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Completed suicides and intranasal esketamine therapy: A case report and case series

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ABSTRACT

Esketamine, formulated as an NMDA receptor antagonist nasal spray, is used in conjunction with an antidepressant for a more rapid reduction of depression symptoms . We report a case of suicide completion and a summary of suicides during industry-sponsored drug trials of esketamine. These cases involved affected patients treated at approved REMS (Risk Evaluation and Mitigation Strategies) clinics where all data about adverse events was complete and reviewed externally. The five suicides were completed at 3 to 20 days after the last dose either during or after therapy. The suicide rate during the 819 patient years was consistent with rates previously reported for major depression. We conclude that patients eligible for esketamine treatment remain at increased suicidality whether during or especially after completion of the course.

Introduction

Major depression is the psychiatric diagnosis most associated with suicide (World Health Organization, 2019). The reported prevalence of suicidal ideation in affected adult patients is as high as 60%, and the lifetime incidence of attempted suicide in this population ranges between 10% and 20% (Holma et al., 2010).

Being an *S*-enantiomer of ketamine, esketamine is an N-methyl-D-aspartate receptor antagonist which confers additional antidepressant effects distinct from that of conventional monoaminergic antidepressants taken coincidentally. Esketamine nasal spray is approved in the United States and European Union for treating adults with treatment-resistant depression (TRD). It is also approved for a moderate to severe episode of a major depressive disorder (MDD), as short-term treatment for the rapid reduction of depression symptoms which according to clinical judgement constitute a psychiatric emergency. Two reports of identically designed, fully powered global studies revealed that esketamine nasal spray reduced depressive symptoms in hospitalized adults with moderate to severe depression and suicidal ≤ideation with intent (Fu et al., 2020; Ionescu et al., 2021).

Despite this promising therapy, suicide intention is possible in this vulnerable- population. In its package insert, the manufacturer has cautioned that use of intranasal esketamine (Spravato®) has not demonstrated a prevention of suicide or reduction of suicidal ideation or behavior. Reports exist of completed suicide during ketamine and esketamine treatment (Cusin et al., 2020; Gastaldon, et al., 2021; Siegel, et al., 2021; Weleff et al., 2022). We are unaware as to how long ketamine or esketamine's antisuicidal effects last. The objective of the present investigation was to report a detailed case and a case series of completed suicide during or after use of intranasal esketamine

Material and methods

This investigation was carried out in accordance with the latest version of the Declaration of Helsinki. Informed consent was obtained from the spouse of the patient in the case report. No identifiers were used.

Case report

Our patient is a 48-year-old White male with a three-year major depressive episode in addition to a generalized anxiety disorder. He had TRD, after being treated unsuccessfully with four antidepressants due to either a lack of efficacy (desvenlafaxine, duloxetine) or side effects (sertraline, venlafaxine). The patient was not treated with a tricyclic or monoamine oxidase inhibitor. He was taking vilazodone (Vibryd®) 40 mg daily and brexipiprazole (Rexulti®) 2 mg daily. Coexisting chronic hypertension was treated with amlodipine (Norvasc®).

The patient had a fear of failure and transferred jobs three years ago after being successful in packaging sales. There were significant fears of driving, leaving his home, and being around others. In the last year he experienced extreme anxiety with things being "out of control."

While feeling "better off dead," he expressed no plans. He denied any violent behavior or crime, mania, chronic pain, substance or alcohol use, traumatic brain injury, self-injury, or prior suicide attempts. Despite a history of childhood adversity, there were no family suicides. He had not

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Table 1
Completed suicides of four persons receiving esketamine during drug trials for major depression.

	Age/sex	Diagnosis	Dose	Study day at death	Days from last dose to death
1.	55/female	TRD	84	Day 188 of SUSTAIN-2	12
2.	41/male	TRD	56	Day 45 of SYNAPSE	20
3.	48/male	TRD	84	Day 26 of SUSTAIN-3	4
4.	53/female	MDDSI	84	Follow-up phase of ASPIRE-1	3

TRD = treatment resistant depression; MDDSI = major depressive disorder with suicidal ideation.

undergone Transcranial Magnetic Stimulation (TMS), Electroconvulsive Therapy (ECT), or psychiatric hospitalization. He was instructed during several clinic visits to remove all guns at home. His relation was stable with his supportive wife and two school-age children. Despite this, he consistently expressed feelings of hopelessness, helplessness, and worthlessness.

He underwent a total of 15 treatments of a full dose (84 mg) of intranasal esketamine (Spravato®). Dosings were initially twice weekly then weekly over the 11-week period while taking his two antidepressants. After many clinic treatments, he stated that esketamine made him not have any suicide ideation but only for the next day. His two providers concluded that the esketamine trial had failed for several reasons: total scores on weekly Patient Health Questionnaires (PHQ-9) remained 22 or higher out of 27; scores on the question, "thoughts that you would be better off dead, or hurting yourself in some way," were always "3″ ("nearly every day"); and neither the patient nor his spouse felt that the medication was helping.

His last visit with a psychiatrist 10 days before his suicide documented discussions about starting weekly psychotherapy, referral for TMS, and removal of all guns. While he repeatedly declined counselling, the patient consented to seeing a licensed professional counselor the day before his completed suicide. He denied suicidal ideation at that intake and was seeking help.

On the 25th day after the last dose of esketamine, the patient ended his life in his bedroom by a self-inflicted shotgun wound to the head. The manner of death after a full autopsy was suicide from the gunshot. Toxicology results included amlodipine, caffeine, and diphenhydramine.

Case series from clinical drug trials

A total of 1708 patients received esketamine in the six phase 2 and 3 TRD and MDD trials (Daly et al., 2019; Fu et al., 2020; Inonescu et al., 2021). Four of the 9 reported deaths were suicides during the 611 patient-years of TRD patients and 452 patient-years of MDD with active suicidal ideation and intent. The suicide completion rate was 0.49 per 100 patient-treatment years.

The age and sex of the patients and relationship between esketamine and death are shown in the Table. Ages ranged from 41 to 55 years among the two men and two women. Treatment was either ongoing or completed. Suicide completion occurred 3 to 21 days after the last of a wide number of esketamine treatments (from 4 to 188). Only one of the cases (case 4) had MDD with acute suicidal ideation with intent and died 3 days after the last of 8 doses. She had a record of 5 previous suicide attempts. Extensive reviews, required by all study site investigators, demonstrated that no suicide was related to esketamine.

Table 1

Discussion

Esketamine nasal spray may address the unmet need for a rapid-acting antidepressant in patients with either TRD or MDD with active suicidal ideation with intent. Two recent double-blind placebo-controlled studies of 226 patients hospitalized for suicide intent and who received esketamine demonstrated promising results during the first 25 days of therapy (Fu et al., 2020; Ionescu et al., 2021). Despite this, suicide completion can occur as reported in the present investigation.

We report a detailed case of a person treated for TRD with esketamine who had no prior suicide attempts and expressed no intent or plan to end his life. Since there was no antidepressant detected in his blood in the toxicology results, the patient may have stopped his medications well before his death. The Naranjo Adverse Drug Reaction Probability Scale was used to determine the likelihood of esketamine contributing to the patient suicide, possibly via withdrawal. The 10-question survey was answered independently by two providers, and the score was 0 which meant that the adverse drug reaction was likely related to factors other than a drug.

The four cases in the series during early clinical trials with esketamine revealed deaths being within three weeks from the last dose. We were limited in not being able to determine any prior suicide attempts, precipitating factors, or mode of death in this group of men and women who were in their 40 s and 50 s. It was not possible to determine whether the availability of "rescue" doses of esketamine would have influenced the eventual outcome.

While the number of completed suicide cases is small and the severity of patient's underlying illness is frequently severe, it is still possible to consider a link between esketamine use and a psychological withdraw. There may be a "disappointment reaction," a phenomenon where patients are left despondent after being failed by this novel medication that offered hope (Weleff et al., 2022). Continued FDA surveillance is necessary to track patients for several years. Despite reporting limitations, post marketing safety data on esketamine from reports made to the FDA Adverse Event Reporting System have revealed a 24.0 increased odds for development of suicidal ideation during treatment with esketamine and a 5.75 increased odds for completed suicide compared with other medications (Gastaldon, et al., 2021).

In summary, anyone taking esketamine for major depression remains at risk for suicide, despite the more rapid action of the medication in reducing depression symptoms and acute suicide ideation or intent. We were encouraged that the successful suicide rate reported here (0.49 per 100 patient-treatment years) is comparable to the background rate (0.47; 95% confidence 0.22–1.0) reported in a meta-analysis of TRD patients (Bergfeld et al., 2018). However, we were unable to answer the question whether coming off the esketamine resulted in a worsening of suicidality or whether prior suicidality returned once esketamine was out of the system. As with other antidepressants, the possibility exists of increased suicidality in some vulnerable patients administering esketamine, even among those who completed esketamine and admitted no intent. Providers can undertake several actions when discontinuing esketamine: talking with the patient's family and friends about this high-risk period, more frequently seeing the affected patients, re-encouraging them to call the clinic with any worsening of suicidality or development of a suicide plan, consideration of a trial of other medications (e.g., lithium or clozapine) with suspected antisuicidal properties, and expediting the use of procedures such as TMS or ECT.

Ethical statement

The study was done as routine clinical practice, and human subjects committee approval was not required due to de-identification of any patients. The patient's family in the case review consented to all information, including accuracy of the presentation and publication of this manuscript.

Conflict of interest

Neither Dr. Rayburn nor Dr. Albright recipes payment for patient care or research from Janssen Pharmaceuticals nor reports any conflict of interest.

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