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Association of C-reactive protein and metabolic risk with cognitive effects of lurasidone in patients with schizophrenia

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ABSTRACT

Background: Accumulating evidence has implicated insulin resistance and inflammation in the pathophysiology of cognitive impairments associated with neuropsychiatric disorders. This post-hoc analysis based on a placebo-controlled trial investigated the effect of inflammation (indexed by CRP) and metabolic risk factors on cognitive performance in patients with schizophrenia treated with lurasidone.

Methods: Acutely exacerbated patients with schizophrenia were randomized to lurasidone (80 or 160 mg/day), quetiapine XR 600 mg/day, or placebo. A wide range CRP test and a cognitive assessment using the CogState computerized battery were performed at baseline and week 6 study endpoint. Associations between log-transformed CRP, high density lipoprotein (HDL), homeostatic model assessment of insulin resistance (HOMA-IR) and treatment response were evaluated.

Results: CRP combined with HDL, triglyceride-to-HDL (TG/HDL) ratio, or HOMA-IR at study baseline were significant moderators of the improvement in cognitive performance associated with lurasidone 160 mg/day (vs. placebo) treatment ($p < .05$). Greater placebo-corrected treatment effect size on the CogState composite score was observed for patients in the lurasidone 160 mg/day treatment group who had either low CRP and high HDL ($d = 0.43$), or low CRP and low HOMA-IR ($d = 0.46$). Interactive relationships between CRP, HDL, TG/HDL, HOMA-IR and the antipsychotic efficacy of lurasidone or quetiapine XR were not significant. There were no significant associations between antipsychotic treatment and changes in CRP level at study endpoint.

Conclusions: Findings of this post-hoc analysis based on a placebo-controlled trial in patients with schizophrenia suggest that baseline CRP level combined with measures of metabolic risk significantly moderated the improvement in cognitive performance associated with lurasidone 160 mg/day (vs. placebo) treatment. Our findings underscore the importance of maintaining a low metabolic risk profile in patients with schizophrenia.

1. Introduction

Cognitive impairments in schizophrenia constitute a substantial source of disease burden, disability, and loss of functional capacity [1,2]. The neurobiologic determinants of cognitive deficits in schizophrenia remain poorly understood. There exists a need to find effective treatments targeting cognitive impairment in schizophrenia and associated heterogeneity in treatment outcomes.

Accumulating evidence has implicated metabolic dysfunction, immune abnormalities, and inflammation in the pathophysiology of schizophrenia, mood disorders [3–6], and cognitive deficits in neuropsychiatric disorders [7–14]. Previous studies have found increased inflammatory risk factors in schizophrenia [11,13–18,21–26]. A meta-analysis found significantly higher C-reactive protein (CRP) levels in patients with schizophrenia versus controls [16]. Cytokine alterations have also been associated with acute exacerbation of schizophrenia [11,17,19,20,22], as well as cognitive dysfunction in multiple psychiatric disorders [12,13,27]. While elevated CRP level has been reported to correlate with obesity and a range of comorbidities in schizophrenia, including cardiovascular disease, metabolic syndrome and

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diabetes [28–31], the relationship of CRP level to cognitive impairment in schizophrenia is not well understood.

Identifying potential biomarkers that can predict cognitive responses to treatment in schizophrenia would provide useful insight into neuroimmune interactions in the pathophysiology of cognitive deficits. In this context, we conducted an exploratory analysis of a randomized, placebo and active-controlled trial to determine if pre-treatment levels of CRP and other selected metabolic parameters predicted responses to lurasidone treatment, a second generation antipsychotic with procognitive effects in schizophrenia [2].

2. Materials and methods

2.1. Design

This is a post-hoc analysis of a 6-week, randomized, double-blind study comparing fixed doses of lurasidone 80 mg/day (n = 125), lurasidone 160 mg/day (n = 121) and quetiapine XR 600 mg/day (n = 120) with placebo (n = 122) (clinicaltrials.gov: NCT00790192) [32]. All study treatment was taken once daily during or within 30 min of the evening meal. The quetiapine XR dose utilized in this study (600 mg/d) fell within the middle of the recommended therapeutic dose range (400 to 800 mg/day) [32]. The analysis population included hospitalized patients age 18–75 with a primary diagnosis of DSM-IV schizophrenia and an illness duration of greater than 1 year. Other inclusion criteria were the presence of a CGI-S score ≥4, a PANSS total score ≥80, and at least two of the following PANSS items rated ≥4 (moderate): hallucinations, delusions, conceptual disorganization, unusual thought content, and suspiciousness at screening and baseline.

2.2. Assessment of CRP and other metabolic parameters

Fasting plasma concentrations of wide range (wr)-CRP were measured in the morning (no food after midnight) at baseline and week 6 study endpoint. The correlation between the wr-CRP assay used in this study and the high-sensitivity (hs) CRP assay is 0.99, showing almost perfect agreement [4,33]. The limit of detection for the wr-CRP assay was 0.12 mg/L, compared to 0.16 mg/L for the hs-CRP assay. Logarithm-transformed values of CRP were analyzed because of the skewed distribution of continuous CRP data [4,5,34]. Stratified CRP was also analyzed using cut-off values suggested in previous studies [4,5,35]. We defined ≤2 mg/L as low CRP group and >2 mg/L as high CRP group.

Other metabolic parameters examined in this analysis included triglycerides (TG), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), total cholesterol, the homeostatic model assessment of insulin resistance (HOMA-IR) [36], and the triglyceride-to-high-density lipoprotein-cholesterol (TG/HDL) ratio. We defined <36 mg/dL as low HDL group and ≥36 mg/dL as high HDL group. Further, we defined ≤3.5 as low HOMA-IR group and >3.5 as high HOMA-IR group [37].

2.3. Statistical methods

The primary objective of this analysis was to evaluate CRP levels combined with other metabolic risk factors at study baseline as moderators of treatment effect (vs. placebo) on cognitive performance in schizophrenia. Analysis was based on the intent-to-treat (ITT) population from a previously reported randomized, double-blind, placebo-controlled trial of lurasidone in patients with schizophrenia [2,32].

Cognitive performance was assessed using the CogState computerized cognitive battery at baseline and week 6 study endpoints [38]. The intent-to-treat analysis was based on a rank transformed CogState cognitive composite and domain task scores, in which early dropouts and/or missing cognitive test scores were imputed with 0, the lowest possible rank. Standard averaging method was used to correct for tied rank values. We applied rank ANCOVA method and a bootstrap sampling-resampling procedure with 3000 replicates to the rank transformed test scores [39,40]. A 95% bootstrap confidence interval was used to test the significance of treatment by CRP-metabolic interaction effects in the rank ANCOVA model. Age, sex, BMI, smoking status, and study site (country regions) were assessed as potential confounders by including these variables as covariates in the ANCOVA analysis. Adjustment for multiple comparisons was not performed due to the exploratory nature of these analyses.

3. Results

3.1. Baseline characteristics

The demographic and clinical characteristics were comparable between the treatment and placebo groups at baseline (Table 1). There were 191 (40%) patients with CRP ≤2 mg/L. An elevated log-transformed CRP was associated with lower HDL ($p < .001$) Supplementary Figure S4, higher TG/HDL-C ($p = .008$), higher BMI ($p < .001$) Supplemetary Figure S3, higher HbA1c ($p < .001$), and higher HOMA-IR ($p < .013$) at study baseline. Age, sex, smoking status and sites (country region) were included as covariates and accounted for in all analyses.

Elevated log-transformed CRP at baseline was associated with greater cognitive impairment (lower ranked CogState cognitive composite score, ANCOVA bootstrap confidence interval [−30.28, −9.27], n = 477, $p < .05$; ANCOVA Generalized Linear Model, n = 477, $p < .001$, $t = -3.58$, df = 467) (Fig. 1). All cognitive tasks showed significant cross-sectional associations with CRP at baseline (ANCOVA bootstrap confidence interval. $p < .05$) Supplementary Fig. S1, with higher CRP level associated with lower performance across cognitive domains.

We found a significant association between log-transformed CRP and PANSS total score at study baseline, with higher CRP level in patients with greater symptom severity (ANCOVA, Student's *t*-test, n = 477, $t = 3.54$, df = 467, $p < .001$) at study baseline Supplementary Figure S2. Higher CRP level was also associated with higher PANSS positive (ANCOVA, Student's t-test, n = 477, $t = 2.39$, df = 467, $p = .017$) and negative subscale scores (ANCOVA, Student's *t*-test, n = 477, $t = 2.29$, df = 467, $p = .023$) but not PANSS excitement component (ANCOVA, Student's t-test, n = 477, $t = 1.55$, df = 467, $p = .123$) at study baseline.

3.2. Pre-treatment CRP and cognitive efficacy

In a bootstrap analysis of the full sample (N = 482), the week 6 change from baseline in rank order of CogState cognitive composite score (RANKCOG) was significantly greater (i.e. improved) in the lurasidone 160 mg/day group versus placebo (ANCOVA bootstrap confidence interval [0.16, 53.98], n = 482, $p < .05$ adjusted for baseline RANKCOG and study sites; ANCOVA, Student's *t*-test, n = 482, $t = 2.04$, df = 439, $p = .042$)(Fig. 2). The treatment effect (vs. placebo) on change in rank cognitive composite score was non-significant for the lurasidone 80 mg/day group (ANCOVA bootstrap confidence interval [−3.26, 47.01], n = 482, $p > .05$ adjusted for baseline RANKCOG and study sites; ANCOVA, Student's *t*-test, n = 482, $t = 1.74$, df = 439, $p = .083$), as well as the quetiapine XR 600 mg/day group (ANCOVA bootstrap confidence interval [−4.69, 43.59], n = 482, $p > .05$ adjusted for baseline RANKCOG and study sites; ANCOVA, Student's *t*-test, n = 482, $t = 1.44$, df = 439, $p = .150$).

CRP combined with HDL level at study baseline was found to moderate the cognitive improvement associated with lurasidone 160 mg/day (vs. placebo) treatment (ANCOVA bootstrap confidence interval [−163.13, −25.53] for LOGCRP-LOGHDL interaction with lurasidone 160 mg/day vs. placebo effect, n = 462, $p < .05$ adjusted for baseline

Table 1
Demographic and baseline characteristics.

	Lurasidone 80 mg/d, N = 125	Lurasidone 160 mg/d, N = 121	Quetiapine XR 600 mg/d, N = 116	Placebo N = 120	P-value
Age, mean ± SE	36.3 ± 1.0	37.9 ± 1.0	37.4 ± 1.0	37.3 ± 1.0	0.64
Gender					
Female	29 (23.2%)	39 (32.2%)	41 (35.3%)	44 (36.7%)	0.10††
Male	96 (76.8%)	82 (67.8%)	75 (64.7%)	76 (63.3%)	
Smoking status, n (%)	80 (64.0%)	70 (57.9%)	64 (55.2%)	63 (52.5%)	0.30
BMI, mean ± SE, kg/m^2	25.8 ± 0.4	25.6 ± 0.4	25.6 ± 0.5	26.0 ± 0.4	0.88
Wr-CRP, mean ± SE, mg/L	3.8 ± 0.4	4.4 ± 0.6	4.2 ± 0.8	2.6 ± 0.3	0.02
Median (IQR)	3.0 (1.0, 3.8)	3.0 (1.0, 4.3)	3.0 (1.0, 3.1)	2.3 (1.0, 3.0)	
≤2 mg/L, n (%)	43 (35.3%)	47 (38.8%)	43 (37.4%)	58 (48.7%)	0.16††
2.1–5 mg/L, n (%)	57 (46.7%)	47 (38.8%)	53 (46.1%)	48 (40.3%)	
>5 mg/L, n (%)	22 (18.0%)	27(22.3%)	19 (16.5%)	13 (10.9%)	
HDL, Mean ± SE, mg/L	45.7 ± 1.0	46.3 ± 1.3	43.5 ± 1.0	46.2 ± 1.3	0.36
Median (IQR)	43.0 (39.0, 52.0)	43.5 (36.5, 54.0)	43.0 (37.0, 50.0)	43.0 (38.0, 52.0)	
HOMA-IR, mean ± SE	3.6 ± 0.4	3.6 ± 0.5	3.3 ± 0.3	3.5 ± 0.5	0.99†
Median (IQR)	2.0 (1.1, 3.9)	1.9 (1.2, 3.7)	1.9 (1.3, 3.4)	1.9 (1.2, 3.8)	
PANSS, mean ± SE	97.6 ± 0.9	97.5 ± 1.1	97.5 ± 0.9	96.6 ± 0.9	0.88

IQR = Interquartile Range.
p-value (treatment group comparison).
† Analysis of covariance on log-transformed parameter values adjusted for sites (country region).
†† Chi-square test.

RANKCOG, age, gender, smoking status and sites (country region)) (Fig. 3). CRP combined with TG/HDL ratio at study baseline was also found to moderate the cognitive improvement associated with lurasidone 160 mg/day (vs. placebo) treatment (LOGCRP-LOGTG/HDL interaction with lurasidone 160 mg/day vs. placebo effect, n = 462, $p < .05$) Supplementary Figure S5. In addition, CRP combined with HOMA-IR level at study baseline was found to moderate the cognitive improvement associated with lurasidone 160 mg/day (vs. placebo) treatment (ANCOVA bootstrap confidence interval [1.19, 68.52] for LOGCRP-LOGHOMAIR interaction with lurasidone 160 mg/day vs. placebo, n = 458, $p < .05$) (Fig. 4). Statistical treatment interaction with either CRP and HDL, CRP and TG/HDL, or CRP and HOMA-IR was not significant for lurasidone 80 mg/day (vs. placebo) or quetiapine XR 600 mg/day (vs. placebo) with regard to the improvement in cognitive performance at week 6.

When patients were stratified based on the cut-offs of pre-treatment CRP and HDL, the placebo-corrected effect size (Cohen's d = 0.43 at week 6) for improving the cognitive composite score with lurasidone 160 mg/day treatment was greatest in patients with lower CRP (≤2 mg/L) and higher HDL (≥36 mg/dL) at study baseline Fig. 3. Likewise, the placebo-corrected effect size (Cohen's d = 0.46 at week 6) for improving the cognitive composite score with lurasidone 160 mg/day treatment was greatest in patients with lower CRP (≤2 mg/L) and lower HOMA-IR level (≤3.5) at study baseline Fig. 4.

When pre-treatment CRP level and other baseline inflammatory risk factors (BMI, HDL, TG, LDL, total cholesterol concentration, and HOMA-IR) were examined *individually* in the analysis, they showed no significant moderating effects on the cognitive response to lurasidone (80 and 160 mg/day) or quetiapine XR 600 mg/day treatment. CRP, HDL and HOMA-IR did not moderate the effect of

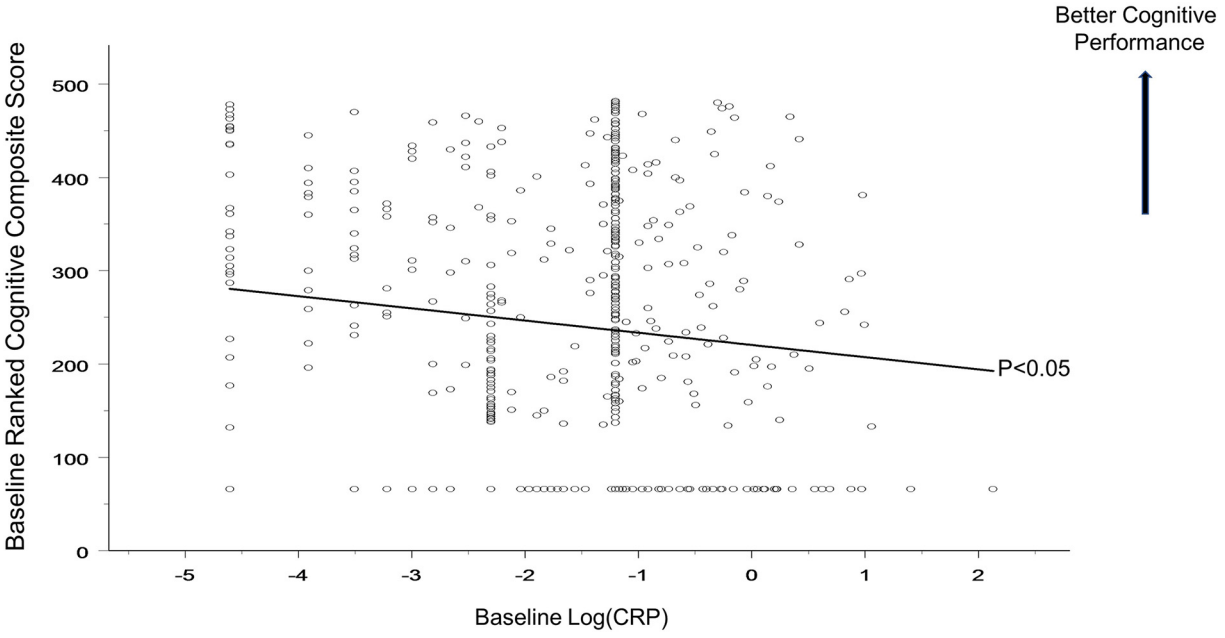

Fig. 1. Cross-sectional association between wr-CRP and cognitive performance (rank score) at study baseline (full ITT sample, N = 477, bootstrap resampling method). $P < .05$ for correlation between log(wr-CRP) and ranked CogState cognitive composite score adjusted for age, gender, BMI, smoking status, sites (country region). Missing CRP values were found in 5 patients at baseline. Non-evaluable scores at baseline and/or week 6, missing cognitive testing scores and/or early dropouts were assigned the lowest possible rank score (=0).

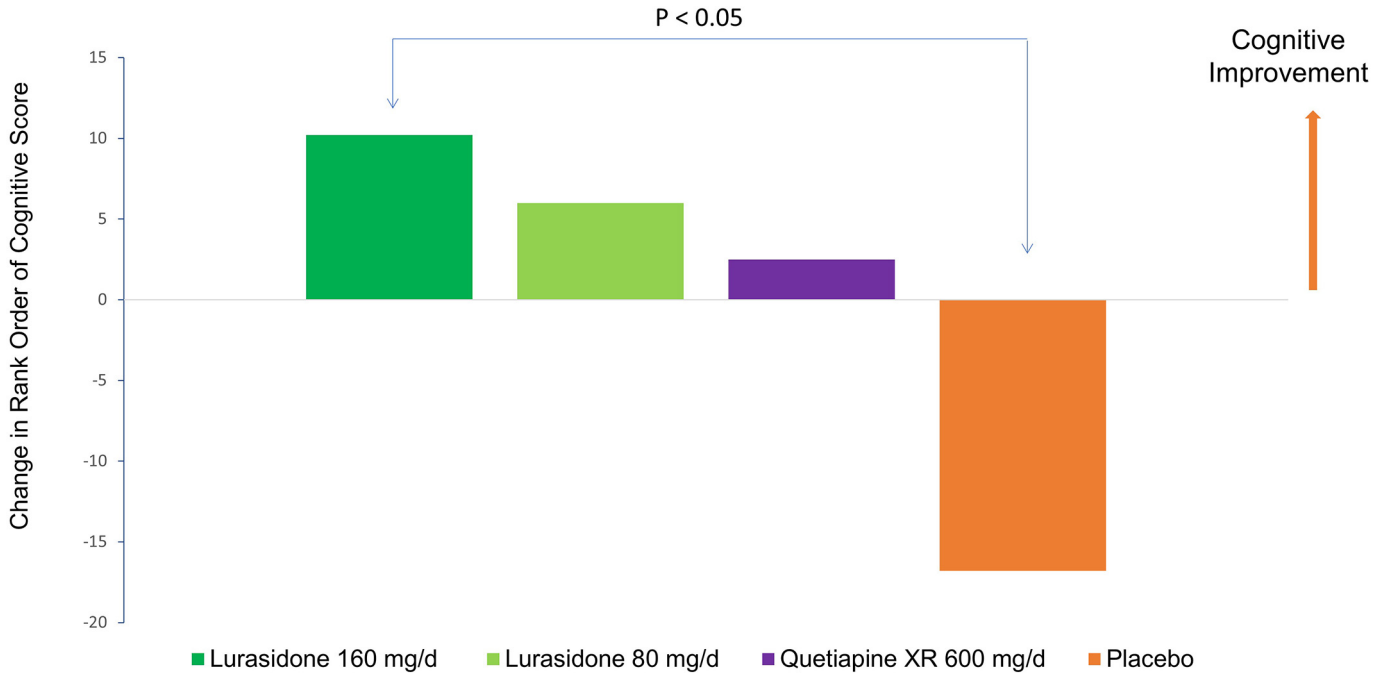

Fig. 2. Lurasidone in the treatment of schizophrenia: change in cognitive performance (ranked CogState cognitive composite score) from baseline to week 6 (N = 482, full ITT sample, bootstrap resampling method). P < .05 (lurasidone 160 mg/day vs. placebo, based on bootstrap 95% confidence interval).

lurasidone or quetiapine XR on change in PANSS total score (ANCOVA, n = 477, F test = 0.5, df = 3430, p = .683 for logCRP interaction with treatment; n = 462, F test = 0.36, df = 3415, p = .779 for TG/HDL interaction with treatment; n = 458, F test = 0.30, df = 3411, p = .878 for HOMA-IR interaction with treatment). Furthermore, CRP, HDL and HOMA-IR did not moderate the effect of lurasidone or quetiapine XR on change in CGI-S score (ANCOVA, n = 477, F test = 0.23, df = 3430, p = .878 for CRP interaction with treatment; n = 462, F test = 0.01, df = 3415, p = .998 for TG/HDL interaction with treatment; n = 458, F test = 0.21, df = 3411, p = .890 for HOMA-IR interaction with treatment), There were also no significant moderating effects of CRP, HDL and HOMA-IR on change in MADRS total score for either lurasidone or quetiapine XR treatment.

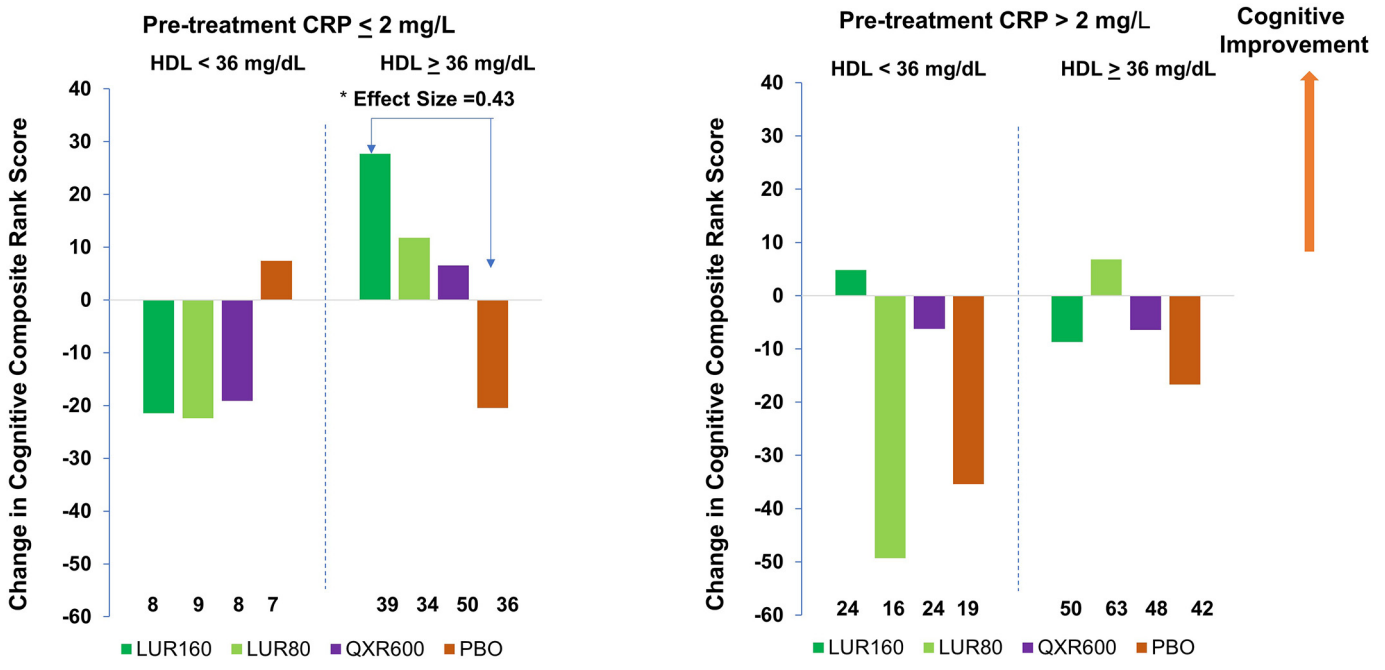

Fig. 3. Association of C-reactive protein and HDL with cognitive effect of lurasidone (N = 477, full ITT sample). *P < .05 for lurasidone 160 mg/day (vs. placebo) treatment effect adjusted for age, gender, smoking status, BMI, and sites (country region). P < .05 for lurasidone 160 mg/day (vs. placebo) treatment interaction with combined Log(CRP) and Log(HDL) effect on change in ranked CogState cognitive composite score from baseline to week 6 adjusted for age, gender, smoking status, BMI, and sites (country region). LUR160: lurasidone 160 mg/d; LUR80: lurasidone 80 mg/d; QXR600: quetiapine XR 600 mg/d; PBO: placebo.

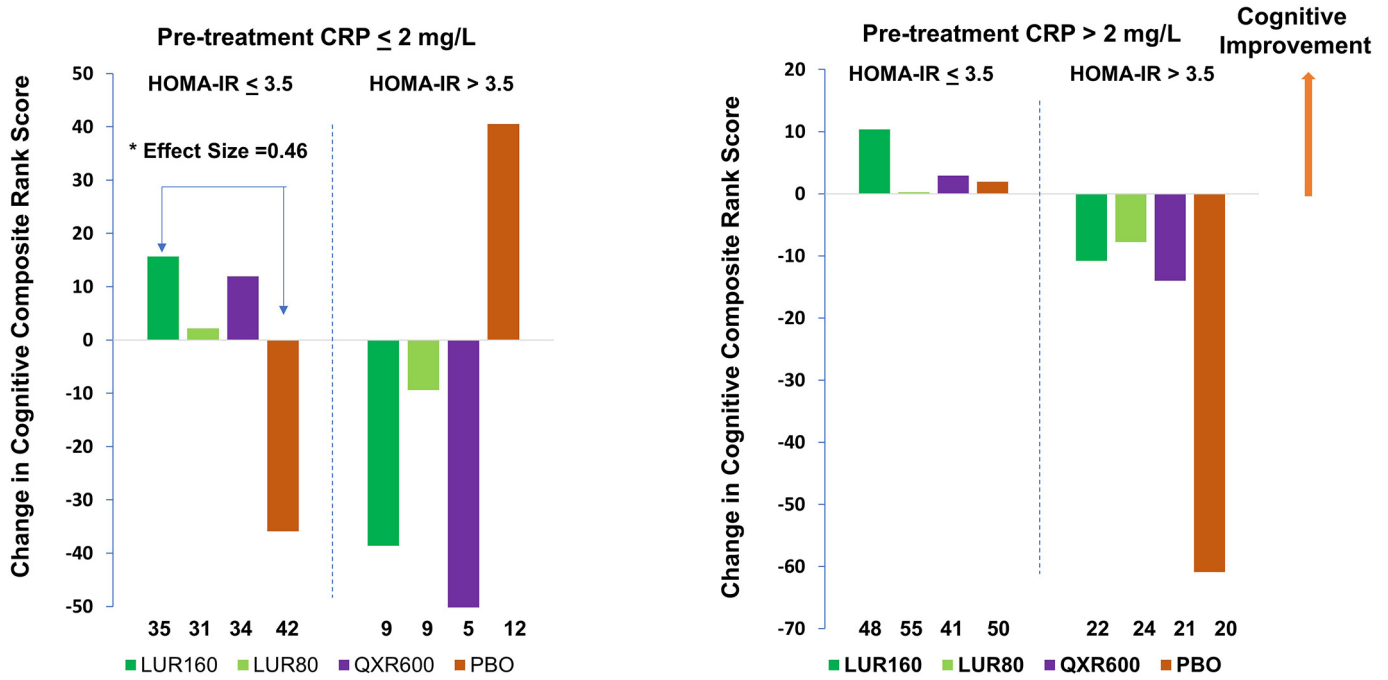

Fig. 4. Association of C-reactive protein and HOMA-IR with cognitive effect of lurasidone (N = 458, full ITT sample). *P < .05 for lurasidone 160 mg/day (vs. placebo) treatment adjusted for age, gender, smoking status, BMI, and sites (country region). P < .05 for lurasidone 160 mg/day (vs. placebo) treatment interaction with combined Log(CRP) and Log(HOMA-IR) effect on change in ranked CogState cognitive composite score from baseline to week 6 adjusted for age, gender, smoking status, BMI, and sites (country region). LUR160: lurasidone 160 mg/d; LUR80: lurasidone 80 mg/d; QXR600: quetiapine XR 600 mg/d; PBO: placebo.

Lurasidone (mean change 1.20-1.30 mg/L) and quetiapine XR (mean change 1.48 mg/L) (vs. placebo, mean change 1.08 mg/L) treatment was not associated with change from baseline in CRP level at week 6 (n= 439, F test=2.05, df=3, 396, p=0.107).

4. Discussion

Multiple studies suggest that the metabolic syndrome is linked to cognitive deficits in neuropsychiatric disorders [7–10,12–14]. There is, however, limited data on the effect of inflammation and metabolic syndrome on cognitive response to treatment in schizophrenia. This post-hoc analysis based on a placebo-controlled trial of lurasidone in schizophrenia [32] is the first study to our knowledge to demonstrate that low levels of inflammation (indexed by CRP) and insulin resistance (indexed by HOMA-IR), as well as a healthy lipid profile (indexed by HDL or TG/HDL ratio) at study baseline predict enhanced cognitive benefit in patients with schizophrenia treated with lurasidone 160 mg/d.

Our findings are consistent with previous studies that show metabolic syndrome (which is closely linked to insulin resistance) increases risk for cognitive deficit in the general population and in neuropsychiatric disease [41–43]. Specifically, we report here that lower log-transformed CRP and log-transformed metabolic risk factors (HOMA-IR, HDL, or TG/HDL ratio) at treatment baseline predicted greater improvement in cognition in subjects treated with lurasidone 160 mg/day. The lurasidone 160 mg/day group demonstrated significant cognitive improvement in subjects with low CRP (≤2 mg/L) combined with lower HOMA-IR (≤3.5, effect size d = 0.46) or higher HDL (≥36 mg/dL, d = 0.43), compared to patients with elevated CRP and metabolic risk parameters. These findings were supported by analysis of CRP and metabolic risk factors as both continuous and categorical variables which were consistent. Our findings suggest a robust link between metabolic risk and cognitive performance in patients with schizophrenia.

Numeric trend to improvement in cognitive performance was also observed in the lurasidone 80 mg/day group with low CRP and metabolic risk factors at baseline. Interestingly, placebo response was relatively low in patients with reduced metabolic risk (lower CRP in addition to higher HDL, lower TG/HDL ratio, or lower HOMA-IR at treatment baseline), suggesting that the procognitive effect of lurasidone in these subgroups may be robust, without confounding by non-specific placebo effects. Taken together, our findings suggest that markers of inflammation and metabolic risk may be useful in predicting cognitive response to lurasidone treatment.

Previous reports indicate that the metabolic syndrome is a proinflammatory state characterized by elevated CRP [44–48]. We found that obesity, insulin resistance, and metabolic syndrome parameters (including HDL or TG/HDL ratio) were significantly associated with low-grade inflammation, indexed by CRP level at study baseline. In contrast to lurasidone, quetiapine XR 600 mg/day treatment had a numerically higher level of change in CRP compared to placebo, and a significantly greater endpoint increase in BMI, cholesterol and triglycerides compared with the placebo group [32].

Growing evidence indicates that inflammation and oxidative stress are linked to cognitive decline and schizophrenia [48–52]. Our findings that increasing CRP levels correlate with increased cognitive impairment and symptom severity at study baseline are consistent with these data, as well as results from recent meta-analyses of cross-sectional studies on associations between CRP (serum or plasma) and schizophrenia [13,53].

Previous studies suggest an association between higher CRP levels in schizophrenia and catatonic features, negative symptomatology, and aggressiveness [25]. We found higher CRP levels were associated with higher PANSS positive and negative subscale scores but not the PANSS excitement component at baseline in the current study.

Strengths of the present post-hoc analysis include the underlying placebo-controlled study design, large sample size, longitudinal assessment of CRP and cognition over 6 weeks, and the availability of several well-established measures of metabolic disturbance. Results from the current study were based on the nonparametric rank analysis of cognitive scores in the full analysis sample of ITT patients, which are consistent with findings based on raw cognitive scores in the evaluable

population [2]. Potential confounding due to early dropouts and moderating effects of age, gender, smoking status, BMI and other measures of lipid disturbance were explored and accounted for in the current analysis.

The present study also has several limitations. This exploratory analysis was not defined a priori to test the hypothesis that CRP and metabolic parameters at study baseline moderated the effect of lurasidone on treatment of cognitive impairment in schizophrenia. Additional studies are needed to confirm and elucidate the complex relationships between inflammation and cognitive impairments in schizophrenia, including in non-acutely ill patient populations. Preferably, this would involve designs with adequate power to test the interactive relationships between biomarkers of inflammation and metabolic risk (including insulin resistance) for prediction of treatment outcomes in schizophrenia.

5. Conclusion

Findings of this post-hoc analysis based on a placebo-controlled trial in patients with schizophrenia suggest that baseline CRP level combined with measures of metabolic risk moderated the improvement in cognitive performance associated with lurasidone 160 mg/day (vs. placebo) treatment. A reduced treatment effect on cognitive performance was observed in patients with higher levels of metabolic risk. Our findings underscore the importance of maintaining a low metabolic risk profile in patients with schizophrenia.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.comppsych.2020.152195.

Declaration of Competing Interest

Dr. Miller received travel expenses to present the work under consideration at the 2017 American College of Neuropsychopharmacology annual meeting. In the past 12 months, Dr. Miller received research support from the Augusta University; the Stanley Medical Research Institute; NARSAD; and the National Institute of Mental Health; and Honoraria from Psychiatric Times. Dr. Siu reports consulting fees from the Chinese University of Hong Kong, and Sunovion. In the last 3 years, Dr. Harvey has received consulting fees or travel reimbursements from Teva, Takeda Pharma, Sunovion Pharma, Sanofi Pharma, Otsuka America (Otsuka Digital Health), Minerva Pharma, Lundbeck Pharma, Jazz Pharma, Intra-Cellular Therapies, Genentech (Roche Pharma), Forum Pharma, Boehringer Ingelheim. Biogen, Allergan, Akili, and Alkermes. He receives royalties from the MATRICS Consensus Battery and the Brief Assessment of Cognition in Schizophrenia. He is the chief scientific officer of i-Function, Inc. He has research grants from the Stanley Medical Research Foundation and Takeda. In the last 3 years Dr. Newcomer has received grant support from Otsuka America Pharmaceutical Co. Ltd., the Substance Abuse and Mental Health Services Administration, and the National Institutes of Health; served as a consultant to Alkermes, Auris, Indivior, Otsuka, and Sunovion; serves on a Data Safety Monitoring Board for Amgen; and has been involved in patent litigation on behalf of Sunovion. and. Drs. Loebel, Pikalov, Tsai, and Tocco are employees of Sunovion Pharmaceuticals Inc.

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