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Bridging the gap: An interdisciplinary perspective on ketamine in psychiatric disorders

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Bridging the gap: An interdisciplinary perspective on ketamine in psychiatric disorders

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Table of contents

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Editorial: Bridging the gap: an interdisciplinary perspective on ketamine in psychiatric disorders

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Editorial on the Research Topic
Bridging the gap: an interdisciplinary perspective on ketamine in psychiatric disorders

While ketamine has emerged as a promising therapeutic for treatment-resistant depression (TRD) and psychiatric emergencies, including suicidality occurring in the course of major depressive disorder (MDD), several issues pertaining to clinical efficacy remain not fully elucidated. These issues include (1) the role of ketamine-assisted psychotherapy (KAP) in enhancing or prolonging antidepressant effects; (2) the therapeutic value of the so-called psychedelic protocols that value the state-altering properties of ketamine; (3) the therapeutic potential of ketamine as a first-line treatment for MDD, other mood diseases, and potentially other psychiatric diagnoses; and (4) the safety and efficacy of home treatment with self-administered ketamine.

This collection of articles extends the currently limited evidence for the efficacy of KAP for MDD, the impact of protocols using doses that induce psychedelic experiences, and the benefits of using both of these approaches with a range of psychiatric diagnoses. The literature on two relatively new treatment options is enriched by a case report illustrating the efficacy of intranasal esketamine, and a study providing early data on safety and efficacy with home use of self-administered oral ketamine. Two frequently discussed risks associated with ketamine treatment are presented with a real-world study examining ketamine's potential for abuse and one study providing guidance for the management of hypertension that may occur in the course of antidepressant treatment with intravenous ketamine. A final case report documented the administration of intranasal esketamine in a 17-year-old female adolescent suffering from TRD, and two articles examined the evidence for differences in the antianhedonic response to ketamine between male and female participants and between individuals with melancholic and non-melancholic depression, representing clinically relevant conditions that are frequently described as predominantly biologically determined manifestations of MDD (1, 2).

In contrast with the scores of studies demonstrating ketamine's efficacy as a fast-acting antidepressant, there is relatively little research on ketamine administered in combination with psychotherapy. There is clear evidence that the addition of psychotherapy to conventional antidepressant psychopharmacotherapy enhances benefits in MDD patients (3–5), although it does not consistently lead to improved outcomes, especially in patients

who are more severely ill (6). Given that ketamine treatment shows efficacy with a substantive percentage of TRD patients (7–11), an added psychotherapy component may prove to be highly effective in selected patient populations.

To date, the most robust evidence for the efficacy of KAP using a psychedelic protocol applied to a wide range of mood and trauma-related conditions comes from a retrospective study of 235 adult patients in three separate private general psychology practices in Northern California and Texas (12). The most common diagnoses in this varied group were MDD and complex post-traumatic stress disorder (cPTSD), and the treatment varied from 1 to 25 sessions. Ketamine was typically administered in doses of either 200–250 mg via sublingual injection or 80–90 mg via intramuscular injection. Mean depression scores on the Beck Depression Inventory (BDI) and Hamilton Anxiety Scale (HAM-A) decreased by more than 50% across this population, with the largest improvements in cases involving cPTSD or developmental trauma. Adverse effects of nausea, vomiting, and agitation were reported by a small percentage of patients, only rarely resulting in the discontinuation of treatment. This study highlights the therapeutic value of pairing psychotherapy with ketamine treatment and points to the real-world potential of KAP at psychedelic doses as a treatment for individuals with a variety of diagnoses.

In a different approach, an overlay of a 10-week, 12-session course of cognitive behavioral therapy (CBT) on a short 2-week course of four ketamine infusions (0.5 mg/kg over 40 min) in an open-label trial resulted in remission in 7 out of 16 self-selected patients with TRD within the first 2 weeks (13); for ketamine responders (8/16), average time to relapse was 12 weeks post-ketamine treatment. This differs from less durable results of ketamine-only treatments in a review of nine trials with patients with TRD using ketamine infusions of varying dosages and frequency; in these trials, the mean time to relapse after ketamine treatment ranged from 16 days to 24 days (14). Wilkinson et al. (13) interpreted their evidence as favorable to the use of psychotherapy as a relapse prevention strategy.

In a novel automated psychosocial intervention (15), 154 adult patients with moderate-to-severe treatment-resistant MDD and below-normal self-reported self-esteem received a single ketamine infusion (0.5 mg/kg over 40 min) followed by eight computer-based sessions of a conditioning intervention designed to reinforce an association between positive traits and the patient's self-perception, both supraliminally and subliminally (automated self-association training; ASAT). Interventions took place in a research office setting, with each intervention lasting 15–20 min and occurring twice on four consecutive days with a 20-min interval between sessions. MADRS depression scores remained stable at a low level over the 30 days of the intervention, with the end-of-study effect size favoring the ketamine + ASAT training against the saline infusion + ASAT training and the ketamine infusion + sham training by a small effect size.

New preliminary evidence for KAP with adolescents is provided in "*Ketamine-assisted psychotherapy in adolescents with multiple psychiatric diagnoses*" by Wolfson et al.. Their study reports on four cases of adolescents aged 13–19 years with conditions ranging from TRD, anxiety, and bipolar disorders to trauma and eating disorders; all adolescents were treated with sublingual ketamine followed by sessions with intramuscular ketamine, at individualized and incrementally higher doses until an experience of ego dissolution was achieved, leading to rapid functional improvements and decreases in symptoms.

The benefits of KAP for the treatment of multiple psychiatric diagnoses are further illustrated, along with an insight into the subjective experience of psychedelic-dose ketamine, in "*Medical student types journals during ketamine infusions for suicidal ideation, treatment-resistant depression, post-traumatic stress disorder, and generalized anxiety disorder*" by Willms et al.. In their study, a 30-year-old man had suffered from suicidal ideation for 5 years, despite prior psychotherapy, lifestyle modifications, and complex psychopharmacology. After an 8-month regimen of ketamine infusions at 1.8 to 2.1 mg/kg/h for 1 h, he experienced remission from suicidality, PTSD, MDD, and GAD. The case includes detailed journals of his subjective experience during four 1-h infusions. While evidence for the relationship between ketamine's alterations of experience and its therapeutic efficacy is mixed (16–19), this study adds rare subjective reports of the client experience.

Ketamine treatment frequently provides sustained clinical improvements independent of psychotherapy, as illustrated by "*Intranasal esketamine for severe major depressive disorder with psychotic features*" by Carter et al.. In their study, a 29-year-old patient with TRD, anhedonia, auditory hallucinations, and suicidal thoughts received 14 intranasal esketamine treatments over 3 months. Her depression symptoms were reduced from severe to mild, and her suicidal ideation and auditory hallucinations resolved; moreover, she continued to be stable for 1 year after treatment.

Many of the efforts to improve ketamine's efficacy are aimed at adjusting treatment protocols or combining ketamine treatment with psychotherapy. A different line of innovation combines ketamine with other drugs, as reported in "*Effectiveness of brexpiprazole and esketamine/ketamine combination: a novel therapeutic strategy in five cases of treatment-resistant depression*" by Chan et al.. Brexpiprazole represents a second-generation antipsychotic agent that, similar to ketamine, can be effectively employed in the course of add-on or augmentation treatment in MDD and that impacts the glutamatergic system with the rapid onset of action. A case series illustrates the potential of synergetic mechanisms offered by this novel drug combination.

A recently pioneered treatment option is sublingual ketamine delivered by mail for self-administration at home. A summary of outcomes with 664 patients who completed at least three ketamine sessions appears in "*Safety, effectiveness and tolerability of sublingual ketamine in depression and anxiety: a retrospective study of off-label, at-home use*" by Hassan et al.. After three twice-weekly treatments with rapid dissolve ketamine tablets delivering 300–450 mg—a range that often induces a psychedelic experience (an altered state that may be accompanied by changes in sense perception and/or sense of self)—the mean depression score for this sample decreased by 47.59% as measured by the Patient Health

Questionnaire (PHQ-9), with similar decreases in anxiety (GAD-7). After six treatments, the PHQ-9 scores dropped to scores of half or less on intake in 65.4% of the 210 patients who completed this extended protocol, with comparable reductions in anxiety. Minor side effects and adverse events such as dizziness and nausea were limited and resolved without medical intervention, providing evidence that, for some patients, this treatment option may offer added convenience, increased privacy, and reduced cost along with good efficacy and safety.[1]

With the rise of at-home treatment comes an appropriate interest in the addiction and abuse potentials of ketamine, which in addition to its clinical uses is also a popular party drug. These concerns are addressed in "*A survey of drug liking and cravings in patients using sublingual or intranasal ketamine for treatment resistant depression: a preliminary evaluation of real-world addictive potential*" by Chubbs et al.. A survey of 33 patients with TRD in current or prior treatment with sublingual or intranasal ketamine found that ketamine was not consistently liked or craved by these patients. While non-parenteral uses of ketamine require diligent monitoring by providers, abuse concerns should be weighed against the potential benefits of treatment. These findings are consistent with other research pointing to negligible risks of abuse associated with ketamine treatment of mood disorders in patients with no comorbid substance use disorders (21).

Another risk factor that is frequently discussed in terms of ketamine treatment is the potential for transient hypertensive episodes. One of the advantages of ketamine as an anesthetic is that, unlike most anesthetics, it does not depress respiration; this makes it an ideal anesthetic for battlefields and other contexts where close monitoring of patients may be difficult. Conversely, ketamine's propensity to raise blood pressure creates risks for individuals prone to hypertension; while hypertension is not necessarily a contraindication for ketamine treatment, it is a frequent comorbid condition that requires appropriate antihypertensive treatment (20). "*Intravenous ketamine for depression: a clinical discussion reconsidering best practices in acute hypertension management*" by Yip et al. offers best practice guidelines for the management of hypertension, which in rare cases may result from ketamine infusions and even less frequently with intranasal esketamine treatment (20, 22).

The case report "*Ketamine as therapeutic option in TRD in minors*" by Skala et al. portrays a 17-year-old student treated with intranasal ketamine at the recommended dose of 28 mg designed to minimize psychoactive effects. After multiple sessions, treatment was discontinued early due to insignificant improvement in assessments of functioning and depression. Some percentage of the treated individuals do not respond to ketamine, and including reports of these in the literature is valuable for understanding how such cases present and progress, providing insights for further treatment optimizations.

Finally, an important dimension of ongoing research into the effects of ketamine is the testing of similar protocols on different populations. A series of six intravenous infusions of subanesthetic ketamine showed no important differences in the antianhedonic effect on male vs. female participants or individuals with melancholic vs. non-melancholic depression, in two respective articles by Zheng et al.(a) and Zheng et al.(b): "*Gender differences in the antianhedonic effects of repeated ketamine infusions in patients with depression*" and "*A comparison of the antianhedonic effects of repeated ketamine infusions in melancholic and non-melancholic depression*".

To date, much of the research on ketamine has focused on the efficacy of one or more series of ketamine only treatments for depression, with doses designed to minimize alterations of mental state. These Articles represent research that engages with a number of additional promising dimensions of ketamine therapy. We offer these in hopes that this will spur further interest, richer dialogue, and a wider range of meticulous studies.

Author contributions

GH conceptualized and wrote the first draft of the manuscript. S-AM and LB contributed to the manuscript revision and read and approved the submitted version. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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1 This treatment approach is in tension with recommendations that suggest close medical monitoring by psychiatrists responsible for confirming indications for the ketamine antidepressant treatment to avoid potentially inappropriate or not indicated administrations (20).

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Case report: Effectiveness of brexpiprazole and esketamine/ketamine combination: A novel therapeutic strategy in five cases of treatment-resistant depression

Lai Fong Chan[1†], Luke Sy-Cherng Woon[1†], Nuur Asyikin Mohd Shukor[2], Choon Leng Eu[2], Nurazah Ismail[3], Song Jie Chin[1], Nik Ruzyanei Nik Jaafar[1*‡] and Azlin Baharudin[1‡]

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A significant proportion of patients with treatment-resistant depression do not attain functional recovery despite administration of multiple steps of pharmacotherapeutic strategies. This highlights the elusiveness of meeting unmet needs in existing pharmacotherapies for treatment-resistant depression. There is accumulating evidence that antidepressant agents involving the glutamatergic system such as brexpiprazole and esketamine/ketamine have more rapid onset of action and potentially improved effectiveness as an augmentation therapy in treatment-resistant depression. This case series aimed to report five complex cases of unipolar and bipolar treatment-resistant depression where conventional treatment strategies were inadequate in managing high risk suicidal behavior and achieving functional recovery. We discussed further the possible synergistic mechanisms of the novel combination strategy of brexpiprazole and esketamine/ketamine, clinical and patient factors that influenced treatment response, challenges with this combination strategy and implications for future practice and research.

KEYWORDS

treatment-resistant depression, effectiveness, ketamine, brexpiprazole, esketamine

Introduction

Unipolar treatment-resistant depression (TRD) is most commonly defined as non-response to at least two adequate courses of sequential antidepressant treatment in a single major depressive episode (1). Bipolar TRD is considered more treatment-refractory and has been defined as failure of sustained symptomatic remission for

8 consecutive weeks after 2 different treatment trials of adequate therapeutic doses, with at least two recommended monotherapy treatments; or at least 1 monotherapy treatment and another combination treatment (2). There is an urgent need for improving the evidence base with regards to our current limited pharmacological options for unipolar and bipolar TRD in view of this population's significant risk of morbidity and mortality, including suicidal behavior (3).

Ketamine, an anesthetic drug; and brexpiprazole, an atypical antipsychotic, are novel pharmacological agents with potential advantages in improving cognition and functionality in treatment-resistant depression. A systematic review by the Canadian Network for Mood and Anxiety Treatments (CANMAT) Task Force found Level 1 evidence for single dose intravenous ketamine as a third-line agent for unipolar TRD. The evidence for multiple IV ketamine doses in unipolar TRD is limited to Level 3 (4). The U.S. Food and Drug Administration (FDA) has approved esketamine, the S-enantiomer of ketamine, as an add-on intranasal therapy to an oral antidepressant in treatment-resistant unipolar depression patients and major depressive disorder (MDD) with suicidal ideation or behavior (5, 6). In terms of treatment-resistant bipolar depression, a handful of studies supported the efficacy of single infusion ketamine, although the meta-analytic evidence for longer term ketamine treatment is mixed (7). Brexpiprazole is FDA-approved for adjunctive treatment of major depressive disorder, with a number needed to treat (NNT) of 12 and a number needed to harm (NNH) of 53 according to a systematic review by (6, 8). Currently, there is a paucity of real-world data on the effectiveness of brexpiprazole in treatment-resistant unipolar and bipolar depression beyond clinical trials (9). To the best of our knowledge, there are no published pre-clinical or clinical studies of brexpiprazole and ketamine/esketamine combination for the treatment of depression. The rationale of this combination is aligned with the Window of Antidepressant Response Paradigm (WARP) (10). Malhi et al. proposed the WARP concept whereby esketamine, as a glutamatergic rapid-acting antidepressant, could potentially be utilized within the immediate-response window in combination with brexpiprazole, a serotonin-dopamine modulator with partial D_2 receptor agonism within the fast-response window as an adjunctive strategy to overcome the delay in conventional selective serotonin reuptake inhibitor (SSRI) or serotonin and norepinephrine reuptake inhibitors (SNRI) antidepressant response (10).

The objective of our case series is to describe the efficacy, tolerability and functional outcome of a novel pharmacological approach involving brexpiprazole as adjunctive treatment to either maintenance intravenous ketamine or intranasal esketamine; in addition to standard biological and psychosocial interventions, in three unipolar and two bipolar TRD patients at an urban public university hospital in Malaysia, an upper middle-income country in South-East-Asia.

Case report 1

Patient 1 is a Malay woman in her 20's. Previous diagnoses included major depressive disorder, complex post-traumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD) and borderline personality disorder (BPD). She experienced unremitting depression with chronic thoughts of self-harm and suicide since 2017. She had been unemployed since she was unable to complete her health-care professional internship in 2020. Systematic physical examination revealed no significant finding. Comprehensive review to rule out potential factors of pseudo treatment resistance depression including presence of substance use disorder and treatment non-adherence were performed. Previous trials of selective serotonin reuptake inhibitors (SSRI) intensified her suicidal ideation and aripiprazole augmentation were unsuccessful. She experienced a severe relapse of a major depressive episode in 2020 with multiple self-harm attempts precipitated by triggers that evoked memories of previous childhood trauma with commanding auditory hallucinations to end her life. Electroconvulsive therapy (ECT) was initiated in view of the high risk of suicide. Her diagnosis was revised to treatment-resistant bipolar type II depression when hypomanic episodes with irritability, reduced need of sleep, increased energy, and increased goal directed activities emerged in December 2020. Trauma-focused psychotherapy was also commenced. She was hospitalized for a suicide attempt during a subsequent severe depressive relapse in March 2021. Brexpiprazole was added to sodium valproate and lamotrigine to target severe depressive symptoms with mood congruent psychosis in the context of bipolar disorder in addition to maintenance ECT. Her mood and obsessive symptoms reduced, but she experienced distressing cognitive impairment on maintenance ECT. In July 2021, ECT was stopped, and her treatment regime was optimized to include intravenous ketamine (0.5 mg/kg, 90-min infusion, weekly to 2-weekly), brexpiprazole 4 mg ON, sodium valproate prolonged release tablet 2 g ON, lamotrigine 200 mg ON, quetiapine 300 mg ON and clonazepam 2 mg PRN, in combination with psychotherapy. Her depression level reduced from very severe to moderate (Self-report Quick Inventory of Depressive Symptomatology, QIDS SR16 scores of 22 to 13) within 5 months (Figure 1). Currently, her mood has significantly stabilized with less debilitating obsessive and PTSD symptoms, as well as a marked reduction in the intensity and frequency of suicidal thoughts. She is also pursuing her interest in baking and realizing her entrepreneurial potential with supported employment.

Case report 2

Patient 2 is a health-science graduate in his 20s. He experienced recurrent brief hypomanic symptoms during his

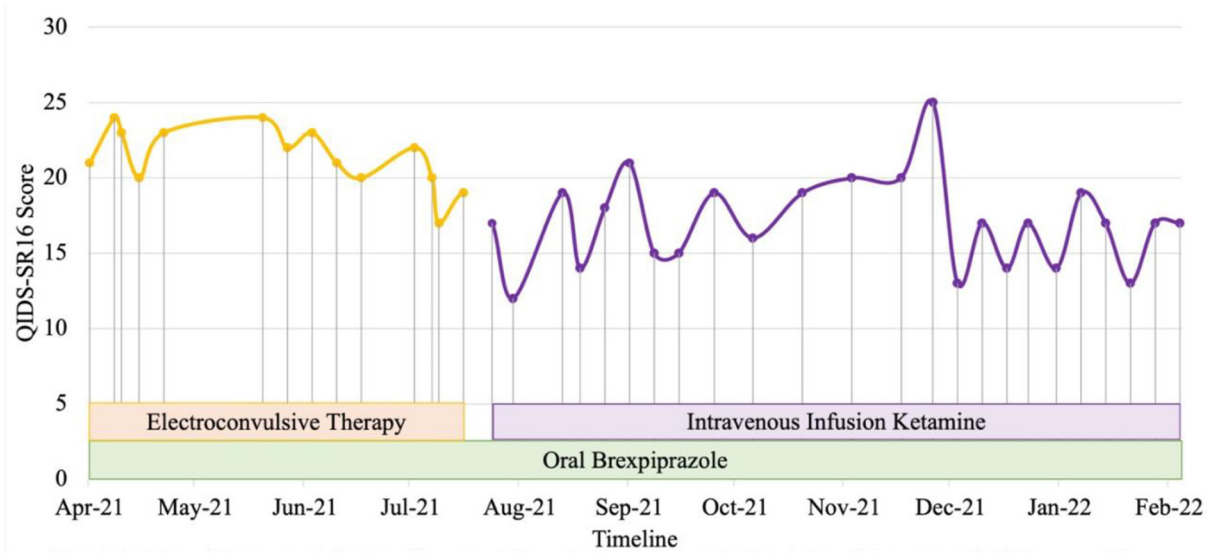

FIGURE 1
Case 1 timeline for longitudinal course of treatment response. Patient 1 is a Malay woman in her 20s with a current diagnosis of treatment-resistant bipolar type II depression with lifetime co-morbid diagnoses of complex post-traumatic stress disorder, obsessive-compulsive disorder and borderline personality disorder. Brexpiprazole was initiated at the dose of 0.5 mg and titrated to a maximum of 4mg. Intravenous infusion ketamine 0.5 mg/kg is initiated at July 2021 to replace ECT due to cognitive impairment as a side effect of ECT. Co-medications include lamotrigine 200 mg, sodium valproate 2 g, quetiapine 300 mg, and clonazepam 2 mg PRN. Currently, she has lesser obsessive, PTSD and depressive symptoms, including marked reduction in intensity and frequency of suicidal thoughts with improvement in her functionality.

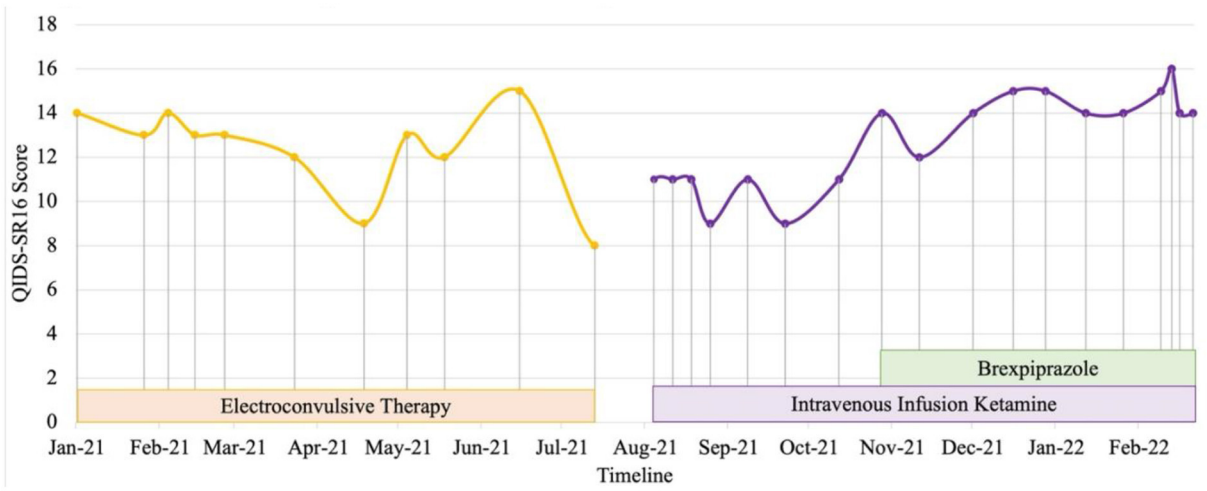

FIGURE 2
Case 2 timeline for longitudinal course of treatment response. Patient 2 is a male in his 20's with a current diagnosis of treatment-resistant bipolar type II depression. Brexpiprazole was initiated at the dose of 0.5 mg and titrated to a maximum of 3 mg in combination with intravenous infusion ketamine 0.5 mg/kg. Co-medications include lamotrigine 300 mg, quetiapine 800mg, vortioxetine 20 mg and clonazepam 0.5 mg with cognitive behavioral therapy and family perticipation in online family support group. Currently, despite fluctuations in mood, he expressed improved levels of satisfaction and self-efficacy in terms of occupational functioning.

undergraduate studies such as feeling energetic, having reduced need of sleep, and spending spree which lasted for about 2 days. He experienced a severe major depression (persistent low mood, anhedonia, hopelessness, worthlessness, social withdrawal and suicidal thoughts) since 2018 and was unable to proceed with internship upon graduation. He was referred to our center in 2020 for inpatient care after an aborted suicide attempt with a lethal method. Systematic physical

examination revealed no significant finding. He was diagnosed with bipolar type II depression during the admission. Previous treatment with escitalopram was unsuccessful. Vortioxetine, quetiapine and lamotrigine were titrated to optimize mood stability as monotherapy with either agent was inadequate to control depressive and hypomanic symptoms. Comprehensive review to rule out potential factors of pseudo treatment resistance depression including presence of substance use disorder, personality disorders and treatment non-adherence were performed. After a serious suicide attempt 4 months later, ECT was commenced. His mood stabilized and suicidal behavior reduced with the addition of maintenance ECT and cognitive behavior therapy (CBT). After 9 months of the above treatment, he was concerned about the impact of ECT cognitive side-effects on his occupational functioning and future career prospects. In view of the significant risk of relapse and suicide, he gave informed consent to switch from maintenance ECT to off-label intravenous ketamine. His depression severity reduced from moderate to mild (QIDS SR16 scores from 11 to 9) after titration of intravenous ketamine (0.5 mg/kg, 90-min infusion) to weekly doses for 6 weeks (Figure 2). He experienced a depressive relapse precipitated by job insecurity and high-expressed emotion in his family. Despite fluctuations in mood, he expressed improved levels of satisfaction and self-efficacy in terms of occupational functioning after adding brexpiprazole 0.5 mg ON and subsequently titrated to maximum of 3 mg ON to vortioxetine 20 mg ON, quetiapine 800 mg ON, lamotrigine 300 mg ON, clonazepam 0.5 mg PRN, and intravenous ketamine twice a month. CBT is ongoing and his family has started participating in an online family support group.

Case report 3

Patient 3 is a single healthcare worker in her 30's with a diagnosis of TRD. She presented to our center in May 2019 with worsening depressive symptoms for 4 months and intense suicidal ideation perpetuated by increased interpersonal conflicts. She had low mood, poor sleep, hopelessness, worthlessness, loss of energy and appetite, and difficulty concentrating for 4 years. She experienced multiple stressors including a burglary, workplace and family interpersonal problems, and bilateral normal tension glaucoma undergone bilateral trabeculectomy and high myopia. There were no manic, hypomanic, psychotic symptoms nor history of substance abuse. Systematic physical examination revealed no significant finding. Since 2016, her significant depressive symptoms persisted despite adequate trials of agomelatine, mirtazapine, fluvoxamine, vortioxetine, aripiprazole, quetiapine, in addition to a brief psychodynamic psychotherapy and hypnotherapy. Comprehensive review to rule out potential factors of pseudo treatment resistance depression including presence of substance use disorder, personality disorders and treatment non-adherence were performed. In 2019, she received acute and maintenance ECT in our inpatient center which significantly reduced her suicidal behavior i.e., resolution of suicidal plans and attempts. However, her depression did not fully remit, compounded by occupational challenges and interpersonal relationship issues. Hence, she was started on intravenous ketamine (0.5 mg/kg, 90-min infusion) in March 2020. The most notable transient side effects during the procedure were dizziness, dry mouth, and dry eyes. She was then switched to maintenance esketamine 84 mg fortnightly when it became available in December 2020. She experienced new side effects, i.e., mild burning sensation in the throat and double vision occurring about 10 min post nasal esketamine administration, which resolved spontaneously within 50 min of observation. However, the effect was short-lived as the negative cognition reemerged by the end of 2nd week post-esketamine administration. There was an overall reduction of depressive symptoms, including suicidal and ruminating thoughts after initiation of ketamine, albeit with fluctuations of these symptoms, perpetuated by psychosocial stressors over the longitudinal course of treatment (Figure 3). Brexpiprazole was subsequently added to address this issue and titrated from 0.5 mg to 3.5 mg, after which she reported more sustainable improvement in her energy, personal care, interpersonal and occupational functioning whereby she was able to establish and sustain her own business.

Case report 4

Patient 4 is in her mid-forties with congenital glaucoma and complete vision loss since she was 6 years old. She developed significant depressive symptoms in her mid-thirties with persistent low mood, anhedonia, poor concentration and excessive guilt. Premorbidly, she was highly independent and functioning very well-occupationally. She sought treatment at our center in February 2019 when she experienced frequent and intense suicidal ideation. Systematic physical examination revealed no significant finding. Previous adequate trials of mirtazapine, agomelatine and vortioxetine were not adequately effective. Comprehensive review to rule out potential factors of pseudo treatment resistance depression including presence of substance use disorder, personality disorders and treatment non-adherence were performed. She received 15 bilateral ECT sessions, which were ineffective and caused significant cognitive impairment. Therefore, intravenous ketamine (0.5 mg/kg, 90-min infusion) was initiated in January 2020 which significantly reduced suicidal ideation intensity. Intravenous ketamine was switched to esketamine in December 2020 when the latter was available. Esketamine was initiated at 56 mg 2-weekly which continued to reduce her suicidal thoughts. She experienced tolerable side-effects such as transient dissociation and headache. Her treatment regime also included mirtazapine 30 mg and agomelatine 50 mg. In addition, aripiprazole 2.5 mg was switched to brexpiprazole 1 mg OD in March 2021 due

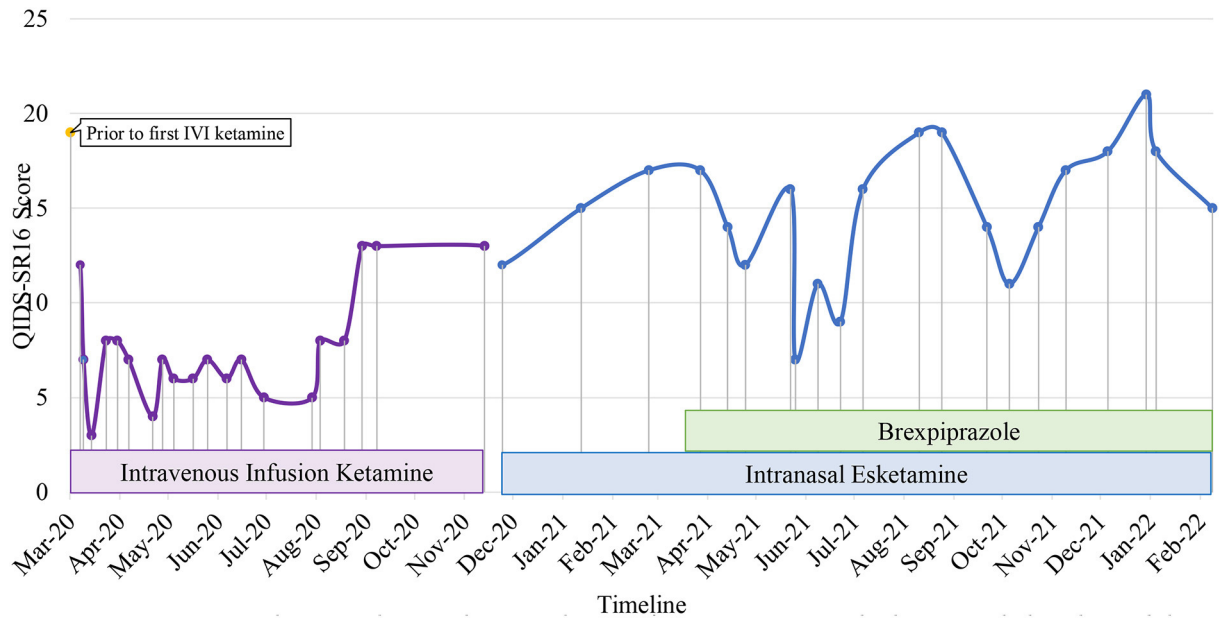

FIGURE 3
Case 3 timeline for longitudinal course of treatment response. Patient 3 is a single woman in her 30s' with a current diagnosis of treatment-resistant unipolar depression with physical co-morbidity of bilateral normal tension glaucoma with high myopia. Brexpiprazole was initiated at the dose of 0.5 mg and titrated to a maximum of 3.5 mg in combine with intranasal esketamine 84mg fortnightly. Co-medications include zolpidem 10 mg, mirtazapine 45 mg, quetiapine 800 mg, vortioxetine 20 mg, and clonazepam 6 mg. There was an overall reduction of depressive symptoms after initiation of ketamine, albeit with fluctuations of these symptoms, perpetuated by psychosocial stressors over the longitudinal course of treatment. She reported more sustainable improvement in her energy, personal care, interpersonal and occupational functioning after brexpiprazole was added to address this issue.

to intolerable side effects such as lethargy and akathisia. Brexpiprazole improved her anxiety symptoms though it could not be further optimized due to lethargy at higher doses. Esketamine was further optimized to 84 mg every 2-weekly in June 2021. Her mood stability and functionality improved with the combination of brexpiprazole and esketamine in her pharmacological regime and Acceptance and Commitment Therapy (ACT)-based psychotherapy (Figure 4).

Case report 5

Patient 5 is a Malaysian Chinese retired educator in her late 50's with a 30-year history of major depressive disorder with anxious distress and recurrent suicidal ideation. Systematic physical examination revealed no significant finding. Comprehensive review to rule out potential factors of pseudo treatment resistance depression including presence of substance use disorder, personality disorders and treatment non-adherence were performed. She was diagnosed with treatment-resistant depression since 2001. Cognitive behavior therapy, family psychoeducation and a total of 131 ECT administrations (79 bilateral and 52 unilateral) were given from 2001 to 2012. Her depressive symptoms partially remitted but she experienced residual cognitive deficits post-ECT which severely impacted her functioning. A previous case series documented her symptomatic remission and significant functional improvement of TRD on intravenous ketamine treatment from 2012-2018 with minimal and transient side-effects (sedation, nausea and dizziness) that resolved within a week (11). Monthly outpatient maintenance intravenous ketamine was withheld in July 2020 due to concerns about contracting COVID-19 from monthly hospital visits. Her depression relapsed (QIDS SR16 score = 12, moderate severity) precipitated by disability due to a sacral fracture and high-expressed emotion in her family. After resuming monthly maintenance ketamine in December to February 2021, she achieved remission (QIDS SR16 score = 8). Maintenance intravenous ketamine was temporarily put on hold from February to May 2021 due to challenging intravenous access which increased her level of distress pre-ketamine infusion. After receiving one maintenance dose of intravenous ketamine in May 2021, the patient was not keen to continue coming to the hospital for treatment during the period of a spike of COVID-19 cases (12). In September 2021 (QIDS SR16 score = 20, severe depression), she was switched to intranasal esketamine 28 mg monthly based on her preferred frequency of hospital visits. Her depressive symptoms and functioning improved after 3 months (QIDS SR16 score = 9, mild depression) though dose optimisation had to be gradually done in view of transient dizziness post-esketamine. In December 2021, Brexpiprazole 0.5 mg on was added to target residual depressive symptoms such as insomnia but was stopped after two doses due to

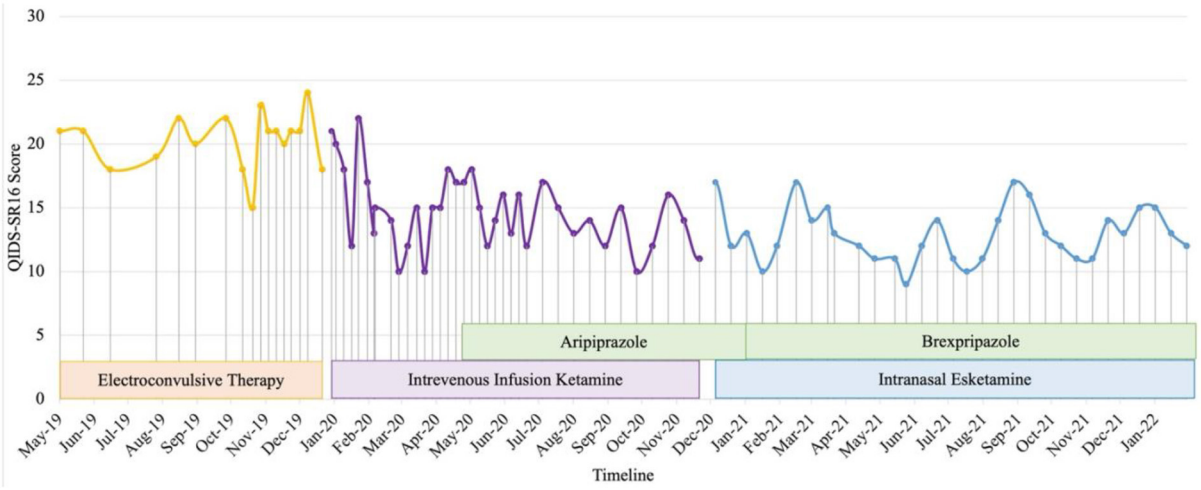

FIGURE 4
Case 4 timeline for longitudinal course of treatment response. Patient 4 is a woman in her 40's with a current diagnosis of treatment-resistant unipolar depression with physical co-morbidity of congenital glaucoma and bilateral complete vision loss. Brexpiprazole was initiated at the dose of 0.5 mg and titrated to a maximum of 1mg in combine with intranasal esketamine 84 mg fortnightly. Co-medications include mirtazapine 30 mg, agomelatine 50 mg. Her mood stability and functionality improved with the combination of brexpiprazole and esketamine in her pharmacological regime and Acceptance and Commitment Therapy (ACT)-based psychotherapy.

intolerable nausea and dizziness. Since February 2022, she has been tolerating esketamine 56 mg od well with no adverse events (QIDS SR_{16} score = 9, mild depression) in combination with agomelatine 50 mg ON, quetiapine extended release 800 mg ON, mirtazapine 45 mg ON, lorazepam 1 mg BD, zolpidem 10 mg ON, and clonazepam 2 mg PRN (Figure 5).

Discussion

Based on our case series, the majority (two unipolar and twobipolar) of TRD patients demonstrated significant improvements in depressive symptoms including suicidal behavior, cognition and functionality with a combination of brexpiprazole and maintenance intravenous ketamine or intranasal esketamine as part of their treatment regime. One patient with unipolar TRD discontinued brexpiprazole due to intolerable dizziness. We employed an infusion regime of 0.5 mg/kg over a longer period of 90 min in our LMIC setting instead of the conventional 40 min as a pragmatic cost effective and less labor-intensive approach without the requirement of full anesthesia monitoring for serial ketamine infusions based on study by Rasmussen et al. (13). All five patients gave written informed consent for publication of the respective case reports.

While brexpiprazole is approved by the FDA as an augmenting agent for MDD patients with 'inadequate response' to standard antidepressant treatments, the evidence-base for the most severe cases of bipolar TRD is currently lacking. An open-label pilot study of brexiprazole (4 mg maximum dose) for bipolar depression by Brown et al. showed improvements in depressive symptoms and quality of life (14). Evidence suggests that through N-methyl-D-aspartate blockade, esketamine upsurges glutamate release leading to increases in α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors stimulation and a rise in neurotrophic signaling that restore synaptic function in brain areas involved with the regulation of mood and emotional behavior. Brexpiprazole, a partial dopamine agonist, also potentiates neurotransmission via the AMPA receptors. However, in contrast to esketamine/ketamine; brexpiprazole also acts on the monoamine pathway; with a faster antidepressant effect than SSRI alone. A single administration of the combination of fluoxetine and brexpiprazole significantly increased the D-serine/L-serine ratio in the frontal cortex, just as a single dose of racemic ketamine (15). Another noteworthy clinical observation of this combination is the apparent cognitive benefits that improve functionality. Pro-cognitive properties of ketamine and brexpiprazole as individual pharmacological agents have been demonstrated by previous preclinical and clinical studies. Cognitive deficits in mice induced by phencyclidine was mitigated by ketamine via activation of brain-derived neurotrophic factor-tropomycin receptor kinase B (BDNF-TrkB) signaling, as well as brexpiprazole via serotonin 1A ($5\text{-}HT_{1A}$) receptors (16, 17). A review by Gill et al. found that subanaesthetic doses (0.5 mg/kg) of intravenous ketamine significantly improved working memory, learning memory, speed of processing and verbal learning memory in TRD patients (18). Improvements in general and cognitive functioning of patients with major depressive disorder treated with adjunctive brexpiprazole was shown in an open-label study by Fava et al. (19). In addition, there is increasing evidence of

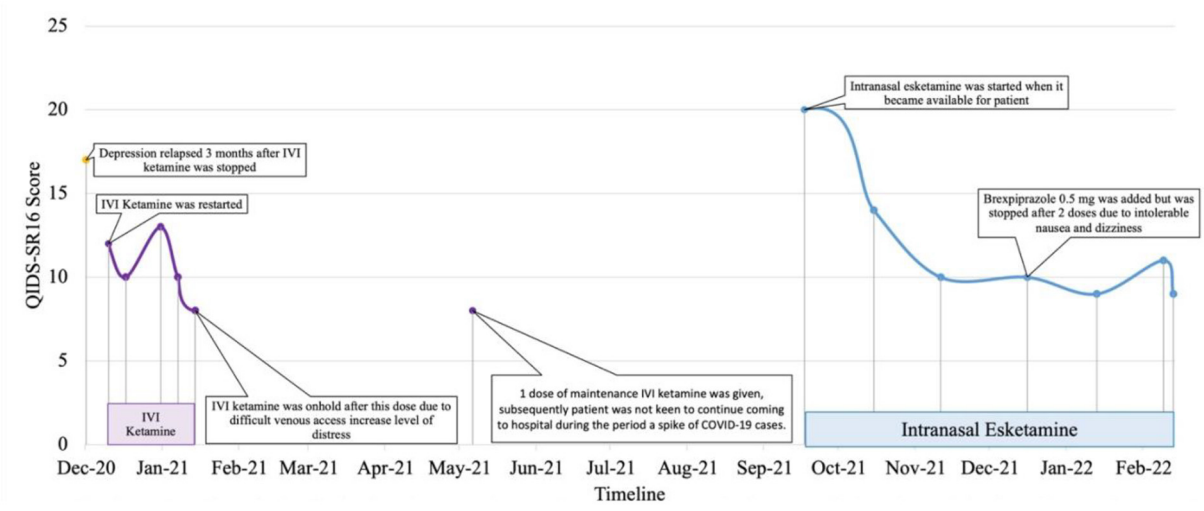

FIGURE 5
Case 5 timeline for longitudinal course of treatment response. Patient 5 is a Chinese female in her late 50's with a current diagnosis of treatment-resistant unipolar depression with physical co-morbidity of sacral fracture. She was on IVI ketamine since 2012 with symptomatic remission as reported in another published case series. IVI ketamine was witheld on July 2020 in view of patient's concern of contacting with COVID-19 cases during hospital visit. Her depression relapsed on Dec 2020 where IVI ketamine was restarted and subsequently reduction of QIDS-SR16 score. Co-medications include esketamine 56mg fortnightly, agomelatine 50 mg, quetiapine 800 mg, mirtazapine 45 mg, lorazepam 1 mg BD, zolpidem 10 mg, and clonazepam 2 mg PRN. Her depressive symptoms and functioning improved after 3 months on intranasal esketamine.

the efficacy of ketamine as a rapid-acting anti-suicidal agent. Patients at very high risk of suicide, particular with bipolar disorder, significantly achieved remission of suicidal ideation with acute intravenous ketamine (20). Currently, there is very limited published data on the role of brexpiprazole as an anti-suicidal medication (21). Future systematic studies are warranted to investigate the potential synergism of ketamine and brexpiprazole as acute and long-term interventions in preventing suicide.

The combination of esketamine/ketamine and brexpiprazole may pose some challenges in view of overlapping side effects. Common adverse events associated with esketamine/ketamine for TRD include vestibular effects (e.g., dizziness, nausea, and vomiting), sympathomimetic symptoms (e.g., tachycardia, hypertension), and psychomimetic symptoms (e.g., hallucinations, dissociative symptom) (Table 1) (22). Based on pharmacovigilance data from the the FDA Adverse Event Reporting System (FAERS), Gastaldon et al. (2021) have raised concerns over esketamine-related serious adverse events such as suicidal ideation and suicide deaths in which the former remained significant when compared to venlafaxine (23). These authors also reported that serious adverse events were more common in cases of esketamine co-medication with antipsychotics, mood stabilizers, benzodiazepines. Other authors have argued that the causal role of esketamine in increasing suicidal risk is still uncertain (24). Nevertheless, this phenomenon underscores the urgency of further research and continued vigilant monitoring of suicidal behavior in patients on esketamine, particularly when combined with other medications (25). Findings from systematic review and meta-analysis suggest that intravenous racemic ketamine was superior in terms of efficacy and treatment retention rates compared to esketamine for unipolar and bipolar treatment resistant depression (26). These authors highlighted the need for future research, including substantively more head-to-head trials of intravenous racemic ketamine vs. esketamine for unipolar and bipolar depression to further elucidate the underlying reasons and mechanisms of such differences in efficacy and acceptability. The evidence is still mixed on whether esketamine has a better tolerability profile compared to intravenous racemic ketamine, compounded by study heterogeneity which complicates arriving at definitive conclusions about the effectiveness of intravenous vs. intranasal ketamine (5, 26, 27). More recently, arketamine, another distinct ketamine enantiomer, has shown some initial potential in animal models and Leal et al's open-label pilot study as a rapid-onset intravenous antidepressant, possibly with a higher response and remission rate and more sustained effects with a better tolerability profile than intravenous racemic ketamine and intranasal esketamine (28). However, these findings need to be confirmed with larger systematic and controlled studies in the future. Postulated mechanisms of action from pre-clinical studies hypothesize that arketamine's antidepressant effects occur via the activation of α-amino-3-hydroxy-5-methyl-4- isoxazolepropionic acid (AMPA) receptors as well as subsequent activation of brain-derived

TABLE 1 The profile of ketamine/esketamine and brexpiprazole.

	Ketamine	Esketamine	Brexpiprazole
Molecular composition/ possible mechanism of action	A racemic mixture of two enantiomers, R-ketamine and S-ketamine/ NMDA receptor antagonist	A purified S-enantiomer/ NMDA receptor antagonist	Serotonin-dopamine activity modulator; dopamine D2 and serotonin 5-HT1A partial agonist; also potentiates neurotransmission via the AMPA-receptors
Route of administration	Intravenous infusion	Nasal, using metered dose spray	Oral
Clinical indications	An anesthetic that has been used off-label for treatment-resistant unipolar and bipolar depression and suicidal behavior	FDA-approved for treatment-resistant unipolar depression and major depressive disorder with suicidal ideation and behavior	FDA-approved for augmentation for inadequate response in treatment of depression
Adverse effects	Vestibular, sympathomimetic & psychotomimetic		Akathisia, somnolence, weight gain, dizziness

neurotrophic factor (BDNF)- tropomyosin receptor kinase B (TrkB) signaling effect, independent of NMDA receptor antagonism as the basis of racemic ketamine and esketamine. According to a meta-analysis by Kishi et al., akathisia, somnolence and weight gain were significant side effects of brexpiprazole (29). In addition, dizziness is another potential side effect although its incidence was not significantly higher compared to placebo. However, adverse event susceptibility varies among individuals and the risk of multiple drug interaction exacerbating overlapping side effects should be considered. This phenomenon is illustrated in case report 5, whereby transient dizziness due to esketamine and ketamine seemed to be exacerbated to an intolerable level with the addition of brexpiprazole which had to be discontinued. Current expert consensus guidelines recommend vigilant surveillance of cognitive changes, vital signs, genitourinary toxicity, hepatic toxicity, progression of suicidal behavior, as well as the risk of abuse liability in patients on maintenance esketamine/ketamine treatment (5, 30). The anecdotal findings from our retrospective case series are limited by a small sample size. Future systematic controlled studies are required to established the effectiveness of the combination of brexpiprazole with ketamine/esketamine.

Sustainable access to esketamine/intravenous ketamine and brexpiprazole is another major challenge. Upscaling of maintenance intravenous ketamine treatment for TRD patients locally is hampered by the labor-intensiveness of service delivery as well as space limitations compounded by the need for adequate physical distancing during the COVID-19 pandemic. In addition, access to non-generic brexpiprazole and esketamine in our case series is based on industry-supported pro-bono compassionate grounds, thus calling into question long-term cost affordability. Future cost benefit analysis of brexpiprazole and esketamine/ketamine combination therapy within healthcare policies is crucial in mitigating the significant economic burden of TRD.

Conclusion

This case-series has highlighted the effectiveness of combining brexpiprazole and maintenance esketamine/intravenous ketamine in the treatment regime for unipolar and bipolar patients with treatment-resistant depression. Effectiveness of this combination appears to be a promising, especially in terms of reducing suicidal behavior and improving cognition as well as functional recovery. Challenges include individual-level sensitivity to specific overlapping adverse events, sustainability in terms of service capacity and cost-effectiveness. Future pragmatic research is required to establish the real-world feasibility of including brexpiprazole and maintenance esketamine/ketamine combination in our therapeutic armamentarium for treatment-resistant depression.

Data availability statement

The original contributions presented in the study are included in the article further inquiries can be directed to the corresponding author.

Ethics statement

Written informed consent was obtained from the individual(s) and/or next of kin for the publication of this case report and any potentially identifiable data included in this article.

Author contributions

NN and LC contributed to conceptualization. LC, LS-CW, NM, CE, NI, and NN wrote the first draft. LC, LS-CW, NM, CE, NI, SC, NN, and AB contributed to the intellectual content, revised, and reviewed the final draft. All authors contributed to the article and approved the submitted version.

Conflict of interest

Brexpiprazole and esketamine were supplied probono to the patients in these case series by Lundbeck and Johnson and Johnson, respectively via patient compassionate programs. The selection and clinical management of patients in this case series were done independently by the respective treating clinicians with no financial compensation from Lundbeck or Johnson & Johnson.

Apart from this case series, LC, LS-CW, CE, NN, and AB have received conference sponsorships, speaker and/or consultancy honoraria from Lundbeck and/or Johnson & Johnson.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Case report: Intranasal esketamine for severe major depressive disorder with psychotic features

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Introduction: About one third of patients with major depressive disorder (MDD) have treatment resistant depression (TRD). The difficulty of treating TRD especially in those with suicidal ideation and psychotic features demands treatments that are fast-acting, safe, and effective. Limited access, lack of viable options, and incomplete characterization of rapid-acting antidepressants has prevented widespread incorporation into treatment of patients with TRD. However, ketamine and its variations have shown promise of being effective treatment options for patients with TRD with psychotic features.

Case description: This 28-year-old patient with TRD with psychotic features received 14 treatments of intranasal esketamine over a 3-month period. This patient initially presented with anhedonia, difficulty sleeping, suicidal thoughts, and auditory hallucinations. The Quick Inventory of Depressive Symptomology (QIDS) was used to assess depression before each session.

Results: After her first two treatment sessions within a week, this patient experienced a reduction in depression from severe to moderate according to the QIDS. Over 14 sessions, she had no significant adverse effects, including no psychotic symptoms during esketamine treatment, and was stabilized to mild depression without suicidal ideations. One year after treatment, she continues to be stable. She has not had auditory hallucinations since the esketamine treatment.

Conclusions: This case report provides an example of a patient with severe TRD with psychotic features that showed significant improvement after treatment with intranasal esketamine. Larger studies are indicated to further elucidate the effectiveness and safety of intranasal esketamine, so it can be more widely used for patients with TRD with psychotic features.

KEYWORDS

esketamine, depression, psychotic, case report, intranasal

Introduction

Over 350 million people in the world suffer from depression (1, 2). Since the COVID-19 pandemic began, there has been an increase in the number of people with depression, with some estimates showing a 27.6% increase per 100,000 (2). About one third of patients with depression have treatment resistant depression (TRD) (1). TRD is

considered to be failure to respond to two antidepressant monotherapies (3). The delayed onset of action of antidepressants leaves patients with TRD at risk for suicidal behavior (4). Finding treatments with shorter onsets of action is essential to better patient care.

Ketamine, an NMDA receptor antagonist, has been shown to have a rapid-acting antidepressant effect that can reduce suicidal thoughts in 1 day (1, 2, 4). The US FDA approved the use of intranasal esketamine for TRD in 2019 (5). Multiple randomized control trials have demonstrated the effectiveness of intravenous ketamine as an antidepressant (3, 6). However, intravenous infusions are not a convenient administration route and can be resource intensive. Alternate administration options have been explored including intranasal ketamine, which has been shown to be a viable alternative (3, 6). Because esketamine, the S-enantiomer of ketamine, is much more potent than ketamine, it can be used at lower doses (1, 4, 5).

The effectiveness and safety of esketamine in the treatment of patient with TRD has not been fully characterized. Due to ketamine's cardiovascular effects including elevations in heart rate and blood pressure, it is important to monitor vital signs during administration (6). Adverse effects, such as dissociative symptoms, have been observed at higher doses (1). It has been previously thought that patients with a primary psychotic disorder or MDD with psychosis should not be started on esketamine due to the potential worsening of the psychotic features. Yet, there has been very limited research into the use of ketamine in TRD patients with psychotic features (7). Some preliminary findings suggests that ketamine treatment for patients with depression with psychotic features is effective and well-tolerated (7). Subcutaneous esketamine treatment for TRD with psychotic features has been found to be safe and effective in small studies (8). However, there has been no research on the use of intranasal esketamine in TRD patients with psychosis. Because ketamine has only been approved for a short period of time, there is still a need to explore how effective and safe it is as a treatment for TRD. There is insufficient data on the effectiveness of ketamine vs. esketamine. In this case report, we discuss a patient with severe MDD with psychotic features that was treated with intranasal esketamine.

Case description

The patient is a 28-year-old African American female with severe MDD with psychotic features and previously diagnosed generalized anxiety disorder (GAD). Her medical history includes essential hypertension and asthma. She has no known family history of mood or psychotic disorders. Several days before her scheduled initiation of esketamine treatment, she presented to the hospital for thoughts about cutting her wrists and cutting her throat with a knife. She was admitted to the crisis center for 3 days.

Before treatment, she had frequent, intrusive thoughts of harming herself and others. She admitted to vivid visual hallucinations of stabbing herself with a knife. Before treatment, she had increasingly frequent episodes of watching herself harm others through her visual hallucinations. The patient admitted auditory hallucinations of being criticized by herself and others. She heard her own voice telling her that she "was not good enough." She heard voices of friends and family telling her the same thing. She also endorsed hearing voices with which she was not familiar. Patient denies previous suicide attempts or a specific plan.

Diagnostic assessment

This patient's symptoms initially included excessive worrying, difficulty sleeping, increased fatigue, and muscle aches. She was diagnosed with anxiety and prescribed Escitalopram. In her mid-twenties, she presented to the emergency department several times for suicidal behavior and the diagnosis of depression was added. Laboratory studies evaluating for endocrine diseases, vitamin deficiencies, and infections were negative for causes of secondary depression. Prior to 2020, she did not receive consistent psychiatric care, thus she was never properly evaluated, diagnosed, or treated. Previous treatment included trials of Desvenlafaxine, Escitalopram, and Nortriptyline without successful reduction in symptoms. In 2020, she presented to the emergency department for hearing voices. Psychotic disorders, such as schizoaffective disorder, and bipolar depression with psychotic features were considered, but her primary symptoms pointed toward a mood disorder. The patient had no manic or hypomanic episodes and her psychotic symptoms occurred during mood episodes. Her symptoms of depressed mood, anhedonia, insomnia, fatigue, and suicidal thoughts in combination with auditory hallucinations best fit a diagnosis of MDD with psychotic features over a primary psychotic disorder.

A range of pharmaceutical and non-pharmaceutical treatment options were considered, including electroconvulsive therapy, transcranial magnetic stimulation, cognitive behavioral therapy (CBT), alternate second-generation antipsychotics, and alternate mood stabilizers. The patient had already tried CBT in combination with a number of antidepressants, antipsychotics, and mood stabilizers without adequate response. Therefore, it was decided that esketamine could be an effective treatment for this patient. Before being started on intranasal esketamine, she was on Bupropion 150 mg, Aripiprazole 10 mg, Trazodone 100 mg, Clonazepam 0.5 mg, and Sertraline 50 mg.

The patient had a total of fourteen treatment sessions with esketamine over a period of 3 months. We followed the FDA labeled treatment protocol in which doses are fixed at 56 mg for induction and 84 mg thereafter. The patient was informed of the benefits and risks of this treatment and agreed to the course.

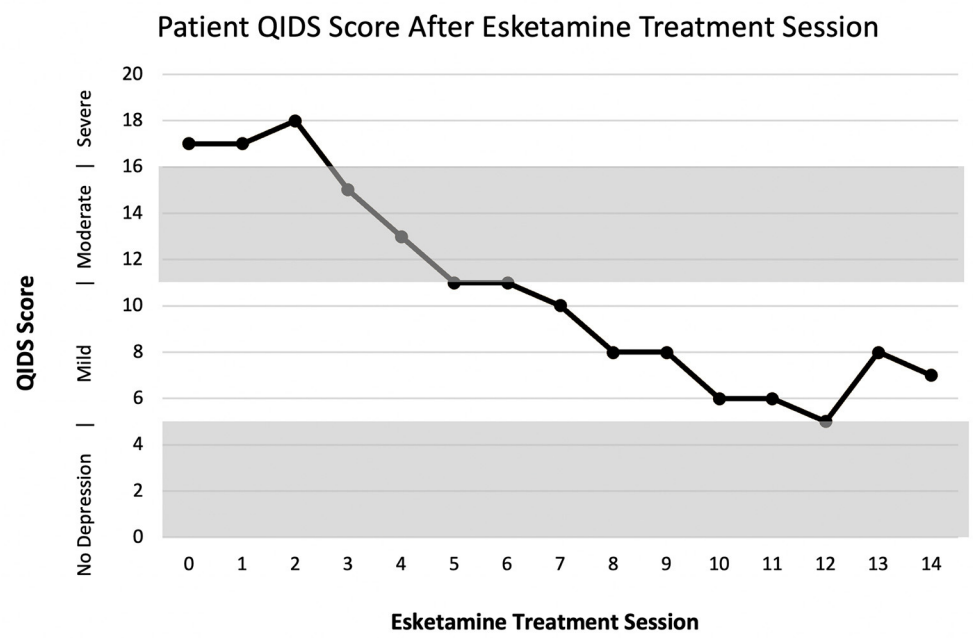

FIGURE 1
Patient QIDS score after treatment with Esketamine.

The first eight sessions occurred biweekly, then four sessions weekly, then two session bimonthly. This regimen was chosen to ensure that the esketamine was safely titrated and tapered. The Quick Inventory of Depressive Symptomology (QIDS) was used to evaluate depressive symptoms. The QIDS was completed at the beginning of each session. The treatment sessions were followed by vital sign monitoring for 2 h and assessment of changes in psychotic symptoms by one-on-one monitoring with a therapist. The patient did not experience any psychotic symptoms during the treatment sessions. She did endorse mild nausea and headache during one of the sessions, but the patient did not experience any significant adverse effects. Even though the patient has comorbid hypertension, she did not experience any significant vital sign changes during the treatment sessions.

Before treatment the patient had a QIDS score of 17, which indicates severe depression (Figure 1). The first two sessions the patient received an esketamine dose of 56 mg without side effects. The subsequent doses were increased to 84 mg and were well-tolerated. One week into treatment at the third session, the patient had a reduction in QIDS to 15, which indicates moderate depression. At her seventh treatment, 3 weeks after initiation of esketamine, she had a further reduction in QIDS to 10, indicating mild depression. The patient continued to show improvement with a decrease in QIDS to 5 at treatment session twelve. There was an increase to eight at treatment session thirteen at which the patient reported difficulty sleeping and having a headache. Nine months after completing treatment, she is stable with a QIDS of eight after discontinuing Bupropion and continuing Aripiprazole 10 mg, Trazodone 100 mg, Clonazepam 0.5 mg, and Sertraline 50 mg.

Since treatment, the patient no longer hears voices. She has had significantly fewer episodes of the visualizations of self-harm. When she has these thoughts, she says that they are not as vivid as before the esketamine treatment and they only occur during periods of stress. She denies any thoughts of harming others.

Discussion

There is growing evidence that ketamine is a viable treatment option for patients with MDD with psychotic features (1, 7, 8). Ketamine treatments can have a quicker onset of action and be used after other treatments have failed. Thus, it is important to understand the safety profile of the various ketamine medications and administration routes to quickly and effective help patients with TRD, especially those at risk for suicidal or homicidal behavior.

We describe a patient with severe TRD with psychotic features that was successfully treated with intranasal esketamine. Before treatment the patient was admitted to the hospital multiple times for suicidal thoughts and auditory hallucinations. She was diagnosed with severe MDD with psychotic features. This patient showed a reduction in depressive symptoms and suicidal thoughts after only two intranasal esketamine sessions. After intranasal esketamine treatment completion,

the patient denied having any auditory hallucinations and has had a significant reduction in the intrusive thoughts of self-harm. The 14 treatment sessions resulted in an overall improvement in her depression to mild according to QIDS. The intranasal esketamine treatment was well-tolerated. It is important to do safety monitoring for patients during intranasal esketamine administration, especially those with psychotic features, and assess for changes in psychotic symptoms. Effectively treating patients with TRD can be difficult, and it is further complicated because there is a reluctance to use ketamine and its derivatives in patients with psychotic symptoms due to adverse effects. However, this case demonstrates that appropriate dosing of esketamine along with careful monitoring can be an effective therapy without eliciting psychotic symptoms during treatment. Further research is warranted to better understand this valuable treatment. For partial recurrence of similar symptoms, we would pursue a shorter series of treatments. For a full recurrence, we would likely plan a repeat course. Should the durability of esketamine not be reasonably sufficient (6 months or more), we would recommend revisiting treatment options. Ultimately our findings support the limited data that suggest that ketamine is a safe and effective treatment for patients with MDD with psychotic features (7, 8).

It is important to do more research to determine the long-term effects of intranasal esketamine treatment, if longer treatment courses would completely reduce depressive symptoms, and if maintenance treatments are required. There are limitations to this study, including the lack of a control. Because this case report only describes one patient, the results here cannot be generalized to the larger population without further investigation. The safety and effectiveness of intranasal esketamine in patients with MDD with psychotic features requires larger studies.

Patient perspective

The patient said that the intranasal esketamine treatment helped her by reducing her suicidal thoughts and allowed her to feel less depressed. She admitted to having nausea and headache during one of the sessions but did not have other side effects. Before treatment, she felt like she had pain in her body but had difficulty finding where the pain was coming from. Sometimes this pain manifested as a headache. After treatment, she says that she can now sit down and think about where the pain is coming from, and it goes away. She says that she is more in tune with how her body is feeling. She has less anhedonia and feels less anxious. She has not had to miss work as often and is able to work more effectively. She is able to spend more time doing things that she enjoys, such as taking care of and playing with her children. She admits that the treatment allowed her to understand reality better. She can now differentiate reality from her hallucinations. Overall, she feels that the treatment was very beneficial and improved her quality of life.

Conclusion

This case report provides an important example of intranasal esketamine being used effectively and safely to treat a patient with severe TRD with psychotic features. The treatment was well-tolerated as the patient did not experience significant side effects. While these results cannot be generalized, this is a promising case of how intranasal esketamine is a rapid-acting treatment that can reduce suicidal thoughts in patients with MDD with psychotic features. There is a need for more in-depth and larger analysis to further investigate the efficacy and safety of intranasal ketamine for patients with MDD with psychotic features.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

MC: conceptualization, data collection and analysis, writing, and editing. KS: data analysis, writing, and editing. NM: conceptualization, editing, and supervision. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Gender differences in the antianhedonic effects of repeated ketamine infusions in patients with depression

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Objectives: Subanaesthetic ketamine (0. 5 mg/kg/40 min intravenous infusion) produces rapid and robust antianhedonic effects in subjects with mood disorders, independent of other depressive symptoms. The objective of this study was to examine potential differences in rate of antianhedonic response to ketamine in males and females, which has not been previously examined.

Methods: A total of 135 patients with depression (68 males, 67 females) who received six intravenous infusions of ketamine (0.5 mg/kg/40 min) during 2 weeks were enrolled. The anhedonia subscale of the Montgomery–Åsberg Depression Rating Scale (MADRS) was utilized to measure anhedonic symptoms. Antianhedonic remission and response were defined as ≥75 and ≥50% improvement of anhedonic symptoms at 24 h after the sixth ketamine infusion (day 13).

Results: Antianhedonic response (50 vs. 47.8%, $p > 0.05$) and remission (26.5 vs. 14.9%, $p > 0.05$) rates did not differ significantly between males and females. A linear mixed model revealed a nonsignificant between-group difference in MADRS anhedonia subscale scores [$F_{(1,132.5)} = 1.1$, $p = 0.30$]. Females reported a significantly larger reduction in anhedonic symptoms than males at the 2-week follow-up ($p < 0.05$).

Conclusion: The rates of antianhedonic response and remission to multiple ketamine infusions for the treatment of depression were similar between males and females. These findings should be verified by future studies, preferably randomized controlled trials (RCTs).

KEYWORDS

ketamine, depression, gender differences, anhedonia, response

Introduction

Major depressive disorder (MDD) is a multisymptom condition that accounts for 40.5% of disability-adjusted life years (DALYs) caused by mental and substance use disorders (1), and females have from a twofold higher risk of MDD than males (2). Numerous studies have observed differences in clinical presentation and comorbidities between females and males with MDD (2, 3). For example, females were likely to have

greater depressive symptom severity, earlier onset of first-episode MDD, and longer duration of depressive episodes than males in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study (3). Alcohol and drug abuse and obsessive compulsive disorder were more common in males than in females (3).

Interestingly, females with MDD were significantly more likely than males to receive antidepressants (2). However, findings on gender differences in outcomes (i.e., response and remission rate, time to response and remission, and adverse drug reactions) of treatment with antidepressants were inconsistent. For example, an increasing number of studies have reported that females are more likely than males to have a positive response to antidepressants, especially selective serotonin reuptake inhibitors (SSRIs) (4–6). Other studies (4, 7) found a significantly greater therapeutic response to the tricyclic antidepressant (TCA) imipramine in males than in females.

The rapid antidepressant response to ketamine (0.5 mg/kg/40 min intravenous infusion), a glutamate N-methyl-D-aspartic acid (NMDA) receptor antagonist for individuals with treatment-resistant depression (TRD), suggests a possible new approach in the treatment of MDD and bipolar depression, which compares favorably to the multiple weeks required for current first-line pharmacotherapies (8–11). Furthermore, both single dose (12–15) and repeated dose (15–17) intravenous ketamine treatments exhibited rapid and sustained antisuicidal and antianhedonic effects. Importantly, Lally et al. found that ketamine's antianhedonic effects are independent of other depressive symptoms (12).

Sex differences in antidepressant response to intravenous ketamine treatment for patients with depression have been investigated, but with inconsistent findings (18). For example, Freeman et al. found no significant difference in antidepressant response to intravenous ketamine infusions in females suffering from TRD, as compared with males with this diagnosis (18). However, a recent systematic review and meta-analysis (437 participants receiving ketamine) found that males appeared to have slightly longer antidepressant responses to a single-dose administration of ketamine than females (19). However, there has been no testing for sex differences in antianhedonic response to ketamine infusions in patients with depression.

In this study we aimed to investigate the impact of sex on the antianhedonic effects of six infusions of 0.5 mg/kg ketamine over two weeks in Chinese patients with MDD or bipolar depression. Based on the findings of Freeman et al.'s study (18), we hypothesized that there is no difference in the efficacy of six ketamine infusions for ameliorating anhedonia levels between females and males with depression.

Methods

This prospective cohort study of consecutive depressed patients with TRD and/or suicidal ideation treated at the Affiliated Brain Hospital of Guangzhou Medical University was initiated in November 2016. The current paper reports on results to date in an ongoing study. This study protocol (Clinical Trials Identifier: ChicCTR-OOC-17012239) was approved by the local ethics committee in accordance with the Declaration of Helsinki. All subjects signed written informed consent.

Patients

The selection of patients has been previously described (20, 21). Briefly, all patients (68 males, 67 females) met the following inclusion criteria: (1) a major depressive episode at the beginning of this study that met the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5) criteria for bipolar disorder or MDD diagnosis without hallucinations or delusions; (2) aged 18 to 65 years, Han Chinese; (3) a baseline Hamilton Depression Rating Scale-17 (HAMD-17) score $\geq$ 17; and (4) inadequate response to two or more sufficient courses of antidepressants and/or a baseline Scale for Suicidal Ideations (SSI)-part I score $\geq$ 2. Patients experiencing TRD and/or suicidal ideation who had a history of alcohol or substance dependence or major medical or neurological diseases (i.e., cancer or infectious disease) were excluded from this study.

Intravenous injections of ketamine

In line with the methodology of previous studies (22, 23), all participants received six intravenous infusions of ketamine during 2 weeks. A detailed description of repeated-dose ketamine infusions in this study has been published in previous studies (20, 21). Briefly, following an overnight fast, all subjects received six intravenous infusions of ketamine hydrochloride administered over a 2-week period (3 times per week) by an intravenous pump. As recommended previously (23), the dose of ketamine was 0.5 mg/kg administered intravenously over a 40-min period. A trained psychiatrist recorded blood pressure, respiratory rate, and pulse frequency for all participants at 10-min intervals during and after each intravenous injection. All participants continued using their previously prescribed psychotropic medications throughout the study.

Anhedonic symptoms

Clinical ratings of anhedonic symptoms were measured by clinical psychiatrists at baseline (day 0), at 4 and 24 h after each infusion of ketamine (0.5 mg/kg over 40 min) and at 2 weeks postinfusion (day 26) using the anhedonia item of the Montgomery–Åsberg Depression Rating Scale (MADRS). The anhedonia item of the MADRS included the following 5 items: inability to feel, concentration difficulties, lassitude, apparent sadness, and reported sadness, which has been utilized

in previous studies and proven useful in evaluating anhedonia symptoms (24–26). A change in the MADRS anhedonia subscale scores from day 0 to 26 was the primary endpoint of this study. The secondary outcomes were as follows: antianhedonic remission rate (defined as a ≥75% reduction in MADRS anhedonia subscale scores at day 13) and response rate (defined as a ≥50% reduction in MADRS anhedonia subscale scores at day 13). For multiple assessments of the MADRS anhedonia subscale scores, the interrater correlation coefficient was > 0.9.

Statistical analysis

SPSS version 24.0 (SPSS Inc., Chicago, United States) was used for all statistical analyses. For descriptive analyses, quantitative and qualitative variables were expressed as the means ± standard deviation (SD) and numbers (percentage) in both the male and female groups. We used Student's *t*-test and/or the Mann–Whitney *U*-test for continuous variables (which included education, age of onset, and duration of illness) and the χ^2 test for categorical variables (which included gender, marital status, family history of psychiatric disorders) to compare the differences in demographic and clinical variables of the male and female groups. The rates of antianhedonic response and remission by gender were analyzed by χ^2 test. Then, we compared the rates of antianhedonic response and remission by gender using odds ratios derived from logistic regression analyses after adjusting for the related variables. We compared the changes in MADRS anhedonia subscale scores from day 0 to 26 between the male and female groups using a linear mixed model after controlling for baseline level. Bonferroni corrections were utilized for multiple tests. A $P < 0.05$ was considered statistically significant.

Results

As shown in Table 1, male patients with depression were more likely to be unmarried ($p = 0.01$, Bonferroni corrected $p < 0.05/7 = 0.007$) and living alone ($p = 0.005$, Bonferroni corrected $p < 0.05/7 = 0.007$) than female patients with depression. Male patients with depression had a higher body mass index (BMI) ($p = 0.003$, Bonferroni corrected $p < 0.05/7 = 0.007$), longer duration of illness ($p = 0.009$, Bonferroni corrected $p < 0.05/7 = 0.007$), younger age of onset ($p = 0.005$, Bonferroni corrected $p < 0.05/7 = 0.007$), more family history of psychiatric disorders ($p = 0.009$, Bonferroni corrected $p < 0.05/7 = 0.007$) and more history of psychiatric hospitalization ($p = 0.01$, Bonferroni corrected $p < 0.05/7 = 0.007$) than female patients with depression. After Bonferroni corrections, living alone, BMI, and younger age of onset remained significant (all $p < 0.007$).

Antianhedonic response rates were 50% (34/68) in male patients with depression and 47.8% (32/67) in female patients with depression. In terms of antianhedonic remission rates, male patients with depression reached 26.5% (18/68), and female patients with depression reached 14.9% (10/67). Antianhedonic response and remission rates did not differ significantly between the two groups (all $p > 0.05$). After controlling for confounders, there were still no significant differences (all $p > 0.05$).

When analyzing the change in anhedonic symptoms over time, a nonsignificant between-group difference was found using a linear mixed model (time: $F_{(13,1684.8)} = 74.6$, $p < 0.001$; group: $F_{(1,132.5)} = 1.1$, $p = 0.30$; group-by-time interaction: $F_{(13,1684.8)} = 1.7$, $p = 0.05$). When compared to baseline, as shown in Figure 1, a significant reduction in anhedonic symptoms was observed from the 1st to 6th injection as well as on day 26 in both groups (all $p < 0.05$). The subgroups did not significantly differ in the improvement of anhedonic symptoms from the 1st to 6th injection (Figure 1). Females were significantly associated with a greater reduction in anhedonic symptoms than males at day 26 ($p < 0.05$) (Figure 1).

Discussion

To the best of our knowledge, this is the first study to determine the gender differences in the antianhedonic effects of ketamine (0.5 mg/kg/40 min intravenous infusion) in female vs. male patients with depression. The main findings of this study included the following: (1) six intravenous infusions of ketamine used in patients with depression are a similarly effective treatment in rapidly ameliorating anhedonia levels for both females and males; and (2) significantly lower MADRS anhedonia subscale scores were found only at the 2-week follow-up in females than in males after receiving six intravenous infusions of ketamine.

Although females appeared to have a significantly higher rate of anhedonia than males (27), no significant gender differences in antianhedonic response and remission rate were found in either females or males after receiving serial ketamine treatments in this study, which was similar to the findings of several studies examining the gender differences in the antidepressant effects of ketamine and esketamine (18, 28). For example, Jones et al. found that the antidepressant effects of esketamine nasal spray are similar in females vs. males suffering from TRD (28). Gender differences in outcomes for the use of other antidepressants such as SSRIs have been investigated, but with mixed findings (4, 5, 7, 29). For example, no gender differences in antidepressant efficacy were reported in some studies (30, 31). However, several studies reported that females responded better than males to SSRIs (5, 29), which was contrary to the findings of previous studies (4, 7). The inconsistent findings across the above studies may be due in part to differences in study design, study drug, and the inclusion criteria of participants.

Although no gender differences in the rates of antianhedonic response and remission to ketamine in patients with depression

TABLE 1 Comparison of demographic and clinical characteristics between male and female patients with depression.

Variables	Male ($n = 68$)		Female ($n = 67$)		Statistics		
	N	%	N	%	χ^2	df	*P*
Married	32	47.1	46	68.7	6.5	1	**0.01**
Employed	26	38.2	26	38.8	0.01	1	0.95
Living alone	10	14.7	1	1.5	7.9	1	**0.005**
No history of psychiatric hospitalization	40	58.8	53	79.1	6.5	1	**0.01**
Having a family history of psychiatric disorders	32	47.1	20	29.9	4.2	1	**0.04**
Antianhedonic responders	34	50.0	32	47.8	0.1	1	0.80
Antianhedonic remitters	18	26.5	10	14.9	2.7	1	0.09
	Mean	SD	Mean	SD	T/Z	df	*P*
Age (years)	33.7	11.0	35.9	12.4	−0.9	—[a]	0.37
Education (years)	12.0	3.1	12.4	3.4	−0.7	133	0.46
BMI (kg/m^2)	23.5	3.6	21.7	3.2	3.1	133	**0.003**
Age of onset (years)	23.3	10.4	29.1	11.9	−2.9	—[a]	**0.004**
Duration of illness (months)	122.4	99.9	81.3	78.3	2.7	133	**0.009**
Baseline HAMD-17 scores	23.0	4.6	24.6	5.5	−1.8	133	0.07
Baseline MADRS scores	32.2	7.4	33.4	8.4	−0.9	133	0.36
Baseline MADRS anhedonia subscale score	20.9	4.9	19.9	4.5	1.1	133	0.25

[a]Mann–Whitney U-test.
Bolded values are $p < 0.05$. BMI, body mass index; HAMD, Hamilton Depression Rating Scale; MADRS, Montgomery–Åsberg Depression Rating Scale.

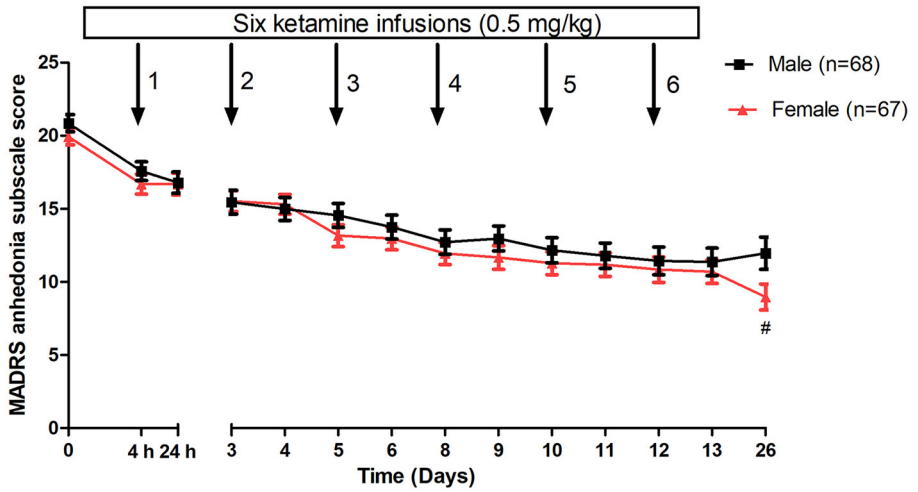

FIGURE 1
Gender differences in changes in anhedonia symptoms in patients with depression following multiple ketamine infusions. All values are presented as mean ± standard error. #A significant difference was found at a given time point between women and men with depression ($p < 0.05$). MADRS, Montgomery-Åsberg Depression Rating Scale.

were found in this study, accumulating studies have found that various factors, including differences in hormone levels, drug metabolism and neuronal circuitry, may account for the disparity in treatment outcomes to other antidepressants between females and males. For example, many studies (32, 33), but not all (34–36), found that both sex hormone therapy and menopausal status were associated with treatment outcomes for antidepressants in females. A recent study found that the antidepressant effects of ketamine were not associated with menopausal status among women (18).

Several limitations are worth considering. First, the sample size of these analyses was relatively small, partly interpreting the negative findings on the rates of antianhedonic response and remission to ketamine in males versus females. Second,

this was an open-label real-world clinical study rather than a randomized controlled trial (RCT). Furthermore, psychotropic medications might potentially affect the antianhedonic effects of ketamine. Third, although several animal studies reported that sex hormones might be related to ketamine treatment response (37, 38), hormone levels such as female oestradiol and female progesterone were not collected in this study. Finally, the current study was a *post hoc* secondary analysis focusing on patients with MDD and bipolar depression.

Conclusion

The rates of antianhedonic response and remission to multiple ketamine infusions for the treatment of depression in males vs. females were similar. These findings should be verified by future RCTs with relatively large sample sizes.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Affiliated Brain Hospital of Guangzhou Medical University. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

Y-PN: study design and critical revision of the manuscript. WZ, Y-LZ, and C-YW: data collection. WZ, X-HY, and L-MG: analysis and interpretation of data. WZ and J-QT: drafting of the manuscript. All the authors: approval of the final version for publication.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Safety, effectiveness and tolerability of sublingual ketamine in depression and anxiety: A retrospective study of off-label, at-home use

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Intravenous and intranasal ketamine have been shown to be effective therapeutic options in patients suffering from treatment-resistant depression (TRD). The use of sublingual (SL), rapid dissolve ketamine tablets (RDT) offers a novel approach for delivery for mental health indications. This study assessed the effectiveness and safety of self-administration of off-label, SL, rapid dissolve ketamine tablets (RDT) at-home for depression and anxiety. Intake scores on the Generalized Anxiety Disorder Screener (GAD-7) and Patient Health Questionnaire (PHQ-9) were compared to scores after treatments of three doses of ketamine RDT, and after six doses of ketamine RDT. After three doses of SL ketamine, 47.6% of patients showed a significant decrease in PHQ-9 scores, and 47.6% of patients showed a significant reduction in GAD-7 scores. Reduction rates were higher in those patients who completed a clinically recommended six doses of RDT ketamine. This study demonstrates that SL ketamine is a novel, safe, and effective treatment for TRD and treatment-resistant anxiety. SL ketamine offers an alternative therapeutic approach to IV ketamine when treating those with TRD.

KEYWORDS

depression, anxiety, ketamine, sublingual, treatment resistant depression (TRD)

Introduction

Major Depressive disorder (MDD) is a common and debilitating psychiatric condition that affects nearly 350 million people globally (1). Approximately 8.1% of Americans aged 20 and over reported depression symptoms in a given 2-weeks period (2). First-line treatment of MDD utilizes antidepressants that prove to be effective in alleviating symptoms in approximately 50% of patients (3). It is estimated 30% of MDD patients fail to respond to at least two antidepressants resulting in treatment-resistant depression (TRD). Suicide risk for TRD patients is higher than that of non-TRD patients diagnosed (4). Range of symptom severity, sequelae, and clinical comorbidity continue to be an area of interest when determining best course of treatment for MDD.

Clinicians have also long recognized that treatment of depression may be unsuccessful if accompanying anxiety disorders are not recognized and addressed (5). Of note, generalized anxiety disorder (GAD) is known to have a high comorbidity rate in patients with TRD (6, 7). Benzodiazepines are commonly utilized in the treatment of depression with anxiety and offer a different pharmacodynamic profile when compared to antidepressants (8), it has been reported that IV ketamine antidepressant effects are interfered with in those concurrently using benzodiazepines (9). The use of benzodiazepines complicates the use of ketamine since anxiety and depression co-occur frequently, and either's symptoms may present as the primary diagnosis. The National Comorbidity Survey demonstrated that an anxiety disorder was comorbid in 58% of the patients diagnosed with MDD at some point in their lifetime (10). These comorbid anxiety symptoms (and potential comorbidity) can complicate the treatment of depression and comorbid anxiety is associated with a greater severity of depressive symptoms and an increased time to recovery. Comorbid anxiety is also associated with a resistance to pharmacological treatment for depression (i.e., TRD), increased incidence of relapse, and suicidal ideation (11). A balanced assessment and approach to TRD also requires an examination of comorbidity issues which may mediate response to treatment.

In recent years there has been increased attention paid to alternative pharmacological interventions for patients with TRD (12). One of these drugs is the anesthetic ketamine (12–16). Ketamine's pharmacodynamic profile is that of a dissociative anesthetic and N-methyl-d-aspartate receptor (NMDA) receptor antagonist (17–19). Berman et al. was the first study to reveal that a single intravenous (IV) dose of ketamine as effective in treating MDD (20). Their randomized, doubl- blind study on a small group of subjects with MDD using IV ketamine hydrochloride (0.5 mg/kg) or saline over 2 days resulted in a significant reduction of depression symptoms as measured by a reduction in Hamilton Depression Rating Scale after ketamine treatment when compared to saline. Reports examining the effectiveness of ketamine in randomized, double-blind controlled trials in the past decade has seen an increase in clinical interest (21, 22). A review of the literature reveals intravenous (IV) infusions of ketamine tend to be the preferred route of administration (23). A systematic review of 288 published studies on IV ketamine's side effects and safety profile reported that acute side-effects were commonly associated with single-dose use ketamine for TRD, though they are generally transient and spontaneously resolve and are relatively understudied (24). A limitation of IV ketamine infusions is that they require a medicalized setting and incur considerable resources and cost. There is sufficient evidence of effectiveness to warrant inclusion as a treatment option with intranasal (IN) esketamine approved by the FDA in 2019 for TRD. Several randomized control trials of racemic ketamine have been published since IN esketamine's approval demonstrating its effectiveness as a tool in treating MDD or TRD (25–36). Studies on transmucosal and sublingual (SL) ketamine provide another alternative to oral ketamine use in the treatment of depression (37–41). Oral ketamine, while less commonly used compared to the gold standard of IV ketamine, has been tested extensively from a pharmacodynamic and pharmacokinetic perspective. Specifically, oral ketamine has been shown to undergo extensive first-pass metabolism and consequently has approximately 10–20% bioavailability, while SL ketamine has a bioavailability of approximately 30% (42, 43), a fact which must be taken into account when designing outpatient oral or SL ketamine treatment regimens. A recently published manuscript has reported similar effectiveness and safety of at-home SL ketamine using a prospective study design (44). The authors found that SL ketamine (three treatments with doses ranging 300–450 mg/kg) in combination with telehealth produced approximately 60% reduction in PHQ-9 and GAD scores at the 4-weeks timepoint compared to baseline scores, roughly comparable with our study. Further work, which we are currently engaged in, will be needed to delineate not only the most effective dosing regimen, but also to identify likely responders based on patient characteristics.

The present study is a retrospective review of patients who had received off-label ketamine using a rapid dissolve tablet for SL delivery treatment at-home for their TRD. The present study examined the effectiveness and safety of the clinical use of at-home, self-administered SL ketamine (300/450 mg) on depression and anxiety symptoms in treatment-resistant patients. This data is related to patients who were treated at home, a model that was created in response to COVID-19 restrictions and using off-label prescription of SL ketamine rapid dissolve tablets, and extends on previous research in that it is the first of its kind examining at-home use of SL ketamine within a clinical context.

Methods

Ethics approval

The protocol for this retrospective study was reviewed by the Wheaton College (Wheaton, IL) Institutional Review Board (Protocol #1828103-1; Exempt Category 4.iii) which follows the ethical principles outlined in 45 CFR 46.104(d). The protocol was approved on 11/15/2021.

Dataset and chart review process

An overview of the dataset analysis and process by which the data was obtained is shown in Figure 1. Data was obtained from a telemedicine practice that offered ketamine treatment that specializes in at-home, SL ketamine use. Between

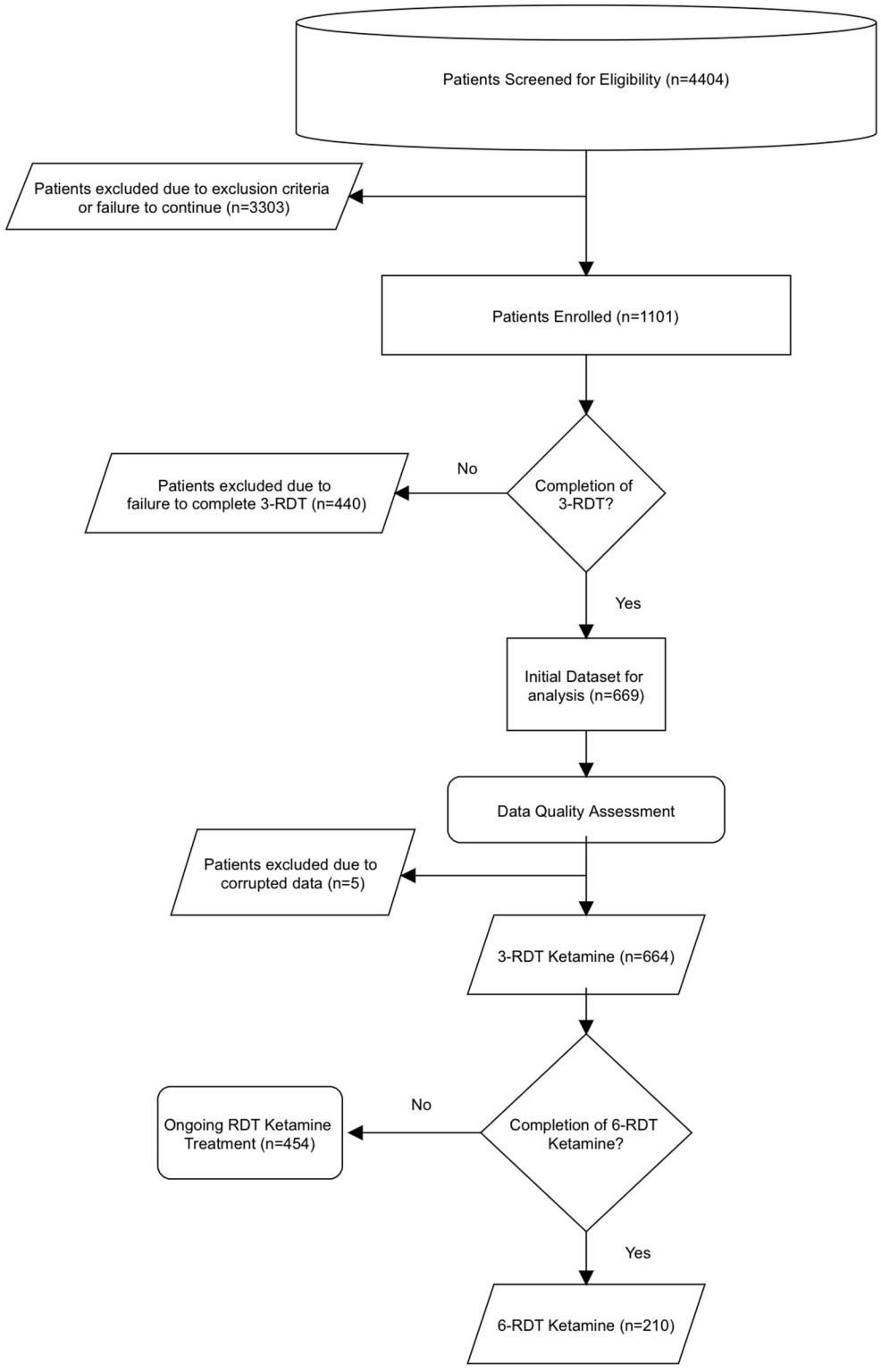

FIGURE 1
Dataset and process flowchart.

12/1/2020-9/30/2021, 1101 individuals experiencing treatment-resistant anxiety or depression sought treatment from the telemedicine practice My Ketamine Home. A new patient registration form including a detailed health history and demographic information was completed, and a telemedicine intake consult was then performed. Relevant medical history was evaluated by Psychiatric Mental Health Nurse Practitioners to diagnose MDD and Generalized anxiety on DSM-5 criteria. This intake also included: (1) any current or presenting medical illnesses or previous psychiatric diagnosis, (2) information about previous failed pharmacological treatments for any depression or anxiety, and (3) other comorbid symptoms. Additionally, respondents were given the Patient Health Questionnaire (PHQ-9) to establish an intake baseline for their depressive symptoms, and the Generalized Anxiety Disorder Screener (GAD-7) to determine baseline anxiety symptoms. Based on this information, an evaluation for the clinical appropriateness of ketamine treatment for depression or anxiety was made by the practice. Exclusion criteria for ketamine consisted of indications of any of the following conditions/symptoms: (1) active suicidal ideation, (2) uncontrolled hypertension (HTN), (3) liver disease, or (4) schizophrenia, active substance use disorder, or other primary psychotic disorder. Uncontrolled HTN was defined as systolic blood pressure $\geq$140 mmHg or an average diastolic blood pressure $\geq$90 mmHg and patients were excluded based on self-reported BP screening. Absence of liver disease was excluded on the basis of available normal liver function test report information and self-reported past medical history. Potential for diversion for abuse was evaluated by psychiatric mental health nurse practitioners by querying state prescription monitoring databases as part of the medical consultation. Patients who were not excluded were provided with information about the ketamine treatment. Terms and conditions for use of data use were addressed during the onboarding process. Patients then signed a detailed informed consent form.

After obtaining informed consent, an express-mailed package containing a 300 mg rapid dissolve tablet (RDT) of ketamine for SL administration with instructions was shipped to the patient. The basis for a treatment course of 6 treatments was based on the extensive evidence showing effectiveness of 6 IV ketamine infusions and to mirror prior treatment schedules as closely as possible in order to minimize unforeseen variables (45). In line with this, a first shipment contained an RDT tab and additional information providing comprehensive instructions on how to safely to self-administer the ketamine RDT. These instructions included careful preparation and creation of an optimal set and setting (i.e. quiet comfortable environment with dedicated time before and after to meditate and/or reflect), safety instructions including fall risk precautions and avoidance of any sharp or dangerous objects or operation of heavy machinery including cars was explicitly prohibited as was the combination of any other psychotropic substance including alcohol or marijuana. Patients on benzodiazepines were instructed to hold this medication on the day of ketamine therapy due to evidence that it may reduce antidepressant effectiveness (46). This guidance instructed patients to consume the RDT in the presence of a sitter who would provide support as needed. This sitter was also provided ketamine safety education by the medical provider which included information about fall risk and the avoidance of drugs or alcohol. After ketamine use, patients were instructed to recline with an eye-covering (i.e., a sleep mask) in a quiet location. Patients were instructed to listen to provider-prepared music using headphones to minimize distraction and support the ketamine experience.

Upon completion of this initial ketamine administration, patients were asked to complete an online experience report for this first ketamine dose for clinical review by the provider. The decision to use ketamine at 300 mg was determined by providers with experiential CME training in ketamine therapy. This training provided the guidance for determination of the clinically recommended course of ketamine treatment (12). Patients were instructed to self-administer their doses twice a week and complete the online experience survey within 2 days of their final dose from the shipment. The duration of therapy ranged from 2–3 weeks to complete the number of doses prescribed. Decisions to increase doses to 450 mg were made collaboratively between the patient and providers. Based on data from the patient's experience report, a clinical judgment was then made by the provider to maintain or increase (up to 450 mg) the dosage of a second shipment containing two additional ketamine RDT.

A second shipment contained either two 300 mg RDT or two 450 mg RDT, and was also express-mailed to patients. Patients repeated the self-administration procedure for the two additional RDT treatments on separate days, bringing their ketamine treatment to three doses (3-RDT). Upon completion, patients were again asked to complete the online experience report which included the PHQ-9 and GAD-7 measures for clinical review, and rank experiences (None, Mild, Moderate, Severe) of several potential side effects. These included: Anxiety, Blurred Vision, Difficulty Speaking, Difficulty Thinking, Dizziness, Loss of Balance, Memory Issues, Nausea, Pain with Urination, Palpitations, and Pelvic Pain.

After a review of the patient report, a clinical determination for a final shipment of 3 additional ketamine RDT (300 mg or 450 mg) was made, and a third shipment was sent. Patients were again instructed to use the three additional doses as directed and then complete another experience report with PHQ-9, GAD-7, and side effect measures after taking their sixth ketamine RDT (6-RDT) within 2 days of their final dose from the shipment. In summary, data from all patients who had contacted the practice and then completed the follow up surveys after at least 3-RDT ketamine were analyzed. Analysis of the data revealed a subgroup of patients that had received an additional three RDT ketamine (raising their total to six; 6-RDT) that had completed follow up surveys was also conducted.

Statistical analysis

SPSS (v28) software was used for frequencies and descriptive measures, and to perform inferential analyses of changes in GAD-7 and PHQ-9 scores between intake levels and post-treatment scores. Wilcoxon Matched Pairs analysis were performed for GAD-7 and PHQ-9 scores for both patients at three-, and six-ketamine RDT treatment times as available. Reductions of $\geq$ 50% of raw score reductions and from intake are also reported, as well % reductions and clinically significant reductions in those patients whose intake GAD-7 and/or PHQ-9 scores placed them in the Moderate to Severe ranges at intake.

Results

Sample characteristics

A total of 4,404 people were assessed for eligibility out of which 1,101 patients were enrolled. A review of their clinical data revealed that 669 patients had completed a course of treatment including at least three SL ketamine RDT (3-RDT) and completed the post-treatment experience report. Of these, 5 patients contained missing or corrupted data and were excluded when analyzing GAD-7 and PHQ-9 measures, however their reports of side effects are included in Table 1. Of the remaining 664 patients remaining for GAD-7 and PHQ-9 data analysis 210 patients had received a third shipment with three additional ketamine RDT. These patients completed an additional post-treatment experience report after completing a clinically recommended six ketamine RDT treatment course (6-RDT, n=210). Based on this process we analyzed a group of patients actively involved in ongoing treatment at the time of data collection who had finished 3-RDT of SL ketamine (n = 464), and a second group of patients who had completed a 6-RDT course of SL ketamine. Demographic characteristics are shown in Table 2.

Safety

A review of systems and follow up visits systematically screened for major adverse events (symptoms requiring medical care including hospitalizations as part of structured clinical interview in follow-up). Minor adverse events and side effects including nausea, dizziness, headache, loss of balance, were assessed on self-report questionnaires for each set of experiences. Side effects of ketamine RDT that were reported as part of the experience report are shown in Table 1. These effects were self-limited and resolved without any further medical intervention.

Impact of three RDT ketamine-induced impact on depression and anxiety

Wilcoxon Matched Pairs analysis of all patients after 3-RDT ($n = 654$) indicated a statistically significant decrease from GAD-7 intake after three ketamine RDT treatment ($z = -18.52$, $p < 0.001$). Average raw GAD-7 score reduction was−4.86, with 47.6% of patients ($n = 316$) having experienced a reduction of 50% or more when compared to their intake GAD-7 score (see Figure 2). As indicated in Table 2, 47.6% ($n = 199$) of patients whose intake GAD-7 scores placed them in the Moderate to Severe range (GAD-7 $\geq$ 10; $n = 418$) reported reductions to at least half of their intake scores. Of these same Moderate to Severe patients, 63% reported clinically significant drops in GAD-7 scores resulting in either None (0–4) or Mild (5–9) anxiety categorization. The remaining 36.4% ($n = 152$) of Moderate to

TABLE 1 Ketamine side effect incidence and severity after 3- or 6-RDT.

3-RDT ketamine ($n = 669$)					6-RDT ketamine ($n = 210$)				
Side effect	**None**	**Mild**	**Moderate**	**Severe**	**Side effect**	**None**	**Mild**	**Moderate**	**Severe**
Anxiety	72.50%	21.30%	5.16%	1.05%	**Anxiety**	76.42%	19.34%	3.46%	0.79%
Blurred vision	45.67%	38.12%	13.53%	2.69%	**Blurred vision**	47.01%	36.01%	13.99%	2.99%
Difficulty speaking	59.57%	33.41%	5.90%	1.12%	**Difficulty speaking**	58.81%	31.76%	7.86%	1.57%
Difficulty thinking	61.43%	29.82%	7.70%	1.05%	**Difficulty thinking**	60.85%	29.56%	8.33%	1.26%
Dizziness	34.98%	43.57%	17.64%	3.81%	**Dizziness**	35.53%	41.98%	19.34%	3.14%
Loss of balance	33.33%	43.05%	20.40%	3.21%	**Loss of balance**	37.11%	40.41%	19.18%	3.30%
Memory issues	83.18%	13.98%	2.69%	0.15%	**Memory issues**	84.43%	13.36%	3.30%	0.47%
Nausea	64.42%	23.09%	9.49%	2.99%	**Nausea**	68.40%	19.81%	8.65%	3.14%
Pain with urination	98.21%	1.57%	0.22%	0.00%	**Pain with urination**	97.48%	2.36%	0.16%	0.00%
Palpitations	90.21%	7.77%	1.87%	0.15%	**Palpitations**	91.19%	7.86%	0.63%	0.31%
Pubic pain	98.21%	1.42%	0.22%	0.15%	**Pubic pain**	98.43%	1.10%	0.31%	0.16%

Percentage of all subjects who reported None, Mild, Moderate, or Severe after their 3rd or 6th RDT of Ketamine.

TABLE 2 Demographic characteristics and GAD-7 and PHQ-9 scores.

		Age							
Gender	***N* (%)**	**<20**	**21–30**	**31–40**	**41–50**	**51–60**	**Over 61**	**Missing**	**Age range**
Female	266 (40.7)	4	49	96	64	31	22	3	19-74
Male	288 (44.0)	2	54	128	59	36	9	0	17-82
Not reported/other	110 (15.3)	1	19	42	27	12	6	0	20-70
Total	664 (100%)								

3-RDT ketamine	***N* (%)**	**Intake GAD-7**	**3-RDT GAD-7**	**GAD-7 change**	**≥ 50% Reduction %**	**Clinically significant reduction/remission %**
All patients after 3-RDT	664 (100%)	11.81 ± 5.50	6.94 ± 5.13	4.86 ± 5.18*	47.60%	-
Moderate to severe GAD-7 intake	418 (64.9%)	15.29 ± 3.45	8.65 ± 5.40	6.64 ± 5.32*	47.60%	63% / 23.9%
	***N* (%)**	**Intake PHQ-9**	**3-RDT PHQ-9**	**PHQ-9 change**	**≥ 50% Reduction %**	**Clinically significant reduction/remission %**
All patients after 3-RDT	664 (100%)	13.24 ± 6.04	7.60 ± 5.34	5.64 ± 5.33*	47.60%	-
Moderate to severe PHQ-9 intake	463 (71.9%)	16.36 ± 4.20	9.13 ± 5.36	7.23 ± 5.33*	49.50%	59% / 20.7%
6-RDT ketamine	***N* (%)**	**Intake GAD-7**	**6-RDT GAD-7**	**GAD-7 change**	**≥ 50% Reduction %**	**Clinically significant reduction/remission %**
Patients after 6-RDT	210 (100%)	11.74 ± 5.47	5.86 ± 4.87	5.88 ± 5.02*	47.60%	-
Moderate to severe GAD-7 intake	133 (63.3%)	15.11 ± 3.61	7.50 ± 5.12	7.61 ± 5.02*	60.20%	69.2% / 33.8%
	***N* (%)**	**Intake PHQ-9**	**6-RDT PHQ-9**	**PHQ-9 change**	**≥ 50% Reduction %**	**Clinically significant reduction/remission %**
Patients after 6-RDT	210	13.90 ± 6.20	6.60 ± 5.19	7.30 ± 5.85*	61.40%	-
Moderate to severe PHQ-9 intake	156 (74.2%)	15.76 ± 5.61	7.88 ± 5.61	7.88 ± 5.85*	65.40%	71.2% / 32.7%

The asterisk (*) indicates statistical significance as cited in the text ($p < 0.001$).

Severe patients at intake did not experience a clinical reduction in anxiety scores after three ketamine RDT treatment.

Analysis of changes in PHQ-9 depression scores revealed statistically significant reductions after three RDT ketamine treatment ($z = -19.71$, $p < 0.001$) when compared to intake scores (Table 2). There was an overall reduction of 47.59% from intake to post-ketamine treatment PHQ-9 scores. In patients whose intake PHQ-9 scores placed them in the Moderate to Severe range ($n = 463$), three RDT ketamine treatment resulted in PHQ-9 scores dropping to at least half of intake scores in 49.5% of patients ($n = 229$). Of these same Moderate to Severe PHQ-9 intake patients, 59% ($n = 273$) reported clinically significant drops that placed them in the None (0–4) to Mild (5–9) depression categories. The remaining 41% ($n = 190$) did not experience a clinical reduction in depression scores after three ketamine RDT.

Impact of six RDT ketamine-induced impact on depression and anxiety

Wilcoxon Matched Pairs analysis of patients who completed a clinically recommended six dose course of RDT ketamine treatment ($n = 210$) revealed a statistically significant decrease in final reported GAD-7 scores when compared to intake after 3-RDT ($z = -10.12$, $p < 0.001$) that was comparable to those reported in the previous group of ongoing patients (see the above 3-RDT). Upon completion of three additional ketamine treatments there was an additional decrease in GAD-7 rank scores ($z = -4.62$, $p < 0.001$; see Figure 2).

As shown in Table 2, average raw GAD-7 score was reduced by 5.88, and 72.4% of those receiving 6 ketamine RDT ($n = 152$) experienced a reduction of 50% or more from their intake GAD-7 score. For patients whose intake GAD-7 scores placed

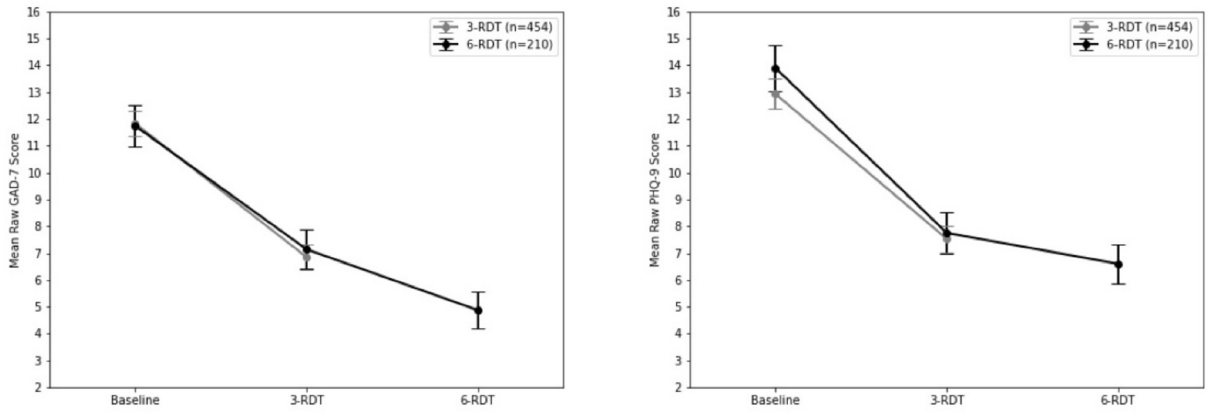

FIGURE 2
Mean GAD-7 and PHQ-9 scores at baseline, after 3-RTD, and 6-RDT ketamine treatments.

them in the Moderate to Severe range (see Table 2; $n = 133$), six ketamine RDT treatment resulted in GAD-7 scores dropping to at least half of intake GAD-7 scores in 60.2% ($n = 80$). For these same patients with Moderate to Severe intake GAD-7 scores ($n = 133$; Table 2), 69.2% ($n = 92$) reported clinically significant reductions resulting in None (0–4) or Mild (5–9) post-treatment anxiety categorization. The remaining 30.8% ($n = 41$) of intake Moderate to Severe patients did not experience a clinical reduction in anxiety after six ketamine RDT treatment.

Similarly, Wilcoxon Matched Pairs analysis of PHQ-9 scores revealed a significant reduction in PHQ-9 scores after three RDT ketamine doses ($z = 10.96, p < 0.001$) and then after 6-RDT ($z = 4.45, p < 0.001$). Of patients whose intake PHQ-9 scores placed them in the Moderate to Severe range ($n = 156$), six ketamine RDT treatment resulted in PHQ-9 scores dropping to at least half of intake scores in 65.4% of patients ($n = 102$). Of these same Moderate to Severe PHQ-9 intake patients, 71.2% ($n = 111$) reported clinically significant drops that placed them in the None (0–4) to Mild (5–9) depression categories. A comparison of 3-RDT only ($n = 454$) and 6-RDT ($n = 210$) GAD-7 and PHQ-9 mean scores from Baseline, 3- and 6-RDT are shown in Figure 2.

Discussion

Previous studies have indicated that IV ketamine infusions can serve as an effective course of treatment for patients with TRD (23, 24). This study aimed to examine the safety and effectiveness of at-home use of SL ketamine for TRD and treatment-resistant anxiety. This study has shown that in as few as three doses of ketamine therapy nearly 50% of patients with moderate to severe depression saw an improvement of reducing their PHQ-9 and GAD-7 scores to half of their intake scores. This reduction rate improved to 60% in patients who completed a clinically recommended six ketamine RDT course of treatment. Of note, for patients with moderate to severe intake GAD-7 scores there was a clinical effect with ketamine therapy of reducing anxiety categorization in as few as three doses, and of those who were with moderate to severe intake GAD-7 scores who completed six ketamine RDT 65.4%, saw their GAD-7 scores reduced to 50% or more of their intake scores. Reductions in scores for those who had only received 3-RDT matched those who had completed 6-RDT (see Figure 2), and it is reasonable to speculate that there would be maintenance of improvement with three additional RDT ketamine treatments.

Our findings indicate that SL ketamine is clinically effective in reducing depression and anxiety in an at-home setting. The use of SL ketamine at home presents a promising approach in the treatment of TRD where treatment resistance may be the result of prior treatment approaches being mismatched with underlying neurobiological etiology. Since most antidepressants target monoaminergic mechanisms, the effectiveness of ketamine's pharmacological profile suggests an underlying role for glutamate in some individuals who experience TRD (47).

Limitations of the study were that it was a retrospective review of chart data from a self-selecting convenience sample. Measures of depression and anxiety relied extensively on self-report, though there was considerable provider care given. There was no placebo/control group, and given the dissociative effects of ketamine, a strong placebo effect is possible. Caution should be exercised whenever treating patients with depression and anxiety, especially those with complicating presenting symptoms (i.e., suicidality) or health problems (i.e., hypertension, substance abuse). While the majority of patients respond after 3 doses, we did not determine whether there are differences in the durability of response based on the number of treatments,; this an active area of investigation. Further work, which we are

currently engaged in, will be needed to delineate not only the most effective dosing regimen, but also to identify likely responders based on patient characteristics and maintain continued analysis of patient data. The researchers also acknowledge the need for continued analysis of patient data. Nonetheless, we argue that SL ketamine offers a safe and effective tool in the treatment of anxiety and depression. This study represents a step toward consideration of at-home, SL ketamine for treatment-resistant depression and treatment-resistant anxiety.

In conclusion, this study adds to a growing literature on the effectiveness of ketamine treatment for TRD (22, 48). The improvements in depression and anxiety symptomology demonstrated in those who received as few as three at-home ketamine RDT present a safe, effective, and reasonable alternative to inpatient IV infusions of ketamine. These improvements in symptoms are further improved with completion of a clinically recommended course of six ketamine RDT. In addition to providing an effective treatment for those with TRD and comorbid anxiety, it also suggests alternative neurobiological modes for understanding MDD and anxiety symptoms. Additional studies including randomized trials, long-term impact on remission rates, combinations with additional psychosocial interventions, other functional outcomes, and cost-effectiveness analysis are needed.

Data availability statement

The datasets presented in this article are not readily available because this data is a retrospective chart study of patient data from a private healthcare provider. Requests to access the datasets should be directed to kh@nue.life.

Ethics statement

The studies involving human participants were reviewed and approved by Wheaton College, Wheaton, IL. The patients/participants provided their written informed consent to participate in this study.

Author contributions

KH: project administration and writing—review and editing. WS: writing—review and editing and formal/statistical analysis. AS: data curation, review, and editing. PD: writing—review and editing. All authors contributed to the article and approved the submitted version.

Conflict of interest

Authors KH, AS, and PD hold restricted shares of Nue Life Health, P.B.C.

The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Intravenous ketamine for depression: A clinical discussion reconsidering best practices in acute hypertension management

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Ketamine is a versatile medication with an emerging role for the treatment of numerous psychiatric conditions, including treatment resistant depression. Current psychiatry guidelines for its intravenous administration to treat depression recommend regular blood pressure monitoring and an aggressive approach to potential transient hypertensive episodes induced by ketamine infusions. While this approach is aimed at ensuring patient safety, it should be updated to align with best practice guidelines in the management of hypertension. This review defines and summarizes the currently recommended approach to the hypertensive emergency, the asymptomatic hypertensive urgency, and discusses their relevance to intravenous ketamine therapy. With an updated protocol informed by these best practice guidelines, ketamine treatment for depression may be more accessible to facilitate psychiatric treatment.

KEYWORDS

ketamine, hypertension, hypertensive emergency, ketamine infusion, treatment resistant depression

Introduction

Ketamine is versatile as both an analgesic and sedating medication. At the lower dosing range, ketamine is an adjunctive pain medication to acetaminophen, non-steroidal anti-inflammatory drugs, and opioids. Ketamine also provides analgesia and sedation for prolonged procedures such as fracture reduction or chest tube insertion. In higher doses of 1–1.5 mg/kg ketamine is used for induction of general anesthesia in both the emergency department and operating room settings. In addition to these various applications, interest is growing in the use of ketamine for its utility in treating psychiatric disorders.

Intravenous ketamine delivered in sub-anesthetic doses (0.5–1.0 mg/kg) has shown effectiveness in reducing depressive symptoms and suicidal ideation in both unipolar and bipolar depression (1–3). Consensus papers from Canada (1), the United States (4), and internationally (5) have recognized its emerging role in the treatment of depression. Unfortunately, administering intravenous ketamine demands significant resources. Monitoring is required due to the potential adverse effects, one of which is a transient episode of hypertension.

Additionally, ketamine has also been used in psychiatric research settings, extensively employed as a model for schizophrenia in humans (6) and non-human primates alike (7). For these studies, ketamine is usually given either as a bolus followed by an infusion or simply a bolus *via* intravenous administration at a sub-anesthetic dose (0.1–0.7 mg/kg) to healthy volunteers (8). Due to the known effect of ketamine to transiently increase blood pressure, studies often mention they record blood pressure but it may not be reported (9–11). When it is reported, the blood pressure changes have been low – reported as transiently increased SBP in one study (mean 18.6 +/- 2.6 mmHg) (12) and transiently increased SBP of ∼20 mmHg in another (13). When compared to the mean SBP elevation of 57 mmHg observed during 9 min of simple exercise in healthy volunteers (14), these small and brief increases caused by ketamine are trivial. As such, while monitoring blood pressure in these healthy volunteers seems to report insignificant transient changes, the recommendations regarding blood pressure monitoring in a research setting are a matter of discourse for the research protocols and ethics committees reviewing them. Clinical studies on IV ketamine for depression are subject to similar ethics boards requirements, and it is important to distinguish the necessity of monitoring for ethical purposes in a research setting vs. clinical need and utility in a clinical setting. This paper reviews the minimal risk of serious complications related to blood pressure in a therapeutic application.

The Canadian Network for Mood and Anxiety Disorders (CANMAT) task force statement on the use of ketamine for depression recommends that blood pressure should be monitored before and during ketamine infusions and for at least 1 h post infusion. In addition, it is recommended that patients with baseline blood pressures <140/90 mmHg should not proceed with treatment (1). An international consensus paper on ketamine treatment also suggests that individuals with other conditions such as uncontrolled hypertension, central aneurysmal disease, significant valvular disease, or New York Heart Association Class III failure should also be excluded from treatment (5). Furthermore, the CANMAT task force statement recommends a blood pressure level of 160/100 mmHg as the threshold to pause infusion and resume treatment when blood pressure falls below 160/100 mmHg, with or without antihypertensive treatment. The concern is that these elevations will cause a complication of elevated blood pressure, the hypertensive emergency. Where blood pressure is a cause for concern, it has been suggested that it may be treated with beta-blockers, alpha agonists, vasodilators, or calcium channel blockers (15).

Based on the recommendations, a practitioner hoping to administer intravenous ketamine for TRD must involve the availability of personnel trained in resuscitation, airway support, and advanced cardiac life support. In addition, uncontrolled hypertension and white coat hypertension in the general patient population is not uncommon. Based on above criteria these patients may not be eligible for ketamine therapy. Data from clinical trials shows that this threshold for pausing infusion is crossed not infrequently. This suggests that applying these parameters to a real-world population would mean that a number of patients would not receive a complete treatment session, or would receive antihypertensive treatment before resuming. Clearly, there are multiple barriers to the routine administration of intravenous ketamine therapy and it is unclear what level of concern is necessary regarding hypertension associated with treatment.

Hypertension is a very common co-morbidity in the emergency department patient (16). The management of asymptomatic hypertension and hypertensive emergencies are an essential part of an emergency physician's skillset. With this experience, emergency medicine (EM) is uniquely well-positioned to provide an objective perspective on the level of concern for blood pressure effects of intravenous ketamine therapy as well as providing guidance for intervention. When comparing the existing literature for hypertensive management in the emergency department to hypertension as an adverse effect of intravenous ketamine therapy, the current recommendations for blood pressure monitoring and treatment from consensus statements in psychiatry should be revisited to align with standards of practice in management of transient hypertension in the emergency setting.

Subsections

Blood pressure elevations in the emergency room setting

The approach to hypertension in the emergency room requires classifying hypertensive patients into those with asymptomatic elevated blood pressure and those in hypertensive emergency. The true hypertensive emergency warrants acute blood pressure reduction and specialist consultation for further workup and management.

A hypertensive emergency is defined as moderate to severe hypertension (systolic blood pressure (SBP) ≥ 180 mmHg, diastolic blood pressure (DBP) ≥ 110 mmHg) with evidence of end organ dysfunction (EOD), most commonly

TABLE 1 Signs or symptoms of hypertensive emergencies, hypertension, and common adverse effects of ketamine.

Signs/Symptoms of hypertensive emergency	Non-emergent hypertensive signs/symptoms	Common adverse effects of ketamine
• Crushing chest pain or pressure	• Headache	• Dissociation
• Decreased (not altered) level of consciousness	• Dizziness	• Anxiety
• Severe abdominal pain	• Epistaxis	• Headache
• Shortness of breath		• Dizziness
• Syncope		• Nausea/vomiting
		• Blurred vision

Only the signs and symptoms of hypertensive emergencies would prompt a blood pressure check.

involving the heart, brain, or kidneys. Specifically, emergency physicians look for signs and symptoms of acute stroke, cardiac ischemia, pulmonary edema, encephalopathy, and congestive heart failure (17). Although frequently accompanied by an elevated blood pressure, symptoms such as headache, epistaxis, and dizziness are not evidence of EOD (Table 1). These symptoms in isolation with an elevated blood pressure, do not constitute a hypertensive emergency nor do they indicate the need for acute blood pressure reduction (17, 18). In contrast to this, patients with hypertensive emergencies are treated with anti-hypertensives such as beta-blockers, calcium channel blockers, and vasodilators. The goal is a maximal reduction of mean arterial pressure by 20–25% within the 1st h and a target blood pressure of 160/100 mmHg by 2–6 h (17).

Outside of a true hypertensive emergency, patients may have elevated blood pressures with or without a history of pre-existing hypertension. In cases where patients present with asymptomatic elevated blood pressure, there is no indication for acute blood pressure lowering. This is supported by the American College of Emergency Physicians policy statement on asymptomatic elevated blood pressure, which recommends that routine emergency department investigations and medical intervention is not required for patients with asymptomatic markedly elevated blood pressure (18). Treating asymptomatic hypertension acutely does not have identified benefits, even in patients with many months of untreated hypertension. A large retrospective cohort study of primary care patients meeting criteria for moderate to severe hypertension (SBP $\geq$ 180 mmHg, DBP $\geq$ 110 mmHg) that went untreated found that rates of major adverse cardiovascular events were extremely low. Specifically, events including acute coronary syndrome, stroke, transient ischemic attack, uncontrolled hypertension ($\geq$140/90 mmHg), and hospital admission occurred in >1% of patients at 7 days, 1 month, and 6 months after diagnosis (19). Clearly, even for asymptomatic hypertensive individuals the hypertensive emergency is extremely rare - even after 6 months of untreated hypertension.

Ketamine in treatment-resistant depression—cardiovascular effects

The adverse effects of intravenous ketamine infusions for treatment-resistant depression (TRD) are well-characterized, most commonly including dissociative effects and transient hypertension. Other common, also transient effects include anxiety, blurred vision, dizziness, headache, and nausea or vomiting (15, 20). Most of these side effects were only mild or moderate, well tolerated, and transient, with all of them ceasing within 4 h post-administration of short-term ketamine for TRD (21, 22).

In randomized trials, typically involving administration of a single dose of intravenous ketamine, transient hemodynamic effects have been observed including increases in heart rate and blood pressure (21). This hypertensive effect may be blunted in the oral formulation of ketamine, however it comes at the cost of potentially lowered efficacy (23). Ketamine's receptor binding profile is quite diverse with at least 8 different cellular receptor systems involved (24). While ketamine's psychoactive effects are primarily attributed to its NMDA antagonism (25), its effects on heart rate and blood pressure have been attributed to a stimulation of the sympathetic nervous system (26) and increased catecholamine release (27). Early experiments have shown that ketamine-induced transient hypertension and tachycardia can be blunted by a co-administration of diazepam (28), a benzodiazepine acting as a positive allosteric modulator of the GABA receptor (29) and a common agent used to counteract sympathomimetic toxicity (30).

Increases in SBP and DBP begin shortly after administration and peak at around 30–50 min with SBP and DBP increases from 10 to 50% above pre-dose values. Increases in blood pressure and heart rate are usually mild and transient, resolving at ~2–4 h after dose administration, with no serious or persistent cardiovascular events reported (1, 21).

A relatively large case series involving 66 participants with 684 total infusions reported that blood pressure peaked at 30 min after infusion starts and only 9% of infusions showed increases

in blood pressure of systolic > 30 mmHg and diastolic > 15 mmHg, with none requiring intervention (31).

However, a higher incidence of elevated blood pressures were observed in a retrospective study that reviewed 203 patients with treatment resistant depression who were treated with intravenous ketamine in a clinical setting. Specifically, 44.3% of all patients exhibited transient "treatment-emergent" hypertension, defined as SBP ≥ 165 mmHg or diastolic blood pressure ≥ 100 mmHg at any point during treatment (32). Twelve percentage of these patients were given labetalol or amlodipine to treat hypertension, but the exact indication for treatment was not clear. Of note, no specific events that would meet the criteria for hypertensive emergency were mentioned in this study.

An earlier report on pooled data from 3 studies of 84 participants and 205 total infusions found mean peak blood pressures of systolic 141.9 mmHg and diastolic 86.4 mmHg with blood pressures returning to baseline at 60–70 min after infusion (33). In this analysis, 30% of participants experienced a "clinically significant" increase in blood pressure, defined as blood pressure >180/100 mmHg or heart rate >110 bpm, with no reports of EOD, thus no instances met the criteria for hypertensive emergency. Similarly, review of cardiovascular effects seen in short-term ketamine for TRD found that some trials showed blood pressure levels exceeding 180/100 mmHg, but this was overall quite rare, and again, no serious or persistent cardiovascular events were reported (21).

Emergency medicine perspective on ketamine associated hypertension

Pre-infusion blood pressure measurement is prudent, but the presence of a hypertensive reading with no signs and symptoms of acute stroke, cardiac ischemia, pulmonary edema, encephalopathy, and congestive heart failure need not be considered an absolute contraindication for treatment. While generally patients receiving non-emergent ketamine treatment should have any pre-existing hypertension treated, patients may commonly have elevations in blood pressure pre-treatment that can even be related to anxiety or white coat hypertension. Recommendations to not proceed with treatment if blood pressure is elevated may be unnecessarily limiting and should be revisited.

Current administration guidelines for ketamine infusions recommend frequent monitoring of vital signs before, during, and after infusion. This is accompanied by a recommendation and suggestions to pause or discontinue infusion, or treat with anti-hypertensives when blood pressures rise above systolic 160 mmHg and/or diastolic 100 mmHg (1), while previously discussed trials utilize a systolic blood pressure ≥ 180 mmHg or diastolic blood pressure ≥ 110 mmHg as a threshold for discontinuing ketamine infusion or initiating treatment with anti-hypertensives. However, in EM these patients would fall under the category of asymptomatic hypertension, in which no medical intervention is recommended.

The intention to treat elevated blood pressure levels during ketamine infusions is well meaning, however, pausing the infusion and/or treating with anti-hypertensives is not without their own adverse effects. Pausing or stopping the infusion because of elevated blood pressure means that the patient may not receive the therapy for their TRD or acute suicidal ideation. It could be argued that leaving either of these conditions untreated also causes an immediate increase in patient morbidity and mortality risk. Additionally, treatment with anti-hypertensives is not benign. A large systematic review examining pharmacologic treatments for hypertensive urgency found that all medications used were associated with side effects. Labetalol, the most frequently used medication to acutely lower blood pressure has been associated with side effects such as dizziness, drowsiness, headache, bradycardia, and pain at the injection site (34). Similar generalized and hemodynamic side effects of anti-hypertensive treatment were seen with other classes of medications such as ACE inhibitors, calcium channel blockers, and vasodilators (34).

Elevated blood pressures that do not meet the criteria for hypertensive emergency should not be treated with antihypertensive agents (18, 35). In addition to side effects of the antihypertensives themselves, they may produce more dangerous hypotensive episodes that could provoke syncope, or worse, if blood pressure is lowered too rapidly in chronically hypertensive patients, stroke or myocardial infarction could occur (36, 37). Routine blood pressure checks mid-infusion offer little benefit and may be distressing to a patient experiencing dissociation. In keeping with the above-described management of hypertension, healthy patients receiving ketamine for depression need not routinely have blood pressure frequently monitored.

Hypertensive emergency has not been documented in IV ketamine trials, so may be considered an extremely rare, though very serious potential adverse event. Rather than monitoring numbers, it is vital for medical personnel administering ketamine infusions to monitor patients for alarming symptoms such as severe chest pressure/pain, acute dyspnea, severe abdominal pain, or significantly decreased (not altered) level of consciousness (that would be defined as a GCS<8). If these occur, blood pressure should be checked. If there is an accompanying hypertensive blood pressure (≥ 180/110 mmHg), anti-hypertensive treatment should be considered with immediate transport to an ED for further workup, management, and evaluation. Anxiety, blurred vision, dizziness, headache, and nausea or vomiting are common ketamine side effects, and not considered signs or symptoms of hypertensive emergencies.

Discussion and future directions for optimal blood pressure management in IV ketamine treatment

Intravenous ketamine administration is a shift outside the realm of traditional psychiatric treatment for depression. Initial guidelines for patient monitoring reflected the anesthetic nature of this medication and erred on the side of caution given the initial experimental and novel nature of the treatment. However, as efficacy data has accumulated, safety data and clinical experience has as well. The approach to blood pressure could be reconsidered, given the previously described best practices for asymptomatic hypertension management. The EM perspective suggests that for patients who are medically stable with no cardiovascular disease, routine continuous cardiac monitoring and/or frequent vital sign measurements are not necessary and may carry potential harms if blood pressure elevations are treated when asymptomatic. Instead, clinical monitoring for worrisome signs and symptoms (Table 1) could alert to a potential hypertensive emergency and are more essential during IV ketamine treatment. If such symptoms are observed, they would serve as a trigger to check the patient's blood pressure. If elevated, it would prompt consideration for treatment and medical specialist consultation for further workup and management of the presumed hypertensive emergency.

Although a hypertensive emergency has not been reported with IV ketamine, it must also be considered that common practice in psychiatric clinical trials and ketamine programs have followed previous recommendations. This includes intervening by pausing an infusion or treating with antihypertensives when blood pressure rises above a threshold. The practice of responding to an asymptomatic elevation is not consistent with the previously described EM best practice, but it must be considered that this approach has prevented any episodes of hypertensive emergency. Any change in practice to reflect EM best practices must be accompanied by vigilance for warning signs and symptoms that would signal a hypertensive emergency and immediate action must be taken if observed.

Another key issue this perspective raises is eligibility for ketamine therapy. Previous exclusion criteria for IV ketamine cited examples as uncontrolled hypertension, unstable medical condition, central aneurysmal disease, significant valvular disease, recent myocardial infarction, or New York Heart Association Class III heart failure (1, 5). In reconsidering the true risks of hypertension (34) and contrasting these eligibility criteria to those for electroconvulsive therapy - where patients are fully anesthetized - it would seem prudent that these instead be relative contraindications considered on a case by case basis, similar to electroconvulsive therapy. Patients with depression often carry other medical comorbidities, in particular a correlation with increased rates of hypertension (38–40) and generalized cardiovascular disease (41, 42), which may preclude treatment under current criteria. While the aim is for hypertension to be properly treated prior to initiating ketamine treatment, it is not uncommon for physical health to be neglected in severe depression. In considering the EM perspective, an elevated blood pressure alone should not necessarily preclude ketamine treatment. As is common practice for electroconvulsive therapy, the presence of multiple comorbidities could prompt medical consultation prior to initiating a treatment course.

The combined accumulation of experience with ketamine for TRD and the EM perspective provided by this paper should provoke a reconsideration of best practices within psychiatry for intravenous ketamine therapy. Although this paper focused on IV ketamine, addressing hypertension associated with similar treatments including intranasal esketamine or non-IV ketamine should be similarly reconsidered through this EM lens. Protocols must balance the minimal risk with healthy individuals, the variety of comorbidities in the depressed patient, the low rate of complications, and the potential harms of treating transient hypertension if it is not a hypertensive emergency. The goal is an appropriate safety monitoring regimen that will not overburden limited resources and will avoid unnecessary interventions which may carry their own risks. Continued interdisciplinary input, both in protocols and individual consultation for at-risk patients will be important to offer optimal care.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

RY wrote the manuscript draft and was supervised by KS. KS and JS contributed to writing of subsequent drafts. RY and KS provided the emergency medicine context for this article. JS, AK, and RM provided the psychiatry context and discussion. RY, JS, AK, RM, and KS reviewed the paper and provided edits. All authors contributed to the article and approved the submitted version.

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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A survey of drug liking and cravings in patients using sublingual or intranasal ketamine for treatment resistant depression: A preliminary evaluation of real world addictive potential

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Ketamine has gained rapid popularity as a treatment option for treatment resistant depression (TRD). Though seen only in limited contexts, ketamine is a potential drug of abuse, addiction and diversion. Clinical ketamine studies to date have not systematically evaluated factors relevant to addiction risk in patients with TRD, but in treating patients with ketamine, risks of potential harms related to addiction must be considered. As clinical access to intravenous ketamine programs is limited in much of Canada, these considerations become even more important for clinicians who elect to offer patients less supervised, non-parenteral forms of ketamine treatment. This study explores factors relevant to addiction risk in a real-world sample of 33 patients with TRD currently or previously treated with sublingual (SL) or intranasal (IN) ketamine in the community. First, patients were surveyed using a Drug Liking and Craving Questionnaire (DLCQ) to assess their level of drug liking and craving for ketamine, and to screen for symptoms of a ketamine use disorder. Second, the pharmacy records of these patients were reviewed for red flags for addiction such as dose escalation or early refills. Third, surveys were administered to the treating psychiatrists of patients who had discontinued ketamine to determine if abuse concerns contributed to reason for discontinuation. Though limited to a small sample, results indicate that ketamine is not a universally liked or craved substance in patients with TRD. Prescribers of non-parenteral ketamine should monitor patients and prescribe

cautiously. Factors related to addiction (as in the DLCQ) should be explored for clinicians to consider individual risk/benefit for judicious use of ketamine in patients with TRD.

KEYWORDS

ketamine, intranasal, sublingual, treatment resistant depression (TRD), addiction, abuse, drug liking, drug cravings

Introduction

Major depressive disorder (MDD) is a common psychiatric disorder with significant disease burden (1). As of early 2021, the global point prevalence of MDD was estimated at 3.2% (2). Approximately 15% of patients suffer from Treatment Resistant Depression (TRD), as defined by a failure to respond to two adequate trials of antidepressants from different pharmacological classes (1, 3). As such, there has been an urgent need to develop alternative treatments to target the TRD population (4).

Ketamine is a commonly used anesthetic agent and *N*-Methyl-D-aspartate (NMDA) receptor antagonist (5) which has demonstrated efficacy in treating depression at sub-anesthetic doses administered intravenously. More specifically, studies have demonstrated that a single infusion of IV ketamine, when administered at doses of 0.5–1.0 mg/kg, may provide antidepressant effects as quickly as 2 h post treatment and lasting up to 1 week, and that multiple IV ketamine infusions may extend this effect (6–11).

Intranasal (IN) esketamine, an enantiomer of ketamine, was recently approved toward the management of TRD (12). While both IV ketamine and IN esketamine represent promising treatment options for individuals with TRD, access is limited, even in urban centers (4), as both must be delivered in a healthcare setting due to monitoring requirements and concerns regarding risks of addiction or diversion (4). The United States Food and Drug Administration (FDA) has noted that subjective "liking" of a drug is the best predictor of its addictive potential (13), and IN esketamine, which has shown similar drug "liking" to ketamine in recreational drug users (14) has been placed under strict federally regulated access guidelines both in Canada and the United States. Esketamine responders are recommended for ongoing maintenance treatment (15), and though data is limited, maintenance ketamine treatment may also be necessary for some patients (11). Access to ketamine or esketamine has been further limited in the context of the COVID-19 pandemic and an associated shift toward the provision of virtual care, which has now often become patient preference.

In addressing these challenges, some physicians have opted to prescribe intranasal or sublingual (SL) forms of racemic ketamine, although evidence for use of non-IV formulations is limited to small randomized controlled trials (RCTs), anecdotal reports and case series (11). Though caution and prudence are advised, these formulations do not require the same level of supervision or monitoring, rendering them more accessible for both patients and the health care system (4). However, with increased access, the potential for abuse, misuse and addiction has been raised as a caution within several expert consensus statements on the use of ketamine for depression (9, 11, 16, 17).

Ketamine has a history as a party drug, particularly in Asian countries such as Hong Kong, Malaysia and China (18–20), and it was the most popular recreational drug of choice in Hong Kong between 2005 and 2014 (21). Despite its popularity in these countries, ketamine accounts for <1% of illicit drug use internationally, and rates of ketamine misuse are decreasing globally (22). In a ranking of overall "harm" from drugs of abuse, ketamine was ranked sixth, just behind alcohol and ahead of benzodiazepines and stimulants, which are commonly cautiously prescribed when clinically indicated in psychiatric practice (23). Another consideration is that recreational doses of ketamine are much greater than antidepressant doses. For example, one study examining 168 ketamine abusers found that they consumed a median dose of 14 g/week (typically snorted or ingested) and up to 140 g/week (24). In contrast, a meta-analysis of studies involving oral ketamine for depression included doses typically in the range of 1–2 mg/kg every 1–3 days. For further context, the largest dosing studied was 7 mg/kg TID (25), which for an 80 kg patient would translate to only 1.68 g/week.

Ketamine has a longer history of use in pain medicine, and meta-analyses from the anesthesia literature have not reported any cases of dependence or addiction to IV ketamine when used for pain management (26, 27). Similarly, two recent reviews on abuse potential for ketamine (4, 28) noted that aside from select case studies, clinical ketamine studies to date have not indicated concern for misuse, dependence, diversion, addiction in patients with TRD, and interestingly, there is emerging evidence that ketamine may be a potential treatment option for addictions (29). Very few studies, however, have included measures related to addiction or abuse in measuring side effect profile. In a systematic review of ketamine side effects, none of 20 randomized controlled trials reviewed included measures related to addiction (30). Taken together, these data make it difficult to place risk into clinical context.

As no study to date has specifically addressed risk factors for addiction in the TRD population, we set out to assess this in a real world population of patients with TRD currently or previously treated with IN or SL formulations of ketamine. To be comprehensive, we completed this study in three parts. These included (1) patient surveys to assess drug liking and craving, desire or history of using amounts of ketamine greater than prescribed, and screening questions for ketamine use disorder, (2) review of pharmacy records to look for red flags such as requests for early refills or significant dose escalation, and (3) Surveys to the psychiatrists of study participants who were no longer taking ketamine to determine whether addiction, diversion or misuse concerns had been reasons for discontinuation of treatment.

Materials and methods

This study was conducted with approval from the University of Alberta's Research Ethics Board. Adult patients who had filled prescriptions for compounded SL or IN ketamine at Crestwood Apothecary Pharmacy in Edmonton, AB, Canada between January 2016 and December 2020 were eligible to take part in the study. This pharmacy was selected as it has handled the majority of SL and IN ketamine prescriptions by physicians who are affiliated with the Intravenous Ketamine Program at the Misericordia Community Hospital. Patients were excluded from the study if they indicated that they had been prescribed SL or IN ketamine for indications other than major depressive episodes in the context of a bipolar spectrum disorder or Major Depressive Disorder.

The pharmacy team reviewed records of ketamine prescriptions within the specified dates to identify eligible patients, who were then contacted to explain the study and request permission to provide their contact information to the study team. Agreeable potential participants were then phoned by a member of our research team (BC) to arrange a secure online Zoom meeting. During this meeting, study information was reviewed, including all three parts of the study. Verbal informed consent was obtained and documented. This consent included all 3 parts of the study; a participant survey, review of pharmacy records, and survey by the treating psychiatrist for any patients who had discontinued ketamine.

Participant survey

The participant survey was informed by a drug liking and craving questionnaire (DLCQ), which has been previously described and is available online (31). In the absence of a validated tool to assess addiction potential for ketamine in the psychiatric population, the DLCQ was created, based on review of the literature and recommendations for assessing abuse potential from the United States Federal Drug Administration (31). Our survey can be found in **Supplementary Appendix A** and included questions of drug liking, craving, desire to use more ketamine than prescribed, screening questions for a ketamine use disorder, and a place for qualitative comments. Consenting participants were sent an online link to the survey via the SurveyMonkey platform.

Pharmacy record review

In the second part of this study, participants' pharmacy records were reviewed (Telus Health Assyst-Rx-S software) for objective markers of ketamine misuse. Data collected included patient initials, the name of the prescribing physician, ketamine treatment route, total number of ketamine treatments, total treatment duration, starting and current/end doses, and the presence or absence of any early refills recorded and any rational for them.

Psychiatrist survey

For participants whose ketamine had been discontinued, a third step in the study was to send the treating physician a survey to determine if concerns regarding misuse or abuse had contributed to treatment discontinuation (**Supplementary Appendix B**). The rationale for the questionnaire and request to complete it was sent from the study team to the physician via secure email, and again administered via the SurveyMonkey platform.

Results

Participation

Sixty-nine individuals were identified as eligible for participation in this research study. One was subsequently excluded due to the patient's report that ketamine was prescribed for an indication other than depression. Fifty-seven of these potential participants were successfully contacted by telephone by the study team. Forty-four individuals consented to participate in this study, including 10 males, 1 individual who identified as non-binary, and 33 females, ranging in age from 25 to 70. Two individuals later withdrew their consent, one without providing a reason and the other reporting that they found the survey confusing and that they were too busy to continue to participate. Of the 13 individuals who declined to participate, reasons included being too busy, too unwell, or simply uninterested in hearing more about the study (n = 6); failing to attend the scheduled virtual meeting where informed consent was to be obtained (n = 6), and absence of a reliable

electronic device via which to complete the survey (n = 1). Of the 42 consenting participants, 37 initiated survey responses and 33 surveys were completed. Thirteen individuals self-reported a diagnosis of bipolar depression and 20 self-reported unipolar depression.

Participant questionnaire

Participants were asked about their "liking" for ketamine on a bipolar visual analog scale (VAS) from 0–100. Scores below 50 signified a dislike for the effects of ketamine, scores between 50 and 60 were interpreted as neutral and scores above 60 were interpreted as relative "liking" for the effects of ketamine. 17/33 participants had a positive "liking" (60–100), 8/33 were neutral (50–60), and 8 reported a negative liking (0–49) (**Figure 1**). The overall mean "liking" of survey respondents was 57.6.

Cravings were measured on a unipolar VAS, with zero as "no craving" and 50 as "neutral," while 100 was "constant desire to use ketamine." Mean degree of cravings was 20.6, with a range from 0 to 75. Only 6 respondents rated cravings above 50, which was designated as neutral, and 4 of these were in the 51–60 range (**Figure 2**). The most commonly reported range was 0–9 (n = 14), and more than half of respondents reported cravings below 19 (**Figure 2**).

Drug liking and cravings have previously been determined to be markers for the risk of dependence to a substance (32–36). As the US FDA has noted drug liking as the best primary measure of abuse potential (13), and challenges have been noted in interpreting subjective reports on cravings (36), we sought to place this in better context by looking at cravings specifically in those with positive drug liking, under the clinical assumption that individuals who both "liked" ketamine and experienced cravings would be the patient population of greater risk for ketamine abuse. Of the 17 participants who reported a positive liking for ketamine (over 60), 14 responded to rate their level of craving. Of these, 5 denied cravings altogether, 3 did not specify their degree of cravings, and 9 reported variable degrees of craving ranging from 3 to 75. Two of these individuals rated their cravings above neutral (**Table 1**). Of the 16 individuals who had negative or neutral liking for ketamine (under 60), average cravings rating was 18.9/100; 6 had no cravings, 2 did not answer, and others ranged from 3 to 54.

Of the 17 individuals who "liked" the effects of ketamine, no participant met more than one substance use disorder (SUD) criterion (**Table 1**). Interestingly, 3 respondents in the group with neutral or negative liking for ketamine (under 60) reported 2 or more SUD criteria. Of the SUD criteria endorsed, 6 participants reported "needing more ketamine over time to get the dissociative effects you want"; 4 reported "spending a lot of time getting, using, or recovering from the use of ketamine"; 3 reported "taking ketamine in larger amounts or longer than is prescribed"; 3 reported "cravings and urges to use ketamine"; 1 reported "wanting to cut down or stop using ketamine but being unable to do so" (for reasons other than worsening depression), and 1 reported "not managing what you should at work, home, or school because of ketamine use." Of note, two of the four participants who reported "spending a lot of time getting, using, or recovering from the use of ketamine" clarified this by noting that it takes them hours to a full day to recover from the effects of their ketamine treatment.

Ten participants failed to respond to the question regarding desire to use ketamine in doses greater than prescribed. Of those who did respond, the majority (16 of 23) reported a low "desire," in the 0–19 range, 1 participant rated their desire in the mild-moderate range at 36, and 6 participants reported "desire" in the moderate-high (50–79) range (**Figure 3**). Three of 30 respondents reported that they had actually used ketamine in amounts greater than prescribed. These three individuals appeared to have similar "liking" for ketamine to the rest of the study population, but their cravings and desire to use more than prescribed were higher. Two of these individuals reported 2 SUD criteria and one endorsed 5 SUD criteria. One of these individuals commented that they had previously discontinued ketamine due to addiction. This participant was currently treated with prescription ketamine but also reported a previous history of "black market ketamine abuse." It was not clear from this participant's answers whether prescription, or solely illicit, ketamine had been previously discontinued due to addiction, or whether the endorsed SUD criteria related specifically to prescription ketamine or the history of illicit ketamine use.

Although 26 participants endorsed experiencing dissociative effects from their SL or IN ketamine, all survey respondents denied having used their prescription ketamine to "get high." No participant had shared their prescription ketamine with others, but two respondents endorsed having "considered" sharing their ketamine. These individuals specified that the reason was so that their loved ones would know what they experience when they take it. One respondent reported that their prescription ketamine had been stolen and specified in the written comments that this was by a family member who also suffered from depression. Several other participants described taking measures such as not telling others they are on ketamine and/or keeping their ketamine locked up to reduce the risk that this medication would be stolen. Finally, of the 33 participants who responded to the question regarding the presence of dissociative side effects, 26 reported that they do experience dissociative effects from ketamine, whilst 7 responded that they do not.

On qualitative review of comments that participants submitted as part of their survey responses, several themes emerged. Perhaps most notably, participants held strong yet opposing views regarding the dissociative side effects from ketamine. For example, six participants used terms such as "relaxing" and "peaceful" to describe their experience of dissociative side effects, whilst six others described such experiences as "unnerving" and "terrifying." Of further interest,

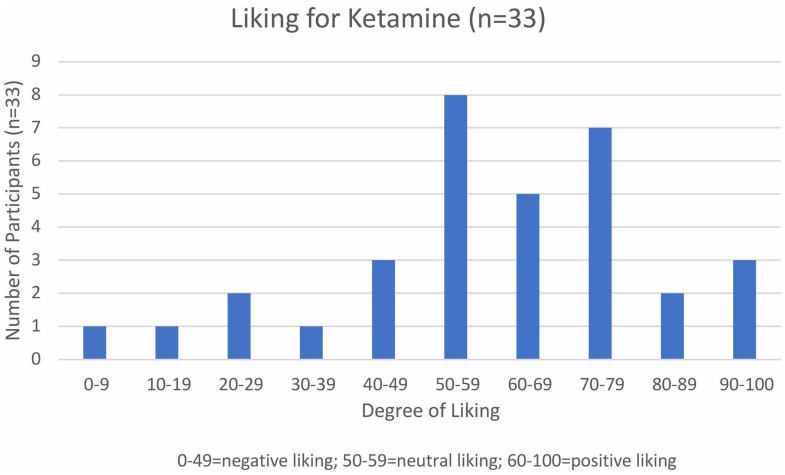

FIGURE 1
Participant ratings of "drug liking" (*n* = 33).

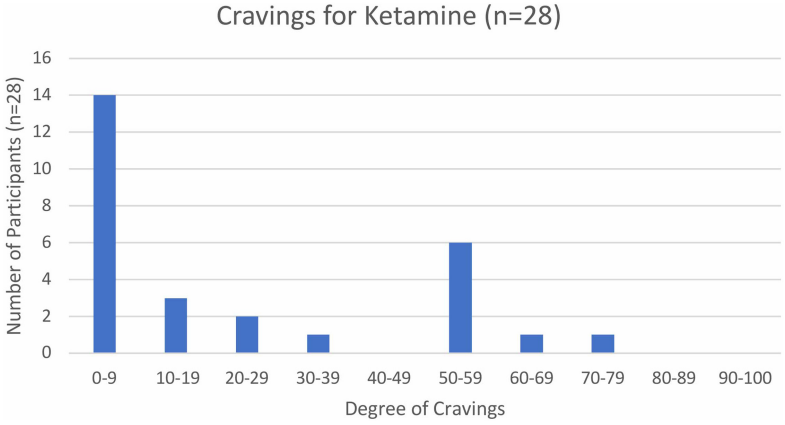

FIGURE 2
Participant ratings of "drug craving" (*n* = 28).

five participants alluded to some "wearing off" of dissociative effects with continued use, six participants suggested that they could "see how" ketamine could become addictive (and cited the "relaxation and peaceful feeling" they experienced following ketamine administration and the "wanting/craving" that can be experienced between treatments to substantiate this concern), and three participants commented that they had not noticed any signs of addiction within their experience of using prescription ketamine. Further, two participants reported taking their ketamine at a dose or frequency lower than prescribed.

Pharmacy record review

Pharmacy records were reviewed for the 42 consenting participants. Of these, 21 participants had ever been prescribed IN ketamine and 37 had ever been prescribed SL ketamine, indicating that some participants had had trials of both. The starting dose of IN for all patients was 100 mg, and it was increased to 150 mg in 5 patients and 140 mg in 1 patient. All others were maintained at 100 mg. The average duration of treatment with IN ketamine was 41.2 weeks, with a range of 5–243 weeks, and 5–389 total treatments. For SL ketamine, the starting doses ranged from 50 to 200 mg with most initial doses at 100 or 150 mg. Fifteen of 37 patients had dose increases to a maximum of 300 mg, while 3 patients had dose decreases. The other 19 participants remained at consistent dosing. The average duration of treatment with SL ketamine was 79.3 weeks, with a range of 4–570 weeks, and 7–990 total treatments. Finally, there were 5 documented early refill requests amongst 5 different participants. Of these, 1 request was to accommodate a pharmacy closure; 1 to accommodate a patient's holiday; 1

TABLE 1 Drug cravings and substance use disorder criteria in patients with positive ketamine drug liking (n = 17)* (positive drug liking defined as liking > 60).

Drug liking > 60	Drug cravings (0–100)	Number of SUD criteria met
60	0	1 (time getting, using)
60	20	1 (cravings)
60	0	–
60	10	–
63	–	0
70	22	1 (tolerance)
70	3	–
70	75	1 (larger amts or longer)
72	11	0
73	65	0
73	0	0
75	0	0
80	–	1 (wanting to cut back)
80	55	1 (tolerance)
90	50	1 (tolerance)
93	–	0
100	0	–

"due to nasal spray liquid not lasting until the estimated time of supply"; and 2 for reasons which were not documented in the pharmacy records.

Physician surveys

Nine physicians were identified as having prescribed ketamine to 15 participants who were "previously treated" with ketamine. Physician surveys were completed for all 15 patients. These surveys indicated no addiction concerns; there were no instances of discontinued ketamine prescribing due to addiction or misuse concerns. Similarly, there were no concerns regarding ketamine diversion and no physicians were aware of participants developing dependency to another recreational substance during their treatment with ketamine.

Discussion

Although this study is descriptive in nature and reports on a small cohort of patients, results suggest that patients prescribed SL or IN ketamine for depression are not universally at risk of drug misuse abuse or diversion. Of the 57 potential participants contacted, only 42 consented and only 33 fully completed surveys. We would posit that this is partially due to the retrospective nature of the survey and the fact it was conducted completely virtually (due to COVID-19), but the possibility for significant response bias exists. Patients with more concerns for addiction/dependence may not have consented to participate or failed to complete their survey. Respondents who were still actively using ketamine treatment may have also under-reported symptoms/signs suggestive of addiction due to concern of having their ketamine prescription changed or discontinued.

Another potential limiting factor was that prospective participants were identified via records from a single pharmacy. This pharmacy has been the primary pharmacy in Edmonton to compound ketamine for psychiatrists who work within Edmonton's ketamine programs, and while participants were the patients of 14 different physicians, data collection from this

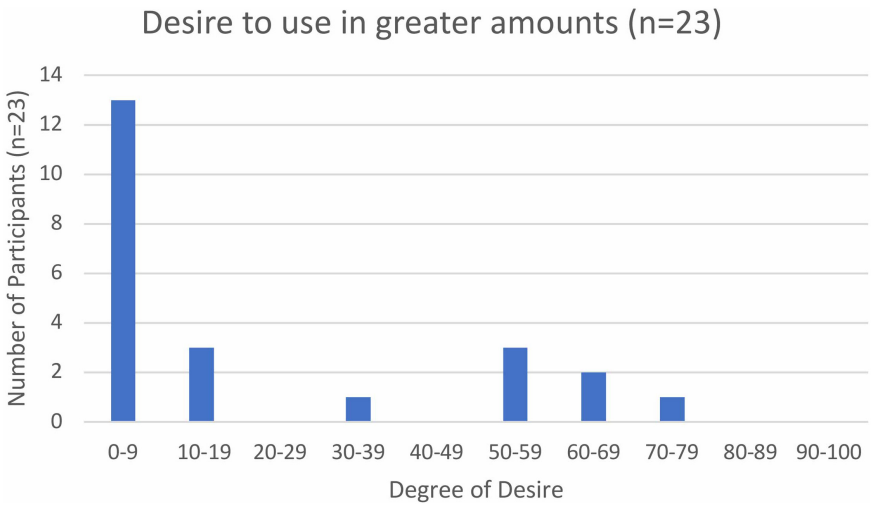

FIGURE 3
Desire to use ketamine in amounts greater than prescribed.

pharmacy alone does limit the pool of prospective participants and prescribers.

The survey itself did not separate experiences with IN or SL ketamine, as many patients had had trials of both. Questions were asked about ketamine in general, and many of these patients had also had previous courses of IV ketamine. In considering abuse/addiction potential, differing pharmacokinetics of the various formulations may impact factors such as liking and craving. Future versions of the survey should also clarify the craving continuum on the VAS to better separate and attribute meaning to those ratings between 1 and 50, as in the current form, they were difficult to interpret. The physician survey was also limited as it was based on clinical judgment only, rather than standardized patient assessment.

Despite multiple limitations, to our knowledge, this was the first study to specifically attempt to assess abuse/addiction potential of ketamine in patients treated with ketamine for TRD. While true level of risk remains unclear, results of this study suggest that prescribing of SL and IN ketamine for TRD need not be viewed with strict prohibition due to addiction concerns, but instead placed within appropriate clinical context of risk/benefit on an individual basis. While this study had a high risk of reporting bias, it remains reassuring that ketamine is not a universally highly liked or craved substance among patient with TRD. Patients surveyed were not using it to "get high" and very few patients desired to use more than prescribed. Ketamine appears not dissimilar to other drugs in psychiatry, such as stimulants or hypnotics, which carry both potential for abuse and for therapeutic benefit for the appropriate patient. Several authors in our group have previously made recommendations for judicious prescribing of non-parenteral ketamine (4), including appropriate patient selection and prescribing considerations. Ketamine prescribers would be advised to use a tool similar to the DLCQ which, though unvalidated and could be improved upon, is a simple tool that can be found online (31). Use of the DLCQ or a similar tool could allow prescribers to routinely monitor patients for signs of drug "liking," "craving," and "desire." Prescribers should also ask patients about misuse of their ketamine, and screen for criteria of a ketamine use disorder. As seen in this study, this data alone is not sufficient due to multiple confounding factors but can be collected as an opening to further discussion to clinically assess abuse/addiction risks for each patient. In the absence of a validated tool, DLCQ or similar scale to assess drug liking could be used in clinical studies to better evaluate and document risk factors related to addiction and misuse of ketamine and esketamine. The DLCQ is currently in use in a real-world study on efficacy of esketamine (37). Though this is a small sample size with qualitative data reporting, **Table 1** would appear to indicate that drug liking is not always associated with craving, and that craving level is quite variable (3–75 range). On review of survey responses, interpretation of cravings rated between zero and 50 is a significant limiting factor in interpretation of our study. In the future, we would suggest adjusting descriptors on the scale to describe intensity and/or frequency along the continuum. We would posit that the largest risk of ketamine misuse or abuse would be in individuals with a high drug liking who also experienced significant cravings for the substance. While there was a subset of patients who did "like" and "crave" the drug, this was not universal. The ketamine treatment experience for TRD appears to be not universally pleasant, enjoyable or desired and this dovetails with many of the authors' significant clinical experience.

As part of this study, we screened for SUD criteria for ketamine. The two most commonly reported SUD criteria were "needing more ketamine over time to get the dissociative effects you want" (i.e., tolerance) and "spending a lot of time getting, using, or recovering from the use of ketamine." In the case of ketamine treatment, tolerance to dissociative symptoms is common and even expected. Clinical experience also indicates that patients may feel more tired the rest of the day following treatment, have side effects such as fatigue or headache, or find the dissociative experience to be emotional. In addition, patients are restricted from driving until the following day after ketamine administration, and thus limited with respect to their usual functioning. As these are common and expected effects following ketamine treatment, they may not be concerning for a SUD. In viewing results in this context, individual positive responses for these one or two SUD seem to carry little relevance in assessing overall risk level, and cannot be interpreted as indicative of a ketamine use disorder in the absence of further data. This is a significant limitation in interpreting this data. Future studies should provide a clear preamble to questions screening for SUD to specify that these statements would NOT relate to any desired dissociative effects for the expected purpose of improved antidepressant efficacy, nor would they relate time required to recover from a standard ketamine treatment.

As no participant endorsed a desire to use ketamine to get "high," we would posit that the most frequent reason a patient would desire to use more ketamine than prescribed would be an expectation that more ketamine could further improve their depression. The patients on maintenance ketamine in this study were a population of highly treatment resistant individuals, and it has been the authors' experience that when individuals with TRD respond to ketamine, much hope is placed in this medication. As part of informed consent for clinical treatment, these patients have also generally been informed by their psychiatrist about the lack of data regarding dosing and duration of treatment for IN and SL ketamine, and this may lead patients to wonder about using more than currently prescribed. Any future studies should include follow up questions as to the reasons why an individual would seek to use extra ketamine to better elucidate level of risk.

Six participants in our study reported needing to use more ketamine over time to achieve a desired dissociative effect, but large dose increases were not seen despite long

durations of treatment. Due to lack of data to guide dosing of these formulations, dose increases likely reflect clinical dosing titration. Further, these 6 individuals were neutral or negative regarding their experience of ketamine, so in this context, this finding likely reflects only tachyphylaxis to dissociation during ongoing ketamine treatment, rather than serving as a red flag for abuse potential. Even if dissociation is not a positive experience, continued dissociative experiences may be desired if patients misattribute the presence of dissociation as an indication that ketamine is "working" for their depression. Though psychedelic psychotherapies, including ketamine psychotherapy, are gaining popularity and rely on dissociation as part of the therapeutic effect, the patients in this study were receiving ketamine only as a part of a pharmacotherapy regimen. Psychoeducation prior to treatment with ketamine should include the concept that dissociative experiences are variable and not necessarily correlated to the antidepressant effects when using ketamine as a pharmacotherapeutic tool. Patient desire to use excess medication should be assessed on an ongoing basis in patients on maintenance ketamine, and reasons for wanting to use more need to be explored by treating physicians to best assess level of risk.

Though no participant endorsed a desire to use their ketamine to "get high," one participant did report a history of illicit ketamine use. Interestingly, in this case, illicit ketamine use in the past did not translate to a desire to abuse prescribed ketamine. In this context, we query whether this individual had used illicit ketamine to self-medicate prior to being prescribed ketamine. Limited access to ketamine programs may stimulate illicit ketamine use by a subset of patients attempting to self medicate a depressive illness, and this uncontrolled use should be strongly discouraged. Increased access to appropriately prescribed SL or IN ketamine may help prevent this uncontrolled use.

Future research assessing ketamine for mental health indications should include measures of addictive potential to further elucidate potential risks so clinicians can better evaluate risks and benefits of treatment.

Data availability statement

The datasets presented in this article are not readily available because Permissions were not obtained from ethics to share data. Requests to access the datasets should be directed to JS, Jennifer.swainson@ualberta.ca.

Ethics statement

The studies involving human participants were reviewed and approved by University of Alberta Health Research Ethics Board. The patients/participants provided verbal informed consent to participate in this study, which was documented by a study investigator over a virtual meeting.

Author contributions

JS, JW, BC, SA, CC, and AK contributed to study design and interpretation of results. SA, JW, and BC contributed to the ethics proposal. BC and MW collected the data. BC wrote the first draft of the manuscript, under supervision and contribution from JS. BC and JS prepared the manuscript revision. All authors reviewed and approved the final manuscript for publication.

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Conflict of interest

AK has received consulting fees and/or speaker honoraria from Abbvie, Bausch, Eisai, Elvium, Jazz, Lundbeck, Otsuka, Paladin, Pfizer, Takeda, and Sunovion and is a medical advisor for the Newly Institute. JS has received consulting fees and/or speaker honoraria from Abbvie, Bausch, Eisai, Lundbeck, Otsuka, and Janssen and is a medical advisor for the Newly Institute.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.1016439/full#supplementary-material

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Case report: Medical student types journals during ketamine infusions for suicidal ideation, treatment-resistant depression, post-traumatic stress disorder, and generalized anxiety disorder

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Suicide is the most common cause of death in male resident physicians and the second most common cause of death in resident physicians overall. Physicians also experience high rates of major depressive disorder (MDD), post-traumatic stress disorder (PTSD), and burnout. These conditions frequently develop during medical school, and threaten not only physicians but the patients they care for. A 30-year-old medical student presented to our clinic with a history of treatment-resistant depression (TRD), generalized anxiety disorder (GAD), PTSD, and 5 years of daily suicidal ideation. Previous treatments included therapy, lifestyle modifications, and various combinations of six antidepressants. These interventions had little effect on the patient's mental health. The patient was treated at our clinic with an 8-month regimen of IV ketamine infusions and ketamine-assisted psychotherapy (KAP). The patient achieved remission from suicidality and PTSD within 1 month; and TRD and GAD within 7 months. The patient's Patient Health Questionnaire (PHQ-9) score decreased from 25 (severe depression) to 1 (not depressed). These findings suggest that ketamine and KAP may represent effective interventions for mental health applications in healthcare professionals. The patient made the unique decision to attempt to type narrative journals during four of his ketamine infusions (doses ranged from 1.8 to 2.1 mg/kg/h IV). The patient successfully typed detailed journals throughout each 1-h ketamine infusion.

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To our knowledge, these journals represent the first independently typed, first-person, real-time narratives of ketamine-induced non ordinary states of consciousness. The transcripts of these journals may provide useful insights for clinicians, particularly in the context of KAP.

KEYWORDS

ketamine, depression, suicidality, medical school, ketamine assisted psychotherapy

Introduction

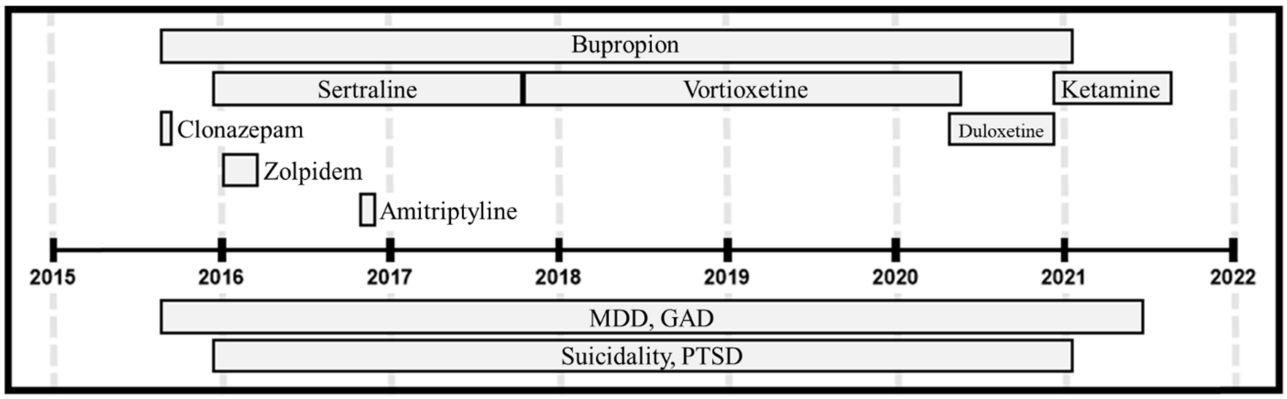
Medical students and physicians experience high rates of mental health disorders. A meta-analysis of 183 studies found that 27% of medical students experience depression, but only 16% of students with depression sought treatment (1). Suicide is the leading cause of death in male resident physicians, and the fourth leading cause of death in female resident physicians (2). A systematic review of 17 studies reported a 12-month prevalence of suicidal ideation in medical students of 7–36%, and a lifetime prevalence of up to 54% (3). Multiple cross-sectional and longitudinal studies report high rates of anxiety in medical students (4–10). A cross-sectional national survey reported positive PTSD screens in 22% of surgical residents, and that an additional 35% of surgical residents were at risk for PTSD (11). Up to 80% of medical students experience humiliation, belittlement, verbal abuse, or discrimination by their superiors, which can lead to symptoms of post-traumatic stress (12–15). Often attributed to stressors such as high workloads, rigorous study requirements, emotional burdens, and financial strains (1), mental health disorders among medical students remains a critically important healthcare concern due not only to impacts on students' quality of life but also to potential repercussions on long-term patient care (6).

First line interventions for MDD, PTSD, GAD, and suicidality include SSRIs, SNRIs, tricyclic antidepressants, atypical antidepressants, psychotherapy, and counseling (16–18). Many patients do not respond well to these treatments (16, 17, 19–27). For example, approximately one-third of MDD patients report inadequate remission rates even after multiple treatment attempts and are said to suffer from treatment-resistant depression (28, 29). For individuals with TRD, cognitive-behavioral therapy (CBT) is the most commonly implemented form of psychotherapy (16), though several studies have reported that CBT may be most effective as an adjunct to pharmacotherapy (30, 31). Although electroconvulsive therapy can be effective for TRD, it is often associated with high cost (32) and adverse cognitive effects (33). Therefore, there is an urgent need for improved therapeutic strategies for patients suffering from TRD.

Burgeoning evidence suggests that psychedelic medications may represent breakthrough treatments for numerous mental health disorders (34–36). (R,S)-Ketamine (ketamine), a dissociative anesthetic with psychedelic properties, reduces symptoms of depression, PTSD, and suicidality when administered at subanesthetic doses (25, 37–40). Extensive research has been published on the pharmacokinetics, pharmacodynamics, and cognitive effects of ketamine (40–43). A wide array of subjective rating scales, cognitive tasks, patient interviews, clinical assessments, and brain imaging techniques have been used to study the effects of ketamine on cognition, dissociation, concentration, verbal fluency, motor coordination, mood, memory, and perception during or shortly after ketamine infusions (44–49). Less is known, however, about the subjective experiences of patients during ketamine-induced altered states of consciousness (i.e., emotional processing, "dreams," meditation, ego dissolution, reliving traumatic experiences, philosophical revelations), in part because these were not traditionally considered to be clinically relevant (34, 50). However, in the context of ketamine-assisted psychotherapy (KAP), clinicians interact with patients who are receiving low-dose ketamine (51–54). In this context, the psychedelic properties of ketamine (i.e., increased receptivity to new ideas, ego dissolution, time-out from ordinary consciousness) represent clinically useful tools, as opposed to problematic side effects (53, 55).

A 30-year-old male medical student was treated for severe depression and suicidality at our clinic with a combination of IV ketamine infusions, KAP, and psychotherapy (**Table 1**). The patient independently chose to type narrative journals (**Supplementary Table 1**: Ketamine Journals 1–4) documenting his subjective experiences during four of his normally scheduled ketamine infusions (doses ranged from 1.8 to 2.1 mg/kg IV over 1 h). These journals include detailed descriptions of what he saw, heard, smelled, felt, and thought during ketamine-induced altered states of consciousness, as well as his perceptions of space, time, and self. In this case study, we report the success of an 8-month regimen of ketamine infusions, KAP, and psychotherapy to reduce suicidality, TRD, and PTSD in a medical student. We also share the transcripts of Ketamine Journals 1–4, conduct quantitative and qualitative analysis of the journals, compare independent typing to established methodologies for evaluating patients

TABLE 1 Timeline of diagnoses and pharmacologic interventions.



Diagnosis/ Intervention	Dose	Start	Stop	Weeks	Response	Notes
MDD	**NA**	**8/27/2015**	**6/21/2021**	**304**	**NA**	First diagnosed on 8/27/2015 by a psychiatrist at TTPPC Monitored by psychiatrists at TTPPC from 2015 to 2016 Monitored by a psychiatrist at an independent clinic from 2016 to 2021 Monitored via PHQ-9 and mood scores at Denovo from 2020 to 2022 (Figure 1) Remission achieved in June of 2021 (after 8 ketamine infusions and 2 KAP sessions)
GAD	**NA**	**8/27/2015**	**6/21/2021**	**304**	**NA**	First diagnosed on 8/27/2015 by a psychiatrist at TTPPC Monitored by psychiatrists at TTPPC from 2015 to 2016 Monitored by a psychiatrist at an independent clinic from 2016 to 2021 Remission achieved in June of 2021 (after 8 ketamine infusions and 2 KAP sessions)
Bupropion	**150–300 mg**	**8/27/2015**	**1/12/2021**	**281**	**No improvement**	**Prescribed for depression, anxiety**
	150 mg	8/27/2015	9/9/2015	2	No improvement	Started patient at 150 mg with a plan titrate dose up as needed
	300 mg	9/9/2015	12/9/2015	13	No improvement	Increased dose due to lack of response
	150 mg	12/9/2015	1/8/2016	4	No improvement	Decreased dose due to side effects
	300 mg	1/8/2016	12/19/2016	49	No improvement	Increased dose due to lack of response
	150 mg	12/19/2016	1/27/2017	6	No improvement	Lowered dose due to side effects, then discontinued due to side effects
	150 mg	5/20/2020	1/12/2021	34	No improvement	Restarted, then discontinued again due to side effects
Clonazepam	**0.5 mg**	**8/27/2015**	**9/17/2015**	**3**	**Minimal response**	**Prescribed for anxiety; patient stopped taking due to concerns about dependence**
Suicidality	**NA**	**Late 2015**	**1/10/2021**	**~267**	**NA**	First reported in late 2015 to a psychiatrist at TTPPC Acute suicidal intention hidden from psychiatrist during crisis visit at TTPPC on 3/2/2016 due to fear of hospitalization Suicide risk assessed seven times from 3/2/2016 to 9/23/2016 at TTPPC Monitored by an independent psychiatrist from 2016 to 2021 Monitored via PHQ-9 question #9 at Denovo from 2020 to 2022 (Figure 1) Remission achieved in December of 2020 (after first ketamine treatment)
PTSD	**NA**	**Late 2015**	**1/10/2021**	**~267**	**NA**	First reported in late 2015 to a psychiatrist at TTPPC Monitored by an independent psychiatrist from 2016 to 2021 Remission achieved in December of 2020 (after first ketamine treatment)
Therapy/Behavioral interventions	**NA**	**9/30/2015**	**2021**	**305**	**Prevented suicide, temporary respite from symptoms**	**Behavioral interventions for the patient included therapy, martial arts, and mentorship**
	Therapy	9/30/2015	9/23/2016	51	No improvement	Patient was seen by a therapist at TTUHSC six times as part of his school's program of assistance, and four times by a psychiatric physician's assistant for CBT. Discontinued in favor of focusing on a relationship with a mentor
	Martial arts	2016	2021	~291	Prevented suicide, temporary respite from symptoms	Patient regularly practiced Brazilian Jiu Jitsu and mixed martial arts. The patient reported that grappling and fighting gave him community, exercise, and temporary mental breaks from depression, anxiety, and suicidality. Training prior to 2016 not reported in this study

(Continued)

TABLE 1 (Continued)

Diagnosis/ Intervention	Dose	Start	Stop	Weeks	Response	Notes
	Mentorship	2016	2021	∼291	Prevented suicide	Patient was seen by a retired psychiatrist on a weekly to monthly basis from 2016 to 2021 in a therapeutic and mentoring capacity. The patient reported that these visits prevented him from committing suicide, but did not resolve his depression, anxiety, or suicidal ideation
Sertraline	**50–100 mg**	**12/9/2015**	**10/17/2017**	**97**	**No improvement**	**Prescribed for depression and anxiety**
	50 mg	12/9/2015	3/2/2016	12	No improvement	Started patient at 50 mg with a plan to titrate dose up as needed
	75 mg	3/2/2016	3/14/2016	2	No improvement	Increased dose due to lack of response
	100 mg	3/14/2016	10/17/2017	83	No improvement	Increased dose due to lack of response, discontinued due to side effects
Zolpidem	**5 mg**	**1/8/2016**	**3/2/2016**	**8**	**Minimal response**	**Prescribed for insomnia; patient stopped taking due to concerns about dependence**
Vortioxetine	**10 mg**	**10/17/2017**	**5/20/2020**	**135**	**No improvement**	**Started for depression, discontinued due to lack of response**
Amitriptyline	**25 mg**	**10/28/2016**	**11/28/2016**	**4**	**No improvement**	**Prescribed for depression, anxiety; discontinued due to side effects**
Duloxetine	**30–60 mg**	**4/29/2020**	**12/10/20**	**32**	**No improvement**	**Prescribed for depression, anxiety**
	30 mg	4/29/2020	10/20/2020	25	No improvement	Started patient at 30 mg with a plan to titrate dose up as needed
	60 mg	10/20/2020	12/10/2020	7	No improvement	Increased dose due to lack of response, discontinued due to side effects
Ketamine	**0.9–1.8 mg/kg/h**	**12/10/2020**	**8/18/2021**	**36**	**Full remission of mental health disorders**	**Patient started 8-month treatment regimen consisting of 12 IV ketamine infusions, 2 KAP sessions, and 2 psychotherapy sessions**
#1 (IV)	0.9 mg/kg/h	12/10/2020	NA	NA	Acute improvement	PHQ-9 decreased from 21 prior to treatment to 5 the next time it was measured (1/10/2021). Patient reported resolution of suicidal ideation
#2 (IV)	1.1 mg/kg/h	12/15/2020	NA	NA	Acute improvement	Infusion 2 was administered as soon as possible after the first infusion. Dose was titrated up
#3 (IV)	1.2 mg/kg/h	12/17/2020	NA	NA	Acute improvement	Infusion 3 was administered as soon as possible after the second infusion. Dose was titrated up
#4 (IV)	1.4 mg/kg/h	1/9/2021	NA	NA	Acute improvement	Patient's schedule delayed Infusion 4. Dose was titrated up
#5 (IV)	1.6 mg/kg/h	2/11/2021	NA	NA	Maintained improvements	Patient's schedule and financial concerns substantially delayed Infusion 5. PHQ-9 score began to rise during this gap in treatment. Dose titrated up
#6 (IV)	1.4 mg/kg/h	3/6/2021	NA	NA	Maintained improvements	Dose titrated down based on patient feedback and long recovery after Infusion 5
#7 (IV)	1.7 mg/kg/h	4/7/2021	NA	NA	Maintained improvements	Dose titrated up based on patient feedback and scheduling constraints (patient would be unable to receive treatment again in the near future)
#8 (IV)	2.1 mg/kg/h	5/13/2021	NA	NA	Maintained improvements	Dose titrated up based on patient feedback and PHQ-9 score beginning to rise during the gap in treatment between Infusions 7 and 8
#9 (KAP)	0.9 mg/kg	5/29/2021	NA	NA	Maintained improvements	First KAP session. Psychotherapy was integrated with a lower dose of ketamine
#10 (KAP)	1.0 mg/kg	6/17/2021	NA	NA	Maintained improvements	Second KAP session. Psychotherapy was integrated with a lower dose of ketamine. Patient's PHQ-9 score reached 1 for the first time after this treatment
#11 (IV)	1.2 mg/kg/h	6/26/2021	NA	NA	Maintained improvements	Dose titrated down from last IV infusion based on patient feedback and to mitigate recovery time
#12 (IV)	1.6 mg/kg/h	7/7/2021	NA	NA	Maintained improvements	Dose titrated up based on patient feedback and therapist's suggestion
#13 (IV)	1.6 mg/kg/h	7/14/2021	NA	NA	Maintained improvements	Dose maintained based on patient feedback and therapist's suggestion
Psychotherapy	NA	7/16/2021	NA	NA	Maintained improvements	No ketamine administered. Patient met with psychotherapist
#14 (IV)	1.6 mg/kg/h	7/27/2021	NA	NA	Maintained improvements	Dose maintained based on patient feedback and therapist's suggestion. Patient's PHQ-9 score reached 1 for the second time after this treatment
Psychotherapy	NA	8/18/2021	NA	NA	Maintained improvements	No ketamine administered. Patient met with psychotherapist

Timing of diagnoses for mental health disorders and timing, dose, and response to medications. Diagnoses and medications were listed in order of when they were first occurred or were prescribed. Responses to medications were based on clinical notes, pharmacy records, and the patient's recollection when necessary. Bupropion, sertraline, amitriptyline, duloxetine, and vortioxetine were taken orally once per day. Clonazepam was taken orally up to twice daily as needed. Zolpidem was taken orally once per day in the evening as needed. Ketamine infusions were administered via IV over 1 h. Ketamine for KAP sessions was administered via a single intramuscular shot. Medications not relevant to the present study (i.e., ibuprofen) were not included. Rows with medications in bold: indicate dose range and total time period over which the medication was prescribed; sub-rows (not in bold) document timing, response, and rationale for changes in dose. Exact dates were reported when available. Ketamine treatments were labeled 1–14 (comprised of 12 IV infusions and 2 KAP sessions) in order of date. TTPPC, Texas Tech Physicians Psychiatry Clinic.

during ketamine infusions, and explore potential implications for clinicians.

Case report

Patient information, clinical findings, and timeline

A 30-year-old, 77-kg, Caucasian male medical student presented to Denovo Therapy (Denovo)[1] with a history of TRD, GAD, PTSD, and 5 years of daily suicidal ideation. The patient reported depressed mood, difficulty concentrating, decreased academic performance, anhedonia, loss of appetite, insomnia, recurrent nightmares, loss of energy, loss of interest in social activities, feelings of worthlessness, grief due to the end of a relationship, and anxiety about the future. The patient perseverated on, fixated on, and re-lived specific traumatic events associated with his medical training. The patient also reported a history of household instability and parental fighting throughout his childhood, and chronic back pain from the ages of approximately 15–30. The patient engaged in heavy binge drinking for 1 month in early 2016 to self-medicate for depression. Over the course of 5 years, the patient was seen by multiple psychiatrists and therapists and was prescribed strategic combinations of seven SSRIs, SNRIs, atypical antidepressants, and benzodiazepines (Table 1). None of these interventions had a meaningful effect on the patient's mental health. The patient was recommended for electroconvulsive therapy, but refused treatment due to time constraints and lack of proximity to a treatment facility.

Diagnostic assessment

Diagnostic methods

Diagnoses for MDD, GAD, PTSD, and suicidality were made using the Structured Clinical Interview for DSM-IV (SCID-I); the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5); and the Columbia-Suicide Severity Rating Scale (C-SSRS) (56–59). TRD diagnosis was made based on inadequate response to multiple antidepressants of different classes taken at adequate doses and durations (Table 1) (60). The Patient Health Questionnaire (PHQ-9), a version of the PRIME-MD diagnostic instrument, was self-administered by the patient using the Osmind electronic health records platform[2] at regular intervals (Figure 1 and Table 2) (61–64). PHQ-9 was used to monitor depression severity, response to treatments, and for diagnostic purposes. Question #9 of the PHQ-9, "Over the past 2 weeks: Thoughts that you would be better off dead, or thoughts of hurting yourself in some way?" and the follow up to Question #9, "Do you have an active intent or plan to harm yourself?" were used to monitor suicidality (Table 2). Subjective mood scores (scale from 1 to 10, where 1 is worst, and 10 is best) with optional journal entries were recorded by the patient daily in Osmind (Figure 2).

1 https://denovotherapy.com/

2 www.osmind.com

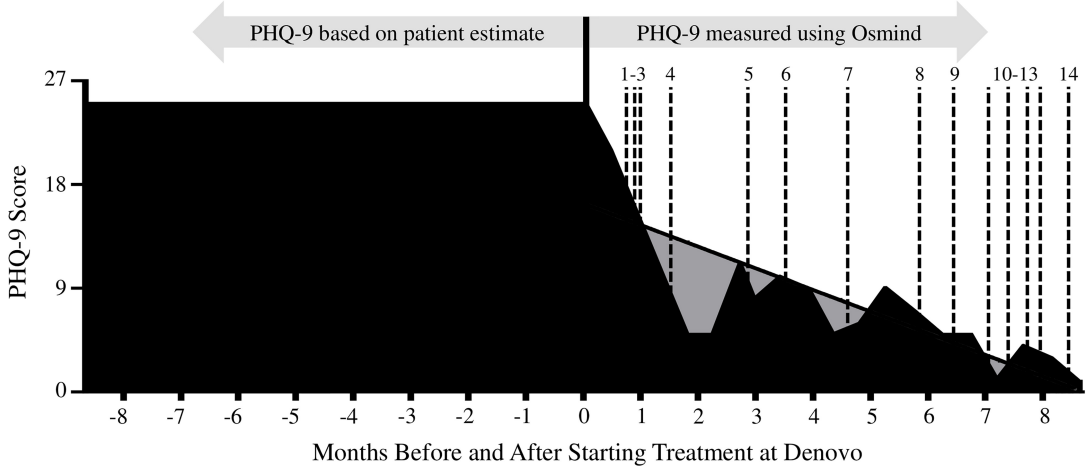


FIGURE 1
The patient's Patient Health Questionnaire (PHQ-9) scores 8 months prior to and after starting treatment at Denovo Therapy. PHQ-9 scores prior to establishing care at Denovo Therapy were based on patient estimates, after establishing care scores were recorded in Osmind. Gray shading: represents the area under a simple linear regression of PHQ-9 data from day 1 (first PHQ-9 measurement; measured 3 weeks prior to first ketamine treatment) to day 258 (last PHQ-9 measurement taken during the 8-month treatment regimen). Dotted lines: correspond to ketamine treatment dates (1–14).

TABLE 2 Long-term impact of ketamine and ketamine assisted psychotherapy (KAP) on the patient's Patient Health Questionnaire (PHQ-9) scores.

Date	Month #	PHQ-9 score	PHQ-9 question #9	Active intent or plan to harm yourself?
PHQ-9 scores during 8-month regimen				
11/18/2020	1	25	4	Yes
12/1/2020	1	21	4	Yes
1/10/2021	1	5	1	No
1/24/2021	2	5	1	No
2/7/2021	2	11	2	No
2/14/2021	2	8	2	No
2/28/2021	3	10	2	No
3/14/2021	3	9	1	No
3/27/2021	4	5	1	No
4/11/2021	4	6	1	No
4/24/2021	5	9	1	No
5/9/2021	5	7	2	No
5/23/2021	6	5	1	No
6/7/2021	6	5	1	No
6/21/2021	7	1	1	No
7/5/2021	7	4	1	No
7/19/2021	8	3	1	No
8/2/2021	8	1	1	No
PHQ-9 scores after 8-month regimen				
8/30/2021	9	6	1	No
9/18/2021	10	5	1	No
10/2/2021	10	3	1	No
10/16/2021	11	7	1	No
10/31/2021	12	1	1	No
11/17/2021	12	2	1	No
12/4/2021	13	10	1	No
12/27/2021	14	6	1	No
1/10/2022	14	5	1	No
3/2/2022	16	4	1	No
3/22/2022	17	5	1	No
4/19/2022	18	3	1	No
5/5/2022	18	2	1	No
5/19/2022	19	4	1	No

Dates, number of months after starting treatment at Denovo, and PHQ-9 scores during and after the 8-month treatment regimen. Responses to PHQ-9 Question #9 "Over the past 2 weeks: Thoughts that you would be better off dead, or of hurting yourself in some way?" were reported individually (1 = not at all, 2 = several days, 3 = more than half the days, and 4 = nearly every day).

Diagnostic challenges

The patient was evaluated at five separate clinics by six psychiatrists, two therapists, and one psychologist prior to intake and treatment at our clinic. The diagnostic tools, reporting methods, and availability of data differed widely from clinic to clinic, limiting the degree to which diagnoses could be compared. The patient reported that he hid the severity of his suicidal ideation from all but one of his mental health providers due to fear of hospitalization; unfortunately this provider did not measure or document the patient's suicidality over time. The patient's rigorous academic schedule was a barrier for the use of structured, standardized diagnostic assessments.

Diagnostic reasoning

The patient presented to our clinic with prior diagnoses of MDD, GAD, PTSD, and suicidality from psychiatrists at independent clinics. Tools used by these clinicians included SCID-I, CAPS-5, and C-SSRS. Depression severity and response to treatment was monitored by Denovo using the PHQ-9 questionnaire and subjective mood scores. Although the PHQ-9 is less sophisticated than other diagnostic tools for depression (i.e., SCID-I), it is brief, does not require a clinician to administer it, and has been validated as a measure of depression severity and for monitoring treatment outcomes (62–64). The brevity and simplicity of the PHQ-9 made it a pragmatic choice to gather data over a long period in a medical student who faced time constraints. No long-term rating scales for GAD or PTSD were administered at our clinic. However, MDD, GAD, PTSD, and suicidality were evaluated by an independent psychiatrist approximately once every 3 months throughout the duration of this study.

Therapeutic intervention

The patient was treated at our clinic with a structured regimen of IV ketamine infusions, KAP, and standard psychotherapy sessions for 8 months. In total, the patient received twelve IV ketamine infusions, two KAP sessions, and two psychotherapy sessions (**Table 1**). The patient's blood pressure, echocardiogram, pulse, and oxygen saturation were monitored throughout each intravenous treatment and prior to each KAP session. An integrative approach to ketamine therapy was used to calibrate ketamine doses, with the goal for the patient to experience meaningful, mystical experiences, noting that the efficacy of ketamine increases with the existence of a mystical/psychedelic experience (65, 66). All treatments employed a multimodal psychedelic model of care, including patient education, a comfortable setting, music, eye shades, and encouragement to find meaning from the experiences (54, 67–69). The patient was encouraged to integrate elements from therapy sessions.

Intervention ketamine infusions

The timing, type of intervention (IV ketamine infusion vs. KAP vs. psychotherapy), and dose for ketamine treatments were determined based on our clinical protocols and the patient's PHQ-9 scores (**Table 1**). The patient's academic schedule, finances, and willingness to participate were also considered. We note that many TRD patients, similar to this case, are unwilling

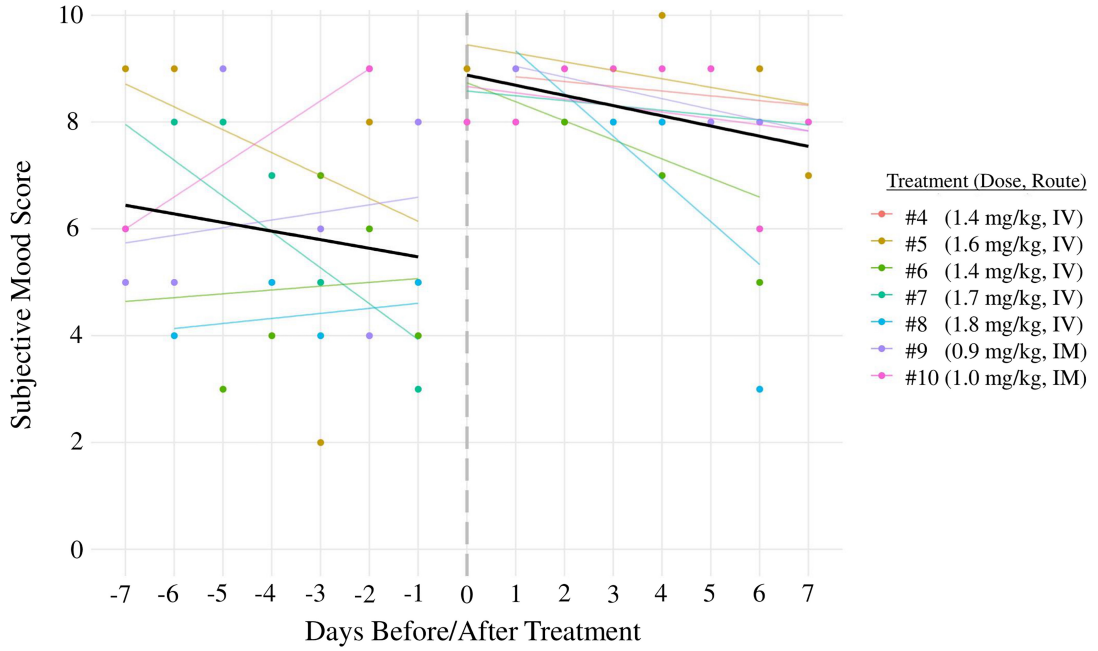


FIGURE 2
Mood scores 7 days before ketamine treatments (**left side** of graph) were compared to mood scores 7 days after (**right side** of graph) for ketamine treatment sessions 4–10. Black lines: linear regression lines (days before/after treatment predicting mood) averaged across all sessions. Colored lines: linear regression lines for each individual treatment session. All treatments were administered over the course of 1 h. Treatments 1–3 were excluded from mood score analysis because the time between sessions was less than 7 days; treatments 11–14 were excluded because the patient did not document his mood scores regularly during that time period.

to try psychotherapy for fear that it will not work for them, either because of previous failed attempts or stigma. Like this case, clinically we observe patients are willing to enter care through the infusion model. Once some results are achieved and a therapeutic relationship is established, we are often able to add other psychotherapeutic modalities. Ondansetron (4–8 mg, sublingual or IV) were administered prior to ketamine treatments to mitigate nausea.

While 0.5 mg/kg (IV infusion) over 40 mins is the most commonly used dose of ketamine for mental health applications, it is not necessarily the optimal dose for every patient (65, 66). Based on the patient's severe depression, acute suicidality, failure to respond to six antidepressants (**Table 1**), and limited time to devote to treatment, we elected to start him at a slightly higher dose of 0.9 mg/kg (IV infusion) over 60 mins. While this mg/kg dose is higher, it is notable that the duration of the infusion is also higher. Considering the example above, a dose of 0.5 mg/kg for 40 mins is 0.0125 mg/kg/min, while 0.9 mg/kg for 60 mins is 0.015 mg/kg/min. Longer infusion times allow the patient to enter the experience more gradually. For most patient populations, this encourages the patient to learn to navigate the altered state of consciousness building trust and partnership with the medicine, the experience, and themselves. Subsequent treatments allow for dose escalation based on the patient's physiological and psychological response. Dose escalations require no previous drop in room air SPO2 below 94%, hemodynamic stability, ambulation within <30 mins of treatment, the patient's ability to retain and relate elements of their experience, and the patient's reporting of psychological benefits. Our protocols are consistent with other researchers who also found that repeated treatments with dose escalation showed increased efficacy for TRD patients (70, 71).

Ketamine-assisted psychotherapy

Including KAP along with two integrative therapy sessions added a depth of understanding to the client's experience by addressing core issues related to psychological disturbance. In a KAP session an initial intention setting time was used to allow the patient and therapist to prepare for the psychological work to be done along with ketamine. The patient's intention in his first KAP was "to notice that even if life feels stressful and stuck, its ok, I'm enough." The therapist acted as a guide encouraging the client toward certain emotional material based on the client's intentions and expressed desire for change. As the session continued, the client was able to identify his ability to hold two polarities of emotion at once: stress over his career/medical school program, and his knowledge of his self-worth regardless of vocation. One of the benefits of KAP was that the client could notice challenging historical and emotional material along with new emerging states of awareness (72). The

therapist encouraged the client to enjoy the break from his ordinary stressors and utilized the idea of "pendulation" (73) to move toward pain points and then out again to his awareness of the ketamine experience.

Psychotherapy

To help the continuity of this new state of expanded reflection, two integration psychotherapy sessions were conducted with the same therapist. The therapist integrated the use of EMDR somatic resourcing to extend the effects of the ketamine experience and the client's new approach to life. Somatic resourcing with bilateral stimulation is a way for the client to have repeated engagement of the ventral vagal state by remembering both external and internal phenomena that bring them comfort and safety. The patient resourced his felt sense of being at the ketamine clinic. The patient recalled the smells of the office, the touch of the blanket, the feeling of being in the reclined chair, and feeling safe in the presence of his providers, which brought him feelings of peace and relaxation. This somatic resourcing process with bilateral stimulation allowed improved access to the ventral vagal state by putting the client in touch with his ability to tolerate negative affect and stress (74). The patient was encouraged to utilize this felt sense of this resource as a tool for when he met challenges around his work as a medical student.

Independent journaling during ketamine infusions

The patient independently chose to document his subjective experiences during ketamine infusions. The patient established his own methodology: while reclining in a chair before the start of each infusion, he used pillows to position his hands on a keyboard. To make typing easier, the patient chose not to capitalize words, replaced almost all punctuation with the return key, and asked the provider monitoring him to reorient his hands if they strayed out of position. The patient created custom musical playlists with "marker songs," and transcribed the lyrics to estimate how long after the start of each infusion he was typing certain sentences. The patient's goals included: describing ketamine-induced altered states of consciousness while experiencing them from a first-person perspective, determining if it was possible to type during ketamine infusions, and determining if he was able to focus his attention on topics discussed with his therapist. Two versions of each journal are included in this report: an unedited version that reflects what the patient was capable of writing during the infusions and a transcript edited by the patient to correct minor errors and clarify text that would have been difficult to interpret (**Supplementary Table 1**: Ketamine Journals 1–4). The patient was careful not to alter the original meaning in the edited transcript.

Results

Long-term impact of ketamine and ketamine-assisted psychotherapy

The patient's PHQ-9 score decreased from 25 (severe depression) to 1 (not depressed) after 8 months of treatment at our clinic (**Figure 1**). A simple linear regression was used to test if time in our treatment regimen significantly predicted the patient's PHQ-9 score over the course of the 8-month treatment regimen. The overall regression was statistically significant [R^2 = 0.6032, $F(1, 16)$ = 24.32, p = 0.0002]. Therefore, it was found that time in our treatment regimen significantly predicted the patient's PHQ-9 score. At 8 months after the first treatment, the patient reported no depression, anhedonia, or generalized anxiety. He no longer experienced recurring nightmares or insomnia. He reported increased energy, ability to focus, and motivation. His academic performance improved, and he reported improvements in interpersonal relationships. The patient's MDD and GAD were considered to be in remission 7–8 months into the treatment regimen based on a PHQ-9 score of 1 and a clinical interview by an independent psychiatrist. Over the following 10 months, the patient maintained an average PHQ-9 score of 4.3 (range 1–10) (**Table 2**).

The patient was suicidal for 5 years prior to treatment at Denovo (**Table 1**). This included an active plan to commit suicide for 3 years and one suicide attempt. The patient's responses to PHQ-9 Question 9, "Over the past 2 weeks: Thoughts that you would be better off dead, or of hurting yourself in some way?" and follow up question "Do you have an active intent or plan to harm yourself?" changed from "nearly every day" and "yes" prior to his first ketamine treatment to "not at all" and "no" immediately after (**Table 2**). The patient responded "not at all" to PHQ-9 Question 9 on all but four questionnaires over the next 18 months (on those four questionnaires, the patient responded "several days"). The patient never responded "yes" to the question "Do you have an active intent or plan to harm yourself?" over the 18 months following his first ketamine infusion.

The patient was diagnosed with PTSD by a psychiatrist at an independent clinic in 2015 (**Table 1**). While no consistent, long-term measure for PTSD was administered by Denovo, the patient reported interacting with and resolving specific traumatic events during his first ketamine infusion. After this infusion, the patient reported that he no longer experienced recurrent, involuntary, or distressing memories about the inciting events, no longer experienced recurrent nightmares related to the inciting events, no longer experienced intense psychological distress in response to external cues that reminded him of the inciting events, no longer avoided memories or external reminders related to the inciting events, no longer experienced persistent negative thoughts about himself, no longer experienced a persistent negative emotional state, no

longer felt detached from others, and reported reductions in self-destructive behavior and difficulty concentrating. The patient reported that these improvements were maintained over the next 18 months. These findings were confirmed by a psychiatrist at an independent clinic using unstructured clinical interviews (**Table 1**).

Short-term impact of ketamine and ketamine-assisted psychotherapy

The short-term effect of ketamine and KAP on the patient's mood was evaluated using subjective mood scores (0–10, higher scores indicate better mood). The patient's subjective mood scores the week prior to treatments 4–10 had an average of 5.94 ± 0.35, compared to 8.20 ± 0.20 the week after, indicating that ketamine treatments had an acute positive effect on the patient's subjective mood ($p < 0.05$; **Figure 2**). Treatments 1–3 were excluded from mood score analysis because the time between them was less than 7 days; treatments 11–14 were excluded due to insufficient data.

Journal transcripts and typing analysis

The patient typed 1,195, 578, 410, and 331 words during the infusions for Ketamine Journals 1–4, respectively. The patient's typing accuracy was calculated by dividing the number of spelling/grammar errors by the total number of words typed during each ketamine infusion. The patient provided a blindfolded typing sample while sober to serve as a positive control (**Supplementary Table 1**). The patient's typing accuracy decreased from 100% while fully conscious to approximately 94, 86, 79, and 84% while typing Ketamine Journals 1–4, respectively.

Ketamine Journals 1–4 included detailed descriptions of the patient's thoughts, feelings, sensations, and perceptions during ketamine emergence at doses from 1.8 to 2.1 mg/kg/h IV. The patient recorded alterations in his visual, auditory, somatosensory, and olfactory senses; attempts to orient himself to time, place, and self; meditation, prayers to a higher power, and repetitive mantras. The patient wrote one poem, transcribed the lyrics of the music he was listening to, and identified his "marker songs." He wrote occasional remarks directed toward the provider who was monitoring him. The patient stated that typing was extremely difficult during infusions: he was generally unaware of the position of his hands, his hands felt like they moved on a time delay, and sometimes he couldn't feel his hands at all. Profound thoughts and deep emotions frequently distracted him from typing. Upon returning to an ordinary state of consciousness after the infusions, the patient did not know if he had successfully typed anything–despite having typed hundreds of words–until removing his blindfold and looking at his computer screen.

Discussion

Established therapies for MDD, suicidality, GAD, and PTSD include SSRIs, SNRIs, tricyclic antidepressants, atypical antidepressants, psychotherapy, and counseling (17, 18), but many patients do not respond well to these interventions (16, 17, 19–27). In particular, the effect of antidepressants on suicidality is complex and age dependent. A recent meta-analysis of randomized controlled trials found that antidepressants actually *increased* risk for suicidality in individuals less than 25 years old and had a neutral effect on individuals 25–64 years old (75). Because most matriculants begin medical school in their early twenties (76), alternatives to traditional antidepressants should be considered for suicidality in medical students.

The positive effects of ketamine were both immediate and long-term for the patient in this report. The patient experienced an acute decrease in depression and suicidal ideation immediately after his first IV ketamine infusion (0.9 mg/kg, administered IV over 1 h), and long-term resolution of his depression and suicidal ideation after 8 months of treatment (**Figure 1** and **Table 1**). These effects are consistent with the broader literature showing that ketamine is an effective intervention for TRD and suicidal ideation (37, 70, 71, 77). Our findings were consistent with a study conducted by Phillips and colleagues in 2019, which found that repeated ketamine infusions were effective to reduce depression in TRD patients (78).

However, our report differs from the established literature regarding the schedule for ketamine treatments, the doses of ketamine used, and the total number of ketamine treatments administered. Most studies on ketamine for mental health applications utilize 0.5 mg/kg of ketamine (IV) over 40 mins (40, 78). For example, Phillips et al., administered six ketamine infusions (0.5 mg/kg over 40 mins) thrice weekly for 2 weeks (78). Patients who responded well to the first six treatments underwent an additional four treatments, for a total of ten. The patient in the present study could not devote 2 weeks to ketamine infusions due to his academic schedule, was severely depressed, and was actively suicidal. Therefore, we chose to modify his treatment schedule to limit interference with school, slightly increase his starting dose of ketamine, and continue maintenance treatments as needed to prevent relapse. After the first treatment, we calibrated subsequent doses of ketamine based on established recommendations (70, 71) and in partnership with the wishes of the patient and his other mental health providers. Our findings suggest that alternative treatment schedules and dosages of ketamine may be effective for patients who are unable to devote weeks to treatment in a single time block.

Ketamine is also emerging as a potential treatment for PTSD, but more research in this area is needed (79–81). One randomized clinical trial found that ketamine rapidly reduced PTSD symptoms (82), and a study on PTSD in burned service

members found that individuals who received perioperative ketamine had a lower prevalence of PTSD than those who did not (83). The patient in the present study was diagnosed with PTSD in 2015, and none of the six antidepressants he took mitigated his symptoms (**Table 1**). He stated that during his ketamine infusions he interacted with and resolved specific traumatic events, and that after infusions he felt a sense of freedom from persistent negative thoughts related to those events. The patient's PTSD fully resolved by the end of the treatment regimen. These findings provide further reason to investigate ketamine for PTSD.

Limitations of this report include the lack an active placebo control (i.e., midazolam); a lack of consistency in selection, administration, and reporting of diagnostic measurements across five separate clinics prior to intake at Denovo; and a lack of long-term, recurring measures for PTSD and GAD. A structured, standardized clinical interview was not used to verify remission of PTSD. The patient's rigorous academic schedule often precluded the use of structured, standardized diagnostic assessments. The patient and providers were not blinded to therapeutic interventions. Because the patient elected to delay KAP and psychotherapy until more than 6 months into his treatment regimen (at which point most symptoms had already improved), it was difficult to compare the therapeutic value of IV infusions, KAP, and psychotherapy. Mood scores were used to monitor short-term changes in the patient's subjective mood (**Figure 2**), but this metric has not been validated as a reliable tool for research and is susceptible to bias. The translatability of our findings may be limited because the patient underwent years of therapy prior to his first infusion (which may have modified his response), and because the patient showed a unique level of engagement with the treatment regimen (i.e., typing journals during infusions). While the patient did not experience any major adverse effects, he was unable to study or attend school on the days he received treatments, which could present a challenge for some students. The risk for adverse events from low doses of ketamine, while extremely low in a clinical setting, cannot be fully ruled out (84, 85).

Strengths of this report include the large amount of PHQ-9 data gathered at regular intervals before, during, and up to 10 months after the 8-month treatment regimen; the large amount of diagnostic information from multiple independent sources; excellent documentation of antidepressant dose, timing, and response for comparison to ketamine therapy; and the dramatic improvements seen in the patient's long term mental health. Ketamine-assisted psychotherapy is an emerging model of care in which providers interact with patients who are experiencing non-ordinary states of consciousness. Unfortunately, relatively little is known about the subjective experiences of patients during psychedelic experiences, limiting the potential for providers to act as guides. To our knowledge, the patient in this study is the first to use real-time typing as a method to report psychedelic experiences. Published methods to document the effects of ketamine include subjective rating scales, cognitive tasks, patient interviews, clinical assessments, brain imaging, and journaling after returning to ordinary consciousness (44–49). Compared to these methods, typing is unique in that it allowed our patient to generate highly detailed, open-ended descriptions of his experiences. Typing is a relatively fast form of communication and allowed the patient to generate large volumes of data per treatment. The patient's reports were less likely to be influenced by the amnestic effects of ketamine because they were typed in real time, an advantage over methods in which patients are interviewed minutes to days after waking up (86, 87). The patient's descriptions were also unique in that they arose from what the patient was motivated to report, as opposed to responding to tightly worded rating scales or questionnaires. In this sense, narrative typing provides insight into what matters about non-ordinary states of consciousness from the perspective of the patient, which could be useful information for KAP providers. However, the authors do not recommend that patients attempt to type during ketamine infusions in general, nor do we recommend typing as a modality for further research. Typed narrative descriptions lack the rigor, reproducibility, and comparability of carefully designed rating scales and cognitive tasks. They also require substantial skill, motivation, and effort on the part of the patient. Our patient reported that typing during infusions was extremely difficult, exhausting, and sometimes retracted from his experience.

The experiential effects of ketamine documented by the patient were largely consistent with the established literature. Similar to other reports, the patient experienced dissociative symptoms (47); psychotomimetic effects (38, 39, 88); alterations in hearing, vision, and proprioception (89–91); and impaired cognition, concentration, and memory (44, 46, 49, 88). The patient also experienced decreased motor coordination (49). However, the patient in this study was unique in that he was able to independently maintain directed attention toward a predetermined goal throughout ketamine infusions at doses as high as 2.1 mg/kg/h (IV). Although there is no way to fully communicate psychedelic experiences to those who have never had them, our patient's detailed, real-time journals may provide helpful insights for providers. Patients who are hesitant to try ketamine therapy may also benefit from reading the experiences of another patient.

Medical students and physicians are a uniquely at-risk population for mental health disorders, and the negative downstream effects of these conditions on their patients and communities cannot be overemphasized (92, 93). Although ketamine and KAP may be expensive and require substantial time investments, they are more affordable than most higher levels of care after first line options have failed. While time constraints for ketamine and KAP are legitimate, our report demonstrates that ketamine treatments can work into a busy schedule where electroconvulsive therapy and in-patient hospitalization would be more difficult. Patients also determine whether ketamine will work for them faster than

antidepressants, which require at least a month to take effect. Perhaps most importantly, ketamine rapidly reverses suicidality (37). For this reason alone, the authors argue that ketamine is a reasonable first line consideration for suicidality and other severe mental health indications in medical students. While no treatment modality can replace the need for substantial reform to a healthcare system that contributes to high rates of mental health disorders in medical students and physicians, ketamine and KAP represent previously untapped treatment modalities that could benefit this population.

Patient perspective

"Traumatic events during my medical training caused me to develop severe depression. I had suicidal thoughts during almost every quiet/non-distracted moment for over 3 years, and I had nightmares almost every night. The constant pressure to perform well in school combined with the rigorous schedule made it nearly impossible for me to find time to grieve, rest, or process my emotions. I was seen by multiple counselors, therapists, and psychiatrists, but my symptoms continued to worsen. Months waiting to see if various iterations of antidepressants would help were months of suffering, and when those treatments failed, I felt hopeless. I began to rationalize ways that I could take my own life but still help people, for example by becoming an organ donor. I decided to try ketamine treatments as a last resort, even though I was highly skeptical that anything could help me. During my first ketamine infusion, I re-experienced and emotionally processed some of the worst traumatic events associated with my training. I told a person who is no longer in my life that I love them, apologized for hurting that person, and forgave myself for past mistakes. Immediately upon waking from this treatment the constant suicidal ideation and self-hatred were gone, like a tumor had been removed from my brain. I was able to sleep peacefully without nightmares, meditate quietly without intrusive thoughts, and reconnect with friends and family who I had been distancing myself from (an attempt to lessen the pain they would feel if I took my own life). I genuinely looked forward to each new day instead of dreading the future, my ability to study greatly improved, and I was also able to process new traumatic experiences without descending into severe depression. Although I experienced mild to moderate depression/anxiety at times over the next year (primarily due to external stressors from school), follow-up treatments with ketamine and psychotherapy prevented me from relapsing anywhere close to my previous state. In my view, the years of cognitive behavioral therapy, counseling, and psychiatric care I underwent prior to ketamine treatments laid the groundwork for improvements to take place; but it was the ketamine that provided the breakthrough necessary to free me from my depression. Before ketamine treatments, I couldn't imagine what it would be like to want to be alive; after, I couldn't imagine what it would be like to want to be dead.

I decided to try to write down what was happening while I was "dreaming" during infusions to help others feel less nervous about ketamine therapy. The staff at Denovo was skeptical that I would be able to type during infusions, but I am grateful that they allowed me to attempt to do so. I also wanted to write during my infusions to document the extraordinary things I experienced, test whether I could direct my focus toward topics I had discussed with therapists, explore what the mind is capable of, and decrease the stigma around ketamine. Each time that I typed a journal, I was surprised that I had typed when I woke up. I was surprised to see pages and pages of notes on my computer screen. Over time though, and after reading my notes, my memories from the ketamine "dreams" partially returned, including what it was like to type. Typing was extremely difficult. It was like trying to remember the name of someone you met only once years ago, and you were at the bottom of the ocean with a 2-mile-long stick attached to a pen trying to write that person's name on a piece of paper on a moving boat–and everything was on a time delay–and you couldn't feel the stick. I am grateful that I can read my notes to reflect on what my experiences taught me."

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding author.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual for the publication of any potentially identifiable data included in this article.

Author contributions

JW collected the data, analyzed transcripts, and wrote initial drafts of the abstract and case description. BM conducted the patient intake and facilitated all treatments at Denovo Therapy. LK conducted KAP sessions. AA calculated the dosages of ketamine and conducted a literature review. PP wrote the initial draft of the introduction and assisted with editing. NS assisted with data collection, assisted with the literature review, and contributed to the introduction. KI designed the figures and tables. MS conducted literature review and assisted with editing.

BM, LK, and JK provided expertise and advice. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.1020214/full#supplementary-material

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A comparison of the antianhedonic effects of repeated ketamine infusions in melancholic and non-melancholic depression

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Objectives: Melancholic depression may respond differently to certain treatments. The aim of this study was to compare the antianhedonic effects of six intravenous injections of 0.5 mg/kg ketamine in patients with melancholic and non-melancholic depression, which remain largely unknown.

Methods: Individuals experiencing melancholic ($n = 30$) and non-melancholic ($n = 105$) depression were recruited and assessed for anhedonic symptoms using the Montgomery–Åsberg Depression Rating Scale (MADRS). The presence of melancholic depression was measured with the depression scale items at baseline based on DSM-5 criteria.

Results: A total of 30 (22.2%) patients with depression fulfilled the DSM-5 criteria for melancholic depression. Patients with melancholic depression had a non-significant lower antianhedonic response (43.3 vs. 50.5%, $t = 0.5$, $p > 0.05$) and remission (20.0 vs. 21.0%, $t = 0.01$, $p > 0.05$) to repeated-dose ketamine infusions than those with non-melancholic depression. The melancholic group had significantly lower MADRS anhedonia subscale scores than the non-melancholic group at day 26 ($p < 0.05$).

Conclusion: After six ketamine infusions, the improvement of anhedonic symptoms was found in both patients with melancholic and non-melancholic depression, and the efficacy was similar in both groups.

KEYWORDS

clinical trial, ketamine, depression, melancholia, response

Introduction

Melancholic features were classified by the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5) as a particular subtype of major depressive disorder (MDD), which may coexist with other patterns of depressive symptoms (1). This concept of melancholic depressive symptoms primarily originated from the historic concept of "endogenous depression" (2). Melancholia can occur in either MDD or major depressive episodes (MDEs) of bipolar depression (BD) (3). Melancholic depression may be associated with a relatively severe clinical manifestation of mood disorder (3).

Patients with melancholic depressive are differentiated from patients with non-melancholic depressive with regard to clinical characteristics, neurocognitive dysfunctions, treatment response patterns, and neuroimaging findings. For example, a recent meta-analysis found that acute episodes of MDD with melancholic features had greater neurocognitive deficits than episodes with non-melancholic features (4). A prospective study reported that subjects with melancholic features have higher excess all-cause mortality than those without melancholic features (5). However, findings on the treatment responses to psychotropic drug treatments between patients with melancholic and non-melancholic features were inconsistent. For example, when compared to those with non-melancholic depression, patients with melancholic depression had similar responses to antidepressants (3, 6) and quetiapine (7), had stronger responses to lithium (8) and electroconvulsive therapy (ECT) (9), and had weaker responses to psychotherapy (10).

Apart from the rapid and robust antisuicidal and antidepressant effects (11–15), accumulating evidence has shown that both single and repeated ketamine injections at a subanaesthetic dose (0.5 mg/kg over 40 min) have rapid and robust antianhedonic effects in individuals suffering from MDD and BD (16–19). Notably, ketamine's antianhedonic effects were independent of other depressive symptoms (16). A recent study found that a single dose of ketamine appears to be effective in treating both melancholic/typical and atypical depressive symptoms (1). However, the differences in the antianhedonic effects of repeated ketamine infusions in patients with melancholic and non-melancholic depression have remained unknown.

In this exploratory study, we divided the participants into melancholic and non-melancholic subtypes and sought to comparatively investigate the antianhedonic effects of multiple intravenous injections of 0.5 mg/kg ketamine in individuals with melancholic and non-melancholic depression. Based on the findings of a recent study (1), we hypothesized that multiple intravenous injections of ketamine effectively treated anhedonic symptoms in both melancholic and non-melancholic depression.

Methods

In this *post hoc* analysis, data were drawn from an ongoing real-world open-label study investigating the efficacy and safety of adjunctive multiple ketamine infusions for the treatment of patients with depression with TRD and/or suicidal ideation, which was initiated in November 2016 and registered in the Chinese Clinical Trail Registry (Clinical Trials Identifier: ChicCTR-OOC-17012239). All patients provided written informed consent, and approval was obtained from the Affiliated Brain Hospital of Guangzhou Medical University respective Institutional Review Board (IRB) (Ethical Application Ref: 2016030).

Patients

Patients with depression were recruited from the Affiliated Brain Hospital of Guangzhou Medical University. The inclusion criteria for this real-world open-label study were as follows: (1) a diagnosis of MDD or BD without hallucinations or delusions according to the DSM-5 criteria; (2) experiencing a MED with a baseline score $\geq$17 on the Hamilton Depression Rating Scale-17 (HAMD-17); (3) aged 18–65 years; and (4) suffering from suicidal ideation with a Beck Scale for Suicide Ideation-part I (SSI-part I) scores of 2 or higher and/or TRD, defined as having failed attempts to achieve a response to two trials of antidepressants. The exclusion criteria were as follows: (1) patients fulfilling the DSM-5 criteria for other serious mental disorders, such as schizophrenia or alcohol/substance use disorder; (2) patients with a positive urine toxicology screen; (3) patients with any serious or unstable somatic diseases, such as cancer or infectious disease; and (4) patients who were pregnant or breast feeding.

Repeated-dose ketamine infusions

The procedures for subanaesthetic intravenous ketamine have been detailed previously (11). In brief, as recommended previously (12), all participants received a course of six intravenous infusions of ketamine hydrochloride (0.5 mg/kg over 40 min) administered thrice weekly over the course of 2 weeks following overnight fasting. A psychiatrist recorded vital signs, including pulse frequency, blood pressure and heart rate, every 10 min throughout the infusion and monitoring period. All subjects remained on stable type and dosage of concomitant psychotropic medication during the infusion treatment.

Clinical interview and assessments

A detailed demographic questionnaire was conducted for patients with melancholic and non-melancholic depression, recording general information and socio-demographic characteristics, such as age, gender, and marital status. Clinical ratings of the severity of anhedonic symptoms measured in a sample of individuals with melancholic and non-melancholic depression at baseline, at 4 and 24 h after each infusion of the study agent, and at 2 weeks postinfusion (day 26) using the Montgomery–Åsberg Depression Rating Scale (MADRS). Following the methodology of previous studies (20–22), the anhedonia items of the MADRS, including assessments of apparent sadness, concentration difficulties, lassitude, reported

sadness, and inability to feel, were utilized to assess the severity of anhedonic symptoms (23, 24). The coprimary endpoints were the comparison of antianhedonic response and remission (≥50 and ≥75% reduction of the MADRS anhedonia subscale scores at day 13, respectively) (25, 26) between individuals with melancholic and non-melancholic depression. The secondary endpoint was the comparison of the severity of anhedonic symptoms between individuals with melancholic and non-melancholic depression. The intraclass correlation coefficient (ICC) for the MADRS anhedonia subscale scores was >0.9, suggesting excellent interrater reliability.

Definition of melancholic depression

As recommended previously (7), baseline scores on the HAMD-17 and MADRS were used to split the population into two subgroups (patients with melancholic and non-melancholic depression). The presence of melancholic depression was defined based on DSM-5 criteria (7), which require anhedonia in nearly all activities (MADRS item 8 $\geq$ 4) and/or non-reactive mood (MADRS items 1 or 2 = 6), and at least three of the following: significant psychomotor retardation or agitation (HAMD-17 items 8 or 9 $\geq$ 2), marked appetite/weight loss (HAMD-17 items 12 or 16 = 2), terminal insomnia (HAMD-17 item 6 $\geq$ 1), and unwarranted or disproportionate guilt (HAMD-17 item 2 $\geq$ 2).

Statistical analysis

In this study, we used SPSS version 24.0 (SPSS Inc., Chicago, United States) for all statistical analyses. Intent-to-treat analysis was conducted in this study. The demographic and clinical variables of individuals with melancholic and non-melancholic depression were compared with Student's *t*-test for continuous variables (including age, body mass index, education, depressive symptoms, anxiety symptoms, and suicidal ideation) and the Chi-square test for categorical variables (including gender, marital status, and rates of antianhedonic response, and remission). The rates of antianhedonic response and remission between individuals with melancholic and non-melancholic depression were analyzed by the Chi-square test. The comparisons of the rates of antianhedonic response and remission between the two groups were performed using odds ratios derived from logistic regression analyses after adjusting for the sociodemographic confounding variables. A linear mixed-effects model was utilized to determine the difference in anhedonic symptoms over time between groups. The covariates in the linear mixed-effects model analysis included baseline demographic and clinical variables that differed between the two groups. We utilized Bonferroni correction to adjust for multiple comparisons and set the significance level α at 0.05.

Results

Demographics of the non-melancholic and melancholic groups

Among 135 patients with depression receiving repeated ketamine infusions, 30 (22.2%) fulfilled the DSM-5 criteria for melancholic depression, and 105 (77.8%) did not. The demographic and clinical characteristics of patients with melancholic depression vs. non-melancholic depression are summarized in Table 1. As expected, the melancholic subgroup had higher baseline HAMD-17 scores ($t = 10.5$, $p < 0.001$), baseline MADRS scores ($t = 7.8$, $p < 0.001$), and baseline MADRS anhedonia subscale scores ($t = 17.4$, $p < 0.001$) (Table 1). The subgroups did not differ with regard to age, sex, education level, or age of onset (all $p > 0.05$).

Antianhedonic response and remission between the non-melancholic and melancholic groups

As shown in Table 1, patients with non-melancholic depression had significantly lower MADRS scores at post-treatment (15.4 ± 10.9 vs. 20.4 ± 12.2, $p < 0.05$) than those with melancholic depression, but significance disappeared after controlling for baseline MADRS scores ($p > 0.05$). Patients with non-melancholic depression had non-significantly lower HAMD scores at post-treatment (11.3 ± 7.0 vs. 13.9 ± 8.1, $p > 0.05$) than those with melancholic depression. Patients with melancholic depression achieved a non-significant lower antianhedonic response to repeated-dose ketamine infusions than those with non-melancholic depression [43.3% (13/30) vs. 50.5% (53/105), $t = 0.5$, $p > 0.05$]. Similarly, patients with melancholic depression met a non-significant lower antianhedonic remission criteria than those with non-melancholic depression [20.0% (6/30) vs. 21.0% (22/105), $t = 0.01$, $p > 0.05$]. No significant differences between the two groups were observed regarding antianhedonic response and remission rates after controlling for confounds (all $p > 0.05$).

Anhedonic symptoms between the non-melancholic and melancholic groups

The linear mixed model with MADRS anhedonia subscale scores showed significant main effects for group-by-time interaction ($F = 3.0$, $p < 0.001$) and time ($F = 64.4$, $p < 0.001$) but not for group ($F = 0.6$, $p = 0.46$). Compared with baseline, significant improvements in anhedonic symptoms were found from day 1 to 26 and from day 3 to 26 in the non-melancholic

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TABLE 1 Comparison of demographic and clinical characteristics between patients with melancholic depression and non-melancholic depression.

Variables	Melancholic ($n = 30$)		Non-melancholic ($n = 105$)		Statistics		
	N	%	*N*	%	χ^2	*df*	*P*
Male	12	40.0	56	53.3	1.7	1	0.19
Married	17	56.7	61	58.1	0.02	1	0.89
Employed	13	43.3	39	37.1	0.4	1	0.54
Living alone	2	6.7	9	8.6	0.1	1	0.74
No history of psychiatric hospitalization	19	63.3	74	70.5	0.6	1	0.46
Having a family history of psychiatric disorders	14	46.7	38	36.2	1.1	1	0.29
Antianhedonic responders	13	43.3	53	50.5	0.5	1	0.49
Antianhedonic remitters	6	20.0	22	21.0	0.01	1	0.91
	Mean	SD	Mean	SD	T/Z	df	*P*
Age (years)	34.7	10.5	34.8	12.1	0.05	133	0.96
Education (years)	12.1	3.9	12.2	3.1	−0.2	133	0.87
BMI (kg/m^2)	22.4	3.4	22.7	3.5	−0.3	133	0.73
Age of onset (years)	26.6	11.4	26.1	11.6	0.2	133	0.83
Duration of illness (months)	94.4	85.5	104.2	93.8	−0.5	133	0.61
Baseline HAMD-17 scores	30.2	4.7	21.9	3.5	10.5	133	
Baseline MADRS scores	41.0	6.7	30.4	6.5	7.8	133	
Baseline MADRS anhedonia subscale scores	24.2	2.6	19.3	4.6	5.5	133	
HAMD-17 scores at post-treatment	13.9	8.1	11.3	7.0	1.7	133	0.09
MADRS scores at post-treatment	20.4	12.2	15.4	10.9	2.2	133	

Bolded values are $p < 0.05$. BMI, body mass index; HAMD, Hamilton Depression Rating Scale; MADRS, Montgomery–Åsberg Depression Rating Scale.

and melancholic groups, respectively (all $p < 0.05$). As shown in Figure 1, the melancholic group had significantly lower MADRS anhedonia subscale scores than the non-melancholic group at day 26 ($p < 0.05$).

Discussion

To the best of our knowledge, this is the first study to examine the differences in antianhedonic response and remission to six intravenous injections of 0.5 mg/kg ketamine over 40 min in individuals with non-melancholic and melancholic depression. The following major findings were obtained: (1) 22.2% (30/135) of subjects reported melancholic depression; (2) similar antianhedonic response and remission rates were found in individuals with or without melancholic depression after six injections of ketamine; and (3) the reduction of anhedonic symptoms in patients with melancholic depression was greater at day 26 than in patients with non-melancholic depression.

Based on the DSM-5 criteria, 22% of participants suffer from melancholic depression, which is relatively lower than the figure (31.7%) reported in a previous study (7). Another study (27) found that 13 of 33 (39.3%) participants were classified as having melancholic depression according to the CORE measure (28). The differences in the presence of melancholic depression between our findings and Spanemberg et al.'s study (27) are mainly attributed to differential diagnosis criteria for melancholic depression. Furthermore, Joyce et al. found that the CORE criteria for melancholia, but not the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV), had greater neuroendocrine dysfunction (29).

In this *post hoc* secondary analysis, significant rapid improvements in anhedonic symptoms in both patients with and without melancholic depression were observed in response to six ketamine infusions in this group of individuals suffering from either MDD or BD. Furthermore, the antianhedonic response and remission to repeated intravenous administration of subanaesthetic doses of ketamine were similar in patients with and without melancholic depression. The fact that this difference did not achieve statistical significance may be due to the relatively small number of melancholic patients in the sample. The potential for a superior result with melancholic patients deserves further study with a larger sample. Similarly, a single

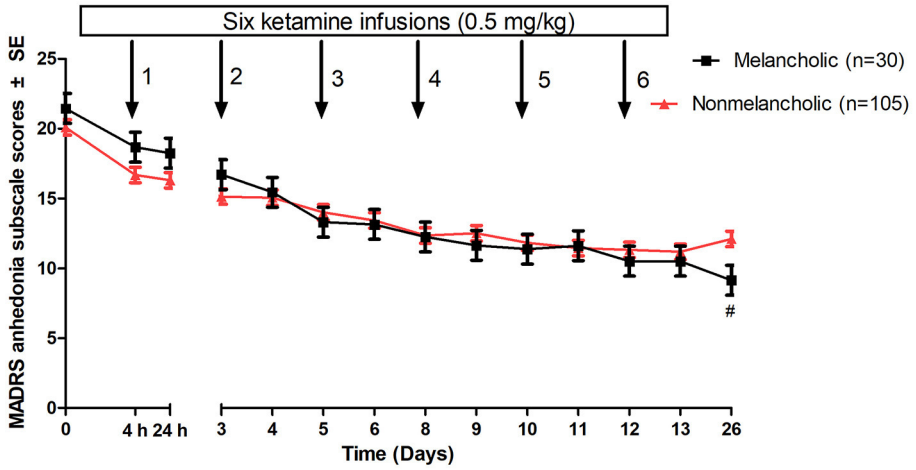

FIGURE 1
Change in ahedonic symptoms in patients with melancholic and non-melancholic depression following multiple ketamine infusions. Values covaried for baseline MADRS anhedonia subscale scores. #A significant difference was found at a given time point between patients with melancholic and non-melancholic depression ($p < 0.05$). MADRS, Montgomery-Åsberg Depression Rating Scale; SE, standard error.

ketamine infusion effectively reduced depressive symptoms in patients with melancholic/typical and atypical depression, with similar efficacy in both groups (1). However, the differences in antianhedonic effects of a single ketamine infusion between the two groups should be investigated in future studies.

The present study has several strengths and limitations. The largest strength of this study is that it is the first to compare the antianhedonic effects of ketamine between patients with melancholic depression and those with non-melancholic depression. The limitations of this study are as follows: (1) open-label design; (2) the sample size for the melancholic group ($n = 30$) was relatively small; (3) the pooling of individuals with MDD and BD increasing sample heterogeneity; (4) the anhedonia items of the MADRS were used to assess anhedonic symptoms rather than a specific scale for anhedonia, such as the Snaith–Hamilton Pleasure Scale (SHAPS) (30–32); and (5) the secondary/*post hoc* analysis of melancholic depression based on scale items.

Conclusion

After six ketamine infusions, an improvement in anhedonic symptoms was observed in patients with melancholic and non-melancholic depression, but with similar efficacy in both groups. These findings are still exploratory, and future studies with a randomized, active placebo-controlled design are warranted.

Significant outcomes

- The prevalence of melancholic depression was 22.2%.
- Ketamine effectively relieved anhedonic symptoms in both patients with melancholic and non-melancholic depression.
- The antianhedonic effects of ketamine was similar in patients with melancholic than non-melancholic depression.

Limitations

- This study was a *post hoc* secondary analysis.
- Participants were pooled across diagnoses (bipolar depression and major depressive disorder).
- This study was conducted based on an open-label design.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by the Affiliated Brain Hospital of Guangzhou Medical University respective Institutional Review Board (IRB) (Ethical Application Ref: 2016030). The patients/participants provided their written informed consent to participate in this study.

Author contributions

Y-PN: study design and critical revision of the manuscript. WZ, Y-LZ, and C-YW: data collection. WZ, X-HY, and L-MG: analysis and interpretation of data. WZ and J-QT: drafting of the manuscript. All authors: approval of the final version for publication.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Ketamine-assisted psychotherapy in adolescents with multiple psychiatric diagnoses

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Ketamine-assisted psychotherapy is a promising new treatment for a variety of mental disorders of adolescence. There is currently an adolescent mental health crisis, with a high prevalence of disorders, diagnostic complexity, and many adolescents failing to respond to conventional treatments. While there is strong evidence for the use of ketamine in adults for a variety of treatment-refractory mental illnesses, research in adolescents is in its early stages. Ketamine-assisted psychotherapy (KAP) has been described in adults with promising results and here we present the first published cases of the use of KAP in adolescents. The four cases include adolescents aged 14–19 at the initiation of treatment, each with a variety of comorbid diagnoses including treatment-resistant depression, bipolar disorder, eating disorders, anxiety, panic, and trauma-related symptoms. They each initially received sublingual ketamine, followed by sessions with intramuscular ketamine. Their courses varied, but each had symptomatic and functional improvements, and the treatment was well-tolerated. Subjective patient reports are included. Rapid resolution of symptomatology and suffering often occurs within months as the result of the application of KAP to adolescent psychiatric care but is not inevitable. Family involvement in the treatment process appears to be essential to success. The development of this modality may have a singularly positive impact that will expand the psychiatric toolbox and its healing potency.

KEYWORDS

adolescent psychiatry, major depressive disorder, bipolar disorder, ketamine-assisted psychotherapy, ketamine, psychedelic psychotherapy, eating disorders, adolescent mental health crisis

Introduction

There is a recognized and alarming crisis in adolescent mental health worldwide (1), both preceding the COVID-19 pandemic (2), and certainly in the midst of it, with evidence suggesting a doubling of the prevalence of depression and anxiety (3). From May 2020 to March 2021, the rate of emergency department visits for suspected suicide attempts increased precipitously for adolescents aged 12–17 compared to the corresponding period in 2019, particularly among female subjects (4).

Mood disorders in adolescents are common, often with multiple comorbidities (5), and are associated with poorer outcomes than those with later onset (6). These disorders are associated with an elevated risk of suicide (7, 8), substantial disability, and societal burden (9). Longitudinal studies demonstrate significant associations between childhood mental disorders and children's health as well as with their caregivers. Prospective and long-term studies of sub-threshold symptomatic adolescents and diagnosed adolescents

indicate significant progression into adulthood of mental disorders, emphasizing the need for treatment, access to care, and the impact of social and economic factors (10–12). Of great concern is that young people are prescribed a panoply of medications for mental health concerns (13), and yet, many do not achieve remission or do not respond to the current evidence-based or FDA-approved treatments (14, 15).

Ketamine has been shown to yield rapid and clinically significant positive effects in adult treatment-resistant mood disorders (16–18). One of the more robust outcomes of treatment with ketamine is a reduction in suicidal ideation (19). A recent large double-blind randomized controlled trial demonstrated that 63% of adults receiving ketamine achieved sustained remission of suicidality ($n = 17$) using a single dose of 0.5 mg/kg of IV ketamine and assessment over 2 weeks (20).

Given the success of ketamine in adults and concerns for the state of the mental health of youth, there is a growing interest in its application to adolescents. A systematic review summarized the nascent research on ketamine for adolescent treatment-resistant mood disorders (21). They concluded that ketamine was shown in adolescents to improve depressive symptoms, decrease acute suicidality, and reduce mood lability, however, a number of subjects did not have significant responses to treatment. This review identified one study concerning bipolar disorder (22)—a retrospective chart review of 12 youth receiving insufflated (30–120 mg) racemic ketamine. The remaining articles were reports of IV ketamine (0.5 mg/kg infused over 40 min) for adolescent treatment-resistant depression. One open-label trial ($n = 13$) (23) and two case reports were presented (24, 25). A supplemental case report of a depressed adolescent who received a continuous IV ketamine infusion over 5 days for chronic pain, but whose depression improved along with the pain, is also mentioned (26). A single intravenous or subcutaneous administration of esketamine to 10 adolescents with a mean age of 15.5 years and a variety of diagnoses and psychiatric and medical comorbidities resulted in a 24-h reduction in depressive symptoms and suicidal ideation (27). A single dose of IV ketamine in adolescents with depression was found to be well-tolerated acutely and with significant short-term (2-week) efficacy in reducing depressive symptoms compared to midazolam as an active placebo (28). Wink et al. (29) provide preliminary evidence for brain correlates of clinical change based on neural flexibility utilizing fMRI. They hypothesize this may underlie symptom relief in adolescents with TRD following six infusions of ketamine.

Autism spectrum disorder (ASD) and ketamine are in early exploration with a report of safety and tolerability of intranasal ketamine in 14–29-year-olds (30) and a single patient report of a dramatic brief remission of the core symptoms of autism (31).

The DiVincenzo meta-analysis of adults and adolescents (19) reports the safety and tolerability of ketamine for adolescents and the improved success of higher doses than the standard 0.5 mg/kg with no substantial adverse effects, nausea being the most common and similar in frequency to adults. They cite a "rapid and robust antidepressant response in adolescents" with "better antidepressant outcomes for individuals who received longer treatment courses and higher doses," which applies to both adolescents and adults. It is worth noting that the review appears to have included the same number of adolescents—33– as in the Kim paper cited earlier (21).

Basic pharmacology of ketamine

Ketamine presents in two enantiomers: the S(+) and the R (–) configurations and as a hydrochloride salt. Historically and in general use for off-label psychiatric indications, as well as for anesthesia and analgesia, is an equimolar racemic mixture of the two enantiomers. Although racemic ketamine has the broadest worldwide use, S(+)-ketamine is available in some European countries and came to market as a commercial patented nasal preparation for psychiatric use in 2019.

Ketamine's most probable mechanism of action is as an N-methyl-D-aspartic acid (NMDA) glutamate receptor antagonist. It may well be that its principal site of action is at a specific NMDA receptor that has a dual capacity as a locus for both antidepressant and dissociative attributes. When NMDA receptors on gamma-aminobutyric acid (GABA)-ergic neurons are antagonized, downstream glutamatergic neurons are disinhibited. This increased glutamatergic activity impacts neural signaling, synaptic plasticity, and connectivity. It is posited based on animal models that ketamine-induced synaptic potentiation and proliferation may play a key role in eliciting antidepressant effects. Ketamine also impacts other neurotransmitter systems, affecting cholinergic, opioidergic, monoaminergic, and GABAergic functions [see Wallach and Brandt for a comprehensive review (31)].

Multiple routes of administration are utilized by practitioners treating depression and other psychiatric conditions, each with its own unique pharmacokinetics, including intravenous, intramuscular, intranasal, sublingual, subcutaneous, epidural, anal, and oral delivery.

Safety of ketamine

McCann and Soriano reviewed the preclinical evidence of the potential for ketamine and other anesthetic agents to induce neurotoxicity in the developing brain (32). While the neurotoxicity of ketamine has been demonstrated in animal models, its clinical relevance is questionable. Examples of studies showing both neurodegeneration and neuroprotection in the developmental period are cited (33, 34). They note that the relevant factors include (1) susceptible developmental age, (2) high dose of the anesthetic, and (3) long duration of exposure. When neurotoxicity is demonstrated, doses are much higher and for a much longer duration than in clinical use. For example, Slikker et al. showed that rhesus monkeys in earlier developmental stages [122 days of gestation and 5 post-natal days (PNDs)] given ~10 times the dose needed for sedation in humans and for a period of 24 h appear more sensitive to ketamine-induced neuronal cell death than at 35 PNDs, and a shorter duration of 3 h of ketamine anesthesia did not result in neuronal cell death at five PNDs (34). Soriano goes on to note that a clinical manifestation or phenotype of anesthetic-induced neurodegeneration has not been identified in humans,

providing reassurance for the continued use of general anesthesia in children (33).

There are numerous clinical studies of ketamine for anesthesia and procedural sedation in children and adolescents indicating its safety (35–38). In addition, a study of nine children inadvertently given 5–100 times the intended dose of ketamine in the emergency department showed no adverse outcomes, although prolonged sedation occurred in all cases and four experienced brief respiratory depression (39).

Importantly, Lee et al. (40) discuss critical time windows for neurocognitive damage in primates and humans, the latter being particularly susceptible during the developmental window from *in utero* to 3 years, with the possibility of more time due to ongoing synaptic plasticity. There is controversy and ambiguity with respect to this with both ketamine and GABA antagonist anesthetics. The byword is caution in neonates and young children. Animal studies contribute to this complexity with evidence of both neurotoxic and neuroprotective impacts from ketamine (40).

Long-term pediatric use of ketamine on a repeated basis has largely been confined to analgesia with the demonstration of its safety. Long-term continuous infusion for pain has been reviewed with three studies of 4–14 days duration without significant side effects—and at doses higher than our episodic intermittent use in adults (41). As clinical use of subanesthetic ketamine has vastly increased for a variety of psychiatric disorders, so too has the need increased for prospective studies of long-term effects.

Given ketamine's episodic, intermittent, and low-dose usage for psychiatric treatment, we would argue that the effects of continuous mood stabilizers, antipsychotics, stimulants, tranquilizers, and antidepressants present a much greater and unassessed risk to adolescent brain maturation. Furthermore, the negative effects of these on emotion and cognition are well described. It is clear that the risks to the youth of emotional disorders and morbidity—including suicide, self-harm, eating disorders, impulsivity, alcohol, and drug abuse—outweigh the potential risk of ketamine use in a controlled clinical application.

Ketamine and KAP

There are many articles on the intravenous use of ketamine for treatment without psychotherapy, generally in medical settings administered by anesthesiologists [(42–44)—as examples]. In this context, attendance to the subjective experience of the ketamine patient is generally absent. Receiving a substance that causes small to large dissociative experiences without the ability to process these experiences tends to diminish their value and often leads to confusion and a sense of "where did I go?" and "what just happened to me?"

In contrast, the value of ketamine embedded in a psychotherapy context is becoming more widely established both clinically and in the literature. We have previously described our process of ketamine-assisted psychotherapy (KAP) and published preliminary data suggesting its effectiveness in the adult population (18). The subjective experience of ketamine, or signature, can be characterized as a spacious time-out from the ordinary mind and its obsessions, with an increased capacity to observe and let go of dysregulated thoughts and behavior patterns. Psychotherapy provides support for a full expression of the subjective experience of ketamine within a conducive non-medicalized setting (18, 45–50). We have used this method in over 1,500 patients and many thousands of sessions in the adult population and have found KAP effective in facilitating new modes of being. This may be particularly relevant in the adolescent population, as most large studies have suggested that the combination of psychotherapy and medication is superior to either treatment on their own for anxiety disorders and depressive disorders. Supporting this furthermore, a recent study of parent perspectives on ketamine suggested that although much of the research to date has been on IV ketamine, parents were more open to less invasive modes of administration, and the authors speculated on the potential for ketamine-assisted psychotherapy to help address some of the understandable parental concerns (50). Our work with adolescents is always in the context of family therapy, including parents and situating adolescents in their homes, schools, and social matrixes.

We work dyadically (i.e., a medical doctor and therapist for each patient) with all adolescents as is customary in working with alternative medicines, such as MDMA (51), and in our practice with ketamine-assisted psychotherapy in adults. KAP sessions are long, generally lasting 3 h or more, and therapist fatigue is a factor mitigated by involving multiple clinicians. The nature of the transference is altered by working dyadically and may offer an emotionally corrective experience of a healthy couple's interaction. Projections based on mother and father experience offer the opportunity for exploration, awareness, and change with processing between therapists and patients.

Generally, adolescents and their families seek our ketamine program after failure with conventional treatment that may include multiple antidepressants, antipsychotics, and mood stabilizing agents, and for a wide variety of clinical presentations. Parents come to us with feelings of confusion, frustration, helplessness, and conflict exacerbated by fear for their child and their own sense of inadequacy. Often, they are in eating disorder programs and have had multiple therapists. While treatment-resistant depression was the major diagnostic category for which intravenous ketamine treatment was based in the adult population (52), ketamine in its general adult application has come to have far greater diagnostic indications than TRD and the literature is voluminous in this regard [see (18, 52, 53)].

Methods

Intake and assessment measures are standardized across patients.[1] We administer a detailed questionnaire along with measures at intake to assess for childhood adverse experiences, resilience, depression, anxiety, and PTSD. We assess changes at each session with repeated measures and our own change of state form, as well as for the effects and presence of mystical experience and depth of ego-dissolution during ketamine experiences. We have our own charting at each session for the

1 Assessments: ACE - adverse childhood experiences; Res - resilience; BDI - Beck Depression Inventory; HAM-A - Hamilton anxiety scale; PCL-C - PTSD checklist/civilian; MEQ - Mystical Experiences Questionnaire; EDI - Ego-Dissolution Inventory/Short.

practitioner assessment of changes in anxiety, depression, PTSD, personality rigidity, sensitivity to ketamine's effects related to dosage, personality rigidity, changes in diagnosis and medication, psychodynamics, social and family system changes and stresses, school experience, friendship statuses, and the patient's view of their experience. We have developed our own Redcap Vanderbilt digital format for recording comprehensive data for each patient, changes in their status, and termination. Diagnosis is made by review of intake materials and medical records, through initial clinical assessment, as well as through consultation with outside treating practitioners, family members, and our weekly case conferences.

Written informed consent is reviewed with parents and adolescents and signed by all involved after satisfying any concerns and questions. The possibility of withdrawal from treatment is present at any time, before, or during treatment, up to the period of administration of the ketamine. Our informed consent is detailed as to effects and potential adverse effects and the rationale for ketamine's use. This is repeated in verbal interaction.

Once appropriateness for treatment has been established, we administer ketamine using two routes of administration: sublingual (SL) or intramuscular (IM) injection. These routes of administration can be administered safely in an office practice where the environment facilitates a comfortable setting for the ketamine experience, in contrast to the often medicalized setting of IV use. Multiple dosing strategies are available for each route of administration and are tailored to patient needs and responses.

We typically initiate treatment with SL administration, using oral dissolving lozenges for dosage assessment and patient familiarity with the effects. Lozenges are held in the mouth for 15 min before spitting or swallowing based on patient preference and increased nausea with the swallowing of larger doses. The SL method provides a slow and gradual onset of effect, enabling close contact between practitioner and patient and minimizing the impact of disorientation as ketamine exerts its effect of moving patients into nonordinary states of consciousness.

If appropriate, the treatment then may include intramuscular (IM) injections. The IM route of administration provides rapid onset of 2–3 min. Generally, the clinician's awareness of sensitivity to ketamine has been established by the sublingual sessions that have preceded the IM use, allowing careful selection of appropriate doses. Up to three injections are typically used for 40 min, with the aim of increasing depth or duration by timing to the rapid metabolism of ketamine.

The choice of route of administration is clinically determined and is provided in a carefully tailored manner beginning with a low first dose and stopping at a dose that is effective for ego-dissolution. IM dosing allows for flexibility of the clinical choice of depth of experience—from mild alteration of consciousness to full ego-dissolution and an internalized experience separated from external sensory input. This state is valued for ketamine's effects for a variety of reasons. Primarily, it is a time-out from the symptomatic and obsessional preoccupations that are the expression of the patient's suffering. In the case of an adolescent, it may be felt as a relief from the pressures causing symptomatic behavior, allowing for a reformation of consciousness and attitudes. With therapeutic guidance, this experience opens new possibilities for self-understanding, self-control, and behavior. The achievement of this generally requires repetition of ketamine experiences, bonding with therapists, and understanding and support for the psychosocial culture and its participants. In addition, the ketamine experience itself confirms the adolescent's inherent capacities and imagination, which have become blocked by the parts that are dysregulated and reactive. The ketamine space is interesting, free of usual concerns, and tends to have a neutral to loving and self-appreciating effect. This positive reclamation may well lead to a reduction in self-loathing, despair, suicidality, and reactivity, opening the door to healing.

A decision to move from SL to IM, or to combine both, is based on successful experiences at the lower doses with minimal side effects and the decision with family and adolescents for a deeper experience based on the perception that there will be a greater impact on symptoms. Patients may have a full therapeutic response with only SL experiences.

There is no accurate method to relate sublingual (or intra-nasal) dosage to intramuscular dosage—estimated at 95%. As with the esketamine intranasal data (54) which indicates a broad range of absorption, the SL method's range of absorption depends on local oral conditions, hydration, the nature, and time for the dissolution of the oral format, and especially the duration of holding the saliva that is the ketamine carrier in the oral cavity. No study has formalized the latter or actually focused on it. In our clinic, we have optimized holding the saliva for 15 min. Our rapid dissolving tablets dissolve in 1–2 min. One product supported study found a median absorption of 29% of the administered dose (55), with another 17–27% (56). Our estimate is of a 15–30% absorption over the duration of exposure. With swallowing, there is a secondary minor absorption from the small intestine with various estimates clustering around 10–15% of swallowed ketamine. As we begin our assessment of ketamine's effect with a low-dose dosage finding procedure, we later can make estimates of the sensitivity to the more rapidly absorbed ketamine administered intramuscularly.

Early in our learning about ketamine, other clinicians noted that several of their patients had abused the prescribed intranasal (IN) ketamine and had become dependent on it. We came to understand that the abuse potential of the IN route was an issue and we prefer the SL method as it is difficult to fill one's mouth with an excessive number of lozenges in contrast to the ease of overuse of the IN administration.

In this regard, the administration of SL lozenges at home is a mainstay of our KAP work. We are aware that at-home ketamine lozenge use has become a major commercial enterprise and is open to critical scrutiny in terms of the thoroughness of the programs that distribute the lozenges, controls on use and dosage, and a lack of psychiatric support. Nonetheless, its use in this context has been recently studied with reports of safety in widespread use (57, 58); however, these articles have come under methodological criticism (59).

Our clinical provision of ketamine for at-home sessions is quite different in being far more supervised and embedded in our face-to-face ongoing KAP program. For our adolescents, this means that parents are in possession of a limited quantity of the lozenges we prescribe, with no opportunity for automatic refilling. Adolescents must request lozenges from parents. Parents

are supervising sessions under the direction of our practitioners. We are available for consultation and the handling of potential crises or safety issues (which have not occurred to date, with at-home use under regular review). The advantages of at-home use are multiple and include an increase in the frequency of sessions and decreased cost, facilitating an increase in the success of our program due to the availability of treatment. At-home work with adults enabled us to provide and continue treatment during the COVID-19 pandemic when in-office sessions were impossible. With careful monitoring of prescriptions and supervising timeframes for use, we have had no safety issues, misuse, or diversion in thousands of at-home sessions in our adult patient population.

At-home strategies for ketamine use for adolescents have three major programs. The first entails supportive sessions at doses of 100–300 mg SL which provide a degree of the time-out experience described earlier. The frequency of such sessions is tailored to the specific therapeutic plan, with more frequent dosing in the early phase of treatment—up to two times per week. These sessions support in-office work and improve outcomes. The second strategy is designed to reduce acute anxiety and consists of a 50–100 mg SL experience which can be repeated at this low dose multiple times per week to reduce the anxiety that results in activated dysregulated behavior. It can be requested by the adolescent or suggested by the parent(s). We limit the number of such sessions and supervise their application. The third strategy is designed to interrupt the impulse to self-harm or indulge in eating-disordered behavior. When the impulse begins to be felt by the adolescent, they have been taught to request a 50–100 mg lozenge which allays the anxiety that attends the potential behavior. This application facilitates a consciousness about the feelings that are about to motivate the behavior and may lead to self-control without ketamine.

This article describes our work with four adolescents with severe and complex presentations and is to our knowledge the first to describe the effects of ketamine-assisted psychotherapy in adolescents. The adolescents discussed as subjects herein were self-referred to our clinic by parents and therapists in our community knowing of our work. No recruitment was made, and treatment was entirely voluntary and conducted with informed consent (IC) that was discussed with parents and adolescents at length. Questions and concerns were addressed to their satisfaction to proceed with KAP treatment. Withdrawal from treatment was always possible as per the IC. No advertising was conducted. The case examples are drawn from the clinical experience of subjects and parents, and when present, in consultation with treating physicians and therapists.

Informed consent

The following proper names are pseudonyms, and any details of identity are obscured for confidentiality. The patients and parents provided their written informed consent to participate in their treatment and for anonymous inclusion of their experiences in this article.

Case examples

Patient Andy—Case report

Keywords: major depression, suicidality, anorexia nervosa, parental conflict, verbally abusive father

Abstract: Abstract: An adolescent with complex self-destructive behavior, actively suicidal, highly reactive to father's verbal abuse and rages, and mother's passivity, who has been successfully treated with ketamine-assisted psychotherapy with relatively rapid resolution of dysregulated behavior and improvement in family stressors with family therapy.

Andy began with us at age 14, in the eighth grade, at the edge of anorexia at 120 lbs. on a 5'9' frame and after two antidepressant failures (treatment-resistant depression by definition). Diagnoses on admission were major depression (F33.2), suicidal ideation (F45), intentional self-harm by a sharp object (X78), and anorexia nervosa (R63). These diagnoses were continuations from the prior treatment and hospitalizations and validated at intake and in the course of treatment.

There were no prior significant medical, birth, developmental, or genetic histories. The family structure is of importance to the dynamics of Andy's struggle. The father is of Latino background, grew up at the edge of the barrio in New York City, and managed to attend prestigious college and law schools by dint of severe self-discipline. The imposition of this in the family was a major source of conflict. In contrast, Andy's mother was of Irish background and much more laissez-faire. Prior treatment focused solely on the eating disorder and hospitalizations for suicidality. A short stint of psychotherapy was abandoned as ineffectual.

Mental status evaluation

Andy appeared agitated and hyperverbal with anger, volubility, and psychomotor agitation. Grooming and dress were appropriate. There were healing cuts on his arms and keloiding of prior lacerations on his legs. He was extremely thin and spoke of restricting food intake. He expressed anger and fear of his very successful father. Andy is highly intelligent, though with a great deal of self-consciousness, denigration, and fear for his abilities. He demonstrated self-awareness and a capacity for introspection. He also was candid about his potential for further cutting and suicidal behavior which made intervention urgent. There was no evidence of hallucinations or delusions, but grandiosity and dramatic expressions were part of his presentation.

Parents were interviewed separately, together, and with Andy present. A 2 year younger daughter was of concern as the parents indicated she was depressed and expressing suicidal thoughts and feelings of worthlessness. She was to start therapy with her own therapist.

On Intake: ACE 2; Resilience 11; BDI 47; HAM-A 35; PCL 59.

At the time of this report (12 months): BDI 2; HAM-A 2; PCL 25.

Andy attributes his depression and subsequent anorexia to sixth grade and his father's dominance, as well as verbal abuse. He made three suicide attempts in 2021—one overdose with 20 Advil and 500 ibuprofen. There were two hanging attempts. Serious ongoing cutting episodes were occurring with deep wounds to thighs and

arms and subsequent keloiding. Andy's compulsion to cut and control his food intake was voiced openly. Parental controls were ineffective, and splitting was both active and passive.

Andy had no history of substance abuse. Medication consisted of a recent prescription of citalopram 20 mg which was discontinued as ineffective after our evaluation. There was no history of alcohol or substance use or abuse. Except for the ketamine, no other medications were administered during the course of treatment.

Working as a dyad, our focus was immediately on the family and Andy's expressions as the identified patient, reflecting his hopelessness, rage, and anxiety. The parents were in a near-constant state of quarreling and yelling with violent verbal abuse. Underneath his resistance to his father's bullying was a terrified sense of not living up to his father's significant successes.

We initiated family, couple, and individual therapy. The father initially begrudgingly took responsibility for his behavior. As he came to a clearer understanding of his own rage and feelings of disrespect, he softened in his relationships. Over time the couple's open friction reduced. Therapy was not particularly successful in assisting the mother in reducing her provocative rebelliousness, this expressed as a compulsion to be late to virtually every scheduled event, which both Andy and his father noted as a source of tension. The success of the focus on the conflictual atmosphere in the home was of tremendous import to the work with Andy as it validated his sense of being harmed by the conflict and reacting to it with his own despair and acting out behavior.

With Andy, KAP therapy focused on increasing his autonomy and self-worth and moving to a position of recognizing the cost to himself and the futility of his self-destruction. His impulses to cut and abstain from eating continued but with less pressure. At the time of writing this, we are at 1 year's treatment without a cutting episode. This has become a source of pride for Andy. There are still occasional thoughts of self-harm but none of suicide. Andy has successfully matriculated into a prestigious high school.

Course

Ketamine's role in the transformation of this family in only several months' time has been profound. Ketamine sessions were initiated with our SL method, commencing at a low dose (100 mg in two tranches based on Andy's response) and building comfort with the inevitable disorientation of ketamine's effects. Andy's intelligence and his increasing self-awareness of his pain, impulses, and the causes of his reactivity at the moment grew rapidly as the work progressed. Ketamine sessions moved to higher doses providing more complete ego-dissolution and relief from the tensions of his ordinary life and obsessions. Andy's intention—always elicited before ketamine administration was: "I would like to understand my depression and be done with it." The SL dose at the second session was increased by 50 mg. Andy moved across the couch swimming like a fish, and overtly happy. At integration, he expressed: "I can be happy if I wanna be in this ketamine space" and, "How can I explain to my dad that I am a fish?" He called his girlfriend and told her "I need to regain cognitive functions."

Given his safe and positive response to ketamine, with parental permission, we initiated a third KAP session with a 50 mg lozenge easing him 20 min later into a 50 mg intramuscular experience. This intentional increase in ketamine was and is designed to induce a state of deeper relief from the pressures and stress of usual consciousness and with a resultant improvement in perspective and reduction of reactive, symptomatic thought and behavior. Andy entered a deeper state than previously without difficulty. At integration, he stated: "I never realized self-harm wasn't going to help. Why is the urge to self-harm there? I never knew when to stop and draw the line to self-harm. My essence is to be kind to myself."

We supported this intention and realization by providing the parents with lozenges to be provided to Andy at a low dose, either at his request to prevent self-harm or by their perception of an increase in tension and stress, raising the possibility of self-harm. The interruption of rising anxiety and the impulse attached to relieve that anxiety by a self-destructive action utilizing a low-dose at-home ketamine experience has become a treatment modality we have incorporated into our therapeutic work. It is entirely under parental control and is described at length above. Andy used ketamine at home on occasion in the low-dose format to reduce the anxiety that would have led to self-harm.

We have completed 13 in-office sessions over 12 months. Our KAP session dose has increased to 90 mg IM with an increase in the depth of each journey that is welcomed by Andy. He values the relief from his stress and the experience of the ketamine journey. We are entering a maintenance phase, with sessions occurring based on struggles and risk for decompensation—which has not occurred. Integration sessions without ketamine, telephone and email support, and consultation with parents continue. Ketamine use at home has always been carefully monitored and has become less frequent. Recently the mother requested a ketamine session and had a remarkable experience benefitting her ability to express herself with a reduction of fear and inhibition. This is having a positive effect on the couple.

The essence of the ketamine phenomenological signature is a time-out enabling freedom from usual concerns and the opportunity for a new view of self and context (1, 18). This provided Andy with the emotional space for him to constitute a sense of personal value separated from the family conflicts, thus resulting in the enhancement of friendships and activities outside the home. Andy has a remarkable capacity to feel and express his inner life. This increased with his sessions as did his sense of imagination and pleasure in his own creative mind. Our 3-h plus sessions included ongoing family work in the post-ketamine period after Andy's reintegration. His transference to us as good parents, the understanding and acceptance that facilitates self-regulation, and a deeper sense of trust in his own judgment and behavior. With Andy's rapid recovery, that sense of trust in us was extended to us from the parents as well, and we enabled a shift in focus to them and an enhancement of mutual kindness and respect. A profound sense of relief was the result. Therapy with the parents continues and our work has had a positive impact indirectly on the younger daughter who was becoming symptomatic.

There were no significant adverse effects. Tapering of ketamine's use has been without withdrawal or cravings.

Ketamine's effect as an anxiolytic and as an interruption of intent has proven to be an effective intervention in this aspect of working with all manner of impulses, including binging, cutting,

suicidal ideation and contemplation, and other potential methods for self-harm. We view the rapidity of effect to be of great therapeutic potential.

Patient Andy's perspective comments

After having multiple in-office ketamine sessions and occasionally taking the at home[sic] ketamine tablets, I have noticed a major reduction (to the point of non-existent) in suicidal thoughts, tendencies, and urges. I have noticed a major reduction (to the point of non-existent) in self harm[sic] thoughts, tendencies, and urges. A major reduction in depressive feelings and depressive mood. Overall better wellbeing feeling.

There were no difficulties in[sic] the medicine apart from nausea on 2[sic] separate occasions.

I did not find difficulty in the journey experience but rather found it to be enjoyable and I found being able to navigate through it to be quite helpful and with relative ease.

I would definitely do this treatment again. I would also highly recommend this treatment to anyone who is troubled by depression, suicide, or self-harm aspects in their life.

I had absolutely no trouble reducing or stopping ketamine use.

Patient Bianca—Case report

keywords: PTSD, anorexia nervosa, panic disorder, divorce, parent alienation syndrome.

Abstract: A highly intelligent, regressed teenager caught between parents who had divorced when she was 1 year old and continued their relationship in a constant struggle over custody, splitting Bianca into a loyalty struggle. Bianca has an extensive history or physical trauma, potential sexual molestation, PTSD from being at a shooter incident, suppression of her individuation and desires for growth and expression, and a great deal of resultant frustration and anger. Her eating disorder commenced as a deliberate attempt to have her parents, particularly the mother, pay attention to her and her determination to have her presence and desires taken seriously. Family therapy with the intention of reducing the parental conflict and unity around Bianca's needs was blocked by the mother who made efforts to stop our work throughout its course. KAP served Bianca over time to verbalize her feelings and needs, to exert her own will through her self-determination, and to gradually leave behind the impactfulness of the anorexia which had taken on a life of its own.

Bianca

Bianca presented to our program as a 14-year-old girl with prior treatment for precocious puberty between ages 7 and 10, a significant history of trauma, with related distrust, hypervigilance, panic symptoms, depression, and an eating disorder. Her diagnoses were PTSD (F43.10), major depression (F33.2), anorexia nervosa (R63), and panic disorder (f41.0). These diagnoses were made in prior treatment and validated by us at Intake and subsequently. There was a history of multiple physical accidents, and possible sexual and physical molestation by her stepfather. Bianca had reported this at age 4 and a Child Protective Service inquiry was inconclusive. Later, she would be open about her fear of her mother's second husband and avoided contact with him, not feeling protected by the mother who had not taken any action on her behalf to protect her from her husband. She had been present at an active shooter incident with a resultant stampede at an amusement park at age 12 that left her with circumstantially related panic attacks.

At intake, she was prescribed Sertraline 50 mg and melatonin for sleep. Prior medications included only sertraline. There was no history of self-damaging behavior; alcohol or substance use or abuse, her sertraline was increased to 75 mg by her eating disorder MD early in our treatment. She is currently in the course of reducing her sertraline dosage. There has been no substance abuse whatsoever during her treatment.

Mental status evaluation at intake indicated an appropriately groomed extremely thin young woman with significant facial acne. She was short adding to the sense of her diminutiveness. Taciturn, withdrawn, with deeply depressed affect and avoidance of eye contact, she huddled in a corner of our couch. Questions were answered minimally, and she offered nothing voluntarily. When her parents left the room and she was alone with the female and male dyadic therapist pair, she came a bit more alive and there was superficial contact and greater responsivity. There was no evidence of a thought disorder, hallucinations, or delusions. Suicidal ideation was acknowledged without current interest in an attempt. Of above-average intelligence, it was only over time that we were able to understand the degree of her intuitive and psychological depth. We rapidly became aware of her strong will, mostly exerted at this time about eating and struggling with the stringency of the eating disorder program which mandated every morsel and type of food she was to consume—a constant struggle. Bianca was in weekly therapy with a female therapist of her mother's choosing for whom she had some fondness. The precocious puberty at 7 had been difficult for her and treatment had continued until age 10.

Her PTSD Checklist (PCL) score at intake was 51, suggesting a high level of clinically significant PTSD symptomatology. It is now 39. BDI has gone from 42 to 14.5; Ham-A from 31 to 15—these last results from our last session, the 38th.

The mother is of Chinese background. The father is of Jewish background. There is no significant mental illness or physical or genetic disorders on either side.

At intake, she was in weekly therapy and in a regimented eating disorder treatment program to which she had become dependent, not eating on her own without direction. Her parents were both present at intake, though her father initiated treatment after being referred to us. Her father was present at most of the sessions, while her mother was present at two sessions.

Her parents divorced when Bianca was 1 year old, and this ongoing protracted contentious divorce, in which Bianca felt that she was in the middle, was a central stressor in her life and presentation. She reported feeling coerced by her mother to choose her side, with threats to the father's custody, including it having been blocked for a time. Contention over the father's ability to act on her behalf and threats to reduce contact was and continues to be major theme throughout her childhood. This splitting and contention continue to the present with Bianca, now

15, with an increasing ability to decide on her life path and choices autonomously. We considered as per Gardner (60) a degree of parental alienation syndrome (PAS) at work.

The unfortunate acrimony between the parents enters directly into our therapy with Bianca. This consists of her father, who throughout her life she experiences mostly as the good parent and her advocate, and the mother as the controlling, negative force. Our efforts to build an alliance with the mother and build unity for the child's sake were rebuffed and the mother has attempted to stop the KAP treatment despite its success and with Bianca's avowed desire to continue with the treatment. This has finally ceased as Bianca has exerted her own determination to continue.

Historically, there were multiple traumas under her mother's care—who remarried when Bianca was 2. These include being bitten by a dog at age 2 at daycare with punishment for wetting her pants—this leading to a life-long fear of dogs; remarkably she reported to her physicians about inappropriate sexual behavior by the stepfather at ages 2, 3, and 4 with an inconclusive report by Child Protective Services—no effective action having been taken to protect her; a concussion, and lack of appropriate response by the mother at age 10; fractures from falling off a bike at age 10, with no examination until the father took her to the emergency department; refusals by the mother to let Bianca attend the school of her choice (where now 3 years later she is happily in attendance); blocking of her successful acting at age 12 by mother; a near continuous battle in the court over custody and its conditions, the mother now attempting to block Bianca's successful and chosen treatment with ketamine.

The event that triggered Bianca into more recent panic attacks was an active shooter event at an amusement park, and her getting lost in the resulting stampede. The school counselor recommended counseling and the mother refused. At age 13, Bianca took direct action by restricting food intake and was outspoken about this being a deliberate attempt on her part to have her health and mental health issues taken seriously and to not be blocked from her choice of schools and acting. She loses 15% of her body weight, stops drinking, is hospitalized, then enters a partial hospital program; then spends over 2 months in a residential eating disorder program; articulates suicidal plans, and ends up in an inpatient unit for a week.

Course

While shy, childlike, and verbally reticent as we began with her, the first session with a single 100 mg lozenge was both well-tolerated and experienced positively as a relief from her usual concerns. Sensitive to ketamine, her experience was significantly dissociative, and she eased into a deep trance state with diminished anxiety and depression as she reintegrated. On the follow-up assessment for the second session, there were very significant reductions in BDI and HAM-A scores. We conducted two more lozenge sessions increasing the dose by 50 mg at each to 200 mg in order to increase the depth of her experience and relief from stress.

Bianca had vivid, imaginative altered states that she enjoyed, feeling a sense of the quality of her imagination and the excitement of her experiences. Bonding with us as therapists enabled early and gentle discussion about family relationships and confidence in our confidentiality and our being for her, with a significant increase in self-disclosure of feelings. Assisting her in building eating autonomy was blocked by her own clarity about wanting the monitoring, nutritional format, and coaching to continue, this having been ingrained as proof of concern for her. Conflicts with her parents in their separate and distant locations would result in regression around food compliance and isolation with depressive and angry moods. This has attenuated.

Given her positive experience with the ketamine lozenges, with her enthusiastic agreement following discussion, we began a course of intramuscular sessions (50 mg) supported by at-home lozenge sessions two times a week with full parental supervision and presence—predominantly the father. This rapidly provided a sense of her own agency and ability to handle the experience with an increasing sense of autonomy. She began attending the school of her choice and after initial nervousness about acceptance, she made friends and has thrived. She resumed her acting and singing. In therapy, she spoke openly about her fear of her mother's irritability, threats to her school about taking her out of it, and bringing her back to the mother's location. Her school choice (an arts and acting focused high school) has unbalanced the custody arrangement as the school's location required living with her father. Her motivation to attend this particular school had occurred before beginning with our treatment, and it was a healthy indication of her beginning moves toward individuation. We discussed the difficulty of her balancing act and its emotional toll. She had become engaged in the therapeutic process. Thoughts of suicide had disappeared early in our treatment. Engagement in living was proceeding.

We reduced in-office session frequency to once per month with our constant availability clear to her. Changes in her dependence on the eating program were occurring and the frequency of meetings with her eating disorder physician decreased. There was a discussion about reducing her antidepressant, initiated by the eating disorder physician and Bianca. We cautioned against it. The program was working. After 5 months, she was eating lunch with her classmates and becoming self-actualizing in her food consumption. Sensitivity to slights by classmates or perceived inadequacies academically caused brief emotional setbacks with reasonably rapid recovery times and processing of these with her father and us. Our ketamine regimen had morphed into two consecutive injections thereby prolonging her sessions—a total of 60 mg—maximizing her time in the journey from 40 min to about 50 min. Ketamine tends to be metabolized at the same rate per person independently of dosage.

Sessions in-office are occurring now every 4–6 weeks and Bianca is slowly reducing the frequency of at-home sessions to once per week. We are all in agreement this is not a long-term process but does include maintenance sessions in future as would be indicated by her needs and her continued psychotherapy with us. This has become a fundamental relationship based on the experience of unwavering trust and support for her autonomy, maturation, and collaboration. Her commitment to her life is sound and strong and her actions reflect this. She will have to manage her balance between her parents but now has the strength to make decisions that further her needs. There will be more work on trauma, pain, and her sense of justice/injustice ahead—no doubt. She is eating entirely on her own and has concluded with her MD and has stopped sessions

with her outside therapist who appeared to Bianca and to us in our contacts with her to have taken sides unfortunately with the mother against the father.

This growth and maturation have happened for the most part in less than a year's time with consolidation now over 16 months of sessions. It feels a bit miraculous to us as therapists. Our relationship is with one parent and is strong. Though we made strenuous efforts, we were not been given the opportunity to work with parents as a unity to foster cooperation in the care of their child.

We have had the profound experience of participating in this adolescent's blooming into life. We do not believe that ketamine treatment on its own could have accomplished this. Ketamine combined with adolescent family psychotherapy has. As therapists, we are all too aware that complex and painful divorces are all too common and children suffer in their midst. Unfortunately, the pain and effects continue too often into adulthood.

The role of medicine in this modality is complex. It has engendered a sense of Bianca's capacities and a mind free of pain and struggle—that this is, indeed, a possibility, an actuality in fact. Embedded in the therapy, it has fostered a sense of safety and trust in us that has extended beyond to father and friends. It has acted to reduce depression, anxiety, rumination, and self-harm. It has antidoted hopelessness and despair. It has strengthened trust in her own judgments and lessened reactivity. It has given a sense of self-regard, self-determination, and allowed for a passion for life to emerge.

Patient Bianca's perspective comments

I've[sic] experienced [sic]better mood, less anxiety, [sic]more contentment.

Sometimes it has affected my sleep, making it harder to sleep directly after usage, some headaches[sic] and nausea.

Some of my difficulty with journeys has been repetitive imagery. Sometimes when taking oral ketamine, I do not experience images at all.

I would recommend this to friends with ongoing symptoms of PTSD, but only for[sic] people who will take it seriously and use it responsibly. Ketamine's nature is different from many other drugs, and it needs to be treated with respect for someone to get healthy results.

There have been periods of time where I have gone a long time without ketamine and not felt any different, there have also been times that the day before I have scheduled ketamine usage, I feel my mood dropping. I haven't[sic] had any trouble lowering my dosage, I think I would be fine if I did. I think if I did stop ketamine usage, my mental health would drop, but if there was a reason, I needed to I would be able to stop just fine.

Patient Chris—Case example

keywords: anxiety, panic, grief.

Abstract: A 16-year-old boy presented with a history of 6 years of increasing anxiety and panic, with decreasing functional capacity over the prior 2 years. He experienced remission within 5 months of treatment with ketamine-assisted psychotherapy and the support of loving parents. The themes of the treatment included acknowledging and working through grief over the loss of his grandmother and reemerging confidence in social settings.

Chris is a 16-year-old boy who presented with his parents for help with anxiety and panic attacks. He had been engaged in a psychotherapy process for 2 years with minimal reported benefit and had no prior treatment with psychiatric medication. There was no history of alcohol or substance use. Family history included the mother having experienced depression and suicidal ideation at age 16.

Chris reported that his anxiety began at age 10 for reasons he could not identify and especially worsened over the last 2 years since entering high school. He emphasized a panic attack while attending a dance which he felt "changed" him, with increasing social anxiety that was further compounded by minimal opportunities for social interaction with peers due to the COVID-19 pandemic. He experienced increasing difficulty talking to new people and developed a fear of crowds. His mother reported that when they would go to grocery stores, he would insist on remaining in close proximity to her and refuse to leave the aisle where she was located. He stopped participating on a sports team that he had enjoyed for 3 years prior, feeling paralyzed as he approached the field. He stopped driving, further limiting access to spend time with friends. His multifactorial presentation did not fit any particular DSM diagnosis, so the working diagnosis of an unspecified anxiety disorder (F41.9) was used. On initial assessment, Chris reported the following measures: BDI 19, Ham-A 19, PCL-5 45, Resilience 14, and ACE 1. Sixteen months after the onset of treatment and over a year after its conclusion, Chris reported a BDI 0, Ham-A 2, and PCL 19.

Mental status examination

At his initial evaluation Chris' mother did most of the talking while he sat quietly and politely. Dress and grooming were appropriate. When we spoke to him alone, despite clearly attempting to be cooperative, he displayed poor eye contact. His speech was quiet, and responses were question-driven and minimal with mild speech latency. His mood was anxious, and his affect was constricted. The thought process was linear, and he expressed a desire to be able to "do more things without fear taking over," as well as openness and optimism about the prospect of working together. Short-term and long-term memories were intact as evidenced by the ability to discuss recent and remote events and what brought him to treatment. There was no evidence of delusions or hallucinations, and he denied suicidal or homicidal ideations. Insight and judgment were fair.

At his first KAP session, Chris was administered a 100 mg rapid dissolve tablet, with a second 100 mg tablet given 22 min later. His experience was peaceful and playful, and he reported pleasant images and memories with a sense of his "brain relaxing."

At his first intramuscular session, he disclosed a severe phobia of needles. Terrified and crying in anticipation, his father held his hand and gently encouraged him. After an hour of working through the fear with determination, Chris was able to receive the injection, resulting in a sense of accomplishment and a pleasant ketamine

experience. In subsequent sessions, he received injections without significant difficulty.

The process of therapy unearthed an awareness of ongoing grief over his grandmother's recent death. He experienced his grandmother's presence during his sessions and felt that she wanted him to know he was "loved by everyone." He gained an intuitive sense of meaningful actions he could take to process her loss; after an at-home session, he asked his mother to take him to her former house and in the yard, he encountered a swarm of dragonflies. He experienced this as a symbol of connection to her, engendering a sense of happiness, peace, and personal specialness.

Over the course of 5 months of treatment, lozenge dosage for at-home sessions ranged from 100 to 200 mg SL two times weekly. The intramuscular dose range was 50–70 mg, with a total of five in-office visits. There were no adverse medical events reported. Some experiences were described as "scary and difficult" but tolerable. The patient and his parents described continuing improvement in his social functioning; he resumed driving, attended large social events including a school dance, spent more time with friends, completed errands on his own, and went on a date. He began to speak more freely as our sessions progressed, stating "I feel like I have come back to life." We terminated treatment in light of his improvement, leaving open the possibility of returning as needed.

Chris provides an example of KAP's utility for anxiety in a patient who had no prior experience with psychiatric medications, emphasizing the possibility for KAP as an effective short-term, intermittent treatment. While ketamine is often reserved for "treatment-resistant" patients, Chris's case suggests that postponing treatment with KAP may not be necessary or beneficial. Family involvement was essential to Chris' ability to participate in and trust the KAP process, as displayed in his session when facing and overcoming his phobia of needles. Finally, although it was not an explicit goal upon entering treatment, he came to recognize and process grief over the loss of his grandmother, with ketamine facilitating transpersonal experiences interacting with her thus fostering a sense of safety, connection, and belonging in the world.

Patient Chris' perspective comments

"One benefit to me after the ketamine experience is that I was able to accomplish many goals and tolerate situations I thought I would never be able to. Another benefit is that I don't[sic] feel as sad or depressed after my grandmother passed away, which put a very negative image in my head that I would think of every day until I got the ketamine therapy. I still get that image in my head today, but it doesn't[sic] make me sad anymore because I believe I have finally moved forward and accepted that she is gone."

"The difficult effects from the medicine are that my whole body becomes numb and that for a while I forget where I am, what I am doing, and even forget who I am. It would sometimes get scary, and I would think that I was being sucked into a black hole and would be trapped in the journey forever. Another effect is when I wake up from the journey, it is hard to walk or even look straight and it takes a little over an hour for the medicine to leave my body after I eat something."

"I will definitely do this again if something comes up in my life where I need to, and I would highly recommend it to troubled friends. Since I started it, I have recommended the psychotherapy to friends I know are going through hard times, and they even asked me questions of[sic] how it works and how it could help them."

"I did not have trouble reducing and stopping the ketamine. The reason is that I felt ready to achieve the things I wouldn't have been able to achieve before."

A comment from Chris's mother in follow-up over a year after conclusion of treatment

"He is driving now and thinking about what he's[sic] going to do after graduation. He has a better personality than before treatment. We are still working on certain things that he needs to get over like going through a drive-through and ordering food and eating out in a restaurant with his friends. He just needs a little push and once he does it and is successful, he is okay. He now gets gas for his car by himself. He is also working every weekend in the same position as before but now he is staying later; he's made friends with some of the prep cooks and stays to eat meals with the other employees. These are all things he would not do before treatment."

Patient Devon—Case example

keywords: bipolar disorder, eating disorder, major depression, ADHD, impulsivity.

Abstract: A now 23-year-old woman began treatment at age 19, with undiagnosed bipolar disorder and a complex history with multiple diagnoses, a history of impulsivity, and substance use, who was hospitalized abroad for a full manic episode early in our treatment of her, and who struggles with medication compliance. Her course of treatment has been erratic despite fluctuating use of valproate. KAP treatment has provided a decrease in the intensity and frequency of depressive episodes, a strong therapeutic bond, and intensive work with her parents has provided a degree of safety. Our perspective is that she will continue to fluctuate with symptoms and impulsivity and will continue to have difficulty sustaining a balanced life. The role of ketamine and KAP with Devon is to provide periods of relief from depression and impulsivity and support for her safety.

Devon is a now 23-year-old woman who began treatment with us when she was 19 years of age. Her treatment is ongoing as she has complex circumstances and comorbidities. Her initial diagnoses were a continuation of those from prior treatment and were validated at intake included major depression (F33.1), moderate to severe anxiety (F41.9), an eating disorder (ED) comprising both binging, purging, and restriction (F50.01 and F50.02), suicidal ideation of fluctuating severity (R45.851), OCD (F42), and ADHD—inattentive type (F90.9). Early in our relationship after a hospitalization abroad for mania with paranoia, her diagnosis was revised to include bipolar I disorder. In view of this, other diagnoses may reflect an earlier less symptomatic course of bipolar I disorder. Binge drinking and regular marijuana use occurred between the ages of 14 and 19. The mother's personal history suggests a bipolar I disorder, as does the maternal grandmother, which has consistently been denied them. The fact that the mother herself suffered from a bipolar illness was considered a culturally shameful idea and

was not easily talked about. There are no other family, genetic, or mental illness issues of relevance. Her parents remain married, and she has one older brother.

Mental status evaluation

At intake, Devon is a 19-year-old Caucasian female who appears as her stated age; she is 5'3", of normal stature, and appears as underweight. She presented with good eye contact, good hygiene, and grooming, and was casually dressed. Her affect at intake was normal and congruent with the topics we discussed. She appeared intelligent and seemed to grasp the impact of her symptoms. She demonstrated insight into problem areas of depression, and at times, impulsivity. She admitted to having difficulty in focus and concentration with her junior college schoolwork at times. She gave a fluent history of her difficulties as a teen. Her speech, while soft-spoken was of normal cadence. There is no history of seizures, periods of loss of consciousness, or any history of developmental delay. Her thought process was fluent with no signs of hallucinations or delusions. She admitted to frequent fleeting suicidal ideation off and on. This appeared to follow the deepening of depressive symptoms and shame. She has a long history of an eating disorder—binge and purge type, as well as restrictive type. She was hospitalized in the past for these disorders. She is very aware of her compulsion to restrict or binge/purge. This stems from the idea of being "too fat" while also acknowledging that she is very slender. She has some difficulty staying asleep and may get up at night when awake to eat, then purge.

Devon's baseline measures: BDI-38, PCL- 36, HAM-A −25, ACE – 3, RES- 8.

Measures at the time of this writing are as follows: BDI-24, PCL-28, HAM -A−17. Her measures tend to fluctuate depending on her stability and swings from depression to hypomania.

Devon

Historically, there have been periods of extreme exercise aimed at achieving an idealized weight in conformity with body dysmorphia. Hospitalized multiple times for eating disorders at inpatient ED rehab centers, she had also attended partial outpatient programs. Her treatment team has included a nutritionist and a therapist focused on her ED. In terms of medications, she had been prescribed many different SSRIs, as well as atypical antipsychotics.

Following the hospitalization for mania, she has prescribed olanzapine, which was reduced during our care of her. She has great concerns about gaining weight and with the subsidence of her mania, olanzapine was reduced, and she came to use it for a time episodically for an increase in symptoms at a low dose. Her determination to use medication as she sees fit is a roadblock to a sustained balance. Olanzapine was discontinued by the patient almost 1 year ago after episodic use at 2.5–5 mg. Of interest is that Devon's weight remained stable despite the olanzapine which is known for its weight gain. Valproic acid ER was added with a dosage between 750 and 1,000 mg. Compliance with this has been an issue at times. Control of manic symptoms has been essential for our ability to utilize ketamine, which has no effect on mania. As she became pregnant at one point, then miscarried, given valproates teratogenicity and erratic use of birth control, a decision to substitute with a trial of lamotrigine was initiated recently with Devon stopping its use at low dose before any possibility of drug effect could occur.

Devon is attractive and somewhat shy, a gifted artist with a striking portfolio of paintings and drawings. She is 5'3" and has weighed between 102 and 110 lbs. Devon has difficulties with focus and concentration, and as a result, has not been able to follow a full school program. However, recently she finished three semesters at the local community college. Recently has dropped out in a depressive episode triggered by an eruption of acne that caused her to feel self-conscious in public.

Devon was referred to us by her parents, who had grown worried and frustrated by her lack of symptom control, the inadequacy of medication management, and confusion about her diagnosis. In addition, Devon and her parents were concerned by her fluctuating symptoms of hypomania, depression, anxiety, difficulty concentrating, inability to follow a consistent path of development, impulsivity, and eating disorder. Her case represents the significant difficulty of treating adolescents with complex disorders and a long history of failed psychiatric and psychotherapeutic interventions.

Previous treatments beginning at age 14 included multiple SSRIs (TRD by definition), atypical antipsychotics, treatment at multiple eating disorder rehabs and with eating disorder specialists, psychotherapy, and behavioral health treatment centers—both inpatient and IOPs.

Devon, a gymnast in elementary and middle schools, had a body shaming incident at the age of 11 that seemed to trigger her anxiety and obsession with her weight and body image. There was also an inappropriate sexual advance from a guidance counselor at age 14 in high school. After that, she began drinking, partying, and having indiscriminate sex, and her eating disorder became prominent.

Excelling in athletics was important in her family. While supportive and concerned, her mother was wary of medications and has continued to emphasize healthy living and will-power as the solution to Devon's problems, complicating treatment and compliance. The maternal family history suggesting bipolar I disorder only came to light later in treatment.

Four months after beginning treatment with KAP, Devon went on a trip abroad to see her mother, brother, and extended family. During this trip, she experienced a full manic episode that required hospitalization. This appears to have been precipitated by the 24 h of daylight during the Scandinavian summer, jet lag, and resulting five nights of sleep deprivation. This break moved us to treat her as having bipolar I disorder, and we came to recognize that her behavior in high school was consistent with this. Age at onset of bipolar I disorder (BPD) typically begins at 12–24 years of age. An earlier presentation of BPD-I may lead to a more severe course (39).

Course

The complexities of her history and emotional and family life led to a multifactorial view of causation and a multipronged treatment approach.

Ketamine treatment followed the relative stabilization of her manic symptoms and proceeded according to our protocol, W began with our SL dosage escalation to assess sensitivity to the medicine. With this established, we developed a closely supervised SL protocol for at-home sessions to further control symptoms of depression, anxiety, and reduce suicidal ideation. In-office sessions moved to IM ketamine administration for a more profound release from her usual concerns and obsessions. Ketamine is usually administered to her in divided doses to sustain the duration of its effect because of her rapid metabolism. Prolonging the duration of ketamine's effect in terms of additional minutes improves the effect of the experience and relief from symptoms.

Devon's course has alternated between periods of relative stability and increased social and personal growth, with periods of severe depression, intense purging, anxiety, and hypomanic symptoms. Both the olanzapine and valproate have been of benefit when used regularly, particularly the valproate which has reduced hypomanic symptoms and prevented another full manic episode. Devon is not alone in her manner of dealing with medication. Adolescents we have treated, often have tended to resist taking medications fearing their effects and at times projecting a lifetime of use. Many have also failed other psychiatric medications and are wary of side effects, having experienced their unpleasantness. In contrast, alcohol, marijuana, and other drugs may be consumed without such concerns despite the problems experienced by their use. In Devon's case, she has continued to use cannabis for anxiety, sleep, and its effects. She also drinks wine at times with family and friends. The former has led to some impulsive acting out that further complicates her life. She has not discontinued use despite our recommendations and the consequences.

While Devon was wary of other medications, she preferred ketamine because of the absence of side effects, the nature of the experience, and because it is not a daily medication. KAP has helped with depression but has not eliminated all episodes. Some of which are sudden and precipitous; conducting KAP sessions when these decompensations occur has reduced their duration.

In another ketamine format, we have implemented a preventative protocol of low-dose ketamine sessions at home to assist with her eating disorder. We are attempting to engage her in blocking self-destructive impulses. When the urge begins to engage in eating disorder behaviors (binging, purging, restricting), Devon is encouraged to put the impulse aside with the relaxing effect of a 50 mg ketamine lozenge. Choosing this action is one of creating awareness and taking agency to diminish the anxiety that precedes binging and purging allaying the impulse based on ketamine's anxiolytic property. This interruption of her pattern combined with higher dose ketamine sessions once or two times per month now has succeeded in eliminating binging and purging episodes.

In-office ketamine IM sessions have resulted in the lessening of depression—shorter and less deep episodes. Her suicidal ideation has markedly decreased and is often not present. Periods of happiness and constructive activity have become more frequent. IM ketamine sessions have been well-tolerated and often enjoyed. Devon has never been agitated or fearful, but rather quite peaceful during and after IM sessions. Her sense of a time-out from her ordinary way of thinking replaced by an experience of traveling and moving through space freely and imaginatively has engendered important changes in her view of herself affecting her identity formation positively.

To date, Devon has had 38 ketamine sessions in-office and many more at home.

Despite setbacks, what has been apparent over the course of these almost 2 years is a substantial increase in insight, clarity, maturity, and self-awareness. Her parents who are involved in her treatment have said "This saved her life." She has now completed three semesters at the local junior college and maintained over a 3.0 average. She has volunteered at an art studio to teach children art and has sold a few of her own pieces. She was involved in two romantic relationships in the past year and ended both when she realized they were unhealthy. One led to pregnancy and miscarriage.

The partial success of treatment with this complex young woman results from several factors: her trusting relationship with her therapist; her honesty with the psychiatrist; the flexibility and advocacy we have shown with her medications; the initiation of mood stabilizers to control her mood swings; her consistency with ketamine and therapy; maturation and containment; insight and agency in handling emotional lability; developing and maintaining the support of her family; and her growth in self-confidence and self-worth. To manage at this young age the constant movement of her center due to bipolar I disorder is truly difficult and the impulsive actions that result from it dislocate her trust in herself and her judgment and necessitate periods for recovery and reorientation. Lack of medication compliance frustrates treatment efforts and makes medication remediation difficult.

We present Devon as an example of the mitigation of a severe mental disorder by ketamine as an assisted psychotherapy. Not its complete remission. Ketamine in such circumstances is not a stand-alone medicine, rather requires a full psychiatric and family therapy treatment approach. As there are so many people who face these sorts of difficult lives, and so many are young when interventions may have more effect, we advocate for exploring KAP's use with this population on a person-by-person basis.

Patient Devon's perspective comments

A few years ago, I was severely depressed. I felt like there was no hope for the future and I would be doing the world a service by committing suicide. I felt so disgusted with myself [sic]all I wanted to do was hide. I'd[sic] tried various medications: Abilify, Celexa, Prozac, Lamictal, Buspar, Geodon—the list goes on. I grew up a very happy child, but I developed an eating disorder around the age of 12 that robbed me of my wellbeing and sanity. Along with this came long depressions[sic] as well as something, I felt was a bit like mania, I would become very obsessive and was anxious a majority of the time. I didn't not[sic] feel I could trust or control my mind at all. When I was depressed, all I could think about was suicide, I spent years in and out of treatment centers and mental hospitals. The last few years, I've[sic] done better with eating, but it is still a struggle. A few years ago, I got diagnosed with bipolar disorder after a manic episode that landed me in the hospital. Since then, I've[sic] stayed out of the hospital, I think largely thanks to my therapist's support as well as the support from my family and friends. I'd [sic]never thought even a year ago that I would be able to say that

I would be able to go 6 months without purging. I feel ketamine has really helped tremendously with my suicidal thinking as well as obsessive thinking and anxiety around food and my body. I feel after a ketamine experience, especially after I am very depressed, I can see life and myself in a new light. I am able to focus more on the good things in life, be more compassionate toward myself and others, and the little voice in my head telling me I'm not good enough seems to fade into the background.

Using the low dose[sic] ketamine, I tend to not crave alcohol, and I have been able to cut down my cigarettes to 1 or 2 a day.

The journey itself can be a beautiful and comforting experience or it can be terrifying. There was one experience when I felt I was on my deathbed, I became extremely panicked trying to find a way to live, [sic]I guess I screamed out "I don't want to die". After this session, I felt like a new person. I was so much more positive and confident in my abilities. I felt that my fears didn't[sic] control me anymore. I have been preoccupied with suicide since I was 12 but I feel my experiences with ketamine have changed something in my brain almost and now I don't[sic] obsess over the idea. I feel that the treatments have helped tremendously with my eating disorder also.

I feel ketamine does help with depression, anxiety, and my obsessive thinking so I notice when I don't[sic] take the medication I have a harder time, but it's[sic] one of the only drugs I think I've[sic] taken that doesn't[sic] have withdrawals so when I stop using it I don't[sic] have a physical craving for it, but I would say I do have a mental craving for it at times because it does help me a lot. I notice I will go to alcohol more often when I'm[sic] not using ketamine to calm my anxiety around food at times.

Discussion

We have presented four case examples of the treatment of adolescents with a wide array of emotional disorders utilizing family-centered KAP methodologies. We have been treating adolescents for over 3 years and there are many more cases we could discuss which resulted in the remission of symptoms and emotional maturation. There are also those with partial successes and failures. Providing therapy to adolescents with significant emotional difficulties tends to be a complex and often arduous undertaking with many variables affecting the course of treatment and its outcome (61).

The ketamine experience itself tends to be the least of the difficulties faced, though we have lost several patients to intractable nausea and vomiting despite our best efforts to ameliorate these symptoms. This is the most common SE occurring in about 5% of our patients overall (18). Ketamine is not for everyone. However, with that caveat, once comfortable with the disorientation and the reduction of contact with this reality and even its transcendence, tolerance and embracing of the ketamine state occur, often with relief and new organization of character and behavior on return and through the support for integration and change by the psychotherapists.

In fact, our adolescent population tends to cope well with the altered states of ketamine. Even those who have significant experience with prior substance use differentiate ketamine experience. We have had no incidents of patient drug-seeking for ketamine outside of our clinical practice. With the essential requirement of close parental control of the SL lozenges we prescribe for at-home use, there has been no diversion to friends or others. Often, our patients have reported that their peers have recognized their positive changes and expressed interest in experiencing therapy.

We are a full-service psychiatric provider, and screening patients for appropriateness prior to initiating KAP treatment is essential. In our experience, factors that may diminish the effectiveness of KAP include recurrent psychotic episodes, a history of untreated/partially treated hypomania, a tendency toward impulsivity and acting out, medication nonadherence, and substance use (18). While we reported on this in our article on adults with 235 patients, hundreds of additional patients and thousands of KAP sessions have continued to provide the same information and will be reported in a forthcoming update of our clinical practice. In this adolescent population, the same factors appear to be impactful.

The formal search for moderators of the effect of ketamine treatment has not yet revealed consistent patient-level clinical or demographic features to help guide the precision application of ketamine (62). Furthermore, while a recent meta-analysis (63) did not detect a difference in response to IV ketamine in bipolar vs. unipolar depression patients, our clinical experience in our particular format for the application of ketamine has suggested that a history of untreated or partially treated bipolar disorders diminishes the effectiveness of KAP. Unstable, stressful, and conflictual family situations are also influential on adolescent emotional integrity and often causative of dysregulated behavior. Economic factors, peer group loyalties, unstable love relationships, a history of abuse, and the presence of perpetrators with a lack of parental protection are all factors and must be addressed along with the actual treatment. Families and parents are often highly stressed by their difficulties in coping with their adolescent(s). Divorce and splitting between parents are among adverse childhood experiences with a significant impact on adolescent mental health and emotional integrity.

In short, the myriad familial, social, and cultural contexts—racism, gender discrimination, and misogyny among them—impact our ability to facilitate autonomy, individuation, and introjection of self-control and self-interest.

In light of the above, administering ketamine as a drug without a strong psychotherapeutic presence is likely not a recipe for success. Engagement in the totality of an adolescent and their situation is essential to the development of trust in the therapist and the success of treatment. Adolescent identity development is predicated on a growing sense of self that is stabilized and leads to commitments to constructive paths. Disruption of this process leads to confused and unstable identity formation (64), and if carried through into adulthood this disintegrated identity leads to poorer or better life integrations and social and physical health (65).

Our work is beginning. Larger numbers and data on how factors including diagnosis and personality characteristics affect treatment will lead to better treatment and patient selection. Reliability in attending treatment sessions and parental involvement in-office and at home is essential to the careful use

of this medicine. Mathai's hopeful survey of parental attitudes (49) indicates the desperation for help with their children. Supporting adolescent needs for respect for their growing independence, and autonomy is imperative for guiding the therapeutic work in the family crucible. We hope awareness of KAP will encourage parents to view this treatment not as the last option prior to giving up or hospitalization, but rather as an early therapeutic opportunity to grow families closer, aiding adolescents in healing from the pain and trauma that has marked their lives.

We expect that this work will generate controversy as "drugs" and children are difficult subjects and there will be concerns raised about the effects on growing minds and bodies, on KAP being a gateway to other substance use, and the ability of an adolescent to handle the potentially disorienting effects of ketamine. These are legitimate concerns. Initial clinical evidence and our experience are reassuring. Uncontrolled adolescent drug use is rampant and can be harmful on the experiential level with detrimental sets and settings (66). We make a point of providing education to our young population not only about ketamine but also about other psychedelics. We teach and inform them about the safe practice at home with ketamine regarding set, setting, safety, dosage, having an alert, and a safe person nearby. We do not promote the use of psychedelics in young people, but we do extrapolate the knowledge of ketamine to other psychedelics-teaching them harm reduction principles should they or their friends at some point in time choose to use psychedelics. Our younger population appreciates this and has given advice to friends and family. They learn to respect the power and intentionality of these medicines.

From NCDAS for 2019 helping us to grasp the situation in the US—a few of their probably low estimate statistics:

- 591,000 teenagers aged 12–17 years old used an illicit drug other than marijuana in the last month.
- 8.7% of eighth graders have used illicit drugs in the last month.
- 21.3% of eighth graders have tried illicit drugs at least once.

By the time they are in 12th grade, 46.6% of teens have tried illicit drugs.

Our KAP process opens the door to adolescents and their families for a frank discussion of drug use, unlike virtually any other setting. Many of our adolescents are drug-naive but drug aware and, in their minds, and social groups, it is looming ahead. Others have been too experienced for their own good. The KAP experience provides a model for a safe and supported set and setting, the essential factors in any drug experience [67]. Teaching it as sacred and a journey into the depths of the mind focuses away from "recreational" use and drug culture, toward conscious thoughtful experience. KAP differentiates "medicine" from "drug." Enabling an honest and open path between parents and their children leads to a non-oppositional stance and an ability to ask for parental support and discussion in advance of drug use. KAP for adolescents provides us with the opportunity to educate, discuss, and exemplify safe use and harm reduction, encouraging postponement of substance use to a time when the brain and mind have more capacity to handle their effects. On the experiential level, it enables our adolescents to experience themselves deeply and to reflect on their lives and choices.

Conclusion

Ketamine-assisted psychotherapy is a new approach to the family-centered adolescent treatment of a variety of mental disorders and acting out states that are afflictive and unique to those in this age range. It offers an opportunity for rapid resolution of suicidality as well. Careful preparation of patients and family, coordination of care, and intensive psychotherapy are component parts of the KAP process. Ketamine itself offers a time-limited respite from the ordinary mind that varies in intensity with dosage and personal sensitivity. This enables relief from obsessional states and preoccupation allowing for a new approach to life through a new experience of self. Ketamine serves as a front-line antidepressant that is administered intermittently, is safe with over a 50-year history of use, and is compatible with most other psychiatric medications given its different neurotransmitter modes of action. We have presented four case examples at length to provide a preliminary sense of our modality.

Data availability statement

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding author.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the individual(s) AND/OR minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

Author contributions

All authors have participated in contributing to the article through their clinical work and writing or the paper including case examples and editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Intranasal esketamine as therapeutic option: a case report of an adolescent with treatment resistant depression

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Depression is among the most common mental health disorders worldwide and treatment resistant depression (TRD) represents a major challenge for both patients and clinicians. In recent years ketamine has received attention as an antidepressant agent, demonstrating promising results in TRD in adults. To date, few attempts have been made in treating adolescent TRD with ketamine and none have used intranasal application. This paper discusses a case of a 17-year-old female adolescent suffering from TRD who underwent treatment with intranasal esketamine application (Spravato 28 mg). As symptoms showed clinically insignificant improvement despite modest gains in objective assessments (GAF, CGI, MADRS), treatment was prematurely discontinued. However, the treatment was tolerable and side effects were scarce and mild. Although this case report does not demonstrate clinical effectiveness, ketamine may nonetheless be a promising substance in treating TRD in other adolescents. Questions regarding the safety of ketamine use in the rapidly developing brains of adolescents still remain unanswered. To further explore the potential benefits of this treatment method a short term RCTs for adolescents with TRD is recommended.

KEYWORDS

ketamine, adolescents, intranasal, treatment resistant depression, off-label

Introduction

Major Depressive Disorder is among the most common mental health disorders worldwide, both in adults, as well as in adolescents. A recent meta analysis reported a global point prevalence of depressive symptoms from 2001 to 2020 of 34% in youth with a point prevalence for major depressive disorder of 8% (1). Throughout the COVID-19 pandemic, these rates are reported to have increased, where, for example, a meta-analysis indicated clinically elevated depressive symptoms in 25.2% of youth (2) highlighting the need for effective evidence-based treatment options.

However, not every youth responds favorably to this treatment approach and nearly 40% of adolescents present with clinically significant depressive symptoms following initial treatment (3), thereby exhibiting a degree of treatment resistance. Definitions of treatment-resistant depression (TRD) vary: For adults, the most common definition is failure of two or more antidepressant medications given at adequate doses for 6–8 weeks during a major depressive episode.

Dwyer et al. (3) have proposed that this category should extend to youth with clinically significant symptoms of depression after a single trial "of an evidence-based psychotherapy and an antidepressant with Grade A evidence for treating depression in pediatric population (fluoxetine, escitalopram, or sertraline)."

While there is little research examining effective treatment methods for adolescents, a staging model has been proposed by Dwyer et al. (3) in which an SSRI is added to psychotherapy. The pharmacological treatment is raised to the maximally tolerated dose before it is replaced by an alternate SSRI and—in the case that no significant effect is achieved—it is combined with alternate antidepressants or augmentation strategies proven to be effective in adult samples (e.g., antipsychotics, lithium, bupropion, mirtazapine or stimulants). Following an escalation approach, this scheme can be further complimented by interventional treatments (such as repetitive transcranial magnetic stimulation), ketamine or electroconvulsive therapy in the highest stage (3, 4).

In recent years ketamine has received attention as an antidepressant agent, showing promising results for TRD in adults (9) as well as having anti-suicidal properties (10). Ketamine is an N-methyl-D-aspartate receptor antagonist with the enantiomers arketamine and esketamine (7). While esketamine has been found to be effective for use in adults with TRD and was thus approved for TRD in adults in several countries, use of this psychopharmacological agent in adolescents has received less attention. A recent review on the therapeutic use of ketamine in children and adolescents identified four studies describing ketamine use by intravenous and subcutaneous application in TRD in minors while naming three additional studies not fulfilling eligibility criteria (11). Results indicate that ketamine improved depressive symptoms, decreased acute suicidality, and reduced mood lability, though a number of subjects remained resistant to its treatment (11). A search of PubMed for "ketamine or esketamine and TRD" yielded five additional publications presenting results from intravenous or subcutaneous use of ketamine in adolescents with TRD and describing a significant reduction in depressive symptoms (7) (see Table 1). A review of existing literature on alternate application methods of ketamine yielded a case series of intranasally administered ketamine in ten males and two females between the ages of six and 19 for the treatment of bipolar disorder. Minimal side effects and clinical improvement were reported (12). As a follow-up to this research, the same group presented data of 45 patients diagnosed with bipolar disorder (both youth and adults between 6 and 37 years with a mean age of 15) who received intranasal ketamine treatment with varying treatment lengths. Results indicate significant reductions of symptoms and (mild) persistent adverse events in 13 cases (13).

A recent online survey of 283 parents explored attitudes regarding the use of ketamine in adolescents and results showed that the use of ketamine for suicidality, bipolar disorder and major depressive disorder in minors exhibited high acceptability among respondents (14). Furthermore, parents reported a preference for less invasive administration modes, with nasal spray as the most preferred application method (14).

Ketamine seems to be a promising substance for the treatment of various affective disorder, yet literature on its use in adolescents is scarce and to our knowledge, no study has sofar investigated intranasally administered ketamine in adolescents.with TDR.

In this paper we describe a therapeutic trial with intranasal ketamine in an adolescent with TRD.

Case study of intranasal esketamine treatment with an adolescent female

M, a 17-year-old Caucasian female student was admitted to our acute psychiatric unit due to chronic suicidal ideation. Suicidal thoughts first emerged at the age of 15 and these had worsened in the weeks prior to admission. She reported symptoms of anxiety beginning 6 years of age and these were present with fluctuations since then. Fears initially revolved around climate catastrophes and war. She currently describes social anxiety and the fear of the death of her parents. At the outset of symptoms she struggled with diurnal incontinence and difficulties initiating and maintaining sleep, which led to seeking mental health treatment. She then attended psychotherapy for 2 years during primary school. Several months prior to hospitalization she first began self-harming. Non-suicidal self-injurious behavior included bruising and scratching her legs and burning her forearms with matches. Prior to intake at the Child and Adolescent Psychiatry (CAP) she had started collecting prescription medication with the intention of taking her own life.

Prior to the worsening of symptoms, the patient had been a good student, with the exception of some difficulties with math. Her parents described gradually emerging difficulties in the school setting. The patient spent more and more time writing excessive lists and planning elaborate systems to become more organized, but was often unable to sustain these goals and reverted to creating new organizational systems.

During the COVID- lockdown in spring 2020, her mental state deteriorated. She spent increasing amounts of time in bed and struggled to motivate herself to do her chores. Her condition continued to worsen in the course of the next school year, specifically during the lockdown in autumn of 2020. Her performance at school significantly deteriorated during the months preceding intake. It proved to be increasingly difficult for her to concentrate and to complete the required tasks; ongoing symptoms of depression and anxiety made it more and more difficult to attend school. She resumed psychotherapy and was able to complete the first term in school, and then failed to participate during the second term. At this point she withdrew, spending her days on the sofa and sleeping. She also gradually withdrew from her friends and ceased all contact a few weeks prior to admission.

In the course of the intake, no history of other psychological disorders, head injury or implantation, seizures, or substance abuse were identified. Additional, her thyroid function test and lab result, EEG and cerebral MRI results were found to be normal.

A family history of depressive disorders in both maternal and paternal relatives were reported. Both grandmothers had suffered

TABLE 1 Studies on ketamine application minors with TRD, based on own PubMed search (FU, follow-up).

References	Age	Study type	Number of participants	Intervention	Finding
Cullen et al. (5)	12–18	Case-series	13	Six ketamine (0.5 mg/kg) infusions over 2 weeks	Average decrease in CDRS-R: 42.5% ($p = 0.0004$). Five (38%) adolescents: clinical response., three responders: sustained remission at 6-week FU
Dwyer et al. (6)	16	Case report	1	Seven infusions over an 8-week hospitalization (days 1, 3, 7, 14, 21, 28, 50).	Rapid reduction in depressive symptoms on first day (61% MADRS reduction; 32% CDRS reduction), treatment gains intensified and persisted
Dwyer et al. (3)	13–17	Randomized, doubleblind, single-dose crossover clinical trial,	17	Single intravenous infusion of either ketamine or midazolam, change to alternate compound 2 weeks later.	Single ketamine:infusion significantly reduced depressive symptoms 24 h after infusion compared with midazolam; (treatment gains remain 14 days Revised). Greater response to ketamine during the first 3 days vs. midazolam (76 and 35%, respectively).
Faria-Guimarāest et al. (7)	Mean age: 15.5 (±1.35)	Case series	10	Single application: 8 patients received subcutaneous esketamine, 2 patients intravenous esketamine	Significant reduction in depressive symptoms (mean total MADRS score) from baseline to 24-h postadministration (mean difference = 12.3; $t = 4.22$; $p = 0.002$; $d = 1.33$).
Zarrinnegar et al. (8)	15	Case report	1	Six ketamine infusions dosed at 0.5 mg/kg per infusion for the course of 3 weeks	Gradual decreases in depressive symptoms (Montgomery–Asberg Depression Rating Scale, Children's Depression Rating Scale)

from major depressive disorder, one uncle had made several suicide attempts, a second cousin had died by suicide, and her mother had struggled with postpartum depression after the patient's birth. At the time of admission, M was living with both her parents as well as her 10 year old brother.

During her inpatient treatment, the patient was also diagnosed with Asperger syndrome, generalized anxiety disorder and major depressive disorder. She exhibited traits of borderline personality disorder but did not meet the full diagnostic criteria.

Prior medication trials included an adequate dose of Sertraline (200 mg/day), Fluoxetine (60 mg/day), Alprazolam (in varying dosages), Venlafaxin (300 mg/day) and Quetiapin (600 mg/day), with Chlorprothixen (100 mg/day), Lorazepam (up to 10 mg/day)and Pregabalin (400 mg/day) as augmentation treatment, each for an adequate duration. After exhibiting refractory responses to various medications, she had attempted to overdose, presumably while experiencing mood congruent auditory hallucinations. Her persistent depressed mood and increased suicidal ideation despite therapy with three different antidepressants in sufficient dosage and over a sufficient period of time resulted in the attempt to administer esketamine.

A nasally administered formulation of esketamine has been approved for treatment of TRD in the adult population. Given the convenience of administration and the possibility of self-administration of the medication (allbeit under close medical supervision), we administered esketamine intranasally as part of an off-label use using the same nasal spray formulation that is approved for adults.

While psychotherapy continued, she received esketamine 28 mg nasal spray (Spravato) according to protocol (28 mg 2×/week with 2 days interval for 4 weeks, then 28 mg once a week for 3 weeks). Medication was applied by a doctor for the first time, then by nurses. The patient remained under close supervision (ECG, blood pressure, saturation) for 1 h after each application.

Side effects included dizziness, which was present after most administrations, occasional nausea and fatigue. All side effects were of short duration (usually 30–60 min). Symptoms of derealization were experienced exclusively after the second administration and lasted for several hours. After one single dose a slight elevation of blood pressure, which also rapidly normalized, was observed.

Clinician ratings were assessed by a clinical psychologist not involved in the treatment of the patient.

To evaluate depressive symptomatology, we used Beck Depression Inventory, (BDI-II) (15) and the Patient Health Questionnaire (PHQ) (16) for self-report and the Montgomery-Asberg Depression Rating Scale (MADRS) (17) for clinician assessment. The severity of mental dysfunction and the general level of functioning were assessed with the Clinical Global Impression Scale (CGI) (18) and the Global Assessment of Functioning Scale (GAF) (19). CGI is a seven-point scale, that requires the clinician to rate the severity of the patient's illness at the time of assessment, relative to the clinician's past experience with patients who have the same diagnosis while GAF describes how much a person's symptoms affect their day-to-day life on a scale of 0–100.

On global scales, an improvement was noted: CGI decreased from 6 (very severe) to 4 (moderately severe)while GAF increased from a raw score of 8 to a score of 20. The results of the ratings of depressive symptomatology differed with regard to self vs. clinician rating. While the self-report measures (BDI-II PHQ-9) remained relatively unchanged (BDI-II: from raw score 49–45; PHQ-9: from

FIGURE 1
Self- and clinician administered rating forms. CGI, Clinical Global Impression Scale; GAF, Global Assessment of Functioning; BDI-II, Beck Depression Inventory; PHQ-9, Patient Health Questionnaire; MADRS, Montgomery-Asberg Depression Rating Scale.

raw score 25–21), MADRS showed a significant decrease (from a raw score of 44–30) in depressive symptomatology (see Figure 1).

No sustained improvement in mood or drive were however identified in the clinical observation. Likewise, no clinically significant changes in anxiety symptoms or in the general level of functioning were noted in subjective ratings and observation.

While tolerability was very good, and psychological evaluation (BDI, MADRS, PHQ) indicated some improvement, subjective ratings and clinical observation showed no clinically relevant persistent change of symptoms. Consequently, treatment was not continued.

Discussion

In light of the high burden of insufficient treatment methods for TRD and the potential adverse effects, it is crucial to complement research on the efficacy of ketamine with research on potential markers for outcome prediction. Using an fMRI approach in 11 adolescents, Roy et al. (20) reported a greater increase in nucleus accumbens entropy in responders ($n = 5$). Within the same sample, better performance in the Word Face Stroop fMRI task (evaluating affective word superimposed on emotionally congruent or incongruent faces) correlated with decreased depressive symptoms, which could point to the direction of an attenuated negativity bias in adolescents responding to treatment (21).

Although the published reports seem promising in offering a potentially efficacious option for adolescents with TRD, questions about the safety of ketamine use in the rapidly developing brains of adolescents still remain unanswered. It has been pointed out that long-term consequences of repeated ketamine use in adolescents are not sufficiently studied and—given that depressive states could also represent a premorbid psychotic symptom—the risk of administering ketamine in vulnerable patient populations is as yet unknown (22). Developing parvalbumin interneurons depend on excitatory input for maturation, meaning that blocking NMDA currents might influence developmental pathways (22). Other clinical data link early life ketamine exposure to neural deficits, such as decreased GMV in the right insula, left inferior parietal lobule, left dorsolateral prefrontal cortex/superior frontal gyrus, left medial orbitofrontal cortex, or frontal white matter abnormalities (23, 24).

These findings call for further well-controlled RCTs in the field of adolescent TRD. So far, there is only one available RCT comparing single administration of ketamine and midazolam, showing a greater reduction of depressive symptoms after ketamine application that lasted up to 14 days (25). Building on these findings, a next step would be to consider short term RCTs for adolescents with TRD using a nasal spray application.

To the best of our knowledge, this is the first case report on an adolescent with TRD using intranasally administered esketamin. Although the assessment of efficacy is complicated by comorbid diagnoses of autism and borderline personality, a case like M's is not atypical in child and adolescent psychiatry. Thus, given the dearth of research exploring ketamine use for TRD in the adolescent population, this case of an adolescent female receiving ready-made available nasal spray application of esketamine proves to be a first step in learning more about the potential benefits of this particular treatment method. While the intranasal application has been licensed for the use in TRD in adults, this drug is still off-label for use with adolescents. However, given the easy mode of administration, intranasal application of esketamine could lead to increased clinical use.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent was obtained from the patient for the publication of this case report.

Author contributions

HE and PP conceived the protocol. KD and HE executed the study. KS wrote the first draft of the paper. KN supervised the trial and contributed substantially to the paper. All authors read and approved the final version.

Conflict of interest

Treatment medication of the patient was covered by medical insurance as part of an off-label use in an inpatient setting. PP is an advisor for Delta4 and Boehringer-Ingelheim. He has received speaker honoraria unrelated to the topic presented here from GSK, Infectopharm, Janssen, and Oral B.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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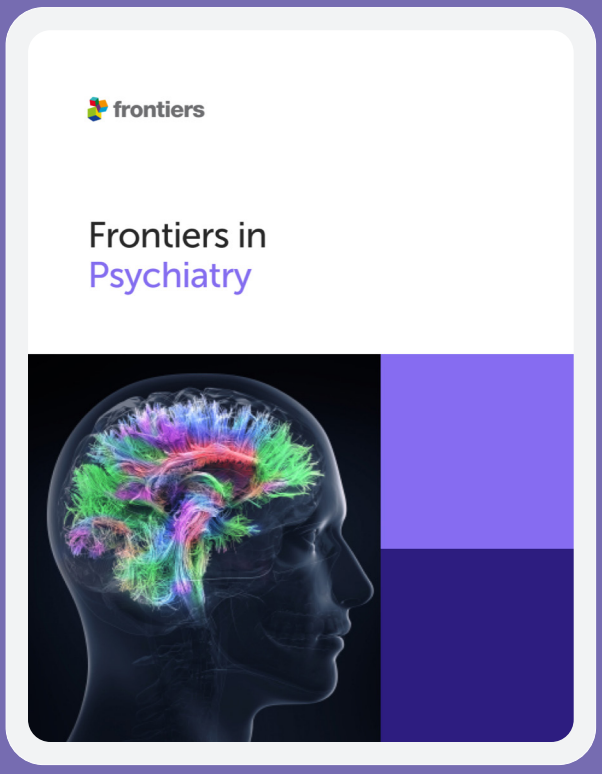

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