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Changes in inflammation with treatment for bipolar II depression: Pilot trial data on differential effects of psychotherapy and medication

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ABSTRACT

Objectives: Limited prospective data, mostly focused on bipolar I disorder, suggests that pro-inflammatory cytokines are elevated in abnormal mood states. We evaluated whether treatment normalizes peripheral markers of inflammation in bipolar II disorder.

Methods: Using data from a randomized clinical trial of Interpersonal and Social Rhythm Therapy (IPSRT) + quetiapine vs. IPSRT + placebo for bipolar II depression, we examined whether these treatments for bipolar II depression impact inflammatory cytokines and whether observed changes in cytokines are associated with changes in depressive symptomatology as measured by the Hamilton Rating Scale for Depression (HRSD-17).

Results: Cytokine values were available for 33 participants who completed baseline and 20-week follow-up visits. After excluding those with CRP values > = 10 mg/L, there were 27 patients available for analysis (IPSRT + quetiapine N = 10, IPSRT + placebo N = 17). Baseline measure of inflammation did not appear to moderate treatment response, nor was change in HRSD-17 score correlated with changes in cytokines. Those who received IPSRT + quetiapine had significantly greater increases in IL-6 ($p = 0.02$) and TNF-α ($p = 0.04$), even after adjusting for changes in body mass index, than the IPSRT alone group. Descriptively, the quetiapine group showed increases in pro-inflammatory and decreases in anti-inflammatory cytokines and the psychotherapy group showed reduced pro-inflammatory cytokines.

Conclusions: Despite both groups showing depression improvement, this small study suggests a more pro-inflammatory cytokine profile over time with quetiapine plus psychotherapy compared to psychotherapy alone. Elevated risk of cardiovascular morbidity and mortality among those with bipolar II disorder underscores the importance of delivering treatments that do not exacerbate these risk factors.

1. Introduction

Once conceptualized as a disorder simply involving fluctuating mood states, it is increasingly apparent that bipolar disorder is a multi-system illness associated with increased risk for diabetes mellitus, metabolic syndrome, sleep disturbances, and cardiovascular disorders (McElroy & Keck, 2014). This high burden of co-occurring medical illnesses (Kilbourne et al., 2004) contributes to increased risk for premature mortality (Angst, Stassen, Clayton, & Angst, 2002). Abnormal levels of immune cells and inflammation have been implicated as a shared pathway to illness across these processes (Leboyer et al., 2012; Snijders et al., 2016), suggesting that underlying pro-inflammatory cascades may explain, at least in part, co-occurring risk for mood, metabolic, and cardiovascular dysregulation in individuals with bipolar disorders.

Serum levels of a variety of pro-inflammatory (and the anti-inflammatory IL-10) cytokines were demonstrated to be elevated in bipolar disorder, relative to healthy controls in a meta-analysis of 30 studies including 1351 participants with bipolar disorder and 1248 healthy controls (Modabbernia, Taslimi, Brietzke, & Ashrafi, 2013). The largest effect sizes were observed for soluble TNF receptor-1 (0.62), TNF-α (0.60), IL-4 (0.46), and the soluble IL-2 receptor (0.41). The few studies that contrasted medicated vs. unmedicated participants with bipolar disorder showed no differences. Another more restrictive meta-analysis of 18 studies comparing those with bipolar disorder to healthy controls found similar results from overlapping studies with the largest standardized mean differences for IL-8 (2 studies, 3.85), IL-4 (3 studies, 1.55), TNF-α (9 studies, 1.52), sIL-2R (3 studies, 0.74), sTNFR1 (7 studies, 0.62), and sIL-6R (4 studies, 0.61) (Munkholm, Brauner, Kessing, & Vinberg, 2013). Neither meta-analysis separated bipolar I from bipolar II disorder and the studies included either focused exclusively on bipolar I disorder (Barbosa et al.,

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2011, 2012; Brietzke, Kauer-Sant'Anna, Teixeira, & Kapczinski, 2009; Brietzke & Teixeira, 2010; Cetin et al., 2012; do Prado et al., 2013; Kapczinski et al., 2011; Kim, Jung, Myint, Kim, & Park, 2007, 2004; Liu et al., 2004; Ortiz-Dominguez et al., 2007; Tsai et al., 1999, 2012; Tsai, Yang, Kuo, Chen, & Leu, 2001), mixed samples with both bipolar I and bipolar II disorder (Breunis et al., 2003; Drexhage et al., 2011; Guloksuz et al., 2010; Hope et al., 2011; Knijff et al., 2006; Rapaport, 1994), included diagnoses other than bipolar disorder (Hung et al., 2007; Kim et al., 2002; Maes, Bosmans, Calabrese, Smith, & Meltzer, 1995; Su et al., 2011), or did not specify bipolar subtype (O'Brien, Scully, Scott, & Dinan, 2006; Rapaport, Guylai, & Whybrow, 1999). Separate consideration of bipolar I and bipolar II disorder is important given a growing body of evidence showing that these subtypes have different genetic and neural determinants as well as distinct courses and outcomes (Altshuler et al., 2006; Charney et al., 2017; Judd et al., 2003; Li et al., 2012).

The more general measure of inflammation, the acute phase reactant, C-reactive protein (CRP) was also not included in the aforementioned meta-analyses. The high sensitivity CRP assay (hsCRP) has been found to be higher in mania compared to euthymia, depression, and healthy controls (Cunha et al., 2008). Another study found elevations in hsCRP in both those with major depressive disorder and bipolar disorder compared to healthy controls (Huang & Lin, 2007). There has been limited prospective study to discern potential state related differences in bipolar disorder, and what is available, consistent with the aforementioned cross-sectional data, suggests that cytokines may be elevated with abnormal mood states, especially mania (Fiedorowicz, 2014; Fiedorowicz et al., 2015; Jacoby, Munkholm, Vinberg, Pedersen, & Kessing, 2016). CRP levels have not been examined separately for those with bipolar II disorder.

If abnormal mood states are related to elevations in cytokines in bipolar disorder, then treatment of these mood states has the potential to normalize these values. In major depressive disorder, a meta-analysis found that IL-6 levels decrease following treatment of major depression (Goldsmith, Rapaport, & Miller, 2016). Cognitive Behavioral Therapy (CBT) was also associated with reductions in IL-6 and TNF-α in one trial of major depressive disorder (N = 97) (Moreira et al., 2015), but only when combined with exercise in another three-arm RCT (N = 98) comparing CBT with exercise to CBT alone to wait list (Euteneuer et al., 2017). Psychological intervention was also associated with reductions in some non-specific markers of inflammation (WBC, neutrophil count, T helper/suppressor ratio) in those with depression and breast cancer (Thornton, Andersen, Schuler, & Carson, 2009). CBT did not reduce cytokines in a large (N = 214) trial of persons with diabetes and subclinical depression, using a diabetes-specific CBT intervention (Hermanns et al., 2015). However, the mean hsCRP was only 0.2 and the lack of any elevation in this general marker of inflammation in this sample with only subclinical depression may have precluded detection of any treatment benefit. An uncontrolled study of mindfulness-based stress reduction (N = 50) secondarily found that session attendance was associated with decreases in IL-6 (Gallegos, Lytle, Moynihan, & Talbot, 2015).

Medications potentially have effects beyond change in mood state. A small (N = 30) RCT of individuals with intermittent explosive disorder showed no change in a panel of 7 cytokines following treatment with fluoxetine or divalproex (Coccaro, Lee, Breen, & Irwin, 2015), suggesting these medications do not have at least large effects. Quetiapine, the medication utilized in this randomized clinical trial, has had limited study of its influence on inflammation in humans. Quetiapine blood levels were marginally associated with CRP in a treated sample (N = 32) (Hefner, Shams, Unterecker, Falter, & Hiemke, 2016). A study of N = 41 participants with bipolar I mania found TNF-α, TGF-β, IL-23, and IL-17 all significantly decreased over 8 weeks in those who responded to treatment with lithium and quetiapine, compared to those who did not respond (Li et al., 2015). In the CATIE trial, exposure to quetiapine was associated with only mild increases in CRP (0.04), which was correlated with changes in BMI and HDL, although mediation was not directly tested (Meyer et al., 2009). Human studies thus hint that any effects of quetiapine may be indirect – i.e., improvements in inflammation with resolution of mania and mild worsening in inflammation secondary to weight gain.

Although there are a paucity of well-established moderators of treatment response in psychiatry, hsCRP shows some initial promise in selecting treatment for major depressive disorder. Uher et al. found that those with lower CRP (< 1 mg/L) were more likely to respond to escitalopram over nortriptyline (NTP) and those with higher CRP were more likely to respond to NTP over escitalopram (Uher et al., 2014). Jha et al. similarly found, through testing of a treatment by biomarker interaction (using the same CRP < 1 mg/L threshold), that those with higher CRP were less likely to respond to an SSRI relative to an SSRI + bupropion combination (Jha et al., 2017).

Experimental study of the impact of treatment on inflammation in bipolar disorder is limited, and absent in those with bipolar II disorder. Using data from a randomized clinical trial of Interpersonal and Social Rhythm Therapy (IPSRT) + placebo vs. IPSRT + quetiapine for bipolar II depression, we sought to assess: 1) if baseline inflammation moderated treatment response, 2) whether changes in cytokines is associated with improvements in depressive symptoms, and 3) whether pharmacologic vs. non-pharmacologic treatments for bipolar II depression differentially impact inflammatory cytokines.

2. Methods

The current analysis presents the results of an ancillary study to a randomized clinical trial, which demonstrated significant improvement in both groups but greater symptomatic improvement and more side-effects with IPSRT + quetiapine compared to IPSRT + placebo (Swartz et al., 2018).

2.1. Participants

Individuals aged 18–65 with a Structured Clinical Interview for DSM-IV (American Psychiatric Association, 2000) confirmed diagnosis of bipolar II were eligible for participation while in a major depressive episode and with a 17-item Hamilton Depression Rating Scale (HDRS-17) score of > = 15 (Hamilton, 1960). Participants were recruited from a research registry, advertisement, and clinician referral. Participants were excluded for having bipolar I or any psychotic disorder, current alcohol/drug dependence, borderline or antisocial personality disorder, suicidal or homicidal ideation requiring a higher level of psychiatric care, pregnancy, other active medical issues that could explain symptoms, or lack of fluency in English. Participants were also excluded if they currently were receiving individual psychotherapy, were on psychotropic medications, or had a history of lack of response to adequate dose IPSRT (> = 12 weeks) or quetiapine (> = 300 mg). All participants provided written informed consent as part of this University of Pittsburgh Institutional Review Board approved protocol.

2.2. Intervention

Each participant received weekly 45-minute manualized and fidelity-verified IPSRT sessions with the same therapist until remission, followed by every other week sessions through week 20. In addition to receiving IPSRT, participants were randomized to either quetiapine or placebo. Medication was administered under double-blind conditions with quetiapine and placebo delivered in identically appearing capsules. Both placebo and quetiapine were flexibly dosed starting at 50 mg/day and titrated weekly in increments of 50 mg/day up to a maximum of 300 mg/day. In the trial, participants received a mean of 11.6 +/- 7.2 psychotherapy sessions over 20 weeks, which did not differ by treatment assignment, and 172 +/- 71 mg/day of quetiapine (Swartz et al., 2018). HRSD-17 assessments were administered by a rater blind to treatment condition at baseline and 20 week follow-up.

2.3. Outcomes

Blood samples were obtained at baseline and at 20 weeks (post treatment) between the times of 09:00 and 15:00. Whole blood venous samples (3 mL) were drawn in non-heparinized Vacutainer collection tubes and allowed to clot before centrifugation. Serum was isolated from centrifugation and kept frozen at -80 °C until assayed. Several cytokines were measured including hsCRP, interferon-gamma (IFN-γ), interleukin-1 (IL-1β), IL-2, IL-4, IL-6, IL-10, IL-12p70, and tumor necrosis factor – alpha (TNF-α) using the Multi-Spot Detection System MSD® (Meso Scale Diagnostics, Rockville, MD, Proinflammatory Panel 1). The lower limits of detection (assay sensitivities) were 0.37 pg/mL for IFN-γ, 0.05 pg/mL for IL-1β, 0.09 pg/mL for IL-2, 0.02 pg/mL for IL-4, 0.06 pg/mL for IL-6, 0.04 pg/mL for IL-10, 0.11 pg/mL for IL-12p70, and 0.04 pg/mL for TNF-α. Consistent with prior analyses, values of zero were imputed for values below the fit curve range while values above the fit curve range were given the value of the highest concentration in the standard curve (Henning et al., 2017). Due to having too many values (> = 25%) outside of the fit curve ranges, measures of IL-1β, IL-2, and IL-12p70 were removed from analyses. The percent of observations outside of the fit curve ranges were 0% for hsCRP, 0% for IFN-γ, 22% for IL-4, 0% for IL-6, 6% for IL-10, and 0% for TNF-α.

2.4. Statistical analyses

Analyses were conducted using SAS 9.4 (SAS Institute, Inc., Cary NC). Due to the extreme skew of cytokine values and consistent with prior analyses, cytokine values were natural log transformed for analyses after right shifting 1 unit such that the lowest possible value following transformation was 0 (ln(1)). Regression diagnostics were conducted on all models to ensure that transformation was adequate to meet assumptions. We excluded any observation for which CRP values (or the hsCRP) were ≥10 mg/L as has been done elsewhere to exclude clinically relevant inflammatory conditions (Arad, Goodman, Roth, Newstein, & Guerci, 2005; Frohlich et al., 2000; Ma et al., 2006; Malkin et al., 2010) and as has been recommended by expert Paul Ridker (Ridker, 2003). There were no identified inflammatory or autoimmune diseases in the final sample. The analyses were conducted after the drafting of an *a priori* statistical analysis plan. Baseline differences between groups were assessed using an independent-sample *t*-test for continuous measures, chi-square for categorical measures, and Mantel-Haenszel test for ordinal measures.

Our primary moderator of interest for Aim 1 was baseline hsCRP, using an established threshold translated to the units of the high sensitivity measure (Jha et al., 2017; Uher et al., 2014) through modeling a treatment by CRP (dichotomous) interaction in linear regression models with change in the HRSD-17, the primary outcome of the trial, as the dependent variable. Secondary analyses pursued other cytokines and CRP through modeling interactions of continuous variables. Models included a main effect of treatment assignment and the relevant cytokine, the components of the tested interaction.

For Aim 2 (to assess relation between change in cytokines and mood), IL-4 served as the primary outcome, given its demonstrated sensitivity to change in treatment of major depressive disorder (Wiedlocha et al., 2018). We secondarily assessed other cytokines. Linear regression models, with change in cytokines as the dependent variable, were used to test the impact of changes in HRSD-17 on change in the cytokine adjusting for the potential confounding effects of age and sex.

For Aim 3 (to assess differential impact of treatment), linear regression models again assessed change in cytokines as the dependent variable and an indicator variable for treatment assignment. Given the limited data upon which to base hypotheses regarding differential effects of treatment, a primary outcome was not selected and the analysis framed as exploratory. A *post hoc* follow-up analyses included a covariate for change in BMI to determine if any apparent effects of quetiapine could be explained by its well-known propensity for inducing weight gain (Abosi, Lopes, Schmitz, & Fiedorowicz, 2018).

Table 1
Baseline sociodemographic participant characteristics within treatment group (27 patients).

	Total Sample (N = 27)	IPSRT plus Quetiapine (N = 10)	IPSRT plus Placebo (N = 17)	P-value
Age (years)	36.5 ± 12.0	40.9 ± 12.9	37.4 ± 11.8	0.53
Body mass index (kg/m^2)	28.1 ± 5.5	28.4 ± 4.6	27.9 ± 6.2	0.78
Sex, n. (%)				
Male	14 (51.8%)	4 (40.0%)	10 (58.8%)	
Female	13 (48.2%)	6 (60.0%)	7 (41.2%)	0.34
Race/Ethnicity, n. (%)				
Asian	2 (7.4%)	0 (0.0%)	2 (11.8%)	
American Indian	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Black	3 (11.1%)	2 (13.3%)	2 (11.8%)	
White	22 (81.5%)	13 (86.7%)	13 (76.4%)	
Unknown	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.51
Hispanic or Latino	1 (3.7%)	0 (0.0%)	1 (5.9%)	
Not Hispanic or Latino	26 (96.3%)	10 (100.0%)	16 (94.1%)	0.43
Education, n. (%)				
Below Some College	1 (3.7%)	0 (0.0%)	1 (5.9%)	
Some College (at least 1 year)	7 (25.9%)	3 (30.0%)	4 (23.5%)	
Technical School/ Associates Degree	5 (18.5%)	2 (20.0%)	3 (17.5%)	
College Diploma	12 (44.5%)	4 (40.0%)	8 (47.1%)	
Graduate/ Professional Degree	2 (7.4%)	1 (10.0%)	1 (5.9%)	0.63†
Marital Status, n. (%)				
Never Married	13 (48.2%)	4 (40.0%)	9 (52.9%)	
Living as Married	7 (25.9%)	3 (30.0%)	4 (23.5%)	
Divorced	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Married	2 (7.4%)	0 (0.0%)	2 (11.8%)	
Separated	4 (14.8%)	3 (30.0%)	1 (5.9%)	
Widowed	1 (3.7%)	0 (0.0%)	1 (5.9%)	0.34
Income, n. (%)				
Less than $10,000	3 (11.1%)	0 (0.0%)	3 (17.6%)	
$10,000-$19,999	7 (25.9%)	3 (30.0%)	4 (23.5%)	
$20,000-$29,999	2 (7.4%)	1 (10.0%)	1 (5.9%)	
$30,000-$39,999	3 (11.1%)	2 (20.0%)	1 (5.9%)	
$40,000-$49,999	2 (7.4%)	1 (10.0%)	1 (5.9%)	
$50,000-$74,999	8 (29.7%)	3 (30.0%)	5 (29.4%)	
$75,000-$99,999	1 (3.7%)	0 (0.0%)	1 (5.9%)	
Above $100,000	1 (3.7%)	0 (0.0%)	1 (5.9%)	> 0.99†

Note. Data are mean ± standard deviation or n. (%). † Mantel-Haenszel chi-square given ordinal nature of data.

3. Results

A total of 33 of participants completed baseline and 20-week follow-up measurements of cytokines. After excluding any observation for which CRP values ≥10 mg/L, there were 27 participants with 54 total observations. Of these, 10 participants were randomized to IPSRT + quetiapine and 17 participants were randomized to IPSRT + placebo. The baseline sociodemographic characteristics of these two groups are detailed in Table 1. There were no clinically or statistically significant differences between groups on variables tested. A slight majority of the IPSRT + quetiapine group was female (60%) compared to a slight minority (41%) in the IPSRT + placebo group, but this difference was not statistically significant. Cytokine values by group at each time point are tabulated in Table 2.

Baseline hsCRP ≥1 mg/L was not found to moderate treatment

Table 2
Cytokine values by group at each time point.

	IPSRT plus Quetiapine (N = 10)	IPSRT plus Placebo (N = 17)
CRP (Continuous)		
Baseline	2.01; 2.94 ± 2.85	1.21; 1.42 ± 1.30
20-Week follow-up	3.46; 3.61 ± 2.79	1.06; 2.05 ± 2.40
Change at wk 20	0.68 ± 2.02	0.63 ± 2.14
IFN		
Baseline	4.28; 5.04 ± 3.36	3.79; 7.25 ± 7.04
20-Week follow-up	5.35; 9.48 ± 13.82	4.08; 5.41 ± 5.58
Change at wk 20	4.44 ± 15.09	−1.84 ± 5.16
IL-4		
Baseline	0.02; 0.06 ± 0.13	0.01; 0.02 ± 0.03
20-Week follow-up	0.02; 0.02 ± 0.01	0.02; 0.02 ± 0.02
Change at wk 20	−0.04 ± 0.13	0.004 ± 0.034
IL-6		
Baseline	0.52; 0.55 ± 0.26	0.45; 1.01 ± 1.60
20-Week follow-up	0.73; 1.55 ± 1.56	0.42; 0.59 ± 0.50
Change at wk 20	1.00 ± 1.55	−0.42 ± 1.63
IL-10		
Baseline	0.22; 0.33 ± 0.35	0.18; 1.70 ± 6.24
20-Week follow-up	0.27; 0.28 ± 0.16	0.16; 0.22 ± 0.25
Change at wk 20	−0.05 ± 0.43	−1.48 ± 6.27
TNF-α		
Baseline	2.61; 2.56 ± 0.63	2.51; 3.12 ± 2.50
20-Week follow-up	2.89; 3.10 ± 0.65	2.45; 2.45 ± 0.68
Change at wk 20	0.54 ± 0.62	−0.68 ± 2.46
BMI		
Baseline	27.04; 28.41 ± 4.56	28.90; 27.95 ± 6.16
20-Week follow-up	27.51; 28.78 ± 5.17	27.94; 28.10 ± 6.26
Change at wk 20	0.37 ± 1.29	0.15 ± 0.90

Note. Values are presented as median ; mean ± standard deviation.

Table 3
Moderation of change in HRSD as modeled through treatment by cytokine interaction from linear regression models.

Cytokine	β_3	SE	p-value
CRP (Dichotomous, Primary)	1.83	5.69	0.75
CRP (Continuous)	3.34	4.83	0.50
IFN	2.59	5.31	0.63
IL-4	29.24	67.30	0.67
IL-6	13.71	13.94	0.34
IL-10	11.54	9.12	0.22
TNF-α	−14.65	12.74	0.26

Note. Cytokine variables are shifted one unit right and natural log transformed for analysis.

response as modeled through a treatment by cytokine interaction on HDRS-17 (p = 0.75). There was no evidence of moderation for hsCRP or any other cytokines modeled as continuous variables (all p's for interaction > = 0.22) as outlined in Table 3.

Change in HDRS-17 was not associated with change in the primary outcome of IL-4 (β = -0.002, SE 0.002, p = 0.35). There were no statistically significant associations between change in HRSD-17 scores and change in any of the other cytokines as shown in Table 4.

In exploration of differential treatment effects, linear regression revealed that assignment to quetiapine instead of placebo with IPSRT was associated with significant elevations in IL-6 (β = 0.49, SE 0.19, p = 0.02) and TNF-α (β = 0.26, SE 0.12, p = 0.04) as highlighted in Table 5. Changes in cytokines by treatment group are illustrated in Fig. 1. These associations remained effectively unchanged in *post hoc* analyses adjusting for change in BMI (β = 0.50, SE 0.20, p = 0.02 and β = 0.27, SE 0.12, p = 0.04, respectively) or change in BMI with change in HDRS-17 (β = 0.48, SE 0.19, p = 0.02 and β = 0.25, SE 0.12, p = 0.04, respectively).

Table 4
Associations between change in HRSD-17 score and change in cytokine values from linear regression models.

Cytokine	β_1	SE	p-value
IL-4 (Primary)	−0.002	0.002	0.35
CRP (Continuous)	−0.01	0.02	0.45
IFN	−0.01	0.02	0.56
IL-6	−0.03	0.02	0.06
IL-10	−0.03	0.02	0.10
TNF-α	−0.016	0.009	0.10

Note. Cytokine variables are shifted one unit right and natural log transformed for analysis. A negative parameter estimate indicates an increase in concentration of the cytokine with a decrease in HRSD-17 score.

Table 5
Changes in cytokines after randomized treatment assignment to quetiapine or placebo with IPSRT. Treatment assignment was modeled such that a positive parameter estimate indicates an increase in the relevant cytokine with IPSRT + quetiapine relative to IPSRT + placebo.

Cytokine	β_1	SE	p-value
CRP (Continuous)	0.02	0.20	0.93
IFN	0.52	0.29	0.09
IL-4	−0.04	0.03	0.17
IL-6	0.49	0.19	0.02*
IL-10	0.14	0.26	0.59
TNF-α	0.26	0.12	0.04*

Note. * P-value < 0.05. Cytokine variables are shifted one unit right and natural log transformed for analysis.

4. Discussion

In this randomized controlled trial of IPSRT + placebo versus IPSRT + quetiapine for bipolar II depression, we did not find evidence that baseline cytokine values moderated treatment response. Although both treatment groups improved over time, we did not identify any correlation between improvements in mood and changes in cytokine values. Interestingly, treatment assignment appeared to differentially impact changes in cytokines. The group assigned to quetiapine with IPSRT demonstrated significant increases in the pro-inflammatory cytokines IL-6 and TNF-α over time relative to the group assigned to placebo with IPSRT. Changes in other pro-inflammatory cytokines, although not statistically significant, were in the same direction as the IL-6 and TNF-α outcomes, supporting a picture of increased inflammation associated with quetiapine exposure. Importantly, these results were independent of changes in BMI. Quetiapine is well-known to be adipogenic and increased adiposity, particularly visceral adiposity, is strongly associated with elevated inflammatory cytokines. Our findings therefore suggest that quetiapine may have pro-inflammatory effects beyond that explained by weight change alone.

There are some biologically plausible mechanisms by which quetiapine could induce inflammation beyond that attributable to weight gain. In vitro data suggests it may induce NF-κβ and NF-κβ1 target genes to enhance secretion of IL-8 and MCP-1, effectively "priming" adipocytes for subclinical inflammation (Sarvari, Vereb, Uray, Fesus, & Balajthy, 2014). Quetiapine may also chemosensitize macrophages, stimulating IL-6 and IFN-γ production (Ogundeji, Pohl, & Sebolai, 2017) and decrease expression of CD68 "scavenger receptors" on monocytes (Bahramabadi et al., 2017). The potential impact of quetiapine treatment itself may not be so straightforwardly pro-inflammatory. In mice, quetiapine and its active metabolite norquetiapine augmented levels of the anti-inflammatory cytokine IL-10, while attenuating IFN-γ following exposure to a lipopolysaccharide stimulus (Jaehne, Corrigan, Toben, Jawahar, & Baune, 2015). In the current analysis, no changes in IL-10 were observed with quetiapine treatment although this stood in contrast to the decreases in the anti-

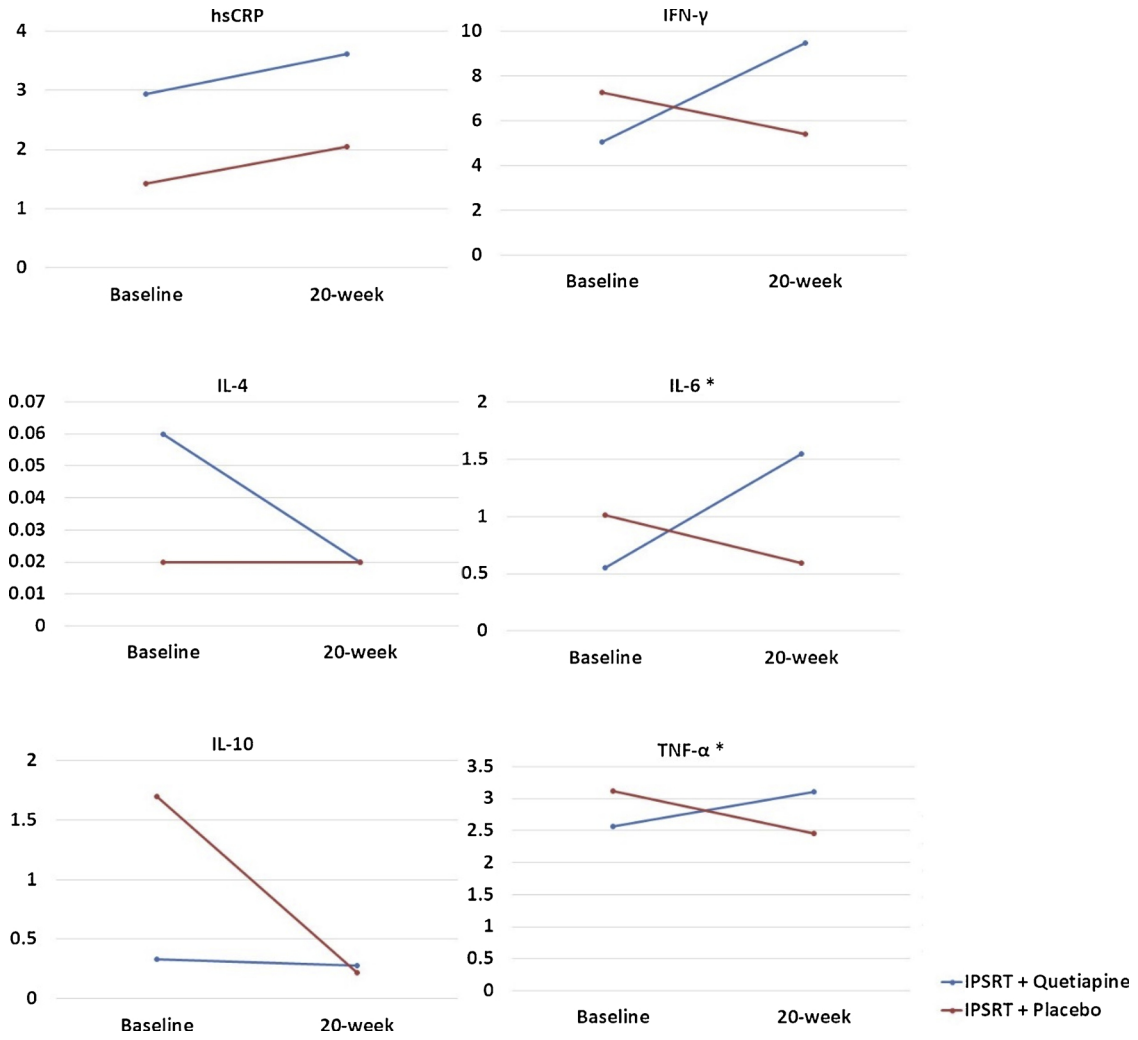

Fig. 1. Changes in cytokines by treatment assignment. This figure illustrates the changes in each cytokine from baseline to week study for those assigned to IPSRT + quetiapine and IPSRT + placebo. * - denotes significant differences with $p < 0.05$.

inflammatory IL-10 observed in those receiving IPSRT + placebo. The findings in our study, with significant increases in IL-6 and TNF-α are perhaps best explained by the aforementioned "priming" of adipocytes and sensitizing of macrophages. Other antipsychotics have been associated with similar cytokine changes (Maes et al., 1997; Pollmacher, Hinze-Selch, & Mullington, 1996; Schmitt et al., 2005), although studies of treatment with antipsychotics in schizophrenia show normalization of a blunted IL-2 response and TNF-α levels (Bresee et al., 2006).

The small sample size represented a key limitation of this analysis, which was powered to detect only large effects, and carries subsequent high risk of Type II error. The lack of association between changes in mood and changes inflammatory measures is subsequently inconclusive. The duration of the trial is a notable strength in this regard, however, as there is reason to believe, from cross-sectional studies of those with depression, that if inflammation is mood state dependent that improvements may take one to six months for values to normalize (Danner, Kasl, Abramson, & Vaccarino, 2003). Thus, this 20-week clinical trial provided a unique opportunity to test this hypothesis in a well-phenotyped and aggressively treated sample with bipolar II disorder. Testing for moderation is even further underpowered. The negative findings for the analysis of inflammation as a moderator for differential response are not definitive. These results are included in this report, however, because it was a primary aim for the ancillary study and part of our *a priori* statistical analysis plan. As noted in the introduction, baseline inflammation holds promise as a potential mediator for treatment response in mood disorders and warrants further study in large samples. Disturbances in circadian integrity are an established feature of bipolar II disorder (Bechtel, 2015; McClung, 2013; Mitterauer, 2000). Lack of information about circadian phase in the current subjects renders us unable to disentangle the effects of circadian rhythm variability on cytokine expression. When able, future studies should consider coupling careful measurement of circadian rhythms with cytokine sampling.

Bipolar II disorder, despite comparable cardiovascular morbidity and mortality to bipolar I disorder, remains grossly understudied. This study is the first to evaluate changes in inflammatory markers in bipolar II disorder, showing a more pro-inflammatory cytokine profile over time with quetiapine plus psychotherapy compared to psychotherapy alone. Although quetiapine is a first line treatment recommended for bipolar II depression (Yatham et al., 2018), it carries risk of clinically significant side-effects. Psychotherapy alone, by contrast, with preliminary evidence of efficacy (Swartz et al., 2018), does not appear to confer added metabolic burdens. Collectively, these data suggest that novel approaches to managing bipolar II depression may be worth considering—for instance a stepped care model that provides a trial of psychotherapy alone to those who wish it, followed by the addition of medication for those who need it, or vice versa (Hoberg, Ponto, Nelson, & Frye, 2013). Examination of these issues warrant follow-up in larger randomized controlled trials.

Authors statement

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HAS and JMC designed the supplemental study. HAS secured funding and conducted the clinical trial. JGF drafted the statistical analysis plan, which was revised with input from all authors. JGF and ZL conducted the statistical analysis. JGF wrote the initial draft of the manuscript which was critically reviewed by all authors. All authors contributed and approved the final manuscript.

Declaration of Competing Interest

All authors have no conflicts of interest to disclose.

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