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THE USE OF GLUTAMATE MODULATING DRUGS IN OBSESSIVE COMPULSIVE DISORDER

Frank P. MacMaster, PhD and

Assistant Professor, Cuthbertson and Fischer Chair in Pediatric Mental Health, Departments of Psychiatry and Pediatrics, University of Calgary, Calgary, AB, Canada

David R. Rosenberg, MD

Professor, Miriam L. Hamburger Endowed Chair of Child Psychiatry, Department of Psychiatry & Behavioral Neurosciences, Wayne State University, Detroit, MI, USA

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Obsessive-compulsive disorder (OCD) is a chronic, severe and debilitating disorder, affecting over 3 million people in the United States. People afflicted with OCD have obsessions and compulsions that impair their functioning in life. According to the World Health Organization, OCD is among the ten most disabling medical conditions worldwide. The National Comorbidity Survey Replication, when examining anxiety disorders, found that OCD had the highest percentage of serious cases (50.6%) (*Kessler et al.*, 2005). Lifetime prevalence estimates of OCD in pediatric and adult populations range from 1% to 3% (*Kessler et al.*, 2005). The clinical presentation of OCD in childhood and adulthood is similar, making findings applicable across the age span. The mean age of onset for OCD in children is between 9 to 11 years in males and 11 to 13 years in females (*Hanna*, 1995). A more negative outcome is associated with an early age of onset. Furthermore, pediatric OCD was found to be chronic and unremitting in up to 87% of cases that failed to receive effective treatment (*Stewart et al.*, 2004). **Finally**, an early diagnosis of OCD is associated with a higher risk for developing other psychiatric disorders into adulthood.

THE CASE FOR NOVEL TREATMENTS OF OCD

Serotonin reuptake inhibitors (SRI) are the only FDA approved medications for OCD. While considered effective in the clinical trial literature, treatment of OCD with SRI's has proven limited in clinical practice. SRIs are only effective in 40 to 60% of patients (*Jenike*, 2004). Obviously, this leaves a considerable number still ill. Additionally, studies often define treatment response as a 20 to 40% reduction in symptoms. Hence, many subjects who are classed as "responders" still have marked symptoms after treatment (*Jenike*, 2004). OCD symptom severity scores, as calculated by the Children's Yale-Brown Obsessive-

Correspondence: David R. Rosenberg, M.D., Wayne State University, Psychiatry 9B, 4201 St. Antoine Boulevard, Detroit, MI 48201; Phone: 313-577-9000, FAX: 313-577-5900, drosen@med.wayne.edu.

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Compulsive Scale (CY-BOCS), normally range from 15 to 20 post-treatment. A score in this range is still indicative of significant impairment. In addition to SRIs, cognitive behavioral therapy (CBT), alone or in combination with SRI, is also considered effective for treating OCD (POTS, 2004). Nonetheless, one-third of pediatric patients remain markedly ill even after receiving the combination of CBT and medication (POTS, 2004). What is more, data indicates that an earlier onset of OCD may be associated with the illness being more treatment refractory (POTS, 2004). Indeed, OCD is one of the few remaining psychiatric disorders for which there is a neurosurgical treatment indication. The persistence of symptoms and the limited nature of treatment response indicates that the serotonin paradigm of understanding OCD cannot fully account for the underlying neurobiology of the illness. Therefore, novel, evidence based approaches are needed to advance treatment of OCD. The glutamate hypothesis of OCD, first developed over a decade ago (Rosenberg & Keshavan, 1998), and resulting biological evidence has recently translated to the application of glutamate modulating agents for the treatment of pediatric OCD.

GLUTAMATE BASED PHARMACOTHERAPY OF OCD

RILUZOLE

Recently riluzole, a glutamate-modulating agent, has shown promise in treating psychiatric disorders (Coric *et al.*, 2003; Coric *et al.*, 2005; Grant, Lougee, Hirschtritt & Swedo, 2007). Riluzole is FDA approved for amyotrophic lateral sclerosis (ALS) and is well tolerated by patients. Riluzole can act in three ways: (1) as an inhibitor of glutamate release, (2) to inactivate voltage dependant sodium channels in cortical neurons, and (3) to block GABA reuptake. In a case report and small open-label trial in adults with OCD (Coric *et al.*, 2003; Coric *et al.*, 2005), riluzole was effective in decreasing OCD symptoms. This was extended to children and adolescents (8 to 16 years) with OCD in a small open-label trial. Again, riluzole was effective at reducing symptoms of OCD and was also well tolerated (Grant *et al.*, 2007). Currently, the National Institutes of Mental health is sponsoring a double blind clinical trial.

TOPIRAMATE

Topiramate has shown some effectiveness in treating OCD symptoms in adults (Hollander & Dell'Osso, 2006; Rubio, Jimenez-Arriero, Martinez-Gras, Manzanares & Palomo, 2006; Van Ameringen, Mancini, Patterson, & Bennett, 2006). In a case study, Hollander *et al.* (Hollander & Dell'Osso, 2006) found that augmentation of paroxetine (40 mg/day) with topiramate (up to 150 mg/day) over nine 9 weeks resulted in a improved clinical condition. In an open label case series, Van Ameringen (Van Ameringen *et al.*, 2006) found topiramate augmentation to be effective in 11 of 16 patients. Rubio *et al.* (Rubio *et al.*, 2006) demonstrated that the combined administration of topiramate with antidepressants significantly improved the symptoms of OCD patients resistant to antidepressant treatments. However, there have been case reports that indicate that certain glutamate modulating medications like topiramate can actually induce OCD-like behaviors (Ozkara, Ozmen, Erdogan & Yulag, 2005; Thuile, Even & Guelfi, 2006).

LAMOTRIGINE

A case report on a patient with treatment resistant OCD found that augmentation of clomipramine (225 mg/day) with lamotrigine (up to 150 mg/day) over 10 weeks resulted in significant clinical improvement (*Uzun, 2010*). Furthermore, lamotrigine may be helpful in reducing obsessive-compulsive symptoms in schizophrenia patients (*Poyurovsky, Glick & Koran, 2010*). Caution is indicated in pediatric patients less than 16 years of age due to an increased risk for potentially life-threatening, disfiguring skin reactions, e.g., Stevens Johnson syndrome.

N-ACETYLCYSTEINE

N-acetylcysteine has also shown promise in the treatment of refractory OCD (*Lafleur et al., 2006*). N-acetylcysteine is converted to cystine. Cystine is a substrate for the glial glutamate/cystine antiporter. The uptake of cystine by glial cells causes the reverse transport of glutamate into the extracellular space. Here, glutamate appears to stimulate inhibitory metabotropic glutamate receptors on glutamatergic nerve terminals, reducing the synaptic release of glutamate (*Moran, McFarland, Melendez, Kalivas & Seamans, 2005*). In a case study of a single patient with serotonin reuptake inhibitor refractory OCD, Lafleur et al (*Lafleur et al., 2006*) found that N-acetylcysteine augmentation of fluvoxamine resulted in a marked decrease in OCD symptoms as measured by the Y-BOCS. The patient had been taking a dosage of 300 mg of fluvoxamine daily for 12 years. Previous trials of fluoxetine, clomipramine, and alprazolam had failed. Previous attempts at behavior modification had also failed. N-acetylcysteine was started at 600 mg PO daily and titrated upward to a total daily dosage of 3 g over 6 weeks and continued at the dosage of 3 g per day for an additional 7 weeks. Aside from a mild, brief right hand tingling, and a single day of xerostomia, no side effects were reported.

D-CYCLOSERINE

D-cycloserine is a partial agonist at the N-methyl-D-aspartate (NMDA) glutamatergic receptor. Kushner et al (*Kushner et al., 2007*) administered D-cycloserine (125 mg) or placebo in a double-blind fashion to OCD patients approximately 2 hours before an exposure therapy session. This was a small trial (N = 14 in the experimental, D-cycloserine group and N = 11 in the placebo group). D-cycloserine treatment decreased the number of exposure therapy sessions needed to achieve clinical milestones and the rate of dropout. After only four exposure sessions, patients in the D-cycloserine group reported significantly greater decreases in symptoms compared with the placebo group. However, the placebo group did catch up to the D-cycloserine group after additional sessions. This work was extended in a randomized, double-blind, placebo-controlled trial examining D-cycloserine augmentation of behavior therapy for OCD (*Wilhelm et al., 2008*). Similar to the above study, relative to the placebo group, the D-cycloserine group's OCD symptoms were significantly more improved at mid-treatment but did not differ from the placebo + behavior therapy group at the end of treatment. D-cycloserine was thought to 'speed up' the effect of treatment and rather than lose its effect of the remaining time, it merely exhausted its clinical utility (*Chasson et al., 2010*).

MEMANTINE

Memantine, a NMDA receptor antagonist, has also shown promise for treating OCD. In the initial case study of memantine in treatment refractory OCD, memantine augmentation (to clomipramine at 300 mg/day and sulpiride at 400 mg/day) was effective in reducing OCD symptoms (Poyurovsky, Weizman, Weizman & Koran, 2005). Memantine was started at 5 mg/day and titrated to 20 mg/day over 2 weeks. No significant side effects were noted and improvement was maintained after 3 months. This held true in a case study in pediatric OCD as well (Hezel, Beattie & Stewart, 2009). In a case study of two patients, memantine was only beneficial to one subject (Pasquini & Biondi, 2006). The authors suggested that subtype may play a role, with the ‘washer’ showing no improvement while the ‘doubter/checker’ did. In an open label trial of memantine in 14 treatment refractory OCD patients, Aboujaoude et al (Aboujaoude, Barry & Gamel, 2009) found six subjects responded to memantine treatment. Side effects were mild and transient. In an open label trial of 10 OCD subjects who received 12 weeks of memantine (10 mg twice daily), as monotherapy or augmentation of their existing medication, Feusner et al (Feusner, Kerwin, Saxena & Bystritsky, 2009) found the OCD patients had a 40.6% reduction in Y-BOCS. Again, memantine was well tolerated. Finally, a single blind case control study found that memantine augmentation was more effective than intent to treat alone (Stewart et al., 2010).

CONCLUSION

Given the above clinical reports, glutamate modulating agents offer particular promise in treating OCD. It is essential to note that usage of glutamate modulating agents is considered off-label and investigational.

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References

- Aboujaoude E, Barry JJ, Gamel N. Memantine augmentation in treatment-resistant obsessive-compulsive disorder: An open-label trial. *Journal of clinical psychopharmacology*. 2009; 29(1):51–55. [PubMed: 19142108]
- Chasson GS, Buhlmann U, Tolin DF, Rao SR, Reese HE, Rowley T, et al. Need for speed: Evaluating slopes of OCD recovery in behavior therapy enhanced with d-cycloserine. *Behaviour research and therapy*. 2010; 48(7):675–679. [PubMed: 20362975]
- Coric V, Milanovic S, Wasylink S, Patel P, Malison R, Krystal JH. Beneficial effects of the antiglutamatergic agent riluzole in a patient diagnosed with obsessive-compulsive disorder and major depressive disorder. *Psychopharmacology (Berl)*. 2003; 167(2):219–220. [PubMed: 12658528]
- Coric V, Taskiran S, Pittenger C, Wasylink S, Mathalon DH, Valentine G, et al. Riluzole augmentation in treatment-resistant obsessive-compulsive disorder: An open-label trial. *Biological psychiatry*. 2005; 58(5):424–428. [PubMed: 15993857]

- Feusner JD, Kerwin L, Saxena S, Bystritsky A. Differential Efficacy of Memantine for Obsessive-Compulsive Disorder vs. Generalized Anxiety Disorder: An Open-Label Trial, *Psychopharmacology bulletin*. 2009; 42(1):81–93. [PubMed: 19204653]
- Grant P, Lougee L, Hirschtritt M, Swedo SE. An open-label trial of riluzole, a glutamate antagonist, in children with treatment-resistant obsessive-compulsive disorder. *Journal of child and adolescent psychopharmacology*. 2007; 17(6):761–767. [PubMed: 18315448]
- Hanna GL. Demographic and clinical features of obsessive-compulsive disorder in children and adolescents. *Journal of the american academy of child and adolescent psychiatry*. 1995; 34(1):19–27. [PubMed: 7860451]
- Hezel DM, Beattie K, Stewart SE. Memantine as an augmenting agent for severe pediatric OCD. *American journal of psychiatry*. 2009; 166(2):237. [PubMed: 19188297]
- Hollander E, Dell'Osso B. Topiramate plus paroxetine in treatment-resistant obsessive-compulsive disorder. *International clinical psychopharmacology*. 2006; 21(3):189–191. [PubMed: 16528143]
- Jenike MA. Clinical practice. Obsessive-compulsive disorder, *The New England journal of medicine*. 2004; 350(3):259–265. [PubMed: 14724305]
- Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of general psychiatry*. 2005; 62(6):593–602. [PubMed: 15939837]
- Kushner MG, Kim SW, Donahue C, Thuras P, Adson D, Kotlyar M, et al. D-cycloserine augmented exposure therapy for obsessive-compulsive disorder. *Biological psychiatry*. 2007; 62(8):835–838. [PubMed: 17588545]
- Lafleur DL, Pittenger C, Kelmendi B, Gardner T, Wasyluk S, Malison RT, et al. N-acetylcysteine augmentation in serotonin reuptake inhibitor refractory obsessive-compulsive disorder. *Psychopharmacology (Berl)*. 2006; 184(2):254–256. [PubMed: 16374600]
- Moran MM, McFarland K, Melendez RI, Kalivas PW, Seamans JK. Cystine/glutamate exchange regulates metabotropic glutamate receptor presynaptic inhibition of excitatory transmission and vulnerability to cocaine seeking. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2005; 25(27):6389–6393. [PubMed: 16000629]
- Ozkara C, Ozmen M, Erdogan A, Yalug I. Topiramate related obsessive-compulsive disorder. *European psychiatry : the journal of the Association of European Psychiatrists*. 2005; 20(1):78–79. [PubMed: 15642451]
- Pasquini M, Biondi M. Memantine augmentation for refractory obsessive-compulsive disorder. *Progress in neuro-psychopharmacology & biological psychiatry*. 2006; 30(6):1173–1175. [PubMed: 16730870]
- POTS. Cognitive-behavior therapy, sertraline, and their combination for children and adolescents with obsessive-compulsive disorder: The pediatric OCD treatment study (POTS) randomized controlled trial. *JAMA : the journal of the American Medical Association*. 2004; 292(16):1969–1976. [PubMed: 15507582]
- Poyurovsky M, Glick I, Koran LM. Lamotrigine augmentation in schizophrenia and schizoaffective patients with obsessive-compulsive symptoms. *Journal of psychopharmacology*. 2010; 24(6):861–866. [PubMed: 19074541]
- Poyurovsky M, Weizman R, Weizman A, Koran L. Memantine for treatment-resistant OCD. *American journal of psychiatry*. 2005; 162(11):2191–2192. [PubMed: 16263867]
- Rosenberg DR, Keshavan MS. A.E. Bennett Research Award. Toward a neurodevelopmental model of of obsessive--compulsive disorder. *Biological psychiatry*. 1998; 43(9):623–640. [PubMed: 9582996]
- Rubio G, Jimenez-Arriero MA, Martinez-Gras I, Manzanares J, Palomo T. The effects of topiramate adjunctive treatment added to antidepressants in patients with resistant obsessive-compulsive disorder. *Journal of clinical psychopharmacology*. 2006; 26(3):341–344. [PubMed: 16702907]
- Stewart SE, Geller DA, Jenike M, Pauls D, Shaw D, Mullin B, Faraone SV. Long-term outcome of pediatric obsessive-compulsive disorder: A meta-analysis and qualitative review of the literature. *Acta psychiatrica Scandinavica*. 2004; 110(1):4–13. [PubMed: 15180774]

- Stewart SE, Jenike EA, Hezel DM, Stack DE, Dodman NH, Shuster L, et al. A single-blinded case-control study of memantine in severe obsessive-compulsive disorder. *Journal of clinical psychopharmacology*. 2010; 30(1):34–39. [PubMed: 20075645]
- Thuile J, Even C, Guelfi JD. Topiramate may induce obsessive-compulsive disorder. *Psychiatry and clinical neurosciences*. 2006; 60(3):394. [PubMed: 16732760]
- Uzun O. Lamotrigine as an augmentation agent in treatment-resistant obsessive-compulsive disorder: A case report. *Journal of psychopharmacology*. 2010; 24(3):425–427. [PubMed: 19010977]
- Van Ameringen M, Mancini C, Patterson B, Bennett M. Topiramate augmentation in treatment-resistant obsessive-compulsive disorder: A retrospective, open-label case series. *Depression and anxiety*. 2006; 23(1):1–5. [PubMed: 16178009]
- Wilhelm S, Buhlmann U, Tolin DF, Meunier SA, Pearlson GD, Reese HE, et al. Augmentation of behavior therapy with D-cycloserine for obsessive-compulsive disorder. *American journal of psychiatry*. 2008; 165(3):335–341. quiz 409. [PubMed: 18245177]

SUMMARY OF GLUTAMATE MODULATING AGENTS IN OBSSIVE COMPULSIVE DISORDER

TABLE 1

Medication	Study	Type of Trial	Sample	Key Results
Riluzole	Coric et al., 2003	Case study (Augmentation)	Adult (47 year old male)	Well-tolerated and reduction in symptoms
	Coric et al., 2005	Open label trial (Augmentation)	Adult (N = 13)	5/13 responders 7/13 > 35% reduction in Y-BOC
	Grant et al., 2007	Open label trial (Augmentation)	Pediatric (N = 6)	4/6 responders – ongoing NIMH double-blind trial now underway
	Hollander & Dell'Osso, 2006	Case study (Augmentation)	Adult (45 year old female)	Well-tolerated and reduction in symptoms
	Van Ameringen et al., 2006	Case series (Augmentation)	Adults (N = 16)	11/16 responders
Lamotrigine	Rubio et al., 2006	Case series (Augmentation)	Adults (N = 12)	10/12 responders
	Uzun, 2010	Case study (Augmentation)	Adult (59 year old female)	Well-tolerated and reduction in symptoms
	Lafleur et al., 2006	Case study (Augmentation)	Adult (58 year old female)	Well-tolerated and reduction in symptoms
N-Acetylcysteine	Kushner et al., 2007	Double blind placebo control (Augmentation)	Adults N = 14 D-Cycloserine N = 11 Placebo	Augmentation to exposure therapy decreased number of sessions needed
Memantine	Wilhelm et al., 2008	Randomized double blind placebo control (Augmentation)	Adults N = 10 D-Cycloserine N = 13 Placebo	Augmentation to exposure therapy decreased number of sessions needed
	Poyurovsky et al., 2005	Case study (Augmentation)	Adult (34 year old female)	Well-tolerated and reduction in symptoms
	Hezel et al., 2009	Case study (Augmentation)	Pediatric (15 year old female)	After 9 months, no evidence of relapse or medication intolerance
	Pasquini & Biondi, 2006	Case studies (Augmentation)	Adults (60 year old female, 27 year old male)	Male did well, female did not respond
	Aboujaoude et al., 2009	Open label trial (Augmentation)	Adults (N = 14)	6 subjects responded
	Feusner et al., 2009	Open label trial (Monotherapy or Augmentation)	Adults N = 10 OCD N = Generalized anxiety disorder (GAD)	3/10 responders, but 7/10 showed a reduction in symptoms; GAD did not respond
	Stewart et al., 2010	Single blind case control (Augmentation)	Adults N = 22 intent to treat N = 22 memantine augmentation	27% decrease in Y-BOC in memantine group compare to 16.5% decrease in intent to treat group