Brain, Behavior, and Immunity xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Brain, Behavior, and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

C-reactive protein and response to lurasidone in patients with bipolar depression

Charles L. Raison[a,b,*], Andrei Pikalov[c,d], Cynthia Siu[e], Joyce Tsai[c,d], Kenneth Koblan[c,d], Antony Loebel[c,d]

[a] School of Human Ecology, University of Wisconsin-Madison, 1300 Linden Drive, Madison, WI 53706, USA
[b] Department of Psychiatry, School of Medicine and Public Health, University of Wisconsin-Madison, 6001 Research Park Blvd, Madison, WI 53719, USA
[c] Sunovion Pharmaceuticals Inc., 1 Bridge Plaza North, Suite 510, Fort Lee, NJ, USA
[d] Sunovion Pharmaceuticals Inc., Marlborough, MA, USA
[e] COS & Associates Ltd., 20/F Central Tower, 28 Queen's Rd, Central District, Hong Kong

ARTICLE INFO

Keywords:
Bipolar depression
Lurasidone
Inflammation
C-reactive protein
Atypical antipsychotics
Predictive biomarkers

ABSTRACT

Prior studies suggest that the inflammatory biomarker c-reactive protein (CRP) holds promise for predicting antidepressant response in patients with major depressive disorder. The objective of this study was to evaluate whether CRP might similarly predict antidepressant responses to lurasidone in patients with bipolar I depression. Serum CRP concentration was measured prior to, and following, 6 weeks of treatment in 485 outpatients with bipolar I depression. Patients were randomized to receive monotherapy with lurasidone 20–60 mg/day (N = 161), lurasidone 80–120 mg/day (N = 162) or placebo (N = 162). CRP was assessed using the wide-range CRP assay (wr-CRP). The primary efficacy endpoint was change from baseline to week 6 in Montgomery-Åsberg Depression Rating Scale (MADRS) score. Mixed models and statistical interaction tests were applied to investigate the moderating effects of pre-treatment wr-CRP on clinical endpoints. CRP was evaluated as a log-transformed continuous variable and by clinically-relevant cut-points. Increasing pre-treatment wr-CRP level predicted a larger overall antidepressant response to lurasidone, as well as an increased response for a number of individual depressive symptoms. These moderating effects of pre-treatment wr-CRP remained significant after adjustment for potential confounds (e.g. baseline BMI and weight change). Treatment with lurasidone did not affect serum concentrations of CRP compared to placebo during the study. Elevated CRP level prior to treatment was associated with an enhanced clinical response to lurasidone in patients with bipolar I depression. If confirmed in future studies, CRP may represent a clinically useful diagnostic and predictive biomarker supporting a precision medicine approach to the treatment of bipolar depression.

1. Introduction

As with major depression and related disorders (MDD), bipolar disorder has been repeatedly associated, in both its manic and depressed phases, with elevated levels of circulating inflammatory biomarkers (Dargél et al., 2015; Hope et al., 2011; Munkholm et al., 2015). Consistent with our growing recognition of the involvement of immune processes in the pathogenesis of mood disorders, many of the biological variables identified as potential predictive biomarkers for response to antidepressants likely index aspects of neuroimmune interactions relevant to the pathophysiology of depression. Consistent with this, immune measures have been reported to predict a differential response to antidepressants. Examples of these measures include gene expression patterns of toll-like receptor pathway molecules (Hung et al., 2017), response elements of the nuclear factor kappa-beta pathway (Koo et al., 2010), multiple combined immune functions (Guilloux et al., 2015; Pettai et al., 2016), and individual proinflammatory cytokines (Cattaneo et al., 2013; Powell et al., 2013), as well as combinations of these cytokines (Cattaneo et al., 2013). Highlighting the potentially unique utility of immune measures for predicting antidepressant response, one direct comparison found that gene expression patterns for inflammatory cytokines predicted treatment response, whereas gene expression patterns for other systems known to be abnormal in MDD, including glucocorticoid signaling and neurotrophic support, did not (Cattaneo et al., 2013).

These findings suggest that immune functioning may contribute to antidepressant responsiveness. It is therefore of great scientific and public health interest to identify an immune biomarker (or -markers)

* Corresponding author at: School of Human Ecology, University of Wisconsin-Madison, 1300 Linden Drive, Room 4174, Madison, WI 53706, USA.
E-mail address: raison@wisc.edu (C.L. Raison).

https://doi.org/10.1016/j.bbi.2018.08.009
Received 7 June 2018; Received in revised form 1 August 2018; Accepted 9 August 2018

that can be tractably implemented in clinical settings. It is in this context that recent findings regarding the predictive value of the acute phase reactant, c-reactive protein (CRP) are potentially important. Unlike more complex assessments, CRP—which provides a good summary measure of overall inflammatory state —is widely available and, importantly, subject to Clinical Laboratory Improvement Amendments (CLIA) standards, assuring its consistency across clinical laboratories.

Several studies now suggest that pretreatment CRP may predict differential patterns of responses to specific antidepressant medications. Indeed, two studies now indicate that low levels of CRP predict response to a selective serotonin reuptake inhibitor (SSRI) and non-response to non-serotonergic antidepressants (i.e. nortriptyline, bupropion), whereas higher levels of CRP predict non-response to SSRIs but enhanced response to non-serotonergic agents (Jha et al., 2017; Uher et al., 2014). Consistent with the possibility that high, as well as low, levels of CRP may prove useful in identifying pharmacologic agents likely to be differentially effective in a given patient with MDD, increased concentrations of CRP have also been shown to predict an increased antidepressant response to the cytokine antagonist infliximab, omega 3 fatty acids and l-methylfolate (Raison et al., 2013; Rapaport et al., 2016; Shelton et al., 2013). Increased pretreatment levels of interleukin (IL)-6, which is the primary stimulus for CRP production, have also been shown to predict response to ketamine in patients with treatment resistant depression (Romeo et al., 2017; Yang et al., 2015).

A single small study found that increased transforming growth factor (TGF)-beta-1 and reduced IL-23 predicted a poor response to either lithium or quetiapine in manic episodes (Li et al., 2015), but to our knowledge the question of whether immune biomarkers in general (or CRP in particular) might hold promise for predicting response to pharmacologic agents in the context of bipolar depression remains unknown. The clinical importance of addressing this issue is highlighted by the fact that few effective pharmacologic options are available for the treatment of bipolar depression (Sidor and Macqueen, 2011; Sienaert et al., 2013), despite the fact that depressive episodes occur more frequently and persistently than other bipolar mood states (Calabrese et al., 2004; Judd et al., 2002), account for the majority of illness burden as measured by social and functional impairment (Fagiolini et al., 2013), as well as direct and indirect healthcare costs (Parker et al., 2013), and are the primary driver of increased suicide risk (Jamison 2000; Leverich et al., 2003).

Given these considerations, the current study utilized a large, placebo-controlled phase 3 trial that evaluated monotherapy treatment with the atypical antipsychotic lurasidone for patients with bipolar depression (Loebel et al., 2014) to investigate whether pretreatment serum concentrations of CRP predict subsequent therapeutic response, as well as whether change in CRP during lurasidone treatment is associated with an improvement in depressive symptoms.

2. Material and methods

2.1. Participants and design of parent study

The analysis population for the current study derives from a randomized, double-blind, placebo-controlled trial of lurasidone monotherapy for the treatment of a major depressive episode in the context of bipolar disorder (Loebel et al., 2014). To qualify for enrollment, participants were required to be between the ages of 18 and 75 and meet DSM-IV-TR criteria for a major depressive episode associated with bipolar I disorder, with or without rapid cycling, without psychotic features and with ≥1 manic or mixed manic episodes. The current depressive episode was required to have persisted for ≥4 weeks, but < 12 months, and participants were required to have a Montgomery-Asberg Depression Rating Scale (MADRS) score ≥ 20 and a Young Mania Rating Scale (YMRS) score ≤ 12 at screening and baseline

This study randomized 485 participants to six weeks of treatment with lurasidone 20–60 mg a day (n = 161), lurasidone 80–120 mg a day (n = 162) or placebo (n = 172). Primary and key secondary study endpoints were change from baseline to week 6 on MADRS and Clinical Global Impression Bipolar Version, Severity of Illness (CGI-BP-S) score (depression), respectively. On both measures, lurasidone significantly outperformed placebo, with no difference in outcomes between the two lurasidone dosage groups (MADRS: lurasidone 20–60 mg, −15.4, effect size (ES) 0.54; lurasidone 80–120 mg, −15.4, ES 0.54; vs. placebo, −10.7; CGI-BP-S: lurasidone 20–60 mg, −1.8, ES 0.61; lurasidone 80–120, −1.7, ES 0.50; vs. placebo, −1.1) (Loebel et al., 2014).

2.2. Assessment of CRP

Blood was withdrawn by venipuncture at baseline (prior to commencing treatment) and again at treatment week 6 to measure serum concentrations of CRP using the wide-range CRP (wr-CRP) assay. This technique is an immunoturbidimetric assay on the ADVIA 1650 chemistry system using Bayer ADVIA kit for wr-CRP (ACM Global Laboratories and Partner Laboratory SRL Diagnostics, Europe-UK and US locations and SRL, India). This assay has been shown to be essentially identical to the more widely-used high-sensitivity (hs) CRP assay, both in medically-ill and healthy adults (i.e. with r values of .99) (Maharshak et al., 2008). The lower limit of detection for the wr-CRP assay is 0.12 mg/L, which compares favorably with a lower limit of detection of 0.16 mg/L for the hs-CRP assay (Maharshak et al., 2008).

2.3. Statistical analysis

As in previous investigations (Raison et al., 2013; Uher et al., 2014), CRP was evaluated as a log-transformed continuous variable because of skewed distribution, and by stratification into three groups according to pretreatment CRP levels as an alternative approach to assessing clinical relevance (Raison et al., 2013). Cross-sectional associations between log-transformed wr-CRP (LOGCRP), body weight, BMI, and MADRS score at study baseline were evaluated using a regression model adjusted for study site effects. To evaluate the moderating effect of pretreatment wr-CRP level on depressive symptom response to lurasidone treatment vs. placebo at week 6, a mixed effects model for repeated measures (MMRM) was employed (Fitzmaurice et al., 2004). The model included terms for treatment, baseline symptom severity score, visit, treatment-by-visit interaction, study site, LOGCRP, LOGCRP-by-visit interaction effect, LOGCRP-by-treatment interaction effect, and LOGCRP-by-treatment-visit interaction effect. Analysis of covariance (ANCOVA) was applied to examine the effect of lurasidone on change in LOGCRP from baseline to week 6. To examine whether treatment-induced changes in wr-CRP mediated differential therapeutic responses to lurasidone vs. placebo, ANCOVA was applied with terms that included treatment, baseline symptom severity score, study site, and change in LOGCRP.

For purposes of illustrating the CRP-treatment interaction effects on treatment outcomes, effect sizes for the difference between lurasidone and placebo were calculated via two stratification strategies. First, participants were stratified based on a standard set of cut-points, specifically < 1 mg/L, 1–3 mg/L and > 3 mg/L (Ridker, 2003). In addition we employed a second stratification strategy that better captured the variance in baseline wr-CRP concentrations in the study population and that more accurately reflects more recent data on the association between CRP and antidepressant responses to cytokine antagonism (Raison et al., 2013). Specifically, we stratified wr-CRP into low (≤2 mg/L), medium (> 2 mg/L ≤ 5 mg/L) and high (> 5 mg/L) subgroups. The high CRP group cut-off value (> 5 mg/L) was chosen based on the finding that this value identifies patients with treatment-resistant MDD who showed an antidepressant response to a cytokine agonist compared to placebo (Raison et al., 2013), and the lower cut-off (≤2 mg/L) was chosen in a post-hoc analysis to optimize the prediction of treatment response and to provide approximately balanced numbers of participants per group.

To further examine the clinical relevance of pre-treatment CRP, we examined whether baseline wr-CRP concentration was associated with clinical response, with response defined as at least 50% improvement in MADRS score from baseline to week 6 endpoint. This metric was evaluated using a logistic regression model, which included terms for baseline MADRS score, site, log(CRP), treatment, and log(CRP)-treatment interaction effect.

Because body mass index (BMI) has been repeatedly associated with CRP levels (O'Connor et al., 2009) and because atypical antipsychotics can induce weight gain (which might secondarily increase peripheral inflammation) (Gao et al., 2016), baseline BMI, as well as age, sex, race, and measures of social support and socioeconomic status (assessed using relevant item scores included in the Quality of Life Enjoyment and Satisfaction Questionnaire [Q-LES-Q]), all of which could influence treatment response, were included as covariates in secondary analyses to better identify the independent effect of baseline CRP levels on treatment outcomes. All analyses were conducted on an intent-to-treat basis.

3. Results

3.1. Baseline characteristics

Table 1 shows baseline demographic and clinical characteristics for the lurasidone and placebo treatment groups. Consistent with multiple reports of elevated CRP in patients with bipolar disorder, both median and mean wr-CRP values were higher than typically observed in the general population (Ong et al., 2013). A total of 118 patients (24.5%) had a baseline wr-CRP serum concentration > 5 mg/L, 216 (44.8%) had a concentration > 2 mg/L and ≤ 5 mg/L, and 148 (30.7%) had a concentration ≤ 2 mg/L, with no significant differences between lurasidone and placebo groups at baseline. Increasing pre-treatment levels of CRP were strongly associated with increasing BMI ($p < 0.001$) and body weight ($p < 0.001$) (Supplemental Fig. S1). No association was found between either CRP ($p = 0.365$) or BMI ($p = 0.853$) and MADRS score at study baseline.

3.2. Association of pre-treatment wr-CRP with clinical response

The statistical interaction between log-transformed baseline wr-CRP level and treatment group was significant for change in MADRS score from baseline to the week 6 study endpoint ($p = 0.007$ for the LOGCRP-by-lurasidone 20–60 mg/d vs. placebo interaction, and $p = 0.011$ for the LOGCRP-by-lurasidone 80–120 mg/d vs. placebo interaction) with a larger placebo-corrected effect size for lurasidone in patients with higher baseline serum concentrations of wr-CRP.

Table 1
Demographic and baseline characteristics.

	Lurasidone (20–60 mg/d or 80–120 mg/d)	Placebo
	n = 323	n = 162
Age, mean ± SE	41.66 ± 0.68	41.20 ± 0.98
Gender		
Female	189 (58.5%)	87 (53.7%)
Male	134 (41.5%)	75 (46.3%)
Race		
White	213 (65.9%)	107 (66.0%)
Black	46 (14.2%)	21 (13.0%)
Other	64 (19.8%)	34 (21.0%)
MADRS, mean ± SE	30.46 ± 0.28	30.47 ± 0.39
CGI-BP-S depression severity, mean ± SE	4.53 ± 0.03	4.48 ± 0.05
Wr-CRP, mean ± SE, mg/L	4.8 ± 0.4	4.5 ± 0.4
Median (Interquartile range)	3.0 (1.3, 5.2)	3.0 (1.7, 4.1)
BMI, mean ± SE	27.44 ± 0.32	27.06 ± 0.45

MADRS, Montgomery-Asberg Depression Rating Scale; CGI-BP-S Score (Depression), Clinical Global Impression Bipolar Version, Severity of Illness score (Depression); wr-CRP, wide-range c-reactive protein; BMI, body mass index; SE, standard error.

No interaction effect was observed between baseline wr-CRP and standard CRP categories (i.e. < 1 mg/L, 1–3 mg/L, > 3 mg/L) for either MADRS or CGI-BP-S score. However, strong interaction effects were observed in a subsequent analysis when study participants were stratified into low (≤ 2 mg/L), medium (> 2 mg/L – ≤5 mg/L) and high (> 5 mg/L) pre-treatment wr-CRP subgroups ($p = 0.003$ for the stratified CRP-by- lurasidone 20–60 mg/d vs. placebo interaction, and $p = 0.008$ for the stratified CRP-by-lurasidone 80–120 mg/d vs. placebo interaction) (Table 2) (All further stratified analyses utilize these cut-points). Both log-transformed and stratified pretreatment CRP also moderated the effect of lurasidone (vs. placebo) on change in CGI-BP-S score ($p = 0.022$ for the LOGCRP-by-lurasidone 20–60 mg/d vs. placebo interaction, and $p = 0.019$ for the LOGCRP-by-lurasidone 80–120 mg/d vs. placebo interaction; $p = 0.003$ for the stratified CRP-by- lurasidone 20–60 mg/d vs. placebo interaction, and $p = 0.004$ for the stratified CRP-by- lurasidone 80–120 mg/d vs. placebo interaction) (Table 3). Interaction effects for both log-transformed and stratified CRP on change in MADRS and CGI-BP-S scores remained significant following adjustment for age, sex, baseline BMI, social support, socioeconomic status and for weight change during treatment. Although pretreatment wr-CRP and BMI were strongly associated, baseline BMI did not predict a differential antidepressant effect size for lurasidone (vs. placebo) ($p = 0.952$, BMI-by-treatment interaction effect).

Because the moderating effect of baseline wr-CRP score was unrelated to lurasidone dosage ($p > .90$) and because the two lurasidone dosage groups produced identical placebo-adjusted reductions in MADRS score (Loebel et al., 2014), we combined these dosage groups to more parsimoniously generate effect size estimates for the impact of lurasidone treatment on MADRS and CGI-BP score in patients with increasing pretreatment CRP levels. As shown in Fig. 1, the effect size for differences between lurasidone and placebo treatment increased with increasing baseline CRP (MADRS: wr-CRP ≤ 2 = 0.0, wr-CRP > 2 – ≤5 = 0.55, wr-CRP > 5 = 0.82; CGI: wr-CRP ≤ 2 = 0.03, wr-CRP > 2 – ≤5 = 0.59, wr-CRP > 5 = 1.05). The interaction of CRP with lurasidone treatment (vs placebo) was significant independent of race ($p = 0.613$ for race by LOGCRP-lurasidone interaction effect).

The statistical interaction between log-transformed baseline wr-CRP level and lurasidone treatment (vs. placebo) was also significant for response rate defined as ≥50% improvement in MADRS score from baseline to week 6 study endpoint ($p = 0.039$ for the LOGCRP-by-lurasidone vs. placebo interaction; $p = 0.043$ for the LOGCRP-by-lurasidone vs. placebo interaction after adjusting for age, gender, and baseline BMI) (Fig. 2).

Moreover, the magnitude of absolute symptom reduction within the lurasidone group increased with increasing levels of pretreatment CRP, with the following concentration–response trend in mean change (SD) from baseline: MADRS: wr-CRP ≤ 2 = −11.66 (9.74), wr-CRP > 2 – ≤5 = −14.22 (9.74), wr-CRP > 5 = −16.08 (9.74); CGI-BP-S: wr-CRP ≤ 2 = −1.39 (1.16), wr-CRP > 2 – ≤5 = −1.59 (1.16), wr-CRP > 5 = −1.86 (1.16). Significant associations between log-transformed baseline wr-CRP level and improvement in MADRS ($p = 0.01$) and CGI-BP-S ($p = 0.04$) scores were also observed within the lurasidone group. A numerically larger placebo response was observed in the low CRP group compared to those with higher levels of wr-CRP but the trend was non-significant ($p = 0.574$) (Fig. 1). Therefore, there was an observed divergence in the trend for within group (lurasidone or placebo) improvement in MADRS score in relation to baseline wr-CRP level.

To evaluate the generalizability of the lower CRP cut-point selected for this study (> 2 mg/L), we examined these alternative cut-points of baseline wr-CRP: ≤1 mg/L, ≤2 mg/L, and ≤ 3 mg/L, with 71 (22.1%), 102 (31.8%), and 202 (62.9%) patients, respectively, in the lurasidone

Table 2
Change from Baseline in Montgomery-Asberg Depression Rating Scale (MADRS).

wr-CRP Group	Covariate(s)	Lurasidone 20–60 mg/day (n = 161)	Lurasidone 80–120 mg/day (n = 160)	Placebo (n = 161)
Low ≤ 2 mg/L (n = 148)	Adjusted for baseline MADRS, site	−11.56 (1.32)	−11.75 (1.42)	−11.63 (1.44)
	Adjusted for baseline MADRS and BMI, site	−12.40 (1.30)	−12.65 (1.41)	−13.96 (1.42)
	Adjusted for baseline MADRS and BMI, age, gender, site	−12.32 (1.31)	−12.23 (1.42)	−12.15 (1.43)
	Adjusted for baseline MADRS, site and weight change during treatment	−11.40 (1.29)	−12.33 (1.39)	−13.61 (1.41)
Medium > 2 to ≤5 mg/L (n = 216)	Adjusted for baseline MADRS, site	−14.57 (1.20)***	−13.91 (1.18)**	−8.89 (1.09)
	Adjusted for baseline MADRS and BMI, site	−13.94 (1.19)**	−14.04 (1.16)**	−8.80 (1.07)
	Adjusted for baseline MADRS and BMI, age, gender, site	−14.31 (1.19)***	−14.00 (1.17)**	−8.78 (1.08)
	Adjusted for baseline MADRS, site and weight change during treatment	−13.95 (1.18)**	−14.07 (1.15)**	−9.12 (1.06)
High > 5 mg/L (n = 118)	Adjusted for baseline MADRS, site	−16.21 (1.54)***	−15.95 (1.47)***	−8.07 (1.67)
	Adjusted for baseline MADRS and BMI, site	−16.07 (1.52)***	−14.88 (1.45)**	−7.82 (1.65)
	Adjusted for baseline MADRS and BMI, age, gender, site	−15.45 (1.53)**	−15.82 (1.46)***	−7.79 (1.66)
	Adjusted for baseline MADRS, site and weight change during treatment	−16.93 (1.51)***	−15.72 (1.44)**	−8.48 (1.64)

Least squares mean change (SE) for treatment comparisons with placebo at week 6 when study participants were stratified into low, medium and high pre-treatment wr-CRP groups: $^{***}p < 0.001$, $^{**}p < 0.01$.
p-values were estimated based on mixed model for repeated measures adjusted for baseline MADRS score, covariates and site: $p = 0.003$ for the stratified CRP-by-lurasidone 20–60 mg/d (vs. placebo) interaction; $p = 0.008$ for the stratified CRP-by-lurasidone 80–120 mg/d (vs. placebo) interaction.
wr-CRP, wide-range c-reactive protein; BMI, body mass index; SE, standard error.

Table 3
Change from Baseline in CGI-BP-S Score (Depression).

wr-CRP Group	Covariate(s)	Lurasidone 20–60 mg/day (n = 161)	Lurasidone 80–120 mg/day (n = 160)	Placebo (n = 161)
Low ≤2 mg/L (n = 148)	Adjusted for baseline CGI-BP-S	−1.42 (0.16)	−1.34 (0.17)	−1.35 (0.17)
	Adjusted for baseline CGI-BP-S and BMI	−1.49 (0.16)	−1.39 (0.17)	−1.41 (0.17)
	Adjusted for baseline CGI-BP-S and weight change during treatment	−1.38 (0.15)	−1.41 (0.16)	−1.61 (0.17)
Medium > 2 – ≤5 mg/L (n = 216)	Adjusted for baseline CGI-BP-S	−1.67 (0.14)***	−1.54 (0.14)**	−0.92 (0.13)
	Adjusted for baseline CGI-BP-S and BMI	−1.64 (0.14)***	−1.54 (0.14)**	−0.91 (0.13)
	Adjusted for baseline CGI-BP-S and weight change during treatment	−1.63 (0.14)**	−1.58 (0.14)**	−0.97 (0.13)
High > 5 mg/L (n = 118)	Adjusted for baseline CGI-BP-S	−1.97 (0.18)***	−1.76 (0.17)***	−0.64 (0.20)
	Adjusted for baseline CGI-BP-S and BMI	−1.88 (0.18)***	−1.71 (0.17)***	−0.57 (0.20)
	Adjusted for baseline CGI-BP-S and weight change during treatment	−2.09 (0.18)***	−1.74 (0.17)***	−0.70 (0.19)

Least squares mean change (SE) for treatment comparisons with placebo at week 6 when study participants were stratified into low, medium and high pre-treatment wr-CRP groups: $^{***}p < 0.001$, $^{**}p < 0.01$.
p-values were estimated based on mixed model for repeated measures adjusted for baseline CGI-BP-S score (depression), covariates and site: $p = 0.003$ for the stratified CRP-by- lurasidone 20–60 mg/d (vs. placebo) interaction; $p = 0.004$ for the stratified CRP-by-lurasidone 80–120 mg/d (vs. placebo) interaction.
Clinical Global Impression Bipolar Version, Severity of Illness (CGI-BP-S) score (depression); CGI-BP-S score (depression), wr-CRP, wide-range c-reactive protein; BMI, body mass index; SE, standard error.

group; and 32 (19.9%), 46 (28.6%), and 104 (64.6%) patients, respectively, in the placebo group. Lurasidone vs. placebo difference in MADRS scores in participants with wr-CRP levels ≤ 1 mg/L, ≤2 mg/L, and ≤ 3 mg/L were −1.57 (Cohen's d = 0.16), −0.01 (Cohen's d = 0.001), and −3.17 (Cohen's d = 0.32), respectively. To evaluate the generalizability of the higher cut-point selected for this study (≤5 mg/L), we found that bifurcating the study sample by this cut-point showed a significantly increased response to lurasidone vs. placebo in the group with baseline wr-CRP > 5 mg/L ($p < 0.05$).

In terms of specific depressive symptoms, there were significant interactions between lurasidone treatment (vs. placebo) and log-transformed baseline wr-CRP for the following MADRS items adjusted for baseline severity and study site: "apparent sadness" (MADRS item 1, p = 0.004), "reported sadness" (MADRS item 2, p < 0.003), "lassitude" (MADRS item 7, p = 0.056), and "pessimistic thoughts" (MADRS item 9, p = 0.003), with improvement in these symptoms favoring lurasidone (vs. placebo) with increasing levels of baseline wr-CRP.

3.3. Effect of treatment on wr-CRP serum concentration

Lurasidone treatment was not associated with significant change in wr-CRP serum concentrations from baseline to week 6 (p = 0.080). Median change from baseline to week 6 in wr-CRP was 0 (inter-quartile range IQR −0.3, 0.8 mg/L) in the lurasidone group, compared to 0 (IQR −0.7, 0.1 mg/L) in the placebo group (p = 0.078). No associations were observed between change in LOGCRP and change in either MADRS or CGI-BP-S score from baseline to week 6 (MADRS: p = .68; CGI-BP-S: p = .63).

All study findings were consistent when evaluated by either ANCOVA or MMRM analyses.

4. Discussion

Results from the current study add to a growing body of evidence indicating that the widely-available inflammatory biomarker CRP may

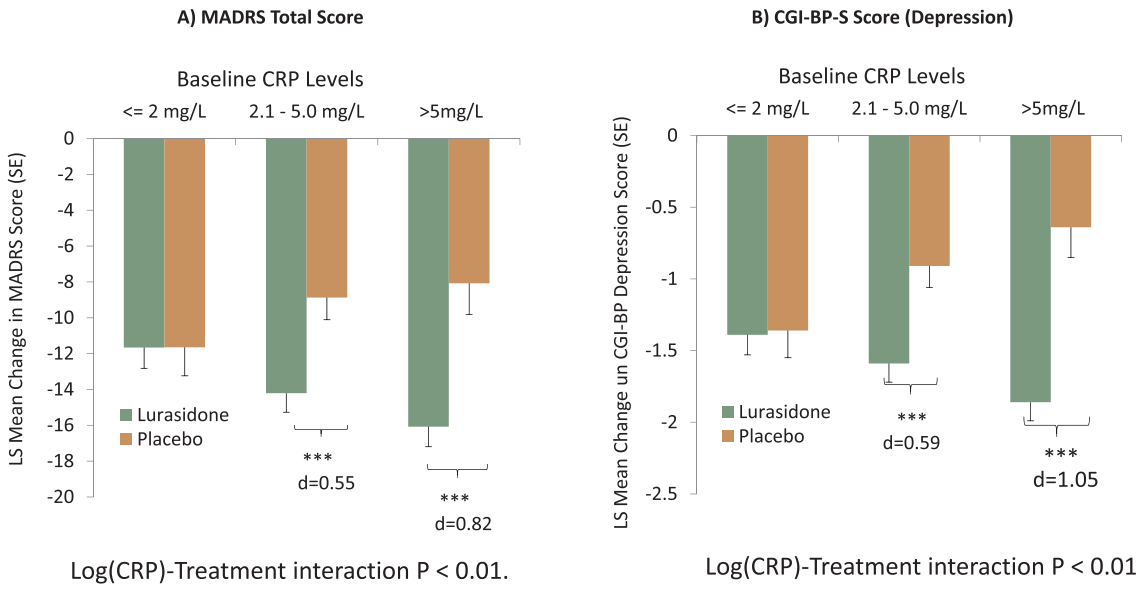

Fig. 1. Baseline C-Reactive Protein Level and Week 6 Change in Montgomery-Asberg Depression Rating Scale (MADRS) Score and Clinical Global Impression Bipolar Version, Severity of Illness (CGI-BP-S) Score (Depression) Associated with Lurasidone (vs. Placebo) Treatment. *p*-values were estimated based on MMRM model adjusted for baseline MADRS score and study site: $p < 0.01$ for both the log-transformed and stratified CRP-by-lurasidone (vs. placebo) interaction effect on week 6 change in MARDS score. $p < 0.01$ for both the log-transformed and stratified CRP-by-lurasidone (vs. placebo) interaction effect on week 6 change in CGI-BP-S score (Depression). Least squares mean change in MADRS and CGI-BP-S scores for lurasidone (20–60 mg/d or 80–120 mg/d) comparisons with placebo at week 6 when study participants were stratified into low, medium and high pre-treatment wr-CRP groups. Lurasidone, lurasidone 20–60 mg/d or 80–120 mg/d; CGI-BP-S Score (Depression), Clinical Global Impression Bipolar Version, Severity of Illness score (Depression); wr-CRP, wide-range c-reactive protein; BMI, body mass index; d, effect size (lurasidone vs. placebo).

hold promise as a clinically useful predictor of response to psychotropic agents used to treat mood disorders. Here we report that in patients with bipolar depression an enhanced antidepressant response to the atypical antipsychotic agent lurasidone was observed with increasing levels of pre-treatment wr-CRP, with this effect being observed across a range of lurasidone doses (20–120 mg/d) utilized in the study. Importantly, although BMI has been reported to influence antidepressant responsiveness (Kloiber et al., 2007) and BMI was strongly associated with CRP in the study sample, the impact of pre-treatment CRP on subsequent response to lurasidone was independent of BMI at baseline, as well as independent of change in BMI with treatment during the study.

Moreover, the predictive value of pre-treatment CRP was clinically relevant. First, increasing log-transformed wr-CRP at baseline was associated with increased clinical response (defined as a ≥ 50% reduction in MADRS score) in patients treated with lurasidone vs. placebo. Second, based on MADRS scores, lurasidone produced an antidepressant response similar to placebo in patients with baseline wr-CRP ≤ 2 mg/L (d = 0, vs. placebo), whereas the medication demonstrated a large effect size (d = 0.82, vs placebo) in patients with wr-CRP > 5 mg/L. In patients with baseline wr-CRP > 2 mg/L to ≤5 mg/L, lurasidone demonstrated a medium effect size (d = 0.55, vs. placebo), which—while not as significant as the advantage seen in the high inflammation group—is still highly clinically relevant, given that

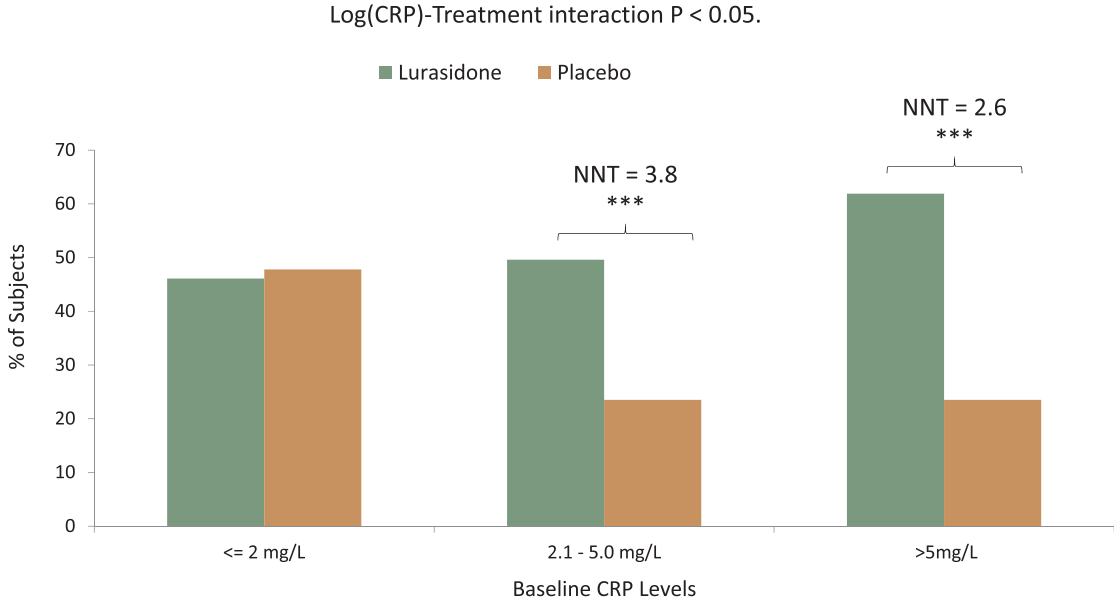

Fig. 2. Baseline wr-CRP and Week 6 Response Rate Associated with Lurasidone (vs. Placebo) Treatment.

it exceeds typical effect size advantage reported for antidepressant agents used to treat MDD (Turner et al., 2008). Similar lurasidone effect sizes were observed for the impact of pretreatment levels of CRP on CGI-BP-S scores, providing convergent evidence for the relevance of CRP as a potential predictive biomarker for response to lurasidone in patients with bipolar depression. Notably, effect sizes associated with lurasidone (vs placebo) treatment increased with CRP ranges from ≤2 mg/L (low) to > 5 mg/L (high) at study baseline. The analysis of CRP as a continuous log-transformed variable has been used in previous studies (Raison et al., 2013; Uher et al., 2014; Jha et al., 2017), which provide similar results as analysis using CRP cut points in the current study. The inclusion of CRP as a continuous variable strengthens our findings by simultaneously demonstrating that the relationship between pre-treatment CRP and outcomes is linear and that the categorical findings (using CRP cut-points included in previous studies) are valid. This linear trend for the effect of CRP on depressive symptom improvement reduces the possibility that the moderating relationship between CRP level and predicted clinical effect found in this study was due to chance.

Nonetheless, we did not find an association between standard CRP cut-points (< 1 mg/L, 1–3 mg/L, > 3 mg/L) and differences in antidepressant response in lurasidone vs. placebo treated patients. This discrepancy likely results from the striking differences in lurasidone/placebo effect size in participants with wr-CRP less than or > 2 mg/L. Below 2 mg/L the effect size difference in depressive symptom change between lurasidone and placebo was zero; between 2 mg/L and 5 mg/L the effect size increased rapidly. Therefore, when participants with CRP levels between 1 and 2 are grouped with participants with CRP levels between 2 and 3 the resultant group is so heterogeneous that the linear relationship between baseline CRP and clinical response is disrupted. On the other hand, the ≤2 mg/L, > 2 to ≤5, > 5 categorization more cleanly "cleaves nature at the joints" in this population, with the cut-off score of 2 representing a potential "optimum cut-off" for predicting treatment response.

Interestingly, placebo response was numerically lowest in the subgroup of patients with highest level of pretreatment CRP. Similar results have been observed in other studies. For example, a study examining the impact of baseline CRP on response to the cytokine antagonist infliximab found that increasing baseline CRP was associated with reduced placebo response (Raison et al., 2013). Similarly, a study of omega-3 fatty acids as monotherapy for MDD found that increased inflammatory biomarkers at baseline predicted better response to placebo than to the active treatment in patients with MDD and low levels of pretreatment inflammation (Rapaport et al., 2016). Interestingly, administration of inflammatory stimuli (e.g. endotoxin) to healthy volunteers has been shown to acutely induce feelings of social disconnection (Eisenberger et al., 2010), raising the intriguing possibility that increased inflammation may interfere with social emotions likely to be involved in the placebo response (Martin et al., 2000). Taken together, these findings suggest that pretreatment CRP may be a biologically relevant predictive variable, not just for predicting response to specific pharmacological agents such as lurasidone, but more generally for predicting response to the wide range of biological and behavioral factors that contribute to placebo response.

Meta-analyses examining the impact of antipsychotics on inflammatory biomarkers provide a somewhat contradictory picture, especially in regard to IL-6, the cytokine most responsible for the production and release of CRP. In schizophrenic populations one meta-analytic study reported that antipsychotic treatment was associated with reduced IL-6 (Miller et al., 2011), while a second study found no effect (Tourjman et al., 2013). Consistent with the second study, a meta-analysis of 85,000 patients with schizophrenia found no impact of antipsychotic treatment on CRP levels (Fernandes et al., 2016).

As the first study to examine the impact of treatment with an atypical antipsychotic on CRP levels in bipolar depression, the current investigation provides additional evidence that these medications may not directly impact CRP or cytokine pathways that stimulate its production and release. Moreover, changes in CRP during treatment showed no association with response to either lurasidone or placebo.

Our finding that pre-treatment levels of CRP predict response to lurasidone, whereas changes in CRP during treatment do not, is consistent with other findings in the literature. For example, Cattaneo et al. identified pre-treatment cytokine gene expression profiles (i.e. IL-1-beta, macrophage inhibiting factor [MIF], TNF) that predicted subsequent response to either escitalopram or nortriptyline in patients with MDD (Cattaneo et al., 2013). Although treatment subsequently impacted expression levels of these biomarkers, these changes were not associated with therapeutic outcomes with either antidepressant.

One explanation for how a biomarker like CRP might predict response prior to—but not during—treatment is that CRP indexes inflammatory pathways that when activated induce downstream physiological changes that are more directly linked to the development of depression and that are targeted by the psychotropic agent. In this scenario, CRP predicts response to lurasidone not because lurasidone directly attenuates inflammatory signaling indexed by CRP, but because it alleviates a bipolar depressive syndrome to which inflammatory processes contribute by activating downstream CNS mechanisms that more directly contribute to the behavioral pathology and that are targeted by the medication. Support for this possibility comes from animal studies showing that inflammation alters glutamatergic activity in the brain and induces indoleamine 2,3-dioxygenase (IDO), which promotes the production/release of kynurenine and its metabolites (which also alter glutamatergic signaling) (Haroon and Miller, 2017; Dantzer et al., 2008). Animal studies demonstrate that blocking these downstream pathways with either ketamine (an antagonist at the glutamatergic N-methyl-D-aspartate (NMDA) receptor) or 1-methyl tryptophan (an IDO inhibitor) abrogates the induction of depressive-like symptoms, while leaving intact the development of sickness behavior, which presumably is more directly related to cytokine signaling (Corona et al., 2013; Walker et al., 2013).

Of direct relevance to the current study, an important downstream mechanism by which inflammation appears to induce depression is impairment of dopaminergic signaling in the ventral striatum (e.g. nucleus accumbens) and disruption of connectivity between this dopaminergically-rich area and ventromedial prefrontal cortex (Capuron et al., 2012; Felger et al., 2016). Along with other atypical antipsychotics, lurasidone has been shown to increase the efflux of dopamine from the nucleus accumbens (Huang et al., 2014). This finding raises the intriguing possibility that lurasidone works preferentially in patients with an inflammation-induced reduction in dopamine signaling within the ventral striatum and/or impairment of the capacity for these signals to reach ventromedial prefrontal cortex. By increasing dopamine signaling within the striatum, lurasidone may counteract this effect, even while leaving the underlying pathology-initiating inflammatory signaling intact, as evidenced in the current study by an increasingly robust antidepressant effect in the absence of any reduction in the inflammatory signaling itself. Future studies could confirm or deny this hypothesis by using neuroimaging to demonstrate either increased dopaminergic activity in the ventral striatum or increased functional connectivity between ventral striatum and ventromedial prefrontal cortex in response to lurasidone treatment in the absence of reduced peripheral inflammation, with this effect being more apparent in those with high pretreatment CRP than in those with low levels of pretreatment CRP.

Convergent data for this possibility comes from two sources. First, the dopaminergic modulator antidepressant bupropion has also been shown to work preferentially in depressed patients with increased pretreatment levels of CRP (Jha et al., 2017), and like lurasidone has been shown to increase extracellular levels of dopamine in the ventral striatum (Kitamura et al., 2010). Similarly, animal studies demonstrate that administration of the dopaminergic agonist pramipexole protects against the development of depressive-like symptoms following an

inflammatory stimuli (endotoxin) (Lieberknecht, 2017). On the other hand, multiple studies confirm that serotonergic antidepressants (which do not have similar effects on either striatal dopamine or connectivity between striatum and ventromedial prefrontal cortex) (Abler et al., 2012) become increasingly ineffective as levels of pretreatment inflammation increase (Cattaneo et al., 2013; Jha et al., 2017; Uher et al., 2014). Second, pretreatment CRP presents a different predictive pattern in the current study than in studies employing agents that more directly modulate inflammatory tone. This is most apparent by comparing current results with those from a randomized trial of the TNF antagonist infliximab in medically-stable patients with treatment resistant MDD. In contradistinction to the current study, which found similar treatment effects for lurasidone and placebo in patients with low pretreatment CRP, the infliximab study reported that placebo significantly outperformed the cytokine antagonist in depressed patients with pretreatment CRP levels < 5 mg/L (Raison et al., 2013). Negative effects on depressive symptoms compared to placebo have also been observed for other agents with anti-inflammatory properties, including omega-3 fatty acids and l-methylfolate (Rapaport et al., 2016; Shelton et al., 2013).

Taken together, these findings raise the possibility that even in patients with elevated inflammation, agents that target pathways downstream from the inflammatory cascade may be more clinically effective than agents that block inflammatory signaling directly, both because agents that target downstream pathways are effective in a larger patient sub-group based on pretreatment CRP (e.g. down to 2 mg/L for lurasidone vs. 5 mg/L for infliximab) and because they do not appear to underperform when compared to placebo in depressed individuals with low levels of inflammation. Moreover, inflammation is almost certainly not the sole pathway by which dopaminergic signaling is altered/impaired in a condition such as bipolar depression, and agents such as lurasidone would be expected to help address these other pathological processes, whereas anti-inflammatory agents would be presumably ineffective.

Several limitations of the current study warrant discussion. Although current findings derive from a large, randomized, placebo-controlled trial, they are based on an exploratory analysis and the study was not primarily designed to assess the predictive power of CRP. Further investigations are needed to confirm that CRP is a useful biomarker for identifying etiologically different subtypes of bipolar depression in relationship to inflammation and predicting antidepressant responses to atypical antipsychotic treatment. Moreover, although levels of CRP tend to demonstrate interindividual stability in populations living in the industrialized world (McDade et al., 2012), it is a limitation that baseline levels of CRP were only assessed once prior to commencing treatment. Similarly, post-treatment CRP levels were only assessed six weeks after commencing treatment. It is possible that changes in CRP earlier in the course of treatment might have shown different associations with therapeutic outcome. Finally, because behavioral data were only collected for six weeks it is unknown whether the predictive power of pretreatment CRP would have increased or diminished over longer-time periods.

4.1. Conclusions

The urgent need to improve our ability to treat bipolar depression is highlighted by its disproportionately large contribution to the disease burden of bipolar disorder, as well as by its recalcitrance to effective treatment (Fagiolini et al., 2013; Jamison 2000; Leverich et al., 2003; Parker et al., 2013; Sidor and Macqueen, 2011; Sienaert et al., 2013). Findings from this placebo-controlled study indicate that lurasidone becomes increasingly effective as levels of pretreatment wr-CRP rise. Lurasidone demonstrated a clinical effect over and above placebo in patients with pretreatment levels of wr-CRP > 2 mg/L. If these findings are confirmed in future prospective studies, CRP may represent a clinically useful diagnostic and predictive biomarker supporting a precision medicine approach to the treatment of bipolar depression.

5. Registration

Clinicaltrials.gov identifier: NCT00868699.

Sunovion Pharmaceuticals Inc. is part of a clinical trial data sharing consortium that facilitates access for qualified researchers to selected anonymized clinical trial data. For up-to-date information on data availability please visit https://www.clinicalstudydatarequest.com/Study-Sponsors.aspx and click on Sunovion.

Acknowledgements

Presented in part at the 19th Annual Conference of the International Society for Bipolar Disorders, May 4-7, 2017, Washington DC, USA; and Annual American Society of Clinical Psychopharmacology Meeting, May 29-June 2, 2017, Miami, Florida; 30th European College of Neuropsychopharmacology (ECNP) Congress 2-5 September 2017, Paris, France.

Role of the sponsor

This study was sponsored by Sunovion Pharmaceuticals Inc. The sponsor was involved in the design and collection of data. This publication is the work of authors. All authors contributed to the analysis and interpretation of data, and gave final approval for the manuscript.

Financial disclosures

Dr. Raison reports that in the prior 12 months he has served as a consultant for Novartis, Alkermes, Shire, Usona Institute, Emory Healthcare and North American Center for Continuing Medical Education. Dr. Siu reports having received consulting fees from Sunovion, Pfizer, the Chinese University of Hong Kong, and the Centre for Addiction and Mental Health, Toronto. Drs. Loebel, Pikalov, Tsai, and Koblan are employees of Sunovion Pharmaceuticals Inc.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.bbi.2018.08.009.

References

Abler, B., Grön, G., Hartmann, A., Metzger, C., Walter, M., 2012. Modulation of frontostriatal interaction aligns with reduced primary reward processing under serotonergic drugs. J. Neurosci. 32, 1329–1335. https://doi.org/10.1523/JNEUROSCI.5826-11.2012.

Calabrese, J.R., Hirschfeld, R.M.A., Frye, M.A., Reed, M.L., 2004. Impact of depressive symptoms compared with manic symptoms in bipolar disorder: results of a U.S. community-based sample. J. Clin. Psychiatry 65, 1499–1504.

Capuron, L., Pagnoni, G., Drake, D.F., Woolwine, B.J., Spivey, J.R., Crowe, R.J., et al., 2012. Dopaminergic mechanisms of reduced basal ganglia responses to hedonic reward during interferon alfa administration. Arch. Gen. Psychiatry 69, 1044–1053. https://doi.org/10.1001/archgenpsychiatry.2011.2094.

Cattaneo, A., Gennarelli, M., Uher, R., Breen, G., Farmer, A., Aitchison, K.J., et al., 2013. Candidate genes expression profile associated with antidepressants response in the GENDEP study: differentiating between baseline "predictors" and longitudinal "targets". Neuropsychopharmacology 38, 377–385. https://doi.org/10.1038/npp.2012.191.

Corona, A.W., Norden, D.M., Skendelas, J.P., Huang, Y., O'Connor, J.C., Lawson, M., et al., 2013. Indoleamine 2,3-dioxygenase inhibition attenuates lipopolysaccharide induced persistent microglial activation and depressive-like complications in fractalkine receptor (CX(3)CR1)-deficient mice. Brain Behav. Immun. 31, 134–142. https://doi.org/10.1016/j.bbi.2012.08.008.

Dantzer, R., O'Connor, J.C., Freund, G.G., Johnson, R.W., Kelley, K.W., 2008. From inflammation to sickness and depression: when the immune system subjugates the brain. Nat. Rev. Neurosci. 9, 46–56. https://doi.org/10.1038/nrn2297.

Dargél, A.A., Godin, O., Kapczinski, F., Kupfer, D.J., Leboyer, M., 2015. C-reactive protein alterations in bipolar disorder: a meta-analysis. J. Clin. Psychiatry 76, 142–150. https://doi.org/10.4088/JCP.14r09007.

Eisenberger, N.I., Inagaki, T.K., Mashal, N.M., Irwin, M.R., 2010. Inflammation and social

experience: an inflammatory challenge induces feelings of social disconnection in addition to depressed mood. Brain Behav. Immun. 24, 558–563.
Fagiolini, A., Forgione, R., Maccari, M., Cuomo, A., Morana, B., Dell'Osso, M.C., et al., 2013. Prevalence, chronicity, burden and borders of bipolar disorder. J. Affect. Disord. 148, 161–169. https://doi.org/10.1016/j.jad.2013.02.001.
Felger, J.C., Li, Z., Haroon, E., Woolwine, B.J., Jung, M.Y., Hu, X., et al., 2016. Inflammation is associated with decreased functional connectivity within corticostriatal reward circuitry in depression. Mol. Psychiatry 21, 1358–1365. https://doi.org/10.1038/mp.2015.168.
Fernandes, B.S., Steiner, J., Bernstein, H.G., Dodd, S., Pasco, J.A., Dean, O.M., et al., 2016. C-reactive protein is increased in schizophrenia but is not altered by antipsychotics: meta-analysis and implications. Mol. Psychiatry 21, 554–564. https://doi.org/10.1038/mp.2015.87.
Fitzmaurice, G.M., Laird, N.M., Ware, J.H., 2004. Applied Longitudinal Analysis. John Wiley and Sons Inc, New Jersey.
Gao, K., Fang, F., Wang, Z., Calabrese, J.R., 2016. Subjective versus objective weight gain during acute treatment with second-generation antipsychotics in schizophrenia and bipolar disorder. J. Clin. Psychopharmacol. 36, 637–642. https://doi.org/10.1097/JCP.0000000000000596.
Guilloux, J.-P., Bassi, S., Ding, Y., Walsh, C., Turecki, G., Tseng, G., et al., 2015. Testing the predictive value of peripheral gene expression for nonremission following citalopram treatment for major depression. Neuropsychopharmacology 40, 701–710. https://doi.org/10.1038/npp.2014.226.
Haroon, E., Miller, A.H., 2017. Inflammation effects on brain glutamate in depression: mechanistic considerations and treatment implications. Current topics in behavioral neurosciences 31, 173–198. https://doi.org/10.1007/7854_2016_40.
Hope, S., Dieset, I., Agartz, I., Steen, N.E., Ueland, T., Melle, I., et al., 2011. Affective symptoms are associated with markers of inflammation and immune activation in bipolar disorders but not in schizophrenia. J. Psychiatry Res. 45, 1608–1616. https://doi.org/10.1016/j.jpsychires.2011.08.003.
Huang, M., Panos, J.J., Kwon, S., Oyamada, Y., Rajagopal, L., Meltzer, H.Y., 2014. Comparative effect of lurasidone and blonanserin on cortical glutamate, dopamine, and acetylcholine efflux: role of relative serotonin (5-HT)2A and DA D2 antagonism and 5-HT1A partial agonism. J. Neurochem. 128, 938–949. https://doi.org/10.1111/jnc.12512.
Hung, Y.Y., Lin, C.C., Kang, H.Y., Huang, T.L., 2017. TNFAIP3, a negative regulator of the TLR signaling pathway, is a potential predictive biomarker of response to antidepressant treatment in major depressive disorder. Brain Behav. Immun. 59, 265–272. https://doi.org/10.1016/j.bbi.2016.09.014.
Jamison, K.R., 2000. Suicide and bipolar disorder. J. Clin. Psychiatry 61 (Suppl. 9), 47–51.
Jha, M.K., Minhajuddin, A., Gadad, B.S., Greer, T., Grannemann, B., Soyombo, A., et al., 2017. Can C-reactive protein inform antidepressant medication selection in depressed outpatients? Findings from the CO-MED trial. Psychoneuroendocrinology 78, 105–113. https://doi.org/10.1016/j.psyneuen.2017.01.023.
Judd, L.L., Akiskal, H.S., Schettler, P.J., Endicott, J., Maser, J., Solomon, D.A., et al., 2002. The long-term natural history of the weekly symptomatic status of bipolar I disorder. Arch. Gen. Psychiatry 59, 530–537.
Kitamura, Y., Yagi, T., Kitagawa, K., Shinomiya, K., Kawasaki, H., Asanuma, M., et al., 2010. Effects of bupropion on the forced swim test and release of dopamine in the nucleus accumbens in ACTH-treated rats. Naunyn Schmiedebergs Arch. Pharmacol. 382, 151–158. https://doi.org/10.1007/s00210-010-0521-x.
Kloiber, S., Ising, M., Reppermund, S., Horstmann, S., Dose, T., Majer, M., et al., 2007. Overweight and obesity affect treatment response in major depression. Biol. Psychiatry 62, 321–326. https://doi.org/10.1016/j.biopsych.2006.10.001.
Koo, J.W., Russo, S.J., Ferguson, D., Nestler, E.J., Duman, R.S., 2010. Nuclear factor-kappaB is a critical mediator of stress-impaired neurogenesis and depressive behavior. Proc. Natl. Acad. Sci. U.S.A. 107, 2669–2674. https://doi.org/10.1073/pnas.0910658107.
Leverich, G.S., Altshuler, L.L., Frye, M.A., Suppes, T., Keck, P.E., McElroy, S.L., et al., 2003. Factors associated with suicide attempts in 648 patients with bipolar disorder in the Stanley Foundation Bipolar Network. J. Clin. Psychiatry 64, 506–515.
Li, H., Hong, W., Zhang, C., Wu, Z., Wang, Z., Yuan, C., et al., 2015. IL-23 and TGF-β1 levels as potential predictive biomarkers in treatment of bipolar I disorder with acute manic episode. J. Affect. Disord. 174, 361–366. https://doi.org/10.1016/j.jad.2014.12.033.
Lieberknecht, V., 2017. Antidepressant-like effect of pramipexole in an inflammatory model of depression. Behav. Brain Res. 320, 365–373. https://doi.org/10.1016/j.bbr.2016.11.007. Epub 2016 Nov 5.
Loebel, A., Cucchiaro, J., Silva, R., Kroger, H., Hsu, J., Sarma, K., et al., 2014. Lurasidone monotherapy in the treatment of bipolar I depression: a randomized, double-blind, placebo-controlled study. Am. J. Psychiatry 171, 160–168. https://doi.org/10.1176/appi.ajp.2013.13070984.
Maharshak, N., Arbel, Y., Gal-Oz, A., Rogowski, O., Shapira, I., Berliner, S., et al., 2008. Comparative analysis of Bayer wide-range C-reactive protein (wr-CRP) and the Dade-Behring high sensitivity C-reactive protein (hs-CRP) in patients with inflammatory bowel disease. J. Dig. Dis. 9, 140–143.
Martin, D.J., Garske, J.P., Davis, M.K., 2000. Relation of the therapeutic alliance with outcome and other variables: a meta-analytic review. J. Consult. Clin. Psychol. 68, 438–450.
McDade, T.W., Tallman, P.S., Madimenos, F.C., Liebert, M.A., Cepon, T.J., Sugiyama, L.S., et al., 2012. Analysis of variability of high sensitivity C-reactive protein in lowland Ecuador reveals no evidence of chronic low-grade inflammation. Am. J. Hum. Biol. 24, 675–681. https://doi.org/10.1002/ajhb.22296.
Miller, B.J., Buckley, P., Seabolt, W., Mellor, A., Kirkpatrick, B., 2011. Meta-analysis of cytokine alterations in schizophrenia: clinical status and antipsychotic effects. Biol. Psychiatry 70, 663–671. https://doi.org/10.1016/j.biopsych.2011.04.013.
Munkholm, K., Weikop, P., Kessing, L.V., Vinberg, M., 2015. Elevated levels of IL-6 and IL-18 in manic and hypomanic states in rapid cycling bipolar disorder patients. Brain Behav. Immun. 43, 205–213. https://doi.org/10.1016/j.bbi.2014.09.021.
O'Connor, M.-F., Bower, J.E., Cho, H.J., Creswell, J.D., Dimitrov, S., Hamby, M.E., et al., 2009. To assess, to control, to exclude: effects of biobehavioral factors on circulating inflammatory markers. Brain Behav. Immun. 23, 887–897. https://doi.org/10.1016/j.bbi.2009.04.005.
Ong, K.L., Allison, M.A., Cheung, B.M.Y., Wu, B.J., Barter, P.J., Rye, K.A., 2013. Trends in C-reactive protein levels in US adults from 1999 to 2010. Am. J. Epidemiol. 177, 1430–1442. https://doi.org/10.1093/aje/kws443.
Parker, G., McCraw, S., Hadzi-Pavlovic, D., Fletcher, K., 2013. Costs of the principal mood disorders: a study of comparative direct and indirect costs incurred by those with bipolar I, bipolar II and unipolar disorders. J. Affect. Disord. 149, 46–55. https://doi.org/10.1016/j.jad.2012.10.002.
Pettai, K., Milani, L., Tammiste, A., Võsa, U., Kolde, R., Eller, T., et al., 2016. Whole-genome expression analysis reveals genes associated with treatment response to escitalopram in major depression. Eur. Neuropsychopharmacol. 26, 1475–1483. https://doi.org/10.1016/j.euroneuro.2016.06.007.
Powell, T.R., Schalkwyk, L.C., Heffernan, A.L., Breen, G., Lawrence, T., Price, T., et al., 2013. Tumor necrosis factor and its targets in the inflammatory cytokine pathway are identified as putative transcriptomic biomarkers for escitalopram response. Eur. Neuropsychopharmacol. 23, 1105–1114. https://doi.org/10.1016/j.euroneuro.2012.09.009.
Raison, C.L., Rutherford, R.E., Woolwine, B.J., Shuo, C., Schettler, P., Drake, D.F., et al., 2013. A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers. JAMA Psychiatry 70, 31–41. https://doi.org/10.1001/2013.jamapsychiatry.4.
Rapaport, M.H., Nierenberg, A.A., Schettler, P.J., Kinkead, B., Cardoos, A., Walker, R., et al., 2016. Inflammation as a predictive biomarker for response to omega-3 fatty acids in major depressive disorder: a proof-of-concept study. Mol. Psychiatry 21, 71–79. https://doi.org/10.1038/mp.2015.22.
Ridker, P.M., 2003. Clinical application of C-reactive protein for cardiovascular disease detection and prevention. Circulation 107, 363–369.
Romeo, B., Choucha, W., Fossati, P., Rotge, J.Y., 2017. Clinical and biological predictors of ketamine response in treatment-resistant major depression: review. Encephale 43, 354–362.
Shelton, R.C., Manning, S.J., Barrentine, L.W., Tipa, E.V., 2013. Assessing effects of l-Methylfolate in depression management: results of a real-world patient experience trial. Prim Care Companion CNS Disord. 15. https://doi.org/10.4088/PCC.13m01520.
Sidor, M.M., Macqueen, G.M., 2011. Antidepressants for the acute treatment of bipolar depression: a systematic review and meta-analysis. J. Clin. Psychiatry 72, 156–167. https://doi.org/10.4088/JCP.09r05385gre.
Sienaert, P., Lambrichts, L., Dols, A., De Fruyt, J., 2013. Evidence-based treatment strategies for treatment-resistant bipolar depression: a systematic review. Bipolar Disord. 15, 61–69. https://doi.org/10.1111/bdi.12026.
Tourjman, V., Kouassi, É., Koué, M.-È., Rocchetti, M., Fortin-Fournier, S., Fusar-Poli, P., et al., 2013. Antipsychotics' effects on blood levels of cytokines in schizophrenia: a meta-analysis. Schizophr. Res. 151, 43–47. https://doi.org/10.1016/j.schres.2013,10.011.
Turner, E.H., Matthews, A.M., Linardatos, E., Tell, R.A., Rosenthal, R., 2008. Selective publication of antidepressant trials and its influence on apparent efficacy. N. Engl. J. Med. 358, 252–260. https://doi.org/10.1056/NEJMsa065779.
Uher, R., Tansey, K.E., Dew, T., Maier, W., Mors, O., Hauser, J., et al., 2014. An inflammatory biomarker as a differential predictor of outcome of depression treatment with escitalopram and nortriptyline. Am. J. Psychiatry 171, 1278–1286. https://doi.org/10.1176/appi.ajp.2014.14010094.
Walker, A.K., Budac, D.P., Bisulco, S., Lee, A.W., Smith, R.A., Beenders, B., et al., 2013. NMDA receptor blockade by ketamine abrogates lipopolysaccharide-induced depressive-like behavior in C57BL/6J mice. Neuropsychopharmacology 38, 1609–1616. https://doi.org/10.1038/npp.2013.71.
Yang, J.J., Wang, N., Yang, C., Shi, J.Y., Yu, H.Y., Hashimoto, K., 2015. Serum interleukin-6 is a predictive biomarker for ketamine's antidepressant effect in treatment-resistant patients with major depression. Biol. Psychiatry 1 (77), e19–e20.