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Effect of memantine on C-reactive protein and lipid profiles in bipolar disorder

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Abstract

Background—Balance in the immune system plays roles in bipolar disorder (BD) and its metabolic co-morbidities. Memantine is an NMDA receptor antagonist with anti-inflammatory

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Contributors

Po See Chen designed the study and wrote the protocol. San-Yuan Huang, Jau-Shyong Hong, and Ru-Band Lu helped to design the study. Shiou-Lan Chen contributed to the statistical analyses. Hui Hua Chang wrote the first draft of the manuscript. Po See Chen, Tzu-Yun Wang, Sheng-Yu Lee, Yen Kuang Yang, and Ru-Band Lu managed the data collection. All authors interpreted the analysis of the results and helped to revise the manuscript.

Conflicts of interest

The authors declare that they have no conflicts of interest in relation to this work. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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effects. However, the effects of memantine adjunct treatment on metabolic status of BD are unclear.

Methods—During the 12 weeks period, a total of 191 BD patients were enrolled and split into valproate (VPA) + placebo and VPA + memantine (5 mg/day) arms. The fasting plasma levels of high-sensitivity C-reactive protein (CRP) and metabolic indices were assessed. BD patients were stratified according to their initial CRP level.

Results—A cut-off value of initial CRP level of 2322 ng/mL discriminated the waist circumference in these BD patients after 12-week VPA treatment. In the high CRP (> 2322 ng/mL) group, patients in the VPA + memantine arm had a significantly decreased in their CRP ($p = 0.009$), total cholesterol ($p = 0.002$), LDL ($p = 0.002$) levels, BMI ($p = 0.001$), and waist circumference ($p < 0.001$), compared to those in the VPA + placebo arm. However, analysis of the low CRP group did not showed the effect.

Limitations—We recruited BD patients in depressed states and the sample size was relative small. The effects of the fixed dose of memantine on metabolic indices were 12-week follow up in BD patients treated with VPA.

Conclusions—BD patients with high initial CRP levels receiving memantine adjunct treatment have a reduced risk of inflammation and metabolic imbalance. Prospective studies are needed to confirm the long-term outcome for memantine adjunct therapy in BD patients.

Keywords

bipolar disorder; memantine; C-reactive protein; metabolic disturbance; clinicaltrials.gov, Identifier: NCT01188148

1. Introduction

Recently, BD has been considered as a chronic multisystemic disease that affects the brain as well as other organs, with a high rate of metabolic disturbances (Bauer et al., 2008; Chang et al., 2009a; Kim et al., 2007; Leboyer et al., 2012b; Salvi et al., 2012). In addition to BD itself, the medication treatment for BD, such as valproate (VPA), may also contribute to the increased risk of metabolic disturbances (Chang et al., 2010a; Citrome et al., 2011). Inflammation might link BD with metabolic disturbance and the underlying pathologic mechanisms of BD as well (Benros et al., 2013; Kapczinski et al., 2011; Stewart et al., 2009; Watkins et al., 2014). In clinical practice, C-reactive protein (CRP) could be a sensitive marker of inflammation and metabolic disturbances (Nordestgaard and Zacho, 2009; Pearson et al., 2003; Wei et al., 2014). Stressful life events, a high number of hospitalizations, and depression recurrence all increase the odds of elevated CRP levels in BD patients (Becking et al., 2013; Halder et al., 2010; Koenders et al., 2014). Moreover, the CRP levels could also be associated with BD mood status and cognitive deficit (Chang et al., 2012; Dargel et al., 2015; Dickerson et al., 2013; Krogh et al., 2014).

Therefore, anti-inflammatory medications have been considered as an adjunct treatment to achieve complete remission and avoid cognitive function deterioration in treating BD (Ayorech et al., 2015). Trials using polyunsaturated fatty acids, cyclooxygenase inhibitors,

anti-TNF alpha and minocycline have been conducted to enhance the treatment response in BD patients (Fond et al., 2014). Studies have proven the effectiveness and tolerance of polyunsaturated fatty acids for the treatment of depression in BD patients (Sarris et al., 2012; Wersching et al., 2010). N-acetyl cysteine also appears to be a safe and effective augmentation strategy for depressive symptoms in BD patients (Berk et al., 2008; Magalhaes et al., 2011). Furthermore, the mood-stabilizing effect of memantine, a noncompetitive NMDA receptor antagonist with an anti-inflammatory effect, has also been suggested (Koukopoulos et al., 2012; Lee et al., 2013b; Sani et al., 2012). Memantine could block neurogenic neuroinflammation in the brain and in the peripheral through both its NMDA-blocking (Xanthos and Sandkuhler, 2014) and non-NMDA blocking effects (Wu et al., 2009; Yu et al., 2015).

Since inflammatory status is associated with metabolic disturbances, here we aimed to investigate whether BD patients receiving memantine adjunct treatment could show metabolic benefits. We also examined whether the initial level of CRP could be a marker to stratify the metabolic outcome in BD patients received memantine add-on treatment. Overall, we examined the effectiveness of add-on memantine on CRP levels, lipid profiles, and body weight in BD patients, stratified by their initial level of CRP.

2. Methods

2.1. Participants

The research protocol was approved by the Institutional Review Board for the Protection of Human Subjects at National Cheng Kung University Hospital and this research was registered with clinicaltrials.gov, Identifier: [NCT01188148](https://clinicaltrials.gov/ct2/show/study?term=NCT01188148). All participants signed written informed consent forms. The BD patients in a depressed state were enrolled as described before (Lee et al., 2013b). Briefly, 191 patients with BD (supplementary Figure 1) were recruited from outpatient and inpatient settings at National Cheng Kung University Hospital between May 2009 and September 2013. All were initially evaluated in an interview by an attending psychiatrist using the Chinese Version of the Modified Schedule of Affective Disorder and Schizophrenia–Life Time in order to determine the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) diagnoses. We also used the 2-day minimum threshold for hypomania in the diagnosis of BD II (Benazzi and Akiskal, 2006; Judd et al., 2003). The exclusion criteria included the presence of other major psychiatric illnesses (such as schizophrenia, BD I), borderline personality disorder, a history of substance or alcohol abuse or dependence, cognitive disorders, severe physical illness, previous or ongoing treatment for metabolic disturbance, females who were pregnant or nursing, and a history of psychotropic agent use.

After a baseline assessment, patients were randomly assigned to parallel-groups to receive either VPA + memantine (daily dose of 5 mg) or VPA + placebo for 12 weeks. A computer-generated list of random numbers was used to allocate the participants to groups. Open-label VPA was administered (500 and 1000 mg daily [50–100 µg/mL in plasma]) starting from the screening phase of the study. Psychiatrists and assistants were blinded to participants' groups. Concomitant lorazepam (<8 mg) was used for nighttime sedation and to treat agitation and insomnia during the study, and fluoxetine (< 20 mg) was permitted for

associated depressive symptoms. In addition, symptom severity and metabolic indices were measured at baseline and 2 weeks, 8 weeks, and 12 weeks after the initiation of pharmacological treatment. The severities of mood symptoms were assessed using the 17-item Hamilton Depression Rating Scale (HDRS) and the 11-item Young Mania Rating Scale (YMRS). Only patients in a depressed state (HDRS ≥ 18) were recruited. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2), and waist circumference was measured at the level midway between the lateral lower rib margin and the superior anterior iliac crest.

2.2. Measurement of metabolic indices

At baseline and 2 weeks, 8 weeks, and 12 weeks after the initiation of pharmacological treatment, fasting blood samples were collected between 0800 and 1000 hours. Ten milliliters of whole blood was withdrawn from the antecubital vein of each patient. Plasma, which was isolated from the whole blood after the samples were centrifuged at $3000 \times g$ for 15 minutes at $4^\circ C$, was immediately stored at $-80^\circ C$. The fasting plasma CRP level was assessed using a high-sensitivity CRP ELISA kit (R&D Systems Inc, USA), for which the mean limit of detection was 0.005–0.022 ng/mL (the mean limit of detection was 0.010 ng/mL), and the intra- and inter-assay coefficients of variation were 5.5% and 6.5%, respectively. The patients' assessments and CRP levels were examined by an independent assistant who was blind to the patients' group allocations. Fasting total cholesterol, high-density lipoprotein (HDL), and triglyceride concentrations were measured by enzymatic methods using the automated analyzer TBA-200FR (Toshiba Lab Medical, Tokyo, Japan). Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald formula. The fasting serum leptin level was measured by ELISA (Linco Research, USA).

2.3. Statistical analysis

We analyzed the data using the Statistical Package for Social Sciences 16.0 for Windows (SPSS Inc, Chicago, IL). Categorical variables were expressed as numbers and percentages, and continuous variables as means $\pm$ Standard Deviation (SD) unless otherwise specified. T test and chi-square analyses were used to compare the demographic and clinical characteristics of the groups. In addition, the receiver operating characteristic (ROC) curve method was used to evaluate the outcomes of metabolic indices at week 12 based on the baseline CRP level. The outcomes of metabolic indices is referred to as central obesity after 12 weeks of treatment, which indicated that BD patients had a waist circumference ≥ 31.5 inches for females or ≥ 35.4 inches for males. Intent-to-treat analyses using the mixed-effects model for repeated measures were used to analyze the metabolic indices as the primary outcome at baseline and after VPA + memantine or VPA + placebo treatment. Data were analyzed using the last observation carried forward (LOCF) method, in which the last observation was entered for missing visits. The level of significance was set at 0.05.

3. Results

One-hundred and ninety-one patients with BD, comprising 123 VPA + placebo and 68 VPA + memantine patients, were enrolled, and the demographic characteristics did not differ significantly between the groups at baseline (Table 1).

To estimate the initial CRP level used for stratification BD patients, a ROC curve analysis was performed that showed a cut-off value of initial CRP level of 2322 ng/mL could discriminate the waist circumference in patients with BD after the 12-week VPA treatment with an area under the curve (AUC) of 0.81 (95% confidence interval: 0.71–0.91) (Figure 1). The sensitivity and specificity were 0.72 and 0.83, respectively. Patients in the high CRP group (> 2322 ng/mL) exhibited worse metabolic indices, including higher BMI, triglyceride levels, and leptin levels, and lower HDL levels, than those in the low CRP (≤ 2322 ng/mL) group.

Then we investigated the effects of 12-week add-on memantine on metabolic indices in BD patients that been stratified into the high (> 2322 ng/mL) and low CRP groups. At baseline, none of the metabolic indices were significantly different between the VPA + placebo arm and the VPA + memantine arm (supplementary Table 1). In the high CRP group, memantine showed significant effect on reducing CRP levels ($p = 0.009$) (Figure 2), lowering total cholesterol ($p = 0.002$) (Figure 3a), LDL ($p = 0.002$) (Figure 3b) levels, BMI ($p = 0.001$) (Figure 4a), and waist circumference ($p < 0.001$) (Figure 4b), compared to those in the VPA + placebo arm. However, these effects were not present in the low CRP group (Figure 2 to Figure 4). Taken together, these results indicate that add-on memantine with VPA treatment for 12 weeks could neutralize inflammation and metabolic disturbances in BD patients with high initial CRP levels.

4. Discussion

The current study showed that BD patients in the high CRP group had abnormal metabolic indices, and add-on memantine could reduce the metabolic disturbances and CRP levels as well. The results also showed the CRP level could be a predictor of metabolic outcome in BD patients receiving low-dose memantine adjunct treatment. It is of clinical importance regarding the high prevalence of metabolic disturbance in BD patients (Chang et al., 2009b; Hung Chi et al., 2013; Vancampfort et al., 2013). CRP plays a pivotal role in aspects of inflammation that appears to be related to BD across several important domains (Chang et al., 2016; Goldstein et al., 2009; Leboyer et al., 2012a). Moreover, inflammation has been proposed to be the underlying mechanism that links BD and metabolic disturbances (Kim et al., 2007; Leboyer et al., 2012a; Lee et al., 2013a), as a previous study revealed apparent metabolic disturbances in BD patients with high CRP levels (Tsai et al., 2014).

Metabolic status has been found to be associated with the BD clinical course and treatment outcomes. BD patients comorbidity with metabolic disturbances have three times greater odds of a chronic course and rapid cycling, and are more likely to be refractory to mood stabilizer treatments than those in a euthymic state (Calkin et al., 2015). Long-term medications use would also increase the risk of metabolic syndrome, that might link to the poor treatment response in late stages of BD (Chang et al., 2010b; Vancampfort et al., 2013). The metabolic imbalance in BD might also increase the risk of neurodegeneration (da Silva et al., 2013; Hajek et al., 2014). Therefore, the findings of the current study suggested the treatment strategy with add-on memantine to the treatment of patients with BD might slow cognitive deterioration, especially in those with high CRP levels (Laurin et al., 2009;

Wersching et al., 2010). It would be of great interest to survey the cognitive effects of memantine in BD patients in a long term follow up study.

In this study, we examined the effect of population stratification and grouped the BD patients according to their CRP level. We found that the anti-inflammation effects and metabolic outcome of add-on memantine were associated with their initial CRP levels. Although BD has been linked to inflammatory processes, it remains unclear as to whether individual differences in the levels of inflammatory biomarkers could assist patients and clinicians to choose beneficial treatments (Fillman et al., 2014). In patients with major depressive disorder, a recent report showed that the CRP level could predict the differential responses to escitalopram and nortriptyline (Uher et al., 2014). Clinical trials of a tumor necrosis factor antagonist and omega 3 fatty acid demonstrated the role of the initial CRP level in predicting individual treatment responses (Raison et al., 2013; Rapaport et al., 2016). Accumulating evidence has shown that blood biomarkers might provide clinically usable peripheral signals in the field of psychiatry (Niculescu et al., 2015). An easily accessible peripheral blood biomarker may contribute to the improvement of outcomes in individuals with mood disorders by enabling personalization of treatment.

4.1. Limitation

There were several limitations in the current study. First, we only recruited BD II patients in depressed states, which might restrict the application of the results to other subtypes of BD patients. Second, the patients with BD were recruited from a single site. Third, the sample size was relatively small, although it achieved adequate statistical power. Fourth, the short duration of treatment and the fixed dose of memantine might restrict the results. In addition, non-medication factors that may have confounded the results of the study, such as smoking and exercise, were not considered. However, table 1 and supplementary table 1 showed, the baseline CRP levels were not significantly different between VPA + placebo and VPA + memantine arms. This indicated the confounding factors that influences CRP levels, such as smoking and exercise, have been normalized by random group design. Therefore, we could investigate the effectiveness of add-on memantine on treatment outcome in BD patients, stratified by their initial level of CRP. Further duplication in prospective studies with a long follow-up period could provide solid evidence of the roles of memantine and CRP level in BD patients.

5. Conclusion

In conclusion, the results suggested that BD patients with high initial CRP levels receiving memantine adjunct treatment have a reduced CRP levels and risk of metabolic imbalance across the treatment course. The initial CRP level could be a predictor of metabolic outcome in BD patients who receive benefits from low-dose memantine adjunct treatment. Using biomarkers would prevent patients who would not benefit from adjunct treatment from being exposed to the unnecessary risks inherent in adjunct medications. Therefore, we could develop personalized treatment regimens for patients in order to maximize the effectiveness of treatments and greatly impact the field of developing individual BD treatments. Further

prospective studies are also needed to confirm the adjunct medications for BD patients in order to achieve the optimal treatment outcome.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- CRP could be a sensitive marker to discriminate metabolic disturbance in BD patients.
- CRP level stratify metabolic outcome in BD received memantine add-on treatment.
- Add-on memantine reduced inflammation and metabolic disturbances in BD with high CRP.

Fig. 1. ROC curve analysis. Receiver operating characteristic (ROC) analysis showed that a baseline C-reactive protein (CRP) level of 2322 ng/L could discriminate the waist circumference in patients with bipolar disorder after 12 weeks of valproate treatment, with an area under the curve (AUC) of 0.81. The sensitivity and specificity were 0.72 and 0.83, respectively.

Fig. 2.

Effect of memantine on fasting level of C-reactive protein in the BD patients. In the high CRP group, CRP level was significantly reduced in the VPA + memantine arm than in the VPA + placebo arm in a 12-week analysis after adjustment for age and gender ($p = 0.009$); in the low CRP group, however, CRP level was not significantly associated with the effects of add-on memantine. Abbreviations: VPA, valproate; CRP, C-reactive protein.

Fig. 3.

Effect of memantine on lipid profiles. In the high initial CRP group, total cholesterol (a) and LDL level (b) were significantly lower in the VPA + memantine arm than those in the VPA + placebo arm in a 12-week analysis after adjustment for age and gender ($p = 0.002$ and $p = 0.002$, respectively). However, in the low CRP group, neither total cholesterol nor LDL level was not significantly associated with the effects of add-on memantine. In addition, add-on memantine did not have significant effect on HDL level and triglyceride level either in the high CRP or low CRP group (data did not shown). Abbreviations: BD: bipolar disorder; VPA, valproate; CRP, C-reactive protein; LDL, low-density lipoprotein.

Fig. 4.

Effect of memantine on body weight of the BD patients. In the high initial CRP group, BMI (a) and waist circumference (b) were significantly lower in the VPA + memantine arm than in the VPA + placebo arm in a 12-week analysis after the results were adjusted for age and gender ($p = 0.001$ and $p < 0.001$, respectively). However, in the low CRP group, neither BMI nor waist circumference was not significantly associated with the effects of add-on memantine. Abbreviations: VPA, valproate; CRP, C-reactive protein; BMI, body mass index.

Table 1

The demographic characteristics of the BD patients at baseline.

Baseline	Total (n=191)	VPA + placebo (n=123)	VPA + memantine (n = 68)	<i>p</i> value	Adjusted <i>p</i> value ^I
Age (yr)	31.9 ± 11.4	31.9 ± 11.4	32.0 ± 11.7	0.953	-
Gender, female (%)	115 (54.5%)	72 (52.6%)	43 (58.1%)	0.471	-
CRP (ng/mL) (Range: ng/mL)	1729.4 ± 1727.5 (0.3–8552.3)	1801.3 ± 1707.8 (0.3–8552.3)	1397.8 ± 1529.2 (0.3–7407.5)	0.107	0.093
HDRS score	19.2 ± 5.5	19.4 ± 5.5	18.8 ± 5.5	0.450	0.346
YMRS score	9.0 ± 4.2	9.2 ± 4.2	8.6 ± 4.2	0.359	0.376
BMI (kg/m ²)	22.7 ± 4.1	22.8 ± 4.4	22.3 ± 3.4	0.349	0.138
Waist circumference (inches)	30.9 ± 4.6	31.3 ± 4.8	30.3 ± 3.9	0.135	0.173
Cholesterol (mg/dL)	179.6 ± 37.2	182.1 ± 36.4	174.9 ± 38.5	0.193	0.336
Triglyceride (mg/dL)	90.5 ± 49.8	90.2 ± 46.8	91.1 ± 55.3	0.904	0.674
HDL (mg/dL)	57.8 ± 15.1	58.3 ± 15.0	56.9 ± 15.2	0.521	0.355
LDL (mg/dL)	107.5 ± 31.1	107.8 ± 30.7	106.8 ± 31.2	0.828	0.596
Leptin (ng/mL)	6.9 ± 7.7	7.4 ± 8.2	6.2 ± 6.5	0.298	0.143

Abbreviations: BD: bipolar disorder; VPA, valproate; CRP, C-reactive protein; HDRS, 17-item Hamilton Depression Rating Scale; YMRS, 11-item Young Mania Rating Scale; BMI, body mass index; Waist, waist circumference HDL, high-density lipoprotein; LDL, low-density lipoprotein.

^I Adjusted for age and gender