

## Caso clinico

# Memantine in the treatment and prophylaxis of bipolar type II mood disorder and co-morbid eating disorder: a case report

## *Memantina nel trattamento e nella profilassi del disturbo dell'umore bipolare di tipo II in comorbidità con disturbo del comportamento alimentare: un caso clinico*

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**SUMMARY.** We have recently reported that memantine has a clinically relevant antimanic and long-lasting mood-stabilizing effect in treatment-resistant bipolar disorders, both as augmenting agent and as a monotherapy. Moreover, we observed an acute antimanic and sustained mood-stabilizing effect also in “naïve” bipolar type I disorder. Here we report a case history of a young woman suffering from bipolar type II mood disorder, associated with a very severe eating disorder, showing an acute antimanic and a long-term prophylactic effect of memantine on bipolar disorder and comorbid eating disorder.

**KEY WORDS:** memantine, bipolar type II mood disorder, eating disorder.

**RIASSUNTO.** Abbiamo recentemente riportato che la memantina ha un effetto antimaniacale clinicamente rilevante e un prolungato effetto profilattico nel disturbo bipolare resistente ai trattamenti convenzionali, sia come “augmenting” terapia sia in monoterapia. Abbiamo, inoltre, osservato un effetto antimaniacale acuto e profilattico a lungo termine in pazienti bipolari di tipo I “naïve”. Qui descriviamo la storia clinica di una giovane paziente con disturbo bipolare di tipo II associato a un grave disturbo del comportamento alimentare, che conferma che la memantina ha un effetto antimaniacale acuto e previene le ricadute del disturbo bipolare in comorbidità con disturbi del comportamento alimentare.

**PAROLE CHIAVE:** memantina, disturbo bipolare di tipo II, disturbo del comportamento alimentare.

### INTRODUCTION

Memantine is a noncompetitive NMDA receptor antagonist currently used in the treatment of Alzheimer disease (AD). Although its actual efficacy on the AD patient's quality of life has proven to be moderate<sup>1</sup>, several pre-marketing and post-marketing studies have demonstrated the excellent safety and tolerability profile of the drug<sup>2</sup>.

We have recently reported that this drug has a clinically relevant antimanic and long-lasting mood-stabilizing effect in treatment-resistant bipolar disorders, both as augmenting agent and as a monotherapy<sup>3-6</sup>. Moreover, we observed an acute antimanic effect, not only as augmenting agent in treatment-resistant patients, but also in “naïve” bipolar type I disorder<sup>6</sup>.

In addition, it has been reported that memantine is effective in different animal models of eating disorders<sup>7-9</sup>, and two open-label clinical studies have observed its efficacy in re-

ducing binge eating, obsessive-compulsive features of binge eating, severity of illness, and disability<sup>10,11</sup> as well as leading to a large reduction in body weight<sup>11</sup>.

Moreover, eating disorders are frequently associated with mood disorders and with negative outcomes that include more severe affective episodes, worsening BP illness course with more residual symptoms between episodes, suicidal ideation and increased risk of suicide<sup>12</sup>.

Such findings suggest the need for differentiated diagnosis and a specific treatment plan for those patients.

These considerations prompted us to use memantine in a young woman suffering from bipolar type II mood disorder (BP II), associated with a very severe eating disorder.

The clinical history of this patient is consistent with our previous observations<sup>3-5</sup> and provides further support to the previously observed clinical effectiveness of memantine in eating disorders<sup>10,11</sup>.

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## CLINICAL CASE

Young woman born in 1976, qualified accountant, suffering from BP II, associated with a very severe eating disorder alternating episodes of anorexia nervosa binge-eating and purging type and bulimia nervosa with purging.

She has a family history of mood disorders: her father suffered from depression, a maternal cousin suffered from BP II disorder with a history of several suicide attempts. The general medical history reveals the patient suffers from psoriasis (diagnosed at age 16).

She had her first affective episode in 1989, at age 13. It was a depression associated with a severe form of anorexia with intense fear of gaining weight, inappropriate eating habits, obsession with having a thin figure, distorted self-image, 6 months of amenorrhea and Body Mass Index (BMI) 18.

After this first episode, she suffered from severe BP II disorder with a continuous circular course characterized by long and severe depressive episodes and short episodes of hypomania, associated with a very severe bulimia nervosa. The patient had daily binge eating, with sensation of losing control, followed by compensatory behavior to prevent weight gain by self-induced vomiting, impaired body image and low self-esteem. She was treated with antidepressants (mainly with selective serotonin reuptake inhibitors, SSRIs) and psychotherapy, without any benefit.

In 2008 she put on 40 kilos because of bulimia and then she underwent partial gastrectomy. After the surgery she lost weight, but the bulimia and the severe mood oscillations remained unchanged.

In fact, she was still having a bulimic symptomatology with binge eating, episodes of loss of control, compensatory behaviors through self-induced vomiting. She was still having low self-esteem and distorted view of her body image.

Because of the disease the patient had to stop working and to reduce her normal social relations.

She came under our care in October 2010. Since 2008 she had been taking fluoxetine (20 mg/day). The patient complained of depressed mood, feelings of worthlessness, irritability, inner tension, psychomotor agitation, insomnia, increased sexual activity, crowded thoughts and severe symptoms of bulimia nervosa.

She was very worried about her body weight and continued to have episodes of loss of control, binge eating, compensatory behaviors through self-induced vomiting. The BMI was in the normal range. Her affective symptoms fulfilled the criteria of Koukopoulos and Koukopoulos for agitated depression<sup>13</sup>, which usually worsens when the patient is treated with antidepressant drugs and improves with antipsychotics and mood stabilizers. Therefore, fluoxetine was discontinued, and we suggested a therapy based on antimanic and mood stabilizer drugs, both as acute treatment and, more important, as a prophylaxis for her bipolar disorder. Moreover, we informed the patient that the administration of lithium could worsen psoriasis and therefore it should be avoided. After discussing with the patient the efficacy, safety and tolerability of the currently used mood stabilizers, alternative to lithium, we proposed the administration of memantine. We obtained the written informed consent from the patient and memantine was administered at a dose increased over 2 weeks to 20 mg/day. After 2 weeks of memantine administration the patient was completely euthymic with recovery from the associated severe eating disorder. In fact, she no longer has manifested neither binge eating, nor purging, nor irrational fear of gaining weight, as well as nor distorted body self-perception. She is still determined to maintain a good weight, but is not obsessive about it. The patient has found a new job in which she is appreciated by her bosses.

At the end of November 2010 a mild depression appeared and spontaneously resolved within one month. From then until June 2012 the patient has been in a state of complete well-being and has returned to work and to a normal social life.

At the end of June 2012, the patient expressed her desire to begin a psychotherapeutic treatment and discontinue drug treatment. We informed the patient that the discontinuation of a mood stabilizer usually leads to an affective recurrence, but she insisted on her decision to discontinue the memantine treatment. We planned a gradual discontinuation of the drug.

At the end of August 2012, after 4 weeks of 10 mg/day reduction of memantine and during her premenstrual period a mild form of agitated depression reappeared, together with an extremely high level of concern about the possible return of the eating disorder. We rapidly increased the memantine dose up to 20 mg/day. After a few days of adjusted memantine dosage the patient returned to her previous state of complete well-being, and has remained euthymic and without eating disorders until now (July 18, 2014). No side effects due to memantine were observed.

## DISCUSSION

This case history provide further support for our previous observations that memantine has an antimanic and mood-stabilizing effect with excellent tolerability and safety profile<sup>3-6</sup>. Moreover it strongly suggests that these effects can be obtained with memantine monotherapy also in BP II disorder.

In addition, our observation is consistent with the reported clinical efficacy of memantine in the treatment of eating disorders<sup>10,11</sup>.

As to the possible mechanism of the antimanic and mood-stabilizing effect of memantine, we have observed that the drug prevents the bipolar-like behaviour induced by antidepressants in rats<sup>14</sup>. Indeed, we have suggested that the dopamine (DA) receptor sensitization induced by antidepressants in rats may be considered an animal model of mania<sup>15</sup>. Moreover we found that the sensitization of dopamine receptors is followed<sup>16</sup>, after antidepressant withdrawal, by a gradual desensitization of these receptors, which is associated with a depressive-like behaviour, assessed in the forced swimming test<sup>17</sup>, a classical animal model of depression. Memantine prevents, like the potent non-competitive NMDA receptor antagonist MK-801, not only the dopamine receptor sensitization, but also its desensitization and the associated depressive-like behaviour<sup>14</sup>. Thus, we suggest that memantine, by suppressing mania, i.e. DA receptor sensitization, prevents the ensuing desensitization associated with depression.

Moreover it has been recently suggested that memantine, as well as lithium, has a neuroprotective action<sup>18</sup> and that mania could be associated with an excessive NMDA receptor stimulation<sup>19</sup>, that may result in a excitotoxic neurodegeneration<sup>20</sup>. According to this hypothesis, it may be suggested that memantine, by blocking NMDA receptors, suppresses mania and prevents the neurodegeneration that may be associated with depression<sup>20</sup>.

Thus, we may suggest that the antimanic and mood-stabilizing action of memantine might be due to its ability to "stabilize" DA receptor sensitivity and to block the excitotoxic effect of the excessive NMDA receptor stimulation.

The observation that memantine has an acute effect in the treatment of agitated depression does not contrast with our

previous report or with the failure to observe an acute antidepressant effect of the drug<sup>5</sup>. Indeed, antidepressant drugs worsen agitated depression, which instead shows a good response to antipsychotics and mood-stabilizing drugs (such as memantine)<sup>13</sup>.

Incidentally, it may be suggested that the conflicting results obtained in the numerous studies<sup>5</sup> aimed at investigating a possible antidepressant effect of memantine could be explained by its efficacy in agitated depression but not in typical (inhibited) major depression.

In line with observations by Hermanussen and Tresguerres<sup>11</sup> at first and Brennan et al.<sup>10</sup> later, in this case history the mood stabilization was associated with the recovery from the severe eating disorder.

Our present observation strengthens the findings of other studies that there is a close relationship between eating disorders and bipolar syndromes.

A detailed description of the postulated pathophysiological hypotheses of eating disorders is beyond the aim of this paper.

However, one might suggest that, in some patients, the same pathophysiological mechanism (such as, for instance, an increased glutamatergic transmission) underlies both mood disorders and eating disorders. Furthermore, it may be worthy to recall that memantine seems to be effective in obsessive compulsive disorders, and its beneficial effect on eating disorder might be due to its anticomulsive action.

The observation that discontinuation of the drug led to the recurrence of the symptomatology argues against the possibility that our observation can be attributed to a placebo effect.

Although we are aware of the limitations of the present observations, we are confident that they are of major clinical relevance and provide further support to our previous observations. These observations have to be confirmed in a large sample of patients and in an RCT, which we are planning.

## REFERENCES

1. Emre M, Mecocci P, Stender K. Pooled analyses on cognitive effects of memantine in patients with moderate to severe Alzheimer's disease. *J Alzheimers Dis* 2008; 14: 193-9.
2. Jones RW. A review comparing the safety and tolerability of memantine with the acetylcholinesterase inhibitors. *Int J Geriatr Psychiatry* 2010; 24: 547-53.
3. Koukopoulos A, Reginaldi D, Serra G, et al. Antimanic and mood stabilizing effect of memantine as augmenting agent in treatment resistant bipolar disorder. *Bipolar Disord* 2010; 12: 348-9.
4. Koukopoulos A, Serra G, Koukopoulos AE, et al. The sustained mood-stabilizing effect of memantine in the management of treatment-resistant bipolar disorders: findings from a 12-months naturalistic trial. *J Affect Disord* 2012; 136: 163-6.
5. Sani G, Serra G, Kotzalidis GD, 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.
6. Serra G, De Chiara L, Koukopoulos A, Serra G. Antimanic and long-lasting mood stabilizing effect of memantine in bipolar I mood disorder: two case reports. *J Clin Psychoph* 2013; 33: 715-7.
7. Bisaga A, Danysz W, Foltin RW. Antagonism of glutamatergic NMDA and mGluR5 receptors decreases consumption of food in baboon model of binge-eating disorder. *Eur Neuropsychopharmacol* 2008; 18: 794-802.
8. Foltin RW, Danysz W, Bisaga A. A novel procedure for assessing the effects of drugs on satiation in baboons: effects of memantine and dexfenfluramine. *Psychopharmacology (Berl)* 2008; 199: 583-92.
9. 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.
10. 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. *Int J Eat Disord* 2008; 41: 520-6.
11. 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. *Econ Hum Biol* 2005; 3: 329-37.
12. McElroy SL, Kotwal R, Keck Jr PE. Comorbidity of eating disorders with bipolar disorder and treatment implications. *Bipolar Disord* 2006; 8: 686-95.
13. Koukopoulos A, Koukopoulos A. Agitated depression as a mixed state and the problem of melancholia. *Psychiatr Clin North Am* 1999; 22: 547-64.
14. Demontis F, Cubeddu A, Serra G. Memantine prevents the "bipolar-like behaviour" induced by chronic imipramine in rats. *Int Clin Psychopharmacol* 2012; 28: e35-e36.
15. Serra G. Memantine for treating bipolar mood disorders resistant to conventional treatments. *EP 2 218 450 A1* (Published 18-08-2010, Bulletin 2010/33).
16. D'Aquila PS, Peana AT, Panin F, et al. Reversal of antidepressant-induced dopaminergic behavioral supersensitivity after long-term chronic imipramine withdrawal. *Eur J Pharmacol* 2004; 458: 129-34.
17. D'Aquila PS, Panin F, Serra G. Long-term imipramine withdrawal induces a depressive-like behaviour in the forced swimming test. *Eur J Pharmacol* 2004; 492: 61-3.
18. La Spada AR. Memantine strikes the perfect balance. *Nat Med* 2009; 15: 1355-6.
19. Ongür D, Jensen JE, Prescott AP, et al. Abnormal glutamatergic neurotransmission and neuronal-glia interactions in acute mania. *Biol Psychiatry* 2008; 64: 718-26.
20. Atmaca M, Yildirim H. Altered neurochemical ingredient of hippocampus in patients with bipolar depression. *Depress Res Treat* 2012; 2012: 485249. doi: 10.1155/2012/485249. Epub 2012 Mar 1.