mhc
MENTAL HEALTH CLINICIAN

CASE REPORT Open Access

Intranasal esketamine use in bipolar disorder: A case report

Courtney Skriptshak, PharmD[1]
Ashley Reich, PharmD, BCPS, BCPP[2]

How to cite: Skriptshak C, Reich A. Intranasal esketamine use in bipolar disorder: A case report. Ment Health Clin [Internet]. 2021;11(4):259-62. DOI: 10.9740/mhc.2021.07.259.

Submitted for Publication: December 28, 2020; **Accepted for Publication:** June 4, 2021

Abstract

Over the past few years, intranasal esketamine has been FDA-approved for treatment-resistant depression as well as MDD with suicidal ideation. In the clinical trials leading to the recent FDA approvals, subjects with a diagnosis of bipolar disorder were excluded from participation in the trial. The manufacturer of intranasal esketamine states that it "has not been studied, and is not indicated, for patients with bipolar disorder." Antidepressants are commonly associated with having the potential to induce rapid cycling in patients with bipolar disorder, though the mechanism is not fully understood. This case report demonstrates the potential safety of intranasal esketamine in combination with mood stabilizer therapy in a patient diagnosed with bipolar disorder without recent history of manic or hypomanic episodes.

Keywords: esketamine, bipolar disorder, treatment-resistant

[1] (Corresponding author) PGY-2 Psychiatric Pharmacy Resident, North Florida/South Georgia Veterans Health System, Lake City, Florida, courtney.skriptshak@va.gov, ORCID: https://orcid.org/0000-0003-1471-746X; [2] Mental Health Clinical Pharmacy Specialist, North Florida/South Georgia Veterans Health System, Lake City, Florida, ORCID: https://orcid.org/0000-0002-1426-781X

Disclosures: The authors have nothing to disclose.

Background

Esketamine nasal spray was approved by the FDA for treatment-resistant depression in March 2019 and MDD with suicidality in August 2020.[1] The 4 trials[2-5] that led to FDA approval for these indications all excluded subjects with psychiatric comorbidities, including bipolar disorder. However, co-occurring disorders are common with depression; a cross-sectional study[6] from 2014 found that 35.3% of subjects with MDD had a psychiatric comorbidity. Additionally, there is mixed data[7-10] regarding the use of antidepressant medications in bipolar disorder because of the potential to induce rapid cycling, which is defined as 4 or more episodes of mania, hypomania, or major depression within the past 12 months. Given that the mechanism of antidepressant-induced rapid cycling is not fully understood, the risk of this warning being extended to intranasal esketamine as well, given its antidepressant effects, cannot be ruled out until it has been more thoroughly evaluated.

There are no data on the use of intranasal esketamine in bipolar disorder, but they could be extrapolated from literature on ketamine in this population. Some studies have looked at ketamine use in patients with unipolar and bipolar depression, and despite positive results in terms of response and remission rates, many of these studies did not separate the 2 subgroups when analyzing the results.[11] One study[12] that looked at 6 0.5 mg/kg ketamine infusions in 16 patients with bipolar disorder demonstrated a 68% response rate and 50.5% remission rate at 24 hours following the last infusion. A literature review[13] from 2020 that analyzed the available data regarding the safety of ketamine and esketamine use in the treatment of bipolar depression found that the most commonly reported adverse events included dissociative symptoms, anxiety, and drowsiness with no reports of symptoms of mania. The following case report aims to shed some light on the potential safety and efficacy of intranasal esketamine treatment in this population, as well as to

TABLE: Patient's past psychotropic medication history

Drug Class	Medications Trialed
Antidepressants	Citalopram
	Bupropion
	Paroxetine
	Sertraline
	Duloxetine
Antipsychotics	Aripiprazole
	Brexpiprazole
	Quetiapine
	Ziprasidone
	Lurasidone
Mood stabilizers	Lamotrigine
	Lithium
Stimulants	Methylphenidate
	Dextroamphetamine and amphetamine
	Modafinil

encourage future trials that include patients with other psychiatric conditions outside of unipolar depression.

Case Report

The patient was a 63-year-old white male with a past medical history significant for bipolar disorder, type 1, current episode depression, as well as PTSD, hyperlipidemia, controlled hypertension, obstructive sleep apnea, and hypothyroidism who presented as lethargic with no interest in anything and felt that he had no quality of life. His labs were largely unremarkable, and his kidney and renal function were stable. The patient was diagnosed with bipolar disorder approximately 2 years prior to initiation of intranasal esketamine treatment, after establishing psychiatric care at this facility and noting the following history consistent with bipolar disorder: "periods of time of months to years where his mood was elevated to irritable, he dressed dramatically differently, thoughts were racing, had decreased need for sleep, was *grandiose*, invented things, engaged in numerous businesses at the same time, was distractible, didn't finish projects, increased religiosity, a new focus on being a survivalist (storing cans of food, etc), was so irritable he was abusive to wife". It is unknown when these manic symptoms began, but he stated that it had been over 10 years since he experienced these symptoms. The patient trialed multiple psychotropic medications in the past (Table), including antidepressants both with and without an active mood stabilizer; notably, the patient reported euphoria and behavioral changes consistent with mania while on citalopram monotherapy. He completed both ECT and transcranial magnetic stimulation treatment in the past with only partial response. He also received pharmacogenomic testing, which did not show any notable abnormalities that would have led to his incomplete response to medications.

The patient met the facility's criteria for intranasal esketamine use, including failure to achieve remission from at least 4 adequate trials of antidepressants plus 2 augmentation trials, and he agreed to REMS requirements. The patient's history of bipolar disorder was considered; he was evaluated by multiple psychiatrists and deemed appropriate for therapy with close monitoring for any signs or symptoms of mania or hypomania given his clinical presentation of treatment-resistant bipolar depression and the lack of reported mania in over 10 years without the use of a mood stabilizer. He had been on multiple psychostimulants, including methylphenidate and dextroamphetamine and amphetamine, over the years without induction of mania and agreed to hold his current psychostimulant (modafinil) on the day of treatment. He was started on lurasidone 40 mg daily about 9 months prior to initiation of intranasal esketamine treatment in order to provide mood stabilization and has remained on this dose of lurasidone throughout treatment; he was also on extended-release bupropion 300 mg daily prior to and throughout the treatment period.

The patient received his first intranasal esketamine dose of 56 mg on day 1 and a second 56 mg dose on day 6. During the work-up for his third appointment, it was documented that "after his intranasal esketamine administration, he continued to feel well, improved mood overall and more active" however, when he woke up on day 7, he noted that his depression had returned, feeling more lethargic and no motivation although it was better than his baseline level of depression prior to the start of intranasal esketamine. After discussion, it was determined to administer an increased dose of 84 mg today (3 devices). The patient continued on 84 mg twice weekly through the end of week 4 for the induction period and then switched to 84 mg once weekly for the remainder of his treatments. Throughout the induction phase and the maintenance phase, the patient continued to endorse benefit from intranasal esketamine treatment for his depression, as evidenced by the self-reported Patient Health Questionnaire (PHQ-9); see the Table and the Figure for more detailed PHQ-9 trends.[14] Prior to induction, his PHQ-9 score was 20, indicative of severe depression; by the end of the induction phase (week 4), the patient's PHQ-9 score dropped down to 0, indicating absence of depression symptoms. Therefore, the team decided to proceed with treatment.

At the 1-year mark, the patient received 46 total doses of intranasal esketamine. It is notable that the patient missed a few weeks of treatment because of concerns about the pandemic as well as severe depression

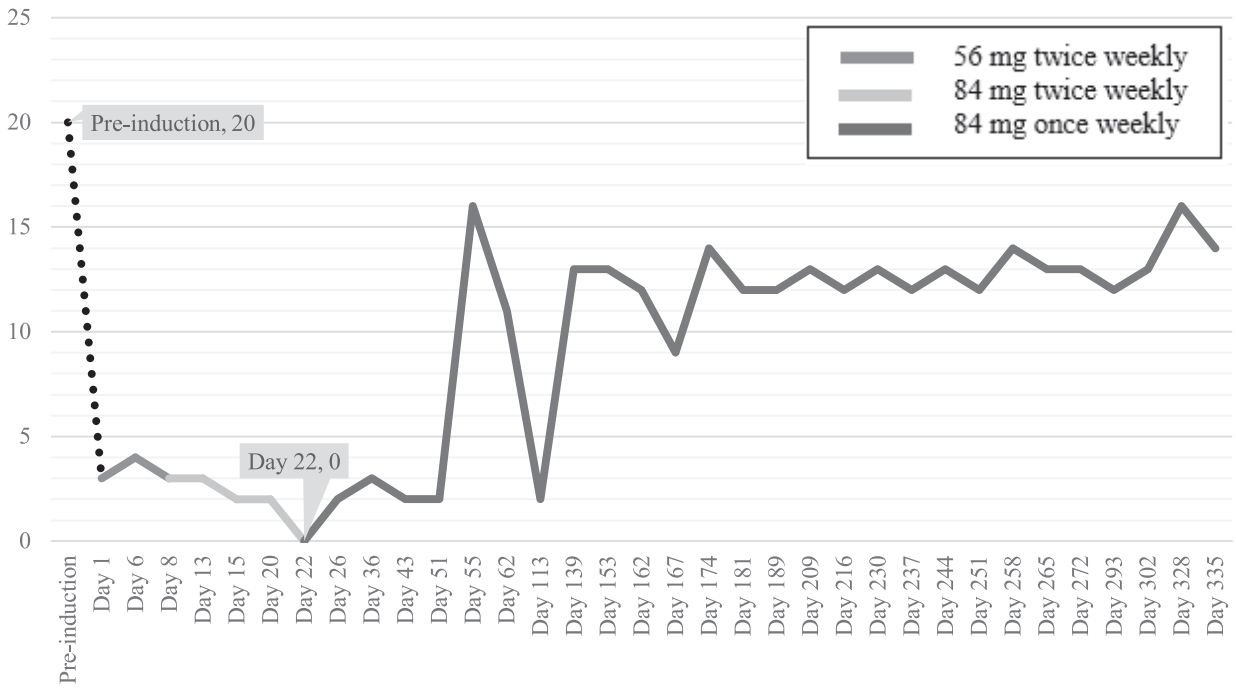

FIGURE: Graphical representation of the self-reported Patient Health Questionnaire (PHQ-9) score trends over time throughout the treatment period, starting with the pre-induction PHQ-9 score through the end of one year of treatment

preventing him from getting out of bed some days (11 nonconsecutive weeks total). The longest interruption in therapy was for 3 weeks in a row. The patient and his wife denied any return of manic or hypomanic symptoms throughout the treatment period, and while the patient continuously endorsed depression symptoms, he noted that they were much better than prior to initiation of intranasal esketamine treatment. There were no notable long-term adverse effects of intranasal esketamine treatment on this patient, and short-term adverse effects were minimal throughout the course of therapy, which included mild blood pressure elevations and subjective reports of dissociation in the first 30 minutes following administration treatment which resolved after 1 hour.

Discussion

Despite the limited data on use of intranasal esketamine in patients with bipolar disorder, this patient's mental health team collaborated and decided that the potential benefits of use outweighed the risks because of multiple treatment failures and lack of manic episodes over the past 10 years. The patient received 46 doses over the past year while on a consistent regimen of lurasidone and bupropion with no return of manic symptoms and continued moderate benefit for his depression. While there did not appear to be any issues with the missed doses throughout treatment, it is possible that the response may have been more significant if he was adherent to his weekly sessions. Adverse effects from esketamine use were minimal and are consistent with the reports of patients included in the literature review by Włodarczyk and Cubała.[13] Because of the documented results of this patient, it may be reasonable to consider intranasal esketamine treatment in other stable patients with treatment-resistant bipolar depression with no recent history of mania who do not have any contraindications for use.

Conclusion

There is a potential place for intranasal esketamine in the treatment of patients with bipolar disorder who are currently in a depressive episode and who have had minimal response to other treatments. This unique case demonstrates that intranasal esketamine may be safe in combination with mood stabilizer therapy in patients with bipolar disorder without recent history of manic or hypomanic episodes. Future intranasal esketamine trials should include subjects with more psychiatric comorbidities so that healthcare professionals can more safely evaluate the role of esketamine in these populations, especially since the prevalence of isolated MDD is a clinical rarity.

References

1. SPRAVATO® [prescribing information]. Titusville (NJ): Janssen Pharmaceuticals, Inc; c2020.
2. Popova V, Daly EJ, Trivedi M, Cooper K, Lane R, Lim P, et al. Efficacy and safety of flexibly dosed esketamine nasal spray

combined with a newly initiated oral antidepressant in treatment-resistant depression: a randomized double-blind active-controlled study. Am J Psychiatry. 2019;176(6):428-38. DOI: 10.1176/appi.ajp.2019.19020172. PubMed PMID: 31109201.
3. Daly EJ, Trivedi MH, Janik A, Li H, Zhang Y, Li X, et al. Efficacy of esketamine nasal spray plus oral antidepressant treatment for relapse prevention in patients with treatment-resistant depression: a randomized clinical trial. JAMA Psychiatry. 2019;76(9):893-903. DOI: 10.1001/jamapsychiatry.2019.1189. PubMed PMID: 31166571; PubMed Central PMCID: PMC6551577.
4. Fu DJ, Ionescu DF, Li X, Lane R, Lim P, Sanacora G, et al. Esketamine nasal spray for rapid reduction of major depressive disorder symptoms in patients who have active suicidal ideation with intent: double-blind, randomized study (ASPIRE I). J Clin Psychiatry. 2020;81(3):19m13191. DOI: 10.4088/JCP.19m13191. PubMed PMID: 32412700.
5. Ionescu DF, Fu D-J, Qiu X, Lane R, Lim P, Kasper S, et al. Esketamine nasal spray for rapid reduction of depressive symptoms in patients with major depressive disorder who have active suicide ideation with intent: results of a phase 3, double-blind, randomized study (ASPIRE II). Int J Neuropsychopharmacol. 2021;24(1):22-31. DOI: 10.1093/ijnp/pyaa068. PubMed PMID: 32861217.
6. Ittasakul P, Thaipisuttikul P, Waleeprakhon P, Wisajun P, Jullagate S. Psychiatric comorbidities in patients with major depressive disorder. Neuropsychiatr Dis Treat. 2014;10:2097-103. DOI: 10.2147/NDT.S72026. PubMed PMID: 25419132; PubMed Central PMCID: PMC4235207.
7. Fountoulakis KN. An update of evidence-based treatment of bipolar depression: where do we stand?. Curr Opin Psychiatry. 2010;23(1):19-24. DOI: 10.1097/YCO.0b013e328333e132. PubMed PMID: 19901836.
8. Licht RW, Gijsman H, Nolen WA, Angst J. Are antidepressants safe in the treatment of bipolar depression? A critical evaluation of their potential risk to induce switch into mania or cycle acceleration. Acta Psychiatr Scand. 2008;118(5):337-46. DOI: 10.1111/j.1600-0447.2008.01237.x. PubMed PMID: 18754834.
9. Salvi V, Fagiolini A, Swartz HA, Maina G, Frank E. The use of antidepressants in bipolar disorder. J Clin Psychiatry. 2008;69(8):1307-18. DOI: 10.4088/jcp.v69n0816. PubMed PMID: 18681751.
10. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington (VA): American Psychiatric Association; 2013.
11. Wilkowska A, Szałach Ł, Cubała WJ. Ketamine in bipolar disorder: a review. Neuropsychiatr Dis Treat. 2020;16:2707-17. DOI: 10.2147/NDT.S282208. PubMed PMID: 33209026; PubMed Central PMCID: PMC7670087.
12. Zheng W, Zhou Y-L, Liu W-J, Wang C-Y, Zhan Y-N, Lan X-F, et al. A preliminary study of adjunctive ketamine for treatment-resistant bipolar depression. J Affect Disord. 2020;275:38-43. DOI: 10.1016/j.jad.2020.06.020. PubMed PMID: 32658821.
13. Włodarczyk A, Cubała WJ. Safety and tolerability of ketamine use in treatment-resistant bipolar depression patients with regard to central nervous system symptomatology: literature review and analysis. Medicina (Kaunas). 2020;56(2):67. DOI: 10.3390/medicina56020067. PubMed PMID: 32050466; PubMed Central PMCID: PMC7073997.
14. Kroenke K, Spitzer RL, Williams JBW. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001;16(9):606-13. DOI: 10.1046/j.1525-1497.2001.016009606.x. PubMed PMID: 11556941.