

## Research paper

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



Hui Hua Chang<sup>a,b</sup>, Po See Chen<sup>c,d,\*</sup>, Tzu-Yun Wang<sup>c,d</sup>, Sheng-Yu Lee<sup>e</sup>, Shiou-Lan Chen<sup>f</sup>, San-Yuan Huang<sup>g</sup>, Jau-Shyong Hong<sup>h</sup>, Yen Kuang Yang<sup>c,d,i,j</sup>, Ru-Band Lu<sup>c,d</sup>

<sup>a</sup> Institute of Clinical Pharmacy and Pharmaceutical Sciences, College of Medicine, National Cheng Kung University, Tainan, Taiwan

<sup>b</sup> School of Pharmacy, College of Medicine, National Cheng Kung University, Tainan, Taiwan

<sup>c</sup> Department of Psychiatry, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan

<sup>d</sup> Addiction Research Center, National Cheng Kung University, Tainan, Taiwan

<sup>e</sup> Department of Psychiatry, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan

<sup>f</sup> Department of Neurology, School of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan

<sup>g</sup> Department of Psychiatry, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan

<sup>h</sup> Laboratory of Pharmacology and Chemistry, National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, NC, USA

<sup>i</sup> Department of Psychiatry, National Cheng Kung University Hospital, Dou-Liou Branch, Yunlin, Taiwan

<sup>j</sup> Institute of Behavioral Medicine, College of Medicine, National Cheng Kung University, Tainan, Taiwan

## ARTICLE INFO

## Keywords:

Bipolar disorder

Memantine

C-reactive protein

Metabolic disturbance

Clinicaltrials.gov, Identifier: NCT01188148

## 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 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.

## 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; Dargél 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

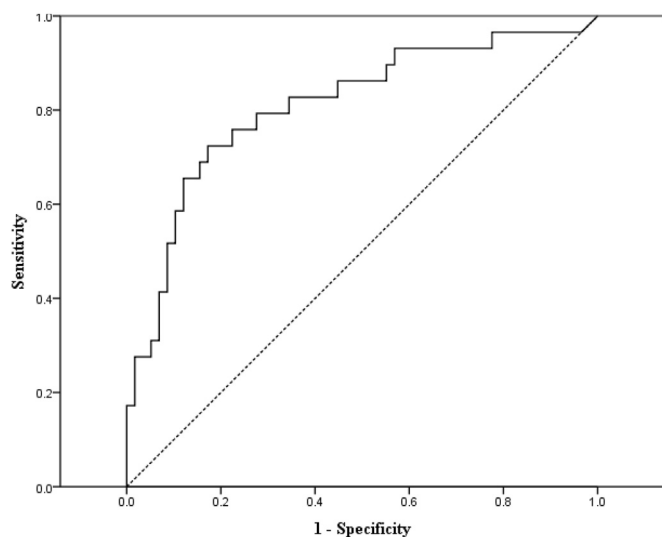
\* Correspondence to: Department of Psychiatry, National Cheng Kung University Hospital, 138 Sheng Li Road, North Dist., Tainan 70403, Taiwan.  
E-mail address: [chenps@mail.ncku.edu.tw](mailto:chenps@mail.ncku.edu.tw) (P.S. Chen).

**Table 1**  
The demographic characteristics of the BD patients at baseline.

| Baseline                     | Total (n =191)  | VPA + placebo (n =123) | VPA + memantine (n = 68) | p value | Adjusted p value <sup>a</sup> |
|------------------------------|-----------------|------------------------|--------------------------|---------|-------------------------------|
| 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)                  | 1729.4 ± 1727.5 | 1801.3 ± 1707.8        | 1397.8 ± 1529.2          | 0.107   | 0.093                         |
| (Range: ng/mL)               | (0.3–8552.3)    | (0.3–8552.3)           | (0.3–7407.5)             |         |                               |
| 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 <sup>2</sup> )     | 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.

<sup>a</sup> Adjusted for age and gender



**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.

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; Werschling 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. 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<sup>2</sup>), and waist circumference was measured at the level midway between the lateral lower rib margin and the superior anterior iliac crest.

Download English Version:

<https://daneshyari.com/en/article/5722002>

Download Persian Version:

<https://daneshyari.com/article/5722002>

[Daneshyari.com](https://daneshyari.com)