

Memantine: New prospective in bipolar disorder treatment

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Abstract

We review preclinical and clinical evidences strongly suggesting that memantine, an old drug currently approved for Alzheimer's dementia, is an effective treatment for acute mania and for the prevention of manic/hypomanic and depressive recurrences of manic-depressive illness. Lithium remains the first line for the treatment and prophylaxis of bipolar disorders, but currently available treatment alternatives for lithium resistant patients are of limited and/or questionable efficacy. Thus, research and development of more effective mood stabilizer drugs is a leading challenge for modern psychopharmacology. We have demonstrated that 21 d administration of imipramine causes a behavioural syndrome similar to a cycle of bipolar disorder, *i.e.*, a mania followed by a depression, in rats. Indeed, such treatment causes a behavioural supersensitivity to dopamine D2 receptor agonists associated with an increase sexual activity and aggressivity (mania). The dopamine receptor sensitization is followed, after imipramine discontinuation, by an opposite phenomenon (dopamine receptor desensitization) and an increased immobility time (depression) in the forced swimming test of depression. Memantine blocks the development of the supersensitivity and the ensuing desensitization associated with the depressive like behavior. On the basis of these observations we have suggested the use of memantine in the treatment of mania and in the prophylaxis of bipolar disorders. To test this hypothesis we performed several naturalistic studies that showed an acute antimanic effect and a long-lasting and progressive mood-stabilizing action (at least 3 years), without clinically relevant side effects. To confirm the observations of our naturalistic trials we are now performing a randomized controlled clinical trial. Finally we described the studies reporting the efficacy of memantine in manic-like symptoms occurring in psychiatric disorders other than bipolar. Limitations: A randomized controlled clinical trial is needed to confirm our naturalistic observations.

Conclusion: We believe that this review presents enough pharmacological and clinical information to consider the administration of memantine in the treatment of bipolar disorders that no respond to standard mood stabilizers.

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Key words: Memantine; Bipolar disorder; Depression; Mood stabilizer; Manic symptoms

Core tip: Memantine, blocks the development of the supersensitivity of dopamine receptors caused by antidepressants and the ensuing desensitization associated with the depressive like behavior. On the basis of these observations we have suggested the use of memantine in the treatment of mania and in the prophylaxis of bipolar disorders. To test this hypothesis we performed several naturalistic studies that showed an acute antimanic effect and a long-lasting and progressive mood-stabilizing action (at least 3 years), without clinically relevant side effects. To confirm the observations of our naturalistic trials we are now performing a randomized controlled clinical trial. Finally we described the studies reporting the efficacy of memantine in manic-like symptoms occurring in psychiatric disorders other than bipolar.

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INTRODUCTION

Mood disorders are one of the leading causes of morbidity, disability and premature mortality^[1] contributing for about 50% of the non-fatal burden of mental disorders^[2]. Bipolar disorder (BD) has a lifetime prevalence of approximately 5%. Eighty-three percent of BD cases are classified as “seriously severe” and 17.1% as “moderately severe”^[3].

Prophylaxis of manic-depressive illness aimed at preventing recurrences of the various phases is a leading clinical and research challenge for contemporary psychopharmacotherapy. With the exception of lithium, it has been difficult to find robust evidences for effective and long-term mood-stabilization in patients with bipolar disorder treated with currently approved mood-stabilizers such as lamotrigine, aripiprazole, olanzapine and quetiapine^[4]. Most antipsychotic drugs and the anticonvulsants carbamazepine and valproate, are currently used for acute manic or mixed-states but lack regulatory approval for long-term prophylaxis. Antidepressants lack evidence of substantial long-term preventive effects^[4-6].

All of these treatments, as well as others sometimes used on an empirical or “off-label” basis, appear to remain incompletely effective, alone or in combinations

and patients with bipolar disorder remain unwell in approximately half of their time even with currently available treatments^[4,7]. Moreover, approximately three-quarters of this unresolved morbidity is depressive, dysthymic, or dysphoric^[4,7].

These considerations highlight the urgent need for more effective treatments that can provide long-term protective effects in patients with bipolar disorder, especially for depressive phases of the disorder that are closely associated with disability, substance abuse, and premature mortality.

MEMANTINE

Memantine is a NMDA receptor blocker in clinical use since 1982. Its pharmacological profile is well known and has been extensively described^[8-16].

DOPAMINE AND THE NEUROBIOLOGY OF BIPOLAR DISORDER

In 1965 Schildkraut^[17] proposed the first neurobiological hypothesis of depression, suggesting that depression could be due to a dysregulation of serotonin and noradrenaline function, but not dopamine.

The first observation suggestive of an involvement of dopamine in the mechanism of action of antidepressants and in the pathogenesis of mood disorders has been reported by Serra *et al.*^[18]. A great deal of pharmacological evidence and clinical observations, confirming the important role of dopamine in the therapeutic effect of antidepressants and in the pathogenesis of mood disorders, has been reported in the last decades^[19-22].

Moreover, a large body of clinical evidences has been accumulated indicating that antidepressant treatments can induce episodes of mania/hypomania, not only in bipolar but also in unipolar patients^[23,24]. In a recent meta-analytic review Tondo *et al.*^[25] reported a rate of antidepressant-induced switching of 12.5%.

Early reports of a possible link between this effect of antidepressants and the induction of a rapid cycling course of bipolar disorders were made by Kukopulos *et al.*^[26] and Wehr *et al.*^[27]. The term rapid-cycling bipolar disorder was coined by Dunner *et al.*^[28] in 1974 to identify lithium non-responders (further research has confirmed that rapid cycling is a factor of poor prognosis). Although some controversies exist^[29], it is now accepted that antidepressants can induce mania/hypomania^[25] and rapid-cycling bipolar disorder^[30]. In keeping with these observations Ghaemi^[30] suggests viewing antidepressants as “mood destabilizers”. Since 1990 we and other groups re-evaluated the effect of chronic antidepressants on dopamine receptor sensitivity and observed that chronic antidepressant treatments sensitize dopamine D2 receptors selectively in the dopaminergic reward system, supporting the hypothesis that an increase activity of this system could underlying both the therapeutic effect and the ability to cause mania/hypomania of antidepressants^[31-41].

Thus, the dopamine receptor sensitization induced by antidepressant should be considered a useful animal model of mania. In fact, it fulfils the McKinney *et al*^[42] criteria to validate a human mental disorder animal model: it resembles the condition it models in its aetiology, biochemistry, symptomatology and treatment. The model is induced by the same treatment that can induce mania in humans, is associated with an increase dopaminergic transmission and, like other models of mania, with an increase protein kinase C (PKC) activity^[43], which appear to be associated with mania. The animal behaviour showed an increase sexual activity^[44,45] and aggressivity (unpublished results), manic symptoms that can be easily observed also in rats. Finally it is sensitive to treatments that seem to have an antimanic effect in humans.

ANTIDEPRESSANTS INDUCE A “BIPOLAR-LIKE” BEHAVIOR

According with clinical observations^[46] D'Aquila *et al*^[47,48] recently reported that the supersensitivity of dopamine receptors induced by antidepressants is followed, after 4 wk of imipramine discontinuation, by a reduced sensitivity of these receptors and a behavioural syndrome that mimics depression in humans.

Antidepressant induced manic episodes in humans^[38,41,49,50] and dopamine receptor sensitization should be considered not a mere iatrogenic phenomenon but the intensification of a spontaneous underlying hypomanic process. In fact, the conversion from unipolar to bipolar course induced by antidepressants persists also after the discontinuation of antidepressant treatment, suggesting that these drugs anticipate a natural phenomenon.

FAILURE OF LITHIUM, CARBAMAZEPINE AND VALPROATE TO PREVENT DOPAMINE D2 RECEPTOR SENSITIZATION

As observed in numerous studies in humans for mania^[25], we observed that currently used mood-stabilizers does not block the behavioural supersensitivity to quinpirole induced by antidepressants in rats^[51-53].

THE ROLE OF NMDA GLUTAMATE RECEPTORS IN THE SENSITIZATION PHENOMENON AND ANIMAL MODELS OF MANIA

The stimulation of the NMDA glutamate receptor is required in the reverse tolerance (or sensitization) to psychostimulants that results in manic-like behaviors in animals and humans, particularly for amphetamine^[54-59], methylphenidate^[60], cocaine^[61-64], apomorphine^[65,66] and other dopamine mimetics^[67,68], nicotine^[69], morphine^[70,71]

and ethanol^[72-74], and some kind of stress^[58,75].

Incidentally, it is worthy to recall that the sensitization (also called reverse tolerance) to psychostimulants (amphetamine-cocaine) result in manic-like behaviors in animals and in manic-like syndromes in humans (indeed, the so called “amphetamine psychosis” considered for a long time as “paranoid schizophrenia”, can be considered, according with the more recent nosography, a manic episode with psychotic symptoms).

ANTIDEPRESSANT-INDUCED DOPAMINE D2 RECEPTOR SENSITIZATION REQUIRES NMDA RECEPTOR STIMULATION

The effects of antidepressant treatments on dopamine receptors are antagonized by MK-801, a non competitive NMDA receptor blocker^[76-78], suggesting that such phenomenon is mediated by NMDA receptor stimulation.

These findings led to hypothesize that the blockade of NMDA receptor could be effective in the treatment of mania and in the prevention of the recurrences of bipolar disorder^[79].

MEMANTINE FOR BIPOLAR DISORDER: PHARMACOLOGICAL RATIONALE

Memantine prevents not only, like MK-801, the increased sensitivity to the selective Dopamine D2 receptor stimulants observed after 21 d of imipramine administration, but also the following desensitization and the associated depressive-like behavior^[80]. A reduction of manic-like behaviour in animals has been observed also by Gao *et al*^[81].

Moreover, Memantine, among the NMDA receptor blockers, possesses the unique ability to prevent the excitotoxic effect of glutamate NMDA receptor stimulation without interfere with the normal synaptic activity. Indeed, by blocking the extracellular NMDA receptor without affecting those inside the synapse, memantine antagonizes the excitotoxic effect due to the excessive stimulation of the NMDA receptor, preserving the normal synaptic function. This effect results in a very potent neurotrophic action and makes memantine the most promising neurotrophic drug^[82].

Thus, memantine may act as antimanic and mood-stabilizer by: (1) Preventing dopamine receptor sensitization (mania) and the ensuing desensitization (depression); and (2) Blocking extracellular NMDA receptors. The NMDA receptor blockage should not only suppress mania but also prevent the excitotoxic effect due to their excessive stimulation associated with mania^[83] and, as a result, the cellular loss and/or atrophy, which seems to underlie the depressive phase of the disorder^[84].

The prevention of neurodegeneration, the increased expression of neurotrophic factors and the promotion of adult neurogenesis are considered to play a key role in the clinical effect of lithium, the gold standard antimanic and mood-stabilizer drugs.

Interestingly, memantine and lithium share a number of pharmacological actions at different physiological levels, that today are considered important targets (such as neuroprotective/neurotrophic action^[85,86], promotion of neurogenesis^[86], increased brain-derived neurotrophic factor^[87], Inhibition of PKC^[88] and glycogen synthase kinase-3^[89]) for the development of antimanic and mood-stabilizing drugs. A detailed description of the shared pharmacological effects of lithium and memantine is beyond the aim of this review.

On the basis of the latter observation it may be suggested that lithium and memantine might have a synergistic effect. Thus, we are planning a randomized, controlled clinical trial to confirm the efficacy, safety and tolerability of the combination of lithium and memantine in bipolar patients resistant to lithium prophylaxis.

Our hypothesis is in contrast with the prevalent idea that suggest the NMDA receptor antagonist as antidepressant^[90], *i.e.*, having an acute antidepressant effect. However, we recently found that memantine failed to reduce immobility time in the forced swimming test after chronic treatment, and to sensitize dopamine receptors^[80], as observed with virtually all antidepressant treatments.

On the other hand, clinical studies aimed at evaluate the possible acute antidepressant effect of memantine have provided contrasting/negative results^[11,12].

MEMANTINE IN TREATMENT-RESISTANT BIPOLAR DISORDER: CLINICAL EVIDENCES

Growing evidences show that memantine might be effective at preventing recurrences of both phases of bipolar disorder and in reducing the manic-like symptomatology associated with several neurological and psychiatric conditions^[11,12,91]. Memantine monotherapy was reported to show evidence of antimanic effects at well-tolerated daily doses (20-50 mg) in a three-week open-label trial in 33 acutely manic patients^[92]. Our group found suggestive evidence of mood-stabilizing actions in 40 BD patients in two unblinded, 6 and 12-mo open label trials when memantine was added to stable, ongoing but inadequately effective treatments^[93,94]. Memantine as a monotherapy also has been reported to show beneficial effects in a few individual patients with bipolar disorder, including after discontinuation of lithium treatment^[95-98]. Another short-term study found memantine to be more effective than placebo when added to lamotrigine for four weeks to treat acute bipolar depression in a randomized, controlled trial, but this effect was no longer significant at 8 wk^[99]. A recent 12-wk trial found little overall difference in effects of small doses of memantine (5 mg/d; $n = 62$) *vs* placebo added to valproate in bipolar II disorder patients for 12 wk^[100]. Finally, we just reported the results of a three-year naturalistic study of adding memantine to 30 treatment-resistant bipolar patients^[91]. In this study memantine showed a long-term and progressive ability to prevent

depressive and mania/hypomania recurrences, in patients who had been resistant to standard treatments for more than 3 years. Memantine decreases the duration of illness, the duration of new episodes, recurrence frequency and symptomatology severity.

Finally, it has been recently reported that memantine improves cognitive dysfunctions and increases hippocampal volume in euthymic bipolar patients^[101].

MEMANTINE IN "MANIC SYMPTOMS" IN PSYCHIATRIC SYNDROMES OTHER THAN BIPOLAR DISORDER: USE OF FORMAL PSYCHOLOGICAL ASSESSMENT

Mood symptoms, irritability, aggressiveness and abnormal manic-like behaviors are widely presented among juvenile and adult patients suffering from diverse neurological and psychiatric disorders^[102]. These category of symptoms are often the main cause for disability, unresolved morbidity and stress for care-givers^[102].

To review the clinical reports on the effect of memantine in manic symptoms in psychiatric syndromes other than bipolar disorder, we use a new methodological approach: Formal Psychological Assessment (FPA)^[103-105]. From a theoretical-mathematical perspective, FPA jointly applies two theories from mathematical psychology: The Knowledge Spaces Theory (KST)^[106-108] and in the Formal Concept Analysis (FCA)^[109,110].

The FPA provides a strong methodological approach based on the construction of a Boolean matrix that relates the so-called objects and attributes. The objects, from a psychological point of view, may be or the items of one or more questionnaires, or a set of clinical disorders. The attributes, which describe them, generally correspond to the decomposition of the diagnostic criteria of a particular clinical disorder. All this can derive from both the diagnostic and statistical manual of mental disorders-5 (DSM-5) and/or representative theories and review of the literature about it.

The procedure that characterizes it consents to give a great help in overcoming the problems of the traditional assessment in various ways. First of all, allows relating the items of a questionnaire to the diagnostic criteria of the disorder it investigates, and then go to see the strengths and weaknesses of both questionnaires and diagnostic criteria of a specific disorder. A second important use of FPA is the construction of new tools for clinical evaluation in an adaptive and effective way. The formal details of FPA are beyond the aims of this paper and can be found in the cited papers about KST, FCA and especially FPA. Third, the FPA gives the possibility to compare all the symptoms of a specific disorder with other disorders, and it help both in differential diagnoses and in the selection of pharmacological therapies that are going to affect not only on the disorder in its entirety but

Table 1 The analysis of relations between the diagnostic criteria of Manic Episode and other specific disorders

Manic episode →	A1	A2	A3	A4	A5	A6	A7	A8	A9	A10	A11	A12	A13	A14	A15	A16	A17	A18	A19	A20	A21	A22	A23	A24	A25
Other clinical disorders																									
D-1			x		x	x		x						x				x	x					x	x
D-2			x		x									x				x	x					x	
D-3								x				x										x			
D-4																									
D-5								x				x										x	x	x	
D-6	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
D-7																									
D-8			x						x					x				x	x						
D-9			x						x					x				x	x						
D-10	x		x				x		x	x	x	x		x			x	x	x						
D-11			x																						
D-12			x						x					x											
D-13			x						x					x											
D-14			x						x					x				x	x						
D-15			x						x					x											
D-16			x									x													
D-17			x																						
D-18																									
D-19			x						x					x				x	x						
D-20			x						x					x											
D-21			x																						
D-22																									
D-23			x																						
D-24			x																						
D-25			x																						
D-26						x			x																
D-27		x	x		x	x			x	x	x		x					x	x						
D-28			x											x											
D-29			x						x																
D-30						x																			
D-31	x														x										
D-32									x																
D-33			x											x											
D-34			x	x																					
D-35			x																						
D-36			x																						
D-37																									
D-38																									
D-39																									
D-40								x																	
D-41			x	x																					
D-42			x																						
D-43																									
D-44			x																						

D-6: It can have all the symptoms of Manic Episode; D-11: It can have many symptoms manic episode and dysthymia.

may act in some symptoms positively changing the course of certain illness; the latter case is what we used in this paper, but there are other papers that demonstrate the validity of this methodological approach in the other two fields described above. For the purposes of this paper, each clinical disorder is a defined object. Each object can be described on the basis of a given theoretical framework. The elements characterizing the objects are named attributes. Attributes are the decomposition of the diagnostic criteria of Manic Episode from DSM-5 and review of the literature about Mania. Each selected disorder may investigate one or more attributes and each attribute can characterize one or more clinical disorders. The "Clinical Context" is the result that we can get from the analysis of relations between the diagnostic criteria of Manic Episode and other specific disorders visible in the formal representation of the matrix (Table 1). The attributes of Manic Episode are placed in the columns of the matrix and all other clinical disorders (in this case are objects) in rows. In this way we can see the similarities and make logical inferences.

Summarizing, this part of the paper is aimed at identifying all clinical disorders that contain Manic Episode symptoms using a well-organized approach. This procedure has a great clinical relevance because it allows us making important associations that can then pour in the therapeutic treatment that psychiatrists play in order to improve the condition of people suffering from certain clinical disorders.

Table 2 contains all the attributes of manic episode. These attributes are derived from the decomposition of the diagnostic criteria for manic episode DSM-5 and a review of the literature on the Mania. Table 3 lists all of the disorders described in the DSM-5, which contain one or more manic symptoms. Table 1, which is also the most explanatory, relates the attributes of the Manic Episode with various clinical disorders with manic symptoms and specific to each disorder in Table 3 which attributes contain of Table 2. Tables 1, 2 and 3 show the results of the matrix summarizing juvenile and adult psychiatric disorders presenting manic symptoms among their diagnostic criteria.

Accordingly, a systematic review of the literature was performed aiming at identifying the effect of memantine in reducing isolated or clustered manic symptoms.

There is large consensus reporting that memantine is highly effective, compared to placebo, in treating and preventing behavioral symptoms of agitation, aggression, delusions and irritability in moderate to severe Alzheimer's Disease^[11-13]. Larsson *et al.*^[14] reported that patients with dementia treated with memantine were less physically active during sleep than patients treated with placebo. Also a large two-year follow-up French study reported a temporal relationship between the onset of memantine treatment and the stabilization of psychotropic drug use in elderly patients^[15].

Memantine improves compulsive buying^[16] and attenuates kleptomania symptomatology^[17].

The combination of memantine and risperidone in the treatment of children with autistic disorders reduces the associated manic-like symptomatology^[18].

Recent reports found memantine might be effective in reducing symptoms of juvenile and adult attention-deficit/hyperactivity disorder (ADHD). On the basis of the results of an open-label 8-wk trial with memantine in 6-12 years old outpatients with ADHD combined type, it has been suggested the use of memantine in children with ADHD^[19]. Memantine was also associated with a statistically significant improvement in the global symptomatology, inattentive and hyperactive symptoms as measured with the Adult ADHD Investigator Symptom Report in a sample of adult ADHD patients. A total of 44% of subjects showed Clinical Global Impression ratings of much or very much improved^[20,21].

Moreover, memantine was reported to be clinically relevant in reducing anxiety symptoms and improving sleep quality when used to treat anxiety disorders^[22].

Finally, memantine have been shown to be effective in a number of catatonia cases resistant to lorazepam and/or electroconvulsive therapy^[23-30].

CONCLUSION

We have reviewed the preclinical and preliminary clinical evidence strongly suggesting that memantine, a safe and well tolerated drug, may be considered a new option for the treatment and long-term prophylaxis of bipolar patients, who failed to respond to standard treatments.

Moreover, we have underscored that memantine seems to be efficacy also in manic symptoms occurring in psychiatric disorders other than in manic episode of bipolar disorder.

In order to confirm our naturalistic clinical observation, we are now starting a randomized controlled, multicenter, clinical trial comparing mood stabilizing effect of memantine vs lamotrigine as adjunctive agents in Bipolar Type I patients who have been resistant to lithium and other current standard treatments.

Table 2 Attributes of manic episode derived from the decomposition of the diagnostic criteria for manic episode DSM-5 and a review of the literature on the manic symptomatology

Attribute	Explanation
A1	Elevated mood
A2	Expansive mood
A3	Irritable mood and Aggressiveness
A4	Increased goal-directed activity
A5	Increased energy
A6	Hyperactivity
A7	Inflated self-esteem
A8	Grandiosity and bizarre ideas
A9	Decreased need for sleep or sleep disturbance
A10	More talkative than usual
A11	Pressure to keep talking
A12	Flight of ideas
A13	Subjective experience that thoughts are racing
A14	Distractibility
A15	Increased sociability
A16	Increased work or school activity
A17	Increased sexual activity or inappropriate sexually
A18	Psychic agitation
A19	Motor agitation
A20	Excessive involvement in activities with high potential for painful consequences
A21	Theatrically and exaggerated expression of emotion
A22	Psychotic features
A23	Catatonia
A24	Disinhibited behavior
A25	Impulsivity

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Table 3 Clinical disorders with manic symptoms

Disorders	Abbreviation
Attention-deficit/hyperactivity disorder	D-1
Autism spectrum disorder	D-2
Brief psychotic disorder	D-3
Schizophreniform disorder	D-4
Schizophrenia	D-5
Schizoaffective disorder	D-6
Catatonia	D-7
Major depressive episode	D-8
Cyclothymic disorder	D-9
Depressive episode, with mixed features	D-10
Disruptive mood dysregulation disorder	D-11
Persistent depressive disorder (dysthymia)	D-12
Premenstrual dysphoric disorder	D-13
Recurrent brief depression	D-14
Generalized anxiety disorder	D-15
Obsessive-compulsive disorder	D-16
Reactive attachment disorder	D-17
Disinhibited social engagement disorder	D-18
Posttraumatic stress disorder	D-19
Acute stress disorder	D-20
Conduct disorder	D-21
Pyromania and kleptomania	D-22
Oppositional defiant disorder	D-23
Intermittent explosive disorder	D-24
Alcohol intoxication	D-25
Alcohol withdrawal	D-26
Caffeine intoxication	D-27
Caffeine withdrawal	D-28
Cannabis withdrawal	D-29
Sedative, hypnotic, or anxiolytic withdrawal	D-30
Stimulant intoxication	D-31
Stimulant withdrawal	D-32
Tobacco withdrawal	D-33
Gambling disorder	D-34
Alzheimer disorder	D-35
Fronto-temporal neurocognitive disorder	D-36
Lewy bodies disorder	D-37
Vascular neurocognitive disorder	D-38
General personality disorder	D-39
Schizotypal personality disorder	D-40
Antisocial personality disorder	D-41
Borderline personality disorder	D-42
Histrionic personality disorder	D-43
Narcissistic personality disorder	D-44
Paraphilic disorders	D-45

Diagnostic and statistical manual of mental disorder-5 containing one or more manic symptom.

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