

## The Urgent Need of New Mood-Stabilizers: The Promising Results of Memantine

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The main aim of pharmacological treatment for Bipolar Disorder (BD) patients is the prevention of manic/hypomanic and depressive episodes by the administration of mood stabilizer drugs.

Unfortunately, after several decades of its serendipitous discovery, lithium remains the only drug with consolidated evidence of mood-stabilizing effect [1]. No important therapeutic innovations (i.e., a drug with major clinical benefit compared with existing drugs, according to the definition of Motola [2] have been introduced in the last 60 years.

Some anticonvulsant medications and atypical antipsychotics are currently approved or used off-label as lithium alternative mood stabilizers. Anticonvulsants have been shown to be of limited efficacy both as a monotherapy and in combination with lithium [1,3-7] and the mood stabilizing effect of atypical antipsychotics has been severely questioned [8,9].

Thus, the research and development of more effective mood-stabilizers for the prophylaxis of bipolar patients resistant to lithium, is an urgent challenge of modern psychopharmacology.

Indeed, even with currently available treatments, patients with BD remain unwell in 50% of their time, with about 75% of this time spent in depression [6].

We have recently suggested that blockade of NMDA receptors by memantine, a drug with excellent safety and tolerability profile [10], could result in an antimanic and mood-stabilizing effect in treatment-resistant BD patients [11,12].

Our group found suggestive evidence of the mood-stabilizing effect of memantine when added to stable, ongoing but inadequately effective standard treatments in 40 BD patients in two 6 and 12-month clinical trials [13,14].

Memantine as a monotherapy also has been reported to show beneficial effects in few individual BD patients, including after discontinuation of lithium treatment [15-18].

Finally, we reported the results of a three-year naturalistic study of adding memantine to 30 treatment-resistant bipolar patients [19]. In this trial, memantine achieves clinically meaningful long-term benefits, for both depressive and mania-like (mania, hypomania) morbidity, in outpatients who had proved resistant to standard treatments for more than 3 years, until memantine (20–30 mg/day) was added to otherwise stable regimens for another 3 years, during which patients improved progressively. Patients under memantine treatment showed a marked, statistically significant decrease of the illness morbidity (total, manic and depressive illness, on average–74.2%), the severity (CGI-BP; –63.1%), the duration (–56.3%) and the number of illness episodes (episodes/year; –55.8%). These findings indicated progressive and impressive improvement in the duration (from about 70% of total illness, 45% of depression, and 25% of mania/hypomania before memantine to less than 10% of total illness, 5% of depression, and 5% of mania hypomania after 3 years of memantine addition) and the severity

of both affective phases of the disorder, with a greater improvement of depression than mania, and evidence of decreased severity of mania. Subjects with previous rapid- ( $\geq 4$  episodes/year) or continuous-cycling were particularly improved.

As for the possible mechanism of antimanic and mood stabilizing effect of memantine, we have demonstrated that chronic treatment with antidepressants sensitizes dopamine D2 receptors in the mesolimbic system, an effect that may contribute to their therapeutic action and may be responsible of their ability to induce switch from depression to mania in humans [11,12,20-24].

Indeed, Tondo et al. [25] reported 12.5% of switch from depression to mania induced by antidepressants, and a great deal of evidence suggests that an increased dopaminergic transmission is associated with mania/hypomania [26-30].

The sensitization of dopamine receptors (mania) is followed by a progressive desensitization of those receptors, associated with a depressive-like behavior assessed in the forced swimming test of depression [31-33].

Thus, antidepressants induce a bipolar-like behavior, mimicking a cycle of the manic depressive illness (mania followed by depression).

Memantine prevents the bipolar-like behavior in rats. Indeed it prevents both the sensitization of dopamine receptors (mania) induced by chronic treatment with imipramine, and the ensuing desensitization associated with the depressive behavior [33].

Moreover it has recently been suggested that memantine, as well as lithium, has a neuroprotective action [34] and that mania could be associated with an excessive stimulation of NMDA receptors [35], which may result in an excitotoxic neurodegeneration [36].

According to this hypothesis, it may be suggested that memantine, by blocking NMDA receptors, suppresses mania and prevents the neurodegeneration [37] that may be associated with depression [36].

Thus, we suggest that the antimanic and mood-stabilizing action of memantine might be due to its ability to “stabilize” dopamine receptor sensitivity and to its blockade of the excitotoxic effect of excessive NMDA receptor stimulation.

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Interestingly, the neuroprotective/neurotrophic effect of memantine may be due not only to the blockade of the excessive glutamatergic stimulation of NMDA receptors, but also to a number of biological effects shared with lithium (the gold standard mood stabilizer), and that are considered involved in a neuroprotective/neurotrophic action, such as, for instance, promotion of neurogenesis [38], increased in neurotrophic factor release in brain [39], inhibition of protein kinase C [40] and glycogen synthase kinase-3 [41].

In keeping with these observation, it may be suggested that lithium and memantine might have a synergistic effect, so that their combination might result in a potentiation of antimanic and mood stabilizing effect.

To conclude, with the exception of lithium the available mood stabilizer drugs are of limited or severely questioned efficacy. We have recently provided very promising data suggesting that memantine, a drug with excellent safety and tolerability profile, has an acute antimanic and a long lasting and progressive mood stabilizing effect in patients with BD resistant to the available treatments.

Moreover, we suggest that memantine and lithium combination might have a synergistic effect.

Accordingly it is tempting to suggest the use of a lithium and memantine combination as a first-line treatment in the severely ill BD patients.

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