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Add-on Memantine Treatment for Bipolar II Disorder Comorbid with Alcohol Dependence: A 12-Week Follow-Up Study

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Abstract

Background: Bipolar disorder (BD), especially BD-II, is frequently comorbid with alcohol dependence. Because BD-II and alcohol dependence are neurodegenerative disorders, agents with

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Trial registration: NCT03043001 (<https://register.clinicaltrials.gov/>). The trial began on 26 Feb. 2014, and is ongoing at National Cheng Kung University Hospital.

Conflicts of Interest

All authors declare that they have no conflicts of interest.

anti-inflammatory and neurotrophic effects might provide effective therapy. We investigated whether add-on memantine to regular valproate (VPA) treatment ameliorated clinical symptoms, reduced alcohol use and cytokine levels, and increased plasma brain-derived neurotrophic factor (BDNF) in BD-II patients with comorbid alcohol dependence.

Method: As a single-arm 12-week clinical trial, BD-II patients with comorbid alcohol dependence undergoing regular VPA treatments were given add-on memantine (5 mg/day). Symptom severity, alcohol use, cytokine (plasma tumor necrosis factor [TNF]- α and C-reactive protein [CRP], transforming growth factor β 1 [TGF- β 1], interleukin-8 [IL-8], IL-10), and plasma BDNF levels were regularly assessed.

Results: Mean within-group decreases in Hamilton Depression Rating Scale (HDRS) and Young Mania Rating Scale (YMRS) scores, alcohol use, CRP, BDNF, and IL-8 levels were significantly different from baseline after 12 weeks of treatment. We found no significant correlation between alcohol use levels and changes in HDRS or YMRS scores. The correlation between reduced alcohol use and reduced TGF- β 1 level was significant ($B = 0.003$, $p = 0.019$).

Conclusions and Relevance: BD-II comorbid with alcohol dependence might benefit from add-on memantine treatment, which significantly reduced clinical severity, alcohol use, and plasma cytokine levels, and increased BDNF levels.

Introduction

Bipolar II disorder (BD-II) is a subtype of BD characterized as “recurrent episodes of depression and hypomania”. BD-II is often misdiagnosed because the diagnosis is frequently made based on recollections of past hypomania when patients present with symptoms of depression (Benazzi, 2001, Benazzi and Akiskal, 2003). Therefore, BD-II is often ineffectively treated (Ghaemi et al., 2000). Patients with BD-II have a greater risk of suicide (Rihmer and Pestalitiy, 1999), a prolonged clinical course, more mood episodes, more major and minor depressive episodes, and shorter inter-episode intervals, than do patients with BD-I (Judd et al., 2003, Pallanti et al., 1999).

Patients with BD frequently have comorbid alcohol use disorders (AUDs) (Di Florio et al., 2014), especially patients with BD-II (Simhandl et al., 2016). Irritable and hyperthymic temperaments might contribute to AUDs in BD (Singh et al., 2015). Comorbid AUDs in BD worsened the clinical presentation with higher rates of mixed episodes, rapid cycling and increased symptom severity (Frye and Salloum, 2006). In addition, we previously reported (Shan et al., 2011) that even in the inter-episode state, BD-II patients comorbid with AUDs performed poorly on verbal, visual, and working memory, psychomotor speed, and attention tests than did BD-II patients without AUDs and normal healthy controls.

BD is proposed as a “neurodegenerative” disease etiologically similar to Alzheimer’s dementia by sharing common neurobiology including brain regions, mechanisms, genes and epigenetic outcomes. Neuroimaging studies showed structural and functional alterations, especially in the hippocampal area in the progression of both BD and Alzheimer’s disease which link to cognitive impairments (Correa-Velloso et al., 2018). BD has been proposed to represent a prodromal state of frontotemporal dementia as well (Papazacharias et al., 2017). Evidence indicates that BD lead to a premature brain aging (Altamura et al., 2015). In

addition, neurodegenerative outcome has been demonstrated in autopsy from patients with BD such as argyrophilic grain-type tauopathy and Lewy body-related alpha-synucleinopathy (Shioya et al., 2015). On the other hand, alcohol is certainly a toxic substance which may lead to brain atrophy. Therefore, comorbid BD and AUDs might lead to detrimental effects likely to increase toxins and nerve damage in various brain areas. On the other hand, neuroinflammation and microglia activation which releases a wide range of pro-inflammatory cytokines has been related to onset and progression of BD (Naaldijk et al., 2016) (Sertzt et al., 2013). The pro-inflammatory cytokines including tumor necrosis factor alpha (TNF- α), and IL-1 β resulted into mitochondria dysfunction, tissue damage and cell death (Rege and Hodgkinson, 2013). Alterations in cytokines levels were proposed to influence mood occurrences and duration in BD (Naaldijk et al., 2016, Soderlund et al., 2011, O'Brien et al., 2006) and as a common biomarker (Altamura et al., 2014). Other evidence (Brietzke and Kapczinski, 2008) points to elevated concentrations of TNF- α in BD as a molecular target for the development of novel treatments. Therefore, inflammation has been thought to be involved in the pathophysiology of, phenomenology of, and treatment response to BD.

We previously reported (Lee et al., 2014b) that alcohol dependence might be categorized into [a] simple, [b] anxiety depression, [c] mixed (bipolar), and [d] antisocial subtypes with genetic variations in Han Chinese populations. The brief descriptions of each type of alcoholism are listed below: 1) Simple alcoholism usually onset in middle adulthood. It is associated with no comorbid mental illnesses and fewer alcohol-related problems. It is similar to Lesch's Type I alcoholics (Lesch et al., 1988). (2) anxiety depression alcoholism: in this subtype, patients almost always have comorbid anxiety or depression before, during, or after drinking; this subtype is associated with more severe alcohol use. The onset is during late adolescence or early adulthood. It is similar to Cloninger's type I alcoholism (Cloninger, 1987). (3) Antisocial alcoholism: comorbid with antisocial personality disorder; onset is usually during early or middle adolescence; associated with more alcohol-related problems, social consequences, and physical consequences. Alcohol abuse might be a symptom of antisocial behavior. This subtype is similar to Lesch's Type IV or Cloninger's type II alcoholism (Cloninger, 1987, Lesch et al., 1988). (4) Mixed bipolar alcoholism: alcoholism comorbid with bipolar disorder or other substance use disorder. This subtype is similar to Lesch's Type III and Babor's type B alcoholism (Babor et al., 1992, Lesch et al., 1988). In our clinical experience, it is more difficult to stop BD patients with the mixed subtype from drinking than it is to stop those with the simple and anxiety depression subtypes. An adequate combination of mood stabilizers plus neuroprotective and anti-inflammatory agents might greatly benefit treatment for BD-II patients with comorbid alcohol dependence.

Memantine is a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist. However, we previously (Wu et al., 2009) reported an alternative mechanism for memantine: it is also an anti-inflammatory agent that downregulates the activity of microglia and upregulates astroglia-released of neurotrophic factors, which are mechanistically remote from an NMDA receptor. We found that low-dose (0.02 mg/kg) memantine abolished morphine-induced conditioned-place-preference behavior in rats because of its IL-6-modulating effect in the medial prefrontal cortex (Chen et al., 2012). We also showed (Lee et

al., 2014a) that low-dose memantine (5 mg/day) added to valproate significantly attenuated plasma cytokines in BD-II patients. In addition, add-on memantine in opioid-dependent patients undergoing methadone maintenance treatment not only significantly downregulated plasma tumor necrosis factor (TNF)- α levels and upregulated transforming growth factor (TGF)- β 1 levels, but also reduced the methadone dose required (Lee et al., 2015).

Because memantine might not only inhibit the overactivity of microglia, but also repair damaged neurons and restore neurogenesis by activating astroglia and upregulating astroglia-released neurotrophic factors, we hypothesize that the neuroprotective and neurotrophic effects of memantine will benefit BD-II patients with comorbid alcohol dependence. In the current study, we investigated whether add-on low-dose (5 mg/day) memantine benefits BD-II patients with comorbid alcohol dependence. The outcome measures included clinical severity, units of alcohol use, and levels of cytokine and plasma BDNF expression.

Methods

The Institutional Review Board for the Protection of Human Subjects at National Cheng Kung University Hospital reviewed and approved the research protocol. All participants were given a detailed description of the study before they signed written informed consent forms.

BD-II patients with comorbid alcohol dependence were recruited from outpatient and inpatient settings in Taiwan. All patients were initially evaluated by an attending psychiatrist and then given a structural interview by a clinical psychologist to determine *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (DSM-IV-TR) diagnoses, using the Chinese version of the Modified Schedule of Affective Disorder and Schizophrenia-Life Time (SADS-L) (Endicott and Spitzer, 1978), which has good inter-rater reliability (Huang et al., 2004). Patients with major mental illnesses other than BD-II and alcohol dependence and who had taken memantine within 1 week before the study began were excluded. Although DSM-IV-TR criteria require a minimum of 4 days of hypomania, current epidemiologic data (Wang et al., 2016, Benazzi and Akiskal, 2006, Angst et al., 2010) suggest that 2 days is more prevalent in community samples; therefore, we used the 2-day minimum for hypomania to diagnose BD-II.

Study Design

Eligible patients were given low-dose (5 mg/day) add-on memantine (5 mg/day) after an initial screening, with open-label valproic acid (VPA) treatment (500 or 1000 mg/day [50–100 μ g/ml in plasma]) which had begun when they joined the study. The severity of mood symptoms was assessed using the Hamilton Depression Rating Scale (HDRS) and the Young Mania Rating Scale (YMRS). Only patients with moderate mood symptoms (HDRS $\geq$ 18 or YMRS $\geq$ 14) were recruited. The exact amount of alcohol used by each patient was assessed using the Chinese version of the Modified SADS-L. Symptom severity and alcohol use were assessed at baseline, and treatment responses were measured on day 7 of weeks 1, 2, 4, 8, and 12. Concomitant benzodiazepine medication (lorazepam $<$ 8 mg) and (chlordiazepoxide $<$ 240 mg) were used for nighttime sedation and withdrawal symptoms during the study. Up

to 20 mg/day of fluoxetine was permitted for associated depressive symptoms, and 1–3 mg of risperidone for hypomanic symptoms.

Ten milliliters of whole blood was withdrawn from the antecubital vein of each patient when clinical severity was assessed: at baseline, and on day 7 of weeks 1, 2, 4, 8, and 12. Plasma, which was isolated from the whole blood after it had been centrifuged at 3000 *g* for 15 min at 4°C, was immediately stored at –80°C. Cytokine levels were quantified using an antibody pair assay system (Flexia; BioSource Intl., Camarillo, CA). Sample processing and data analysis were done according to the manufacturer's instructions. The immunological parameters—plasma TNF- α , CRP, TGF- β 1, IL-8, IL-10, and BDNF—were analyzed.

Statistical Analysis

The demographic and clinical characteristics of the patients—baseline and endpoint YMRS and HDRS scores, alcohol use, and cytokine levels—are presented as means $\pm$ standard deviation (SD).

The intent to-treat (ITT) analysis set included all patients who had taken at least one dose of a study drug, and had undergone one baseline assessment and at least one post-baseline assessment. All outcome variables—HDRS, YMRS, cytokine levels, plasma BDNF levels, and metabolic parameters—in the ITT set were analyzed. Missing data were filled in using the last observation carried forward (LOCF) method.

The overall within-group changes of each outcome over the 12 weeks were analyzed using generalized estimating equations (GEEs). We ran 9 models with each outcome as a dependent variable. In each model, treatment duration, gender, and age were included as independent variables, and controlled for use of valproate before trial, administration of fluoxetine, risperidone and lorazepam. The covariance structure used was the autoregressive (AR[1]) model. The significance of change of each outcome over 12-week follow-up was represented by the variable “treatment duration”. Linear regression analysis was used to analyze correlations between changes in alcohol use with changes in cytokine and BDNF levels in 12 weeks. Changes in alcohol use were dependent variables, and changes in HDRS and YMRS scores, and in plasma cytokine and BDNF levels (controlled for gender, age, and baseline clinical severity), concomitant medicine use, were independent variables. SPSS 22.0 for Windows was used for all statistical computations. Significance was set at $p < 0.05$.

Results

We initially screened 99 patients: 39 were excluded because they did not meet the inclusion criteria and 15 because they refused to participate. Forty-five BD-II patients with comorbid alcohol dependence were treated with low-dose (5 mg/day) memantine for 12 weeks. Twenty-six (57.8%) of them completed the 12-week follow-up, and 19 (49.6%) dropped out: 17 refused follow-up, and 2 travelled abroad. The flow chart of the study can be seen in Figure 1.

Patient's baseline and endpoint demographic and clinical characteristics, HDRS and YMRS scores, alcohol use, cytokine and BDNF levels are presented in Table 1. All patients received

lorazepam with mean dosage 2.89 mg/day (standard deviation 1.35). Six patients took valproate before the beginning of the study. The dosage ranged between 500–1000mg (average: 875mg) per day and average duration of valproate use before trial 17.1 weeks. Only one patient was administered fluoxetine during the study, while 32 patients were administered with risperidone during the study. After 12 weeks of treatment, mean within-group decreases in clinical severity (HDRS and YMRS scores) ($p < 0.001$), alcohol use ($p < 0.001$), CRP ($p = 0.012$), and IL-8 levels ($p = 0.021$) were significant (Table 2). BDNF levels were significantly ($p = 0.018$) higher (Table 2). Controlling for use of valproate before trial, administration of fluoxetine, risperidone, and lorazepam, we found no significant correlation between changes in alcohol use levels or HDRS and YMRS scores. The correlation between changes in alcohol use and in TGF- β 1 levels, however, was significant ($B = 0.003$, $p = 0.022$) (Table 3 and Figure 2).

Overall, 15 patients (33.3%) stopped drinking during the first week of memantine treatment. After 12 weeks of treatment, all of the patients greatly reduced their alcohol use $> 50\%$, and 22 patients (84.6%) reduced their alcohol use to 0 unit.

Discussion

Our most important finding was that low-dose (5 mg/day) add-on memantine treatment seemed to significantly attenuate clinical severity, reduce alcohol use and plasma cytokine levels, and increase BDNF levels. We also found a significant correlation between reductions in alcohol use and in plasma TGF- β 1 levels. Our study, as a pilot study, provides the first evidence that low-dose add-on memantine for BD-II patients with comorbid alcohol dependence is associated with reduced alcohol use, attenuated clinical symptoms, and downregulated cytokine levels.

We found no correlation between attenuated clinical severity and reduced alcohol use, which indicates that the changes in alcohol use might not be associated with BD-II treatment. One clinical study (Bisaga and Evans, 2004) reported that pretreatment with memantine might reduce craving for alcohol. An animal study (Alaux-Cantin et al., 2015) also reported that, in post-dependent (PD) rats, a memantine injection (25 mg/kg) reduced alcohol drinking during acute withdrawal, but did not reduce relapses of alcohol dependence after protracted abstinence. However, a pilot double-blind trial using up to 40 mg/day of memantine (Evans et al., 2007) did not significantly reduce alcohol use compared with placebo. Whether our findings support those of these three studies is unclear, because patients were given only 5 mg/day of memantine. Patients' plasma memantine concentrations were about 10–50 ng/ml (0.05–0.2 μ M). This ultralow level of plasma memantine was insufficient to block NMDA receptors (50% inhibition concentration [IC₅₀] of memantine = 2–3 μ M) (Parsons et al., 1999).

We previously (Wu et al., 2009) reported an alternative mechanism for memantine: an anti-inflammatory effect by reducing the activity of microglia and an increase in the release of neurotrophic factors by astroglia, which are mechanistically remote from an NMDA receptor. We hypothesize that the decline in alcohol use in the current study might be the result of memantine's anti-inflammatory or neurotrophic effect, not its function as an

NMDA-receptor blocker. We therefore further analyzed the correlation between changes in alcohol use and changes in cytokine levels.

We found a significant correlation between reductions in alcohol use and decreases in plasma TGF- β 1 levels. TGF- β 1 is a potent anti-inflammatory cytokine that inhibits cytokine production (Yang et al., 2012). Plasma TGF- β 1 levels were higher in alcohol-dependent than in non-dependent patients (Kim et al., 2009) and rats (Kuhn and Sarkar, 2008). The increase in TGF- β 1 might, however, be a predictor of alcohol-induced liver damage, because TGF- β 1 mediates hepatic apoptosis and fibrogenesis, and suppresses hepatocyte proliferation (Schuster and Kriegelstein, 2002). Our finding of a positive correlation between reduced alcohol use and reduced TGF- β 1 levels suggests that decreasing one's use of alcohol reduces alcohol-induced liver fibrosis and hepatocyte apoptosis. We hypothesize that the anti-inflammatory and neurotrophic effect of low dose add-on memantine is involved in reducing plasma TGF- β 1 levels, which, in turn, might contribute to reducing alcohol use. However, TGF- β 1 levels were found with no correlation with mean daily alcohol consumption (Kim et al., 2009). Therefore, the mechanism how TGF- β 1 decrease alcohol use still requires further investigation.

Our study has some limitations. First, this is a single-arm trial that has no placebo group to better demonstrate the effect of memantine. Although we tried to limit concomitant treatment medication to only two drugs, it is difficult to confirm that the attenuation of clinical symptoms and reduction of alcohol use is related only to the effect of add-on memantine. However, our review of the literature showed no reports which suggested that valproate sodium (Depakine) might attenuate drinking behavior; thus, we inferred that memantine reduced alcohol use and helped treat alcohol dependence. Randomized double-blind trials are required to confirm this. Second, our study sample is small and, typical of BD-II and alcoholism clinical trials, had a high drop-out rate. Studies with larger samples are needed to confirm our findings. Third, we sampled only peripheral BDNF and cytokines instead of central nervous system samples because the former samples were easier to obtain. In addition, it has been suggested (Pan et al., 1998, Pan and Kastin, 1999) that changes in central BDNF and cytokine levels might be partly reflected by the changes in peripheral levels. Finally, because of our small sample size, if we correct for multiple comparisons using Bonferroni, our positive findings of reduced cytokine levels and the correlation between reductions in alcohol use and plasma TGF- β 1 levels might not survive. However, if we use the less conservative method, Benjamini-Hochberg method of the false discovery rate (FDR) to correct for multiple comparison, the significance of our result remains if we set $FDR(R)=0.25$. The Q value is $=0.25*1/8=0.03125$ and our result ($P=0.022<Q$ value) would survive multiple comparison.

Conclusion

This appears to be the first pilot study which shows that low-dose add-on memantine (5 mg/day) treatment for BD-II patients with comorbid alcohol dependence significantly attenuated clinical severity, reduced alcohol use and plasma cytokine levels, increased BDNF levels. We also found a significant correlation between reduced alcohol use and reduced plasma TGF- β 1 levels. However, we are not able to confirm whether was related to add-on

memantine. Additional studies with larger samples and a randomized double-blind design are required.

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Figure 1.
Consort diagram of the current study.

Figure 2.
Correlation between changes in alcohol use (unit) and changes in TGF-β1 levels in BD-II patients after a 12-week follow-up.

Table 1.

Demographic and clinical characteristics of the patients at baseline and endpoint

Variable	Baseline (n = 45)		Endpoint (n = 26)	
	Mean	SD	Mean	SD
HDRS	14.4	3.9	9.4	3.2
YMRS	13.8	2.5	9.4	2.9
Alcohol use (unit)	73.9	58.3	11.8	38.8
TNF-α	2.64	2.07	2.66	1.85
CRP	2960.48	1983.52	2382.29	1666.26
BDNF	16196.64	10699.20	18910.46	11743.63
IL-8	17.64	37.93	10.22	25.60
TGF-β1	30884.32	18941.671	27653.85	17175.710
IL-10	2.09	2.080	1.92	2.333

SD: standard deviation; HDRS: Hamilton Depression Rating Scale; YMRS: Young Mania Rating Scale; TNF- α : tumor necrosis factor α ; CRP: C-reactive protein; BDNF: brain-derived neurotrophic factor; IL-8: Interleukin-8; TGF- β 1: Transforming growth factor- β 1; IL-10: Interleukin-10.

Table 2.

Changes in clinical severity, alcohol use, and cytokine levels over 12 weeks of treatment

Variable	B	P	P [†]
HDRS	−5.0	< 0.001**	< 0.001**
YMRS	−4.4	< 0.001**	< 0.001**
Alcohol use	−61.99	< 0.001**	< 0.001**
TNF-α	0.04	0.89	0.88
CRP	−610.08	0.012*	0.013*
BDNF	3096.04	0.018*	0.016*
IL-8	−7.86	0.021*	0.021*
TGF-β1	−3586.37	0.080	0.079
IL-10	−0.182	0.605	0.63

HDRS: Hamilton Depression Rating Scale; YMRS: Young Mania Rating Scale; TNF- α : tumor necrosis factor α ; CRP: C-reactive protein; BDNF: brain-derived neurotrophic factor; IL-8: Interleukin-8; TGF- β 1: Transforming growth factor- β 1; IL-10: Interleukin-10.

[†] controlled for use of fluoxetine, risperidone, lorazepam, and before trial use of depakine.

Table 3.

Relationship between changes in alcohol use vs. changes in cytokine levels

Variable	B	P
HDRS	-1.02	0.77
YMRS	2.12	0.57
TNF-α^a	-4.15	0.53
CRP^a	0.003	0.75
BDNF^a	0.002	0.29
IL-8^a	0.51	0.38
TGF-β1^a	0.003	0.022*
IL-10^a	4.35	0.54

HDRS: Hamilton Depression Rating Scale; YMRS: Young Mania Rating Scale; TNF- α : tumor necrosis factor α ; CRP: C-reactive protein; BDNF: brain-derived neurotrophic factor; IL-8: Interleukin-8; TGF- β 1: Transforming growth factor- β 1; IL-10: Interleukin-10.

Controlled for age and gender, and use of fluoxetine, risperidone, lorazepam and before trial use of depakine.

^aControlled for age, gender, baseline HDRS and YMRS scores, and use of fluoxetine, risperidone, lorazepam, and before trial use of depakine.