Three-Year, Naturalistic, Mirror-Image Assessment of Adding Memantine to the Treatment of 30 Treatment-Resistant Patients With Bipolar Disorder

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ABSTRACT

Background: Developing safe and effective long-term treatments for bipolar disorder remains a major challenge. Given available treatments, patients with bipolar disorder remain unwell in half of long-term follow-up, mostly in depression. As memantine, an *N*-methyl-D-aspartate (NMDA)–glutamate receptor antagonist used to treat dementia, has been proposed for testing in bipolar disorder, we carried out a 3 + 3-year, mirror-image, chart-review study of the effects of adding memantine to stably continued, but insufficiently effective, ongoing mood-stabilizing treatments.

Method: Outpatients diagnosed with *DSM-IV-TR* bipolar disorder (I or II), followed intensively at the Lucio Bini Mood Disorder Center, Rome, Italy, had responded consistently unsatisfactorily to standard treatments (lithium, anticonvulsants, antipsychotics, antidepressants, and electroconvulsive therapy) for ≥ 3 years (2005–2013). Memantine (20–30 mg/d) was added clinically to otherwise stable regimens for another 3 years. On the basis of chart review, we compared morbidity measures and Clinical Global Impressions scale for Bipolar Disorder (CGI-BP) score before versus during memantine treatment.

Results: The 30 bipolar I (n = 17) and II (n = 13) subjects showed consistent morbidity for 3 years before memantine, but improved progressively ($r = 0.28$, $P < .01$) over 3 years with memantine (23 ± 4.8 mg/d). Markedly decreased (all P values ≤ .01) were (1) percentage of time ill (total, mania, or depression; averaging –75.0%), (2) CGI-BP severity scores (–67.8%), (3) duration of new episodes (–58.6%), and (4) episodes/year (–55.7%). Subjects with previous rapid or continuous cycling were particularly improved ($t = 2.61$, $P = .016$). Adverse effects were mild and rare.

Conclusions: Memantine added substantial long-term benefits by preventing or ameliorating depressive as well as mania-like morbidity in previously consistently poorly responsive patients with bipolar disorder. Further testing in randomized, controlled trials is required.

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Long-term treatment of bipolar disorder (BD) aimed at preventing recurrences of the various phases of this complex illness is a leading clinical and research challenge for contemporary psychiatry. With the possible exception of lithium carbonate, it has been difficult to develop unambiguous evidence for effective, long-term mood stabilization in BD uncomplicated by artifacts associated with trials involving treatment-discontinuation designs, particularly following incomplete recovery from acute episodes of illness.[1] Treatments with evidence of long-term beneficial effects and with current regulatory approval for prophylactic applications include lithium carbonate, lamotrigine, aripiprazole, and olanzapine, as well as quetiapine as an adjunctive agent.[1–3] Most antipsychotic drugs and the anticonvulsants carbamazepine and valproate are useful in acute manic or mixed-states but lack regulatory approval for long-term applications in BD and have variable effects in acute bipolar depression.[4] Antidepressants remain controversial for use in acute bipolar depression and lack evidence of substantial long-term preventive effects.[1,5,6]

All of these treatments, as well as others sometimes used on an empirical or "off-label" basis, appear to be incompletely effective, alone or in various combinations. It is remarkable that, even with currently available treatments used by community standards of care, patients with BD remain unwell in approximately half of weeks of long-term follow-up, both during the midcourse of the illness and from onset.[7] Moreover, fully three-quarters of this unresolved morbidity is depressive, dysthymic, or dysphoric.[7] These considerations underscore the urgent need for more effective treatments that can provide long-term protective effects in BD patients, particularly for depressive components of the disorder that are closely associated with disability, substance abuse, and premature mortality.[8–10]

One potential candidate is memantine (1-amino-3,5-dimethyladamantane hydrochloride; Namenda and others), currently indicated for the treatment of some forms of dementia. This pharmacologically complex adamantane derivative was first synthesized in the 1960s.[11] It is a low-affinity, rapidly dissociating, voltage-dependent, uncompetitive antagonist at glutamate *N*-methyl-D-aspartate (NMDA) receptors, which inhibits neuronal influx of Ca^{2+} ions, but does not prevent functioning of glutamate excitatory neurotransmission.[11,12] Memantine also has noncompetitive activity at some cerebral nicotinic acetylcholine receptors (including α_7) that is followed by their rapid up-regulation, perhaps contributing to antidementia effects. In addition, memantine has noncompetitive antagonistic activity at serotonin 5-HT_3 receptors, of unknown significance, with additional agonistic actions at dopamine D_2 receptors.[11] A proposed laboratory model of BD involves up-regulation of dopamine D_2 receptors by repeated treatment with antidepressants, associated with increased, possibly mania-related, behavioral responsiveness of laboratory animals to dopamine

Clinical Points

- Memantine may have substantial, long-term, mood-stabilizing effects in otherwise treatment-resistant bipolar disorder (BD) patients and had excellent tolerability at daily doses of 20–30 mg.
- Clinical improvements with memantine occurred in both type I and II BD patients, including reduction of the number, duration, and severity of episodes in both mania-like and depressive morbidity, and were independent of initial clinical status at the start of memantine treatment.
- Subjects with previous rapid or continuous cycling were particularly improved with memantine treatment.

agonists, followed by a "depressive" state after discontinuing antidepressants.[13] Such effects of antidepressant treatment are prevented by cotreatment with NMDA antagonists including memantine, but not by standard mood-stabilizing drugs.[14,15]

In daily doses of 10–30 mg, memantine is used in the treatment of moderate-to-severe,[16] but not mild,[17] Alzheimer's disease with a favorable efficacy/risk ratio; it also may be effective in other types of nonvascular dementia.[18] Memantine undergoes little hepatic metabolism and has a relatively long elimination half-life (60–100 hours). It appears to be less likely than other NMDA antagonists, such as phencyclidine and ketamine, to induce psychotic reactions, although such effects may occur infrequently with memantine.[19] Memantine has been considered for use in the treatment of various psychiatric disorders, usually with inconsistent or inconclusive findings, particularly in schizophrenia.[20,21] In patients with dementia, clinical benefits may include reduction of irritability, agitation, aggression, and some psychotic symptoms, as well as a reduced need for other psychotropic drugs.[22,23]

Studies of effects of memantine in BD, specifically, remain limited and tentative, though suggestive. Memantine monotherapy was reported to show evidence of antimanic effects at well-tolerated daily doses (20–50 mg) in a 3-week open-label trial in 33 acutely manic patients.[24] Our group found suggestive evidence of mood-stabilizing actions in 40 patients with BD in an unblinded, 12-month trial when memantine was added to stable, ongoing, but inadequately effective, treatments.[25] Memantine as a monotherapy also has been reported to show beneficial effects in mania and possibly for long-term mood stabilization in a few individual BD patients, including after discontinuation of lithium treatment.[26,27] Another short-term study found memantine (20 mg/d; n = 14) to be more effective than placebo (n = 15) when added to lamotrigine for 4 weeks to treat acute bipolar depression in a randomized, controlled trial, but this effect was no longer significant at 8 weeks.[28] A recent 12-week trial found little overall difference in effects of small doses of memantine (5 mg/d; n = 62) versus placebo (n = 73) added to valproate in patients with bipolar II disorder for 12 weeks.[29]

The few studies that have evaluated effects of memantine in BD, therefore, are inconsistent regarding short-term effects but vary in the current morbid status of subjects tested, doses of memantine, and duration of treatment. More prolonged treatments might have been more helpful. Given this suggestive but inconclusive background of possible beneficial effects on mania and bipolar depression, we evaluated the effects of adding memantine clinically for 3 years to stable, ongoing, mood-stabilizing treatments that had proved to be consistently unsatisfactory over several preceding years in types I and II BD patients in varied states of initial morbidity. We hypothesized that adding memantine in such circumstances might yield long-term reductions of morbidity involving manic and possibly also depressive recurrences based on selected outcome measures.

METHOD

Subjects were evaluated and treated as outpatients at the Lucio Bini Mood Disorder Center in Rome, Italy (2005–2013). In an effort to improve their clinical status, patients were given memantine augmentation clinically and individually after failing to respond satisfactorily to prolonged trials of standard mood-stabilizing treatments over several years. Patients provided informed consent for the off-label administration of a drug with regulatory approval for other indications and for possible future anonymous analysis of their clinical data and its reporting in aggregate form. These procedures are consistent with current Italian law pertaining to individually, clinically decided, off-label use of marketed drugs. The study was a retrospective chart review of clinically acquired data that was collected prospectively by the same expert psychiatrist (A.K.).

Memantine was given to patients meeting *DSM-IV-TR* diagnostic criteria for type I or II BD, aged 18–70 years, lacking major, unstable medical illnesses, and with adequate contraception for women of childbearing age. The same clinician (A.K.) had followed all study patients personally for several years and documented their clinically unsatisfactory responses to standard mood-stabilizing treatments for several years before considering them for addition of memantine. He then added memantine on an individually decided, clinical basis to clinically unsatisfactory treatment regimens, not according to a formal protocol. Treatments were held constant throughout the 3 years of addition of memantine in this open-label, naturalistic, clinical study. Assessments were made regularly and prospectively to compare clinical status in the 3 years during versus the 3 years before memantine. We evaluated morbidity on a per-time-at-risk basis, evaluated consistency of observed changes before, and tested for possible temporal changes during memantine treatment. Ongoing treatments included standard mood-stabilizing agents, including lithium at daily trough serum concentrations of 0.6–1.0 mEq/L, selected anticonvulsants (carbamazepine, lamotrigine, and valproate), or antipsychotic agents (in various combinations, usually adjunctively in low doses), as well as antidepressants when required. A third of the subjects (10/30) had also received trials of electroconvulsive shock treatment in the past, consistent with relatively severe illness. All study subjects were considered to respond consistently

unsatisfactorily for at least 3 years prior to trial entry based on clinical assessments and repeatedly elevated ratings of overall morbidity with the Clinical Global Impressions scale for Bipolar Disorder (CGI-BP-total[30]), with scores of > 5 at the point of starting memantine. A majority of participants (20/30) had been ill more than half of the time during the 3 years prior to starting memantine.

Data collected for each subject included the number, type (polarity), and estimated duration of episodes of BD illness based on regular assessments every 2–4 weeks for the 3 years before memantine treatment was given and every 2 weeks during the 3 years of prospective memantine treatment based on semistructured clinical assessments and recording of clinical status using life charts.[31] In addition, all subjects were rated with the CGI-BP scale at least once yearly to assess the average interval severity of overall illness, as well as that of manic and depressive episodes. Clinical assessments were recorded systematically and prospectively before and during memantine and summarized in life charts, all in accordance with the standard clinical practices of the study center; these records provided data for the present analyses.

Memantine hydrochloride at daily oral doses of 20–30 mg was added to ongoing, mood-stabilizing treatment, which was held constant across the 3 years of the trial but for adjusting doses to current clinical requirements. For new acute episodes of BD illness, temporary addition only of treatments that had been given previously to the same patient for similar acute illnesses was allowed, including an antipsychotic agent for mania and an antidepressant for acute major depression based on the discretion of the senior treating psychiatrist.

We compared the number of illness episodes and the estimated duration of episodes considered as mania-related (mania, hypomania, psychosis) or depression-related (depression with or without psychosis, dysthymia, dysphoric-agitated mixed-states), as well as their severity based on CGI-BP ratings. Systematically collected and recorded clinical assessment data allowed quarterly estimates of episode counts and durations and computation of the percentage of months of mania-related illness, depression, and all affective illness. These measures were averaged for 12-month intervals and compared yearly for the 3 years before versus 3 years during treatment with memantine added.

Averages for individual subjects were compared between times before versus during memantine treatment using paired *t* tests. We also employed linear regression to test for changes in percentage of time ill and of mean CGI-BP scores versus year of observation during periods before and during memantine treatment. Finally, we considered selected factors (age, sex, diagnosis, total years of illness, polarity of episodes closest to the start of memantine, and predominant cycling pattern) in preliminary bivariate comparisons for before versus during memantine treatment, followed by multivariate, linear regression modeling of factors tentatively associated with change in total percentage of time ill. Data are means (SDs) or medians with interquartile ranges (IQR), unless stated otherwise. Statistical analyses were made with commercial software (Stata.12, StataCorp, College Station, Texas; including spreadsheets based on Statview.5, SAS Institute, Cary, North Carolina).

RESULTS

Subject Characteristics

We reviewed and analyzed the medical records of 30 patients with *DSM-IV-TR* bipolar I (n = 17) or II (n = 13) disorder to compare morbidity during 36 months of illness course before to 36 months with memantine added to otherwise stable, but clinically unsatisfactory, treatment regimens. A total of 44 BD patients had been started on memantine augmentation at the study center through 2013. Ten patients discontinued or were lost at follow-up before 3 years of treatment, at 6–18 months after starting memantine. Of these, 4 patients were rated as unchanged (CGI-BP improvement score of 4) at their last assessment; 1 patient was minimally improved (CGI-BP improvement score of 3), and 5 patients (50.0%) were rated as very much or much improved (CGI-BP improvement score of 1 or 2). Reasons for dropout included complaints of drowsiness (1 patient), lack of immediate efficacy (2 patients), and loss of hypomania (1 patient). Another 4 subjects with major changes in other medications also were omitted but appear elsewhere in case reports.[26,27]

Participant age averaged 46.9 years, with a mean of 23.7 years from illness onset, and assessment and treatment at the study site averaged 7.53 ± 7.19 years; 70.0% of participants were women (Table 1). The subjects had been consistently symptomatic in the 3 years before memantine treatment was added: median percentage of time ill was 66.7% (IQR: 23.3%–100%); 66.7% had been ill > 50% of the time and 33.3% for > 90%. A high proportion of subjects (56.7%) had shown rapid (≥ 4 discrete episodes/year) or continuous cycling at some time during the 6 years of study; when a course pattern could be identified, it was characterized as being dominated by episodes of mania preceding depression episodes or the opposite.[31] Overall, CGI-BP scores averaged 6.41 ± 1.05 at the start of memantine treatment. These several measures indicate relatively high levels of previous and initial morbidity. Initial clinical states at the start of memantine treatment were hypomanic or manic in 40.0% of patients, depressive in 33.3% of patients, and more or less euthymic in 26.7% of patients.

The proportions and average doses of other treatments were typical of patients with BD and very similar before and during addition of memantine, thus supporting the conclusion that treatments were substantially held constant (Table 1).

Morbidity Before Versus During Memantine Treatment

Several measures indicated marked differences in morbidity between the years during versus the years before starting adjunctive memantine treatment, consistently in the direction of less severe illness with memantine (Table 2). These outcome measures included episodes/year (total,

Table 1. Subject Characteristics

Characteristic	Measure
Subjects, N	30
Women, % (n = 21)	70.0
Current age, mean ± SD, y	46.9 ± 14.3
Diagnosis, %	
Bipolar I (n = 17)	56.7
Bipolar II (n = 13)	43.3
Course types, %	
Rapid cycling (n = 14)	46.7
Continuously cycling (n = 3)	10.0
Irregularly cycling (n = 1)	3.33
MDI or DMI sequences (n = 12)[a]	40.0
Initial clinical state, %[b]	
Hypomanic, manic, or psychotic (n = 12)	40.0
Depressed (n = 10)	33.3
Euthymic (n = 8)	26.7
Initial CGI-BP score, mean ± SD[b]	6.41 ± 1.05
Treatments before vs with memantine, %[c]	
Lithium carbonate (before n = 23; with n = 24)	79.3 vs 82.8
Anticonvulsants (before n = 21; with n = 21)	72.4 vs 72.4
Antipsychotics (before n = 22; with n = 16)	75.9 vs 55.2
Mean doses before vs with memantine, mg/d[d,e]	
Lithium carbonate (before n = 23; with n = 24)	500 ± 380 vs 614 ± 330
Anticonvulsants (before n = 21; with n = 21)	642 ± 558 vs 551 ± 448
Antipsychotics (before n = 22; with n = 16)	84.2 ± 73.7 vs 49.7 ± 108
Memantine dose, mean mg/d ± SD	23.3 ± 4.79

[a]Course-sequences: (hypo)mania-depression-euthymia (MDI); depression-(hypo)mania-euthymia (DMI); others are rapid, continuous, or irregularly cycling (60% of cases).
[b]When memantine started.
[c]For all agent-types, $\chi^2 \leq 2.70$, $P < .10$.
[d]Doses are mg/d for lithium carbonate, and standardized for anticonvulsants (as divalproex-equivalents) and antipsychotics (as chlorpromazine-equivalents).[1]
[e]Lithium dose increased by 22.8% (paired $t = 1.69$, $P = .10$), anticonvulsants decreased by 14.2% ($t = 1.22$, $P = .20$), and antipsychotics decreased by 41.0% ($t = 1.91$, $P = .07$).
Abbreviation: CGI-BP = Clinical Global Impressions scale for Bipolar Disorder.

Table 2. Morbidity Before and During Treatment With Memantine

Measure	Before	During	% Change	*t* Score[a]	*P* Value
Episodes/y					
Total	2.46 ± 2.18	1.09 ± 0.78	−55.7	3.25	.003
(Hypo)manic	1.17 ± 1.13	0.57 ± 0.46	−51.3	2.65	.01
Depressive	1.29 ± 1.13	0.51 ± 0.53	−60.5	3.70	.0009
Episode duration, mo					
All episodes	4.25 ± 3.49	1.76 ± 1.03	−58.6	3.57	.0004
(Hypo)manic	2.93 ± 1.64	1.66 ± 1.16	−43.3	3.07	.002
Depressive	5.37 ± 5.50	1.77 ± 1.17	−67.0	2.94	.0025
Percentage of time ill					
All illness	61.2 ± 29.1	15.3 ± 12.7	−75.0	8.01	< .0001
(Hypo)mania	23.2 ± 16.3	7.40 ± 8.35	−68.1	4.22	.0002
Depression	38.1 ± 23.7	7.94 ± 10.3	−79.2	7.40	< .0001
CGI-BP scores					
Overall	6.22 ± 1.04	2.00 ± 0.91	−67.8	17.3	< .0001
Mania	3.86 ± 1.58	1.59 ± 0.64	−58.8	7.52	< .0001
Depression	5.36 ± 1.79	1.77 ± 0.81	−67.0	10.6	< .0001

[a]The *t* scores are based on paired comparisons, except for episode durations (unpaired since some subjects had no recurrences with memantine).
Abbreviation: CGI-BP = Clinical Global Impressions scale for Bipolar Disorder.

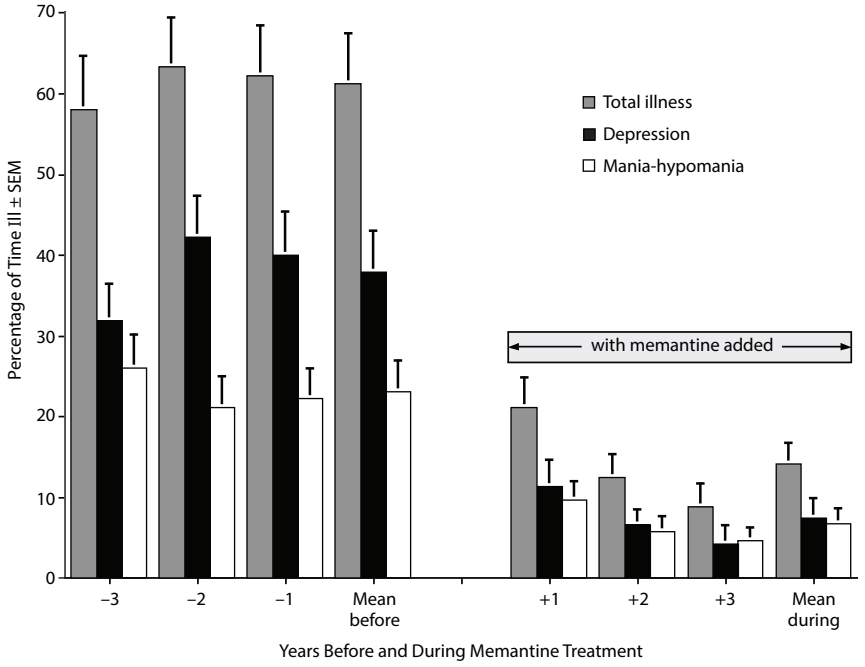
depressive, and manic or hypomanic), estimated average duration of episodes (total and specific types), proportion of time ill (and time in depressive or manic illness), and mean annual CGI-BP scores for overall morbidity, as well as for mania-like and depression-related illness states. Improvements ranged from a low of 43.3% shorter mania-like recurrences to a high of 79.2% less time in depression; all of the changes were highly significant, based on paired comparisons (Table 2). Several of the previously treatment-resistant study participants (4/30; 13.3%) had no new illness recurrences in the 3 years of treatment with memantine; a substantial proportion (12/30; 40.0%) were ill ≤ 10% of the entire 3 years during such treatment, and 33.3% (10/30) were illness-free in at least 1 of the years during memantine treatment (all in years 2 and 3).

As expected,[7,9] time in depressive states was much greater than time in mania-like states before adding memantine, but, surprisingly, this difference was much less during memantine treatment (Table 2). This change reflects the particularly noteworthy finding that depressive morbidity tended to be reduced by at least as much, and possibly more than mania-like illness, in terms of episodes/year, months/episode, and in percentage of time ill (percentage change in time depressed decreased by 79.2%, and in time manic by 68.1%; $t = 1.29$, $P = .21$; Table 2). These findings suggest substantial long-term improvements in all aspects of BD morbidity, with somewhat greater effects on depressive than on mania-like illness.

That episode recurrences decreased by an average of 55.7%, and their duration decreased by 58.6% during versus before memantine treatment, with similar decreases in both mania-like and depression-like episodes, suggests that the duration and perhaps severity, as well as risk of new episodes, were reduced during treatment with memantine (Table 2). The impression that the intensity of morbidity may have been reduced is further suggested by indications that in type I BD patients, the rate of recurrence of manic episodes decreased markedly with memantine (by 89.3%, from 0.58 ± 0.48 to 0.06 ± 0.13 episodes/year; paired $t = 4.04$, $P = .001$), whereas recurrences of hypomania tended to *increase* (by 66.7%, from 0.38 ± 0.42 to 0.63 ± 0.48 episodes/year; paired $t = 2.02$, $P = .06$; not shown). There were no instances of increased hypomania among BD type II patients (percentage time in hypomania was reduced by 75.7%, $t = 2.56$, $P = .03$, and the number of hypomanic recurrences was reduced by 69.6%, $t = 2.05$, $P = .05$). That is, there was an evident shift from mania to hypomania, adding to the impression that the severity of mania was reduced.

Overall morbidity as well as the proportion of time in mania-like and depression-like states before and during addition of memantine for each of the 3 years before and 3 years during addition of memantine is illustrated (Figure 1). These findings indicate that morbidity was quite stable over the 3 years of observation before memantine, but has declined over the years of memantine treatment. This hypothesis was tested by regressing the proportion of time ill versus years, separately, for before and during memantine treatment. Before memantine, there was no significant change over time ($r = 0.050$, $P = .638$), whereas during the 3 years of

Figure 1. Morbidity (percentage of time ill ± SEM; N = 30) as Total Affective Illness (gray bars), Depression (black bars), and Mania (white bars) in Each of 3 Years Preceding Versus 3 Years During Added Memantine Treatment (and the 3-year averages of each morbidity type)[a]



[a]For total morbidity averaged across the 3 years before versus during memantine treatment, paired $t = 8.01$, $P < .0001$.

Table 3. Factors Associated With Greater Percentage Improvement of Overall Percentage of Time Ill With Memantine Added to Treatment of Bipolar Disorder Patients

	Percentage Improvement (n)		*t*	*P*
Factor[a]	Factor Present	Factor Absent	Score	Value
Rapid or continuous cycling	78.8 ± 16.8 (16)	49.4 ± 46.2 (10)	2.33	.028
Bipolar II diagnosis	79.9 ± 16.1 (13)	58.5 ± 38.1 (17)	1.89	.069
Age > 40 y[b]	73.6 ± 18.4 (16)	61.0 ± 42.4 (14)	1.08	.288
Ill > 20 y[c]	73.0 ± 18.9 (15)	62.5 ± 41.3 (15)	0.896	.378
Male sex	75.5 ± 15.2 (9)	64.4 ± 36.8 (21)	0.869	.392
Memantine started in (hypo)mania[d]	72.7 ± 35.8 (12)	64.4 ± 29.9 (18)	0.682	.501

[a]Factors are listed in descending order of significance.
[b]Linear regression of improvement vs age: $r = 0.166$, $P = .380$.
[c]Linear regression of improvement vs years of illness: $r = 0.010$, $P = .958$.
[d]Improvement vs initial status: (hypo)mania 72.7% ± 35.8% (n = 12); depression 68.7% ± 16.4% (n = 10); euthymia 59.1% ± 42.0% (n = 8).

memantine treatment, morbidity declined significantly over time ($r = –0.288$, $P = .006$). Similar relationships were found for changes of yearly-averaged CGI-BP ratings of overall morbidity: before ($r = 0.059$, $P = .603$) versus during memantine treatment ($r = –0.244$, $P = .03$).

Factors Associated With Improvement

We compared the mean 3-year percentage change in overall proportion of time ill with versus before memantine-treatment as an outcome measure (Table 3). In bivariate comparisons, only rapid or continuous cycling (vs slower or erratic cycling) was significantly associated with greater benefit with memantine (possibly an artifact of greater initial deviance). There also was a nonsignificant tendency for somewhat better responses among subjects diagnosed with type II versus type I BD. Other factors *not* significantly associated with percentage change in overall proportion of time ill included sex, current age, years of illness, and clinical status (in mania-like or depressive episodes, or euthymic) at the start of memantine treatment (Table 3). In multivariate linear regression modeling of factors even suggestively associated with the outcome measure in the preliminary bivariate analyses, only a rapid or continuously cycling course type remained significantly associated with superior outcome, regardless of other covariates included (Table 4).

Table 4. Multivariate Linear Regression Model of Factors Associated With Reduction in Overall Percentage of Time Ill Among Treatment-Resistant Bipolar Disorder Subjects[a]

Factor	Slope Function, β [95% CI]	*t* Score	*P* Value
Rapid or continuous cycling	32.4 [7.74 to 58.1]	2.61	.016
Male sex	19.6 [–7.26 to 46.5]	1.51	.145
Years of illness	0.095 [–0.981 to 0.790]	0.22	.825
Initial (hypo)mania	0.255 [–16.0 to 15.5]	0.03	.974

[a]Outcome = percentage change of overall percentage of time ill during vs before memantine treatment, with modeling based on factors identified preliminarily (Table 3), including unassociated factors of interest.

DISCUSSION

The present findings support a growing body of evidence suggesting that memantine may have substantial long-term benefits for a variety of measures of morbidity among BD patients (Table 2). In this long-term, open, naturalistic study, standard treatments had been persistently unsatisfactory in reducing BD morbidity for at least 3 years before memantine

was added to otherwise stable treatment regimens (Figure 1). Addition of memantine, even to relatively complex treatment regimens, was remarkably well tolerated for 3 years.

In the present multiyear study, improvements were seen among both type I and II BD patients in mania-like and depressive morbidity and were independent of initial clinical status at the start of memantine treatment. In addition, there were indications that illness severity may have diminished with memantine in that recurrences were briefer, and there appeared to be a substantial shift from manic to hypomanic recurrences. Given the difficulty of long-term control of the depressive components of BD and their major clinical importance in terms of disability and excess mortality,[8–10,32,33] it may be particularly significant that improvements in depressive morbidity, on average, were somewhat greater than in mania-like morbidity (Table 2). On the other hand, this observation may reflect a statistical consequence of the generally higher starting levels of depressive morbidity.

Previous clinical observations had suggested possible antimanic and mood-stabilizing effects of memantine in BD patients,[24–27] as well as reduction of possibly mania-like manifestations associated with other neuropsychiatric disorders.[22,23,34,35] The antimanic effects of memantine may exceed those in *acute* depression in short-term studies,[28,36,37] in contrast to the rapid antidepressant actions of the more potent NMDA-antagonist ketamine.[38] However, in the present observation, *long-term* benefits appeared to be at least as great against bipolar depression as for mania-like morbidity. The present long-term benefits for depressive aspects of BD associated with adding memantine to other standard treatments for BD might also reflect reductions of mixed, agitated-dysphoric features, or indirect amelioration of depression secondary to prevention or amelioration of manic aspects of the disorder. Broader effects of preventing mania, including on bipolar depression, have been hypothesized previously.[39,40]

As the reported mechanisms of action of memantine are complex and implicate neurotransmission through glutamate, serotonin, dopamine, and nicotinic acetylcholine receptors, it is not clear why this agent should have mood-stabilizing effects. It is also not clear whether its beneficial effects in dementia are based on pharmacodynamic actions similar to its apparent effects in BD. Mechanisms that may plausibly be considered include modulation of dopaminergic neurotransmission,[15,41,42] perhaps neurotrophic or neuroprotective effects,[43,44] or reduction of proposed pathophysiologic excitotoxic effects.[45–47]

Clinical questions arising from this study that remain to be examined are whether memantine will prove useful in the long-term treatment of BD as a monotherapy or in specific and limited combinations with other agents, as well as its optimal dosing. Also remaining to be determined is the extent to which memantine may exert short-term antimanic compared to antidepressive effects in BD. These questions require additional, adequately designed and controlled trials.

Limitations of the present study are clear and substantial. They include a lack of adequate controls or blinding and a small number of patients who may not be representative of broader samples of BD patients. On the other hand, striking benefits were found in a particularly challenging sample of patients who had shown clinically inadequate responses to standard treatments for several years. Lack of a randomly assigned placebo control group led to use of a within-subject analytic design based on paired comparisons. Moreover, unresolved morbidity had been stable for at least 3 years before showing not only major, but also progressive improvements with memantine (Figure 1). These aspects of the findings tend to support their plausibility.

In conclusion, this preliminary, naturalistic study evaluated effects of adding memantine in doses used to treat dementias in type I and II BD patients who had consistently shown clinically unsatisfactory responses to standard mood-stabilizing treatments for at least 3 years. It found major improvements in recurrence rates, duration, and possibly the severity of both mania-like and depressive morbidity that were sustained and may have increased over the 3 years of memantine treatment. Particularly important may be suggestions of superior benefits in the especially hard-to-treat depressive components of BD illness.

Drug names: aripiprazole (Abilify), carbamazepine (Carbatrol, Equetro, and others), divalproex (Depakote and others), ketamine (Ketalar and others), lamotrigine (Lamictal and others), lithium (Lithobid and others), memantine (Namenda), olanzapine (Zyprexa), quetiapine (Seroquel).

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Potential conflicts of interest: **Dr Gino Serra** has applied for a patent for use of memantine to treat bipolar disorder. **Dr Girardi** has received grant/research support from Eli Lilly and Janssen; has received honoraria from Eli Lilly and Organon; and has served on the speakers or advisory boards for Eli Lilly, Organon, Pfizer, and Schering. **Drs Giulia Serra, A. E. Koukopoulos, De Chiara, Tondo, Baldessarini,** and **Gino Serra** and their immediate family members have no current financial relationships with commercial entities that might appear to represent potential conflicts of interest with the material presented. **Dr A. Koukopoulos** had no conflicts of interest.

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