A Rapid-Acting Anti-Obsessive Agent for Obsessive-Compulsive Disorder: Reviewing the Effects of Ketamine in OCD

Gabriel Luiz Bundies[1], Himanshu Tyagi[2,3,4]

1. UCL Division of Psychiatry; 2. UCL Institute of Neurology; 3. National Hospital for Neurology and Neurosurgery, Queens Square London; 4. University College London Hospitals NHS Foundation Trust

Introduction

Obsessive-compulsive disorder (OCD) describes a common neuropsychiatric disorder that is characterised by intrusive reoccurring anxiogenic feelings and thoughts, often followed by anxiolytic-acting compulsions[7].

Problems with OCD Treatment

Serotonin Reuptake Inhibitors (SRIs) are the pharmacological agents of choice as the first line treatment of OCD. Despite their widely confirmed effectiveness in most patients, their anti-obsessive effects are delayed, with an average lag period of eight to 12 weeks[11]. A single pharmacological agent with rapid anti-obsessive action would be an ideal candidate to manage this treatment gap.

Ketamine: A Novel Treatment Approach

Ketamine is a Non-competitive N-methyl-D-aspartate receptor (NMDAr) antagonist[15]. Initially used as an anaesthetic, ketamine was found to have significant implications in the rapid treatment of (treatment-resistant) depression[3,8]. Although its mechanisms are not fully understood, ketamine enhances the synthesis of neurotrophins in the cortex by modulating glutamatergic activity, thereby increasing synaptic plasticity[15].

OCD and Glutamate

It appears that the pharmacological properties of ketamine match the neurobiological profile of OCD.

OCD is suggested to find its origin in elevated glutamatergic transmission within the cortico-striatal-thalamo-cortical[9,16]. The use of glutamate antagonists is a novel approach on treating obsessive-compulsive symptoms and has already revealed potentially beneficial effects in animals model of OCD treatment[16].

Study Aim

This study reviewed the current state of evidence on rapid anti-obsessive treatment effects resulting from ketamine administration in OCD.

Results may guide future research as suggestions for further investigations will be stated.

Methods

Literature Search

To identify studies investigating rapid anti-obsessive effects of ketamine, the databases Embase, MEDLINE(R), and PsycINFO were searched. ClinicalTrials.gov was further searched for grey literature. Other reviews were excluded. The search terms used were as follows: (ketamine) AND ((Obsessive-Compulsive Disorder [Mesh]) OR ocd). The search was Limited to: human studies; studies published in English. Identified studies were selected, discussed in a group and evaluated.

Analysis

Due to the small numbers of studies that qualified for this review, full meta-analyses could not be performed. Instead, changes in available OCD scores were combined to provide a quantitative estimate effect. To provide a precise estimate, authors of included studies have been contacted to request data that was not provided in the original publication.

Table 1. Anti-obsessive effects of ketamine per study

Study	Anti-Obsessive Effects	Sustained Anti-Obsessive Effects
Adams, Bloch, & Pittenger (2017)*	✓	—
Best (2015)	✗	✗
Bloch (2014)	✓	✗
Best et al. (2012)	✓✓	✗
Goldberg (2020)	—	✗
Niciu, Grunschel, Corlett, Pittenger, & Bloch (2013)	✓✓	✗
Rodriguez, Kegeles, Flood, & Simpson (2011)	✓✓	✗
Rodriguez et al. (2013)	✓✓	✓
Rodriguez et al. (2016)	✓✓	✗

*Table 1. Listing all studies with individual study results on effects of ketamine in OCD. One check mark (**green**) confirms reductions in OCD scores; two check marks indicate significant rapid onsets of action; crosses (**red**) indicate no effects; dashes (**blue**) imply insufficient data. * Intranasal ketamine trial.*

Results

Search Outcomes & Descriptive Data

The literature search yielded 182 studies from which nine studies qualified for this review (four case reports; two controlled trials; three uncontrolled trials). Eight studies utilised intravenous (IV) and one intranasal (IN) ketamine.

The total *n* of participants is 54 (49 adults & five adolescents; gender distribution unclear). Sample sizes per study range from one (case reports) to 15. The common dose of ketamine was 40 minutes of 0.5mg/kg IV-ketamine.

Effects of Ketamine in OCD

Seven studies indicate reductions in OCD scores, following ketamine of which five reveal significant rapid-acting anti-obsessive effects (Table 1). Within the first 60min post IV-ketamine injection, OCD scores fell by 63.84%, however, increased again by 48.83% at follow-up (Figure). Hence, Anti-obsessive effects occurred rapidly, but were not maintained. A summary of effect can be found in Table 2.

Additional Results

For comorbid depression, ketamine initiated a sustained reduction in depressive symptoms and suicidality. Furthermore, one trial reported an extended length and margin of anti-obsessive effect when combined with cognitive behavioural therapy in 9 patients.

Figure

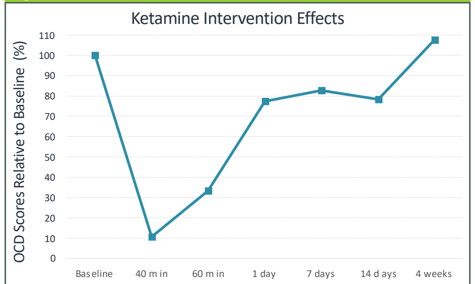

Figure 1. Displayed are percentual levels of the Y-BOCS and OCD-VAS scales. Baseline (n participants=54) is displayed at 100%. Post-ketamine induction scores are indicated at 40 minutes (n=16), 60 minutes (n=27), 1 day (n=39), 7 days (n=29), 14 days (n=15), and 4 weeks (n=1).

Limitations & Clinical Implications

Four studies yield no significant rapid anti-obsessive effects, with one study testing longitudinal IN-ketamine use. Furthermore, samples were small with 4 studies being case reports and only two studies were placebo-controlled, reducing precision and generalisability. The few selected studies display strong methodological heterogeneity, making conclusive comparisons difficult.

Despite limitations, this review points out potential benefits of ketamine in OCD treatment. Nonetheless, greater awareness and randomised controlled trials are required before recommending the use of ketamine in OCD treatment

Table 2. Summary: Anti-obsessive effects of ketamine

Pooled Reduction in OCD Scores (%)	Time to Peak Effect	Duration of Effect
- 62.84%	20-60 minutes	1–3 days

Table 2. The pooled reduction in OCD scores measured post IV-ketamine induction in 38 OCD patients is displayed (excluding studies reporting longitudinal data only). An estimate of time required to reach the peak of effect and the duration of that effect are further presented.

Conclusion

1. **Support for rapid anti-obsessive effects through IV-Ketamine administration in OCD**
2. **Effects of IV-Ketamine in OCD are not sustained**
3. **Available clinical trials are exceptionally small and methodologically heterogenous**
4. **Larger trials investigating ketamine in OCD are needed**

Contact: Gabriel Luiz Bundies

Phone: +49 171 2233388
Email: gabriel.bundies.19@ucl.ac.uk
LinkedIn: www.linkedin.com/in/gabriel-luiz-bundies-123a6b13b

References

1. Adams, T. G., Bloch, M. H., & Pittenger, C. (2017). Intranasal Ketamine and Cognitive-Behavioral Therapy for Treatment-Refractory Obsessive-Compulsive Disorder. *Journal of clinical psychopharmacology, 37*(2), 269–271. doi:10.1097/JCP.0000000000000659
2. Best, S., (2015). Combined ketamine and transcranial magnetic stimulation for treatment resistant depression in the context of chronic OCD: a case report. *Neuropsychiatric Electrophysiology, 1*(1). doi: 10.1186/s40810-015-0003-y
3. Björkholm, C., Monteggia, L. M. (2016). BDNF – a key transducer of antidepressant effects. *Neuropharmacology, 102*. doi:10.1016/j.neuropharm.2015.10.034
4. Bloch, M. H. (2014). *Ketamine Infusion for Obsessive-Compulsive Disorder* (ClinicalTrials.gov Identifier NCT01349231). Retrieved from www.clinicaltrials.gov/ct2/show/study/NCT01349231
5. Bloch, M. H., Wasylink, S., Landeros-Weisenberger, A., Panza, K. E., Billingslea, E., Leckman, J. F., Krystal, J. H., Bhagwagar, Z., Sanacora, G., & Pittenger, C. (2012). Effects of ketamine in treatment-refractory obsessive-compulsive disorder. *Biological psychiatry, 72*(11), 964–970. doi:10.1016/j.biopsych.2012.05.028
6. Goldberg, P. (2020). *Ketamine Treatment for Pediatric-Refractory Obsessive-Compulsive Disorder (OCD)* (ClinicalTrials.gov Identifier NCT02422290). Retrieved from www.clinicaltrials.gov/ct2/show/NCT02422290
7. Huey, E., Zahn, R., Krueger, F., Moll, J., Kapogiannis, D., Wassermann, E., & Grafman, J. (2008). A psychological and neuroanatomical model of obsessive-compulsive disorder. *The Journal of Neuropsychiatry and Clinical Neurosciences, 20*(4). doi:10.1176/appi.neuropsych.20.4.390
8. Kishimoto, T., Chawla, J., Hagi, K., Zarate, C., Kane, J., Bauer, M., & Correll, C. (2016). Single-dose infusion ketamine and non-ketamine N-methyl-d-aspartate receptor antagonists for unipolar and bipolar depression: A meta-analysis of efficacy, safety and time trajectories. *Psychological Medicine, 46*(7), 1459-1472. doi:10.1017/S0033291716000064
9. Marinova, Z., Chuang, D. M., & Fineberg, N. (2017). Glutamate-Modulating Drugs as a Potential Therapeutic Strategy in Obsessive-Compulsive Disorder. *Current neuropharmacology, 15*(7), 977–995. doi:10.2174/1570159X15666170320104237
10. Niciu, M. J., Grunschel, B. D., Corlett, P. R., Pittenger, C., & Bloch, M. H. (2013). Two cases of delayed-onset suicidal ideation, dysphoria and anxiety after ketamine infusion in patients with obsessive-compulsive disorder and a history of major depressive disorder. *Journal of psychopharmacology (Oxford, England), 27*(7), 651–654. doi:10.1177/0269881113486718
11. Pittenger, C., & Bloch, M. H. (2014). Pharmacological treatment of obsessive-compulsive disorder. *The Psychiatric clinics of North America, 37*(3), 375–391. doi:10.1016/j.psc.2014.05.006
12. Rodriguez, C. I., Kegeles, L. S., Flood, P., & Simpson, H. B. (2011). Rapid resolution of obsessions after an infusion of intravenous ketamine in a patient with treatment-resistant obsessive-compulsive disorder. *The Journal of clinical psychiatry, 72*(4), 567–569. doi:10.4088/JCP.10l06653
13. Rodriguez, C. I., Kegeles, L. S., Levinson, A., Feng, T., Marcus, S. M., Vermes, D., Flood, P., & Simpson, H. B. (2013). Randomized controlled crossover trial of ketamine in obsessive-compulsive disorder: proof-of-concept. *Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology, 38*(12), 2475–2483. doi:10.1038/npp.2013.150
14. Rodriguez, C., Wheaton, M., Zwerling, J., Steinman, S., Sonnenfeld, D., Galfalvy, H. and Simpson, H., (2016). Can Exposure-Based CBT Extend the Effects of Intravenous Ketamine in Obsessive-Compulsive Disorder?. *The Journal of Clinical Psychiatry, 77*(03), pp.408-409. doi:10.4088/JCP.15l10138
15. Sleigh, J., Harvey, M., Voss, L. and Denny, B., 2014. Ketamine – More mechanisms of action than just NMDA blockade. *Trends in Anaesthesia and Critical Care, 4*(2-3), pp.76-81. doi:10.1016/j.tacc.2014.03.002
16. Ting, J. T., & Feng, G. (2011). Neurobiology of obsessive–compulsive disorder: Insights into neural circuitry dysfunction through mouse genetics. *Current Opinion in Neurobiology, 21*(6), 842-848. doi:10.1016/j.conb.2011.04.010