KETAMINE AS A POTENTIAL THERAPEUTIC AGENT IN OBSESSIVE-COMPULSIVE DISORDER

C. Fernandes Santos, N. Descalço, F. Fernandes Martins

Department of Psychiatry and Mental Health, Hospital Garcia de Orta – Almada, Portugal

OBJECTIVES

To review the **clinical evidence** for **therapeutic utility** of **ketamine** as an **augmentation** or **monotherapy** in patients with **obsessive-compulsive disorder** (OCD).

BACKGROUND

OCD is a **clinically heterogeneous neuropsychiatric disease**, affecting **1-3%** of the population and being a **leading cause of illness-related disability**^{1,2,3}.

It can be treated using **pharmacotherapy**, **specialized psychotherapy**, **anatomically targeted treatments**, or their **combination**⁴.

One-third of patients with OCD **fail to experience significant clinical benefit** from **first-line interventions** – **cognitive behavioral therapy** (CBT) and pharmacotherapy with the **selective serotonin reuptake inhibitors** (SSRIs)^{1,5,6}.

Unfortunately, even with optimal treatment, many patients continue to experience **significant symptoms**. **Remission of moderate or severe OCD is uncommon**, and **long-term management is often necessary**. The development of new, more effective treatment interventions represents an **urgent clinical need**^{1,4,5,7,8,9}.

Converging lines of evidence from brain-imaging, genetic, and pharmacological studies implicate a fundamental **dysregulation of glutamate homeostasis** in the **pathogenesis of OCD**^{1,2,4,6,7,8,9}.

Glutamate-modulating agents, such as **ketamine**, have been shown to **improve OCD symptoms**^{10,11} and this work aims to review its **therapeutic utility**.

MATERIALS AND METHODS

Non-systematic review of literature published in 2010-2019, on *PubMed/MEDLINE*, corresponding to 'obsessive-compulsive disorder' and 'ketamine'.

RESULTS

Glutamate is the **primary neurotransmitter** within the **cortico-striatal-thalamic circuits**, implicated in **OCD**^{2,8,11}.

Ketamine is a **potent noncompetitive antagonist** of the **N-methyl-D-aspartate (NMDA) glutamate receptor** and its neuropsychiatric interest derives from effects at **subanesthetic doses** (0.5 mg/kg infused over 40 minutes)^{1,2,3,6,7,8,11}.

EFFICACY

- The results from trials on **intravenous ketamine efficacy** in **OCD** are **contradictory**^{6,8}:

Rapid decrease in symptomatology (**50%** met criteria for treatment response: $\geq 35\%$ decrease in the *Yale–Brown Obsessive Compulsive Scale* [Y-BOCS]⁸).

Sustainability of its effect over a clinically meaningful period of time differed greatly – from **1-3 days** to **one week** after infusion.

- Individuals with **constant intrusive obsessions** may represent an OCD subtype **more sensitive** to ketamine's effects⁸;
- OCD patients with comorbid depression** may represent a subtype of illness that is ironically **less responsive** to **ketamine effects on OCD symptoms**⁸.

SIDE EFFECTS^{3,6,8}

- During infusion:** mild elevations in blood pressure and pulse; dissociation (feelings of unreality, distortions of time - level of dissociation may influence ketamine's effects in OCD), psychotic symptoms (unusual thought content, conceptual disorganization, manic symptoms (elevated mood));
- Post-infusion:** dizziness, nausea, vomiting, headache.

CONCLUSIONS

Ketamine can have **rapid anti-obsessional effects** that persist for **one week in some patients with OCD**^{2,3,4,6,8}.

Future research is needed to clarify the mechanism of ketamine's acute effects and why some – but not all – patients benefit. Ketamine may provide a useful tool to study the glutamatergic mechanism implicated in OCD and, if proven effective, may help identify novel drug targets.

REFERENCES: 1. Tosta CL, et al. S-ketamine reduces marble burying behaviour: Involvement of ventromedial orbitofrontal cortex and AMPA receptors. *Neuropharmacology*. 2019 Jan;144:233-243. Epub 2018 Oct 29. 2. Marinova Z, Chuang DM, Fineberg N. Glutamate-Modulating Drugs as a Potential Therapeutic Strategy in Obsessive-Compulsive Disorder. *Curr Neuropharmacol*. 2017;15(7):977-995. 3. Rodriguez CI, et al. Rapid resolution of obsessions after an infusion of intravenous ketamine in a patient with treatment-resistant obsessive-compulsive disorder. *J Clin Psychiatry*. 2011 Apr;72(4):567-9. 4. Pittenger C, Bloch MH. Pharmacological Treatment of Obsessive-Compulsive Disorder. *Psychiatr Clin N Am*. 2014;37:375-391. 5. M Koran L, Aboujaoude E. Promising Treatments for Obsessive-Compulsive Disorder: A Call for Additional Research. *Curr Med Chem*. 2018;25(41):5690-5697. 6. Bloch MH, et al. Effects of ketamine in treatment-refractory obsessive-compulsive disorder. *Biol Psychiatry*. 2012 Dec 1;72(11):964-70. 7. Rodriguez CI, et al. In vivo effects of ketamine on glutamate-glutamine and gamma-aminobutyric acid in obsessive-compulsive disorder: Proof of concept. *Psychiatry Res*. 2015 Aug 30;233(2):141-7. 8. Rodriguez CI, et al. Randomized controlled crossover trial of ketamine in obsessive-compulsive disorder: proof-of-concept. *Neuropsychopharmacology*. 2013 Nov;38(12):2475-83. 9. Pittenger C. Glutamatergic agents for OCD and related disorders. *Curr Treat Options Psychiatry*. 2015 Sep;2(3):271-283. 10. Rodriguez CI, et al. Challenges in Testing Intranasal Ketamine in Obsessive-Compulsive Disorder. *J Clin Psychiatry*. 2017 Apr;78(4):466-467. 11. Pittenger C. Glutamate modulators in the treatment of obsessive-compulsive disorder. *Psychiatr Ann*. 2015 Jun;45(6):308-315.

catiafersantos@gmail.com