Differential Efficacy of Memantine for Obsessive-Compulsive Disorder vs. Generalized Anxiety Disorder: An Open-Label Trial

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ABSTRACT - Objective: A substantial proportion of patients with obsessive-compulsive disorder (OCD) and generalized anxiety disorder (GAD) do not respond to, or are intolerant of, standard treatments. Additional treatment strategies are therefore necessary. Excessive action of the excitatory neurotransmitter glutamate may play a role in the pathophysiology of OCD and possibly GAD. Memantine blocks the excitatory action of glutamate at the N-methyl-D-aspartate (NMDA) receptor under pathological conditions. The objective of this study was to compare the efficacy and safety of memantine in OCD and GAD, and to probe relative effects on OCD and anxiety symptoms. Method: Ten OCD and 7 GAD subjects received 12 weeks of open-label memantine 10 mg twice daily, as either monotherapy or augmentation of their existing medication. Primary outcome measures were the Yale-Brown Obsessive Compulsive Scale (YBOCS) for the OCD group, the Hamilton Anxiety Rating Scale (HARS) for the GAD group, and the Clinical Global Impression-Improvement Scale (CGI-I) for both groups. Results: The OCD group experienced a significant mean 40.6% reduction in YBOCS scores at endpoint ($t = 4.75$, $p < 0.001$). Three of 10 of OCD subjects were classified as responders, although 7 of 10 experienced a $\geq 45\%$ reduction in YBOCS scores. The GAD group experienced a mean 22.4% reduction in HARS scores ($t = 3.56$, $p = 0.012$). None of the GAD subjects were responders, and none experienced a $\geq 50\%$ reduction in HARS scores. Memantine was well tolerated, and there were no serious adverse effects. Conclusions: These results suggest that memantine may have preferential efficacy in the treatment of OCD versus GAD. These preliminary findings warrant larger, placebo-controlled studies in OCD. Psychopharmacology Bulletin. 2009;42(1):81–93.

INTRODUCTION

Obsessive-compulsive disorder (OCD) and generalized anxiety disorder (GAD) belong to the category of anxiety disorders, the most common class of...
psychiatric conditions.\textsuperscript{1} Anxiety disorders are usually chronic and cause significant disability, functional impairment and decrease in quality of life.\textsuperscript{2,3} OCD is characterized by recurrent obsessions and compulsions that cause marked distress and/or interfere with daily functioning.\textsuperscript{4} GAD is characterized by persistent and excessive worry, along with chronic physical arousal.\textsuperscript{4} At least 9 million people suffer from one of these disorders in the U.S. alone.\textsuperscript{1}

Effective treatments for OCD and GAD include serotonin reuptake inhibitor (SRI) medications and cognitive-behavioral therapy (CBT).\textsuperscript{5,6} However, 40–60\% of OCD patients do not have an adequate response to SRI medications\textsuperscript{7,8} and over 40\% of GAD patients show limited or no response to conventional treatments.\textsuperscript{9} In addition, many patients who do respond to SRIs experience troublesome side effects such as impairment in sexual functioning and weight gain that may interfere with adherence. These factors necessitate the development of additional treatment strategies that are effective, safe, and well-tolerated.

Understanding the pathophysiology of anxiety disorders can assist in the development of medications that can target abnormally functioning neural pathways. The functional neuroanatomy and pathophysiology of OCD have been the most studied of the anxiety disorders. Functional neuroimaging studies of OCD have consistently shown higher than normal glucose metabolism in the orbitofrontal cortex (OFC), caudate nucleus, and thalamus that decreases in responders to treatment with SRI medications, CBT or neurosurgery.\textsuperscript{10} Interventions that provoke OCD symptoms increase activity in these same brain regions. The glucose metabolic signal is thought to predominantly reflect transmission of the excitatory neurotransmitter glutamate.\textsuperscript{11} Abnormally high cerebrospinal fluid levels of glutamate have been found in patients with OCD, compared to healthy controls.\textsuperscript{12} In addition, magnetic resonance spectroscopy (MRS) studies of pediatric OCD patients have found elevated glutamate concentrations in the caudate nuclei that decreased dramatically after successful treatment with SRIs.\textsuperscript{13} Thus, pre- to post-treatment decreases in orbitofrontal-subcortical circuit activity seen in neuroimaging studies of OCD appear to reflect decreased release of glutamate in these regions. This suggests that alterations in glutamate transmission in the caudate may play a role in the pathophysiology and response to treatment of OCD.

Such excessive glutamatergic activity along cortico-striato-pallido-thalamic circuits has been postulated to be central to the pathophysiology of OCD,\textsuperscript{10,12} but has not been implicated in GAD. Studies of the pathophysiology of GAD are much more limited. Nevertheless, several functional neuroimaging studies have demonstrated abnormally high activity in the right prefrontal cortex as evidenced by metabolic hyperactivity at
rest, abnormal metabolite ratios, and greater activation in response to angry faces. It is possible that this hyperactivity is mediated by glutamate, given its role as the primary excitatory neurotransmitter, although no published studies to date have examined glutamate concentrations in GAD.

The objective of this study was to obtain preliminary open-label data on the efficacy and tolerability of memantine, an anti-glutamatergic medication with a unique pharmacodynamic profile, in individuals with OCD and individuals with GAD. Because glutamatergic hyperactivity in frontal and frontal-subcortical circuits may play a role in the symptomatic expression of OCD, and possibly GAD, agents that reduce glutamatergic neurotransmission may provide unique anti-obsessional and anti-anxiety benefits. Memantine is a specific, uncompetitive antagonist at the NMDA receptor that blocks sustained activation of the NMDA receptor by high concentrations of glutamate under pathological conditions but rapidly leaves the NMDA channel upon transient physiological activation by low concentrations of glutamate. NMDA receptors are densely expressed on all neurons in the human striatum. Memantine may thus reduce excessive cortico-striatal glutamate transmission in OCD. Memantine also enhances intracortical inhibition, which is deficient in OCD.

There is very little published data of memantine treatment of either OCD or GAD. Two case reports described memantine treatment of OCD; Poyurovsky et al. reported improvement with memantine augmentation in one patient with treatment resistant OCD, while Pasquini and Biondi noted improvement in one OCD patient with checking compulsions but not in one with contamination obsessions. There have been no case reports of memantine for GAD reported thus far. Neither have there been any open-label or controlled trials of memantine for OCD or GAD reported.

We chose to study memantine in these two anxiety disorder groups in order to compare relative efficacy for OCD vs. GAD symptoms. We hypothesized that treatment with memantine would result in significant symptom reduction in both OCD and GAD.

MATERIALS AND METHODS

Study Design

This study utilized a 12-week, open-label, flexible-dosing design to evaluate the efficacy of memantine in the treatment of OCD and GAD. Participants were recruited from May 2005 to January 2008 from the UCLA Anxiety Disorders Program at the Semel Institute for Neuroscience and Human Behavior. UCLA’s Institutional Review Board approved the study.
Board provided permission to conduct this study. All eligible subjects provided approved written consent prior to the initiation of any study-related procedure.

**Patient Selection**

Male or female outpatients aged 18 to 64 years were eligible if they had a current diagnosis of OCD or GAD. The MINI interview was conducted at screening to confirm diagnoses. OCD and GAD patients were eligible if they had a score ≥ 16 on the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) or the Hamilton Anxiety Rating Scale (HARS), respectively, and a Clinical Global Impression of Severity (CGI-S) score of at least 5 ("markedly ill"). Both groups were also required to have a score of < 17 on the 17-Item Hamilton Depression Rating Scale (HDRS) at baseline. We included subjects with lower HARS scores than have typically been used in GAD clinical trials (i.e., HARS > 20) to include milder cases of GAD, in order to improve the external validity of these results to clinical practice. Subjects were excluded if they had a primary diagnosis meeting DSM-IV criteria for any other Axis I disorder other than OCD or GAD, or if they met DSM-IV criteria for mental retardation or any pervasive developmental disorder, or had a neurological impairment. Also excluded were those with a current diagnosis or recent (6 month) history or of drug or alcohol dependence or abuse, current suicidal ideation and/or history of suicide attempt, or any personality disorder of sufficient severity to interfere with participation in the study. Other exclusion criteria included the presence or history of a medical disease that might put the patient at risk or compromise the study. Pregnant or breastfeeding women and those of childbearing potential who were not practicing a reliable form of contraception were excluded from the study. Subjects were permitted to continue taking an SRI or serotonin and norepinephrine reuptake inhibitor (SNRI) if they had been on a stable, therapeutic-range dose for at least 3 months and were still symptomatic. Subjects who had been using as-needed benzodiazepines were permitted to enter the study only if the frequency of use did not exceed two times per week. Subjects with 2 or more prior failed trials of SRI medication (of 6 weeks or longer) were excluded, due to the exploratory nature of this pilot study and to decrease clinical heterogeneity in the small sample.

**Treatment**

Subjects who met all of the eligibility criteria at screening were enrolled into the treatment phase and were dispensed study medication. We instructed subjects to begin treatment with memantine (Namenda®) 2.5 mg by mouth in the morning and the evening. The dose titration
schedule was based on clinical response and tolerability, with a target dose for all subjects of 20 mg/day. We provided subjects with a scheduled titration to increase the dose to 5.0 mg twice daily by day 8, 7.5 mg twice daily by day 15, and 10.0 mg twice daily by day 22. We monitored compliance with pill counts. For the duration of the study, we did not permit any changes to subjects’ concomitant medications.

At the study visits at weeks 2, 4, 6, 8, and 12, the study physician determined if the subject should continue with the scheduled dose increase, remain at the current dose, or decrease the dose. Doses were increased if subjects tolerated the medication and were not responding adequately, as defined by a rating of anything other than “much improved” on the Clinical Global Impression of Improvement Scale (CGI-I). If the subject tolerated the medication and had a rating of “much improved,” the dose remained the same. If the subject was not tolerating the dose, it was decreased to the previously tolerated level.

Assessments

The primary efficacy measure for subjects with OCD was the Y-BOCS; for those with GAD it was the HARS. We administered these instruments at baseline and weeks 2, 4, 6, 8, and 12. An additional primary outcome measure, the CGI-I, was administered at weeks 4, 8 and 12. The secondary efficacy measures for both groups were the Four Dimensional Anxiety and Depression Scale (FDADS) and the HDRS for both groups, and the HARS for the OCD group. The FDADS is a self-rated measure of anxiety and depression that has been tested in the general population as well as in clinical samples. It assesses four dimensional components of anxiety and depression: cognitive, physical, emotional, and behavioral. It consists of a depression subscale (FDADS-D) and an anxiety subscale (FDADS-A). It demonstrates sound psychometric properties with good internal consistency and test-retest reliability, and has demonstrated validity relative to other measures of anxiety and depression. The FDADS was administered at baseline and weeks 2, 4, 6, 8, and 12. We administered the HDRS at baseline and at weeks 8 and 12.

OCD subjects were classified as “responders” to treatment if they showed a ≥35% decrease in Y-BOCS score and were rated as “much improved” or “very much improved” on the CGI-I. GAD subjects were classified as “responders” to treatment if they showed a ≥50% decrease in HARS score and were rated as “much improved” or “very much improved” on the CGI-I.

Safety measures included a physical exam and routine chemistry, hematology, and urinalysis laboratory assessments, both at screening and endpoint. We also performed a pregnancy test and urine toxicology screen at baseline and endpoint. We monitored subjective reports on
the United Kingdom Unified (UKU) Side Effect Rating Scale and vital signs at all study visits.35

**Statistical Methods**

Demographic and clinical variables were compared between diagnostic groups with students’ t-tests for independent samples. Gender distribution and proportion of subjects on SRI medications were compared between groups with Fisher’s exact tests. Pre- to post-treatment changes in symptom rating scale scores were evaluated in each diagnostic group with paired t-tests.

**RESULTS**

Twenty-one individuals expressed interest in the study and engaged in an initial telephone screen. Twenty percent (n = 4) of these individuals were deemed ineligible to participate. Reasons for ineligibility included age (n = 2; 9%), psychiatric comorbidity (n = 1; 4%), and exclusion for concomitant medication (n = 1; 4%). Seventeen participants (10 OCD, 7 GAD) enrolled and received memantine treatment. After a preliminary analysis of treatment effects for 7 GAD patients, we terminated enrollment due to lack of response. Of the 17 individuals enrolled in the study, 11 (64%) were female, and 6 (35%) were male. Twelve participants (70%) had been taking psychotropic medications (SRIs n = 10; benzodiazepine n = 1, SRI and benzodiazepine n = 1) for at least 3 months prior to enrollment and continued throughout the study. Seven in the OCD group were taking concomitant medications and 5 in the GAD group (p = 1, Fisher’s exact test). All participants (n = 17) completed the study, and all were able to achieve the target dose of 10 mg twice a day. All were compliant with treatment, according to pill counts. Adverse events were generally mild in severity, mostly consisting of dizziness (n = 6) and somnolence (n = 3). Vital signs and pre- and post-treatment laboratory results were all within normal limits.

Demographics and primary outcome measure results for the OCD and GAD groups are presented in Tables 1 and 2, respectively. There were no significant differences between groups in mean age (OCD: 38.6 ± 11.8; GAD: 37 ± 14.3; t = 0.25, p = 0.81) or gender distribution (OCD: 4 males and 6 females; GAD: 2 males and 5 females; p = 1, Fisher’s exact test). There were also no significant differences in baseline mean HDRS scores (OCD: 9.2 ± 3.1; GAD: 8.7 ± 2.2; t = 0.36, p = 0.72) or baseline mean FDADS-A (OCD: 28.8 ± 5.9; GAD: 33.7 ± 4.4; t = 1.87, p = 0.081). However, the GAD group had significantly higher mean FDADS-D (OCD: 15.7 ± 2.7; GAD: 22.3 ± 5.7; t = 3.21, p = 0.0058) and HARS (OCD: 14.6 ± 2.6; GAD: 24.3 ± 1.1; t = 9.05, p < 0.001) scores at baseline.
### TABLE 1

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Mean ± SD: 38.6 ± 11.8

Paired t-test: t = 4.75, p = 0.001

*Participants classified as responders.
†Participants with ≥45% reduction in YBOCS scores from week 0 to week 12.

Abbreviations: YBOCS, Yale Brown Obsessive Compulsive Scale; OBS, YBOCS obsessions subscale; COMP, YBOCS compulsions subscale; CGI-I, Clinical Global Impression of Improvement scale.
The OCD group showed a significant, mean 40.6% reduction in YBOCS scores at endpoint (t = 4.75, p < 0.001). Three of 10 (30%) of OCD subjects were classified as responders, although 7 of 10 (70%) experienced a ≥35% reduction in YBOCS scores. In fact, these same 7 individuals each experienced a ≥45% reduction in YBOCS scores. The GAD group had a mean 22.4% reduction in HARS scores (t = 3.56, p = 0.012) at week 12. None of the GAD subjects were classified as responders to memantine treatment; no GAD subjects experienced a ≥50% reduction in HARS scores, and only one was rated as “much improved” on the CGI-I (see Table 2).

Both the OCD and GAD groups showed significant but modest decreases in depressive symptoms, as measured by HDRS and FDADS scores. The two groups showed similar improvements on the HDRS by endpoint, with a mean 27.2% reduction in the OCD group (t = 3.1, p = 0.013) and a 25% reduction in the GAD group (t = 2.9, p = 0.027). On the FDADS-D, there were mean 14% (t = 2.5, p = 0.03) and 29.8% (t = 2.8, p = 0.03) reductions by endpoint for the OCD and GAD groups, respectively. There were similar significant but modest decreases in anxiety in both groups. On the FDADS-A, there were mean 18.7% (t = 2.8, p = 0.02) and 22.9% (t = 3.2, p = 0.019) reductions by endpoint for the OCD and GAD groups, respectively. In the OCD group, the mean decrease on the HARS by endpoint was 19.7% (t = 4, p = 0.005).
DISCUSSION

The major finding of this study was that memantine appeared to be effective for treatment of OCD but not GAD. 70% of the OCD subjects treated with memantine experienced significant improvement of their OCD symptoms. OCD symptoms decreased to a greater extent than GAD symptoms, and to a greater extent than anxiety or depressive symptoms in either group.

These findings are consistent with prior case reports of improvement in OCD with memantine treatment. In addition, several case reports and an open-label trial have reported efficacy of other anti-glutamatergic medications for the treatment of OCD. In an open-label trial of riluzole, a glutamate release inhibitor, seven of 13 adult patients with OCD improved, and five were categorized as treatment responders. Another open trial found riluzole to be effective for four of six children with treatment-refractory OCD. N-acetylcysteine, an agent that likely attenuates glutamate neurotransmission, was effective as an augmentation in one patient with OCD.

Although preliminary, it is possible that memantine may have specific properties responsible for reducing obsessions and compulsions. If so, this may relate to its specific and preferential blockade of NMDA receptor ion channels when they are excessively open due to pathological stimulation by tonic, low-amplitude glutamate transmission. Functional neuroimaging studies will be required to determine whether memantine treatment decreases excessive activity in the orbitofrontal cortex and caudate, thought to be a final common pathway for OCD symptom improvement. Moreover, memantine was well tolerated, and no subjects dropped out of the study. Therefore, double-blind, placebo-controlled studies of memantine for OCD are now warranted.

Contrary to our hypotheses, memantine did not appear to have a strong anxiolytic effect, either in GAD patients or OCD patients. Although the decreases in FDADS-A and HARS scores were statistically significant for both groups, the magnitude of improvement (19–23%) was not clinically significant. The statistical significance is likely due to the fact that the variance was small. The same can be said for the FDADS-D and HDRS for both groups. The minimal antidepressant effect of memantine in this study is consistent with a previous study that found no difference between memantine and placebo for treatment of major depression, although low pre-treatment depression ratings in the current study limit this interpretation.

In contrast, riluzole has been found in open trials to be helpful for GAD, as well as OCD and major depression. In an open-label trial of riluzole treatment in 18 patients with GAD, twelve...
patients responded and eight achieved remission.\textsuperscript{41} Riluzole has a broader mechanism of action than memantine, with other, non-glutamatergic actions\textsuperscript{44} that may convey broader efficacy for other anxiety and mood disorders.

Only one other study of a glutamatergic agent in GAD has been published. In a double-blind, controlled study LY354740, a metabotropic glutamate receptor 2/3 (mGlu2/3) agonist, was significantly more effective than placebo for GAD.\textsuperscript{45}

There was relatively little improvement in overall anxiety for the OCD group, which likely accounted for the fact that 7 of 10 subjects experienced a ≥45% decrease in YBOCS scores, yet only 3 of these were rated “much improved” or “very much improved” on the CGI-I. The CGI-I was based on the overall clinical picture, not just the OCD symptoms.

There also appeared to be a slightly greater magnitude in improvement in the compulsive, relative to the obsessive, subscale of the YBOCS (mean 6.5 point vs. 4.2 point improvements, respectively). Future, larger studies will need to confirm if memantine confers differential efficacy for these two main OCD symptom categories, as well as for different symptom dimensions.

This study had several limitations. The sample size was small, especially for the GAD group. However, this was due to the apparent lack of efficacy of memantine in the GAD group. We stopped enrolling GAD subjects after none of the first seven GAD subjects showed a significant positive response to memantine. The inclusion of 12 subjects who were taking SRIs and benzodiazepines could potentially produce a confound in the interpretation of our results. However, no subject in this study had any change in medications or doses for at least twelve weeks prior to study entry, nor were changes in other medications allowed during the twelve-week memantine treatment period. Another limitation is that the open-label design of this study does not allow for a determination of efficacy separate from placebo effect. If placebo effects solely accounted for improvements, however, we would have expected a higher response rate in the GAD group than the OCD group, based on placebo response rates from previous controlled studies.\textsuperscript{46,47}

This study had several strengths that afford confidence in its findings. To our knowledge, this was the first standardized trial of memantine treatment for either OCD or GAD. The study design comparing two anxiety disorders provided an exploratory means for testing if memantine has specific anti-obsessional properties, as opposed to non-specific anxiolytic or antidepressant properties that might be seen across diagnostic groups. Another strength is that subjects with comorbid disorders were excluded.
In sum, results from this study suggest that memantine may have preferential efficacy in treatment of OCD, as opposed to only minimal effects on anxiety symptoms in GAD. These preliminary findings warrant confirmation from larger, placebo-controlled studies in OCD.

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REFERENCES

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