

CASE REPORT

New use for an old drug: oral ketamine for treatment-resistant depression

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SUMMARY

Treatment-resistant depression (TRD) is a disabling disorder that can interfere with a patient's capacity to understand and participate in medical care and thus negatively impact individual morbidity and mortality. Hospitalised patients with TRD may require rapid alleviation of severe symptomatology, particularly when suicidal or if unable to participate in care decisions. Ketamine is well known for its anaesthetic effects and its use as a 'street' drug; however, its action as an N-methyl-D-aspartate receptor antagonist makes ketamine a potential therapy for TRD. The majority of studies investigating ketamine for TRD have used intravenous drug delivery, demonstrating benefit for rapid alleviation and sustained response of depression symptoms. Oral ketamine for urgent alleviation of TRD symptoms is less reported. We describe rapid alleviation of severe TRD with oral ketamine in a severely ill postoperative hospitalised patient, and review the current literature on 'off-label' use of ketamine for treatment of refractory depression.

BACKGROUND

In 2014, 15.7 million (6.6%) US adults aged 18 years or older had at least one major depressive disorder (MDD) episode in the last year.¹ A significant number of patients who fail to respond or achieve remission with conventional therapies for MDD are subsequently classified as treatment-resistant depression (TRD). The exact prevalence of TRD is unknown, but it is estimated that 10–30% of all patients with unipolar depression fail to respond to at least two different antidepressants prescribed at maximum dose for at least 1-month.^{2–5}

The WHO ranks depression as a top cause of disease burden worldwide and a significant source of disability in adults.⁶ TRD is associated with increased morbidity and mortality^{7 8} and can negatively impact an individual's ability to participate in medical decision-making.^{9 10} Patients with TRD are twice as likely to be hospitalised with overall medical costs estimated at six times that of patients without TRD.⁵ Multiple treatment options for TRD exist, including use of multiple conventional antidepressant drugs, adjunct antipsychotic therapy, psychostimulant drugs, electroconvulsive therapy and even brain stimulation. However, alternative treatments may be needed for rapid alleviation of TRD in severely ill hospitalised patients, particularly in cases of suicidality or when severe refractory depression prohibits therapeutic shared decision-making.

Ketamine is a well-known intravenous anaesthetic that acts as a high-affinity N-methyl-D-aspartate

(NMDA) receptor antagonist.¹¹ The drug interacts with cholinergic, noradrenergic and serotonergic reuptake inhibition, resulting in rapid alleviation of depressed mood. Thus, ketamine has emerged as a potential therapy for acute alleviation of suicidal ideation as well as TRD. The majority of reports describe intravenous use of ketamine in subanaesthetic doses for treatment of TRD.^{2 12–14} Oral ketamine has been used to treat TRD and severe anxiety in outpatient psychiatric and hospice settings,^{12 13 15 16} but has not been described for treatment of severe TRD in the hospitalised patient with severe medical illness. We believe the following case is important in highlighting oral ketamine as a potential therapy for a severely ill patient with TRD in the hospital setting.

CASE PRESENTATION

A 62-year-old man was admitted to the inpatient surgical service for worsening abdominal pain and distension. Approximately 1-year previously, he was admitted with gallstone pancreatitis complicated by pancreatic necrosis and retroperitoneal abscess formation, requiring open cholecystectomy and pancreatic necrosectomy. He had an extended postoperative course lasting several months due to complications of aspiration pneumonia, chronic respiratory failure requiring tracheostomy, recurrent abdominal abscesses, *Clostridium difficile* infection and malnutrition requiring percutaneous endoscopic gastrostomy (PEG) tube placement. The patient was eventually discharged to a long-term acute care hospital but developed liver function abnormalities which resulted in multiple readmissions for endoscopies and imaging studies. Over the next several months, his health status declined from complications of repeated infections and severe malnutrition, causing liver failure and portal hypertension, subsequent abdominal distension, pain and ascites. He lost more than 80 lb and developed increasing apathy, depression and anxiousness.

His medical history was significant for long-standing MDD, chronic anxiety, chronic pain and diabetes secondary to recurrent pancreatitis. Medications included: citalopram 40 mg daily, mirtazapine 30 mg at night, lorazepam 0.5 mg two times a day, trazodone 50 mg at night as needed for insomnia, oxycodone-acetaminophen 5/325 mg two tablets every 4 hours as needed for pain and insulin for diabetes.

INVESTIGATIONS

Pertinent findings on this admission included tachycardia 110 bpm, normal blood pressure and diffuse



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abdominal tenderness. Laboratory studies noted elevated alkaline phosphatase of 1927 U/L, albumin of 1.6 g/dL, pre-albumin of 3.4 mg/dL and elevated International Normalized Ratio (INR) of 1.8. Admission aspartate aminotransferase (AST) was 27 U/L and alanine aminotransferase (ALT) 16 U/L, with elevated lipase of 1190 U/L. Imaging demonstrated continued pancreatic necrosis with development of fistulous tracts to the stomach, retroperitoneum and abdominal wall. The patient was treated medically, and with endoscopic intervention for creation of postpancreatic drainage tube placement.

His recovery period was prolonged with multiple medical and psychological setbacks, which resulted in worsening of his anxiety, depression and impaired decision-making. A psychological evaluation revealed flat affect with intermittent emotional lability and inconsistent responses to questions. He expressed suicidal ideation and required a bedside sitter, and became unable to participate in medical decision-making. Palliative medicine services were consulted.

The palliative team administered the Hospital Anxiety and Depression Scale (HADS), which has been used to assess anxiety and depression in the hospital setting. Scores for the HADS range from 0 to 21 for the two subscales of anxiety (HADS-A) and depression (HADS-D) and high scores (>15) are indicative of severe symptomatology.¹⁷ Our patient scored 16 on HADS-D baseline testing, signifying severe symptoms and emotional distress despite multidrug therapy with therapeutic doses of citalopram, mirtazapine and lorazepam, consistent with a diagnosis of TRD stage 2, as defined by the Thase-Rush TRD Staging Method.⁵

TREATMENT

Following discussion with the patient and family, oral ketamine 0.25 mg/kg was added in an attempt to provide rapid relief from severe depressive symptomatology. The ketamine dose was reduced by 50% from the recommended starting dose used in prior studies due to hepatic dysfunction from his severe malnutrition, so that he was taking ketamine 5 mg orally every 8 hours. At 48 hours, a repeat HADS-D was scored as 10 (38% change) and ketamine was continued at the same dose. Notably, the patient was taking opioids, but following addition of ketamine, the opioid dose was reduced by 75%. The patient was able to participate in therapy and better articulate his ultimate wishes to his family members who expressed satisfaction with the significant improvement seen in the patient's mood.

OUTCOME AND FOLLOW-UP

Unfortunately, over the next week, the patient's clinical condition deteriorated with resultant escalation of anxiety and depression. Nine days after initiation of ketamine, repeat HADS-D score was 13 and ketamine was increased to 10 mg every 8 hours. However, given his grim prognosis associated with his pancreatic disease, the patient and family decided to focus on comfort care only. Ketamine was discontinued and the patient expired.

DISCUSSION

This case demonstrates successful off-label use of oral ketamine to provide rapid alleviation of severe TRD in a significantly ill patient in the hospital setting. The pathogenesis of depression remains unclear, but is considered multifactorial in aetiology with evidence of dysfunctional serotonergic, noradrenergic and dopaminergic communications in the midbrain and brainstem. NMDA receptors, a subtype of fast-signalling glutamate receptors located in the central nervous system (CNS), are the main mediators of presynaptic monoamine levels involved in the

neuroplasticity and neuronal changes responsible for the development of major depression.^{2 18-20} NMDA receptor blockade results in rapid mood elevation,²¹⁻²³ as well as remodelling and repair of damaged neuronal transmission pathways, which can result in long-term physiological change.¹⁸ Thus, ketamine's action as an NMDA receptor antagonist allows use as a novel treatment for TRD.

Prior investigations of ketamine for treatment of suicide, unipolar and bipolar depression, post-traumatic stress disorder (PTSD) and other anxiety disorders have been reported.²⁴⁻²⁷ The majority of studies describe use of either single or sequential ketamine infusion therapy.²⁰ In 2000, Berman *et al*²⁸ published a small double-blinded, placebo-controlled trial with intravenous ketamine, which produced a rapid and marked antidepressant effect when given at subanaesthetic doses as compared to the placebo group. A 2006 randomised, double-blind, placebo-controlled crossover trial demonstrated that a single ketamine infusion produced significant and sustained therapeutic effect compared to placebo.²¹ Successful use of oral ketamine is reported in only small numbers of patients, [table 1](#). Paskalis *et al*²⁹ first described oral ketamine as adjunctive therapy for poorly controlled anxiety and depression in four patients in 2010. Subsequently, oral ketamine has been used for therapy of pain, anxiety and depression without significant untoward effect in small numbers of patients in the outpatient and hospice settings.³⁰ Use in severely ill hospitalised patients has not been formerly described.

It is important to consider that different studies report different methods to measure ketamine success for TRD or MDD treatment, including: the Montgomery-Asberg Depression Rating Scale, Beck Depression Inventory, Hamilton Depression Rating Scale and the Hospital Anxiety Depression Scale (HADS). The HADS has been validated in the hospital setting and measures depression (HADS-D) and anxiety (HADS-A), and has been regarded as a 'global measure of psychological distress'.^{17 33} The total score is of 42, with 21 points related to anxiety (HADS-A) and 21 to depression (HADS-D). Higher scores indicate greater levels of anxiety or depression with cut-off scores of eight or above in the initial test construct and in reviews evaluating internal consistency.^{17 34 35} The SE of measurement is 1.37-2,³⁶ and retest reliability (when carried out in 0-2 weeks) is excellent.³⁷

Similar to work performed by Irwin *et al*,¹³ we used the HADS score to determine effectiveness of ketamine therapy. Studies have not validated a minimally clinically important difference of the HADS-D score to determine efficacy of treatment; however, Irwin *et al*¹³ found that a 30% reduction in HADS scores correlated with a treatment response defined as a clinically meaningful reduction in symptoms as determined by 'qualified mental health experts'. Applying this to our patient, an early, immediate improvement was noted by physician clinical judgement and a 38% reduction in the HADS-D score. At day 10, the HADS score of 13 (20% reduction from initial testing) correlated with clinical escalation of symptoms secondary to deterioration of medical condition. It is unclear if further escalation of the ketamine dose would have improved relapsing symptomatology, but the patient and family wished to decline any additional treatment, opting for comfort care. Repeated dosing of intravenous formulations of ketamine have demonstrated success at sustained improvement for TRD in several reports,⁵ but further investigation is necessary to determine success of oral ketamine at providing sustained relief or symptom remission. In our case, immediate alleviation of symptoms allowed our patient the ability to participate in care decisions, and was thus considered to provide positive effect.

Table 1 Studies reporting oral ketamine use for treatment of depression

Study	Number of patients	Dose and frequency	Side effects	Results	Conclusions
Paslakis <i>et al</i> ²⁹ Severe depression, chronic MDD, recurrent depressive disorder HAMD used for assessment	4	Starting dose: 10 mg TID, maximum dose: 1.25 mg/kg TID for 12–14 days	No psychotomimetic effects	Pt 1: Pretreatment HAMD 24, repeat HAMD 8, sustained Pt 2: Pretreatment HAMD 24, repeat HAMD 19 Pt 3: Pretreatment HAMD 19, repeat HAMD no change Pt 4: Pretreatment HAMD 21, repeat HAMD 8, sustained	Potential 'add-on' therapy in patients on conventional antidepressant medication.
Irwin and Iglewicz ¹² Severe depression HADS used for assessment	2	0.5 mg/kg, single dose	No side effects reported	Pt 1: Pretreatment HADS 18, repeat HADS 7 at 60 min, repeat HADS 9 at 15 days Pt 2: Pretreatment HADS 33, repeat HADS 21 at 60 min, repeat HADS 13 at 8 days	Improved pain, anxiety and depression scales in hospice patients (home setting).
McNulty and Hahn ¹⁶ Severe depression	1	0.5 mg/kg daily for 2 months	No side effects reported	Pretreatment 'depression score' 8; post-treatment 0	Improved pain, anxiety and depression in outpatient palliative and hospice patient.
Irwin <i>et al</i> ¹³ Depression HADS _{≥15} used for assessment	14	0.5 mg/kg daily for 28 days	Mild increase in diarrhoea, trouble sleeping and sitting still	8 patients completed the study, 100% demonstrated a $\geq 30\%$ decrease in HADS depression scale	Proof of concept in population of hospice patients (home and skilled nursing facility).
Lara <i>et al</i> ¹⁵ Refractory unipolar depression Likert scale used for assessment: 0=very sad/distressed; 10=cheerful/positive/peaceful	26	Starting dose: 10 mg daily, titrated by 5 mg increments; variable dosing frequency, no maximum dose reported, longest treatment was 6 months	Transient agitation and light-headedness	20 patients: remission or 'clear response' 3 patients: moderate or partial response 3 patients: no response	Low doses of oral ketamine may achieve remission and be sustained after cessation.
De Gioannis and De Leo ³¹ Bipolar depression, chronic suicidal ideation MADRS used for assessment	2	0.5–3 mg/kg, every 2–4 weeks	No side effects reported	Pt 1: Pretreatment MADRS 36, repeat MADRS 17 at 24 hours, sustained 'remission' of suicidal ideation. Pt 2: Pretreatment MADRS 31, repeat MADRS 10 at 24 hours, no suicidal ideation	Sustained remission of suicidal ideation.
Nguyen L <i>et al</i> ³² MDD, TRD DSM-IV-TR used for diagnosis; assessment of response based on clinician opinion and drug refill history; standardised test not used	17	0.5–1 mg/kg of ketamine held for as long as possible in mouth prior to swallowing	No notable side effects	13/17 (76%) deemed responders 4/17 non-responders Patients classified as 'responders' or 'non-responders' on clinical basis/opinion and/or drug refill history	Improved depression using transmucosal delivery of liquid oral ketamine in an outpatient psychiatric clinic setting.

DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (Text Revision); HADS, Hospital Anxiety Depression Scale; HAMD, Hamilton Depression Rating Scale; MADRS, Montgomery-Asberg Depression Rating Scale; MDD, major depressive disorder; Pt, patient; TID, three times a day; TRD, treatment-resistant depression.

Multiple formulations of ketamine are under investigation for antidepressant properties including intravenous, oral, intramuscular, sublingual and, most recently, intranasal.³⁸ Ketamine undergoes hepatic metabolism to an active metabolite, norketamine, a non-competitive NMDA receptor antagonist with one-third the affinity of ketamine.³⁹ Ketamine and norketamine are renally excreted. Ketamine's bioavailability differs greatly by route of administration. The bioavailability of sublingual, intramuscular and intranasal routes are estimated at $32 \pm 17\%$, 93% and 30% , respectively. The bioavailability of oral ketamine is $23 \pm 9\%$, but increases to $59 \pm 16\%$ when considering contribution from norketamine.⁴⁰ Several factors can affect oral bioavailability of oral dosing, including whether liquid or tablet form is used and individual cytochrome phenotype.³⁰ Following oral dosing, onset of symptom relief typically occurs at 120 min¹² with effects lasting up to 1-month in some cases.¹³

In addition to antidepressant properties, ketamine has analgesic and antianxiety effects. The metabolite norketamine has

been linked with improved analgesia by decreasing pain perception at the dorsal horn and reversing opioid tolerance by inhibiting nitric oxide synthesis.^{41–43} We were able to reduce opioid dose in our patient with ketamine addition. Ketamine augments gamma-aminobutyric acid (GABA) receptors, which can potentiate benzodiazepines and other anxiolytics.⁴⁴

There are no published standardised dosing recommendations for either intravenous or oral ketamine use for TRD. Concerns about habituation and tolerance have been noted, and repeat dosing strategies remain unclear.^{5 30} Most studies suggest weight-based dosing using 0.5 mg/kg, but De Gioannis and De Leo³¹ reported successful treatment of two patients with suicidal ideation using a maximum dose of liquid ketamine at 3 mg/kg. Further study is necessary to determine optimal dosing strategies, both frequency and maximal dose. However, dose reduction of 25–50% is recommended in the presence of mild-to-moderate renal or hepatic dysfunction and in patients taking opioids or benzodiazepines, as ketamine augments effect

of these drugs via NMDA receptor antagonism.³⁹ Increased myocardial demand and cerebral blood flow occur secondary to ketamine-releasing endogenous catecholamines and recommendations include dose reduction or avoidance in patients with coronary ischaemia or a history of stroke.³⁹ Finally, dose reduction is recommended in elderly individuals.

Adverse events are generally mild when ketamine is administered at subanaesthetic doses, and are usually dose-related, occurring with doses >1 mg/kg. Side effects include sedation, nausea, tachycardia, respiratory depression, hypersalivation, increased lacrimation and analgesia.^{39–41} Psychotomimetic side effects have been reported with intravenous administration, but do not persist beyond the infusion.¹⁴ Oral, sublingual and intranasal ketamine have a decreased side effect profile due to lower bioavailability and rapid metabolism to norketamine.⁴⁵ Over time, ketamine induces and enhances its own metabolism, and hepatic injury with repeated dosing has been documented. The exact pathophysiology leading to hepatic impairment is unclear, but close monitoring of hepatic enzymes is recommended.^{39–41} Long-term effects of repeated ketamine dosing are under investigation.³⁸ In cases of misuse, prolonged ketamine has been associated with neurocognitive impairment and white matter changes.³⁰ Repeated ketamine dosing can also cause irritation of the urinary tract mucosa, leading to interstitial cystitis and detrusor overactivity, but these symptoms generally subside after drug cessation.⁴¹

Private ketamine clinics have emerged offering outpatient infusions to patients with suicidality, TRD, MDD and bipolar depression, raising concerns about cost and addictive potential.^{30–46} This off-label procedure is not covered by most insurances, and out-of-pocket costs range from US\$400 to US\$1700 per infusion.⁴⁷ Ketamine's pharmacological attributes are also similar to the potent psychotomimetic drug phencyclidine,²⁰ and its dissociative, psychogenic and μ -receptor-binding capacity at high doses make its use controversial.²³ Death from toxicity is rare, but ketamine misuse has the potential to cause significant burden on the healthcare system. Emphasis must be placed on selection of the 'right' patient for ketamine therapy. A 2014 multivariate analysis suggested that clinical predictors associated with more favourable response to intravenous ketamine therapy of MDD or TRD include increased body mass index, family history of alcohol use and no prior history of suicide attempt.⁴⁸ These characteristics will also need to be defined in the context of oral use if ketamine is to become more available for administration by a broad range of practitioners.

Ketamine is not currently FDA approved for use in the treatment of TRD. We used this medication off-label given the failure of conventional treatments, severity of our patient's symptoms and need for rapid amelioration of TRD. Safety and efficacy of long-term use of ketamine is lacking; however, ketamine's effect of rapid mood elevation highlights the need for continued investigation of NMDA receptor antagonists for short-term use in the hospital setting and for long-term efficacy in alleviation of severe or treatment-resistant major depression.

Patient's perspective

The patient expired and consent for case presentation was obtained from the patient's sister who was the power of attorney for the patient. She and other family members were asked to provide written comments, but informed the authors that they had no additional information to provide.

Learning points

- ▶ Treatment-resistant depression (TRD) is a disabling disorder that affects up to 10–30% of patients with depression and adversely affects mortality and morbidity in affected patients.
- ▶ N-methyl-D-aspartate (NMDA) receptors mediate presynaptic monoamine levels which are involved in neuroplasticity and neuronal changes seen with development of major depression.
- ▶ Ketamine acts as an NMDA receptor antagonist and its various formulations (intravenous, oral, intranasal and intramuscular) have been used to treat severe depression providing rapid alleviation of symptoms and sustained improvement.
- ▶ Ketamine dose reduction is necessary in elderly individuals, those with renal or hepatic dysfunction, and in patients with a history of coronary ischaemia or history of stroke, and cost and addictive potential must be carefully considered if using as off-label therapy for TRD.
- ▶ Although not currently FDA approved for treatment of TRD, oral ketamine administration resulted in rapid improvement of TRD in a severely ill hospitalised patient, highlighting the need for continued investigation of oral ketamine use in similar settings.

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