Memantine in the management of affective recurrences of bipolar disorders after the discontinuation of long-term lithium treatment: three case histories

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Introduction

Discontinuation of long-term lithium treatment leads to early and severe affective recurrences [Baldessarini *et al.* 1999], and to a bipolar disorder course more severe than that before lithium treatment with an increased risk of suicide [Post, 2012], which is often resistant not only to other mood stabilizers, but also to the reinstitution of lithium treatment at the prior effective serum lithium level [Post, 2012].

Unfortunately, the currently available lithium-alternative mood stabilizers are of limited (anticonvulsants) [Geddes *et al.* 2010; Kessing *et al.* 2011; Greil and Kleindiest, 1999], or questionable (atypical neuroleptics) [Goodwin *et al.* 2011] efficacy.

We have recently provided clinical observations strongly suggesting that memantine, a noncompetitive N-methyl D-aspartate receptor antagonist, has a clinically relevant antimanic and a sustained mood-stabilizing effect in treatment-resistant bipolar disorder with excellent safety and tolerability [Koukopoulos *et al.* 2010, 2012; Sani *et al.* 2012; Serra *et al.* 2013].

More recently we have observed a long-lasting mood-stabilizing effect of memantine after lithium discontinuation in a bipolar I patient [Serra *et al.* 2013].

In order to evaluate further the effect of memantine in the prophylaxis of affective recurrences occurring after long-term lithium discontinuation, we administered the drug to three patients who had to discontinue lithium because of severe renal complications (two patients) or excessive tremor (one patient).

These case histories confirm our previous observations, and suggest that memantine may be considered a useful lithium substitute to prevent the affective recurrences after lithium discontinuation.

Case 1

Woman born in 1930, suffering from a bipolar II disorder with rapid cycling course.

She has a family history of bipolar disorder.

Her first affective episode was a depression in May 1979 (aged 49 years), followed by a hypomania until January 1980. She started lithium prophylaxis and had a very good response to lithium.

In June 2009 lithium was gradually reduced to 150 mg every 2 days (serum lithium level 0.2 mmol/L) and then withdrawn because of renal impairment. After we had obtained the informed written consent, she was put on 20 mg/day memantine and lamotrigine (250 mg/day). She started with rapid cycling recurrences until May 2010. Since then she has been well and stable on memantine 20 mg/day, lamotrigine 250 mg/day and lithium 150 mg every 2 days (lithium serum level 0.2 mmol/L).

Case 2

Woman born in 1934, suffering from a bipolar II disorder with rapid cycling course.

She has a family history of mood disorder.

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She had her first depressive episode in 1985. In 2000 she started having hypomanias and depressions with a rapid cycling course. Then she was totally stabilized with lithium therapy. In February 2004 lithium was reduced because of renal impairment and valproic acid was added at 600–900 mg/day.

In November 2008 the patient started having a rapid recurrence of hypomanic and depressive episodes and in November 2009 lithium had to be finally withdrawn because of the worsening of renal impairment.

In March 2010, after we had obtained the informed written consent, memantine 20 mg/day was added to valproic acid. She had a depressive episode milder than the previous one. Currently mood oscillations persist but are much milder than those she had before lithium treatment and before memantine.

Case 3

Woman born in 1937, retired teacher, suffering from a bipolar II disorder with rapid cycling course.

Her mood disorder started in 2006 (aged 68 years) with a major depressive episode.

Subsequently her unipolar depression converted to a bipolar type II disorder with a rapid cycling course. In June 2009 she started treatment with lithium 300 mg/day (serum lithium level 0.4 mmol/L), lamotrigine 200 mg/day and clonazepam 0.5 mg/day. Although maintaining a rapid cycling course, her mood episodes became milder, but she started suffering from a disabling tremor due to lithium, and she had a severe skin reaction due to lamotrigine (rapidly discontinued). After we had obtained written informed consent, memantine was added and titrated to 20 mg/day within a week. The rapid course was stopped. She had another mild euphoria immediately interrupted by adding valproic acid (600 mg/day). In March 2011 lithium was gradually discontinued because of disabling tremors. Since June 2011 she has been completely euthymic with memantine 20 mg/day and valproic acid 450 mg/day.

Discussion

These observations suggest that memantine could effectively replace lithium and stabilize the course of bipolar disorder in patients who discontinue long-term lithium treatment.

In case 1 we added memantine and lamotrigine to treat rapid recurrences triggered by lithium discontinuation, which led to severe recurrences that had to be treated with *electroconvulsive therapy*. This clinical condition is usually resistant to conventional mood stabilizers, including the reinstitution of lithium [Post, 2012]. In combination with lamotrigine and a subtherapeutical serum lithium level, memantine was able to stop this malignant course.

In case 2 valproic acid was not able to stop rapid recurrences due to lithium discontinuation. The rapid cycling was stopped with the addition of memantine.

In case 3 the patient had a rapid cycling bipolar II disorder treated with lithium and lamotrigine with poor response. She had to discontinue both drugs because of adverse reactions. The rapid cycling course was stopped with memantine and a small dose of valproic acid.

Moreover, we previously observed that the drug might be effective also as monotherapy in the prevention of affective recurrences occurring after lithium discontinuation [Serra *et al*. 2013].

Although we observed a good response to memantine administration 4 months after lithium discontinuation (case 2), the mood-stabilizing effect of memantine seems to be more effective (as a monotherapy [Serra *et al*. 2013]) when it is administered before lithium discontinuation (case 3: 9 months before). In case 1 memantine was added immediately after lithium discontinuation and the stabilization of the rapid cycling bipolar course was obtained with the reinstatement of a subtherapeutic dose of lithium (serum level 0.2 mmol/L).

Although memantine is used in combination with another mood stabilizer, it does not diminish the clinical relevance of our observations. In our patients lithium discontinuation led to a malignant course that did not respond to valproic acid as monotherapy. We observed a potent mood-stabilizing action of the combination of memantine with lamotrigine or valproic acid, drugs that usually are not able to stop the rapid cycling course when used as monotherapy [Kemp *et al*. 2012].

Moreover, even lithium, before its discontinuation and the addition of memantine, was administered in combination with another mood stabilizer, because of the severity of the bipolar disorder course.

These case histories are consistent with our previous observations suggesting that memantine has a long-lasting mood-stabilizing effect.

As to the mechanism of action, we have observed that memantine prevents the bipolar-like behaviour induced by antidepressants in rats [Demontis *et al*. 2012], and suggested that the prevention of dopamine antagonist receptor sensitization (mania) by memantine results in an antimanic effect, which, in turn, prevents the following desensitization associated with depression [Serra, 2010].

Regardless of the mechanism of action, these case reports confirm our previous observations, and suggest that memantine may be considered a useful replacement for lithium in the prevention of affective recurrences observed in patients who have to discontinue long-term lithium prophylaxis because of severe medical complications.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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