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

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

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

Following the fourth week of treatment and at the end
of the study, the patient provided written informed con-
sent 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 disso-
ciation 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 reas-
ured 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 coordi-
nator 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 treat-
ment, and 30 minutes after the second esketamine nasal
spray device was administered, the patient again began to
experience symptoms of dissociation. Her symptoms lasted
for a total of 55 minutes (Table 1). The patient sug-
gested that she would like to try listening to music on
her iPhone to distract herself from the unpleasant disso-
ciative sensations she was experiencing. The patient pro-
ceded 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 disso-
ciative 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 con-
fusion or anxiety during all subsequent treatment visits.

While the patient continued to experience dissociative
symptoms, after the introduction of music, the associ-
ated 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 reas-
surance has been used to successfully manage confusion
and agitation associated with dissociation with other pa-
ents at our clinic.

### Discussion

Esketamine nasal spray is a noncompetitive N-methyl-
D-aspartate receptor antagonist. Unlike currently avail-
able 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, treat-
ment 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 disso-
ciative 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.
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).

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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.