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Memantine: A New Mood Stabilizer for Treatment-Resistant Bipolar Disorders

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1. Introduction

Memantine is a non-competitve NMDA receptor antagonist, but, at variance with the most potent NMDA receptor blockers, such as Ketamine, Phencyclidine and MK-801, has a low affinity for the receptor and its action is voltage/use dependent (Gillin et al., 2009; Johnson & Kotermanski, 2006; Rammes et al., 2008) . Moreover it has been recently demonstrated that this compound selectively blocks the extrasynaptic (excitotoxic) receptor but preserves the normal synaptic function (La Spada, 2009).

These peculiar pharmacological properties explain the lack of psychotomimetic/psychedelic effect and of interference with the normal physiological functions [memory and learning, synaptic plasticity, etc. etc. (Van Dongen, Editor, 2009)].

The drug has been on the market in Germany as Akatinol Memantine since 1982 for the treatment of Parkinsonism, cerebral and peripheral spasticity, and organic brain syndrome, without apparent cause for concern before its approval in 2002 and 2004 by EMEA and FDA for the treatment of moderate to severe Alzheimer's Disease.

Although its actual efficacy on the AD patient's quality of life has proven to be moderate (Emre et al., 2008; Kaduszkiewicz & Hoffmann, 2008), several pre-marketing and post-marketing studies have demonstrated the excellent safety and tolerability profile of the drug (Farlow & Phillips, 2008; Jones, 2010).

Moreover, the drug has been used off-label in a number of neurological and psychiatric conditions, including depression, with conflicting and inconclusive results (Zdanis & Tampi, 2008).

We have recently suggested, on the basis of preclinical experimental evidence obtained in our laboratory (Serra 2009, 2010) the use of memantine, as having an antimanic and mood-stabilizing effect, in treatment-resistant bipolar disorder. This use is absolutely at variance with the prevalent hypotheses which take NMDA receptor antagonists to be potential antidepressant drugs [mainly on the basis of their effect on the forced swimming test (Rogoz et al., 2002, Reus et al., 2010), a widely used animal model of depression].

In keeping with our experimental pharmacological evidence we have observed in bipolar patients a significant clinical antimanic and sustained mood-stabilizing effect of memantine, as augmenting agent, in treatment-resistant bipolar disorders.

Lithium is the drug of choice for the treatment of mania and the prophylaxis (as a mood stabilizer) of manic and/or depressive recurrences of Bipolar Disorders (BD) and Unipolar Depression (Goodwin, 2002). In cases of severe mania with a strong component of psychomotor agitation and/or psychotic symptoms, antipsychotic drugs are generally combined.

Anticonvulsants (carbamazepine, valproic acid, lamotrigine) are used [in mania and/or as mood stabilizers (Rapoport, 2009)] in combination with lithium when the latter does not produce a satisfactory response or in monotherapy in patients for whom lithium is contraindicated. The effectiveness of these drugs, both as antimanics and mood stabilizers, is however modest, and therefore patients who do not respond adequately to lithium (Koukopoulos et al. 1995, Tohen et al., 2005) today constitute the real problem of long-term treatment of mood disorders.

The use of antipsychotics as mood stabilizers is not advisable both because of their dubious efficacy (Culpepper & Ghaemi, 2011) and their long-term safety and/or tolerability.

Traditional antipsychotics, as well as having undesirable effects of a psychiatric type (emotional blunting, etc.), may, if administered for a long time, provoke sometimes debilitating and irreversible neurological damage (Serra & Gessa, 1990). The so-called atypical antipsychotics, on which the jury is still out on whether they do not cause long-term neurological damage (Gardener et al., 2005), have the drawback (except for some) of being able to cause what is called "metabolic syndrome" (Gardner et al., 2005) which constitutes a serious cardiovascular risk factor and thus risk of early death (which is aggravated by the fact that BD patients *per se* have an increased cardiovascular risk). Finally, it should be stressed that most antipsychotics, whether traditional or atypical, may cause, albeit rarely, death by sudden cardiac arrest (Ray et al., 2009).

Concern has also been raised by a recent alarm (FDA Alert, 2008) over the possibility that anti-epileptics may bring a two-fold increase in suicide risk compared to placebo.

Along with the approved old anticonvulsants a plethora of "new" antiepileptics [Gabapentin, Oxcarbazepine, Clonazepam, Pregabaline, Tiagabine, Topiramate, etc. (Kaufman, 2011)] are usually used off-label in combination with lithium, anticonvulsants and antipsychotics, when these associations fail to produce a satisfactory clinical response. Thus, the overwhelming majority of bipolar patients, today, receive a combination of 4 or 5 drugs or even more, often with questionable pharmacological rationale and little additional relevant clinical benefit.

The problem of the therapy and prophylaxis of mood disorders in patients who do not respond to lithium, whose numbers appear to be continually rising, therefore remains unsolved (Koukopoulos et al., 1995; Ghaemi, 2008).

Indeed, while the acute phases of the manic/hypomanic and depressive episodes of the illness appear to be relatively easy to control, the failure on the stabilization of treatment-resistant bipolar disorders is becoming an emergengy of psychiatry today and represents an increased risk of suicide.

Unfortunately, the currently available lithium-alternative mood-stabilizers not only are of limited efficacy, but have a number of acute troublesome and sometimes long-term severe side effects along with clinically relevant drug-drug interaction (Mc Namara, 2011).

Hence, the need for new more effective and safe mood-stabilizing drugs.

2. Treatment-resistant bipolar disorders

Mood disorders are currently classified (DSM IV TR) as Depressive Disorders and Bipolar Disorders. Depressive Disorders include Major Depressive Disorder (single or recurrent) and Dysthymic Disorder.

Bipolar Disorders comprise: BD I (which presents with an alternation of episodes of major depression and recurrent episodes of mania); BD II (which is made up of episodes of major depression and recurrent hypomanias); Cyclothymic Disorder (for at least two years several hypomanic and depressive episodes which must not be major). Further, a Mixed Episode is when symptoms of major depression and mania are present in the same episode.

The depression that manifests in BD is also commonly defined as Bipolar Depression, while that of Major Depressive Disorder is often called Unipolar Depression (or Unipolar Depressive Disorder).

Since affective disorders are often highly recurrent prophylaxis is of primary importance. Many cases, however, do not respond to current mood stabilizing treatments.

Cole et al. (1993) identified four different patterns of treatment-resistant Bipolar Disorder: rapid cycling (37%), other form of cycling (32%), chronic depression (26%) and mixed states (6%). They identified some risk factors for treatment resistant Bipolar Disorder, including female gender (for rapid cycling), high prevalence of family history of affective disorders (72%) and electroencephalografic abnormalities (54% of recordings).

Particularly resistant to prophylactic treatments are the patients with rapid cycling course.

Dunner and Fieve (1974) defined as Rapid Cyclers those patients that have a course with four or more affective episodes in the 12 previous months, and this course specifier was adopted by DSM-IV.

Today, most clinicians waive the duration criterion of episodes and intervals because in many cases the episodes become progressively shorter and we see ultra-rapid (within the course of weeks or days) and ultradian cyclers (mood shifts within 24 hours). Some patients indeed show an alternation of phase within a few hours.

The general impression of clinicians today is that the course of recurrences of manic-depressive illness has substantially changed in the last 40 years. The recurrences of many patients have become more frequent. One sees more manias and hypomanias and therefore more bipolar cases than before, more rapid cyclers, and more chronic depressions (Koukopoulos et al 1983; Ghaemi, 2008). This phenomenon is called today mood destabilization.

In his monograph on *la folie a double forme,* Ritti (1883) presented only 17 cases with a rapid course; he collected them from various French and German authors. Kraepelin (1913)

illustrated one case with a rapid cycling course in his graphs of type of course. This was case C, and he commented, "I had to seek for a long time in my cases until I finally found at least one course of the type that case C represents.' In a meta-analysis of 8 studies including 2054 bipolar patients, Kupka et al. (2003) found a percentage of 16.3% of rapid cyclers. Women and bipolar II patients were slightly but significantly more prevalent. Maj et. al (1994) found a prevalence of 19.5% of rapid cyclers among BPI patients.

Among the first 500 BP patients of the STEP-BD study 20% were rapid cyclers while in 2008 among 1,742 BD patients the percentage at entry was 32% (Schneck et al, 2008).

Among women, rapid cycling is more frequent than among men and the age of onset of the bipolar disorder is earlier than among non-rapid cycling patients (Yildiz et al, 2004).

Particularly frequent is rapid cycling among prepubertal and early adolescent bipolar patients. Geller at al. (1998) found a proportion of 83.3% rapid, ultra-rapid or ultradian cyclers among such young patients.

Rapid cycling is more frequent among BPII than among BPI and in patients with hyperthymic and cyclothymic temperament. They are very energetic, very emotional and reactive (Kukopoulos et al., 1983). One could posit the hypothesis that they are equally reactive to chemical stimulations. Because of this temperament they are diagnosed often as borderline personality disorders and in the past as hysterics. In patients with cyclothymic temperament the rapid-cycling course could be viewed as the accentuation of longstanding subclinical mood oscillations.

Patients that more likely remain rapid-cyclers for many years are those with a DMI (depression-mania-interval) or DmI (depression-hypomania-interval) cycle patterns, those with a switch process and/or agitated depression in their course and those who have not been stabilized after the first year of an adequate treatment.

The investigation of the course of manic-depressive illness is a difficult task in itself, and the investigation of possible factors that influence this course is extremely difficult given the variability of the spontaneous course. Yet the above-mentioned changes and the general increase of bipolar cases today make this investigation necessary. Of all the possible factors that unfavorably influence the course of the disease what most urgently needs to be studied are the treatments themselves, firstly because they certainly influence the disease, and second, because treatments are given by the doctor and therefore can be easily modified. This is certainly not the case of other factors like menopause, older age, life situations, and so forth.

The increase of substance abuse, including alcohol and cannabis among young people certainly plays an important role in the worsening of the course of affective disorder.

Antidepressant treatments should also be reconsidered. They have been largely employed in the treatment of affective disorders during the last five decades, although many authors observed an increase of the frequency of episodes compared to the course of the disease before the introduction of antidepressants *(*Arnold & Kryspin Exner, 1965; Freyhan, 1960; Heinz & Grunze, 2008; Hoheisel, 1966; Lauber, 1964; Till, 1970).

Particularly associated to the use of antidepressants is the rapid cycling course (Kukopulos et al., 1983). The stabilization of rapid cyclers is often very difficult. It requires prolonged

effort: it is necessary to know the life of the patient, his premorbid temperament and personality, the history of his illness and its course, the treatments used in the past, and the events and treatments associated with the onset of rapid cycling.

Patients with rapid cycling course are usually of cyclothymic or hyperthymic temperament, therefore particularly excitable and emotional persons. It is important to advise them to avoid coffee, tea, alcohol and all psychostimulant substances, intense physical exercise and also to avoid, as much as possible, stressful situations and events. Sleep is particularly important and they should go to sleep early and try to sleep as long as possible.

The resistance of rapid cyclers to all mood-stabilizing treatments is well established. None of these treatments (carbamazepine, lithium, lamotrigine, topiramate and valproate) showed a clear advantage over the others (Baldessarini et al, 2000; Tondo et al, 2003). Also the efficacy of atypical antipsychotics as mood stabilazers in maintenance therapy has not been demonstrated, and current data do not support their use as maintenance agents (Zupancic , 2011). The authors, however, agree with Muzina (2009) about the fundamental importance of lithium in the treatment of rapid cyclers.

We apply the following strategy. Given that most cases of rapid cycling are induced by antidepressants, it is of primary importance to suspend the antidepressants and to continue the treatment with mood stabilizing agents. In most cases without antidepressants the depressive phase will last longer but the following mania/hypomania will be less intense. The anti-manic action of mood stabilizers will be more effective in the absence of antidepressants. Gradually, both the excitatory and the depressive phase will be attenuated and stabilization will eventually be achieved, over a variable period of time. This therapeutic strategy is based on the idea that the suppression of the excitatory phase prevents or attenuates the following depression (Koukopoulos & Ghaemi, 2009). Indeed, all mood stabilizers like lithium, anticonvulsants, calcium antagonists, old or new antipsychotics (Koukopoulos & Ghaemi, 2009), and also memantine (Koukopoulos et al., 2010) are essentially anti-excitatory agents .

In the presence of suicide risk, electroconvulsive therapy (ECT) could be used to end the depressive phase and immediately afterwards mood-stabilizing treatment should be administered. A study from Sainte-Anne hospital in Paris shows that maintenance ECT is effective against the RC course, with full or partial remission for 100% of RC patients (Vanelle et al, 1994). Other authors have shown that maintenance ETC is effective against rapid cycling course: Minnai et al. (2011) found a percentage of remission of 58% of patients, and other similar results were obtained by Fazzari (2009, *personal comunication*). Continuous treatment was more effective against mania/hypomania than against depression, yet in all persisting rapid cycler cases the mania/hypomania remitted only partially.

3. Memantine as antimanic and mood-stabilizer: Pharmacological rationale

3.1 Dopamine and bipolar disorders

The first evidence-based hypothesis of the neurobiology of depression was proposed by Schildkraut in 1965 (Schildkraut, 1965). Mainly on the basis of the supposed mechanism of therapeutic effect of tricyclic antidepressants and MAO inhibitors (blockade of serotonin and noradrenaline reuptake or inhibition of MAO, respectively) he suggested that

depression may be associated with a decreased function of serotonin and noradrenaline transmission. Further support for this hypothesis is provided by the observation that reserpine, which induces depression in humans, causes a depletion of the neurotransmitters in monoaminergic neurons.

As a consequence of this hypothesis the role of dopamine (DA) in the pathophysiology of mood disorders has long been neglected although reserpine also depletes dopaminergic neurons.

In 1975 Randrup et al (1975) suggested that mania might be associated with increased dopaminergic transmission, while depression could be associated with decreased DA transmission.

In 1979 (Serra et al, 1979) we first reported that antidepressant drugs act not only on serotonin and noradrenaline, but also activate dopaminergic transmission. In fact we found that chronic treatment with antidepressants, by inducing a dopamine autoreceptor subsensitivity, potentiates dopaminergic transmission in rats, and suggested that this effect may play an important role both in the therapeutic action and in the capacity of antidepressants to induce mania/hypomania.

Since then, in the last three decades, an amount of preclinical and clinical evidence has been accumulated strongly suggesting a key role of dopamine in the pathophysiology of bipolar disorders (Berk et al, 2007; Cousins & Butts, 2009; Dihel & Gerson, 1992).

A detailed description of this clinical and preclinical evidence supporting a key role of dopamine in the pathophysiology of bipolar disorders is beyond the aim of this chapter: the reader may find such a description in a number of excellent recent reviews (Berk et al, 2007; Cousins & Butts, 2009; Dihel & Gerson, 1992; Dunlop & Nemeroff, 2007).

3.2 Antidepressants sensitize mesolimbic dopamine D2 receptors

In our first report (Serra et al, 1979) we observed that chronic treatment with antidepressants reduces the sedative effect of apomorphine and potentiates its stimulatory action on locomotor activity, thus potentiating dopamine transmission. We interpreted these effects as a consequence of a development of sedative dopamine autoreceptor subsensitivity, and suggested that the potentiation of dopamine transmission may play an important role in the capacity of these drugs both in therapeutic action and in inducing switching from depression to mania/hypomania.

Subsequent studies in the following 30 years have produced conflicting results (Chiodo & Antelman, 1980a, 1980b; Diggory & Buckett, 1984; Dziedzicka-Wasylewska, 1997; Holcomb et al, 1982; Muscat et al., 1988; Serra et al, 1980, 1981a, 1981b; Spyraki & Fibiger, 1981) on the ability of ADs to induce subsensitivity in DA autoreceptors.

However numerous studies have confirmed the capacity of virtually all AD treatments (TCAs, MAO-inhibitors, Mianserine, SSRI/NSRI, electroconvulsive shock, REM-sleep deprivation), to increase the motor-stimulant effect of DA receptor agonists (Collu et al., 1997a; D'Aquila et al., 2000a; Gershon et al., 2007; Spyraki & Fibiger, 1981; Serra et al., 1990, 1991, 1992; Willner, 1997). In particular, Spyraki and Fibiger in 1981 (Spyraki & Fibiger, 1981) observed that chronic Desipramine treatment potentiated dopaminergic transmission by inducing a supersensitivity of postsynaptic dopamine receptors in the mesolimbic system.

Strong evidence now exists suggesting a key role of mesolimbic DA in the mechanism of action of antidepressants (Collu et al., 1997b; D'Aquila et al, 2000a; Fibiger & Philips, 1981; Gershon et al, 2007; Spyraki & Fibiger, 1981; Serra et al, 1990, 1992; Willner, 1997)

Gerson et al. (2007) recently published an elegant review on the experimental and clinical evidence indicating the role of dopamine D2 receptors in the mechanism of action of antidepressants.

In 1990 the availability of selective agonists for DA receptor subtypes prompted us to re-evaluate the effect of chronic antidepressant treatments on pre- and post-synaptic dopamine receptor sensitivity (Serra et al, 1990). We found that chronic antidepressant treatment does not induce a subsensitivity of dopamine autoreceptors, but, confirming the results of Spiraki and Fibiger (1981), we observed that such a treatment sensitizes dopamine D2, but not D1, receptors selectively in the mesolimbic system The key role of mesolimbic DA D2 receptor sensitization in the mechanism of action of antidepressants is now widely accepted (Collu et al., 1997a; D'Aquila et al, 2000a; Fibiger & Philips, 1981; Gershon et al, 2007; Spyraki & Fibiger, 1981; Serra et al, 1990, 1991, 1992; Willner, 1997).

In keeping with these observations it may be suggested that the increased dopaminergic transmission in the mesolimbic system (the reward system) due to D2 receptor sensitization, induced by antidepressants, may contribute to their therapeutic effect, and in particular for such symptoms as anhedonia, loss of motivation, decreased libido and psychomotor retardation. (Collu, 1997b; D'Aquila, 2000a; Serra et al. 1990, 1992).

Moreover, the sensitization of mesolimbic dopamine D2 receptors induced by antidepressants may be responsible, in "vulnerable subjects" (bipolar disorder, the presence of previous mixed states, early age at onset, a cyclothymic or hyperthymic temperament, genetic factors?), for the switches from depression to mania/hypomania (Collu et al, 1997b; D'Aquila e al, 2000a; Gessa et al, 1995; Serra et al, 1990, 1992, Serra & D'Aquila, 2008; Serra, 2009, 2010) which, in turn, trigger a rapid-cycling course (Serra et al, 2008; Serra, 2009, 2010).

3.3 Antidepressants induce a "bipolar-like behaviour"

Koukopoulos et al. (1980) suggested that "The intensification of an underlying hypomanic process by antidepressants would precipitate another depression and establish continuous circularity".

In accordance with this hypothesis we recently found that chronic treatment with imipramine induced a 'bipolar-like behaviour' (i.e. a cycle of mania-depression) in rats (D'Aquila et al, 2003; D'Aquila et al, 2004). In fact, as expected, imipramine induces a sensitization of dopamine D2 receptors (mania/hypomania), which is followed after 12, 33 and 40 days of imipramine withdrawal by a progressive desensitization of dopamine D2 receptors (depression) (D'Aquila et al, 2003) associated with a depressive-like behaviour as assessed in the forced swimming test animal model of depression (D'Aquila et al, 2004).

This observation provides strong experimental support for the hypothesis that antidepressant-induced mania/hypomania is the trigger phenomenon of rapid-cycling course (Collu et al, 1997b; Serra & D'Aquila, 2008; Serra, 2009, 2010) and that the prevention

of both spontaneous or antidepressant-induced mania/hypomania (Koukopoulos & Reginaldi, 1973; Koukopoulos & Ghaemi, 2009) (in neurobiological terms, dopamine D2 receptor sensitization) is essential to avoid the development of a rapid-cycling bipolar disorder.

The prevention of mania, whether induced by antidepressants or spontaneous, is the essential element in the therapy and prophylaxis of bipolar disorders (Koukopoulos & Reginaldi, 1973; Koukopoulos & Ghaemi, 2009). When, in fact, treatments currently in use do not achieve this aim the course of the disorder becomes 'malign', i.e refractory to treatment, as in the rapid-cycling course.

According with the clinical observations that demonstrate the ineffectiveness of currently used mood stabilizers in preventing antidepressant-induced switch from depression to mania (Leverich et al., 2006; Tondo et al., 1981, 2010), we found that the concomitant administration of lithium (D'Aquila et al, 2000b), carbamazepine (D'Aquila et al., 2001), valproate (D'Aquila et al 2006), lamotrigine (unpublished results) with imipramine fails to prevent the development of dopamine D2 receptor sensitization. Actually, carbamazepine seems to be effective, but its effect is due to the reduction of imipramine plasma levels due to the induction of the drug metabolism.

3.4 Memantine prevents the "bipolar-like behaviour" induced by antidepressants

These observations led us to further investigate the mechanism by which antidepressants induce dopamine receptor sensitization. In fact, this mechanism may represent a possible target to develop drugs effective in preventing this phenomenon as potential new antimanic and mood stabilizing agents.

There is ample experimental evidence showing that the NMDA glutamate receptor plays an essential role in the phenomenon of sensitization. Its stimulation is, in fact, necessary for the sensitization of amphetamine (Battisti et al., 2000; Groning et al., 2004; Ohmori et al, 1994; Pacchioni et al, 2002; Vezina & Quen, 2000; Wolf et al, 1994), methylphenidate (Gaytan et al, 2000), cocaine (Heusner & Palmiter 2005; Li et al, 2000; Kim et al, 1996; Rompré & Bauco 2006), apomorphine (Acerbo et al, 2004; Pacchioni et al, 2002; Voikar et al, 1999) and other dopamine mimetics (Kalivas, 1995; Rockhold, 1998), nicotine (Kelsey et al, 2002), morphine (Jeziorski et al, 1994; Trujillo, 2002) and ethanol (Broadbent & Weiemier, 1999; Camarini et al, 2000; Kotlinska et al, 2006), as well as several types of stress such as, for instance, 'restraint stress' (Pacchioni et al, 2002) and 'social defeat stress' (Yap et al, 2005).

The stimulation of NMDA receptors is required for the development of dopamine receptor sensitization induced by antidepressants. Indeed, we found that the administration of MK-801, a selective non-competitive NMDA receptor blocker, completely prevents the dopamine receptor sensitization induced by imipramine (D'Aquila et al, 1992) and by electroconvulsive shock (D'Aquila et al, 1997).

These observations strongly suggest that the non-competitive blockade of NMDA receptors should result in an anti-manic and mood stabilizing action, and that it should also be effective in the treatment of the disorders resistant to currently used antimanic and mood stabilizers.

Consistent with this hypothesis, we have recently found that memantine prevents both the up-regulation induced by chronic imipramine (Malesa & Serra, 2011) and the down-regulation (Demontis & Serra, 2011) of dopamine D2 receptors associated with a depressive-like behaviour (Cubeddu & Serra, 2011) observed after imipramine withdrawal.

These observations provide strong experimental evidence supporting the hypothesis of the antimanic and prophylactic effect of memantine in bipolar disorders resistant to conventional treatments.

Moreover, an antimanic-like activity of memantine has been observed in other animal models of mania by Gao et al.,(2011).

These observations prompted us to suggest the use of memantine, the only safe and well-tolerated non-competitive NMDA antagonist that may be proposed for long-term clinical use, as antimanic and mood-stabilizer in treatment-resistant bipolar disorder (Serra, 2009, 2010).

In addition, it may be interesting to recall that memantine, like the "gold standard" antimanic and mood-stabilizer, lithium, seems to posses a powerful neuroprotective activity (La Spada, 2009), an effect that may contribute to its mood-stabilizing properties. Indeed, in accordance with the neurotrophic hypothesis of mood-disorders (Dumas, 2004; Serra & Fratta, 2007), an excessive glutamatergic stimulation of NMDA receptors [that seems to be associated with mania (Ongur et al., 2009)]could result in a neurodegeneration that appears to be associated with depression (Dumas, 2004, Macqueen, 2003, Videbech & Ravnkilde, 2004) and can be reversed by an effective antidepressant treatment (Sheline et al., 2003; Malberg, 2004, Malberg & Blendy, 2005; Paizanis et al., 2007).

Thus, it may be suggested that memantine, by blocking NMDA receptors, prevents both the up (mania) and down (depression) regulation of dopamine D2 receptors, and the neurodegeneration that results from the excessive glutamatergic neurotransmission during mania, which might underlie the following depressive phase.

4. Memantine, a drug with excellent safety and tolerability

4.1 Pre-marketing data

"This module reflects the initial scientific discussion for the approval of Ebixa (EMEA, 2004). The product has been on the market for nearly twenty years in a European country without apparent cause for concern, which can be considered as giving some reassurance. In addition there has been clinical exposure in the older clinical trials.

The most frequent adverse events reported with memantine have been dizziness, followed by headache and fatigue. Agitation occurred less with memantine than with placebo. There is no suggestion of a psychedelic effect that could be feared as a result of activation of the NMDA receptors. Even if the target population would have had difficulties in reporting this kind of effects the fact that the levels of agitation were decreased is in favour of absence of such theoretical psychedelic effects. Despite the absence of studies formally addressing the question of withdrawal and dependence, there are no signals in the data available suggesting its existence. Taking into account the indication granted, the clinical evidence available gives reassurance of a sufficient safety profile."

4.2 Post-marketing data

A recent review (Jones, 2010) of the most recent safety/tolerability data for memantine (derived from meta-analyses, pooled analyses, European SPCs, and EMEA publications) confirmed that memantine has a favorable tolerability profile when used in monotherapy or in combination with other agents. Moreover, results of studies of a total treatment period of up to two years show that memantine is safe and tolerated, with an adverse event profile almost indistinguable from that of placebo. Side effects are usually mild to moderate in severity, and are commonly (1-10%) represented by dizziness, constipation, headache, hypertension and somnolence.

The incidence of serious adverse events (SAEs) was slightly lower for memantine than for placebo.

Warnings and precautions are few: caution is recommended in epileptic patients or with a former history of convulsions or predisposing factors for epilepsy. Close supervision is recommended in patients with myocardial infarction, uncompensated congestive heart failure or uncontrolled hypertension.

There are no contraindications for the use of memantine, apart from the sensitivity to tablet excipients. However, due to the lack of clinical experience, the drug should be avoided in patients with severe hepatic impairment.

Drug-drug interactions: memantine should not be administered alongside other compounds acting at NMDA receptors such as amantadine, ketamine and dextromethorphan, due to the risk of psychotic symptoms. Moreover memantine might enhance the effects of antiparkinson drugs such as levodopa, dopamine agonists and anticholinergic compounds. On the contrary, the effects of neuroleptics and barbiturates might be reduced. Finally, memantine may also influence the effect of baclofen and dantrolene (antispamodic agents).

5. Memantine as antimanic and mood stabilizer in treatment-resistant bipolar disorder: Clinical studies

We have recently carried out 3 naturalistic clinical studies in order to evaluate the antimanic and mood stabilizing effects of memantine, as augmenting agent, in treatment-resistant bipolar disorder.

In the first study (Koukopoulos et al, 2010) we administered memantine (10-30 mg/day), as augmenting agent, to 18 treatment-resistant bipolar patients monitored for 24 weeks. The severity of the patients' condition before memantine and the change after memantine augmentation was evaluated on the Clinical Global Impression-Bipolar (Spearing et al., 1997) Overall Bipolar Illness scale.

The patients had been ill for an average of 21 years and had been resistant to very intense standard treatments (lithium, anticonvulsants, typical and atypical antipsychotics, electroconvulsive therapy, and antidepressants). Of these 18 patients, 13 were bipolar I and 5 bipolar II, 10 were rapid cyclers, 5 were continuous circular with long cycles, and 3 had a course with free intervals. Thirteen patients exhibited psychotic symptoms. The 10 rapid cyclers had a mean duration of rapid cycling course of 11 years.

The average of CGI-BP score before memantine was 6.6, which indicates a very severe condition. After 24 weeks of memantine addition 72.2% of patients were very much or much improved. Among the rapid cyclers 60% reached stability. The mean time to improvement was 55 days.

The second study (Koukopoulos et al, 2011) encompassed 40 treatment-resistant bipolar patients monitored for 12 months. Of these 40 patients 21 were bipolar I and 19 bipolar II, 19 were rapid cyclers, 9 were continuous circular with long cycles, and 12 had a course with free intervals. Nineteen exhibited psychotic symptoms. All patients had been resistant for many years to very intense long-term standard treament. The mean duration of illness was 22 years, while the average duration of rapid cycling course of rapid cyclers was 8.6 years.

The average of CGI-BP Overall Bipolar Illness score before the memantine addition was 6.7, indicating a very severe condition.

After 6 months of memantine augmentation (10-30 mg/day added to ongoing treatment which was left unmodified) 72.5% of patients were very much or much improved and remained stabilized for 12 months. Among the rapid cyclers 68.5% reached stability after 6 months and remained free of recurrences for 12 months.

Finally, in order to evaluate the long-term effect of memantine, we studied the action of the drug on 22 treatment-resistant bipolar patients with a follow-up of 24 months (Serra, 2011). Of these 22 patients 16 were bipolar I, 6 bipolar II, 10 were rapid cyclers, 6 continuous circular with long cycles, and 6 had a course with free intervals, 15 exhibited psychotic symptoms. Almost all patients were very severely ill (average CGI-BP Overall Bipolar Illness score before memantine addition 6.6). All patients had been resistant for many years to very intense standard treatments (including lithium, anticonvulsants, typical and atypical antipsychotics, electroconvulsive therapy, antidepressants).

The mean duration of illness was 22.4 years, and the duration of rapid cycling course of rapid cyclers was 11 years. After 6 months of memantine augmentation 77.3% were very much or much improved and 60% of rapid cyclers reached stability. The mean time to improvement was 69 days. Similar results were obtained on the evaluation at 12, 18, and 24 months.

All patients who were very much or much improved at 6 months and continued on memantine remained free of recurrences at 12 and 18 months, and all but one at 24 months.

The side effects observed during our studies are the already described dizziness (one patient), constipation (one patient) and drowsiness (one patient), thus confirming the excellent safety and tolerability profile of the drug, also when used in combination with other drugs currently used in the treatment of bipolar disorders.

Our results strongly suggest that memantine, as augmenting agent, was associated with clinically substantial antimanic and sustained mood-stabilizing effects in treatment-resistant bipolar disorder patients with excellent safety and tolerability.

The significant clinical relevance of our observations is not diminished by the use of memantine as augmentation treatment, considering the long history of drug-resistance of the study patients.

As in all naturalistic studies, the limitation of our clinical observations is the lack of a placebo control. Hovewer, the prior history of treatment resistance of the study patients and the long-lasting effect of the drug argues against a placebo effect contributing in any substantial way to what we observed. Nevertheless, we are going to start an RCT to confirm our naturalistic observations.

Consistent with our results is the observation by Keck et al (2009) of an antimanic effect of memantine monotherapy in bipolar disorder patients.

In addition, our results are consistent with a recent analysis on the effect of memantine on the management of behavioural disorders in AD patients (Gauthier et al., 2010) which suggest an antimanic and mood-stabilizing effect of memantine.

In fact, the analysis demonstrates that memantine reduces "manic" symptoms such as agitation, aggression, irritability, lability, and even delusions and hallucinations in AD patients. Moreover, suggestive of a prophylactic/ mood-stabilizing effect, the observation that patients who do not exhibit such symptoms at baseline, showed a reduction of their emergence.

Taken together these clinical observations and considering the safety/tolerability and the drug-drug interaction of the drug, we are tempted to suggest, pending the results of our controlled clinical trial, the use of memantine, as augmenting agent, in treatment-resistant bipolar disorders, which have no therapeutic alternative

Discontinuation of long-term lithium treatment leads to early and severe affective recurrences (Baldessarini & Tondo, 1998), which are often resistant to other mood stabilizers. In order to evaluate the effect of memantine in this condition we administered the drug to three patients who are lithium responders, but discontunued lithium because of severe renal complications (two patients) or excessive tremor (one patients).

Case 1) A woman born in 1930 suffered of BD II with rapid cycling course. She was perfectly stable on Lithium and Valproic acid since 1980. In june 2009 Lithium was withdrawn because of renal impairment. She was put on 20 mg/day Memantine. In Dec.2009 she had a depressive recurrence treated with six ECT and in May 2010 she had a second depressive recurrence treated with thirteen ECT. Since then she is well and stable on Memantine 20 mg/day and Valproic acid 600mg.

Case 2) A woman born in 1934, suffering from BD II, was stable on lithium since 2001 In Nov. 2009 lithium was withdrawn because of renal impairment. A hypomanic and a depressive relapse followed. In june 2010 Memantine 20 mg/day was added to Valproic acid. She is still having mood oscillations but much milder than those she had before Lithium and before Memantine.

Case 3) A woman born in 1937 and suffering from BD II was started on Lithium and Valproic acid on June 2009. On May 2010 Memantine 20 mg/day were added and her mood oscillations became milder. On March 2011 Lithium was withdrawn because of tremor. A short depressive phase followed and for the moment she is well.

These observations suggest that memantine could stabilize the course of bipolar disorder in patients who discontinued long-term lihium treatment.

However, further studies in a large population sample are needed, before suggesting the use of memantine to prevent recurrences due to lithium discontinuation.

6. Conclusions

Memantine is a non-competitive NMDA receptor antagonist, with peculiar pharmacological properties, which explain its excellent safety and tolerability profile, at variance with the most potent NMDA receptor blockers such as Ketamine, Phencyclidine and MK-801.

The drug has been used in Germany since 1982, and approved by EMEA in 2002 and by FDA in 2004 for the treatment of moderate to severe Alzheimer's Disease.

Moreover it has been recently used off-label in a number of neurological and psychiatric disorders, including depression, with conflicting and inconclusive results.

At variance with the hypothesis that, mainly on the basis of the effect of these compounds in the forced swimming test animal model of depression, suggests that NMDA receptors antagonist might have an antidepressant activity, we have recently demonstrated that MK-801 and Memantine show an antimanic and mood-stabilizing-like effect in an animal model of bipolar disorder resistant to standard treatments.

Thus, we have suggested (Serra, 2009, 2010) the use of Memantine as antimanic and mood-stabilizing agent in the treatment of resistant bipolar disorders.

This hypothesis prompted us to carry out three naturalistic trials to test memantine as augmenting agent, in the management of treatment resistant bipolar disorders.

The results of these studies strongly suggest that memantine has a clinically relevant antimanic effect and a long-term prophylactic action in treatment of resistant and very severe bipolar patients, with very good safety and tolerability.

Although our naturalistic observations lack placebo control and need to be confirmed by an RCT (which we are going to start), we believe that they provide enough information to suggest the safe use of memantine augmentation in severely ill bipolar patients, who are resistant to conventional treatments and have not therapeutic alternative.

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8. References

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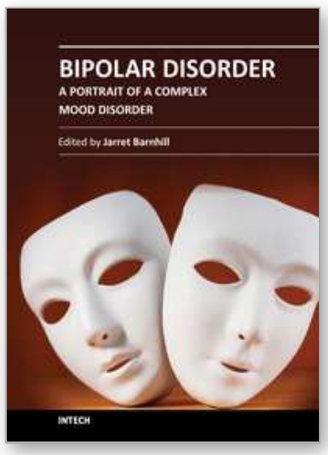

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Bipolar Disorder: Portrait of a Complex Mood Disorder is a step towards integrating many diverse perspectives on BD. As we shall see, such diversity makes it difficult to clearly define the boundaries of BD. It is helpful to view BD from this perspective, as a final common pathway arises from multiple frames of reference. The integration of epigenetics, molecular pharmacology, and neurophysiology is essential. One solution involves using this diverse data to search for endophenotypes to aid researchers, even though most clinicians prefer broader groupings of symptoms and clinical variables. Our challenge is to consolidate this new information with existing clinical practice in a usable fashion. This need for convergent thinkers who can integrate the findings in this book remains a critical need. This book is a small step in that direction and hopefully guides researchers and clinicians towards a new synthesis of basic neurosciences and clinical psychiatry

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