Concerns About Ketamine Treatment Practices in the Community: A Report of Two Cases

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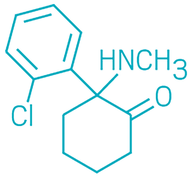
Patient Case #1

Patient #1: A 22 year-old female with 15-year history of celiac disease and endometriosis, post traumatic stress disorder (PTSD), and generalized anxiety disorder (GAD) presented for initial outpatient psychiatric evaluation. Abdominal discomfort persisted and, after thorough work-up, was determined to not be related to either endometriosis or celiac. This was instead attributed to "stress" by her gastroenterologist. She for psychiatric evaluation with initial episode of moderate major depressive disorder (MDD). ***She works as an administrative assistant at the gastroenterology clinic where she is also a patient for celiac disease.*** She was previously treated with psychotherapy and sertraline 25mg daily from her PCP for several months, which was ineffective. In the last year she received amitriptyline 25mg daily for several weeks from her gastroenterologist without improvement in cognitive, emotional, or physical symptoms of anxiety before discontinuation. ***She received 6-9 undocumented, free-of-charge, ketamine infusions (unknown dose/rate) from a certified nurse anesthetist (CRNA) over three weeks with several "booster" infusions afterward. She also reported being provided prescription of intranasal ketamine 125mg, two puffs each nostril twice daily for 30 days for home use.*** The compounding pharmacy clarified prescription was for 2 puffs each nostril, once daily (4.17mg total daily dose). She reported feeling "out of the fog for the first time in years". The patient discontinued morning dose due to difficulty driving secondary to blurred vision. She continued evening dose. There was no Risk Evaluation and Mitigation Strategy (REMS) system available for intranasal ketamine. After psychoeducation she chose to stop ketamine and try an adequate trial of sertraline for generalized anxiety disorder (GAD), PTSD, and possible initial episode of MDD. The compounding pharmacy confirmed that ketamine refills had not been filled and expired two days after the evaluation.



Ketamine
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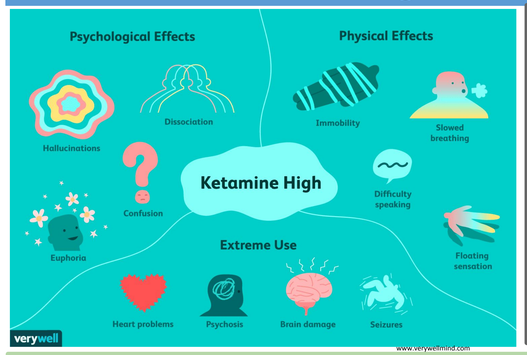
Patient Case #2

Patient #2: A 24 year old female with history of chronic PTSD from physical and sexual trauma in childhood and sexual assault as an adult, MDD, GAD, unspecified bipolar disorder (BP) and borderline personality disorder (BPD) was evaluated at an outpatient clinic following psychiatric hospitalization status post intentional overdose. She reported more than six inpatient psychiatric hospitalizations in the previous year, including one following attempted hanging. She had multiple past medication trials but at the time of evaluation was on venlafaxine, olanzapine, hydroxyzine, and trazodone. ***The patient received six ketamine infusions and intranasal ketamine HCL for home use from the same gastroenterologist and CRNA as patient #1 for treatment of MDD as diagnosed at the gastroenterology clinic. She received ketamine HCL powder 125mg, for intranasal administration, daily for one week, then twice daily as needed. Suicidal ideation worsened six weeks post-infusion and she received a booster infusion. Intranasal ketamine dosage was increased to unknown and undocumented amount.*** The patient reported improvement in suicidal ideation with the fourth infusion. Her venlafaxine dose was increased and lithium was added by the psychiatry outpatient clinic. She presented to the ED with suicidal intent several weeks later following alcohol and cocaine use, but could not recall how she sustained superficial cuts to her wrists. She was admitted to an inpatient psychiatric hospital. Electroconvulsive therapy (ECT) was considered on an outpatient basis, but she had been denied twice previously that year due to comorbid BPD diagnosis. Following discharge she received another ketamine infusion without therapeutic benefit. At the time of psychiatric evaluation, her diagnosis was consistent with Bipolar I most recent episode depressed with mixed features. The patient decided to discontinue ketamine due to lack of efficacy for suicidal ideation, but only after finishing her home supply of intranasal ketamine.

Background



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- **Ketamine is a class III controlled substance and NMDA receptor antagonist that has gained attention in clinical and academic settings for its role in treatment-resistant depression (TRD), suicidality, and other psychiatric indications**
- **It is widely available intravenously, orally, intranasally, parenterally, rectally, and topically. Intranasal esketamine was recently FDA-approved for treatment resistant depression (TRD).**
- **It has also been popularized as a club drug, "special K"**

Monitoring, administration, and safety of racemic ketamine and esketamine:

- Patients receiving intranasal esketamine must be enrolled in the Risk Evaluation and Mitigation Strategy (REMS) through a certified clinic
- Patients receiving esketamine must be monitored by a medical professional trained in ACLS and behavioral emergencies for ≥2 hrs following administration. ***Those receiving racemic ketamine intranasally do not have any such regulations that we know of as it is widely available generically***

Patient selection and consent:

- Selection should be limited to those who are unresponsive to antidepressant trials and should include a comprehensive biopsychosocial assessment (Wilkinson & Sanacora 2017)
- Patients should be informed of little long-term safety data of ketamine use in psychiatric conditions (Sanacora 2017)

Prescribing practices Survey:

- In a survey of clinicians utilizing ketamine treatment, most (87.7%) used IV ketamine (0.5mg/kg over 40-45 minutes) for indications of Major Depressive Disorder (72.2%), Bipolar Disorder (15.1%), and PTSD (5.7%) (Wilkinson et al 2017)
- Of those prescribing ketamine, 66.7% were trained in psychiatry, 22.8% were trained in anesthesiology, 3.5% in emergency medicine, and 3.5% in family medicine

PTSD

- **Ketamine IV (0.5mg/kg) improves PTSD symptoms (Feder 2014) vs midazolam at 24 hours**
- **Possible role in prophylaxis of "contextualized fear reconsolidation" in rat models (Duclot et al. 2016) via downregulation of early growth response 1 in the CA1 region of the hippocampus and BDNF mRNA prelimbic and infralimbic cortices.**
- **hyperarousal and dissociation side effects could be harmful in the context of PTSD (Banov et al. 2019)**

Anxiety

- **Long-term data for ketamine treatment of anxiety disorders (including OCD and PTSD) is limited and typically under-powered. Careful screening of appropriate patients is critical and should be limited to those with treatment-resistant symptoms (Banov et al. 2019)**
- **IV ketamine may improve cognitive, emotional, and physical symptoms of anxiety for patients with treatment resistant Generalized Anxiety Disorder and Social Anxiety Disorder (Glue 2017)**

Bipolar

- **Studies of intravenous & intranasal ketamine demonstrated more robust response to symptoms of unipolar depression vs bipolar depression (McGirr et al. 2015) The meta-analysis did not clearly distinguish TRD from major depressive episodes in general**

Discussion

- **Ketamine is an exciting treatment option, but this case series highlights knowledge gaps in management which exist regarding use for other psychiatric conditions.**
- **Wide availability due to generic status, lack of required REMS program, multiple formulations, and increasing presence in popular media are unique challenges to ketamine use.**
- **Psychiatrists need to consider:**
  - **Approach to patients who have received ketamine at concerning doses, without sufficient monitoring**
  - **Consideration of reporting to licensing agencies in situations outside of scope of practice**
  - **Management of addiction/withdrawal: Withdrawal similar cocaine: no discernable physical harm, but intense cravings (Jansen 2011)**

Discussion (cont)

- **Prescribers may feel pressure to provide enthusiastic patients with what they believe to be a cutting edge treatment (Shak et al. 2017)**
- **Some may advocate for additional access to ketamine/esketamine given rising rate of suicide & generally good tolerability (Wan et al 2015)**
- **Well documented risks of poor monitoring, addictive potential, driving following administration, and severe desensitization (Shak et al 2016)**
- **A balanced view of the evidence, risks, benefits, and alternatives for each patient must be at the forefront of treatment decisions including ketamine**


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Future Directions

- Ketamine and esketamine research should continue for psychiatric conditions which are refractory to current treatments
- Long-term safety and outcome data will be critical for assessing appropriateness of this treatment option.
- Evaluation may be needed to determine if BPD is a contraindication
- Work to identify who may be at highest risk of adverse events with ketamine/esketamine
- Development of a registry for ketamine treatment of psychiatric conditions


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