Published in final edited form as:

J Psychiatr Res. 2013 October ; 47(10): 1343–1348. doi:10.1016/j.jpsychires.2013.06.017.

Add-on memantine to valproate treatment increased HDL-C in bipolar II disorder

Sheng-Yu Lee^a, Shiou-Lan Chen^{a,b}, Yun-Hsuan Chang^c, Po See Chen^a, San-Yuan Huang^d, Nian-Sheng Tzeng^d, Yu-Shan Wang^b, Liang-Jen Wang^e, I. Hui Lee^a, Tzung Lih Yeh^a, Yen Kuang Yang^a, Ru-Band Lu^{a,b,c,f,*}, and Jau-Shyong Hong^g

^aDepartment of Psychiatry, National Cheng Kung University, Tainan, Taiwan

^bInstitute of Behavioral Medicine, National Cheng Kung University, Tainan, Taiwan

^cInstitute of Allied Health Sciences, College of Medicine and Hospital, National Cheng Kung University, Tainan, Taiwan

^dDepartment of Psychiatry, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan

^eDepartment of Child and Adolescent Psychiatry, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan

^fAddiction Research Center, National Cheng Kung University, Tainan, Taiwan

^gLaboratory of Toxicology and Pharmacology, NIH/NIEHS, Research Triangle Park, NC, USA

Abstract

Memantine is a noncompetitive NMDA receptor antagonist. As an augmenting agent, it has an antidepressant-like and mood-stabilizing effect. Memantine also reduces binge eating episodes and weight. We investigated whether memantine added on to valproate (VPA) is more effective than VPA alone for treating BP-II depression and improving the patient's metabolic profile. This was a randomized, double-blind, controlled study. BP-II patients undergoing regular VPA treatments were randomly assigned to one of two groups: VPA plus either add-on [1] memantine (5 mg/day) ($n = 62$) or [2] placebo ($n = 73$) for 12 weeks. The Young Mania Rating Scale (YMRS) and Hamilton Depression Rating Scale (HDRS) were used to evaluate clinical response. Height, weight, fasting serum glucose, fasting total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides were followed regularly. Multiple linear regressions with generalized estimating equation methods were used to analyze the

*Corresponding author. Institute of Behavioral Medicine, Department of Psychiatry, Addiction Center, College of Medicine and Hospital, National Cheng Kung University, 138 Sheng-Li Road, Tainan 70428, Taiwan. Tel.: +886 6 235 3535x5108; fax: +886 6 302 8012., rblu@mail.ncku.edu.tw (R.-B. Lu).

Trial registration: NCT01188148 (<https://register.clinicaltrials.gov/>), Trial date was from 1st August, 2008 to 31st July, 2012 in National Cheng Kung University and Tri-Service General Hospital.

Author contributions

The authors SYL and RBL wrote the first draft. The authors SYL, SLC, YHC, SHC and CHC managed the lab work and statistics. The authors YSW, SYH, NST, PSC, IHL, TLY and YKY managed the participant recruitment. The author, JSH supervised this work and edited the manuscript.

Conflict of interest

All authors declare that they have no conflicts of interest.

effects of memantine on clinical performance. There were no significant differences in pre- and post-treatment YMRS and HDRS scores between the VPA + memantine and VPA + placebo groups. Although there were no significant differences in the pre- and post-treatment values of most metabolic indices between the two groups, there was a significant increase of HDL-C ($p = 0.009$) in the VPA + memantine group compared with the VPA + placebo group. This increase remained significant even after controlling for body mass index (BMI) ($p = 0.020$). We conclude that add-on memantine plus VPA treatment of BP-II depression increases the blood level of HDL-C even in the absence of change in affective symptoms.

Keywords

Bipolar II disorder; Memantine; Treatment; HDL-C

1. Introduction

Bipolar II disorder (BP-II), defined as recurrent episodes of depression and hypomania, is frequently misdiagnosed in clinical settings (Akiskal and Pinto, 1999; Angst et al., 2003; Benazzi, 2001a; Benazzi and Akiskal, 2003). Depression prompts patients to seek treatment, while hypomania is often perceived as ego-syntonic, and patients tend to experience it as positive (American Psychiatric Association, 2000; Angst, 2007; Angst et al., 2003). Scholars believe BP-II is greatly under-diagnosed in clinical practice and lacks in-depth research because BP-II has been regarded as a “milder form of Bipolar I disorder (BP-I)” (Angst, 2007; Vieta and Suppes, 2008). Long-term follow-ups show that patients with BP-II have a more chronic course, more mood episodes, more major and minor depressive episodes, and shorter inter-episodes, all of which last longer than those of patients with BP-I (Judd et al., 2003; Pallanti et al., 1999; Vieta et al., 1997). Psychosocial impairments also significantly increase with each increment in the severity of the symptoms of depression (Judd et al., 2005).

Although the pharmacological guidelines for treatment for bipolar disorder are well-established (American Psychiatric Association, 2002; Kowatch et al., 2005; Yatham et al., 2005), the treatment in practice remains less than ideal. Most patients still have breakthrough episodes or significant residual symptoms while on medication, and functional deficits often remain even when patients are in remission (Bauer et al., 2002). Increasing evidence suggests the glutaminergic receptor system, especially the N-methyl-D-aspartic acid (NMDA) receptor complex, may be involved in the pathogenesis of bipolar disorder (Schiffer, 2002). Memantine, a noncompetitive NMDA receptor antagonist, has an antidepressant-like effect in animal models (Rogoz et al., 2002; Tsapakis and Travis, 2002). Memantine is increasingly being used in a variety of psychiatric disorders, including bipolar disorder (Sani et al., 2012). Memantine monotherapy is efficacious and well tolerated in patients with acute manic episodes (Keck et al., 2009). The meaningful antimanic and mood-stabilizing effect of memantine, as an add-on augmenting agent for treatment-resistant BP-I and BP-II has been reported in open-label naturalistic observations (Koukopoulos et al., 2010, 2012). These clinical observations suggest that the efficacy of memantine in bipolar disorder needs replication in future randomized clinical trials. Although a possible

antidepressant effect of memantine was reported in an animal model (Quan et al., 2011), memantine's antidepressant effect is still controversial (Ferguson and Shingleton, 2007; Zarate et al., 2006a, 2006b).

Patients with bipolar disorder have a higher prevalence rate of metabolic syndrome than does the general population (Ferguson and Shingleton, 2007; Zarate et al., 2006a, 2006b). Obesity is prevalent in bipolar disorder and is associated with a worse prognosis as well as with suicide attempts (Fagiolini et al., 2005). Metabolic syndrome is associated with increased risks for diabetes mellitus and cardiovascular diseases. Therefore, minimizing the increased risk of metabolic abnormalities in bipolar disorder is an important clinical priority. Memantine is effective for reducing weight (Hermanussen and Tresguerres, 2005) and the number of binge episodes (Brennan et al., 2008). However, the effectiveness of memantine in reducing the risk of metabolic abnormalities during the treatment of bipolar disorder remains unknown.

We evaluated the efficacy of memantine as an augmenting agent for treating BP-II. We conducted a double-blind, placebo-controlled study of VPA plus add-on memantine treatment in patients with BP-II undergoing a depressive episode. We also assessed the metabolic profile in each BP-II patient during the follow-up period. We hypothesized that adding memantine to VPA is more effective than using VPA alone for treating BP-II depression, and that memantine attenuates the risk of metabolic abnormalities in BP-II patients.

2. Methods

2.1. Patient selection

The research protocol was approved by the Institutional Review Board for the Protection of Human Subjects at Tri-Service General Hospital and at National Cheng Kung University Hospital. After the study had been completely described to the participants, they all signed written informed consent forms.

BP-II patients were recruited from outpatient and inpatient settings. All were initially evaluated in an interview by an attending psychiatrist, and followed-up in a more detailed interview by a clinical psychologist 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), to determine Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV), diagnoses. The Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960, 1967) and the Young Mania Rating Scale (YMRS) (Young et al., 1978) were used to evaluate the severity of mood symptoms. Only patients who scored over 18 on the HDRS were recruited. Patients with major mental illnesses, borderline personality disorder, drug dependence, and cognitive disorders other than BP-II were excluded. Patients who had taken memantine within 1 week before the first dose of the double-blind medication were excluded. Patients taking over-the-counter medications, such as statins, that might affect their metabolic profile were also excluded.

Although DSM-IV-TR (American Psychiatric Association, 2000) criteria require a minimum duration of 4 days of hypomania, current epidemiologic data suggest that a 2-day duration is more prevalent in community samples (Akiskal et al., 1977, 1979; Angst, 1998; Angst et al., 2003; Benazzi, 2001b; Judd et al., 2003); therefore, we used a 2-day minimum for hypomania in the diagnosis of BP-II.

2.2. Study design

After a baseline assessment, patients were randomly assigned add-on treatment with memantine (5 mg/day = 0.1 mg/kg) or a placebo for 12 weeks while they continued their open-label VPA treatment (500 mg or 1000 mg daily [50–100 µg/ml in plasma]), which had begun when they joined the study. We used memantine at a very low dose (usually it is used at 20–30 mg/day) because we recently showed that using a low dose of memantine (0.02 mg/kg) 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). Our preliminary clinical data showed that 5 mg/day of oral memantine added to methadone maintenance therapy given to heroin-dependent patients significantly attenuated plasma cytokines, the methadone replacement dose, and combined opiate use (Chen et al., unpublished data). Because of its reported anti-inflammatory and neuroprotective effects, we hypothesized that 5 mg/day of add-on memantine would therapeutically benefit patients with bipolar disorder.

Symptom severity was assessed at baseline and followed by measurements of treatment responses on day 7 of weeks 1, 2, 4, 8, and 12. The severity of current symptoms was assessed using the YMRS and HDRS scores. Concomitant benzodiazepine medication (lorazepam < 8 mg) was used for nighttime sedation, agitation, or insomnia during the study. Up to 20 mg/daily of fluoxetine was permitted for associated depressive symptoms.

Height, weight, waist circumference (midway between the iliac crest and the lower costal margin), blood pressure, fasting serum glucose, fasting total cholesterol, high-density lipoprotein (HDL-C), low-density lipoprotein (LDL-C), and triglycerides were measured at baseline and at the end of the 2nd, 8th, and 12th weeks. Serum levels of valproate were measured at the end of the 2nd, 8th, and 12th weeks.

2.3. Statistical analysis

The demographic and clinical characteristics of the patients, their basic scores on the YMRS and HDRS, and their biochemical indices were compared between groups using one-way analysis of variance (ANOVA) for continuous variables and χ^2 tests for categorical variables. YMRS and HDRS total scores were used as measures of response to add-on memantine. Potential prognostic factors included the treatment duration (weeks 0–12), use of memantine, baseline YMRS and HDRS scores, gender, and age. To evaluate the possible effects of the prognostic factors on the response values, a multiple linear regression model, which is capable of controlling for other prognostic factors, was used. Because there were repeated assessments, multiple linear regressions with the generalized estimating equation method (Zeger et al., 1988) was used to control for time effects, baseline psycho-pathology, and other patient-related variables. The association between memantine treatment and

changes in the patients' metabolic indices was also evaluated using multiple linear regressions with the generalized estimating equation method after controlling for time effects, severity of mood symptoms, blood level of valproate, and other patient-related variables. SPSS version 16.0 was used for statistical computations. Significance was set at $p < 0.05$. The power analysis was done using G-Power 3 software (Buchner et al., 1996; Faul et al., 2009), and the effect-size conventions were determined according to Buchner et al. (1996).

3. Results

One hundred thirty-five patients were recruited and randomly assigned to groups given either add-on memantine (5 mg/day) (VPA + memantine; $n = 62$) or placebo (VPA + placebo; $n = 73$) for 12 weeks (Fig. 1). All BP-II patients were first diagnosed without a history of taking mood stabilizers or memantine. Eighty-four (62%) of the 135 patients completed the double-blind phase and 51 (38%) dropped out, primarily because of a lack of efficacy (placebo, 44%; memantine, 25%) and a failure to return for scheduled appointments (placebo, 41%; memantine, 75%). The demographic and clinical characteristics, baseline HDRS and YMRS scores, and biochemical indices of the patients were similar in both groups at baseline (Table 1).

We analyzed the treatment effect of VPA + placebo and VPA + memantine in BP-II depression. In both groups, the YMRS and HDRS scores significantly decreased after 12 weeks of treatment, but they were not significantly different between the groups (Table 2).

We also analyzed the association between the effect of memantine with the course of illness: onset age, number of episodes, and baseline mood symptoms. The interaction effect of number of episodes and treatment group was inversely and significantly associated with the change of HDRS score (Wald $\chi^2 = 4.28$, $p = 0.039$), but not with the change of YMRS score (Wald $\chi^2 = 2.5$, $p = 0.11$). If we analyze patients with over 4 previous episodes, the change of HDRS in the VPA + memantine group did not differ from the VPA + placebo group (Wald $\chi^2 = 2.00$, $p = 0.157$). Neither baseline HDRS nor YMRS scores, however, were associated with endpoint changes in those scores: HDRS (Wald $\chi^2 = 2.3$, $p = 0.13$); YMRS (Wald $\chi^2 = 1.7$, $p = 0.19$). In addition, the onset age was not associated with the effect of memantine on endpoint HDRS (Wald $\chi^2 = 0.9$, $p = 0.34$) or YMRS scores (Wald $\chi^2 = 3.3$, $p = 0.07$).

After changes in the HDRS and YMRS scores and in the blood level of valproate had been controlled for, endpoint HDL-C levels in the VPA + memantine group had significantly increased compared with those in the VPA + placebo group (Fig. 2; Table 3, model 1; $p = 0.009$). After controlling for BMI as well, the increase remained significant (Table 3, model 2; $p = 0.020$). However, no other changes in the metabolic indices were associated with add-on memantine treatment.

We analyzed the differences in HDL-C levels during each visit in both groups. There were significant differences between endpoint HDL-C (12th week) and baseline ($p = 0.036$), 2nd-week ($p = 0.012$), and 8th-week ($p = 0.029$) HDL-C levels in the VPA + memantine group, but not in the VPA + placebo group.

The study had a power of approximately 0.92 to detect a small effect, and 0.98–1.00 to detect medium and large effects in ANOVA analysis ($N = 135$) for the two groups. For multiple regression analysis, the study had a power of 0.37 to detect a small effect, 0.99 to detect medium effect, and 1.00 to detect large effects. In this power analysis, the effect-size conventions were determined according to Buchner et al. (1996) as follows: small effect size = 0.1, medium effect size = 0.25, large effect size = 0.4 for ANOVA ($\alpha = 0.05$); and small effect size = 0.02, medium effect size = 0.15, large effect size = 0.35 for the multiple regression model ($\alpha = 0.05$).

4. Discussion

In the 12 weeks of treatment, we found that adding memantine to VPA was no more effective than VPA alone for symptom improvement for BP-II depression. Although there were no significant differences in the changes of most metabolic indices between the VPA + memantine and VPA + placebo groups, the VPA + memantine group showed a significant increase in the endpoint HDL-C level, a parameter of metabolic syndrome, but the VPA + placebo group did not. Our study provides initial evidence that 5 mg/day of memantine may raise HDL-C levels in patients with BP-II depression. The HDL-C changes observed in the current study occurred at a dose lower than that generally associated with affective changes. In addition, the relatively large sample size resulted in analyses with good statistical power, which may have decreased the risk of type II errors. However, the reason we found that memantine had no antidepressant effect on our patients might be that the dose was only 5 mg/day, but a standard dose is 20–30 mg/day.

Memantine has not been associated with an increase in HDL-C in prior studies. In a rat model of binge eating (Popik et al., 2011), memantine reduced the consumption of highly palatable food. Schaefer et al. (2007) reported that memantine reversed clozapine-induced weight gain in humans. We found no association between memantine and body-weight or BMI changes; however, it has been suggested (Atmaca et al., 2002; Cassidy and Carroll, 2002; Ghaemi et al., 2000; Pae et al., 2004) that serum lipids are important in the pathophysiology of mood disorders. Chen and Zhou (2001) reported that, in the general population, women with low levels of HDL-C had more depressive symptoms than did women with normal lipid levels. However, the association between bipolar disorder and total cholesterol, HDL-C, LDL-C, and triglyceride levels is still controversial (Atmaca et al., 2002; Pae et al., 2004; Sagud et al., 2007). Lower (Maes et al., 1997) or unaltered (Oxenkrug et al., 1983) serum cholesterol levels were found in prior studies of major depression. Sagud et al. (2009) suggested that low HDL-C levels and a high LDL-C/HDL-C ratio (atherogenic index) might be a hallmark of affective disorders, but this point is still being debated. No effective biomarker is currently available for bipolar disorder, but our finding suggests that serum cholesterol level may be one of the potential markers. The relatively easy and inexpensive sampling methods for serum cholesterol levels would be advantageous should cholesterol be confirmed a practical and clinically useful biomarker candidate for bipolar disorder.

The plasma level of HDL-C has been inversely associated with the risk of cardiovascular diseases, which implies that HDL-C is both cardioprotective and cerebroprotective

(Franceschini, 2001; Sacco et al., 2001; Wannamethee et al., 2000). Furthermore, endogenous HDL-C is known as a scavenger of superoxide anions (Chander and Kapoor, 1990). Reconstituted HDL-C protected neurons against excitotoxic and ischemic damage in a rat model of stroke (Paterno et al., 2004). The mechanism of action through which memantine might affect serum HDL-C levels is not known. Because memantine is an NMDA antagonist, one possibility is that it regulates HDL-C levels by reducing NMDA-receptor-mediated neuronal excitotoxicity (Brennan et al., 2008) and overstimulating glutamate receptors (Choi, 1990). One mechanistic study (Wu et al., 2009) reported that the high potency of a small dose of memantine may have dual actions: an anti-inflammatory effect by reducing the activity of microglia and an increase in the release of neurotrophic factors, such as brain-derived neurotrophic factor (BDNF) and glial-cell-derived neurotrophic factor (GDNF) by astroglia. We hypothesize that memantine improves serum HDL-C levels through its peripheral neurotrophic effect; however, additional large studies are needed to confirm this.

Neurodegeneration is increasingly recognized as one pathogenetic source of bipolar disorder (Burke and Wengel, 2003). Imaging studies (Beyer and Krishnan, 2002; Drevets et al., 1997; Stoll et al., 2000) suggest that ongoing neuronal atrophy accompanies bipolar disorder. Moreover, neurodegeneration has been associated with disturbances in cholesterol metabolism (Bjorkhem et al., 2009); for example, hypercholesterolemia is an important risk factor for developing Alzheimer's disease (Launer et al., 2001; Pappolla et al., 2003). Taking the above findings together, neurodegeneration seems to be a common pathophysiology of disturbance presented in both cholesterol metabolism and bipolar disorder. However, additional investigations of the association, such as genetic links between cholesterol levels and bipolar disorder, are needed.

We found that add-on memantine was not associated with changes in HDRS and YMRS scores. The assessment tool in the current study was only the sum of the scores of the YMRS and HDRS, which makes it difficult to detect specific improvement in individual symptoms. Additional factorial analysis for clustered symptoms is required to explore specific differences in the effect of add-on memantine in depressed BP-II patients. Our negative finding is similar to that of Zarate et al. (2006b), who reported no antidepressant effect of memantine in the treatment of major depression. However, studies (Koukopoulos et al., 2010, 2012) have proposed that memantine may be more effective in patients with more severe illness. Although not associated with the patient's age at onset or baseline mood symptoms, we found that an increase in the number of episodes was associated with a significant decrease in HDRS scores in the VPA + memantine group compared with the VPA + placebo group. Our findings support the notion that memantine is effective in BP-II patients with a more severe course of illness, such as more previous symptoms. Further study evaluating the association of the effect of memantine and other factors connected with the course of illness, such as rapid-cycling, is required to clarify the mood stabilizing effect of memantine in bipolar disorder.

Our study has some limitations. This is the first randomized double-blind study investigating the benefit of add-on memantine treatment on BP-II depression, but our study population was not large enough to allow us to draw strong conclusions. Additional studies study with

larger study populations are required to confirm our positive findings. Given the small effect size = 0.02 for the multiple regression model ($\alpha = 0.05$), we have calculated that a total of 776 participants would be needed to detect change in affective symptoms as statistically significant. Because all the BP-II patients in the current study were first diagnosed without a history of taking mood stabilizers or memantine, our study is not comparable to studies of memantine in treatment-resistant bipolar disorder. Although we tried to control for factors that may affect the change of metabolic profiles, we did not control for the amount and variety of exercise or food intake. Another limitation is that some were given up to four drugs: lorazepam (up to 8 mg/day), memantine (5 mg/day), valproate, and fluoxetine (20 mg/day). Because the plasma concentration of the concomitant medication was not assessed, the influence of these medications on the metabolic profile may not be ruled out. Therefore, our findings should be interpreted with caution. In addition, because the present study was a fixed-dose comparison without dose-assessment trials, the definitive effects of add-on memantine and their clinical efficacy require additional studies. To investigate the possible neurotrophic and anti-inflammatory effects of add-on memantine when treating BP-II, changes in cytokine levels and inflammatory markers should also be monitored to clarify the mechanism of memantine in BP-II.

In conclusion, we found that treating BP-II depression with valproate plus add-on memantine may increase the blood level of HDL-C, but that it had little effect on affective symptoms and other metabolic parameters. We hypothesize that the neuroprotective effect of memantine is involved in the change of serum HDL-C levels. However, additional mechanistic studies such as changes in cytokine levels and inflammatory markers are necessary to confirm our hypothesis.

Acknowledgments

Role of funding source

This work was supported in part by grant NSC98-2314-B-006-022-MY3 (to RBL) from the Taiwan National Science Council, grant DOH 95-TD-M-113-055 (to RBL) from the Taiwan Department of Health, grant NHRI-EX-97-9738NI (to RBL) from the Taiwan National Health Research Institute, and the National Cheng Kung University Project for Promoting Academic Excellence and Developing World Class Research Centers.

We thank Dr. Liang-Jen Wang, Ms. Shin-Feng Yang and Huei-Yu Chuang for their assistance in preparing this manuscript.

References

- Akiskal HS, Djenderedjian AM, Rosenthal RH, Khani MK. Cyclothymic disorder: validating criteria for inclusion in the bipolar affective group. *American Journal of Psychiatry*. 1977; 134:1227–33. [PubMed: 910973]
- Akiskal HS, Pinto O. The evolving bipolar spectrum. Prototypes I, II, III, and IV. *Psychiatric Clinics of North America*. 1999; 22:517–34. vii. [PubMed: 10550853]
- Akiskal HS, Rosenthal RH, Rosenthal TL, Kashgarian M, Khani MK, Puzantian VR. Differentiation of primary affective illness from situational, symptomatic, and secondary depressions. *Archives of General Psychiatry*. 1979; 36:635–43. [PubMed: 444017]
- American Psychiatric Association. *Diagnostic and statistical manual of mental disorder-IV-TR*. 4. Washington: American Psychiatric Association; 2000.
- American Psychiatric Association. *Diagnostic and statistical manual of mental disorder-IV-TR*. 4. Washington: American Psychiatric Association; 2002.

- Angst J. The emerging epidemiology of hypomania and bipolar II disorder. *Journal of Affective Disorders*. 1998; 50:143–51. [PubMed: 9858074]
- Angst J. The bipolar spectrum. *British Journal of Psychiatry*. 2007; 190:189–91. [PubMed: 17329735]
- Angst J, Gamma A, Sellaro R, Lavori PW, Zhang H. Recurrence of bipolar disorders and major depression. A life-long perspective. *European Archives of Psychiatry and Clinical Neuroscience*. 2003; 253:236–40. [PubMed: 14504992]
- Atmaca M, Kuloglu M, Tezcan E, Ustundag B, Bayik Y. Serum leptin and cholesterol levels in patients with bipolar disorder. *Neuropsychobiology*. 2002; 46:176–9. [PubMed: 12566933]
- Bauer M, Unutzer J, Pincus HA, Lawson WB. Bipolar disorder. *Mental Health Services Research*. 2002; 4:225–9. [PubMed: 12558008]
- Benazzi F. Bipolar II depression in late life: prevalence and clinical features in 525 depressed outpatients. *Journal of Affective Disorders*. 2001a; 66:13–8. [PubMed: 11532528]
- Benazzi F. Is 4 days the minimum duration of hypomania in bipolar II disorder? *European Archives of Psychiatry and Clinical Neuroscience*. 2001b; 25:32–4. [PubMed: 11315516]
- Benazzi F, Akiskal HS. Refining the evaluation of bipolar II: beyond the strict SCID-CV guidelines for hypomania. *Journal of Affective Disorders*. 2003; 73:33–8. [PubMed: 12507735]
- Beyer JL, Krishnan KR. Volumetric brain imaging findings in mood disorders. *Bipolar Disorders*. 2002; 4:89–104. [PubMed: 12071514]
- Bjorkhem I, Cedazo-Minguez A, Leoni V, Meaney S. Oxysterols and neurodegenerative diseases. *Molecular Aspects of Medicine*. 2009; 30:171–9. [PubMed: 19248803]
- Brennan BP, Roberts JL, Fogarty KV, Reynolds KA, Jonas JM, Hudson JI. Memantine in the treatment of binge eating disorder: an open-label, prospective trial. *International Journal of Eating Disorders*. 2008; 41:520–6. [PubMed: 18433015]
- Buchner A, Faul F, Erdfelder E. G-Power: a priori, post hoc, and compromise power analyses for the Macintosh. Trier, Germany: University of Trier; 1996. Version 2.1.1. ed
- Burke WJ, Wengel SP. Late-life mood disorders. *Clinics in Geriatric Medicine*. 2003; 19:777–97. vii. [PubMed: 15024812]
- Cassidy F, Carroll BJ. Seasonal variation of mixed and pure episodes of bipolar disorder. *Journal of Affective Disorders*. 2002; 68:25–31. [PubMed: 11869779]
- Chander R, Kapoor NK. High density lipoprotein is a scavenger of superoxide anions. *Biochemical Pharmacology*. 1990; 40:1663–5. [PubMed: 2171536]
- Chen HH, Zhou JF. Low cholesterol in erythrocyte membranes and high lipoperoxides in erythrocytes are the potential risk factors for cerebral hemorrhagic stroke in human. *Biomedical and Environmental Sciences*. 2001; 14:189–98. [PubMed: 11723718]
- Chen SL, Tao PL, Chu CH, Chen SH, Wu HE, Tseng LF, et al. Low-dose memantine attenuated morphine addictive behavior through its anti-inflammation and neurotrophic effects in rats. *Journal of Neuroimmune Pharmacology*. 2012; 7(2):444–53. [PubMed: 22205542]
- Choi DW. Possible mechanisms limiting N-methyl-D-aspartate receptor over-activation and the therapeutic efficacy of N-methyl-D-aspartate antagonists. *Stroke*. 1990; 21:III20–2. [PubMed: 2146778]
- Drevets WC, Price JL, Simpson JR Jr, Todd RD, Reich T, Vannier M, et al. Subgenual prefrontal cortex abnormalities in mood disorders. *Nature*. 1997; 386:824–7. [PubMed: 9126739]
- Endicott J, Spitzer RL. A diagnostic interview: the schedule for affective disorders and schizophrenia. *Archives of General Psychiatry*. 1978; 35:837–44. [PubMed: 678037]
- Fagiolini A, Frank E, Scott JA, Turkin S, Kupfer DJ. Metabolic syndrome in bipolar disorder: findings from the Bipolar Disorder Center for Pennsylvanians. *Bipolar Disorders*. 2005; 7:424–30. [PubMed: 16176435]
- Faul F, Erdfelder E, Buchner A, Lang A. Statistical power analyses using G*Power 3.1: tests for correlation and regression analyses. *Behavior Research Methods*. 2009; 41:1149–60. [PubMed: 19897823]
- Ferguson JM, Shingleton RN. An open-label, flexible-dose study of memantine in major depressive disorder. *Clinical Neuropharmacology*. 2007; 30:136–44. [PubMed: 17545748]

- Franceschini G. Epidemiologic evidence for high-density lipoprotein cholesterol as a risk factor for coronary artery disease. *American Journal of Cardiology*. 2001; 88:9N–13N.
- Ghaemi SN, Shields GS, Hegarty JD, Goodwin FK. Cholesterol levels in mood disorders: high or low? *Bipolar Disorders*. 2000; 2:60–4. [PubMed: 11254022]
- Hamilton M. A rating scale for depression. *Journal of Neurology, Neurosurgery, and Psychiatry*. 1960; 23:56–62.
- Hamilton M. Development of a rating scale for primary depressive illness. *British Journal of Social and Clinical Psychology*. 1967; 6:278–96. [PubMed: 6080235]
- Hermanussen M, Tresguerres JA. A new anti-obesity drug treatment: first clinical evidence that, antagonising glutamate-gated Ca²⁺ ion channels with memantine normalises binge-eating disorders. *Economics and Human Biology*. 2005; 3:329–37. [PubMed: 15886075]
- Huang SY, Lin WW, Ko HC, Lee JF, Wang TJ, Chou YH, et al. Possible interaction of alcohol dehydrogenase and aldehyde dehydrogenase genes with the dopamine D2 receptor gene in anxiety-depressive alcohol dependence. *Alcoholism Clinical and Experimental Research*. 2004; 28:374–84.
- Judd LL, Akiskal HS, Schettler PJ, Coryell W, Maser J, Rice JA, et al. The comparative clinical phenotype and long term longitudinal episode course of bipolar I and II: a clinical spectrum or distinct disorders? *Journal of Affective Disorders*. 2003; 73:19–32. [PubMed: 12507734]
- Judd LL, Akiskal HS, Schettler PJ, Endicott J, Leon AC, Solomon DA, et al. Psychosocial disability in the course of bipolar I and II disorders: a prospective, comparative, longitudinal study. *Archives of General Psychiatry*. 2005; 62:1322–30. [PubMed: 16330720]
- Keck PE Jr, Hsu HA, Papadakis K, Russo J Jr. Memantine efficacy and safety in patients with acute mania associated with bipolar I disorder: a pilot evaluation. *Clinical Neuropharmacology*. 2009; 32:199–204. [PubMed: 19620854]
- Koukopoulos A, Reginaldi D, Serra G, Sani G. Antimanic and mood-stabilizing effect of memantine as an augmenting agent in treatment-resistant bipolar disorder. *Bipolar Disorders*. 2010; 12:348–9. [PubMed: 20565444]
- Koukopoulos A, Serra G, Koukopoulos AE, Reginaldi D. The sustained mood-stabilizing effect of memantine in the management of treatment resistant bipolar disorders: findings from a 12-month naturalistic trial. *Journal of Affective Disorders*. 2012; 136:163–6. [PubMed: 22030128]
- Kowatch RA, Fristad M, Birmaher B, Wagner KD, Findling RL, Hellander M. Treatment guidelines for children and adolescents with bipolar disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2005; 44:213–35. [PubMed: 15725966]
- Launer LJ, White LR, Petrovitch H, Ross GW, Curb JD. Cholesterol and neuropathologic markers of AD: a population-based autopsy study. *Neurology*. 2001; 57:1447–52. [PubMed: 11673587]
- Maes M, Smith R, Christophe A, Vandoolaeghe E, Van Gastel A, Neels H, et al. Lower serum high-density lipoprotein cholesterol (HDL-C) in major depression and in depressed men with serious suicidal attempts: relationship with immune-inflammatory markers. *Acta Psychiatrica Scandinavica*. 1997; 95:212–21. [PubMed: 9111854]
- Oxenkrug GF, Branconnier RJ, Harto-Truax N, Cole JO. Is serum cholesterol a biological marker for major depressive disorder? *American Journal of Psychiatry*. 1983; 140:920–1. [PubMed: 6859316]
- Pae CU, Kim JJ, Lee SJ, Lee C, Paik IH, Lee CU. Aberration of cholesterol level in first-onset bipolar I patients. *Journal of Affective Disorders*. 2004; 83:79–82. [PubMed: 15546649]
- Pallanti S, Quercioli L, Pazzagli A, Rossi A, Dell'Osso L, Pini S, et al. Awareness of illness and subjective experience of cognitive complaints in patients with bipolar I and bipolar II disorder. *American Journal of Psychiatry*. 1999; 156:1094–6. [PubMed: 10401459]
- Pappolla MA, Bryant-Thomas TK, Herbert D, Pacheco J, Fabra Garcia M, Manjon M, et al. Mild hypercholesterolemia is an early risk factor for the development of Alzheimer amyloid pathology. *Neurology*. 2003; 61:199–205. [PubMed: 12874399]
- Paterno R, Ruocco A, Postiglione A, Hubsch A, Andresen I, Lang MG. Reconstituted high-density lipoprotein exhibits neuroprotection in two rat models of stroke. *Cerebrovascular Diseases*. 2004; 17:204–11. [PubMed: 14707423]
- Popik P, Kos T, Zhang Y, Bisaga A. Memantine reduces consumption of highly palatable food in a rat model of binge eating. *Amino Acids*. 2011; 40:477–85. [PubMed: 20571841]

- Quan MN, Zhang N, Wang YY, Zhang T, Yang Z. Possible antidepressant effects and mechanisms of memantine in behaviors and synaptic plasticity of a depression rat model. *Neuroscience*. 2011; 182:88–97. [PubMed: 21440043]
- Rogoz Z, Skuza G, Maj J, Danysz W. Synergistic effect of uncompetitive NMDA receptor antagonists and antidepressant drugs in the forced swimming test in rats. *Neuropharmacology*. 2002; 42:1024–30. [PubMed: 12128003]
- Sacco RL, Benson RT, Kargman DE, Boden-Albala B, Tuck C, Lin IF, et al. High-density lipoprotein cholesterol and ischemic stroke in the elderly: the Northern Manhattan Stroke Study. *JAMA*. 2001; 285:2729–35. [PubMed: 11386928]
- Sagud M, Mihaljevic-Peles A, Pivac N, Jakovljevic M, Muck-Seler D. Platelet serotonin and serum lipids in psychotic mania. *Journal of Affective Disorders*. 2007; 97:247–51. [PubMed: 16820211]
- Sagud M, Mihaljevic-Peles A, Pivac N, Jakovljevic M, Muck-Seler D. Lipid levels in female patients with affective disorders. *Psychiatry Research*. 2009; 168:218–21. [PubMed: 19560828]
- Sani G, Serra G, Kotzalidis GD, Romano S, Tamorri SM, Manfredi G, et al. The role of memantine in the treatment of psychiatric disorders other than the dementias: a review of current preclinical and clinical evidence. *CNS Drugs*. 2012; 26:663–90. [PubMed: 22784018]
- Schaefer M, Leopold K, Hinzpeter A, Heinz A, Krebs M. Memantine-associated reversal of clozapine-induced weight gain. *Pharmacopsychiatry*. 2007; 40:149–51. [PubMed: 17694477]
- Schiffer HH. Glutamate receptor genes: susceptibility factors in schizophrenia and depressive disorders? *Molecular Neurobiology*. 2002; 25:191–212. [PubMed: 11936559]
- Stoll AL, Renshaw PF, Yurgelun-Todd DA, Cohen BM. Neuroimaging in bipolar disorder: what have we learned? *Biological Psychiatry*. 2000; 48:505–17. [PubMed: 11018223]
- Tsapakis EM, Travis MJ. Glutamate and psychiatric disorders. *Advances in Psychiatric Treatment*. 2002; 8:189–97.
- Vieta E, Gastó C, Otero A, Nieto E, Vallejo J. Differential features between bipolar I and bipolar II disorder. *Comprehensive Psychiatry*. 1997; 38:98–101. [PubMed: 9056128]
- Vieta E, Suppes T. Bipolar II disorder: arguments for and against a distinct diagnostic entity. *Bipolar Disorders*. 2008; 10:163–78. [PubMed: 18199235]
- Wannamethee SG, Shaper AG, Ebrahim S. HDL-Cholesterol, total cholesterol, and the risk of stroke in middle-aged British men. *Stroke*. 2000; 31:1882–8. [PubMed: 10926951]
- Wu HM, Tzeng NS, Qian L, Wei SJ, Hu X, Chen SH, et al. Novel neuroprotective mechanisms of memantine: increase in neurotrophic factor release from astroglia and anti-inflammation by preventing microglial activation. *Neuro-psychopharmacology*. 2009; 34:2344–57.
- Yatham LN, Goldstein JM, Vieta E, Bowden CL, Grunze H, Post RM, et al. Atypical antipsychotics in bipolar depression: potential mechanisms of action. *Journal of Clinical Psychiatry*. 2005; 66(Suppl 5):40–8. [PubMed: 16038601]
- Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. *British Journal of Psychiatry*. 1978; 133:429–35. [PubMed: 728692]
- Zarate CA Jr, Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA, et al. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Archives of General Psychiatry*. 2006a; 63:856–64. [PubMed: 16894061]
- Zarate CA Jr, Singh JB, Quiroz JA, De Jesus G, Denicoff KK, Luckenbaugh DA, et al. A double-blind, placebo-controlled study of memantine in the treatment of major depression. *The American Journal of Psychiatry*. 2006b; 163:153–5. [PubMed: 16390905]
- Zeger SL, Liang KY, Albert PS. Models for longitudinal data: a generalized estimating equation approach. *Biometrics*. 1988; 44:1049–60. [PubMed: 3233245]

Fig. 1.
Enrollment, randomization, withdrawals, and completion of the 2 treatment phases.

Fig. 2.

Improvement of high density lipoprotein cholesterol (HDL-C) compared with baseline in the valproate (VPA) + memantine and VPA + placebo groups.

Table 1

Characteristics of depressed BP-II patients taking VPA + memantine or VPA + placebo at baseline and endpoint.

	Baseline		Endpoint	
	VPA + Memantine	VPA + Placebo	VPA + Memantine	VPA + Placebo
Number (<i>n</i>)	62	73	48	36
Gender (male/female) (<i>n</i>)	30/32	41/32	26/22	24/12
Age, mean (SD), (years)	32.7 ± 11.7	30.6 ± 10.8	32.6 ± 11.7	30.3 ± 10.8
Age of onset (years)	16.4 ± 3.1	17.5 ± 5.4		
Number of episodes	5.7 ± 4.6	4.3 ± 2.6		
HDRS ¹ score, mean (SD)	20.6 ± 3.5	20.9 ± 3.9	8.0 ± 6.8	9.7 ± 6.9
YMRS ² score, mean (SD)	6.8 ± 3.3	7.7 ± 3.5	4.7 ± 3.4	5.1 ± 4.0
BMI, mean (SD), (kg/m ²)	21.8 ± 3.4	23.0 ± 4.9	22.6 ± 3.3	24.8 ± 4.9
Glucose AC, mean (SD), (mg/dL)	87.7 ± 14.7	89.6 ± 22.9	83.7 ± 12.3	85.5 ± 12.2
Triglyceride, mean (SD), (mg/dL)	113.6 ± 116.9	112.1 ± 121.8	123.0 ± 116.6	121.7 ± 73.9
Cholesterol (total), mean (SD), (mg/dL)	180.5 ± 39.3	184.2 ± 36.6	182.7 ± 40.5	187.2 ± 39.6
HDL-C, mean (SD), (mg/dL)	55.5 ± 16.0	55.5 ± 15.6	60.4 ± 20.5	50.7 ± 14.9
LDL-C, mean (SD), (mg/dL)	109.3 ± 29.8	111.5 ± 28.8	105.3 ± 32.2	117.1 ± 33.2
LDL-C/HDL-C ratio	2.1 ± 0.8	2.2 ± 0.8	2.0 ± 0.9	2.5 ± 1.1
HbA1C, mean (SD), (%)	5.5 ± 0.4	5.6 ± 0.7	5.6 ± 1.3	5.6 ± 0.6
Body weight, mean (SD), (kg)	60.7 ± 13.2	63.6 ± 15.1	62.1 ± 12.4	70.6 ± 15.8
Systolic BP, mean (SD), (mmHg)	116.0 ± 17.1	111.6 ± 22.6	114.3 ± 22.4	115.2 ± 13.3
Diastolic BP, mean (SD), (mmHg)	74.5 ± 12.9	72.4 ± 13.2	72.9 ± 11.3	72.4 ± 9.7
Waist, mean (SD), (cm)	30.5 ± 3.9	31.5 ± 5.1	31.1 ± 3.7	33.6 ± 5.0
Depakine level, mean (SD), (mg/L)			56.2 ± 32.0	54.5 ± 36.0

VPA: valproate; HDRS: Hamilton Depression Rating Scale; YMRS: Young Mania Rating Scale; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol.

Table 2

Changes in HDRS and YMRS scores from baseline after 12 weeks of VPA + memantine or VPA + placebo treatment in depressed BP-II patients.

	<i>B</i>	Wald χ^2	<i>p</i> -Value
Changes in HDRS scores			
Medication $\times$ Treatment Course	−0.016	0.001	0.976
Age	0.005	0.022	0.882
Gender	0.121	0.023	0.880
Changes in YMRS scores			
Medication $\times$ Treatment Course	0.230	0.524	0.469
Age	−0.052	7.334	0.007
Gender	−0.760	2.309	0.129

VPA: valproate; HDRS: Hamilton Depression Rating Scale; YMRS: Young Mania Rating Scale. Reference group: VPA + placebo group.

Table 3

Changes in metabolic indexes from baseline after 12 weeks of VPA + memantine or VPA + placebo treatment in BP-II depressed patients.

Metabolic indexes	Model 1			Model 2		
	B	Wald χ^2	p-Value	B	Wald χ^2	p-Value
BMI (kg/m ²)	-0.07	0.47	0.49			
Glucose AC (mg/dL)	0.03	0.001	0.97	-1.43	1.12	0.27
Triglyceride (mg/dL)	1.19	0.04	0.84	5.95	0.62	0.43
Cholesterol (total) (mg/dL)	-0.07	0.001	0.98	-0.53	0.06	0.81
HDL-C (mg/dL)	2.157	6.85	0.009*	1.89	5.44	0.02*
LDL-C (mg/dL)	-1.93	1.05	0.31	-1.69	1.00	0.32
LDL/HDL ratio	-0.8	2.94	0.09	-0.22	2.68	0.10
HbA1C (%)	0.07	1.03	0.31	0.02	0.08	0.78
Waist (cm)	-0.15	1.09	0.30	-0.02	0.01	0.93
Body weight (kg)	-0.18	0.66	0.42	-0.13	0.38	0.54

VPA: valproate; HDRS: Hamilton Depression Rating Scale; YMRS: Young Mania Rating Scale.

* $p < 0.05$.

Reference group is VPA + placebo group.

Model 1: Controlled for treatment course, gender, age, HDRS score, YMRS score, blood level of valproate.

Model 2: Controlled for treatment course, gender, age, HDRS score, YMRS score, BMI, and blood level of VPA.