Antipsychotics and Metabolics in the Post-CATIE Era

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Abstract Schizophrenia patients have high prevalence of cardiovascular (CV) disease risk factors and high CV mortality, with increasing concern over the contribution of antipsychotic medications to cardiometabolic risk. The design of the NIMH-sponsored Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Schizophrenia Trial was driven by a need to understand the efficacy and safety differences between atypical antipsychotics, and between atypical and typical antipsychotics. The CATIE data indicated differences between olanzapine and other antipsychotics in phase 1 on the primary outcome measure, time to drug

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discontinuation, yet olanzapine was not superior to risperidone in the phase 2 tolerability arm, and was inferior to clozapine in the phase 2 efficacy arm. However, CATIE provided clear confirmation of the metabolic liability for olanzapine and also quetiapine, particularly on measures associated with insulin resistance: fasting triglycerides and central adiposity. Current research is focused on analyzing the adiposity-independent impact of certain antipsychotics on glucose–insulin homeostasis, and the disease-specific biological factors that predispose schizophrenia patients to metabolic dysfunction. The CATIE data also highlighted the high prevalence of metabolic disorders in chronic schizophrenia patients, and the moderating role of gender and race or ethnicity in antipsychotic-associated metabolic adverse effects. In the post-CATIE era, safety concerns remain the primary driver of antipsychotic prescribing habits. Absent compelling efficacy data that differentiates between antipsychotics for nonrefractory schizophrenia, the CATIE results reinforce the need for additional metabolically neutral antipsychotic treatment options, and the importance of ongoing physical health monitoring for schizophrenia patients.

Keywords Antipsychotic · Cardiovascular · C-reactive protein · Insulin · Metabolic · Metabolic syndrome

1 Introduction

The diagnosis of schizophrenia is associated with early mortality related to suicide and medical illnesses (Allebeck 1989; Brown 1997). Among the medical conditions which are overrepresented in patients with schizophrenia, recent research has convincingly established cardiovascular (CV) disease as the leading natural cause of excess mortality, with standardized mortality ratios for CV causes twofold greater than the general population (Colton and Manderscheid 2006; Osby et al. 2000a, b). As mounting evidence indicates that the mortality gap may be widening between schizophrenia patients and their peers (Saha et al. 2007), the psychiatric community has increasingly focused on means to improve the physical health of patients with schizophrenia (Marder et al. 2004; Meyer and Nasrallah 2009) with the expressed goal of monitoring for cardiometabolic risk, and mitigating medical comorbidity and high CV mortality rates.

Multiple factors contribute to CV risk in schizophrenia patients (Newcomer and Hennekens 2007), including high cigarette smoking prevalence (Brown et al. 1999), undertreatment of medical conditions (Druss et al. 2000; Nasrallah et al. 2006), and inherent metabolic dysfunction associated with schizophrenia (van Nimwegen et al. 2008), yet it is the metabolic effects of antipsychotic treatment that have emerged as one of the most important and contentious elements in the risk equation. By the 1960s, it was apparent that low-potency phenothiazines had deleterious effects on weight, serum lipids, and glucose (Clark et al. 1967; Efron and Balter 1966;

Mefferd et al. 1958; Schwarz and Munoz 1968), but the lessons learned were lost in the ensuing decades as use of metabolically neutral high-potency typical antipsychotics eclipsed that of low-potency agents (Meyer and Koro 2004). In the mid-1990s, the availability of a new generation of antipsychotics, derived from clozapine's pharmacological properties of high $5HT_2$ affinity and low D_2 potency, heralded a new age of schizophrenia treatment with markedly reduced risk for neurological adverse effects. By decade's end, it became apparent that these newer compounds had lower rates of extrapyramidal side effects and tardive dyskinesia, but were at times accompanied by weight gain, and significant derangements in lipid and glucose metabolism (Jin et al. 2002; Meyer 2001a, b). Aside from case reports, the largest data sets with metabolic outcomes were from industry trials, whose restrictive enrollment criteria often precluded generalizability to the broader spectrum of schizophrenia patients. It was in this context that many looked to the NIMH-sponsored Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Schizophrenia Trial to provide data on antipsychotic health outcomes from a broad array of atypical antipsychotics, using unbiased entry criteria that promoted enrollment of schizophrenia patients with medical comorbidities (Lieberman et al. 2005) (see Fig. 1). The randomized, double-blind nature of the study, and the large sample size ($n = 1{,}460$) offered a unique opportunity to resolve many unaddressed issues regarding the relative metabolic impact of atypical antipsychotics; in doing so, the CATIE results confirmed the high prevalence of cardiometabolic risk in

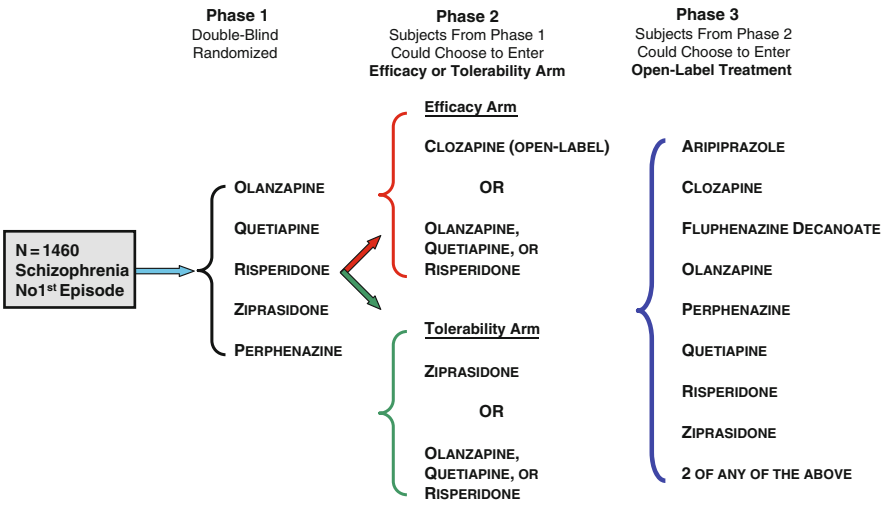

Fig. 1 CATIE Schizophrenia Trial design. *Notes*: (a) Ziprasidone was added to phase 1 after 40% of subjects had been randomized. (b) Subjects with baseline tardive dyskinesia were not randomized to perphenazine in phase 1. (c) Subjects who failed perphenazine in phase 1 were randomized to an atypical (phase 1B) before eligibility for phase 2. (d) Subjects who discontinued phase 1 medication for efficacy reasons were offered treatment in the efficacy arm of phase 2. If they chose not participate due to the possibility of clozapine exposure, they were randomized in the phase 2 tolerability arm. (e) All subjects in phase 2 received a different medication than phase 1

schizophrenia patients, and highlighted those parameters of greatest import to health monitoring during antipsychotic treatment.

The post-CATIE view of antipsychotics is very different from that which engendered the study. Metabolic safety concerns now drive antipsychotic choice, with many providers concluding that there are, at best, limited efficacy differences between atypical antipsychotics (clozapine excepted), and between typical and atypical agents. The purpose of this chapter is to review the current understanding of sources for cardiometabolic risk, and discuss the implications of CATIE data on antipsychotic metabolic outcomes in light of ongoing research into medication and disease mechanisms underlying metabolic dysfunction in schizophrenia patients.

2 Sources of Cardiovascular Risk

The November 20, 2008 issue of the New England Journal of Medicine published findings from a double-blind, placebo-controlled study of rosuvastatin treatment for individuals who did not meet usual criteria for lipid-lowering therapy (Ridker et al. 2008). The findings of this trial, its conceptualization, and its early termination by the safety monitoring board due to markedly lower CV event rates in the rosuvastatin arm represent a paradigm shift in our understanding of CV risk. For decades, clinical CV risk assessment was based on risk factors derived from large longitudinal studies such as the Framingham Heart Study (Wilson et al. 1998). Smoking, hypertension, total cholesterol, and high-density lipoprotein (HDL) cholesterol levels emerged as the most robust predictors of CV events, and were included in empirically derived risk algorithms (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults 2001; Wilson et al. 1998), yet there were limitations to these predictive models. Cardiologists were troubled by the fact that 20% of subjects in the Framingham Heart Study experienced major CV events without one major CV risk factor (Wilson et al. 1998). While low-density lipoprotein (LDL) serves as the primary target for lipid-lowering therapy (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults 2001), it was perplexing that there was a poor correlation between baseline LDL and future myocardial infarction risk during statin treatment (Heart Protection Study Collaborative Group 2002); moreover, 46% of CV events in large longitudinal studies occurred in those with low serum LDL (<130 mg/dL) (Ridker et al. 2002).

These issues, combined with the knowledge that atherosclerotic disease burden increases serum levels of inflammatory markers such as interleukin-6 (IL-6) and C-reactive protein (CRP), prompted investigators to examine the association between inflammation and CV outcomes. Prospective data from several statin studies confirmed that CRP possessed significant predictive power for CV events, that CRP levels were superior to LDL, HDL, total cholesterol:HDL ratio, and IL-6 for risk prediction, and that CRP was second to systolic blood pressure and ahead of smoking as a predictor of CV risk (Boekholdt et al. 2006; Cook et al. 2006; Ridker et al. 2002). That CRP might be an independent predictor of CV risk was also raised

by data, indicating that patients with lower CRP levels after statin treatment sustained fewer CV events than those with higher CRP, regardless of LDL levels (Ridker et al. 2005).

These data served as justification for enrolling 17,802 apparently healthy men and women with normal serum LDL (<130 mg/dL), but with serum CRP above population median levels (>2 mg/L), into a long-term, placebo-controlled trial of the high-potency statin, rosuvastatin. The study was intended as a 4-year trial, but was terminated less than 2 years after commencement by the finding of 37% lower CV events in the rosuvastatin arm, a finding that was consistent across all demographic risk groups (e.g., gender, age, smokers, those with metabolic syndrome, etc.). The appreciation of CRP as a target for CV risk reduction is very recent, but is rapidly assuming relevance for CV monitoring of schizophrenia patients based on the rosuvastatin trial outcome, combined with CATIE data illustrating antipsychotic effects on CRP and other inflammatory markers (Meyer et al. 2009a); moreover, as will be discussed later, there is emerging evidence that elevated levels of systemic inflammation may have deleterious neurocognitive effects, providing another reason to consider CRP reduction as a therapeutic target in schizophrenia patients (Dickerson et al. 2007; Gunstad et al. 2006; Weuve et al. 2006).

Another important source of cardiometabolic risk of relevance to schizophrenia treatment is that related to insulin resistance. Type 2 diabetes mellitus (DM) has long been recognized as a strong predictor of future CV events (Epstein 1967; Kannel and McGee 1979). Current CV risk algorithms deem type 2 DM a coronary heart disease (CHD) risk-equivalent condition, based on findings that the long-term myocardial infarction risk (>20%) is virtually identical to that in patients without DM but with a prior history of myocardial infarction (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults 2001). Many are aware of the concerns regarding diabetes risk with atypical antipsychotics, but most are unaware that serum glucose is a relatively insensitive marker of increasing insulin resistance over short periods of time (e.g., <1 year). Given the twofold higher DM prevalence in schizophrenia patients (Bushe and Holt 2004), clinicians are correct in asserting the need to monitor serum glucose, but if the goal is to forestall the onset of diabetes, other laboratory and clinical data provide a more sensitive picture of declining insulin sensitivity.

The metabolic syndrome concept was first elaborated over two decades ago (Reaven 1988), and describes the fact that, in certain susceptible individuals, central (visceral) adiposity results in compensatory hyperinsulinemia, and a cluster of other findings including hypertension, atherogenic dyslipidemia (decreased HDL cholesterol, elevated triglycerides – TGs), and increased serum levels of prothrombotic proteins and inflammatory markers (Table 1). These metabolic parameters define a continuum of risk – those individuals who have more features of this syndrome appear more greatly predisposed to type 2 DM (de Vegt et al. 2001) and CV disease (Ford 2004). There has been an ongoing debate in recent literature over the value of the metabolic syndrome concept (American Heart Association et al. 2005; Kahn et al. 2005), since the metabolic syndrome diagnosis itself confers no greater predictive value for CV events than traditional estimating algorithms

Table 1 National cholesterol education program metabolic syndrome criteria (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults 2001)

Criterion	Threshold
Abdominal obesity (waist circumference)	
Men	>40 in.
Women	>35 in.
Fasting triglycerides	≥150 mg/dL
HDL	
Men	<40 mg/dL
Women	<50 mg/dL
Blood pressure	≥130/85 mmHg or use of antihypertensive medication
Fasting glucose[a]	≥110 mg/dL or use of insulin or hypoglycemic medication

[a]Recently lowered to 100 mg/dL (Grundy et al. 2004)

(Wannamethee et al. 2005). Nonetheless, there is a strong association between the number of metabolic syndrome criteria met and increased CHD risk (Girman et al. 2005); moreover, the concept is of value by highlighting clinical findings that, by themselves, may not generate significant attention, and are associated with future risk for DM and CHD, in particular hypertriglyceridemia (Lorenzo et al. 2007). Among laboratory markers of CV risk in schizophrenia patients, hypertriglyceridemia assumes particular importance due to (a) the association with metabolic syndrome and insulin resistance and (b) the fact that elevated TGs may be frequently seen during treatment with certain atypical antipsychotics (Meyer and Koro 2004).

Serum TGs have not been included in CV risk algorithms since, by itself, the predictive power of serum TG levels was inferior to that of total cholesterol and HDL; however, there are data to indicate that, for any level of HDL, elevated TG confers additional CV risk (Jeppesen et al. 1998). Importantly, fasting TG levels highly correlate with insulin resistance among nondiabetics using sophisticated means to measure insulin sensitivity (McLaughlin et al. 2003). This relationship is the direct result of adipocyte insulin resistance to the inhibitory effects on insulin-dependent lipase. As insulin resistance worsens, inappropriately high levels of lipolysis release excess free fatty acids into circulation that are hepatically transformed into TG (Smith 2007). Elevated fasting TG levels thus become a sensitive marker of insulin resistance, but fasting TG to HDL ratios $\geq$ 3.0 perform better than fasting TGs in identifying prediabetic individuals in the highest tertile of insulin resistance (McLaughlin et al. 2003). Increased TG levels interfere with important regulatory functions governing the production of apolipoprotein B100 (ApoB100), a core lipoprotein in very low, intermediate, and LDL particles (Smith 2007). The overproduction of ApoB100 results in more of these TG-rich particles, and the greater presence of these light TG-rich lipoproteins causes the transfer of TG to HDL at the expense of HDL cholesterol content. After passage through the liver, where TG is cleaved by enzymatic processes, the remaining HDL particle is smaller than normal and more readily cleared in the kidney, resulting in the characteristic low serum HDL levels seen with insulin-resistant states (Smith 2007). The TG:HDL ratio thus reflects the combined effects of low HDL and elevated TG seen in insulin-resistant patients.

While fasting TG values provide important information on insulin resistance, both fasting and nonfasting TGs are associated with CV risk. Nonfasting TG in particular may be more relevant to the development of atherosclerosis and subsequent CV risk than fasting TG levels. The basis of this assertion lies in the concept that arterial injury may occur primarily during the postprandial period, when TG-rich particles reach their highest levels and penetrate arterial intimal cells (Eberly et al. 2003). As serum TG levels require more than 8 h to return to baseline after a meal, individuals are in a nonfasting state most of the day with respect to TG values (Nordestgaard et al. 2007). Supporting clinical data are seen in results from a large ($n = 13{,}981$) European trial with mean 26 years of follow-up that found a significant correlation between nonfasting TG levels and risk of major CV events (Nordestgaard et al. 2007). Moreover, prospective data from the Women's Health Study ($n = 26{,}509$) found no relationship between increasing fasting TG values and CV risk over the 11.4 years of follow-up when fully adjusted for CV risk factors; however, using adjusted models, a significant association was found between nonfasting TG and CV risk (Bansal et al. 2007), particularly, TG levels measured 2–4 h postprandially.

There is little debate on the value of established CV risk factors, including older age, low serum HDL, elevated total cholesterol, hypertension, smoking, and the moderating impact of gender (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults 2001), but, as the prior discussion illustrates, these factors do not encompass all aspects of CV risk prediction. As will be discussed, CATIE not only provided ample data on traditional CV risk factors and those associated with the metabolic syndrome, but also provided the first introduction for the psychiatric community to the role of nonfasting TG and inflammation in assessing the CV risks of antipsychotic treatment.

3 The Cardiovascular and Metabolic Risk Profile of Subjects Entering the CATIE Schizophrenia Trial

When the CATIE Schizophrenia Trial concluded in fall 2004, it was already evident that schizophrenia patients had 2–4 times higher metabolic syndrome prevalence than general population estimates (Cohn et al. 2004; Heiskanen et al. 2003), but the largest published study at that time was from a Canadian sample of 240 subjects (Cohn et al. 2004). Of 1,460 subjects with baseline data, 689 CATIE subjects had fasting laboratory measures at study baseline to examine metabolic syndrome criteria, and these subjects were matched 1:1 on the basis of age, gender race, and ethnicity with subjects randomly drawn from the Third National Health and Nutrition Examination Survey (NHANES III) to perform comparative analyses. Overall metabolic syndrome prevalence among the CATIE subjects was 40.9% (McEvoy et al. 2005), but was significantly higher in CATIE females (51.6%) than CATIE males (36.0%) ($p = 0.0002$). When compared with the matched NHANES cohort,

Table 2 Comparison of metabolic syndrome data between CATIE subjects and matched NHANES III subjects (McEvoy et al. 2005)

	Males ($n = 509$)			Females ($n = 180$)		
	CATIE (%)	NHANES (%)	p	CATIE (%)	NHANES (%)	p
Metabolic syndrome prevalence	36.0	19.7	0.0001	51.59	25.1	0.0001
Met waist circumference criterion	35.5	24.8	0.0001	76.3	57.0	0.0001
Met triglyceride criterion	50.7	32.1	0.0001	42.3	19.6	0.0001
Met HDL criterion	48.9	31.9	0.0001	63.3	36.3	0.0001
Met BP criterion	47.2	31.1	0.0001	46.9	26.8	0.0001
Met glucose criterion	14.1	14.2	0.9635	21.7	11.2	0.0075

CATIE male subjects were twice as likely to have metabolic syndrome (OR 2.38; 95% CI 1.78–3.18), while CATIE females had three times greater odds for metabolic syndrome (OR 3.51; 95% CI 2.19–5.62). The CATIE subjects also had greater prevalence of every metabolic syndrome criterion when compared to the NHANES sample (Table 2), with fasting glucose among males the sole exception. An additional analysis using the Framingham CV risk algorithm found that 10-year CHD risk was significantly elevated in male (9.4 vs. 7.0%) and female (6.3 vs. 4.2%) schizophrenia patients in the baseline CATIE sample compared to their matched NHANES peers ($p = 0.0001$) (Goff et al. 2005), and significantly higher rates of smoking (68 vs. 35%), diabetes (13 vs. 3%), and hypertension (27 vs. 17%) compared to NHANES subjects ($p < 0.001$). Despite the known cardiometabolic risk factors seen in schizophrenia patients, analysis of the CATIE baseline sample also revealed high rates of nontreatment that ranged from 30.2% for diabetes, to 62.4% for hypertension, and 88.0% for dyslipidemia (Nasrallah et al. 2006).

4 The Impact of Antipsychotic Treatment on Cardiovascular and Metabolic Outcomes in the CATIE Schizophrenia Trial

4.1 Metabolic Outcomes

The initial CATIE publications provided data on changes weight, serum cholesterol, hemoglobin A1C, glucose, and TG (Lieberman et al. 2005; Stroup et al. 2006), and confirmed olanzapine's deleterious effects on weight and TG, but failed to find significant differences between treatments (olanzapine, perphenazine, quetiapine, risperidone, and ziprasidone) for serum glucose. The increased serum TG levels during olanzapine exposure indicate worsening insulin sensitivity, but over the short periods of exposure for subjects in CATIE phase 1, these did not translate into significant between-treatment changes in serum glucose. Ziprasidone exposure

was associated with metabolic improvement, as noted in prior switch studies (Weiden et al. 2003, 2008), an effect not related to any weight or lipid-lowering properties of ziprasidone, but rather the removal of prior drug effects combined with ziprasidone's metabolic neutrality. Prior to CATIE, consensus opinion had concluded that risperidone and quetiapine possessed equivalent metabolic profiles, and that both had greater metabolic impact than ziprasidone, but were more benign than olanzapine (American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, North American Association for the Study of Obesity 2004); however, the initial CATIE data indicated that quetiapine had an adverse impact on TG not seen with risperidone.

Subsequent detailed analysis of the CATIE phase 1 data focusing on metabolic syndrome components (Meyer et al. 2008b) noted that, after 3 months, there were significant between-drug differences for the change in proportion meeting metabolic syndrome status. The metabolic syndrome prevalence increased for olanzapine-exposed subjects from 34.8 to 43.9%, but decreased for ziprasidone (from 37.7 to 29.9%) ($p = 0.001$). To examine the effect of longer exposure on change in metabolic parameters, an analysis was performed using the last phase 1 data available for each subject. These data were obtained, on average, 9 months from baseline, and the findings were consistent with those at 3 months for mean changes in waist circumference and fasting TG, although between-group differences now emerged for HDL and systolic BP (Table 3). A repeated measures analysis of waist circumference change was also performed which found a significant impact of baseline value on changes in waist circumference: patients who were more centrally obese tended to become thinner. For subjects with baseline values below the median (<39 in.), olanzapine caused greater increases in central adiposity (+1.92 in.) compared to every other medication [range +0.35 in. (ziprasidone) to +0.97 in. (quetiapine)]. Among subjects with baseline waist circumference at or above the median (≥39 in.), only the olanzapine-exposed cohort did not experience an adjusted mean decrease in waist circumference; moreover, perphenazine (−0.97 in.) was found to be significantly superior to both olanzapine (+0.17 in.; $p < 0.0001$) and quetiapine (−0.01 in.; $p = 0.0007$). The exploratory analysis of CATIE phase 1 nonfasting TG samples noted greater increases in median and adjusted mean nonfasting TG levels among those randomized to quetiapine (mean +54.7 mg/dL, median +26 mg/dL) and olanzapine (mean +23.4 mg/dL, median +26.5 mg/dL), with a significant between-group difference for perphenazine versus olanzapine ($p = 0.002$) (Meyer et al. 2008a).

4.2 Framingham Cardiovascular Risk

Since the greatest metabolic impact of atypical antipsychotics is on weight (Newcomer 2005) and serum TG, but much less on cholesterol measures (Meyer and Koro 2004), an important question is whether there would be between-treatment differences in calculated CV risk, given the fact that neither weight, waist circumference, nor

Table 3 Mean changes in individual metabolic criteria at end of CATIE phase 1 visit (Meyer et al. 2008a)

	Waist circumference[a] (in.)		Systolic BP[a] (mmHg)		Diastolic BP (mmHg)	HDL[b,c] (mg/dL) (whites)	HDL[b] (mg/dL) (nonwhites)	Fasting glucose (mg/dL)	Fasting triglycerides[a] (mg/dL)	
	Below median	Above median	Below median	Above median					Below median	Above median
Mean exposure (months)	8.9	8.7	8.7	9.1	8.9	9.2	9.9	9.9	9.9	9.8
OLANZ	1.9 (SE = 0.2) (n = 146)	0.4 (SE = 0.3) (n = 147)	6.0 (SE = 1.0) (n = 159)	−3.6 (SE = 1.2) (n = 146)	0.1 (SE = 0.6) (n = 305)	−1.7 (SE = 0.6) (n = 171)	−0.9 (SE = 0.9) (n = 115)	4.5 (SE = 2.3) (n = 94)	49.0 (SE = 10.8) (n = 42)	5.2 (SE = 17.4) (n = 51)
RISP	0.9 (SE = 0.2) (n = 145)	−0.7 (SE = 0.3) (n = 143)	5.6 (SE = 1.1) (n = 136)	−9.0 (SE = 1.1) (n = 162)	−1.3 (SE = 0.6) (n = 298)	0.1 (SE = 0.6) (n = 162)	0.9 (SE = 0.9) (n = 109)	−0.4 (SE = 2.6) (n = 74)	19.7 (SE = 11.2) (n = 39)	−67.1 (SE = 21.2) (n = 35)
QUET	0.7 (SE = 0.2) (n = 142)	0.0 (SE = 0.2) (n = 157)	8.6 (SE = 1.0) (n = 158)	−8.0 (SE = 1.2) (n = 145)	−0.1 (SE = 0.6) (n = 303)	−0.2 (SE = 0.6) (n = 186)	0.1 (SE = 1.1) (n = 85)	−1.8 (SE = 2.4) (n = 88)	29.8 (SE = 10.8) (n = 42)	−13.0 (SE = 18.4) (n = 46)
ZIP	0.0 (SE = 0.3) (n = 77)	−0.4 (SE = 0.3) (n = 78)	8.8 (SE = 1.5) (n = 78)	−7.6 (SE = 1.6) (n = 80)	−0.4 (SE = 0.8) (n = 158)	0.6 (SE = 0.9) (n = 90)	4.3 (SE = 1.4) (n = 51)	0.0 (SE = 3.5) (n = 39)	26.0 (SE = 15.6) (n = 20)	−96.4 (SE = 28.5) (n = 19)
PER	0.6 (SE = 0.2) (n = 126)	−1.1 (SE = 0.3) (n = 110)	6.0 (SE = 1.2) (n = 107)	−6.4 (SE = 1.2) (n = 137)	0.0 (SE = 0.6) (n = 243)	2.7 (SE = 0.7) (n = 130)	−1.3 (SE = 1.0) (n = 88)	−1.0 (SE = 2.7) (n = 68)	28.7 (SE = 11.6) (n = 36)	−27.5 (SE = 22.3) (n = 31)
Overall treatment difference	<0.001[d]	0.001[e]	NS	0.017[f]	NS	<0.001[g]	0.012[h]	NS	NS	0.011[i]

Table entries are ANCOVA least-squares adjusted means. All models include time to treatment discontinuation as a covariate, as well as baseline value of outcome. Demographic variables were analyzed, but only age and race entered the models for HDL, SBP, and DBP, and gender for HDL and SBP

Note: *NS* not significant ($p \geq 0.05$)

[a]Data presented in separate columns due to significant baseline by treatment effect. Median WC = 39 in., median SBP = 122 mmHg, and median TG = 148 mg/dL

[b]Data presented in separate columns due to significant race by treatment effect

[c]There was a significant ziprasidone cohort effect, but the between-group results were not different for cohorts enrolled prior to, or after the introduction of ziprasidone

[d]Between-group comparison significant for olanzapine versus risperidone ($p = 0.001$), quetiapine ($p < 0.001$), ziprasidone ($p < 0.001$), and perphenazine ($p < 0.001$)

[e]Between-group comparison significant for perphenazine versus olanzapine ($p < 0.001$), perphenazine versus quetiapine ($p = 0.003$), and olanzapine versus risperidone ($p = 0.003$)

[f]Between-group comparison significant for olanzapine versus risperidone ($p = 0.001$)

[g]Between-group comparison significant for perphenazine versus olanzapine ($p < 0.001$) and perphenazine versus quetiapine ($p = 0.002$)

[h]Between-group comparisons significant for ziprasidone versus olanzapine ($p = 0.002$) and ziprasidone versus perphenazine ($p = 0.001$)

[i]Between-group comparisons significant for olanzapine versus ziprasidone ($p = 0.003$)

TG are part of Framingham-based CV risk algorithms (Daumit et al. 2008). The other question is whether, over a relatively short time frame, the magnitude of any changes in CHD risk will be significant in those with higher baseline levels of risk (range 8.1–9.1% across antipsychotic treatments). Using the 3-month outcomes, there were significant differences between treatments for covariate-adjusted mean change in 10-year CHD risk (Daumit et al. 2008). Olanzapine was associated with an absolute increase in risk of 0.5% (SE 0.3) and quetiapine, a 0.3% (SE 0.3) increase; whereas risk decreased in patients treated with perphenazine, −0.5% (SE 0.3), risperidone, −0.6% (SE 0.3), and ziprasidone, −0.6% (SE 0.4). The difference in 10-year CHD risk between olanzapine and risperidone was statistically significant ($p = 0.004$).

4.3 Outcomes with Novel Biomarkers

The enormity of the data collected in the CATIE Schizophrenia Trial means that new findings will continue to emerge for years to come. As of this writing, samples are being analyzed to examine various markers associated with cardiometabolic risk, and the first of these to yield important results is the examination of CRP changes during phase 1. As mentioned in Sect. 2, recent clinical data on CRP have greatly influenced our understanding of CV risk, and of possible targets for risk modification. As with waist circumference and HDL, baseline CRP among CATIE subjects was a significant predictor of 3-month CRP change ($p < 0.001$), yet the 3-month analysis still found significant treatment differences in change from baseline after adjustment for baseline CRP ($p = 0.011$) (Meyer et al. 2009a). At 3 months, both olanzapine and quetiapine had the numerically greatest increases. There were no significant treatment differences in those with higher baseline levels of systemic inflammation (CRP $\geq$ 1 mg/L), but for those with lower baseline CV risk (CRP $<$ 1 mg/L), pairwise comparisons were significantly different for olanzapine versus perphenazine ($p < 0.001$) and versus risperidone ($p = 0.001$). The 12-month repeated measures analysis confirmed the association between baseline CRP and outcomes, and the deleterious impact of olanzapine compared to perphenazine ($p < 0.001$) and ziprasidone ($p = 0.003$) in those with baseline CRP $<$ 1 mg/L.

5 The Post-CATIE Era

5.1 Clinical Conclusions

The CATIE data confirm the fact that metabolic differences exist between various atypical antipsychotics, and pinpoint the metabolic outcomes (adiposity, TGs) most greatly influenced by medications. Among patients with clinical and laboratory

findings suggestive of insulin resistance, use of olanzapine is associated with further deterioration in metabolic status, while risperidone and quetiapine have intermediate effects, and ziprasidone appears to be metabolically neutral. Prior consensus panels found equivalent metabolic risk between quetiapine and risperidone (American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, North American Association for the Study of Obesity 2004), but the CATIE data suggest that quetiapine, when used at doses >400 mg for schizophrenia treatment, has significant adverse effects on nonfasting TG, HDL (in white subjects), and central adiposity in a manner not seen with risperidone.

Prior literature noted minimal effects of atypical antipsychotic treatment on blood pressure compared to other metabolic parameters, and this is confirmed by CATIE. Weight gain is associated with hypertension, but the time frame of this study may be inadequate to manifest this effect. The absence of a significant signal for HDL changes in prior antipsychotic studies may have been the result of limited duration of exposure and smaller sample sizes (Meyer and Koro 2004), since a deleterious impact of olanzapine and quetiapine was seen for serum HDL in whites, and significant improvement in HDL with ziprasidone in nonwhites. CATIE also provided the first controlled data on the metabolic effects of a medium potency typical antipsychotic published in the past 40 years, with evidence that perphenazine is generally metabolically neutral. The lack of significant between-group differences for glucose should not reassure clinicians that there are no differences in future DM risk between antipsychotics. As previously described, DM develops over 10−20 years, so short-term changes in serum glucose may not be seen despite worsening in other parameters associated with insulin resistance, especially waist circumference and TG. Lastly, the CATIE phase 1 analysis of inflammatory markers and nonfasting TG revealed patterns of changes that paralleled the known metabolic liability for each antipsychotic medication. It should also be noted that aripiprazole was not studied in the first two phases of CATIE, but clinical data indicate a benign metabolic risk profile very similar to ziprasidone (Newcomer 2005).

One of the paramount conclusions from CATIE is that schizophrenia patients possess high levels of CV risk, and that antipsychotic choice may have significant influences on cardiometabolic health over short time frames. One intended outcome for CATIE was to demonstrate whether significant between-drug differences existed for efficacy measures, but the results of CATIE, the British CUtLASS study (Jones et al. 2006), and the recent TEOSS trial in first-episode subjects (Sikich et al. 2008) have caused many to question whether significant efficacy differences exist among atypical antipsychotics (with the exception of clozapine for treatment refractory patients), and between atypical and typical antipsychotics. An unintended outcome, but important for future schizophrenia treatment, is that no novel agent with known metabolic adverse effects is likely to progress very far down the developmental pathway toward approval.

Another useful finding from CATIE relates to demographic factors that moderate metabolic risk. In the general population, gender is associated with differential risk for metabolic syndrome, with the prevalence in US women 27% compared to

22% in men according to recent estimates (Ford et al. 2004). The CATIE baseline analysis not only revealed markedly higher metabolic syndrome prevalence among chronic schizophrenia patients compared to matched peers in the general population, but also a significantly greater gender discrepancy within the CATIE cohort, with CATIE women having 42% higher prevalence than CATIE men (McEvoy et al. 2005). The differential sensitivity to metabolic risk on the basis of race and ethnicity was also seen in the baseline analysis of metabolic syndrome prevalence (McEvoy et al. 2005), and in the analysis of phase 1 metabolic outcomes (Meyer et al. 2008b). The increased vulnerability for black and Hispanic schizophrenia patients to antipsychotic metabolic effects has also been demonstrated in a recent retrospective analysis of a prospective, 26-week, randomized aripiprazole versus olanzapine trial (Meyer et al. 2009b). As treatment of all medical conditions moves into the era of personalized medicine, recognition of sensitivity to antipsychotic adverse effects, and possibly differential psychiatric outcomes on the basis gender and race/ethnicity present significant opportunities for further clinical research.

5.2 *Hypotheses on Schizophrenia and Metabolic Risk, and Adiposity-Independent Drug Effects*

Patients with schizophrenia exhibit higher metabolic syndrome prevalence than the general population (Cohn et al. 2004; De Hert et al. 2006; Hagg et al. 2006; Heiskanen et al. 2003; Mackin et al. 2007; McEvoy et al. 2005; Meyer et al. 2006; Saari et al. 2005; Srisurapanont et al. 2007; Suvisaari et al. 2007; Tirupati and Chua 2007), and the age of metabolic syndrome onset occurs much earlier than the general population (McEvoy et al. 2005). As these data are primarily accrued in antipsychotic treated individuals, there has been an ongoing debate whether there is any biological contribution of mental illness toward metabolic disease risk that exists independently of other disease-related risks such as medications, inactivity, smoking (Willi et al. 2007), and dietary habits.

Early data from samples of neuroleptic-naïve and drug-free schizophrenia patients showed contradictory findings regarding the presence of fasting hyperinsulinemia, increased central adiposity, and other abnormalities (e.g., hypercortisolemia) (Arranz et al. 2004; Ryan et al. 2003, 2004; Thakore et al. 2002; Zhang et al. 2004), but recent studies performed in neuroleptic-naïve first-episode schizophrenia patients have found evidence of pretreatment metabolic dysfunction. In a Canadian study of nine predominantly drug-naïve schizophrenia patients compared to nine matched controls, mean insulin sensitivity was 42% lower in the schizophrenia patients ($p = 0.026$), although acute insulin response to glucose did not differ between the groups ($p = 0.752$) (Cohn et al. 2006). Oral glucose tolerance testing of 38 drug-naïve, first-episode Irish schizophrenia patients and 38 matched controls found that the prevalence of impaired glucose tolerance was 10.5% in the schizophrenia patients, compared to 0% in the controls (Spelman et al. 2007).

The investigators found no significant differences on any lipid measure, leptin, hemoglobin A1C, or fasting glucose between patients and controls, but there were differences for fasting cortisol, baseline insulin, and 2-h postload insulin. Fasting plasma glucose, insulin, insulin-like growth factor-1 (IGF-1), and cortisol levels were examined in 44 neuroleptic-naïve schizophrenia patients (mean age 33.3 years) in India, and 44 matched control subjects, with schizophrenia patients exhibiting significantly higher fasting insulin and cortisol levels, but lower IGF-1 levels (Venkatasubramanian et al. 2007). Most recently, a study of seven first-episode neuroleptic-naïve Dutch schizophrenia patients and seven matched controls found no between-group differences on insulin-mediated peripheral glucose uptake; the schizophrenia patients had significantly greater endogenous glucose production (van Nimwegen et al. 2008). The failure of insulin to suppress hepatic glucose production (the primary source of endogenous glucose) indicates a level of hepatic insulin resistance existing prior to the effects of treatment.

One major research question not addressed by CATIE relates to adiposity-independent effects of atypical antipsychotics on glucose–insulin homeostasis. An early detailed analysis of new onset diabetes cased culled from the FDA MedWatch database showed that 78% of those on clozapine or olanzapine exhibited reversal of their metabolic derangements after antipsychotic discontinuation (Koller et al. 2001; Koller and Doraiswamy 2002). This was followed by a review (Jin et al. 2002) of the published literature that noted a significant proportion of atypical antipsychotic-associated new onset DM cases occurred literally within weeks of treatment initiation, again suggesting a direct antipsychotic effect on glycemic control.

These data were indicative of direct antipsychotic impact on glucose–insulin homeostasis, but the case literature is always clouded by confounding variables, including prior drug exposure, baseline obesity, and health habits which increase diabetes risk. To address these issues, Houseknecht et al. (2007) performed a series of euglycemic clamps in laboratory rats exposed to single doses of clozapine, olanzapine, ziprasidone, or risperidone. In the euglycemic clamp, a fixed intravenous insulin infusion is administered, and a simultaneous infusion of 20% glucose is also given, with the glucose infusion rate (GIR) adjusted to achieve a predetermined serum glucose level in the euglycemic range (typically 90 mg/dL in humans). The GIR thus becomes a measure of insulin effectiveness, and therefore the extent of insulin resistance, with low GIR representing a high degree of insulin resistance. In animal models, GIR equilibrium is reached after 90 min, at which point Houseknecht administered a single parenteral antipsychotic dose to each rat. This single dose design examined the acute antipsychotic impact on insulin sensitivity, completely eliminating the confounding effects of prior drug exposure and any possible effect of weight gain (Houseknecht et al. 2007). A significant impact of olanzapine on whole body insulin sensitivity was seen after injections at $t = 100$ min, as evidenced by a mean 43% decrease in GIR. A similar impact on GIR was also seen with clozapine (mean decrease of 65.2%), but not with risperidone or ziprasidone. The investigators followed this discovery by looking for evidence of impaired insulin action on target tissues. A main effect of insulin is to suppress

de novo glucose production by the liver, and individuals who are insulin resistant continue to have inappropriately high levels of endogenous hepatic glucose production. In animals and humans, hepatic glucose production can be studied using labeled glucose tracers (e.g., [6,6-$^{2}H_{2}$]-glucose) that are infused prior to and during the clamp procedure. Changes in hepatic glucose production during the clamp procedure are measured as percentage increase in endogenous glucose production from baseline. Following a single dose of ziprasidone, there was no change in hepatic glucose production compared to baseline, but a single dose of olanzapine or clozapine significantly impaired the ability of insulin to inhibit hepatic glucose production, with an 18.5-fold (olanzapine) and 22.7-fold (clozapine) increase in hepatic glucose production, a result consistent with severe hepatic insulin resistance.

This constellation of findings provided the first compelling biological data to support the concept of adiposity-independent effects of certain antipsychotics on glucose–insulin homeostasis. As this research is extended into human models, it may provide useful information on the molecular basis of antipsychotic induced disturbances in metabolic functioning, and potentially elucidate specific markers to predict differential risk among patients exposed to medication with known metabolic liabilities (e.g., clozapine and olanzapine). The ability to identify individuals at low risk for metabolic dysfunction from clozapine in particular might permit certain treatment-resistant schizophrenia patients to be transitioned more quickly to clozapine, after having failed adequate trials of other antipsychotics.

6 Conclusions

Safety concerns exert considerable influence over antipsychotic prescribing practices, particularly in the absence of compelling effectiveness differences between agents. Results of the CATIE trial confirmed the high prevalence of cardiometabolic risk among chronic schizophrenia patients, and the immediate impact of antipsychotics on certain parameters related to insulin resistance, especially central adiposity and triglyceride levels. Emerging data have augmented the information provided by CATIE on demographic factors that increase risk for adverse metabolic effects from antipsychotic treatment, even with metabolically more benign medications. Regardless of medication choice, the burden remains on clinicians to monitor all metabolic parameters associated with increased CV risk in schizophrenia patients. In the post-CATIE era it is important that psychiatrists are mindful that many patients with severe mental illnesses receive limited primary care services, and psychotropic medications are one of many contributors to increased CV risk.

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