Potential Risks of Poorly Monitored Ketamine Use in Depression Treatment

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At the time of his initial presentation to a tertiary medical center in 2012, "Mr. A" was a 52-year-old divorced man with a 30-year history of recurrent major depressive disorder, persistent depressive disorder, and a remote history of outpatient treatment for alcohol use disorder as a young adult. His first episode of major depression occurred at age 22 in association with a suicide attempt (he jumped off a four-story building) and subsequent hospitalization. Mr. A's medical history was significant for corrected hypothyroidism. The prospective course of illness encompassed four subsequent psychiatric admissions at our medical center, annually from 2012 to 2014, illustrating clear treatment-resistant depression and a reemerging pattern of substance misuse (alcohol, benzodiazepines, and ketamine).

Mr. A's admission in the summer of 2012 focused on consultation for depression and consideration of ECT. Prior medication trials of optimal dose and duration included trazodone, escitalopram, bupropion, and mirtazapine with lamotrigine and aripiprazole augmentation strategies. Mr. A reported negligible alcohol consumption (a single drink on rare occasions). He received seven bilateral ECT treatments, and his symptoms improved; his score on the Hamilton Depression Rating Scale declined from 37 on admission to 8 at discharge. He was discharged after 18 days on mirtazapine monotherapy with recommendations to maximize his dosing of mirtazapine and to add lithium for augmentation following his ECT course. He received three additional ECT treatments prior to self-discontinuing his ECT course and being lost to follow-up.

Mr. A's 2013 admission, 15 months later, was for major depression with suicidal ideation with intent to overdose on prescribed medications. Mr. A reported drinking 1–2 beers a day and misuse of lorazepam (he was taking 5 mg daily, although it was prescribed at 1 mg twice daily). However, on admission, his urine drug abuse test was negative, including absence of alcohol and benzodiazepines. During hospitalization, Mr. A reported that earlier in the year, he participated in an out-of-state research study in which he received a single intravenous ketamine infusion, which he reported provided antidepressant benefit for 4–5 days. Because of his perceived mood improvement, he left the study and sought out a ketamine prescriber. A neurologist in another state prescribed intranasal ketamine for depression, and Mr. A reported taking the prescribed ketamine intranasally with continued benefit. In contrast to the previous admission, ECT was not instituted in 2013. Discharge recommendations after this 5-day admission included follow-up with outpatient prescribers, changing lorazepam to clonazepam at 1 mg twice daily, and abstinence from alcohol. He did not receive ketamine while hospitalized.

Mr. A's next admission for major depression, 3 months later in early 2014, differed from previous admissions based on a reemergence of increasing alcohol use (he reported consuming four drinks daily). On admission, his urine drug abuse test was negative, including absence of alcohol. He admitted to using ketamine beyond the prescribed recommendations, although ketamine screening was not included in the urine drug abuse test. We contacted the out-of-state prescriber, who verified prescribing ketamine, 150 mg/mL, 0.5–1 mL intranasally every 4 hours as needed for depression. However, Mr. A reported using higher than prescribed doses of ketamine and more frequently (10–12 times a day) before admission, which he said he needed to relieve his depressive symptoms. He reported that the antidepressant benefit of ketamine lasted 2–3 hours after administration, but noted transient dissociative side effects lasting up to 20 minutes ("feeling like I am in a dreamy state" and "trippy effect … can be kind of intense"). He mentioned using intranasal ketamine in his car and stated that his mother had concerns about his driving during those times ("She thought I was swerving"). His family reported that ketamine was "ripping his life apart" and that he had "no control over it [ketamine use]." Mr. A met criteria for ketamine dependence based on his use of increased amounts of and increased tolerance to ketamine, driving while using despite concern from family, and loss of employment due to ketamine use. We discussed our concerns

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with the patient and his ketamine prescriber, who agreed to cease prescribing. Mr. A insisted that ketamine was the only prescribed substance that had helped his depression, and he reported his intention to seek more ketamine despite his treatment team's recommendations. A petition for civil commitment was not supported by the court. During the hospitalization, we discussed alternative medication recommendations to consider, including ECT, which Mr. A. declined because of memory difficulties associated with his previous treatment. After he was discharged from a 7-day admission, Mr. A participated in an outpatient program, but he often appeared to be intoxicated in group sessions, and he acknowledged continued use of prescribed ketamine. He was occasionally asked to leave group sessions because of an inability to maintain sobriety from ketamine.

Mr. A's fourth admission for depression, a month after the previous admission, was associated with a suicide attempt by alcohol and overdose of prescribed eszopiclone. A urine drug test was negative, including for alcohol. Mr. A reported that he had discontinued ketamine because he was unable to obtain the drug. He reported moderate alcohol consumption (1–2 beers two or three nights a week) but adamantly denied alcohol abuse or dependence. The treatment team again petitioned for civil commitment. A stay of commitment was granted, which meant that the court would not enforce commitment as long as Mr. A participated in recommended voluntary treatment, including outpatient chemical dependency evaluation and medication management.

We were notified of his death from a single-car crash 3 months later. Autopsy findings included a blood alcohol concentration of 0.133% (well over the 0.08% legal limit), tetrahydrocannabinol, and bupropion (prescribed); tests for ketamine and norketamine were negative. The family indicated the belief that Mr. A's death was a suicide facilitated by alcohol.

Discussion

The morbidity and mortality of depression are staggeringly clear. Yet, other than atypical antipsychotic augmentation and transcranial magnetic stimulation programs, little novel research has been proposed to develop successful treatments (1). Ketamine is an anesthetic medication with rapid antidepressant effects that are robust, rapid, and nonsustained (2). There has been recent interest in large-scale drug development of ketamine. While debate continues on the therapeutic mechanism of action and potential liability (3), early clinical data have been impressive and have supported development of large-scale, well-designed programs of intranasal esketamine, the *S*(+) enantiomer of ketamine, for treatment-resistant depression and major depression with suicidality. While ketamine and esketamine are available in highly regulated clinical trials, the use of ketamine for treatment of depression and chronic pain in clinical practice, in various delivery models, is increasing. The case presented here illustrates the potential unintended consequences and risks of ketamine prescribed for depression before optimal dosing, routes of administration, and specific indications have been established.

Pharmacologically, ketamine is a derivative of phencyclidine, and in addition to its primary mechanism of *N*-methyl-D-aspartate receptor antagonism, it may also increase levels of dopamine, norepinephrine, and serotonin in the brain (4). While likely multifactorial, ketamine's dopaminergic effects may promote euphoria and contribute to risk of dependence via the dopamine reward pathway (5, 6). The abuse potential of different formulations has not been determined. However, the pharmacokinetic properties of intranasal drug delivery, including rapid onset of action and improved bioavailability, may increase its abuse potential (7).

Ketamine's established availability as an anesthetic presents a dilemma for prescribers who otherwise would not have prescription access to an investigational medication for depression. Many argue that the only current recommendation is simply not to prescribe ketamine, given a lack of clinical evidence. Others believe that ketamine's robust antidepressant effects warrant immediate prescribing for treatment of depression. Current unregulated practice and lack of phase III clinical trial data challenge each recommendation.

If esketamine, a schedule III controlled substance, does attain FDA approval for treatment of depression, we hope this case report will promote discussion for monitoring ketamine use.

An Internet search with the words "ketamine and pharmacy" yields multiple web sites through which patients may contact prospective ketamine prescribers and pharmacies. Mr. A's access to ketamine and experience with his ketamine prescriber was not unique. He received monthly ketamine shipments, across state boundaries, of intranasal and sublingual formulations prescribed for multiple doses each day, with infrequent medication management appointments or telephone calls with his prescriber.

It is impossible to know the number of patients who receive prescriptions for ketamine for depression outside of research settings. Given the types of ketamine formulations that are typically dispensed in the community, including intranasal formulations, it is likely that most prescriptions are sold from compounding pharmacies. Traditional retail pharmacies are not able to manipulate the dosage form or access the

raw ketamine compounding powder, but compounding pharmacies have the infrastructure to create ketamine formulations. The role of compounding pharmacies and ketamine was highlighted in a recent report in which a patient obtained intranasal ketamine after being referred to a neurologist for ketamine based on her history of migraines and to treat her severe depression (8).

The Internet provides today's patients easy access to early research data on ketamine's antidepressant effects. Although there are positive aspects of patients being informed, this access may amplify the pressure or arguable ethical dilemma some prescribers may feel when patients request cutting-edge treatments. This is particularly challenging for patients like Mr. A, who have experienced varying degrees of depression and then experience a treatment like ketamine with an immediate, robust antidepressant effect.

Although the treatment team's position is not to recommend off-label use of ketamine for maintenance treatment of depression, the team did not interfere with Mr. A's receiving ketamine until there were concerns about misuse and dependence. Mr. A expressed frustration that the treatment team did not understand that ketamine was the only prescribed substance that had ever treated his depression.

Mr. A's use of alcohol became more apparent later in the course of his treatment. Underreporting of alcohol use (9) and co-occurrence of alcohol use and depression (10) are both common and consistent with the literature. However, Mr. A's lack of interest in addiction treatment made the dual diagnosis treatment challenging (11). Additionally, individuals with dual diagnoses are more likely to die by accidents compared with those with a single diagnosis (12). Mr. A was unwilling to consider changes in his antidepressant regimen or initiate dependence treatment, particularly when recommendations included ending his ketamine prescription. Patients in this situation may perceive that a practitioner who does not prescribe ketamine for treatment of depression simply does not understand the extent of their suffering, and thereby is withholding treatment.

Prescribing ketamine for depression is currently off label, which is defined as prescribing for an indication, dosage, or dosage form that has not been approved by the Food and Drug Administration (FDA) (13). Off-label drug use is common in psychiatry; however, a clear monitoring plan should be in place to avoid or manage serious adverse events. In this particular case, minimal monitoring occurred as Mr. A received monthly supplies of ketamine without being seen for follow-up.

If esketamine, a schedule III controlled substance, does attain FDA approval for treatment of depression, we hope this case report will promote discussion for monitoring ketamine use. Ketamine dependence has been reported in the literature with descriptions of tolerance, but not with withdrawal (14). This was the case with Mr. A, as he had symptoms of tolerance without any specific, apparent withdrawal symptoms. Knowing the warning signs of ketamine dependence is important, especially if ketamine becomes a mainstream treatment method. Given the potential for misuse and addiction, close follow-up and monitoring of ketamine prescribing will be essential.

This case report should encourage ongoing dialogue about ketamine prescribing in non-research settings. Outside of registered clinical trials, ketamine is currently being prescribed for depression treatment with no mechanism to report outcomes, either positive or negative (15). At what point does prescribing a schedule III medication with addictive potential, in a manner that lacks clear dosing parameters, lead to more harm than benefit? This case illustrates the potential harm of current, off-label, poorly regulated ketamine prescribing. Additionally, Mr. A's history of alcohol misuse with a remote history of alcohol addiction treatment may have made him a less than ideal candidate for ketamine. Without additional research and safety data, patients with a history of substance use may not be good candidates for ketamine therapy. Continued scientific, registered, clinical investigation regarding the use of ketamine and esketamine for treatment of depression and suicidality will be critical for drug development.

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