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The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Schizophrenia Trial: Clinical comparison of subgroups with and without the metabolic syndrome

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Abstract

The metabolic syndrome (MS) is highly prevalent among patients with schizophrenia (current estimates 35–40%), yet no data exist on the correlation of this diagnosis with illness severity, neurocognitive or quality of life measures in this population.

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Methods: Using baseline data from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Schizophrenia Trial, assignment of MS status was performed using an updated definition derived from the National Cholesterol Education Program (NCEP) criteria. Those with and without MS were compared on the basis of primary and secondary variables of interest from baseline data encompassing psychiatric, neurocognitive and quality of life measures.
Results: Of 1460 subjects enrolled at baseline, MS status could be reliably assigned for 1231 subjects, with a prevalence of 35.8% using the NCEP derived criteria. After adjustment for age, gender, race, ethnicity and site variance, those with MS rated themselves significantly lower on physical health by SF-12 ($p < .001$), and scored higher on somatic preoccupation (PANSS item G1) ($p = .03$). There were no significant differences between the two cohorts on measures of symptom severity, depression, quality of life, neurocognition, or self-rated mental health. Neither years of antipsychotic exposure nor alcohol usage were significant predictors of MS status when adjusted for age, gender, race, and ethnicity.
Conclusions: The metabolic syndrome is highly prevalent in this large cohort of schizophrenia patients and is strongly associated with a poor self-rating of physical health and increased somatic preoccupation. These results underscore the need for mental health practitioners to take an active role in the health monitoring of patients with schizophrenia to minimize the impact of medical comorbidity on long-term mortality and on daily functioning. Outcomes data from CATIE will provide important information on the metabolic and clinical impact of antipsychotic treatment for those subjects with MS and other medical comorbidities.

Keywords: Schizophrenia; Metabolic syndrome; Health; Rating; Comorbidity

1. Introduction

More than any period in the past 50 years, there has been a resurgence of interest in medical comorbidity among patients with schizophrenia, with numerous papers (Goldman, 1999; Le Fevre, 2001; Lambert et al., 2003; Jones et al., 2004; Marder et al., 2004) and an edited book (Meyer and Nasrallah, 2003) solely devoted to this topic. One stimulus has been the recent concern regarding the metabolic effects of atypical antipsychotics (Allison and Casey, 2001; Jin et al., 2004; Meyer and Koro, 2004), and the differential impact of these newer therapies on cardiovascular risk and overall health of patients with schizophrenia (American Diabetes Association et al., 2004; Melkersson et al., 2004). There is also a body of literature on excess mortality related to the diagnosis of schizophrenia, with recent methodologically rigorous data confirming excess mortality from natural causes, particularly cardiovascular disease (Allebeck, 1989; Mortensen and Juel, 1990; Newman and Bland, 1991; Mortensen and Juel, 1993; Simpson and Tsuang, 1996; Brown, 1997; Brown et al., 2000; Osby et al., 2000a,b).

While mortality and side effect researches have been published consistently since the mid-20th century, a more recent addition to the literature on medical comorbidity in schizophrenia has focused on the underdiagnosis and treatment of common medical conditions among patients with schizophrenia (Druss et al., 2000, 2001; Cradock-O'Leary et al., 2002). In addition to the direct physiological burden, patients with schizophrenia suffer functional sequelae from medical comorbidity. Data from the large Patient Outcomes Research Team (PORT) study revealed that, among the 719 patients with schizophrenia studied, the number of medical problems present at time of interview was associated with worse perceived physical health, greater severity of psychotic and depressive symptoms, and greater likelihood of a history of a suicide attempt (Dixon et al., 1999). Moreover, the effect of medical comorbidity was significant even after controlling for psychiatric disease severity. Among acute inpatients, medical comorbidity is associated with longer hospital stays and more psychiatric symptoms and functional impairment at discharge, effects which also persisted after statistical adjustment for clinical severity at time of admission (Lyketsos et al., 2002). Persistent medication related medical side effects, such as weight gain, also play an active role in schizophrenia treatment outcomes by affecting adherence (Robinson et al., 2002; Weiden et al., 2004).

Given this confluence of findings, investigators have sought to study the functional impact of specific disease entities among patients with schizophrenia, particularly those which are highly prevalent in this

population. Type 2 diabetes mellitus has received significant attention in the recent literature, in part related to the association with atypical antipsychotic therapy, and concern over long-term health burden in patients with schizophrenia, especially the marked increase in cardiovascular disease risk (Jin et al., 2002, 2004). The prevalence of this disorder in patients with schizophrenia is approximately 10–15%, or twice that of the general population (Dixon et al., 2000; Bushe and Holt, 2004), and retrospective analysis of the PORT data sample confirmed a linkage between a diagnosis of diabetes, other medical comorbidities, and poor self-perception of physical health (Dixon et al., 2000).

With this recent focus on metabolic disorders in patients with schizophrenia, investigators have turned their attention to another clinical entity, the metabolic syndrome, which may be up to three times more prevalent than diabetes among schizophrenia patients, and poses a substantial risk of cardiovascular morbidity and mortality. The metabolic syndrome, also called the insulin resistance syndrome, dysmetabolic syndrome or Syndrome X, is diagnosed in those who meet 3 or more of the clinical criteria: increased abdominal or visceral adiposity (measured by waist circumference), low serum high density lipoprotein (HDL), elevated fasting triglycerides, hypertension, impaired fasting glucose or overt diabetes mellitus (DM) (Expert Panel, 2001). The definition from the National Cholesterol Education Program (NCEP) is commonly used (Table 1), although recent consensus panels suggest incorporating the new lower threshold for impaired fasting glucose of 100 mg/dl (Grundy et al., 2004). The age-adjusted prevalence of metabolic syndrome in the U.S. population is 23.7%, with the lowest prevalence (6.7%) in the cohort ages 20–29, and the highest (43.5%) in those ages 60 and over (Ford et al., 2002). Most importantly, those diagnosed with the metabolic syndrome are at significant future risk for development of type 2 diabetes mellitus (if not already diabetic), and cardiovascular mortality. Cross-sectional data obtained in the U.S. found the prevalence of coronary heart disease to be significantly higher among nondiabetic patients with the metabolic syndrome (13.9%) than in diabetic patients who did not meet criteria for the syndrome (7.5%), implying that the metabolic syndrome poses a greater risk from cardiovascular disease than DM (Alexander et al., 2003). Moreover, prospective data reveal that a diagnosis of the metabolic syndrome was associated with a 3-fold increased risk for both coronary heart disease and stroke over a median of 6.2 years of follow-up (Isomaa et al., 2001).

Table 1
Diagnostic criteria for the metabolic syndrome derived from NCEP (Expert Panel, 2001) (≥3 criteria must be present to establish diagnosis)

Risk factor	Defining measure
Abdominal obesity	
Men	>40 in.
Women	>35 in.
Fasting triglycerides	≥150 mg/dl
High density lipoprotein (HDL)	
Men	<40 mg/dl
Women	<50 mg/dl
Blood pressure	≥130/85 mm Hg or on antihypertensive medication
Fasting glucose	≥100 mg/dl or on insulin or hypoglycemic medication

The metabolic syndrome is of interest to those who care for patients with schizophrenia for two important reasons: 1) it appears to be highly prevalent in this patient population; and 2) it is associated with increased risk for future diabetes and cardiovascular mortality. There are three published prevalence studies of the metabolic syndrome in schizophrenia patients as of this writing, two of which have small samples sizes which call into question the reliability of the data; nonetheless, these published estimates correlate with unpublished meeting abstracts, and indicate that among schizophrenia patients ages 40–49, the prevalence of the metabolic syndrome may be as high as 50%, or more than twice the prevalence of the age-matched U.S. cohort ages 40–49 of 24% for males and 20% for females (Ford et al., 2002, 2004; Cohn et al., 2004). The first estimate is from Heiskanen et al., who published metabolic syndrome prevalence data among from a sample of 35 Finnish outpatients with schizophrenia using the NCEP criteria for the metabolic syndrome (Heiskanen et al., 2003). The sample prevalence of 37% was 2 to 4 times higher than the prevalence reported for the surrounding geographical area in Eastern Finland. The second published study assessed 33 outpatients with schizoaffective disorder (mean age 44.5 years) enrolled in a clinical trial, and noted a prevalence of 42.4% (Basu et al., 2004). The best published estimate

is from Cohn et al. Canadian study of 240 subjects with schizophrenia or schizoaffective disorder (65% male, mean age 43.3 years), which found a prevalence of 42.6% for males and 48.5% for females using the NCEP criteria (Cohn et al., 2004).

The mechanism for this increased prevalence is not entirely clear, but hypotheses include lifestyle factors which promote obesity (e.g., poor dietary habits, lack of exercise or limited activity due to negative symptoms of schizophrenia), the direct metabolic effects of antipsychotic medications (Basu et al., 2004), increased propensity for storing excess fat as intraabdominal (visceral) adiposity (Ryan and Thakore, 2002; Thakore et al., 2002), or abnormalities of the hypothalamic–pituitary–adrenal (HPA) axis (Elman et al., 1998; Kaneda et al., 2002) leading to hypercortisolemia and its phenotypic expression of truncal obesity, poor glycemic control (Rosmond, 2002) and possible effects on hippocampal volume (Starkman et al., 1999; Brown et al., 2004).

The HPA hypothesis in particular has been considered by a number of investigators as a means of unifying the features of truncal obesity and glucose intolerance (Chrousos, 2000; Ryan et al., 2003), with recent data indicating an association between depression and the metabolic syndrome, all of which may be mediated by elevated serum cortisol levels. While the association between metabolic syndrome and abnormal glucocorticoid feedback has not been definitively established, an association with this syndrome and psychological stress or depression has emerged in recent studies. In one prospective study of middle-aged women, those with high baseline levels of depression, tension and anger, and ongoing anger during the 7.4 years of follow-up had significantly elevated risk for developing the metabolic syndrome (Raikkonen et al., 2002). Analysis of data from the Third National Health and Nutrition Examination Survey comprising 3186 men and 3003 women, ages 17 to 39, also revealed that women with a history of depression, but not men, were twice as likely to have the metabolic syndrome (Kinder et al., 2004).

Given the association between medical comorbidity and poor self-perceived physical health, and the likelihood that the metabolic syndrome is highly prevalent in patients with schizophrenia, there is a need for studies with large sample sizes to more appropriately assess the impact on clinical and quality of life variables in this patient population. The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Schizophrenia Trial is a large multicenter study, sponsored by the National Institute of Mental Health (NIMH), designed to examine a multitude of variables in patients with schizophrenia (Stroup et al., 2003; Swartz et al., 2003). With the broad recruitment strategy of the CATIE Schizophrenia Trial, its multisite design, and large sample size, the baseline data obtained offers an excellent opportunity to explore the impact of the metabolic syndrome among U.S. patients with schizophrenia. Specifically, we hypothesized that those with the metabolic syndrome, as has been described with diabetes, might report worse quality of life and self-perceived physical health; moreover, if the metabolic syndrome is related to HPA axis dysfunction, we hypothesized that this might result in greater psychiatric symptom severity and neurocognitive impairment than in patients without the metabolic syndrome.

2. Methods

The methods for the CATIE Schizophrenia Trial have been published in detail previously (Stroup et al., 2003). Briefly, the CATIE Schizophrenia Trial is a national, multisite, NIMH-sponsored prospective trial of antipsychotic effectiveness in patients with schizophrenia which broadly assesses metabolic, symptom, neurocognitive and functional outcomes. Institutional Review Board approval was obtained at each site, and subjects voluntarily enrolled after having been provided informed consent in verbal and written form. Baseline demographic information collected on each subject included age, gender, NIH designations of ethnicity (Hispanic or non-Hispanic) and race (white, black or African American, Asian, American Indian or Alaskan Native, Hawaiian or Pacific Islander, or two or more races), illness duration, years since first antipsychotic use, and current antipsychotic medication. Neither duration of current antipsychotic regimen, nor historical information regarding duration of previous antipsychotic trials was obtained. Identifying information was removed from databases prior to analysis to preserve subject confidentiality. Data from one site (33 patients) were excluded from all analyses because of concerns about their integrity.

CATIE subjects were asked to present in a fasting state for laboratory evaluations, but there was a significant range recorded for time since last meal. Published data support the use of 8 h or more since last meal as an appropriate definition of fasting (Troisi et al., 2000), so this was used at the cutoff for determination of fasting status. The definition of the metabolic syndrome itself, derived from the National Cholesterol Education Program (NCEP) Third Adult Treatment Panel (ATPIII), involves satisfying 3 or more of the criteria noted in Table 1, and is the one most commonly used in published U.S. prevalence studies (Ford et al., 2002; Alexander et al., 2003; Park et al., 2003). With the recent change in the definition of impaired fasting glucose from 110–125 to 100–125 mg/dl, expert panels have recommended a similar change in the fasting glucose criterion of the metabolic syndrome (Grundy et al., 2004), so we have used this definition of the metabolic syndrome which contains this lower fasting glucose threshold (Malik and Kashyap, 2003; UK HDL-C Consensus Group, 2004). Blood pressure was performed as a single, seated determination, and waist circumference measured at the narrowest point. All metabolic laboratory measures were performed at one central laboratory.

For those subjects whose baseline laboratory values were not obtained in a fasting state by the definition above ($n=771$), we sought to classify their metabolic syndrome status using the available data in order to enlarge the pool of subjects with which to conduct the comparison of functional outcomes, consonant with the purpose of this analysis [NB: a companion paper on metabolic syndrome prevalence in the fasting cohort of subjects ($n=689$) is published separately. Only prevalence estimates from fasting subjects are comparable with other metabolic syndrome prevalence papers in the literature]. The blood pressure, waist circumference and high density lipoprotein (HDL) criteria are not affected by fasting status, and could be accurately assessed for nonfasting subjects. Both serum glucose and triglycerides are affected by recent food ingestion, and present some challenges for interpretation. The glucose criterion was considered met for the nonfasting subjects only if they were prescribed hypoglycemic medications or insulin. The glucose criterion was considered not met if the random (nonfasting) serum glucose was less than 100 mg/dl. Similarly, the triglyceride criterion was considered not met if the random serum value was less than 150 mg/dl. Random glucose values greater than 100 mg/dl (in those not taking antidiabetic medications), and random triglyceride values of 150 mg/dl or greater were considered uninterpretable, and were not counted positively or negatively for the respective criteria.

Based upon the above analysis of the metabolic syndrome criteria for nonfasting CATIE subjects, metabolic syndrome status could accurately be classified for 1231 of the 1460 subjects with baseline data (689 fasting subjects plus 542 nonfasting subjects). The 229 unclassifiable subjects represent those nonfasting subjects who met 1 or 2 of the blood pressure, waist circumference and HDL criteria, but could not be classified accurately on either the glucose or triglyceride criteria (or both), to make a determination of metabolic syndrome status, or who had missing data which precluded classification.

2.1. Statistics

Variables of interest were divided into a small set of five primary outcomes which were compared between the two cohorts on the basis of metabolic syndrome status. The number of primary comparisons was kept small (five), and the p-values were adjusted for multiple comparisons. The overall significance level of these 5 primary hypotheses was maintained at .05 by a Hochberg adjustment for multiple comparisons. The smallest p-value was compared to $0.05/5=0.01$ (Hochberg, 1988). These primary comparisons were: years of antipsychotic exposure, Positive and Negative Syndrome Scale (PANSS) total score, Heinrichs–Carpenter Quality of Life Scale score, Neurocognitive Composite Score (see note below), and self-rating of physical health using the Short Form-12 (SF-12) (Swartz et al., 2003). The SF-12 was developed as an abbreviated version of the SF-36, to lessen administration time, and contains a subset of 12 questions from the SF-36 which evaluate both physical and mental components. Although used less often than the SF-36, the SF-12 has been found to be reliable and valid (Note: the Neurocognitive Composite Score is an average of the five subscale composite results after conversion to z-scores. The five separate composite scores were: 1). *Processing Speed*: the average of three components: grooved pegboard, the WAIS-R Digit Symbol Test, and the average of the

Controlled Oral Word Association Test (COWAT) and Category Instances. 2). *Verbal Memory*: Hopkins Verbal Learning Test (average of 3 trials). 3). *Vigilance Summary Score*: Continuous Performance Test (CPT) d-prime scores (average of 2-digit, 3-digit, and 4-digit). 4). *Reasoning Summary Score*: average of Wisconsin Card Sorting Test and WISC-R Mazes. 5). *Working Memory Summary Score*: average of a computerized test of visuospatial working member (sign reversed) and letter number sequencing.).

The secondary comparisons incorporated subscale scores of the above batteries, alcohol use, Calgary Depression Scale for Schizophrenia score, and the item on somatic preoccupation from the PANSS (General Psychopathology item 1), and were not adjusted for multiple comparisons, but were adjusted for age, gender, race (white vs. non-white), Hispanic ethnicity and site variance based on ANCOVA. The *p*-values for these secondary parameters are presented for descriptive purposes only, since there is no adjustment for multiple comparisons. Those with and without the metabolic syndrome were descriptively compared on both the primary and secondary outcomes using a one-way ANOVA with $df=1$. Alcohol use was compared using a chi-square test. Since it was hypothesized that years of antipsychotic exposure and alcohol use might be predictors of MS status, adjusted comparisons of these parameters were assessed based on a logistic regression model, with MS status as the binary outcome, and age, gender, race and ethnicity as covariates. Additional exploratory analyses were performed for the two genders separately. All statistical analyses used SAS version 8.2.

3. Results

For the 1231 subjects who could be classified on the basis of metabolic syndrome status, the metabolic syndrome prevalence was 35.8%. When compared on the basis of demographics (Table 2), those with the metabolic syndrome, were older, had higher proportion of female gender, and also were more likely to be white. There was no significant difference in the proportion of those with Hispanic ethnicity based upon metabolic syndrome status. Table 3 provides data on the primary and secondary variables of interest, with unadjusted and covariate-adjusted levels of significance. While several unadjusted comparisons were significant at the $p=.05$ level, only one primary comparison variable, the SF-12 Physical score ($p<.001$), and one secondary comparison variable, the PANSS rating of somatic concern (item 1 of the 16 general psychopathology items) ($p=.03$), were significant after adjustment for demographic variables. Importantly, the patients with metabolic syndrome as a whole did not differ from other patients on the basis of depressive symptomatology, neither were there differences when this analysis was repeated on gender-specific cohorts. In the logistic models, with MS status as the binary dependent variable, neither years of antipsychotic exposure nor self-reported alcohol predicted MS status, but age, race, and ethnicity all emerged as significant covariates. While the majority of the secondary comparisons were not significant, the importance of including the site of enrollment in the model was seen in the fact that in every linear regression model, study site emerged as a significant covariate.

4. Discussion

The results of this study, from the baseline CATIE Schizophrenia Trial sample, represent the first data set

Table 2
Comparison of baseline CATIE subjects on the basis of metabolic syndrome classification

Parameter	Metabolic syndrome ($n=441$)	No metabolic syndrome ($n=790$)	*p*
Age	42.8 ± 10.2	39.4 ± 11.6	<0.0001
Gender (% male)	66.2%	78.4%	<0.0001
Race (% white)	66.6%	54.3%	<0.0001
Ethnicity (% Hispanic)	11.8%	11.0%	0.679
Systolic BP (mm Hg)	129.9 ± 14.8	120.8 ± 16.0	<0.0001
Diastolic BP (mm Hg)	83.2 ± 10.4	76.4 ± 10.5	<0.0001
Waist circumference (in.)	44.2 ± 6.0	36.1 ± 4.8	<0.0001
Body mass index (kg/m^2)	34.4 ± 6.9	26.6 ± 5.5	<0.0001
HDL (mg/dl)	36.4 ± 9.0	49.0 ± 14.0	<0.0001
Glucose (mg/dl)	115.4 ± 59.0	90.0 ± 27.6	<0.0001
Triglycerides (mg/dl)	276.0 ± 192.1	138.0 ± 93.2	<0.0001

Table 3
Comparison of mean baseline values for CATIE subjects by metabolic syndrome status

Variables	Metabolic syndrome status		Significance (p)	
	No (n=790)	Yes (n=441)	Unadjusted	Adjusted
Primary variables				
PANSS total score	75.9 ± 17.6 (n=782)	74.4 ± 17.5 (n=438)	.158	.207
Neurocognitive composite score	−.008 ± .657 (n=721)	−.055 ± .632 (n=402)	.240	.765
Quality of life (QOL) total score	2.72 ± 1.07 (n=790)	2.79 ± 1.01 (n=441)	.270	.333
SF-12 physical score	49.59 ± 9.59 (n=777)	46.20 ± 10.63 (n=432)	<.0001	<.0001
Years of antipsychotic use	13.40 ± 10.82 (n=755)	15.98 ± 10.50 (n=433)	<.0001	NS*
Secondary variables				
PANSS Positive symptom score	18.5 ± 5.6 (n=782)	18.1 ± 5.6 (n=438)	.155	.231
PANSS Negative symptom score	20.3 ± 6.5 (n=782)	19.9 ± 6.4 (n=438)	.270	.598
PANSS general psychopathology score	37.0 ± 9.3 (n=782)	36.4 ± 9.4 (n=438)	.299	.213
PANSS item G1-somatic concern	2.22 ± 1.29 (n=782)	2.40 ± 1.37 (n=438)	.023	.026
Neurocognitive — Verbal Memory	−.030 ± .900 (n=721)	.021 ± .889 (n=402)	.367	.768
Neurocognitive — Processing Speed	.037 ± .756 (n=721)	−.071 ± .725 (n=402)	.020	.212
Neurocognitive — Working Memory	−.009 ± .868 (n=721)	−.016 ± .843 (n=402)	.782	.674
Neurocognitive — Reasoning	.041 ± .793 (n=721)	−.074 ± .778 (n=402)	.019	.578
Neurocognitive — Vigilance	−.044 ± .891 (n=721)	−.088 ± .869 (n=402)	.441	.894
QOL — interpersonal relations	2.50 ± 1.28 (n=790)	2.60 ± 1.29 (n=441)	.193	.153
QOL — instrumental role	1.72 ± 1.65 (n=790)	1.78 ± 1.60 (n=441)	.557	.389
QOL — intrapsychic foundations	3.11 ± 1.22 (n=790)	3.10 ± 1.16 (n=441)	.828	.597
QOL — common objects and activities	3.27 ± 1.24 (n=790)	3.49 ± 1.08 (n=441)	.003	.075
SF-12 mental score	40.94 ± 11.71 (n=777)	40.61 ± 11.59 (n=432)	.640	.719
Calgary depression score	4.42 ± 4.33 (n=783)	4.76 ± 4.61 (n=438)	.203	.718
Alcohol use (% prevalence)	34.6% (n=790)	26.3% (n=441)	.003**	NS***

NS=not significant.
* p=.332 for variable in logistic regression model predicting MS status, with age, gender, race and ethnicity as covariates.
** χ^2 df=1.
*** p=.087 for variable in logistic regression model predicting MS status, with age, gender, race and ethnicity as covariates.

to systematically examine the impact of the metabolic syndrome on clinical, cognitive, and quality of life variables in patients with schizophrenia. While much of the recent literature on metabolic dysfunction in patients with schizophrenia has focused on diabetes (Dixon et al., 2000), the metabolic syndrome is much more prevalent, and deserving of increased scrutiny. The metabolic syndrome should be of concern for the psychiatric community because it represents a significant source of cardiovascular risk, and, as these data illustrate, because of the associated psychic burden imposed on patients with schizophrenia. Although the metabolic syndrome cohort was older, and had a greater proportion of whites and females, the effect of this syndrome on somatic concerns and self-rated health remained statistically significant after controlling for age and other demographic variables.

The results presented here are consistent with the PORT study findings that schizophrenia patients with co-occurring medical illness report lower self-ratings of physical health (Dixon et al., 1999). What was not seen, after adjustment for demographic variables, was a relationship between the presence of the metabolic syndrome and symptom severity or neurocognitive dysfunction. Neither was there an association between depressive symptoms and metabolic syndrome status for the entire group or the female cohort, implying that the perception of poor physical health was not driven by mood symptoms. Whether the increased prevalence of the metabolic syndrome in patients with schizophrenia is related to HPA axis abnormalities and hypercortisolemia remains a matter of debate (Ryan et al., 2003), but the findings here do not support an impact on cognition, particularly hippocampal-mediated functions related to memory.

Although CATIE was designed to examine a large array of treatment outcome variables related to schizophrenia, one item, which would have been beneficial, is reliable documentation at study entry of duration of current antipsychotic use. With the

reported association between metabolic adverse effects and use of atypical antipsychotics, especially the dibenzodiazepine derived agents (American Diabetes Association et al., 2004), it would have been useful to explore whether there are symptom or quality of life differences between patients on stable antipsychotic regimens for extended periods. The metabolic syndrome clearly has an impact on patient somatic concerns, but this analysis cannot provide guidance on how modification of psychotropic treatment might impact the metabolic syndrome criteria. The failure to collect duration of current antipsychotic (or other psychotropic medication use) is a significant limitation, but without such information, attempts to make causal inferences regarding associations between use of certain medications and clinical variables will generate uninterpretable data.

Multiple studies indicate that patients with severe mental illness are not highly motivated to address obesity (Meyer, 2002), and, when motivated to enter a behavioral program for weight loss, experience high drop-out rates with limited success (Loh et al., in press). The outcomes data from CATIE will address the medication-related issues in a prospective manner, and thereby provide useful information on the effects of antipsychotic switching on medical comorbidity and associated symptom and quality of life measures. Until such time, clinicians are advised to heed the recent expert consensus recommendations on metabolic and general health monitoring for patients with schizophrenia (American Diabetes Association et al., 2004; Marder et al., 2004), and be attentive to the psychic impact which medical comorbidity may have on their patients with severe mental illness.

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