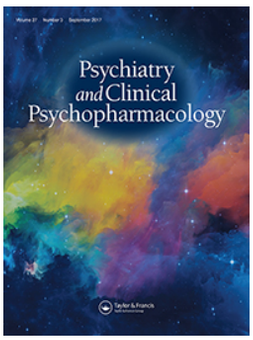

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EDITORIAL

Ketamine and rapastinel: NMDA receptor modulators in the rapid treatment of obsessive-compulsive disorder

Obsessive-compulsive disorder (OCD), which is characterized by repetitive thoughts (obsessions) and repetitive behaviours (compulsions) [1] and is known to be associated with dysfunction in the fronto-striatal circuitry [2]. OCD commonly has its onset in childhood, and research studies have documented the significant disruption to interpersonal relationship and functioning. Comorbidity is common in OCD, occurring in up to 90% of patients; the most common comorbidities include major depressive disorder, panic disorder, social phobia and other phobias, and alcohol use disorder [3]. OCD patients experience significant social and academic difficulties and emotional toll associated with OCD goes beyond the practical disruption of social and occupational daily life. It is intuitive to learn that intrusive thoughts are more frequent contributors to family impairment than compulsive rituals. At its worst, OCD is associated with stress, anxiety, sadness, and frustration for the individual and the family members. For the practicing clinician, this is a reminder of the fragile emotional state of individuals and their families struggling with the challenge of OCD. It also can help explain the difficulties often encountered by mental health providers in introducing and implementing therapeutic interventions.

Specialized cognitive-behavioural therapy and pharmacotherapy with selective serotonin reuptake inhibitors are both first-line treatments, and approximately two-third of patients will benefit significantly from these interventions [1]. Partial responsers and fluctuating course of response together with substantial comorbidity highlight the urgent need for new treatments. Established pharmacological strategies in OCD mostly target the brain's serotonin and dopamine neuromodulatory systems. Efforts to identify other neurochemical systems in OCD have led to studies of other classes of medications such as glutamate modulators, the brain's primary excitatory neurotransmitter, as potential therapeutics in refractory OCD [4].

Ketamine is a noncompetitive N-methyl-D-aspartate (NMDA) glutamate receptor antagonist which has been used clinically as an anesthetic and in pain control [5]. Activation of NMDA receptors is required for the induction of a form of synaptic plasticity called long-term potentiation, a potential mechanism underlying memory formation [6]. Interest in ketamine as a treatment for psychiatric disorders stemmed from the serendipitous observation that it produced rapid (relatively short-lived) antidepressant effects, in patients with treatment-resistant depression [7]. Hoping to find a similar finding in treatment-resistant OCD patients, Rodriguez et al. initially reported improvement in a medication-free patient with severe OCD after intravenous (IV) ketamine infusion [8]. This was followed by the first systematic examination of ketamine infusion in OCD by Bloch et al. and the researchers reported a statistically significant but clinically trivial effect in a group of severely affected patients, many of them had comorbidities and were medicated [9]. Subsequently, Rodriguez et al. reported a clear and clinically significant response in a randomized placebo-controlled study in unmedicated patients with less severe OCD symptoms [10]. In a subsequent study, Rodriguez et al. examined whether an intranasal delivery system is a practical alternative to IV infusion. Only 2 patients out of 23 enrolled OCD patients completed the study and in these patients' nasal delivery system were poorly tolerated and neither of these completers met the OCD response criteria one week following the ketamine administration [11].

Better understanding of OCD could be key to the development of novel interventions in the treatment of this disorder. In order to examine the neurochemical effects of ketamine in OCD patients, Rodriguez et al. used proton magnetic resonance spectroscopy (^{1}H MRS) to dynamically monitor the changes in the levels of gamma-aminobutyric acid (GABA) and glutamate + glutamine (Glx) in the medial dorsolateral prefrontal cortex (MPFC) of 17 medication-free patients with OCD during administration of ketamine and saline [12]. Levels of the inhibitory neurotransmitter GABA and the excitatory neurochemicals Glx were acquired in the MPFC. A mixed effects model found that MPFC GABA/W significantly increased over time in the ketamine compared with the saline infusion. One particularly poignant message from Rodriguez et al.'s study was that models of OCD pathology should consider the role of GABAergic abnormalities in the fronto-striatal brain circuits in OCD patients.

On the other hand, one of the potential limitation of ketamine use in OCD is that occurrence of transient dissociation – a sense of detachment from one's self,

or an out-of-body experience. Rapastinel, a glutamate receptor modulator and experimental drug, might reduce symptoms of OCD without the dissociative side effects reported by patients treated with ketamine. According to a recent study, rapastinel, currently being evaluated for the treatment for major depression, might relieve the symptoms of OCD rapidly and with fewer side effects. In this small, preliminary clinical study, the experimental drug rapastinel (formerly GLYX-13), a putative NMDA receptor functional glycine site partial agonist and important in learning, memory and synaptic plasticity, rapidly reduced symptoms of OCD, although the effect was not long-lasting. The drug was well tolerated, causing none of the dissociative side effects associated with ketamine. Seven patients with OCD received a single 3- to 5-minute IV push of rapastinel (10 mg/kg). At baseline, 90 minutes post-infusion, and 230 minutes post-infusion, patients self-rated the severity of their OCD symptoms using the Yale-Brown Obsessive Compulsive Challenge Scale (YBOCS) [13], a 10-item self-report form that assesses OCD symptoms. Treatment response was defined a priori as a reduction of more than 35% in YBOCS scores. Rapastinel was well tolerated with no reported side effects (e.g. transient dissociation, dizziness, nausea, vomiting, or headache) and within hours of treatment, the severity of patients' symptoms declined significantly. Rapastinel reduced the severity of patients' obsessions and compulsions, as well as symptoms of anxiety and depression. However, while rapastinel's effects on OCD symptoms were rapid, they were not long-lasting. Rapastinel did not have significant effects on OCD symptoms measured at 1 week post-infusion. In order to emphaize clinical value, glutamate modulators should refine molecular targets for rapid and sustained action while minimizing side effects further. The OCD researchers claim that the crucial next steps would be testing the effects of these drugs with repeated dosing and working to develop related drugs that reduce OCD symptoms over a sustained period.

In the treatment of refractory OCD patients, the evidence of NMDA receptor modulation pathways seem to be promising; alas clinical decisions must be made through careful balancing of risks and uncertainty, but plausible benefits.

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