Case report

Memantine augmentation for refractory obsessive–compulsive disorder

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Abstract

Glutamatergic hyperactivity hypothesis in obsessive–compulsive disorder (OCD) has been proposed but not tested. Memantine is an uncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist. We report two cases of refractory obsessive–compulsive disorder treated with an augmentation of memantine at 15 mg/day. The first case did not benefit from such treatment, while the second showed immediate and substantial improvement. Contrasting results, reflecting different subtypes of OCD, are discussed. We hypothesized that in certain OCD subtypes an agent that enhances memory for actions may promote a reduction in orbitofrontal activation.

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1. Introduction

A large proportion of obsessive–compulsive disorder (OCD) patients do not respond to standard treatment. Moreover, clinical presentations of OCD are heterogeneous, with subtypes characterized by different pathophysiological mechanisms and treatment outcomes (Lochner and Stein, 2003; Pujol et al., 1999). The role of serotonin in the pathophysiology of OCD has been largely supported by pharmacological studies. Recently it has been suggested that the glutamatergic neurotransmission may have a role in the pathogenesis of OCD. More specifically the supposed hyper-glutamatergia in the orbitofrontal cortex could be influenced by the acetylcholine activity (Girod et al., 2000; Araki et al., 2002; Mansvelder et al., 2002). At present no data are available supporting this hypothesis. However improvement among resistant OCD patients, after nicotine treatment, has been reported (Carlsson, 2001; Lundberg et al., 2004; Pasquini et al., 2005). Memantine is an uncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist, which reduces glutamatergic excitotoxicity, thus protecting against the excitotoxic destruction of cholinergic neurons. Moreover memantine interacts with more than one class of sites on the nicotinic acetylcholine receptors (alpha7* nAChRs), one voltage sensitive, and, therefore, likely to be within the receptor channel, the other voltage insensitive, and, thereby, likely to be in the extracellular domain of the receptor (Aracava et al., 2005). Furthermore, in animal models, memantine increases striatal dopamine.

Poyurovsky et al. (2005), first, reported the case of a OCD resistant patient who improved with memantine augmentation. The patient treated was a 34-year-old woman affected by fear of harm to her daughter and compulsive checking behavior.

We report our experience in two patients treated with memantine as an add-on treatment.

2. Case reports

The first case is a 60-year-old female patient who suffered from OCD, with good insight, for 30 years. Her primary obsession is fear of possible contamination of body parts or personal objects by germs, with consequent washing compulsions. She spends many hours washing everything that has been touched by others; and there is only one clean area where she can do the washing. Her life is completely absorbed by her disorder and her husband is also involved in her rituals. Dysthymic disorder co-occurs. We used the Structured Clinical Interview for DSM-IV to establish diagnosis. She was treated for thirty years with several medications: clomipramine 250 mg/day, fluoxetine 80 mg/day, fluvoxamine 350 mg/day, paroxetine 60 mg/day, sertraline 250 mg/day, and venlafaxine 350 mg/day. Each medication has been taken for...
at least 12 weeks. Several augmentation strategies with atypical and typical antipsychotics were tried, such as haloperidol 20 mg/day, risperidone 6 mg/day, olanzapine 20 mg/day, and with anticonvulsants as valproate 1300 mg/day or topiramate 250 mg/day. Improvements with these regimens were minimal. Current treatment was 300 mg/day of venlafaxine, and her Y-BOCS (Yale Brown Obsessive Compulsive) score was 38. After she signed an informed consent, regarding the off-label prescription of memantine, this was started at 5 mg/day and titrated for 3 weeks to 15 mg/day. After 2 months of the latter therapy the OCD symptoms did not improve (Y-BOCS score = 36), and treatment was discontinued.

The second case is a 27-year-old male, OCD onset at 15 years, with severe compulsions of checking behaviors, related to pathologic doubt. The patient feels compelled to check doors, windows, light switches, electrical outlets; and his obsessions were fear of harm to others. In addition, he repeats actions over and over in an attempt to get it “just right”. He recognizes that his compulsions are unreasonable. The Structured Clinical Interview for DSM-IV was used to establish diagnosis.

He was previously treated with multiple medications and was hospitalized twice. Several antipsychotic therapies were prescribed: fluoxetine 80 mg/day, sertraline 200 mg/day, citalopram 60 mg/day, paroxetine 60 mg/day and clomipramine 225 mg/day; risperidone 3 mg/day added to sertraline 150 mg/day, olanzapine 10 mg/day added to paroxetine 60 mg/day. Fifty weekly sessions of cognitive therapy according to Salkovskis’ model (1999), including Exposure and Response Prevention (E/RP), were unsuccessful.

Current treatment consists in citalopram 60 mg/day. His Y-BOCS score is 34.

After he signed an informed consent, regarding the off-label prescription of memantine, the treatment started with 5 mg/day titrated for 2 weeks to 10 mg/day. After 3 weeks of treatment an evident improvement was seen in compulsions, his Y-BOCS score has fallen from 34 to 19. More specifically the Y-BOCS items regarding time spent for compulsions, interference from compulsions and distress from compulsions greatly decreased. Memantine dosage was increased to 15 mg/day. After 1 month at 15 mg/day a dysphoric state, rather than a hypomanic state, with psychomotor agitation and insomnia was observed. For this reason the memantine dosage was decreased to 5 mg/day; in a few days the dysphoric state disappeared and improvement on compulsions was maintained, without withdrawal effects.

3. Discussion

Taken together, these two cases show contrasting results. The first patient was a chronic OCD washer patient with intrusive thoughts of contamination; while the second patient suffered from pathologic doubts and checking compulsions. Even though these are both OCD patients, they differ in their clinical picture and it could be hypothesized that they have different patterns of functional brain abnormalities. However neither neuropsychological tests to evaluate potential cognitive deficits, nor neuroimaging studies were applied in these two patients. These methodological issues may limit the interpretation of our findings.

As suggested by several authors, checkers patients have deficits in their memory for actions (Tallis et al., 1999; Zitterl et al., 2001), hence they have low confidence in their own memories (Tolin et al., 2001). We suggest that in some cases an agent that acts to enhance memory for actions may lead to a reduction in the orbitofrontal activation. Being an NMDA receptor antagonist, memantine at low concentrations, by blocking the effect of abnormal glutamate activity, may preserve memory and learning. Abnormal glutamate activity has been suggested to be associated to neuronal cell death and cognitive dysfunction. It must also be stressed in this context that the effects of memantine involving other transmitter systems, as dopamine in the striatum, could be dysfunctional in OCD patients (Carlsson, 2001). The kinetics and the affinity are the key-factors for memantine action, because it blocks the effects of excessive glutamate while preserving physiologic activation of NMDA receptors (Kumar, 2004).

Antagonists of postsynaptic glutamate receptors, and drugs that reduce the presynaptic release of glutamate are among the candidate medications under development as potential antidepressant (Kuipers et al., 2005). However, in a recent double-blind, placebo-controlled, study, memantine was not effective in the treatment of major depressive disorder (Zarate et al., 2006).

Although glutamatergic therapy to OCD symptoms has not been used yet, the pharmacological action of memantine suggests that testing this drug in larger samples may be appropriate.

4. Conclusions

The two cases of treatment-resistant OCD treated with a memantine augmentation showed contrasting results. The subtypes of OCD should be taken into consideration in the assessment of the effectiveness of this treatment. Further studies on the potential usefulness of memantine in the management of OCD are needed to establish whether certain subtypes of patients may be responsive to intervention of this nature.

References


