NIH Public Access
Author Manuscript

Biol Psychiatry. Author manuscript; available in PMC 2013 August 14.

Inflammatory Markers in Schizophrenia: Comparing Antipsychotic Effects in Phase 1 of the CATIE Schizophrenia Trial

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Abstract

Background—C-reactive protein (CRP), intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and E-selectin are systemic inflammatory markers (IM) that positively correlate with cardiovascular (CV) risk. Despite the known CV effects of atypical antipsychotics, there is limited prospective data on IM changes during treatment.

Methods—IM outcomes were compared between antipsychotic treatment groups in the CATIE Schizophrenia Trial phase 1 using subjects with laboratory assessments at baseline and 3 months (n=789).

Results—There were significant treatment differences in CRP, E-selectin and ICAM-1 at 3 months, with a differential impact of baseline values on the CRP and ICAM-1 results. In overall comparisons, quetiapine and olanzapine had the highest median levels for CRP, and olanzapine for E-selectin and ICAM-1. Olanzapine was significantly different after baseline adjustment than perphenazine (p=0.001) for E-selectin, and, in those with low baseline CRP (< 1 mg/L), olanzapine was significantly different than perphenazine (p<0.001), risperidone (p<0.001) and ziprasidone (p=0.002) for CRP. Perphenazine had the lowest 3-month ICAM-1 levels in subjects with baseline ICAM-1 above the median, but the differences were not statistically significant vs. olanzapine (p=0.010), quetiapine (p=0.010) and risperidone (p=0.006) after controlling for multiple comparisons. The 18-month repeated measures CRP analysis confirmed the significantly higher values for olanzapine in those with low baseline CRP.

Conclusions—This analysis provides further evidence for differential antipsychotic metabolic liabilities as measured by changes in systemic inflammation. CRP may emerge as a useful target for CV risk outcomes in schizophrenia patients.

Keywords

antipsychotic; schizophrenia; cardiovascular risk; inflammation; C-reactive protein; ICAM-1; VCAM-1; E-selectin

Introduction

Schizophrenia is associated with twofold greater cardiovascular (CV) mortality (1), with life expectancies 25–30 years less than expected (2). Modifiable risk factors and undertreatment of CV risks (e.g. dyslipidemia) contribute to this public health problem (3). Increasingly, consensus panels insist that treatment of schizophrenia patients addresses medical illness to minimize common causes of excess mortality, especially CV disease (4).

Cardiovascular risk prediction has been greatly enhanced by the development of algorithms derived from prospective trials, such as the Framingham Heart Study (FHS) (5). Therapy for modifiable risk factors is crucial to risk reduction and focuses on decreasing low-density lipoprotein (LDL) cholesterol; however, there are aspects of CV risk not captured by cholesterol markers. Particularly problematic is the fact that 20% of FHS subjects experienced major CV events without evident major risk factors (6), that 46% of CV events in the Women's Health Study occurred in those with serum LDL <130 mg/dL (7), and the lack of correlation between baseline LDL and myocardial infarction (MI) risk during statin treatment (8).

The search for means to refine CV risk assessment has centered on inflammatory markers (IM) such as intracellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), E-selectin, and C-reactive protein (CRP). Underlying this focus is evidence that atherosclerotic disease is a chronic inflammatory state involving components of vascular tissue (endothelial cells, smooth muscle cells) (9). Physiological stresses and inflammatory cell recruitment are the primary causes of vascular injury, and precede changes in most markers of vascular inflammation. The first step in monocyte recruitment is the presentation of E-selectin on endothelial cell surfaces in response to cytokines, oxidative stress from mechanical injury (e.g. turbulence, shear), or from phospholipids such as LDL and its oxidative byproducts (10). E-selectin binds to selective receptors on lymphocyte surfaces, slowing their movement along the endothelial surface (11). Subsequent adhesion of immune cells to vascular endothelium is mediated by increased expression of cellular adhesion molecules such as ICAM-1 and VCAM-1, the upregulation of which also occurs as a response to mechanical or oxidative stress (9,12). The expression of ICAM-1 appears more sensitive to LDL and oxidative LDL byproducts than mechanical injury, while VCAM-1 expression is increased by disturbed flow, other cytokines, and cholesterol (13,14). Since these three markers have limited expression in normal endothelium, increases in soluble forms measured in plasma serve as atherosclerosis markers (15).

Elevated IM levels are seen in various states associated with increased CV risk, including metabolic disturbances in glucose-insulin homeostasis (15–17). Serum ICAM-1 and VCAM-1 levels are elevated in patients with coronary heart disease (18), with higher ICAM-1 levels predictive of greater CV risk (19), and increased levels of both ICAM-1 and VCAM-1 associated with greater carotid atherosclerotic disease burden (20). Importantly, serum levels of soluble E-selectin and ICAM-1 positively correlate with central adiposity, and successful lifestyle modification that decreases body mass also lowers levels of both markers (21), and of C-reactive protein (CRP) (22).

CRP is a circulating acute phase reactant produced in hepatic cells in response to interleukin-6 and leptin, and also in arterial smooth muscle cells, with the highest expression in areas of atherosclerotic plaque (23). While CRP is an inflammatory marker, it accentuates atherosclerotic injury through multiple mechanisms (24) including binding to, and subsequent interference with leptin's activity at target receptors (25). The CV risk associated with CRP is continuous, but risk stratification typically divides patients into tertiles: <1 mg/L (lowest risk), 1–3 mg/L, and >3 mg/L. The highest tertile is associated with twofold greater risk (RR 1.9; 95% CI 1.5–2.3) for nonfatal MI and CV death compared to the lowest tertile after controlling for traditional factors. Markedly elevated values (>>10 mg/L) are typically ignored and repeated later, as they may reflect acute conditions (e.g. infection) and not baseline systemic inflammation levels (26). Persistent values >15 mg/L are rarely encountered.

CRP quantification of using high sensitivity assays (hS-CRP) has shown superior predictive power by itself than other IM (27), and the use of CRP provides added CV risk information after controlling for traditional CV risk factors (7). In global risk models, hS-CRP is second to systolic blood pressure and ahead of smoking as a CV risk predictor (28,29). The hS-CRP results from large statin trials also question whether the CV benefits from lipid reduction are driven by LDL changes or changes in CRP. Patients in a large randomized pravastatin vs. atorvastatin trial with lower post-treatment CRP experienced fewer CV events than those with higher CRP, regardless of LDL levels (30); moreover, agents which reduce LDL but increase CRP (e.g. hormone replacement therapy) are associated with increased CV risk. Convincing evidence for CRP as a mediator of CV risk has also been recently demonstrated by results of the JUPITER trial. This randomized, placebo-controlled study found that statin-induced CRP reduction was associated with significantly reduced CV event risk among individuals with low baseline LDL (<130 mg/dL) but elevated CRP (2 mg/L) (31).

Despite the cardiometabolic risk associated with atypical antipsychotics, there is limited published information on IM changes in response to antipsychotics with varying metabolic liabilities. Preliminary data from a 5-month randomized risperidone vs. olanzapine trial (n=42) found few patients with CRP >1 mg/L at any time point, and no between-drug differences in CRP at any time point by independent t-test, or repeated measures analysis of drug by time effects (32). However, a cross-sectional analysis of IM in 88 chronic schizophrenia patients found higher mean CRP levels: clozapine 5.2±5.0 mg/L (n=29), olanzapine 4.9±2.9 mg/L (n=29), typical antipsychotics 6.9±4.2 mg/L (n=30) (33). While varying assay methods and subject demographics create difficulties in comparing CRP levels between the two trials, CRP levels in the latter study correlated positively with central adiposity and negatively with serum high-density lipoprotein (HDL) cholesterol levels, thus demonstrating a consistent association between dysmetabolic states and increased systemic inflammation.

The large sample and randomized nature of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Schizophrenia Trial phase 1 offers an opportunity to examine antipsychotic effects on IM. The *a priori* hypothesis for this analysis is that there will be significant between-drug differences in 3-month IM changes. Secondary analyses will examine the association between IM changes and changes in individual metabolic parameters.

Methods and Materials

Recruitment and enrollment criteria for the CATIE Schizophrenia Trial have been previously described (34). Blood for IM was collected at screening and months 3, 6, 12, 18 and end of phase 1 (up to 18 months). Plasma was analyzed for soluble levels of CRP,

ICAM-1, VCAM-1 and E-selectin on the Bioplex Xmap system (Bio Rad) using Luminex bead-based assays. CRP levels were determined with an Invitrogen/Biosource (Carlsbad, CA) kit as a single-plex assay with initial plasma dilution of 1:500 per the manufacturer's instructions. Subject samples were compared to a serial 1:3 dilution standard curve of CRP (10.97–8,000 pg/mL). ICAM-1, VCAM-1 and E-selectin levels were determined with a Linco/Millipore (Chicago, IL) kit as a three-plex assay with initial plasma dilution of 1:100 per the manufacturer's instructions. Subject samples were compared to a serial 1:5 dilution standard curve of ICAM-1, VCAM-1 and E-selectin (80–250,000 pg/mL). For both assays, four-point logarithmic curve fits were performed on all standard curves of expected concentration versus median fluorescence intensity per bead set. The minimum detectable level of CRP was 2 pg/mL, of ICAM-1 9 pg/mL, of VCAM-1 16 pg/mL, and of E-selectin 79 pg/mL. Seventy-four distinct assays were performed over a 4-month period with the following median interassay coefficients of variation (6 test measurements per run): CRP-4.1%, ICAM-3.8%, VCAM-5.5% and E-selectin-3.7%. Reported final results were corrected for the initial sample dilution in either assay. Samples with results outside this range were assayed after further dilution, and results were extrapolated.

The primary analysis was conducted in subjects with non-extrapolated IM values at baseline and 3 months. The 3-month value was chosen as the time point for the analyses to maximize subject retention, while providing a physiologically meaningful period to assess antipsychotic impact. E-selectin, ICAM-1, VCAM-1 are sensitive to prandial effects, so only subjects with fasting laboratory measures (last meal >8 hours) at baseline and 3 months could be used (n=268). CRP has a half-life of 19 hours, with limited diurnal and prandial effects (36), so all non-extrapolated specimens were used in the primary analyses, regardless of fasting status (n=789) except for 2 samples with CRP 15 mg/L, due to their probable association with acute infectious or inflammatory processes. Only CRP and E-selectin had extrapolated data. A supportive analysis included the extrapolated data, but with values truncated to the lowest or highest nonextrapolated value. The exclusion of extrapolated values from the primary analysis removed 28 subjects (3.4% of 817) for CRP and 72 subjects (27% of 268) for E-selectin. As a result of the skewed distribution for CRP, E-selectin, and ICAM-1, the data for these IM underwent log transformation prior to analysis.

Analysis of variance (ANOVA) and Spearman correlations were used to examine the relationship between IM levels and metabolic syndrome (MS) criteria. Initial treatment group comparisons of IM at baseline and 3 months were made using (ANOVA) (4 df). Adjusted comparisons of IM at 3 months were performed using a 4 df Analysis of Covariance (ANCOVA), which adjusted for baseline IM values and allowed for consideration of age, gender, other baseline antipsychotic medications, and two CATIE design measures (study entrance after the ziprasidone treatment option was added, and having tardive dyskinesia at baseline) (35). For all treatment group comparisons, if the analysis yielded an overall treatment group difference (p<0.05), the 10 possible pairwise comparisons between treatments were performed with a Bonferroni correction, yielding an α of .05/10 = 0.005 as the threshold for significance. Due to the conservative nature of the Bonferroni correction, p-values between 0.005 and 0.01 are noted for the reader's discretion.

Potential interactions between baseline covariates and treatment group were explored and, if identified, treatment groups were compared within levels of the covariate using additional ANCOVA models. If an interaction was identified between baseline level of CRP and treatment group, treatment comparisons were made with additional models for those with low (<1 mg/L) and moderate/high (1 mg/L) baseline CRP values. This cutoff point was selected *a priori* because of its clinical significance to CV risk. Unlike CRP, for which well-established risk cutpoints exist based on population norms, these do not exist for the other markers. Therefore, when necessary, other cutpoints were based on the sample median.

Because IM data at 3 months was not available for all randomized patients, a sensitivity analysis of the primary treatment group comparison was performed, and ANCOVA models further adjusted for baseline covariates that were found to be predictive of patient dropout. These significant covariates (p<0.10) were identified with logistic regression models that predicted which patients had baseline and 3-month laboratory data, both overall and limited to fasting samples.

The ability to use all gathered data for CRP permitted a secondary mixed model analysis to be performed using non-extrapolated values collected at any post-baseline visit, combined into time intervals corresponding to 3, 6, 12 and 18 months as in prior CATIE metabolic analyses (37). Due to the paucity of fasting samples, mixed model analyses could not be performed for the other markers. CRP change from baseline was compared across treatment groups with a mixed model including terms for baseline CRP, time (treated as a classification variable), and terms representing baseline-by-time, treatment-by-time, and baseline-bytreatment interactions. A random subject effect and a spatial power covariance structure were used to adjust standard errors for correlation of observations within individual. No treatment-bytime interaction was found, and therefore treatment effects were averaged over visits for comparisons.

Results

Subjects with fasting values at baseline and 3-month assessments (fasting cohort) were similar on all demographic variables with subjects who had nonfasting laboratory values at one or both time points (Table 1). Those with baseline and 3-month CRP values were also similar to other CATIE phase 1 subjects, but were older (+1.4 years) than those without follow-up CRP ($T_{1,347}$=2.25, p=0.025). At 3 months, median CRP levels were significantly higher in patients who met MS criteria (Table 2), and higher CRP values positively correlated with greater number of MS criteria (r_S=0.27, p<0.001) (Figure 1). Among the other IM, only fasting E-selectin levels were correlated with greater number of MS criteria (r_S=0.15, p=0.027).

The olanzapine and quetiapine groups had the highest median CRP at the 3-month assessment, and the greatest numerical increase from baseline (Table 3). In the primary analysis, there was a significant overall treatment difference in 3-month CRP values after adjustment for the significant effect of baseline CRP and gender (p=0.013). Pairwise comparison revealed a statistically significant difference between olanzapine and risperidone (p=0.004). Given the differential impact of baseline CRP on the relationship between treatment and 3-month outcome ($F_{4,779}$=2.56, p=0.037), the same ANCOVA model was repeated separately for those subjects with low baseline CV risk (CRP <1 mg/L, n=500) and higher risk (CRP 1 mg/L, n=289). For subjects with lower baseline CRP, pairwise treatment comparison found significant differences for olanzapine vs. perphenazine (p<0.001), vs. risperidone (p<0.001), and vs. ziprasidone (p=0.002) (see Table 4). The overall test of treatment difference was not significant for patients with higher CRP values at baseline (p=0.511). The supportive analysis, including extrapolated values truncated at the lower or higher nonextrapolated value, did not find a significant overall treatment difference for CRP ($F_{4,810}$=1.98, p=0.095). However, for those subjects with low baseline risk, significant differences (with Bonferroni correction) for olanzapine vs. perphenazine (T_{231}=3.37, p=0.001) and vs. risperidone (T_{245}=3.39, p=0.001), but not ziprasidone (T_{195}=2.46, p=0.014), were confirmed.

There were also significant treatment differences for fasting E-selectin in the 3-month analysis. Olanzapine and quetiapine patients had the highest median E-selectin value at 3 months, and treatment pairwise comparison was statistically significant for olanzapine vs.

perphenazine (p=0.001) and noteworthy for olanzapine vs. risperidone (p=0.010), although not significant after Bonferroni correction (Table 3). The supportive analysis of E-selectin outcomes including truncated extrapolated values confirmed the significant between-group differences for olanzapine vs. perphenazine (T_{97}=2.91, p=0.004), and found noteworthy differences for olanzapine vs. risperidone (T_{116}=2.65, p=0.009), for quetiapine vs. perphenazine (T_{91}=2.80, p=0.006) and for quetiapine vs. risperidone (T_{109}=2.72, p=0.007). Due to a significant effect for TD status in this model ($F_{1,201}$=4.67, p=0.032), all comparisons involving perphenazine excluded patients with TD.

For ICAM-1, there were significant differences for perphenazine vs. quetiapine (p=0.002), and vs. risperidone (p=0.001) and a noteworthy difference, but not significant after Bonferroni correction, vs. olanzapine (p=0.006). As with CRP, there was a differential effect of baseline ICAM-1 value on treatment effects ($F_{4,258}$=2.87, p=0.024), with trends for treatment differences occurring only in those patients with baseline ICAM-1 above the median (273 ng/ml); however, these differences fell short of statistical significance due to Bonferroni correction: perphenazine vs. quetiapine (p=0.010), vs. olanzapine (p=0.010), and vs. risperidone (p=0.006) (Table 4). There were no significant between group differences for VCAM-1 in the 3-month analysis after adjusting for baseline levels (Table 3).

In a supportive logistic regression analysis, age, white race, and baseline total Positive and Negative Syndrome Scale (PANSS) score were found to be significant predictors of having baseline and 3-month laboratory values, while gender and baseline PANSS score were associated with having fasting laboratory values at baseline and 3 months. Inclusion of these covariates in the ANCOVA models revealed that none of the predictors were significantly associated with change in IM at 3 months (p>0.05 for all), yielding results consistent with the original findings.

Given the association between metabolic dysfunction and IM, we examined the Spearman correlation between 3-month changes in each of the four IM and changes from baseline in metabolic parameters: adiposity measures (waist circumference, body mass index {BMI}), systolic and diastolic BP, fasting lipids (total cholesterol, triglycerides and HDL) and fasting glucose. Only data from the fasting cohort was used for the 3 IM that are sensitive to prandial effects (E-selectin, ICAM-1, VCAM-1) and for correlations between CRP and metabolic parameters that require fasting samples (glucose, lipids). Among these correlations, there were small associations between 3-month change in E-selectin with waist circumference (r_S=0.20, p=0.007) and BMI (r_S=0.26, p<0.001). CRP itself does not require fasting samples, so all available data (fasting and random samples) were used in the correlation analysis for change in CRP and change in adiposity and blood pressure measures. The 3-month change in CRP was weakly correlated with both change in BMI (r_S=0.073, p=0.044) and change in HDL (r_S=−0.11, p=0.004). After adjusting for baseline IM value, the correlations with CRP and E-selectin were nonsignificant.

To account for prior antipsychotic medications, especially the large number taking olanzapine (24%) or risperidone (21%) at study baseline who were randomized to the same medication in phase 1 (8% and 5%, respectively), prior antipsychotic was considered as a potential covariate in the rank ANCOVA model for each IM at 3-months. However, in all cases, it was neither statistically significant nor did it alter the treatment effects.

The repeated measures analysis of change in CRP up to 18 months found an overall significant treatment effect over time ($F_{4,1086}$=2.86; p=0.023), with pairwise comparisons revealing a trend for higher values in olanzapine versus perphenazine ($T_{1,058}$=2.57; p=0.010). As with the 3-month analysis, an interaction between treatment and baseline CRP was identified ($F_{4,986}$=4.68; p=0.001), and treatment comparisons were made stratifying on

baseline CRP risk level. There were significant between group differences among 694 subjects with CRP values <1mg/L at baseline ($F_{4,671}=4.51$, p=0.001) (Figure 2, Table 5). Pairwise treatment comparisons found significant differences for olanzapine vs. perphenazine ($T_{657}=3.83$, p<0.001) and vs. ziprasidone ($T_{681}=3.03$, p=0.003). There was no treatment difference in the cohort with baseline CRP 1 mg/L ($F_{4,387}=0.25$; p=0.910, n=394).

Discussion

Presented here is the first analysis of data from a randomized study to examine the comparative impact of multiple antipsychotic therapies on changes in systemic inflammation. While certain metabolic effects from antipsychotic exposure are known, this is the first attempt to examine other pathophysiological elements that may underlie excess CV morbidity and mortality in chronic schizophrenia patients, and may be associated with antipsychotic treatment, particularly second-generation agents. The importance of CRP for CV risk prediction has been firmly established (31), but this is the first data set to confirm that atypical antipsychotic therapy may have differential effects on other IM, with olanzapine consistently emerging as a treatment with higher risk across several IM. Over the 3-month time frame, only the VCAM-1 results did not reveal any differences between antipsychotics.

As seen in larger samples (38), there is a correlation among CATIE subjects between increasing numbers of MS components and measures of systemic inflammation, specifically levels of E-selectin and CRP, so the expectation is that antipsychotics which adversely affect MS risk will result in concomitant changes in these IM. Olanzapine is associated with deleterious metabolic effects (39), while earlier CATIE analyses indicated that perphenazine, risperidone and ziprasidone are relatively more benign (37), so the findings seen here are consistent with the metabolic properties of these medications. Little historical metabolic outcomes data was available for perphenazine, but the findings from this and other CATIE studies confirm that perphenazine treatment is associated with reduction in markers of CV risk, including CRP and E-selectin (34,37). There were also noteworthy numerical differences when 3-month ICAM-1 levels for perphenazine were compared to those of other treatments among subjects with high baseline ICAM-1 levels, although these fell short of significance due to Bonferroni correction. It is also worth pointing out that the quetiapine cohort the numerically highest 3-month VCAM-1 level and the numerically highest 3-month CRP level (which it shared with olanzapine), and was the only treatment in which the median E-selectin level at 3 months was not lower than baseline.

Aside from the link between psychotropic-induced weight gain and central histamine H_1 antagonism (40), with additive effects of $5HT_{2C}$ antagonism (or $5HT_{2C}$ receptor polymorphisms) for medications with high H_1 affinity (41,42), the mechanisms underlying antipsychotic-induced dyslipidemia and hyperglycemia are unclear; nonetheless, these data indicate that alterations in IM are likely to accompany antipsychotic changes. The absence of strong correlations between change in any IM and change in metabolic variables may be due to a number of factors. Small sample sizes for the fasting analyses are one contributor. As shown in prior 3-month CATIE metabolic analyses (37), the mean changes in metabolic syndrome parameters across all drug arms was modest (waist circumference −0.4 – +0.7 inches; systolic BP −2.9 – −0.5 mmHg; diastolic BP −1.4 – +0.1 mmHg; HDL −2.3 – −0.1 mg/dL; fasting glucose −1.1 – +4.7 mg/dL; fasting triglycerides −32.1 – +21.5 mg/dL), so these small changes individually may not correlate with IM alterations; however, the fact that significant associations were found between certain IM and medication suggests that the combined effects of antipsychotic-induced changes on multiple metabolic parameters, or possibly direct drug effects on cytokine regulation, can accrue significant physiological

impact. Given the impact of CRP on metabolic functioning, the findings of these analyses also open the door to the possibility that certain antipsychotic metabolic effects are mediated through inflammatory cytokines such as CRP (24). Further research might clarify why significant antipsychotic effects on CRP were only seen in those with low baseline CRP, while greater effects on ICAM-1 were only found for those with high baseline ICAM-1.

These data clearly indicate that, among subjects with lower CRP levels, changes in antipsychotic therapy can improve or worsen CV risk as early as 3 months after treatment initiation through changes in CRP; moreover, there may be concomitant changes in other IM, the clinical significance of which is still being elucidated. Clinicians are thus provided with another reason to be judicious in the use of antipsychotics, and to be diligent in metabolic monitoring. For patients with metabolic abnormalities who cannot switch medications, the limited studies on statin treatment in dyslipidemic schizophrenia patients show expected improvements in LDL cholesterol (43,44). In general population studies for patients with type 2 DM or coronary heart disease, statin therapy has been proven to reduce LDL cholesterol and IM (15,30). Unfortunately, the published literature is silent on whether statin treatment achieves comparable IM reduction in antipsychotic treated patients. Given the association between insulin resistance, central adiposity and systemic inflammation (45–47), medications that improve insulin sensitivity have been proposed as one way to address elevated IM in the context of antipsychotic mediated metabolic dysfunction; however, two placebo-controlled studies of adjunctive metformin during olanzapine treatment failed to establish any significant impact on CRP (48,49), although the metabolic benefits noted in some trials (50) might certainly influence other IM.

One limitation of this analysis derives from the fact that, at study baseline, nearly half of CATIE subjects were taking either olanzapine or risperidone, and 13% were randomized to the same medication in phase 1, diminishing the extent of any change from baseline noted in those medication arms. In addition, analyses of fasting IM, and in particular E-selectin, were hindered by small sample sizes, as were stratified analyses used to explore treatment effects in the presence of interaction with baseline IM values. In general, there was also reduced power to find differences between ziprasidone and the other treatments due to its addition to CATIE after 40% of subjects had been enrolled. While certain baseline variables were predictive of drop-out, these did not have a significant influence on IM outcomes; however, unequal subject attrition for assigned treatments may have injected some bias, as more data was available for olanzapine-treated subjects than for other medication assignments. The assay method employed for these analyses is used for research purposes only, so the magnitude of any treatment effect found here may differ from that using other forms of laboratory analysis.

Nonetheless, differences exist between various antipsychotics on measures of systemic inflammation, and emerge after relatively brief exposure. When antipsychotic switching is not an option, the available evidence points towards lifestyle modification and standard pharmacotherapy as the best means to address elevated IM in the context of antipsychotic therapy. For many patients with schizophrenia, the greatest impediments to effective medical management of antipsychotic treatment are the failure to perform routine laboratory monitoring (51) and undertreatment of common risk conditions (3). The present data not only reinforce the need for aggressive metabolic monitoring during antipsychotic treatment, but also foreshadow the importance of inflammation in our understanding of CV risk changes during antipsychotic therapy (52).

Acknowledgments

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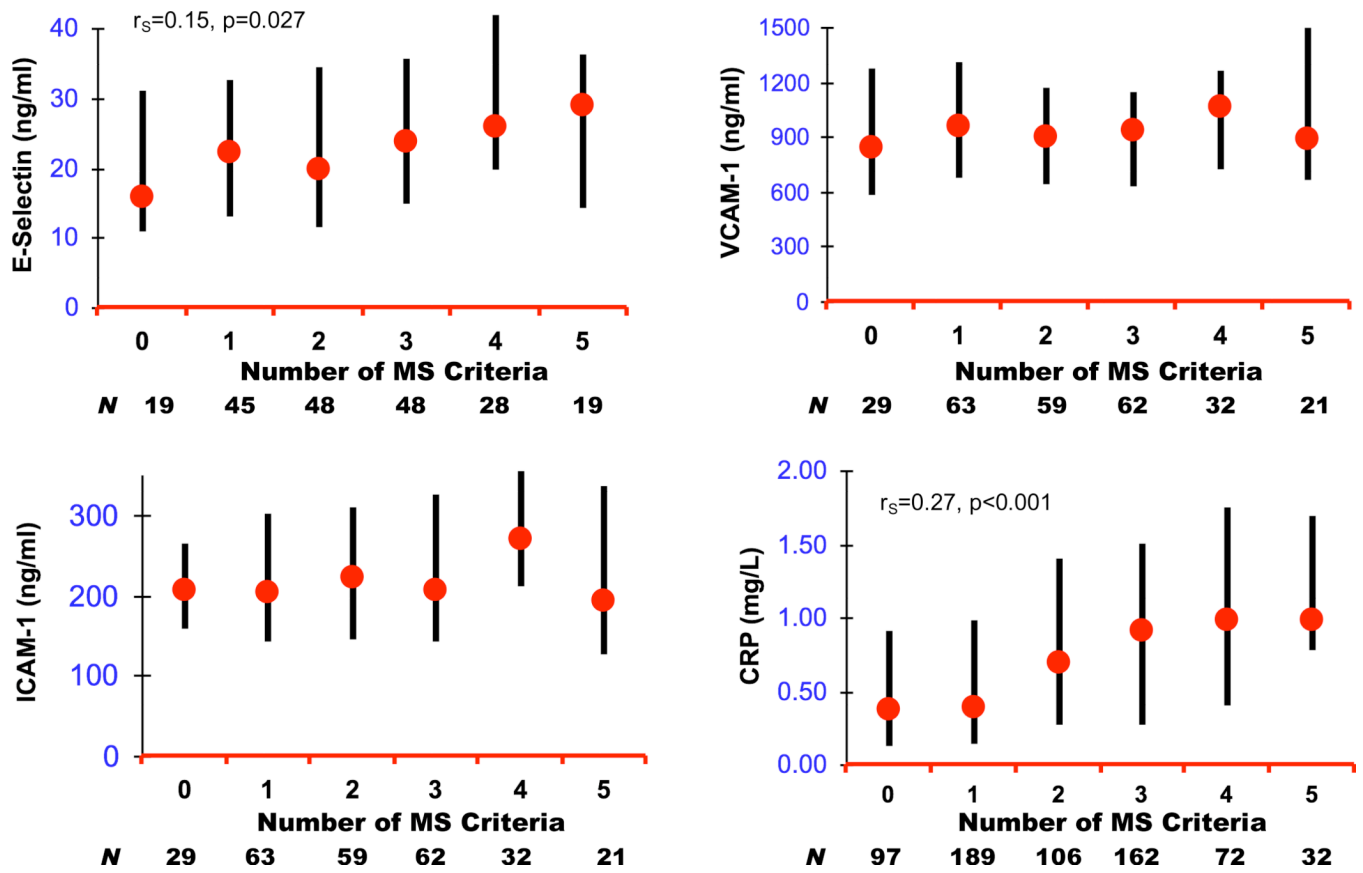
Figure 1.
Distribution of Median and Interquartile Range for Inflammatory Marker Values According to Number of Metabolic Syndrome (MS) Criteria at 3 months
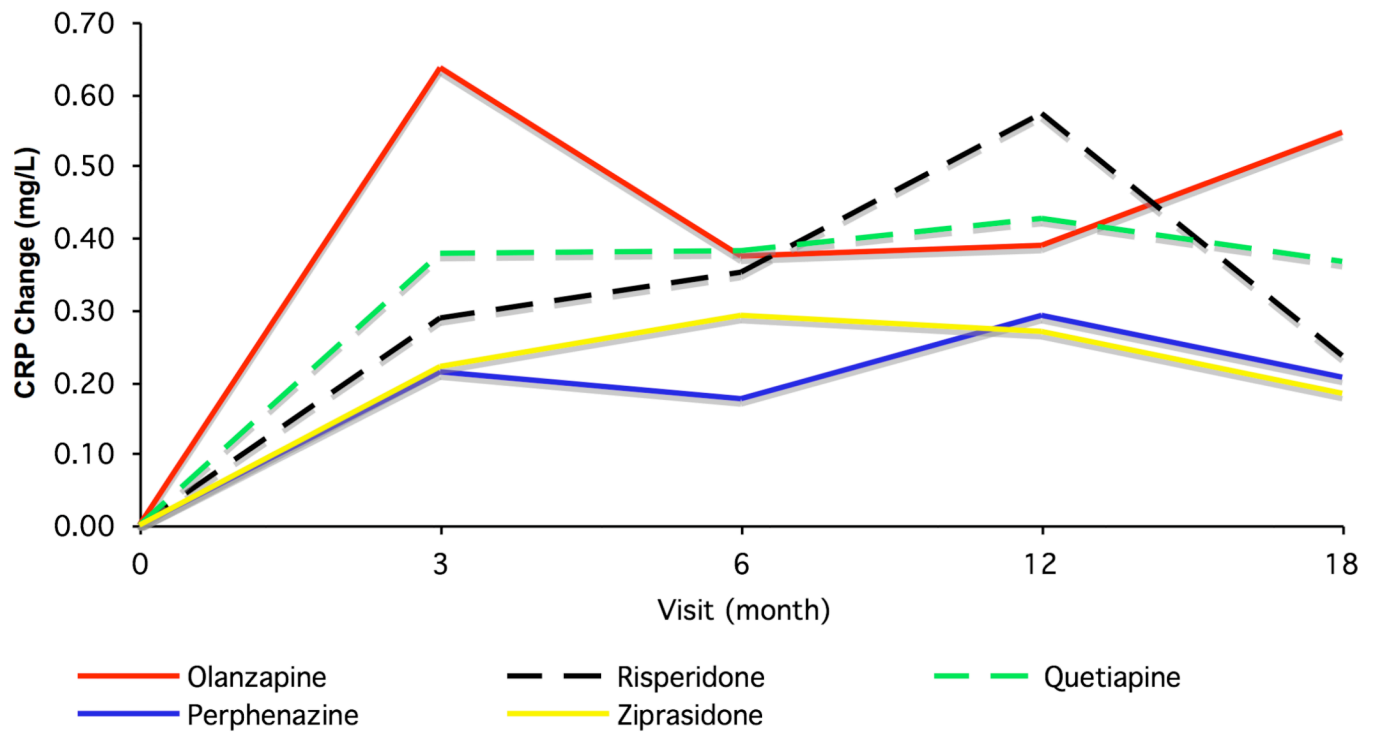
* Mixed model estimated least squares means.

Overall treatment difference: p=0.001.
Pairwise treatment comparisons significant for olanzapine vs.
perphenazine (p<0.001) and olanzapine vs. ziprasidone (p=0.003).

Figure 2.
Repeated Measures Model of C-Reactive Protein (CRP) Changes After Adjustment for
Baseline CRP (Subjects With Baseline CRP < 1 mg/L)*

Table 1

Demographics of CATIE Subjects with Baseline and 3-month Fasting ICAM-1, VCAM-1 and E-selectin Values (Fasting Cohort), and Baseline and 3-Month C-Reactive Protein Values (CRP) [*]

Parameter	Fasting Cohort	CRP
Age	40.6 ± 11.1 (N=268)	41.2 ± 10.8 (N=789)
Gender (% Male)	78.4% (N=268)	74.5% (N=789)
Race (% White)	64.6% (N=268)	62.8% (N=788)
Ethnicity (% Hispanic)	11.6% (N=268)	11.3% (N=789)
Years of Education	12.3 ± 2.0 (N=266)	12.1 ± 2.3 (N=785)
Years Since First Antipsychotic Treatment	14.2 ± 10.7 (N=259)	14.5 ± 10.9 (N=759)
Smoking	58.9% (N=260)	59.2% (N=770)
Hypertension	34.7% (N=268)	33.2% (N=789)
Diabetes	11.6% (N=268)	13.2% (N=789)
Body Mass Index (kg/m^2)	29.5 ± 6.9 (N=265)	30.0 ± 6.9 (N=780)

Note: Table entries are Mean ± SD or %.

[*] Excluding extrapolated data

Table 2

Median Marker Levels (Interquartile Range) By Presence or Absence of Metabolic Syndrome Criteria[†] and Smoking Status at 3 Months[1]

	CRP (mg/L)	E-Selectin (ng/mL)	ICAM-1 (ng/mL)	VCAM-1 (ng/mL)
Central Obesity				
Present	**0.95** (0.40–1.66) n=382	**23.7** (15.6–36.5) n=99	**246.5** (144.7–337.7) N=118	**925.0** (668.6–1216.8) N=118
Absent	**0.42** (0.16–1.03) n=390	**21.9** (12.6–33.0) n=105	**209.9** (152.2–294.2) N=145	**933.0** (676.1–1289.9) N=145
Test Statistic; p-value[††]	**$F_{1,770}$ =56.44; *p*<0.001**	$F_{1,202}$ =2.90; *p*=0.090	$F_{1,261}$ =2.01; *p*=0.158	$F_{1,261}$ =0.062; *p*=0.803
Elevated Triglycerides				
Present	**0.79** (0.33–1.47) N=188	**24.1** (14.9–35.5) N=111	**237.4** (155.4–335.6) N=128	**971.9** (678.2–1275.5) N=128
Absent	**0.46** (0.18–1.23) n=360	**21.3** (12.5–34.7) N=98	**207.9** (134.2–305.2) N=140	**904.2** (639.1–1268.7) N=140
Test Statistic; p-value[††]	**$F_{1,546}$ =8.78; *p*=0.003**	$F_{1,207}$ =1.01; *p*=0.316	**$F_{1,266}$ =4.23; *p*=0.041**	$F_{1,266}$ =0.77; *p*=0.382
Low HDL				
Present	**0.74** (0.28–1.53) n=450	**21.8** (14.0–35.9) N=116	**235.5** (147.2–331.0) N=147	**914.5** (639.7–1199.9) N=147
Absent	**0.48** (0.17–1.20) n=330	**23.7** (13.0–32.9) N=93	**212.1** (148.2–311.7) N=121	**960.4** (693.4–1302.4) N=121
Test Statistic; p-value[††]	**$F_{1,778}$ =13.89; *p*<0.001**	$F_{1,207}$ =0.00; *p*=0.972	$F_{1,266}$ =6.50; *p*=0.421	$F_{1,266}$ =0.57; *p*=0.450
Elevated Glucose				
Present	**0.79** (0.29–1.47) n=164	**26.8** (14.3–41.1) N=67	**208.3** (148.2–332.8) N=83	**965.2** (705.1–1341.4) N=83
Absent	**0.59** (0.20–1.31) n=503	**21.6** (13.0–32.6) N=141	**224.7** (145.7–316.9) N=184	**909.3** (636.3–1227.3) N=184
Test Statistic; p-value[††]	**$F_{1,665}$ =4.48; *p*=0.035**	**$F_{1,206}$ =3.95; *p*=0.048**	$F_{1,265}$ =0.61; *p*=0.435	$F_{1,265}$ =1.70; *p*=0.193
Elevated BP				
Present	**0.86** (0.32–1.55) n=382	**25.2** (14.3–36.5) N=103	**231.7** (148.0–327.2) N=128	**958.7** (690.0–1275.5) N=128
Absent	**0.50** (0.19–1.18) n=400	**21.0** (12.1–33.8) N=103	**211.3** (145.6–302.6) N=137	**899.9** (658.1–1275.5) N=137
Test Statistic; p-value[††]	**$F_{1,780}$ =17.98; *p*<0.001**	$F_{1,204}$ =2.58; *p*=0.110	$F_{1,263}$ =0.54; *p*=0.463	$F_{1,263}$ =1.36; *p*=0.244
Metabolic Syndrome [*]				
Present	**0.93** (0.40–1.64) N=266	**25.0** (15.6–37.9) N=95	**237.3** (147.9–337.7) N=115	**969.0** (672.6–1216.8) N=115
Absent	**0.42** (0.16–1.14) n=392	**20.6** (12.2–32.9) N=112	**211.3** (144.4–298.7) N=151	**905.9** (664.4–1293.4) N=151
Test Statistic; p-value[††]	**$F_{1,656}$ =40.13; *p*<0.001**	**$F_{1,205}$ =5.09; *p*=0.025**	$F_{1,264}$ =1.76; *p*=0.186	$F_{1,264}$ =0.28; *p*=0.595
Current Smoker [**]				
Yes	**0.69** (0.25–1.41) n=470	**21.9** (13.1–32.9) N=119	**246.4** (161.2–327.8) N=15	**928.3** (668.6V1220.3) N=157

	CRP (mg/L)	E-Selectin (ng/mL)	ICAM-1 (ng/mL)	VCAM-1 (ng/mL)
No	**0.61** (0.21–1.32) n=309	**24.1** (13.7–36.5) N=89	**199.5** (138.4–311.7) N=109	**937.5** (693.4–1299.1) N=109
Test Statistic; p-value [††]	$F_{1,777} = 1.24$; $p=0.266$	$F_{1,206} = 0.86$; $p=0.355$	$F_{1,264} = 2.50$; $p=0.115$	$F_{1,264} = 2.53$; $p=0.113$

[1]
Excluding extrapolated data

[†]
Metabolic Syndrome Criteria

Central Obesity: Male and waist circumference > 40 inches, or female and waist circumference > 35 inches

Elevated Triglycerides: Fasting triglycerides   150 mg/dL

Low HDL: Male and HDL <40 mg/dL, or female and HDL <50 mg/dL

Elevated Glucose: Fasting glucose   100 mg/dL or random glucose value   200 mg/dl, or on insulin or hypoglycemic medication

Elevated BP: 130/85 mm Hg or on antihypertensive medication

[††]
P-values based on ANOVA on the log transformation, except for VCAM-1, which was normally distributed and not transformed.

[*]
Metabolic syndrome diagnosis based on all subjects with sufficient data to be classified (i.e. met   3 criteria).

[**]
Patients were considered current smokers if they smoked five or more cigarettes daily over the previous week.

Table 3

Median Baseline and 3-Month Marker Levels (Interquartile Range) By Treatment[1]

	CRP (mg/L)		E-Selectin (ng/mL)		ICAM-1 (ng/mL)		VCAM-1 (ng/mL)	
	Baseline	**3 months**	**Baseline**	**3 months**	**Baseline**	**3 months**	**Baseline**	**3 months**
Olanzapine	(n=202)	(n=202)	(n=54)	(n=54)	(n=70)	(n=70)	(n=70)	(n=70)
Level	**0.63** (0.17–1.36)	**0.77** (0.26–1.57)	**29.2** (18.5–46.7)	**28.4** (19.3–40.5)	**360** (231–479)	**270** (173 – 347)	**1330** (915–1668)	**928** (713–1308)
Change		0.09 (−0.44–0.50)		−1.4 (−23.8 – 10.8)		−78 (−201 – 49)		−240 (−598 – 51)
Perphenazine	(n=143)	(n=143)	(n=36)	(n=36)	(n=51)	(n=51)	(n=51)	(n=51)
Level	**0.54** (0.19–1.34)	**0.51** (0.22–1.30)	**36.3** (21.7–60.3)	**15.9** (11.7–34.0)	**317** (218–424)	**211** (134 – 262)	**1336** (850–1866)	**964** (624–1278)
Change		−0.06 (−0.31–0.30)		−11.7 (−28.3 – 1.2)		−119 (−211 – −23)		−359 (−904 – 90)
Quetiapine	(n=180)	(n=180)	(n=40)	(n=40)	(n=65)	(n=65)	(n=65)	(n=65)
Level	**0.71** (0.30–1.41)	**0.77** (0.37–1.38)	**25.7** (16.4–36.2)	**26.4** (15.8–41.3)	**245** (176–357)	**215** (161–328)	**1125** (842–1553)	**1089** (755–1418)
Change		0.04 (−0.39–0.48)		+0.9 (−9.2 – 11.1)		−32 (−112 – 70)		−55 (−414 – 204)
Risperidone	(n=178)	(n=178)	(n=32)	(n=32)	(n=51)	(n=51)	(n=51)	(n=51)
Level	**0.53** (0.17–1.51)	**0.53** (0.15–1.40)	**29.8** (23.2–42.8)	**19.9** (13.1–31.5)	**223** (152–307)	**201** (150–326)	**685** (453–921)	**878** (604–1074)
Change		−0.03 (−0.46–0.30)		−9.7 (−19.4 – 1.7)		+1 (−70 – 102)		+133 (−35 – 480)
Ziprasidone	(n=86)	(n=86)	(n=17)	(n=17)	(n=31)	(n=31)	(n=31)	(n=31)
Level	**0.64** (0.23–1.23)	**0.60** (0.22–1.04)	**25.7** (15.7–40.1)	**21.0** (13.3–25.5)	**188** (113–280)	**194** (118–263)	**533** (370–750)	**705** (576–1008)
Change		−0.06 (−0.36–0.26)		−4.6 (−20.9 – 2.6)		−2 (−85 – 82)		+214 (−132 – 470)
Overall Difference:								
Unadjusted[†]								
Test Statistic; p-value	$F_{4,784}=0.54$; p=0.706	$F_{4,784}=2.83$; p=0.024	$F_{4,174}=1.42$; p=0.231	$F_{4,174}=2.45$; p=0.048	$F_{4,263}=7.28$; p<0.001	$F_{4,263}=2.30$; p=0.059	$F_{4,263}=25.85$; p<0.001	$F_{4,263}=3.82$; p=0.005
Adjusted[†]								
Test Statistic; p-value		$F_{4,782}=3.20$; p=**0.013**[*]		$F_{4,173}=3.96$; p=**0.004**[**]		$F_{3,231}=4.65$; p=**0.004**[***]		$F_{4,262}=1.77$; p=0.136

[1] Descriptive statistics excluding extrapolated CRP and E-selectin data

[†] An ANCOVA on the log transformation was used to compare treatments, except for VCAM-1, which was normally distributed and not transformed. The adjusted models included the log transformation of the baseline IM values (except for VCAM-1, which was not transformed), as well as gender in the CRP model, and a ziprasidone cohort effect in the ICAM-1 model. These were the only significant covariates of those considered for inclusion.

[*] Between group comparison at 3 months was statistically significant for olanzapine vs. risperidone (T_{379}=2.89, p=0.004).

[**] Between group comparison at 3 months was statistically significant for olanzapine vs. perphenazine (T_{89}=3.28, p=0.001) and numerically different (but not statistically significant with Bonferroni correction) for olanzapine vs. risperidone (T_{85}=2.59, p=0.010).

[***] Between group comparison at 3 months statistically significant for perphenazine vs. quetiapine (T_{115}=3.22, p=0.002), risperidone (T_{101}=3.26, p=0.001), and numerically different (but not statistically significant with Bonferroni correction) for perphenazine vs. olanzapine (T_{120}=2.76, p=0.006). A significant ziprasidone cohort effect was found for this model ($F_{1,231}$=7.98, p=0.005). No significant differences were found between ziprasidone and the other treatments in the ziprasidone cohort (N=143).

Table 4

Median 3-Month Marker Levels and Change from Baseline (Interquartile Range) By Treatment Stratified on Baseline Marker Level

	CRP (mg/L)		ICAM-1 (ng/mL)	
	Baseline <1 mg/L	**Baseline 1 mg/L**	**Baseline < 273 ng/ml**	**Baseline 273 ng/ml**
Olanzapine	(n=127)	(n=75)	(n=24)	(n=46)
Level	0.61 (0.19–1.23)	1.27 (0.50–1.89)	221 (120–298)	305 (205–440)
Change	0.27 (−0.01–0.85)	−0.72 (−1.29–0.13)	44 (−40–102)	−174 (−260- −52)
Perphenazine	(n=95)	(n=48)	(n=18)	(n=33)
Level	0.31 (0.15–0.77)	1.31 (0.78–2.10)	194 (132–250)	241 (148–297)
Change	0.04 (−0.15–0.32)	−0.39 (−1.08–0.18)	6 (−48–41)	−190 (−339- −118)
Quetiapine	(n=111)	(n=69)	(n=34)	(n=31)
Level	0.51 (0.23–0.99)	1.23 (0.78–1.88)	197 (152–249)	299 (188–374)
Change	0.13 (−0.07–0.53)	−0.44 (−1.27–0.29)	35 (−41–85)	−118 (−188- −32)
Risperidone	(n=109)	(n=69)	(n=36)	(n=15)
Level	0.26 (0.12–0.78)	1.14 (0.54–1.94)	189 (146–279)	358 (199–550)
Change	0.04 (−0.09–0.46)	−0.73 (−1.60–0.04)	7 (−36–100)	−12 (−187–179)
Ziprasidone	(n=58)	(n=28)	(n=23)	(n=8)
Level	0.43 (0.14–0.87)	0.91 (0.41–2.19)	146 (91–237)	273 (179–448)
Change	0.11 (−0.16–0.38)	−0.56 (−1.39- −0.09)	15 (−69–82)	−113 (−195–40)
Overall Treatment Difference[†] *Test Statistic; p-value*	**$F_{4,493}=5.57$; p<0.001** [*]	$F_{4,282}=0.82$; p=0.511	$F_{4,129}=1.26$; p=0.287	**$F_{3,119}=3.82$; p=0.012** [**]

[†]An ANCOVA on the log transformation was used to compare treatments. The adjusted models included the log transformation of the baseline IM values, as well as gender in the CRP model and a ziprasidone cohort effect in the ICAM-1 model where baseline 273 ng/ml. These were the only significant covariates of those considered for inclusion. E-Selectin and VCAM-1 are not included in table due to absence of significant treatment by baseline interaction.

[*] Between group comparisons at 3 months were statistically significant for olanzapine vs. perphenazine ($T_{221}=4.02$, p<0.001), risperidone ($T_{235}=3.57$, p<0.001), and ziprasidone ($T_{184}=3.17$, p=0.002).

[**] Between group comparison at 3 months were numerically different (but not statistically significant with Bonferroni correction) for perphenazine vs. olanzapine ($T_{78}=2.61$, p=0.010), quetiapine ($T_{63}=2.60$, p=0.010), and risperidone ($T_{47}=2.80$, p=0.006). A significant ziprasidone cohort effect was found for this model ($F_{1,119}=6.04$, p=0.015). No significant differences were found between ziprasidone and the other treatments in the ziprasidone cohort (N=63).

Table 5

Sample Sizes by Visit and Treatment for Subjects with Baseline CRP < 1 mg/L

Visit	3	6	12	18
Olanzapine	154	114	83	71
Perphenazine	124	78	46	34
Quetiapine	143	89	60	40
Risperidone	144	97	71	53
Ziprasidone	81	46	35	20
TOTAL	646	424	295	218