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C-reactive protein and response to lurasidone treatment in children and adolescents with bipolar I depression: Results from a placebo-controlled trial

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A B S T R A C T

This study sought to investigate associations between levels of high-sensitivity c-reactive protein (hsCRP) prior to treatment and change in depressive symptoms and cognition in a short-term, double-blind, placebo-controlled study of lurasidone in children and adolescents with bipolar I depression. Patients 10–17 years of age with a DSM-5 diagnosis of bipolar I depression were randomized to 6 weeks of double-blind treatment with flexibly dosed lurasidone (20–80 mg/day) (n = 173) or placebo (n = 170). The primary efficacy measure was change from baseline to week 6 in the Children's Depression Rating Scale, Revised (CDRS-R). Treatment response was defined as 50% or greater improvement on the CDRS-R from baseline to week 6. Cognitive function was evaluated with the computerized Brief Cogstate Battery at baseline and week 6. Analyses were adjusted for baseline BMI, as well as age. HsCRP was evaluated as a logarithmically transformed continuous variable and as a categorical variable dichotomized into lower (< 1 mg/L) and higher (≥1 mg/L) subgroups. A significant interaction was found between baseline hsCRP and treatment group for change in CDRS-R score at study endpoint, with larger placebo-corrected effect sizes for lurasidone in the higher baseline hsCRP group (≥1 mg/L). A significant BMI-by-hsCRP-by-treatment interaction was found for response rate with higher baseline hsCRP levels associated with greater antidepressant response to lurasidone (vs. placebo) in the normal BMI range subgroup (NNT = 2 in higher hsCRP vs. NNT = 5 in lower hsCRP groups) but not in the overweight/obese patients (NNT = 6 in higher hsCRP vs. NNT = 5 in lower hsCRP). Similarly, a significant interaction effect was observed for the combination of hsCRP and BMI on the procognitive effect of lurasidone, with higher baseline hsCRP levels being associated with improvement in cognitive function for lurasidone (vs placebo) in the normal BMI range subgroup but not in overweight/obese patients. These results suggest that young patients with bipolar depression with normal weight and higher levels of pre-treatment CRP may show a greater placebo-adjusted improvement in depressive symptoms and cognitive performance when treated with lurasidone. If these findings are confirmed in future prospective studies, CRP and BMI may prove to be useful diagnostic and predictive biomarkers in the treatment with lurasidone of children and adolescents with bipolar depression.

1. Introduction

Pediatric bipolar disorder is a prevalent condition with significant negative implications for public health. Approximately 14% to 28% of patients with bipolar disorder experience an onset of illness before age 13, and 50% to 67% experience an onset before age 19 (Leverich et al., 2007). An earlier age of onset has been associated with features that contribute to a more severe and impairing course of illness, including faster cycling, more days depressed, greater frequency of lifetime manic and depressive episodes, increased risk of substance abuse and other comorbidities, as well as a higher lifetime risk of suicide attempts (Leverich et al., 2007).

C-reactive protein (CRP) is an acute phase reactant that is a non-specific, but sensitive, marker of systemic inflammation. The role of inflammation in adult mood disorders has been examined more extensively in unipolar depression than in bipolar disorder; however significant data indicate that changes in immune function are at least as common in bipolar as in unipolar conditions, and that both manic and depressive phases of the illness are characterized by increased inflammation (Dargél et al., 2015; Hope et al., 2011; Munkholm et al., 2015; Cattaneo et al., 2013; Powell et al., 2013; Misiak et al., 2018). There is, however, far less evidence in relation to the impact of inflammation in pediatric bipolar disorder, and the data are mixed. Indeed, a recent review of eight cross-sectional studies (N ranged from 10 to 231 per study) and one longitudinal study (N = 47) found insufficient evidence to confirm causal relationships between alterations of inflammatory markers and bipolar disorder in young adult patients (minimum age ranged from 7 to 18 years old) (Serra et al., 2015).

In a short-term clinical trial of adults with bipolar depression randomized to receive flexibly dosed lurasidone (20–120 mg/d) or placebo, lurasidone-treated patients with high baseline CRP levels demonstrated a larger treatment effect compared to patients with lower

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baseline CRP levels (Raison et al., 2018). The current analysis explores whether similar associations pertain between pre-treatment CRP and lurasidone efficacy in pediatric bipolar depression, using a placebo-controlled randomized clinical trial that demonstrated efficacy for lurasidone in the treatment of children and adolescents with bipolar depression (DelBello et al., 2017). In addition to examining associations between pre-treatment high-sensitivity CRP (hsCRP) and antidepressant efficacy, the current study also examines whether baseline levels of CRP were associated with the impact of lurasidone vs. placebo on cognition.

2. Material and methods

2.1. Participants and study design

As previously reported, patients 10 to 17 years of age with bipolar I depression were randomized to 6 weeks of double-blind treatment with once-daily, flexibly dosed lurasidone (20–80 mg) or placebo (DelBello et al., 2017). Study participants were required to meet DSM-5 criteria for diagnosis of bipolar I disorder; with the most recent episode being depressed without psychotic features, with or without rapid cycling (≥4 episodes of mood disturbance but < 8 episodes in the previous 12 months). Diagnosis was confirmed with the Schedule for Affective Disorders and Schizophrenia for School-age Children-Present and Lifetime (K-SADS-PL). Participants were required to have a Children's Depression Rating Scale, Revised (CDRS-R) total score ≥ 45 and ≤ 85 at screening and baseline, as well as Young Mania Rating Scale (YMRS) score ≤ 15 (with YMRS Item 1 [elevated mood] score ≤ 2) at screening and baseline. Potential subjects were excluded for any clinically significant neurologic, endocrine, or other significant medical disorders.

The primary efficacy outcome measure was change from baseline to week 6 in the CDRS-R. Clinical response was defined as 50% or greater improvement on the CDRS-R from baseline to week 6. Cognitive function was evaluated as a secondary outcome measure using the computerized Brief Cogstate Battery at baseline and week 6 (Maruff et al., 2009). A standardized composite score was calculated as the mean of the standardized scores of 4 individually administered tests in 4 MATRICS cognitive domains, i.e., psychomotor speed, attention, learning/memory, and working memory. If two or more domain test scores were missing at a visit, the composite score was considered missing. A hsCRP assay was used to assess levels of systemic inflammation.

2.2. Statistical analysis

The analysis population included all randomized subjects who received at least one dose of study medication and had at least one post-baseline assessment for any efficacy variable. Based on prior studies examining associations between CRP and treatment response, hsCRP was evaluated as both a logarithmically transformed continuous variable and as a categorical variable dichotomized into lower (< 1 mg/L) and higher (≥1 mg/L) subgroups (Jha et al., 2017; Raison et al., 2018). Multiple regression analysis was performed to examine cross-sectional associations between log-transformed hsCRP, body weight, BMI, CDRS-R score and cognitive composite score at study baseline. To evaluate whether hsCRP level at study baseline moderated therapeutic responses to lurasidone at week 6, statistical interaction tests were applied for treatment-by-hsCRP and/or treatment-by-hsCRP-by-BMI based on ANCOVA and Mixed Model for Repeated Measures (MMRM), adjusted for baseline BMI, age and age strata (10 to 14 years or 15 to 17 years at screening), gender and study sites (country). Percentiles for BMI categories were derived based on the WHO 2007 growth reference for 5 to 19 years old.

Table 1
Demographic and Clinical Characteristics of the Study Sample.

Characteristic	Lurasidone 20–80 mg/d (N = 173)	Placebo (N = 170)
Male, n (%)	88 (50.9%)	87 (51.2%)
Age, years, mean + SE	14.17 ± 0.17	14.25 ± 0.16
Race, %		
White	134 (77.5%)	125 (73.5%)
Black/African American	15 (8.7%)	18 (10.6%)
Other	24 (13.9%)	27 (15.9%)
Baseline Scores, mean + SE		
CDRS-R Total Score	59.23 ± 0.63	58.59 ± 0.63
CGI-BP-S Depression Score	4.58 ± 0.05	4.48 ± 0.04
Young Mania Rating Scale	5.49 ± 0.29	5.06 ± 0.25
Cognitive Composite Standardized Score	−0.79 ± 0.10	−1.05 ± 0.11
hsCRP, mean ± SE, mg/L	1.49 ± 0.27	1.03 ± 0.23
hsCRP ≥ 1 mg/L, n (%)	50 (29.8%)	37 (22.2%)
BMI, mean	21.5 ± 0.26	21.5 ± 0.27

Children's Depression Rating Scale, Revised (CDRS-R); CGI-BP-S depression severity, Clinical Global Impression Bipolar Version, Severity of Illness (CGI–BP-S) score (depression); high-sensitivity c-reactive protein (hsCRP); BMI, body mass index; SE, standard error.

3. Results

3.1. Baseline characteristics

Baseline demographic and clinical characteristics of the lurasidone and placebo treatment groups are shown in Table 1. Eighty-seven participants (26.0%) had a baseline hsCRP serum concentration ≥ 1 mg/L, and 118 (36.2%) were obese/overweight, with no significant difference between the treatment groups on either hsCRP or BMI at study baseline. At baseline, overweight and obese range BMI was significantly associated with higher hsCRP ($p < 0.001$, $F = 30.43$, $df = 1, 306$) and CDRS-R total score ($p = 0.013$, $F = 6.26$, $df = 1, 314$), but not with cognitive composite score. There was a significant positive association between age and log-hsCRP at baseline ($r = 0.19$, $p < 0.001$). Associations between hsCRP, CDRS-R and cognitive performance were not significant at study baseline. Lurasidone was initiated at a daily dose of 20 mg for seven days, with flexible dosing in the range of 20 to 80 mg/day permitted after seven days, based on blinded clinical judgment and clinical response. The modal daily dose of lurasidone during the double-blind study period was 20 mg in 52.3% of patients, 40 mg in 26.2% of patients, 60 mg in 12.8% of patients, and 80 mg in 8.7% of patients. Based on the modal dose, there was no significant dose effect on change in CDRS-R score ($p = 0.2156$, change in CDRS score: −20 for 20 mg/d; –23.5 for 40 mg/d; −24.7 for 60 mg/d, and −18.8 for 80 mg/d). Of the 347 subjects who received study drug (lurasidone or placebo), 177 (51.0%) received one or more concomitant medications during the study. There were 39 (11.2%) subjects who received benzodiazepines. The most commonly reported concomitant medications by preferred name were ibuprofen (9.8%), paracetamol (9.8%), lorazepam (8.9%), and melatonin (6.1%). No other concomitant medications were used by ≥ 5% of subjects overall.

3.2. Associations of pre-treatment hsCRP, BMI and depressive symptom improvement

A significant interaction was found between baseline stratified hsCRP and treatment group for change in CDRS-R score between baseline and study endpoint, with lurasidone demonstrating a larger placebo-corrected effect size in the higher baseline hsCRP group (≥1 mg/L) than in participants with baseline hsCRP < 1 mg/L ($p = 0.017$, $F = 5.73$, $df = 1, 302$) (Fig. 1). The interaction effect between log transformed hsCRP and lurasidone was non-significant ($p = 0.212$, $F = 1.57$, $df = 1, 302$). Baseline hsCRP did not moderate the effect of

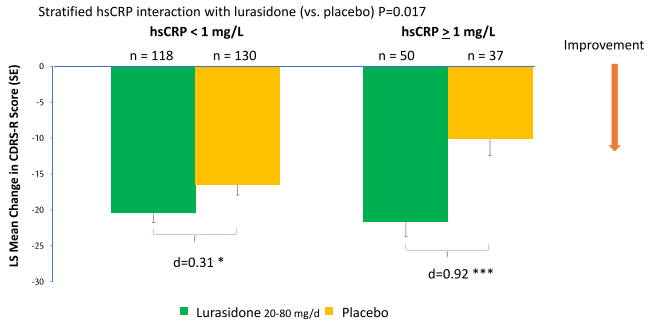

Fig. 1. Baseline C-Reactive Protein Level and Week 6 Change in CDRS-R Score Associated with Lurasidone (vs. Placebo). P-values were estimated based on ANCOVA model adjusted for baseline CDRS-R score, baseline BMI, age, gender and study sites (country) in the analyses: P = 0.017 for stratified hsCRP interaction with lurasidone (vs. placebo). *** P < 0.001, * P < 0.05.

treatment group on clinical response (defined as a 50% or greater reduction in CDRS score). Similarly, baseline BMI did not moderate the effect of treatment group on either clinical response or change in CDRS-R score.

Although neither stratified hsCRP nor BMI predicted clinical response, a significant interaction was observed between pre-treatment BMI, stratified baseline hsCRP and treatment group for clinical response (p = 0.043, chi-square = 4.080). Increased hsCRP (≥1 mg/L) was associated with an enhanced clinical response to lurasidone compared to placebo in participants with normal BMI (NNT = 2 for hsCRP ≥ 1 mg/L vs. NNT = 5 for hsCRP < 1 mg/L, p = 0.003 for treatment-by-hsCRP interaction effect, chi-square = 0.886), but not in overweight/obese participants (NNT = 6 for hsCRP ≥ 1 mg/L vs. NNT = 5 for CRP < 1 mg/L, p = 0.785 for treatment-by-hsCRP interaction effect, chi-square = 0.075) (Fig. 2). Similar interactions were observed between BMI, stratified baseline hsCRP and treatment group for placebo-corrected change in CDRS-R score (normal weight participants: *d* = 1.2 for hsCRP ≥ 1 mg/L vs. *d* = 0.4 for hsCRP < 1 mg/L, p = 0.038 for treatment-by-hsCRP interaction effect, F = 4.32, df = 1, 299; overweight/obese participants: d = 0.75 for hsCRP ≥ 1 mg/L vs. d = 0.12 for hsCRP < 1 mg/L, p = 0.105 for treatment-by-hsCRP interaction effect, F = 2.64, df = 1, 299).

Among normal weight patients in the placebo group, lower levels of pre-treatment hsCRP were associated with a larger clinical response (p = 0.010, chi-square = 6.64) and a greater mean improvement in CDRS-R score (p = 0.017, F = 5.75, df = 1, 299). Among normal weight patients in the lurasidone group, no significant associations were found between pre-treatment hsCRP and either clinical response (p = 0.196, chi-square = 1.673) or with mean improvement in CDRS-R score (p = 0.323, F = 0.98, df = 1, 299). On the other hand, among overweight/obese patients in either the lurasidone or placebo groups, no associations were observed between pre-treatment hsCRP and either clinical response (p = 0.816, chi-square = 0.054 for lurasidone; p = 0.239, chi-square = 1.385 for placebo) or mean change in CDRS-R score (p = 0.392, F = 0.73, df = 1, 299 for lurasidone; p = 0.550, F = 0.36, df = 1, 299 for placebo). Furthermore, age-hsCRP interaction with lurasidone effect (vs. placebo) on clinical response was non-significant (p = 0.6867, chi-square = 0.1626).

3.3. Association between pre-treatment hsCRP, BMI and change in cognitive function

Neither log transformed nor stratified baseline hsCRP was associated with change in any cognitive function measure in response to treatment. On the other hand, a significant interaction was observed between baseline BMI and improvement in cognitive composite score with lurasidone treatment when compared to placebo (p = 0.03, F = 4.69, df = 1, 310), with greater lurasidone effect size (placebo-corrected) for improvement of cognitive composite score (effect size = 0.50, t = 2.99, df = 101, p = 0.009) and psychomotor score (effect size = 0.50, t = 2.62, df = 300, p = 0.009) in overweight/obese participants. Moreover, significant interactions were observed between treatment group, baseline BMI, and baseline log-hsCRP on change in the composite score (p = 0.014, F = 6.15, df = 1, 298) (Fig. 3). Significant interactions were also observed between treatment group, baseline BMI, and baseline log-hsCRP for the psychomotor speed task score (p = 0.029, F = 4.85, df = 1, 297). In the normal/underweight subgroup, increasing baseline hsCRP levels were associated with improvement in cognitive composite (p = 0.039, F = 4.29, df = 1, 298 for log-hsCRP interaction with treatment) and working memory domain scores (p = 0.042, F = 4.18, df = 1, 299 for log-hsCRP interaction with treatment) for lurasidone treated patients compared to those treated with placebo (p < 0.05, for log-hsCRP interaction with treatment). No interactions were observed between stratified hsCRP, BMI and treatment for any of the cognitive measures. No interaction was observed between age and hsCRP for lurasidone effect on improvement of cognitive composite score (p = 0.1742, F = 1.86, df = 1, 292).

Finally, when compared to placebo, treatment with lurasidone had no effect on plasma concentrations of hsCRP.

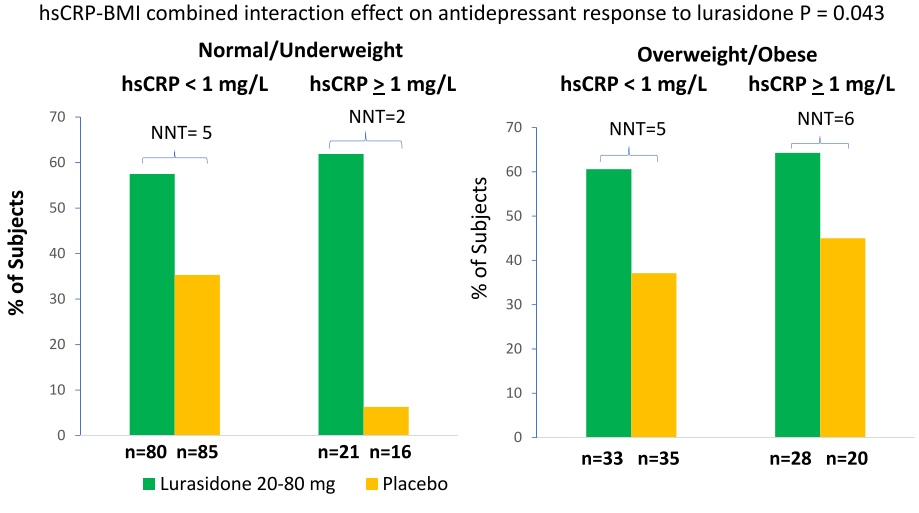

Fig. 2. Baseline C-Reactive Protein Level Combined with BMI and Week 6 Response Rate Associated with Lurasidone (vs. Placebo). P-values were estimated based on logistic regression model adjusted for baseline CDRS-R score, baseline BMI, age, gender and study sites (country) in the analyses: P = 0.043 for hsCRP and BMI combined interaction effect on antidepressant response to lurasidone (vs. placebo) treatment.

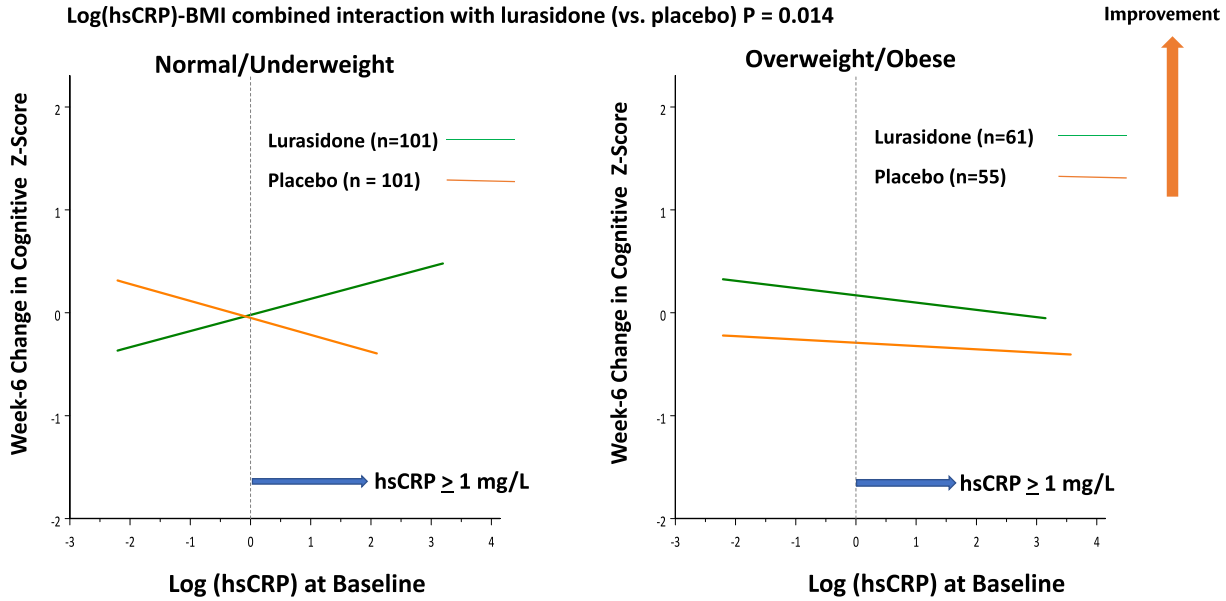

Fig. 3. Baseline C-Reactive Protein Level Combined with BMI and Week 6 Change in Cognitive Performance Associated with Lurasidone (vs. Placebo). P-values were estimated based on ANCOVA model adjusted for baseline cognitive score, baseline BMI, age, gender and study sites (country) in the analyses: P = 0.014 for the log-transformed hsCRP) and BMI combined interaction with lurasidone (vs. placebo).

4. Discussion

The role of inflammation in the pathogenesis and treatment of mood disorders has been in the focus of attention of numerous studies over last decade (Bauer and Teixeira, 2019; Jha and Trivedi, 2018; Slavich and Irwin, 2014; Miller and Raison, 2016; Enache et al., 2019). However, a limited number of studies have examined the role of inflammation in pediatric depression in general, and in pediatric bipolar disorder in particular (Peters et al., 2019). Indeed, to the best of our knowledge, this post hoc analysis of a randomized, placebo-controlled trial of lurasidone is the first study to examine the potential utility of an inflammatory biomarker for guiding pharmacologic treatment in children and adolescents with a mood. Consistent with findings in adult patients with mood disorders, we found that pre-treatment hsCRP was associated with clinical outcomes in the study population. Specifically, increasing levels of hsCRP at baseline predicted an increased antidepressant response to lurasidone when compared to placebo. These findings add to a growing database indicating that—as in adults—increased inflammatory biomarkers in children and adolescents may identify a clinically meaningful subgroup of mood disorder patients, with symptom trajectories and—based on the current study—responses to treatment that differ from patients with lower levels of inflammation.

Results from the current study are both consistent with, and differ, from a prior study examining the impact of pre-treatment CRP on responses to lurasidone in adults with bipolar I depression (Raison et al., 2018). As in the current report, increasing CRP was associated with an enhanced placebo-adjusted antidepressant response to lurasidone in adult patients. Indeed, lurasidone was indistinguishable from placebo in patients with wide-range (wr)-CRP levels $\leq$ 2 mg/L, whereas the medication demonstrated an increasingly large placebo-adjusted effect size as wr-CRP levels increased (e.g. d = 0.82 for wr-CRP > 5 mg/L). Importantly, this effect reflected the fact that lurasidone became increasingly effective with higher levels of pre-treatment CRP (i.e. based on larger pre-post treatment reductions in CDRS-R score in the lurasidone-treated group). Moreover, although BMI and wr-CRP were highly correlated, the predictive effect of pre-treatment CRP was independent of BMI.

In contrast, in the current study, although lurasidone demonstrated a larger placebo-adjusted effect with higher pre-treatment levels of hsCRP (e.g. d = 0.31 in hsCRP < 1 mg/L vs. d = 0.92 in hsCRP $\geq$ 1 mg/L), lurasidone outperformed placebo regardless of inflammatory status, in terms of both antidepressant and procognitive effects. Moreover, the absolute antidepressant effect of lurasidone (measured as pre-post treatment change) was not significantly impacted by pre-treatment hsCRP. Rather, higher levels of hsCRP were associated with a reduced placebo response. Many factors influence the generation of a placebo response in clinical trials. Classical conditioning and expectancy are two frequently hypothesized neurobiological and psychological mechanisms that contribute to the placebo effect (Dodd et al., 2017). Current results suggest that inflammatory processes may impair the ability to access these types of processes. Convergent data for this possibility come from studies indicating that inflammation alters the processing of clinically-important social information, as evidenced by associations between increased inflammatory biomarkers and reduced responses to psychotherapy (Zahn et al., 2016; Harley et al., 2010), as well as findings that immune activation induces feelings of social isolation (Moieni and Eisenberger, 2018).

Moreover, in this younger population the influence of hsCRP on depressive and cognitive outcomes was not independent of BMI. Interestingly, the association of increased hsCRP with a larger placebo-adjusted benefit of lurasidone treatment was only apparent in normal and underweight participants. As in the sample as a whole, the association of increased hsCRP with a larger placebo-adjusted antidepressant response to lurasidone was accounted for by a marked reduction in the placebo response with increasing levels of hsCRP. On the other hand, in normal/underweight participants, increasing log-hsCRP was associated with greater improvement of cognitive functioning in the lurasidone-treated group, and a reduction in cognitive functioning in participants randomized to placebo.

The reasons for these discrepancies between adult and child/adolescent patients with bipolar I depression are unknown, but several observations warrant consideration. Children/adolescents in the current study had significantly lower levels of CRP and were leaner than adult patients with bipolar I depression in the prior study. This finding is of scientific interest in and of itself, given the paucity of data regarding both the inflammatory status of children/adolescents with bipolar disorder and the course of inflammation in bipolar disorder across the lifespan. Prior studies have suggested that inflammation increases as chronicity increases in mood disorders (Berk et al., 2011; Setiawan et al., 2018). Whether findings in children/adolescents vs. adults reflect

a similar process in bipolar disorder or are better explained by normative changes with age cannot be answered by the current data. In regard to the utility of CRP as a predictive biomarker, several prior studies suggest that the predictive power of CRP may be maximal at higher levels of pre-treatment inflammation than were normative in the current study sample, which may account—at least in part—for why pre-treatment CRP was less predictive of lurasidone response in the current study than in the prior trial of adults with bipolar depression (Raison et al., 2013; McFarland et al., 2019).

BMI consistently shows a positive association with circulating levels of CRP (Rethorst et al., 2014). Less consistent, however, are the associations between CRP, BMI and depression, with some studies reporting independent effects of CRP on symptom status or treatment response, while other studies fail to find these effects (Liu et al., 2014; Qin et al., 2017; Haroon et al., 2018; Ambrósio et al., 2018; Delgado et al., 2018; Moraes et al., 2017). The current study is unusual in finding that accounting for BMI actually increased and/or unveiled a direct effect of hsCRP on the placebo-adjusted response to lurasidone on both depressive symptoms and cognition. The reason for this is unknown, but it is intriguing to speculate that whereas hsCRP in overweight/obese children/adolescents may primarily index body mass, in underweight/normal weight individuals increased hsCRP may more directly reflect activation of peripheral immune pathways known to impact both behavior and cognition. The glucose and lipid profiles for the adolescents in the current study were in the normal ranges, and their endpoint changes from baseline were similar for the lurasidone and placebo groups (DelBello et al., 2017). This allows for the detection of significant BMI-dependent effects of hsCRP on treatment response without confounding by the cardiovascular and metabolic co-morbidities.

Rising rates of placebo response over the last several decades have posed a considerable challenge for antidepressant drug discovery (Walsh et al., 2002; Iovieno and Papakostas, 2012; Weimer et al., 2015). Results from the current study add to a growing database indicating that peripheral inflammation, whether indexed by CRP or other immune biomarkers, may be of direct relevance to this problem, given the repeated finding that patients with increased inflammation demonstrate a reduced placebo response (Raison et al., 2013; Raison et al., 2018; Rapaport et al., 2016). Enrolling depressed patients with even mildly elevated levels of CRP may reduce the placebo response and might be especially beneficial for identifying true drug effects when studying medications reported to show enhanced antidepressant efficacy in patients with elevated inflammatory biomarkers (i.e. ketamine, bupropion, nortriptyline, lurasidone, cytokine antagonists) (Rong et al., 2018; Yang et al., 2015; Jha et al., 2017; Uher et al., 2014; Raison et al., 2018, Raison et al., 2013). At the least, including pre-treatment levels of inflammatory biomarkers as co-factors in multivariate analyses may strengthen drug-placebo differences.

The current investigation has several limitations. Our findings are primarily based on an exploratory analysis and the study was not designed to assess the predictive power of either CRP or BMI on treatment response. Further prospective studies are needed to confirm the clinical relevance of CRP combined—or not—with BMI, for identifying subtypes of bipolar depression with different therapeutic responses to atypical antipsychotic treatment. Moreover, because CRP was only evaluated at baseline and week 6 study endpoints, the current study provides no insight into potential associations of treatment responses with early changes in CRP in the course of treatment is unknown.

In summary, findings from this large placebo-controlled study indicate that young patients with bipolar I depression who had normal weight and higher levels of pre-treatment CRP showed an enhanced placebo adjusted improvement in depressive symptoms and cognitive impairment. If these findings are confirmed in future prospective studies, CRP and BMI may prove to be useful diagnostic and predictive biomarkers in the treatment with lurasidone of children and adolescents with bipolar depression.

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Role of the sponsor

This study was sponsored and funded 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 Usona Institute, Emory Healthcare, Sage Pharmaceuticals and North American Center for Continuing Medical Education. Dr. Siu reports having received consulting fees from Sunovion, the Chinese University of Hong Kong, and the Centre for Addiction and Mental Health, Toronto. Drs. Loebel, Pikalov, and Tocco are employees of Sunovion Pharmaceuticals Inc.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2019.12.010.

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