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Journal of Pharmacology & Clinical Toxicology

Short Communication

Esketamine Effects on Buprenorphine Treatment in a Comorbid Case of Opioid Addiction with Depression, Obsessive-Compulsive Disorder and Chronic Pain

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Submitted: 02 March 2023
Accepted: 29 March 2023
Published: 31 March 2023
ISSN: 2333-7079

Keywords
- Opioid addiction
- Buprenorphine
- Glutamate
- Esketamine
- Depression
- OCD
- Chronic pain

Abstract

Ketamine is a N-methyl-D-aspartate glutamate receptor antagonist that has efficacy against chronic major depression. Its mechanism of action likely depends on changes in glutamate-mediated transmission and plasticity in circuits involved in a wide range of neuropsychiatric disorders and addictions. Although ketamine can reduce opioid requirements in a pain context, no prior reports have documented its impact in the context of treatment of opioid addiction. We describe treatment outcomes with esketamine in a patient with treatment-resistant depression, obsessive-compulsive disorder, chronic pain and opioid addiction treated with the partial opioid agonist buprenorphine/naloxone. During esketamine treatment, the patient spontaneously self-tapered his buprenorphine/naloxone (16/4 mg to 8/2 mg) without experiencing withdrawal or rebound pain, and with some improvement in his obsessive compulsive disorder. Short term modulation of the glutamate system with esketamine or other novel compounds should be more systematically tested for efficacy in patients with complex comorbidities of mental illness and addiction.

ABBREVIATIONS

NMDA: N-methyl-D-aspartate: OCD: Obsessive Compulsive Disorder; MDD: Major Depressive Disorder; OUD: Opioid Use Disorder; FDA: Food and Drug Administration; REMS: Risk Evaluation and Mitigation Strategy

INTRODUCTION

Ketamine, an N-methyl-D-aspartate (NMDA) glutamate receptor antagonist, was first reported as producing rapid and sustained efficacy against major depressive disorder (MDD) over 20 years ago [1]. This finding has been thoroughly and rigorously replicated, representing one of the most significant breakthroughs in terms of novelty of mechanism, and robustness of efficacy in psychiatric pharmacology over these two decades [2]. Unfortunately, high risk misapplication of this treatment conducted outside of psychiatric expertise, direct medical supervision, or appropriate scientific observation, especially involving custom preparations of racemic ketamine, has been a growing concern that is now reaching attention in major news media [3]. Still, given the novel mechanism of action of this drug in targeting glutamate neurotransmission and neuroplasticity in brain circuits that are positioned at the nexus of addictions and mental disorder pathologies [4], it is important to fully explore the therapeutic potential of this drug, and others like it carefully, with a solid observational approach and clinical standards

Here, we report a case experience in the use of esketamine, the intranasally-delivered enantiomer of ketamine that is the FDA-approved version (for chronic depression). Esketamine has been developed from research using the racemic form of ketamine (typically delivered orally, or intravenously that is *not* FDA-approved for depression). Notably, comparison studies between racemic ketamine and FDA-regulated esketamine have not identified major differences in efficacy (5 2538). In this case, we treated a patient with longstanding treatment refractory depression, who was also suffering with several other neuropsychiatric comorbidities including obsessive-compulsive disorder (OCD), chronic pain syndrome, opioid addiction (i.e. opioid use disorder (OUD)), and nicotine addiction (tobacco use

disorder). As such, this patient represented a fairly typical case of severe, treatment refractory depression, that is often complicated by other psychiatric comorbidities and addiction. However, cases like this, which could warrant esketamine treatment, would provide a substantial challenge to most psychiatric or addiction treatment programs in the U.S. which typically do not provide integrated addiction and mental health care [5,6]. In this case, the patient with complex, 'dual diagnosis', comorbidities was treated with esketamine in a fully integrated addiction psychiatry clinic that provides a full spectrum of mental illness, addictions, and comorbidity care provided by board certified addiction psychiatrists and fellows [7]. To our knowledge, there are no prior reports of esketamine's efficacy in a patient with OUD, depression, and other neuropsychiatric comorbidities while being treated with buprenorphine/naloxone.

MATERIALS AND METHODS

A 37-year-old, single, white male, living on disability income for psychiatric illness, had been treated successfully for his OUD over 2 years in our university-affiliated addiction psychiatry clinic, with buprenorphine/naloxone (a standard partial opioid agonist medication for the maintenance treatment of opioid addiction) at 16/4 mg daily. His treatment compliance and freedom from opioid relapses, was confirmed as steady and excellent by regular random drug testing and serial evaluations by the addiction psychiatrists. However, his depression, beginning in his teens with a suicide attempt at age 16, had been largely treatment-refractory and complicated by OCD that could encompass hours of rituals, cleaning and counting every day. As with most patients with opioid addiction, especially those with co-occurring mental illness, his opioid use disorder began iatrogenically (i.e., by medical over-prescribing) [8,9], in his teens and grew steadily during his 20's via medically obtained prescriptions for back pain.

Given the steady severity of his major depressive disorder that had been refractory to prior standard medication trials, our team and the patient elected to proceed with a treatment course of intranasal esketamine (Brand name Spravato), with registration in the FDA-required Risk Evaluation and Mitigation Strategy (REMS) program. In this case, as an addiction psychiatry program, we were able to rigorously observe for and mitigate the risk of giving a controlled, psychoactive, and potentially addictive substance for a mental illness (esketamine), to a patient who was also suffering with 2 other comorbid addictions (to opioid and nicotine). Thus, the patient was only given the intranasal esketamine treatments under direct medical supervision in the clinic as per FDA-guidelines, while engaging in comprehensive addiction psychiatry services and monitoring.

Over an 8-month period, we delivered 17 doses of intranasal esketamine (56 mg) while the patient was continued on his baseline psychiatric medications, which were implemented to target his MDD and OCD (fluoxetine 60 mg and risperidone 3 mg daily). His treatment plan generally followed a pattern of receiving 2 treatments a week (separated by 2 days) for about 4 weeks, followed by one treatment a week for 4 weeks, then once monthly treatment for 5 months. A given treatment session would include the delivery of 14 mg of esketamine insufflated up each nostril (for total of 28 mg) in a first dosing round, followed by a second round 5 minutes later (another 28 mg) for total dosing of 56 mg. Vital signs were checked at baseline and at 40 and 120 minutes after treatment to monitor for blood pressure elevations that can occur with esketamine. The patient was required to stay in his treatment room for 2 hours after dosing and could read or use devices to listen to music or watch videos during that time. As with many patients receiving esketamine treatment, this patient did typically experience a state of mild pleasant euphoria acutely after treatment that was not cognitively impairing and resolving in about an hour to 90 minutes. This was followed by some degree of relief of depressive feelings that sustained for several days. Over the 17-session treatment course we employed commonly used rating scales for measuring symptom levels of MDD, OCD, and pain, always done 30 minutes prior to esketamine dosing, to observe for long-term trends that the treatment may be generating that could not have been produced by acute intoxication.

Consent was provided by the patient to have his case documented in the medical literature, reported without his identifying information.

RESULTS AND DISCUSSION

Remarkably, after the 4th esketamine session, the patient unexpectedly and without direction from the treatment team self-tapered his buprenorphine/naloxone from 16/4 to 8/2 mg daily over about a week, without experiencing opioid withdrawal, cravings, or worsening of pain (Table 1). While his MDD ratings remained fairly consistent with a transient improvement in the middle of his treatment course, his OCD severity decreased substantially in a more sustained pattern. After the 17 esketamine sessions, his buprenorphine/naloxone dosing never rebounded upward past the 8/2 mg daily dosing he established during the treatment, for the subsequent 2 years to present.

Table 1: Esketamine treatments per month with corresponding outcome scale values.

Month	#ESK Treatments	PHQ-9	OCI-R	Pain Intensity	SBX Dose, mg
August	3	23	69	9	16
September	6	25	63	8	16 to 8
October	3	22	66	8	8
November	1	NA	NA	NA	8
December	1	16	59	8	8
January	1	NA	NA	NA	8
February	1	21	59	9	8
March	1	22	56	8	8

Abbreviations: Column results for depression, OCD and Pain intensity are averaged for each month due to limited variation. #ESK Treatments (number of sessions delivering 56 mg intranasal); PHQ-9 (Patient Health Questionnaire-9, depression scale), OCI-R (Obsessive Compulsive Inventory-Revised), pain intensity (subjective score, 0 (none) to 10(max)); SBX dose (daily dose of Buprenorphine-naloxone, 4/1 mg ratio); NA = Not Assessed, patient received treatment on date senior author not present.

Ketamine has previously shown efficacy in reducing total opioid burden in chronic pain patients and in post-surgical opioid requirements when given intraoperatively [10]. This case builds upon this literature by documenting for the first time, a spontaneous 50% reduction in buprenorphine/naloxone dosing in a patient with opioid addiction. Although his MDD did not improve in a sustained way, his OCD did, also consistent with recent observations [11]. The intersection of MDD and OCD is a common [12], and likely reflects shared neuropathological substrates involving prefrontal cortical and striatal circuits that are "stuck" or overactive in representing perseverative thought content underpinning ruminative thinking and obsessions [13]. The intersection of chronic pain and depression is also very common, likely based on similar overlapping neuropathological substrates [14]. In this patients' case it is interesting that his OCD responded better to esketamine in a more sustained way than his core MDD symptoms, although it is not unusual for complex psychiatric syndromes and their comorbidities to have specific components that improve differentially to treatments over time.

CONCLUSION

The glutamate neurotransmitter system is fundamental to information processing and neuroplastic change in the brain. This system is a shared substrate in the integrated pathogenesis of many forms of mental illness and addictions that show convergent circuity and bidirectional causal interactions, particularly within frontal-cortical, ventral-striatal circuits, that mediate decision-making, affective awareness and motivational control [15,16]. Thus, medications that can produce enduring changes in information professing and plasticity mediated by glutamate neurotransmission within these circuits, like esketamine, may have multi-faceted potential to improve a range of mental illness and addiction disease trajectories. This report suggests the therapeutic value of esketamine, and other glutamatergic agents for complex comorbidities of mental illness and addictions, to enhance phasic transitions through recovery trajectories [17]. Further study of ketamine and other glutamate modulators, done while adhering to FDA guidelines, executed buy well-trained clinicians with attention to ethical standards, and a commitment to scientific reporting, should be conducted over an array of indications and patients with various forms of dual diagnosis comorbidities. Addition psychiatry treatment programs may be ideally suited to this given their expertise in comorbid patients, and rigorous balanced attention to monitoring for both mental illness and addiction-disease outcomes.

ACKNOWLEDGMENTS

NB is a beneficiary of an HRSA-Addiction Medicine Training grant (T25HP37617) on which RAC is PI. RAC is also supported by NIDA UG3 DA050923 (as PI).

We thank our patient for allowing his clinical story to be shown in the literature.

REFERENCES

1. Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS, et al. Antidepressant effects of ketamine in depressed patients. Biol Psychiatry. 2000; 47: 351-354.
2. Iadarola ND, Niciu MJ, Richards EM, Vande Voort JL, Ballard ED, Lundin NB, et al. Ketamine and other N-methyl-D-aspartate receptor antagonists in the treatment of depression: a perspective review. Ther Adv Chronic Dis. 2015; 6: 97-114.
3. Hamby C. Ketamine Treatment, and Abuse, Made Easier by Telemedicine. New York Times. 2023 Feb. 20, 2023; Sect. A.
4. Chambers RA. Impulsivity, dual diagnosis, and the structure of motivated behavior in addiction. Behavioral and Brain Sciences. 2008; 31: 443-444.
5. Correia-Melo FS, Leal GC, Vieira F, Jesus-Nunes AP, Mello RP, Magnavita G, et al. Efficacy and safety of adjunctive therapy using esketamine or racemic ketamine for adult treatment-resistant depression: A randomized, double-blind, non-inferiority study. J Affect Disord. 2020; 264: 527-534.
6. Canady V. SAMHSA NSDUH report findes increases in mental health, co-occurring disorders. Mental Health Weekly. 2020; 30: 1-3.
7. Chambers RA. The 2 x 4 model: a neuroscience-based blueprint for the modern integrated addiction and mental health treatment system. First edition. ed. New York, NY: Routledge; 2018.
8. Wright ER, Kooreman HE, Greene MS, Chambers RA, Banerjee A, Wilson J. The iatrogenic epidemic of prescription drug abuse: county-level determinants of opioid availability and abuse. Drug Alcohol Depend. 2014; 138: 209-215.
9. Davis MA, Lin LA, Liu H, Sites BD. Prescription Opioid Use among Adults with Mental Health Disorders in the United States. J Am Board Fam Med. 2017; 30: 407-417.
10. Culp C, Kim HK, Abdi S. Ketamine Use for Cancer and Chronic Pain Management. Front Pharmacol. 2020; 11: 599721.
11. Bandeira ID, Lins-Silva DH, Cavenaghi VB, Dorea-Bandeira I, Faria-Guimaraes D, Barouh JL, et al. Ketamine in the Treatment of Obsessive-Compulsive Disorder: A Systematic Review. Harv Rev Psychiatry. 2022; 30: 135-145.
12. Overbeek T, Schruers K, Vermetten E, Griez E. Comorbidity of obsessive-compulsive disorder and depression: prevalence, symptom severity, and treatment effect. J Clin Psychiatry. 2002; 63: 1106-1112.
13. Macpherson T, Hikida T. Role of basal ganglia neurocircuitry in the pathology of psychiatric disorders. Psychiatry Clin Neurosci. 2019; 73: 289-301.
14. Feingold D, Brill S, Goor-Aryeh I, Delayahu Y, Lev-Ran S. The association between severity of depression and prescription opioid misuse among chronic pain patients with and without anxiety: A cross-sectional study. J Affect Disord. 2018; 235: 293-302.
15. Chambers RA, Bickel WK, Potenza MN. A scale-free systems theroy of motivation and addiction. Neurosciene and Biobehavioral Reviews. 2007; 31: 1017-1045.
16. Chambers RA, Sentir AM, Conroy SK, Truitt WA, Shekhar A. Cortical-striatal integration of cocaine history and prefrontal dysfunction in animal modeling of dual diagnosis. Biol Psychiatry. 2010; 67: 788-792.
17. Chambers RA, Toombs C. Deep Network Pharmacology: Targeting Glutamate Systems as Integrative Treatments for Jump-Starting Neural Networks and Recovery Trajectories. J Psychiatr Brain Sci. 2021; 6.