

Managing dissociative symptoms following the use of esketamine nasal spray: a case report

Sophia Pereira, Emily Brennan, Anjali Patel, Melissa Moran, Jenny Wallier and Michael R. Liebowitz

Patients with treatment-resistant depression (TRD) treated with esketamine nasal spray commonly experience transient symptoms of dissociation. Manifestations of dissociation, such as feelings of detachment from the environment, can cause considerable anxiety for patients. Nonpharmacologic interventions may help clinicians to manage associated anxiety and confusion due to dissociation following administration of esketamine nasal spray. We present the case of a 64-year-old woman with major depressive disorder who participated in a clinical trial evaluating the efficacy and safety of esketamine nasal spray in conjunction with an oral antidepressant for TRD. The patient received flexible doses of esketamine nasal spray (56 or 84 mg) twice weekly for 4 weeks. On treatment day 1, the patient was administered 56 mg of esketamine nasal spray using two nasal spray devices (28 mg per device). Twenty minutes after the first esketamine nasal spray device was administered, the patient experienced a dissociative episode lasting

40 minutes that caused anxiety and confusion. The patient was encouraged to listen to music during treatment sessions, which resulted in notable improvement of her symptoms. Listening to music of choice immediately following esketamine nasal spray administration along with reassurance from staff may help manage confusion and anxiety associated with dissociation. *Int Clin Psychopharmacol* 36: 54–57 Copyright © 2020 The Author(s). Published by Wolters Kluwer Health, Inc.

International Clinical Psychopharmacology 2021, 36:54–57

Keywords: anxiety, confusion, dissociation, esketamine nasal spray, music

Department of Psychiatry, The Medical Research Network LLC, New York, New York, USA

Correspondence to Sophia Pereira, The Medical Research Network, LLC, 134 East 93rd Street, Suite 201A, New York, NY 10128, USA
Tel: +212 595 5012 x238; fax: +212 595 5013;
e-mail: SPereira@MedicalResearchNetwork.com

Received 28 May 2020 Accepted 3 June 2020

Background

Patients with treatment-resistant depression (TRD) who are prescribed esketamine nasal spray may experience side effects that temporarily impair their functioning. In double-blind clinical trials of esketamine nasal spray combined with an oral antidepressant, dissociation was reported as an adverse reaction in 41% of the esketamine plus oral antidepressant group (SPRAVATO, 2020). The group receiving 84 mg of esketamine nasal spray experienced higher rates of dissociative symptoms than the group receiving 56 mg (Fedgchin *et al.*, 2019). While dissociative symptoms generally peaked at 40 minutes following esketamine administration and resolved within 1.5 h (Fedgchin *et al.*, 2019), the associated confusion, loss of awareness of external environment, and other dissociative symptoms can be overwhelming for some patients (Park *et al.*, 2019). Ketamine-associated dissociation typically resolves without pharmacologic intervention, suggesting that nonpharmacologic approaches could play a more central role in its management (Park *et al.*, 2019).

Here, we describe the management of a patient affected by confusion, agitation, and anxiety due to dissociation after receiving an administration of esketamine nasal spray. To our knowledge, this strategy has not been reported in the literature and presents a simple, nonpharmacologic, inexpensive solution to a frequently occurring problem.

Case presentation

A 64-year-old woman with a medical history of hyperthyroidism and irritable bowel syndrome and a psychiatric history of major depressive disorder presented in December 2018 with unresolved symptoms of depression. She had a history of several failed antidepressant treatments (venlafaxine, bupropion, and citalopram) in the current major depressive episode and sought to alleviate her current depressive symptoms. She provided written informed consent to participate in a randomized, double-blind study (NCT03434041) to evaluate the efficacy, pharmacokinetics, safety, and tolerability of flexible doses of esketamine nasal spray in conjunction with an oral antidepressant in adults with TRD. She met trial eligibility criteria and was randomly assigned to receive either esketamine or placebo nasal spray; she also simultaneously began treatment with the oral antidepressant duloxetine. Nasal spray study medication was initiated

This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CC-BY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

on treatment day 1 beginning at a dose of 56 mg administered using two nasal spray devices (28 mg per device), with dosing (flexible doses of 56 or 84 mg) thereafter twice weekly for 4 weeks. The patient did not respond to treatment (where response = improvement of $\geq 50\%$ in the Montgomery-Åsberg Depression Rating Scale total score) and did not experience dissociation while participating in the double-blind trial.

Following the fourth week of treatment and at the end of the study, the patient provided written informed consent to participate in an open-label, long-term extension safety study of esketamine nasal spray for TRD. During the induction phase of the subsequent open-label trial, the patient was administered flexible doses of esketamine nasal spray (56 or 84 mg) twice weekly for 4 weeks. She received 56 mg of esketamine nasal spray on day 1 and was titrated to 84 mg on day 11. On day 1 of treatment, the patient experienced agitation and confusion due to dissociation that began 20 minutes after esketamine nasal spray administration and persisted for 40 minutes (Table 1). The coordinator and doctor who were with the patient reassured her that the dissociative symptoms would soon subside and reminded her that she was safe in the clinic.

We note that the patient experienced dissociation during the second treatment session, but do not have the timing of onset recorded. During the third treatment session, the patient was apprehensive regarding treatment because of the dissociative symptoms she had experienced during the first and second treatment sessions. The study coordinator and investigator reassured the patient that she was safe in the clinic and would be monitored by staff until her symptoms subsided. The patient continued treatment, and 30 minutes after the second esketamine nasal spray device was administered, the patient again began to exhibit symptoms of dissociation. Her symptoms lasted for a total of 55 minutes (Table 1). The patient suggested that she would like to try listening to music on her iPhone to distract herself from the unpleasant dissociative sensations she was experiencing. The patient proceeded to play music and continued to listen to the music for the duration of her stay at the clinic. Approximately

5 minutes after listening to music, the patient appeared noticeably calmer and was no longer confused or agitated by the dissociation she was experiencing. The patient reported that she was better able to tolerate the dissociative symptoms while listening to music of her choice. This marked a notable improvement from the previous dosing sessions, when the patient did not listen to music while experiencing dissociative symptoms. This strategy continued to be employed to alleviate feelings of confusion or anxiety during all subsequent treatment visits.

While the patient continued to experience dissociative symptoms, after the introduction of music, the associated symptoms of anxiety and agitation were no longer recorded. Subsequent experiences of agitation or anxiety were considered related to an increase in the patient's dose of esketamine (from 56 to 84 mg) and were not related to the experience of dissociation. Since that time, playing music in addition to providing patients with reassurance has been used to successfully manage confusion and agitation associated with dissociation with other patients at our clinic.

Discussion

Esketamine nasal spray is a noncompetitive N-methyl-D-aspartate receptor antagonist. Unlike currently available oral antidepressants, esketamine nasal spray has rapid onset of antidepressant effects (Daly *et al.*, 2018). However, notable side effects are associated with the use of this drug, such as dissociation (41%), dizziness (29%), nausea (28%), and sedation (23%) (SPRAVATO, 2020). Vertigo and headaches were also commonly reported in phase 3 double-blind esketamine trials (Fedgchin *et al.*, 2019; Popova *et al.*, 2019). In the case of this patient, treatment was aimed at managing dissociation. We identified music as a simple, inexpensive, nonpharmacologic way to reduce the symptoms of dissociation.

Playing music for patients is one of the most effective alternative interventions that we have employed at our clinic. Previous research has suggested that music enhances the quality of recovery and acceptance of dissociative symptoms after ketamine anesthesia (Kumar

Table 1 Timing of dissociative symptoms after administration of first esketamine nasal spray device

Visit (study phase/week)	Total dosage administered (mg)	Time until onset of symptoms (minutes)	Time until resolution of symptoms (minutes)
Phase 1/week 1	56	20	40
Phase 1/week 2	56	30	55
Phase 1/week 2	84	14	76
Phase 2/week 18	84	25	78
Phase 2/week 19	84	18	64
Phase 2/week 20	84	20	25
Phase 2/week 22	84	21	38
Phase 2/week 24	84	35	16
Phase 2/week 25	84	30	5
Phase 2/week 30	84	26	32
Phase 2/week 36	84	15	40

Phase 1 = induction phase (patient dosed twice weekly).

Phase 2 = optimization/maintenance phase.

On average, symptoms of dissociation were reported by the patient approximately 23 minutes after the first device was administered and lasted approximately 43 minutes.

Table 2 Managing associated symptoms of dissociation after esketamine dosing

Associated symptoms of dissociation	Management approaches
Confusion	1. Patient requested to listen to music on her mobile device when feelings of confusion/agitation arose after dosing and for the duration of her time at the clinic
Agitation	2. Relieved symptoms of agitation and discomfort associated with dissociation within several minutes
Anxiety	a. Kept room at cool temperature b. Had patient lie down/prop up feet on couch c. Patient asked coordinator to hold her hand d. Coordinator and investigator spoke to patient in calm, reassuring manner e. Coordinator and investigator explained to patient that symptoms were normal and that they would subside within an hour f. Ensured patient's safety. Investigators and coordinator repeatedly explained that the patient was safe in the clinic

et al., 1992). Patients who are experiencing dissociative symptoms for the first time may have difficulty accepting these symptoms and may even fear them. Music can help alleviate those fears and anxiety. In addition, research has shown that music may lower stress hormones such as cortisol, adrenaline, and noradrenaline and can stimulate the release of endorphins (McCraty *et al.*, 1998). While the exact physiological mechanism behind the effectiveness of music in allaying the confusion and anxiety due to dissociation is unknown, we hypothesize that music's ability to lower stress hormones and release endorphins may lead to an alleviation of the symptoms of confusion, agitation, and anxiety resulting from esketamine-induced dissociation.

In addition to encouraging the patient in this case report to listen to music during treatment visits, our site provided the patient with a comfortable environment for all treatment sessions, which included maintaining the room at a cool temperature, minimizing the brightness of the room, and providing the patient with a couch to lay upon (Table 2). Furthermore, both the coordinator and investigator provided the patient with reassurance by informing her that the unpleasant symptoms she was experiencing were normal and would subside within an hour (Table 2). Explaining to the patient that she was safe in the clinic and that staff would not leave the room until her symptoms subsided provided her with feelings of comfort and security while she was experiencing the dissociative symptoms.

We acknowledge that adverse events such as confusion, agitation, and anxiety cannot be resolved in all patients with dissociation by listening to music and receiving reassurance from staff, but we note that this individual patient's request to listen to music while having staff present and ensuring her safety helped relieve her symptoms of agitation, confusion, and anxiety that had resulted from dissociation. We also recognize that we did not conduct a controlled experiment of this treatment, and did not try to 'rechallenge' the patient by having her subsequently undergo esketamine administration without listening to music to control for the possibility that she tolerated later treatments better simply because she had more experience with them. Nevertheless, given our experience with this patient, we utilized listening to music and offering reassurance to subsequent patients in

our clinic experiencing troubling symptoms of dissociation, and found it helpful in these instances as well. In sum, we believe this strategy presents a simple, affordable approach to solving a frequent problem associated with esketamine administration.

Conclusion

Clinicians may consider managing dissociation related to esketamine administration through simple, low-risk, nonpharmacologic interventions. Specifically, listening to music based on patients' personal preferences and being provided with reassurance successfully controlled confusion, agitation, and anxiety resulting from dissociation.

Other adjustments utilized that varied between patients were temperature and light preference (i.e. cooler, darker rooms).

Acknowledgements

The authors thank ApotheCom (Yardley, PA) for editorial services, which were funded by Janssen Scientific Affairs.

Janssen Scientific Affairs funded editorial support for the preparation of this case report. The studies (NCT03434041 and NCT02782104) that the patient in this case report participated in were conducted at 35 centers across the USA and China. The study protocols and their amendments were approved by the local ethics committees. The studies were conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, consistent with Good Clinical Practice guidelines and applicable regulatory requirements. All participants provided written informed consent before participation.

SP, EB, AP, MM, JW, and MRL were all involved in the conduct of this study, as well as the preparation, review, and final approval of the manuscript. All authors read and approved the final manuscript.

Consent for publication: Not applicable, as the information presented in this case report is fully anonymized.

The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at <https://www.janssen.com/clinical-trials/transparency>. As noted

on this site, requests for access to the study data can be submitted through the Yale Open Data Access (YODA) Project site at <http://yoda.yale.edu>.

Conflicts of interest

S.P., E.B., A.P., and J.W. are all employees of The Medical Research Network. M.M. is a former employee of The Medical Research Network. M.R.L. is the owner and Managing Director of The Medical Research Network.

References

- Daly EJ, Singh JB, Fedgchin M, Cooper K, Lim P, Shelton RC, *et al.* (2018). Efficacy and safety of intranasal esketamine adjunctive to oral antidepressant therapy in treatment-resistant depression: a randomized clinical trial. *JAMA Psychiatry* **75**:139–148.
- Fedgchin M, Trivedi M, Daly EJ, Melkote R, Lane R, Lim P, *et al.* (2019). Efficacy and safety of fixed-dose esketamine nasal spray combined with a new oral antidepressant in treatment-resistant depression: results of a randomized, double-blind, active-controlled study (TRANSFORM-1). *Int J Neuropsychopharmacol* **22**:616–630.
- Kumar A, Bajaj A, Sarkar P, Grover VK. (1992). The effect of music on ketamine induced emergence phenomena. *Anaesthesia* **47**:438–439.
- McCraty R, Barrios-Choplin B, Atkinson M, Tomasino D (1998). The effects of different types of music on mood, tension, and mental clarity. *Altern Ther Health Med* **4**:75–84.
- Park LT, Falodun TB, Zarate CA Jr (2019). Ketamine for treatment-resistant mood disorders. *Focus (Am Psychiatr Publ)* **17**:8–12.
- Popova V, Daly EJ, Trivedi M, Cooper K, Lane R, Lim P, *et al.* (2019). 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* **176**:428–438.
- SPRAVATO (2020). *SPRAVATO (esketamine) nasal spray [prescribing information]*. Titusville, NJ: Janssen Pharmaceuticals, Inc.