is small, data were missing (particularly during the FGA period), and certain of the metabolic measurements (BMI and total cholesterol) were suboptimal. BMI is insensitive to the specific location of fat deposition. Measures of central obesity (abdominal circumference) would have been the measurement of choice because this metric is more clearly correlated with glucose-insulin homeostasis (45, 46). Absence of high density lipoprotein measures throughout most of the study is another limitation. The sample demographics are also a limiting factor. Our sample was comprised of an older, chronically psychotic inpatient population, and, as a result, the findings may not generalize to younger clozapine-treated populations who have received other atypical antipsychotics and possibly were never treated with FGAs. The lack of a control group is an important limitation, and the small sample limited statistical power and increased the risk of statistical error. It will be crucial to replicate these findings in a larger clozapine-treated sample and compare the findings with those from a sample that has remained on FGA treatment and those treated with other second-generation antipsychotic medications.

With these limitations in mind, the findings still have important clinical implications. The results suggest that gender, dose, duration, and age are important considerations when initiating clozapine treatment. Generally, females were found to have a higher risk for metabolic dysregulation with clozapine treatment, as reported by others (21, 24). Higher doses of clozapine and longer treatment duration are associated with increased long-term metabolic risk. Also, older individuals may have a greater metabolic risk. These are important considerations when starting clozapine treatment.

But, the more common dilemma facing clinicians has to do with individuals already being treated with clozapine. What should be done when metabolic problems arise? Does the clinician attempt to treat the metabolic problem itself? Should the patient be switched to a medication with different side effects? Are the emergent metabolic problems related to clozapine exposure rather than aging or some other developmental risk factor? These are issues with complicated implications, and unfortunately, there is little evidence to guide these "real-life" decisions. Many individuals successfully treated with clozapine will not be willing to change to a different antipsychotic given their history of treatment

failure. Fortunately, the diagnosis of schizophrenia is not a contra-indication for receiving treatment for metabolic dysregulation. Within the general population, treatments and prevention programs have been shown to have benefits in management of the MetS. These strategies should not be forgotten for people with schizophrenia, even though the implementation is challenging and requires a multidisciplinary approach involving both physical and mental health services.

In conclusion, the high prevalence of metabolic dysregulation observed in clozapine-treated individuals is real and has serious long-term health implications. These afflicted individuals have a significant increase in risk for cardiovascular disease and all-cause mortality. But, unfortunately, even with regular metabolic monitoring there is little evidence to guide the "real-life" next steps when faced with these emergent concerns. In the past, clozapine was often simply replaced with a lower risk antipsychotic agent. This is a common sense approach—clozapine is presumed to be the causal risk factor. And, in fact, this "switching" strategy has gained empirical support as a method for managing metabolic problems arising with other atypical antipsychotic agents (47). However, clozapine is a special case. These individuals usually have not responded meaningfully to numerous prior antipsychotic agents and, therefore, the risk/benefit considerations of "switching" are vexing. Thankfully, clinical practice is beginning to include metabolic screening for metabolic dysregulation; with "baseline" metabolic information available, research should be stimulated that will lead to a better understanding of the complex interactions among the effects of schizophrenia, medications, lifestyle, and individual pharmacogenetics. Many important questions remain unanswered, including appropriate and feasible screening approaches, prevention, and forms of optimal metabolic treatment. These answers will not come easily. Yet, progress has already accelerated and the developing insights will begin to unlock fundamental questions to eventually bring relief from metabolic burden.

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