ORIGINAL CONTRIBUTION

A Single-Blinded Case-Control Study of Memantine in Severe Obsessive-Compulsive Disorder

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Background: Obsessive-compulsive disorder (OCD) is a common debilitating psychiatric illness that typically improves but does not remit with first-line medication and behavioral treatments. Serotonergic agents including selective serotonin reuptake inhibitors and clomipramine have provided the mainstay of OCD medication management for decades. Combined dopamine/serotonergic agents such as atypical antipsychotics are presently the only OCD-augmenting strategies proven effective via randomized controlled trials. Despite increasing evidence for a pathogenic role of glutamate in OCD, no controlled trials of glutamatergic augmenting agents have been reported.

Methods: An intent-to-treat sample included 44 subjects receiving standard treatment at the McLean/Massachusetts General Hospital Intensive Residential Treatment (IRT) program, 22 of whom also received memantine augmentation. Admission, monthly and discharge measures of OCD, depression, and psychosocial functioning were collected by raters blinded to augmentation status. Matched controls were selected based on sex, initial OCD severity, psychosocial functioning, and timing of admission. The Clinical Global Improvement Scale captured global clinical change.

Results: Mean (SD) Yale-Brown Obsessive Compulsive Scale score decreases were 7.2 (6.4) among the cases and 4.6 (5.9) among the matched controls, reflecting mean clinical improvement among the cases (27.0% decrease) but not the controls (16.5% decrease). Mean (SD) depression severity score decreases were 5.8 (9.5) among the cases and 4.7 (9.9) among the controls. Initial intrusive obsessions were significantly more severe among marked responders compared with limited response or nonresponse cases (4.4 vs 2.9; t = 2.15; P = 0.048).

Conclusions: This study provides preliminary supportive evidence for the effectiveness of memantine as a glutamatergic augmenting agent in severe OCD. Future randomized double-blind placebo-controlled trials are warranted.

Key Words: obsessive-compulsive disorder (OCD), memantine, glutamate, augmenting agents, anxiety disorders, treatment

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Obsessive-compulsive disorder (OCD) is a common and debilitating psychiatric condition that affects 1% to 3% of the population worldwide,† making it the fourth most common psychiatric disorder.‡ First-line OCD treatments, including selective serotonin reuptake inhibitors (SSRIs), cognitive–behavior therapy (CBT), and their combination, are effective in approximately 42% to 50%,§ 62%, and 70% of cases, respectively.¶ However, symptoms often persist and full remission is uncommon with first-line approaches.¶ When symptoms remain severe, a medication switch or use of augmenting agents may become necessary. Switching from one SSRI to another benefits approximately 40% of OCD patients.¶ Although successful trials of atypical antipsychotics have demonstrated further symptom reduction, no controlled studies of glutamatergic agents as augmenting agents for standard OCD pharmacotherapy have yet been reported.

Obsessive-compulsive disorder augmenting strategies reported in randomized controlled trials to date include the atypical antipsychotics risperidone, octapirazine, and olanzapine, which act on serotonergic-dopaminergic systems. Open-label studies and reports have also supported use of trazodone, aripiprazole, zipirimate, and mirtazapine, in partial responders and nonresponders. Open-label trials of the glutamatergic agents riluzole, n-acetylcysteine, and memantine have emerged in recent years, but no controlled studies of these agents have yet been reported in OCD.

Several lines of evidence implicating glutamatergic neurotransmission as a putative etiologic factor in OCD. Increased glutamate levels in cerebrospinal fluid, in the prefrontal and orbitofrontal cortex and the striatum, and reversible dysfunction in the glutamate-mediated corticostriatothalamic circuit have been reported. Significant associations with OCD have been identified for genes including the glutamate receptor, ionotropic, N-methyl-d-aspartate 2B (GRIN2B); glutamate receptor, ionotropic kainite 2 (GRIK2) genes. Knockout mice for the striatum-expressed SAPAP3 gene, coding for a postsynaptic scaffolding protein at corticostriatal glutamatergic excitatory synapses, also developed facial lesions, repetitive grooming behaviors, and anxiety that were reversed with an SSRI and with gene replacement.

Memantine is a glutamate receptor antagonist that has been reported to reduce OCD symptoms in case studies of treatment-resistant individuals. In this intent-to-treat, single-blinded, naturalistic case-control study, we examine the effectiveness of memantine as an augmenting agent to standard intensive residential treatment of severe OCD.

MATERIALS AND METHODS

Subjects

The study population comprised 44 subjects receiving standard treatment at the McLean Hospital/Massachusetts General Hospital OCD Institute Intensive Residential Treatment (IRT) program, admitted between May 1999 and December 2007. Frequencies of other prescribed standard OCD medications among the case patients and the control subjects at trial initiation were 59.1% (n = 13 case patients) versus 72.7% (n = 16 control subjects) for SSRI or clomipramine (P = 0.34), 36.4% (n = 8 case patients) versus 27.3% (n = 6 control subjects) for...
benediazepines (P = 0.52), and 27.3% (n = 6 case patients) versus 22.7% (n = 5 control subjects) for atypical antipsychotics (P = 0.73). There were no significant differences between the case and control groups with respect to non-memantine medication dose changes, initiations or discontinuations during the memantine trial (P > 0.05). The threshold criteria for admission to the OCDI include the presence of severe OCD-related impairment and inadequate prior response to standard treatment modalities. These criteria are established via admission package information, Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) severity scores, and collateral information from family members and treating clinicians and are subsequently confirmed by OCDI psychiatrist assessments. In general, the program exclusion criteria include conditions that preclude significant engagement in IRT, such as severe mental retardation, primary psychotic illness, active substance dependence, or suicidality. The OCDI comprises intensive behavioral, medication, and milieu OCD treatment provided by a multi-disciplinary team of psychiatrists, behavior therapists, social workers, nurses and counselors, with a highly structured program that enables close monitoring of treatment adherence. All residents participate in 2 to 4 hours of CBT daily and weekly psychopharmacology assessments by OCD expert psychiatrists to monitor medication efficacy and adverse effects. More extensive details of this treatment program have been provided elsewhere.\textsuperscript{36}

**Study Design**

Among consecutive patients requiring medication augmentation, 22 gave informed consent to an IRT psychiatrist (M.A.J.) for an off-label trial of the augmenting agent, memantine. To control for confounding effects of nonmedication therapeutic aspects of the OCD program, matched IRT controls were selected based on sex, Y-BOCS, and Work and Social Adjustment (WSA) scores at admission (±1 point). The most recent subject from the OCDI research database found to meet these criteria for each case was identified as the matched control. These matching criteria were preliminarily established based on previous research at this program that identified OCD severity, psychosocial functioning, and sex as predictors of IRT outcome.\textsuperscript{37}

**Measures**

The following standard admission, monthly and discharge psychometric IRT program outcome measures were used in this study. Measures were administered by trained and experienced IRT staff members. The Y-BOCS is a 10-item measure rating each item between 0 (lowest severity) and 4 (highest severity). It has a high convergent validity with the National Institute of Mental Health Obsessive-Compulsive Scale (r = 0.67)\textsuperscript{35} with excellent reliability.\textsuperscript{38,39} The Y-BOCS checklist has more than 60 items organized into 2 miscellaneous categories and 13 other categories according to thematic content. The Beck Depression Inventory (BDI) is a 21-item depression severity scale with a reliability of 0.92, a construct validity correlation with the Symptom Checklist-90-Revised of 0.76, sensitivity of 100%, and specificity of 89% (using a cutoff score of 16).\textsuperscript{22,40,41} The Obsessive-Compulsive Rating scale is a questionnaire-based measure that rates the severity of OCD symptom categories between 0 and 10. This measure has good internal consistency with a Cronbach α of 0.83 for the total severity score and good convergent validity with the Y-BOCS.\textsuperscript{42} The WSA scale is a 5-item measure assessing functional impairment and quality of life, with test-retest reliability of 0.73, convergent validity with clinician interviews of 0.81 to 0.86, and increasing scores that reflect worse functional impairment.\textsuperscript{43} The Clinical Global Impression (CGI) scale provides an assessment of overall impact of treatment rated between 1 (very much improved) and 7 (very much worse). The aforementioned study instruments were administered by experienced, bachelor level IRT counselors in the IRT program who were randomly assigned to study subjects and supervised by PhD level psychologists with OCD expertise.

**Analyses**

Data were coded from completed measures at admission, monthly intervals, and discharge and were subsequently double-entered into a database and verified. The primary study outcome measure was defined as percent change in Y-BOCS OCD severity scores between admission and discharge. For a small minority of subjects, discharge measures of OCD severity were not obtained because of causes including premature discharge from the program. When unavailable, a last observation carried forward (LOCF) approach was used to define proxy discharge scores for analyses. In those cases, the similar time point for the matched control was used as the final discharge/LOCF score for comparison in an attempt to match the cases and the controls as closely as possible on all relevant variables (given that the IRT program has multiple modalities that may potentially impact OCD severity in a time-dependent manner). Moreover, any subjects without at least 1 pre-memantine and 1 post-memantine OCD severity score were excluded from study. Secondary outcomes of interest included changes in comorbid depression severity as measured by the BDI, psychosocial functioning changes as measured by the WSA scale, and global improvement as measured by the CGI scale. Clinically significant treatment response was defined by a Y-BOCS score decrease of at least 25% (as used in previous studies\textsuperscript{10}) and marked response was defined by a 50% Y-BOCS score decrease. Descriptive and comparative analyses were conducted between the case and control groups and also between the responders and the nonresponders in the entire group and in the cases alone, using t tests and χ² tests and a cutoff of P = 0.05 to indicate statistical significance.

**RESULTS**

For the 44 matched study subjects at admission, mean (SD) scores were 26.8 (5.2) for the Y-BOCS, 18.2 (9.1) for the BDI, and 28.2 (5.3) for the WSA. The mean (SD) admission length was 62 (37.3) days, and 68.2% (n = 30) of subjects were male. There were no notable or serious adverse effects or related discontinuations of memantine.

Admission and discharge (or LOCF) scores reflecting OCD severity, psychosocial functioning, and self-reported improvement were compared between the case and the control groups. There were no significant differences identified between the case and the control groups on any admission (preaugmentation) measures (P > 0.2). The mean (SD) Y-BOCS decrease was equal to 7.2 (6.4) for the cases and 4.6 (5.9) for the controls. These data represent a clinically significant (≥25% decrease) mean improvement for the case group (27.0% decrease) but not the control group (16.5% decrease). The mean starting dose of memantine was 5 mg. The mean duration to the first dose increase was 7.6 days and the mean final memantine dose was 18.0 mg.

Among the responders in both groups, those in the case group were significantly more likely to have a 50% OCD severity decrease compared with those in the control group (22.7% of the case group vs 4.5% of the control group; χ² = 4.27, P = 0.04). According to available CGI discharge scores (n = 31), all the case patients had at least a minimal improvement. Moreover, 35.3% (n = 6) of the case patients were...
TABLE 1. Clinical Characteristics for Nonresponders, Responders, and Marked Responders in the Memantine Case Group

<table>
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<tr>
<th>ID #</th>
<th>OCD Symptom Type Severity</th>
<th>Comorbidity</th>
<th>Other Medications</th>
<th>Medications at Memantine Start</th>
<th>Medication Added (+) or Removed (−)</th>
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<tr>
<td></td>
<td>Intrusive Obsessions (0−10)</td>
<td>Sexual Obsessions (0−10)</td>
<td>Checking Compulsions (0−10)</td>
<td>MDD†</td>
<td>BDD</td>
</tr>
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<td>*By score ≥16 on the BDI.</td>
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<td>†By self-report on the tic symptom checklist.</td>
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Atypical indicates atypical antipsychotic; BDD, body dysmorphic disorder; Benzo, benzodiazepine; MDD, major depressive disorder; n/a, unavailable data or not applicable; NDRI, norepinephrine dopamine reuptake inhibitor; PTSD, posttraumatic stress disorder; SARI, serotonin antagonist reuptake inhibitor; SNRI, serotonin norepinephrine reuptake inhibitor; TCA, tricyclic antidepressant; Trich, trichotillomania; WSA, work and social adjustment scale.
very much improved” compared with 7.1% (n = 1) of the control subjects. The likelihood of being rated as very much improved was 3.8 times higher in the case group versus the control group (P = 0.05). None of the case patients and 14.3% (n = 2) of the control subjects demonstrated worsening or no change at discharge. Clinical characteristics of the nonresponder, the responder, and the marked responder case patients are summarized in Table 1, including details of OCD symptom types, comorbidities, psychosocial functioning and other medications.

No differences in OCD symptom category type were identified between the responders and the nonresponders in the overall sample or in the case group alone. Furthermore, no OCD symptom type differences were identified between the responders in the case and the controls groups (P > 0.05). Symptom types with the highest mean (SD) severity scores (rated out of 10) among the case and the control groups included washing (6.1 [4.3]), repeating (5.9 [3.9]), and telling/asking/confessing (5.7 [3.7]) obsessions and compulsions. Marked responders (with at least 50% OCD improvement) had significantly higher intrusive obsession scores (4.4 vs 2.9, t = 2.15, P = 0.048) versus the subjects without a marked response. Among these marked responders, the most severe subtypes were sexual obsessions (7.5 [5.0] vs 4.1 [4.2] for poorer response) and checking compulsions (6.0 [2.3] vs 5.5 [4.6] for poorer response).

Depression severity was not significantly different between the case patients and the control subjects upon admission (P = 0.82) or at discharge (LOCF; P = 0.64). However, both discharge (LOCF) depression severity (t = 2.12, P = 0.04) and psychosocial functioning WSA (t = 5.9, P < 0.001) scores were significantly lower among the IRT (case and control groups) OCD responders versus the nonresponders. In examining the responder versus the nonresponder case patients only, the discharge (LOCF) WSA scores were also significantly improved among the responders (t = 5.4, P < 0.001), although the depression severity did not significantly differ (t = 1.8, P = 0.09).

**DISCUSSION**

Results from this controlled single-blinded study demonstrate memantine as an effective augmenting agent to standard IRT treatment in severe OCD. This expands upon previous open-label trials and case reports suggesting the drug’s efficacy. A mean OCD severity improvement of at least 25%, denoting clinically significant improvement, was noted among the case patients but not the control subjects.

From a clinical perspective, this finding suggests promise for the use of memantine in OCD. This medication was approved by the Food and Drug Administration in 2003. Its safety profile and patient tolerability are very good, with no known cardiotoxic, hepatotoxic, or serious adverse effects. It is not associated with physiologic tolerance and is not metabolized by the cytochrome P450 system, thus increasing its ease of use in combination with other medications. Memantine has not been approved specifically for use in children, which is a concern given that OCD frequently begins in childhood. However, a recent case report of its safe, effective use in an adolescent has been published.

Although the mean Y-BOCS score decrease among the case patients represented a clinically significant improvement, only 36.4% (n = 8) of the case patients were responders (>25% Y-BOCS decrease). This suggests that the responders predominantly had greater than the minimum threshold of 25% improvement, driving the mean score change for the entire case group. As such, memantine and other glutamatergic agents may be preferentially beneficial to as of yet undefined OCD subtypes.

Ideally, this study would explore response predictors for memantine and examine its effectiveness and tolerability. For example, an augmentation study of risperidone (acting on dopaminergic and serotoninergic neurotransmitter systems) demonstrated response in a subsample (n = 4 of 9) of OCD patients with lower striatal metabolism and higher anterior cingulum metabolism. The relatively small sample size in the present study precluded a thorough examination of symptom dimensions, age of onset, or focal metabolism as potential treatment response predictors. No differences in OCD symptom types were identified between the case responders (>25% Y-BOCS improvement) and the nonresponders (<25% Y-BOCS decrease; P > 0.07), although the marked responders (>50% Y-BOCS decrease) had significantly higher intrusive obsession scores (4.4 vs 2.9, P = 0.048) compared with the other case patients (<50% Y-BOCS decrease). Among the marked responders, the most severe obsessions were sexual (7.5 vs 4.1 for the poorer response group) and compulsions were checking (6.0 vs 5.5). Interestingly, these symptoms and intrusive obsession symptoms are all represented in the “sexual/religious/aggressive/somatic/checking” symptom dimension previously described in adult and child samples. Given the cognitive benefits of memantine in Alzheimer’s disease, it could be postulated that this agent may be preferential for use in OCD patients with prominent cognition-related obsession symptoms within this symptom dimension, rather than for those with more physical or stand-alone rituals. However, this hypothesis will require testing in future larger randomized controlled trials.

Percent decrease in depression severity after IRT treatment was not significantly different between the case group (32.1%, SD 46.7) and the control group (12.8%, t = -1.1, P = 0.28). However, the depression improvement was significantly greater among the combined case-control OCD responders (45.3% BDI decrease) versus the nonresponders (14.4% BDI decrease; t = 2.99, P = 0.006). This pattern was also seen in the case-only responders (58.7%) versus the nonresponders (5.5%; t = 2.7, P = 0.02) but was not seen in the control-only responders (32.0%) versus the nonresponders (9.2%; t = 1.7, P = 0.12). Discharge (or LOCF) psychosocial functioning scores were better among the IRT responders versus the nonresponders (t = 5.4, P < 0.001) regardless of the case-control status.

This study examines in vivo effectiveness of memantine as an augmenting agent with standard IRT in complex, severely ill OCD patients with comorbidities, rather than studying efficacy in a higher functioning, comorbidity-free population. Although subjects are atypical from those included in double-blinded, randomized placebo-controlled trials, this study was designed to increase generalizability of its findings to individuals with severe OCD that warrants treatment augmentation.

From a research perspective, this study provides an additional line of converging preliminary evidence implicating the glutamate pathway as a potential target in OCD treatment. It has been well established that excess interneuronal glutamate levels may result in excitotoxicity for neurons. Memantine is a noncompetitive antagonist of glutamate receptors of the N-methyl-D-aspartate type. As such, it is a logical choice for use in moderate to severe Alzheimer disease, for which it is approved by the Food and Drug Administration. Altered glutamate receptor levels have been found in OCD-implicated brain areas, the OCD-associated GRIK2 glutamate receptor gene has messenger RNA that is prominent in these areas (striatum and caudate), and the OCD-associated GRIK receptor gene...
is known to influence glutamate-induced neuronal degeneration in the basal ganglia. Glutamate also interacts with previously implicated monoamine systems in OCD pathology (including serotonin and dopamine) in a complex manner. Glutamate agonists facilitate presynaptic synthesis and release of dopamine in the prefrontal cortex. Moreover, glutamate receptor antagonism leads to an enhancement of 5-HT2A receptor-mediated transmission; 5-HT2A agonism leads to reduced glutamatergic transmission and 5-HT receptor activation reduces the excitatory effect of glutamate on cellular activity. It is this interaction that is believed to contribute to some mechanisms of psychiatric symptoms.

Given the previously reported white matter abnormalities and white matter volume decreases in OCD, it could also be hypothesized that this is a direct or indirect product of cytotoxic damage. However, such claims would be premature at present and require future study. Nonetheless, memantine has reportedly been effective in a randomized placebo-controlled study of schizophrenia, another psychiatric illness in which white matter abnormalities have been implicated.

Limitations of this study must be acknowledged. Specifically, the cases comprise a convenience sample of individuals placed on memantine during IRT for OCD. However, all IRT participants received regular admission and monthly and discharge measures (not administered by the treating physician) such that the control subjects, and the raters were blinded to their involvement in these analyses and to medication status. The case patients were aware of their treatment with memantine, thus introducing a potential placebo effect. All the case patients and control subjects (in response to a standard offer to all new IRT patients) initially gave written consent to the anonymous release of their clinical data for research purposes. The decision to conduct matching of the cases to the controls occurred only after the discharge of all participants, such that randomization to the treatment groups did not occur. However, this does not preclude measurement bias regarding potential memantine effects. Matching variables were defined before selection of the control group. Given that this augmentation occurred in the context of IRT, which incorporates both the standard OCD medication and the CBT approaches, examining the improvement of the case patients alone would provide inadequate specificity regarding impact of memantine. Thus, careful matching inclusive of all variables found to be associated with IRT outcome was conducted in an attempt to isolate the effect of memantine. Although there was no medication matching, this factor did not previously yield significant differences in predicting IRT outcome. Despite these efforts, it is possible that some selection bias may have remained as a consequence of lack of randomization in the study design. Owing to the study approach, no weekly measures were available to accurately determine time to effect. Moreover, although the sample size had sufficient power to detect a difference between groups, the limited numbers precluded analyses to identify memantine response predictors.

CONCLUSION

This single-blinded matched case-control study of standard IRT with versus without memantine in a severe OCD sample demonstrates promise for memantine as an augmenting agent. Moreover, it provides a further converging line of evidence pointing to a putative pathological role of glutamate in OCD. Future randomized controlled trials attempting to replicate these findings and to identify memantine response predictors in a larger OCD sample are warranted.

AUTHOR DISCLOSURE INFORMATION

Dr Evelyn Stewart has received support from the Anxiety Disorders Association of America (ADAA), the Obsessive-Compulsive Foundation (OFC), the American Academy of Child and Adolescent Psychiatry (AACAP), and a nonindustry, not-for-profit private fund. The other authors report no competing interests.

REFERENCES


