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Impact of antipsychotic treatment on nonfasting triglycerides in the CATIE Schizophrenia Trial phase 1

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Abstract

Background: Recent literature documents a stronger association between nonfasting triglycerides (TG) and cardiovascular risk compared to fasting TG. Given concerns over antipsychotic effects on serum TG, this analysis explored changes in nonfasting TG in phase 1 of the CATIE Schizophrenia Trial.
Methods: Change in nonfasting TG, adjusted for baseline value, was compared between antipsychotic treatment groups using subjects with nonfasting laboratory assessments at baseline and 3 months.
Results: Among the 246 subjects there were significant treatment differences in 3-month change from baseline ($p=0.009$). The greatest

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increases in median and adjusted mean nonfasting TG levels were seen 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), while ziprasidone was neutral (mean+0.0 mg/dl, median+8 mg/dl), and decreases were seen with risperidone (mean −18.4 mg/dl, median −6.5 mg/dl) and perphenazine (mean −1.3 mg/dl, median −22 mg/dl). Pairwise comparisons indicated a significant between-group difference for perphenazine vs. olanzapine ($p=0.002$) and a trend for perphenazine vs. quetiapine ($p=0.006$).

Conclusions: This analysis provides further evidence for differential antipsychotic metabolic liabilities, and confirms signals for the effects of olanzapine and quetiapine on serum TG seen in earlier CATIE analyses. Future consensus recommendations will clarify the role of nonfasting TG monitoring in routine clinical practice.

Keywords: Antipsychotic; Schizophrenia; Cardiovascular risk; Lipids; Triglycerides; Nonfasting

1. Introduction

Fasting triglyceride (TG) values are a marker of insulin resistance, and moderate elevations are associated with increased cardiovascular (CV) risk independent of high density lipoprotein cholesterol levels (Jeppesen et al., 1998). However, there is evidence to indicate that atherosclerosis may be a postprandial phenomenon in which atherogenic remnant lipoproteins (chylomicrons and very low-density lipoproteins) play a critical role (Eberly et al., 2003). These triglyceride-rich particles are smaller than other lipid components, and more readily penetrate arterial intimal cells. Individuals are in a nonfasting state most of the day with respect to serum TG, since fat tolerance testing notes that TG levels peak 4 h after an oral fat load, and return to basal values only after 8–10 h (Nordestgaard et al., 2007).

Data from the Copenhagen study ($n=13,981$, mean follow-up 26 years), indicate a significant linear correlation between nonfasting TG values and directly measured remnant lipoproteins (Nordestgaard et al., 2007), providing the impetus to examine the association between nonfasting TG and CV risk. Over the course of the study follow-up, there was a significant relationship between nonfasting TG levels in men and women and risk of major CV-related events including ischemic heart disease, myocardial infarction (MI), and mortality (Nordestgaard et al., 2007). Compared to those with nonfasting TG<1 mmol/l (88.5 mg/dl), women and men with levels of 2–2.99 mmol/L (177.0–264.6 mg/dl) had adjusted hazard ratios for MI of 2.5 and 1.6 respectively. The superiority of nonfasting TG over fasting TG is seen in prospective data from the Women's Health Study ($n=26,509$, median follow-up 11.4 years) (Bansal et al., 2007). While there was no relationship between increasing tertiles of fasting TG values and risk of CV events in fully adjusted models, nonfasting TG tertiles were significantly associated with CV risk, with TG levels measured 2–4 h postprandially showing the strongest association.

Schizophrenia patients are a high-risk group for CV mortality, with lifestyle factors and treatment playing additive roles (Goff et al., 2005; Newcomer and Hennekens, 2007). Given the differential impact of antipsychotics on fasting TG (Meyer et al., 2008) and random serum TG levels (Lieberman et al., 2005) in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Schizophrenia Trial phase 1, the *a priori* hypothesis for this analysis is that there would be significant between-drug differences for nonfasting TG changes.

2. Methods

The recruitment criteria for the CATIE Schizophrenia Trial and enrollment methods have been previously described (Lieberman et al., 2005). 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. Only subjects who ate <8 h prior to phlebotomy at the baseline and 3-month assessment were used for this analysis. The 3-month time point was chosen to maximize subject retention, while providing a physiologically meaningful time frame to assess the impact of antipsychotic treatment. Due to the skewness of the nonfasting TG data, treatment groups were compared with a nonparametric test, rank analysis of covariance (Koch et al., 1982). Multiple factors were examined to assess the influence on outcome (age, gender, race/ethnicity, smoking status, baseline antipsychotic medication, baseline nonfasting TG), and treatment group comparisons were adjusted for those factors that were statistically significant ($p<0.05$). A supportive unadjusted Kruskal–Wallis rank test was also performed. In both analyses, if the overall 4 *df* test for treatment group was significant at 0.05, then the 10 between-drug comparisons were evaluated using a Bonferroni correction, yielding an alpha of $0.05/10=0.005$. Due to the relatively conservative nature of this correction, *p*-values between 0.005 and 0.01 are also identified for the reader's

Table 1
Demographic comparison of CATIE subjects with nonfasting triglyceride levels at both baseline and 3-month assessments vs. other subjects with baseline and 3-month data

Parameter	Nonfasting TG	Other subjects	*p*
Age	43.0±10.7 (*n*=246)	40.4±11.0 (*n*=687)	0.001
Gender (% male)	73.6% (*n*=246)	74.1% (*n*=687)	NS
Race (% White)	55.7% (*n*=246)	63.1% (*n*=686)	0.040
Ethnicity (% Hispanic)	9.4% (*n*=246)	12.5% (*n*=687)	NS
Years since first antipsychotic treatment	16.2±11.6 (*n*=236)	13.9±10.7 (*n*=663)	0.006
Baseline DM diagnosis	12.6% (*n*=246)	13.5% (*n*=687)	NS
Smoker	55.0% (*n*=242)	59.4% (*n*=667)	NS
Body Mass Index (kg/m^2)	30.3±6.6 (*n*=246)	29.9±7.3 (*n*=677)	NS
Baseline TG (mg/dl)	216.9±162.7 (*n*=246)	200.5±166.8 (*n*=645)	NS

Table entries are mean±SD, or %.
p-values for comparison of means are from a *t*-test; those for comparison of proportions are from a chi-square test with 1 *df*.
NS=not significant ($p \geq 0.05$).

discretion. All metabolic laboratory measures were performed at the Quintiles central laboratory.

3. Results

Demographic comparison between subjects with nonfasting TG at both time points (*n*=246) and other subjects with baseline and 3-month data (*n*=687) showed similar distributions by gender, ethnicity, body mass index, diabetes mellitus and smoking prevalence, but the nonfasting TG cohort was older by 2.6 years, with 2.3 years longer drug exposure, and had fewer white subjects (Table 1). At study entry, 28.1% of the 246 subjects were on no antipsychotic, 19.1% on olanzapine, 4.9% on quetiapine, 19.5% on risperidone, 17.5% on other antipsychotics, and 11.0% on antipsychotic combinations. The distribution of median nonfasting TG is comparable to general population studies (Nordestgaard et al., 2007), and shows serum values peaking 2–4 h from last meal, with the numerically highest peak seen in subjects reporting last meal 2–3 h prior to laboratory determination (Fig. 1).

Among the demographic factors examined, only baseline nonfasting TG values were significantly associated with 3-month changes in this variable, and this was utilized in adjusted analyses. Table 2 presents median, and baseline-adjusted mean 3-month nonfasting TG changes, although all statistical testing is nonparametric (rank transformation) due to the skewness of the data. The greatest increases in median and adjusted mean nonfasting TG levels were seen 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), while ziprasidone was neutral (mean+0.0 mg/dl, median+8 mg/dl), and decreases were seen in subjects exposed to risperidone (mean −18.4 mg/dl, median −6.5 mg/dl) and perphenazine (mean −1.3 mg/dl, median −22 mg/dl). Adjustment for baseline nonfasting TG values with a ranked ANCOVA revealed overall significant treatment differences ($p=0.009$), with a

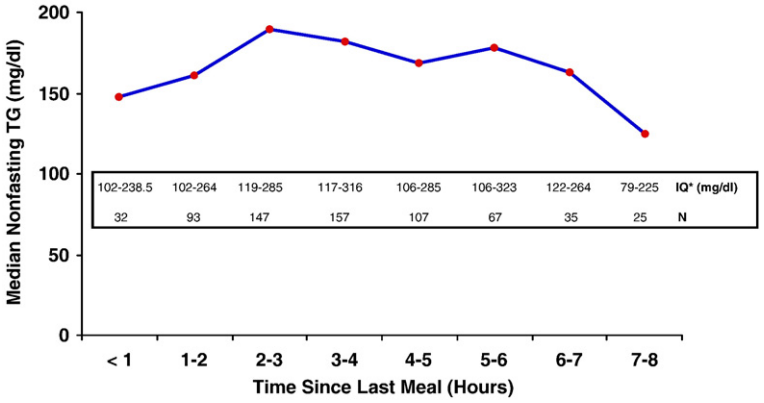

Fig. 1. Median baseline nonfasting triglyceride (TG) values by time since last meal. *IQ = interquartile range 25th–75th percentile.

Table 2
3-month changes from baseline in nonfasting triglycerides (mg/dl) by treatment group

		Observed		Adjusted[a]
	N	Median (interquartile range)	Mean±SD	Least squares mean±SE
Olanzapine	62	26.5 (−20 to 80)	33.1±159.1	23.4±22.8
Perphenazine	39	−22 (−81 to 24)	−3.7±243.8	−1.3±28.6
Quetiapine	59	26 (−34 to 96)	36.0±264.0	54.7±23.5
Risperidone	56	−6.5 (−52 to 38)	−7.9±85.3	−18.4±24.0
Ziprasidone	30	8 (−48 to 58)	0.4±145.0	0.0±32.7
Overall treatment difference		0.016[b]		0.009[c]

[a] Model adjusted for baseline triglycerides. Age, gender, race, ethnicity, baseline antipsychotic medication and smoking were allowed to enter the model but were not significant. The interaction between baseline triglycerides and treatment was also explored and was not significant.
[b] Unadjusted comparisons using the Kruskal–Wallis rank test revealed overall significant treatment differences ($p=0.016$). Individual pairwise comparisons revealed a significant difference for olanzapine vs. perphenazine ($p=0.002$).
[c] Rank ANCOVA adjusting for baseline triglycerides revealed overall significant treatment differences ($p=0.009$). Individual pairwise comparisons revealed a significant difference for perphenazine vs. olanzapine ($p=0.002$). The change in nonfasting TG was also numerically different for perphenazine vs. quetiapine, although not statistically significant with the Bonferroni correction ($p=0.006$).

significant between-group difference for perphenazine vs. olanzapine ($p=0.002$). The change in nonfasting TG was also numerically different for perphenazine vs. quetiapine, although not statistically significant with the Bonferroni correction ($p=0.006$). A supportive unadjusted analysis was similar: $p=0.016$ overall, $p=0.002$ for perphenazine vs. olanzapine, and $p=0.012$ for perphenazine vs. quetiapine.

For phase 1, there was a distinct possibility that subjects could be randomized to the same medication taken at study baseline, and be unlikely to experience significant changes in outcome measures compared to those who switched medications. Among the 246 subjects, there were 37 nonswitchers (13 olanzapine, 14 risperidone, 8 quetiapine, 2 other), so the data were reexamined after excluding these subjects (Table 3). In this analysis, the between-drug treatment differences at 3 months became more pronounced ($p=0.001$, adjusted for baseline). The pairwise comparisons now revealed significant differences for olanzapine vs. perphenazine ($p<0.001$), olanzapine vs. risperidone ($p=0.002$), and quetiapine vs. perphenazine ($p=0.003$). Unadjusted results were similar (overall $p=0.001$). Due to the small number of nonswitchers, and the unbalanced composition (predominantly olanzapine and risperidone at baseline), comparisons of switchers vs. nonswitchers were not performed.

4. Discussion

Presented here are the first data to examine the impact of antipsychotic therapy specifically in subjects with

Table 3
3-month changes from baseline in nonfasting triglycerides (mg/dl) by treatment group excluding nonswitchers

		Observed		Adjusted[a]
	N	Median (interquartile range)	Mean±SD	Least squares mean±SE
Olanzapine	49	30 (−4 to 87)	64.3±137.3	61.5±24.0
Perphenazine	39	−22 (−81 to 24)	−3.7±243.8	−2.4±26.7
Quetiapine	51	27 (−32 to 96)	57.5±179.6	59.8±23.5
Risperidone	42	−10.5 (−76 to 31)	−12.2±79.8	−13.1±25.7
Ziprasidone	28	8 (−64 to 56)	−2.0±149.6	−1.8±31.5
Overall treatment difference		0.001[b]		0.001[c]

[a]Model adjusted for baseline triglycerides. Age, gender, race, ethnicity, baseline antipsychotic medication and smoking were allowed to enter the model but were not significant. The interaction between baseline triglycerides and treatment was also explored and was not significant.
[b]Unadjusted comparisons using the Kruskal–Wallis rank test revealed overall significant treatment differences ($p=0.001$). Individual pairwise comparisons revealed a significant difference for olanzapine vs. both perphenazine ($p<0.001$) and risperidone ($p=0.001$). The change in nonfasting TG was also numerically different for perphenazine vs. quetiapine, although not statistically significant with the Bonferroni correction ($p=0.008$).
[c]Rank ANCOVA adjusting for baseline triglycerides revealed overall significant treatment differences ($p=0.001$). Individual pairwise comparisons revealed a significant difference for olanzapine vs. both perphenazine ($p<0.001$) and risperidone ($p=0.002$), and quetiapine vs. perphenazine ($p=0.003$).

nonfasting serum TG values. The concept that postprandial hyperlipidemia best reflects the role of triglyceride-rich particles in atherogenesis is quite new, and has only recently been born out by large, long-term clinical trials (Eberly et al., 2003; Bansal et al., 2007; Nordestgaard et al., 2007). Most studies of antipsychotic lipid effects have focused on fasting TG values (Meyer and Koro, 2004), and rightfully so, due to the association between fasting TG and the metabolic syndrome (McEvoy et al., 2005) or directly measured insulin sensitivity (McLaughlin et al., 2003).

Olanzapine treatment has been associated with deleterious impact on lipid profiles (Meyer and Koro, 2004), but recent findings from a large first-episode trial (McEvoy et al., 2007) and CATIE phase 1 raised concerns that, at dosages used to treat schizophrenia, quetiapine is also associated with significant increases in random TG (Lieberman et al., 2005; Correll, 2007) and fasting TG (McEvoy et al., 2007; Meyer et al., 2008). With the stringent Bonferroni correction, the quetiapine vs. perphenazine comparison ($p=0.006$) did not meet the required 0.005 level of significance, but the numerical change in nonfasting TG seen in the adjusted analysis (+54.7 mg/dl), and the significant result when nonswitchers were excluded (quetiapine vs. perphenazine $p=0.003$), suggests that quetiapine has a lipid profile distinct from risperidone (−18.4 mg/dl) in a manner not appreciated several years ago, when the American Diabetes Association/American Psychiatric Association consensus paper on antipsychotic metabolic effects found these agents comparable on the basis of the available data (American Diabetes Association, 2004). That ziprasidone, risperidone and perphenazine treatment did not significantly increase nonfasting TG was expected, although it is surprising that ziprasidone in particular did not decrease nonfasting TG.

One limitation of this study is that the small sample size of each drug arm precludes stratification by time since last meal, age, gender or race. These effects can be managed with controlled prospective studies using fat tolerance testing or other means to examine lipid metabolism. The findings from the recent large clinical trials (Nordestgaard et al., 2007; Bansal et al., 2007) demonstrate a robust association between nonfasting TG and CV risk. Whether nonfasting TG will replace fasting TG measurements, or used in addition to fasting TG to provide added information on CV risk, and the optimal time since last meal to obtain this result, awaits consensus recommendations. Nonetheless, this study provides confirmation of the differential metabolic impact of atypical antipsychotics, and the need for clinicians to routinely monitor parameters associated with metabolic risk.

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The CATIE Trials were supported by National Institute of Mental health (NIMH) grant #N01MH90001. The NIMH and study principal investigators are responsible for the design and conduct of the trial, and the primary analyses. There is no industry involvement in these activities.

Contributors

Drs. McEvoy, Stroup and Lieberman are the CATIE principal investigators and were involved in the study design and creation of the protocol, and oversaw data collection, with input and support from co-investigator Drs. S. Davis and M. Swartz, and collaborators Drs. Hsiao and Goff. Dr. V. Davis performed the statistical analyses. Drs. Meyer, V. Davis, Goff, McEvoy, Nasrallah, S. Davis and Daumit were involved in the interpretation of findings and outline of the manuscript. Dr. Meyer wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

Jonathan M. Meyer, M.D.: Dr. Meyer reports having received research support from Bristol-Myers Squibb and Pfizer, Inc., and has received speaking or advising fees from Bristol-Myers Squibb, Janssen Pharmaceutica, Organon, Pfizer, Inc., Vanda, and Wyeth.

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