Development of the primary care/psychiatry collaborative ketamine clinic for treatment-resistant depression

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Patients with treatment-resistant depression (TRD) have limited treatment options. Subanesthetic doses of ketamine have been shown to have rapid and sustained antidepressant effect in some patients with TRD. Both the intravenous and intramuscular ketamine treatments administered in a clinical setting, where the dose, frequency, and patients’ response can be monitored by the clinical staff, provide safe and effective treatment. The availability of intramuscular ketamine allows the expansion of TRD treatments to the primary care settings, especially in rural communities where access to specialized treatment modalities is limited. This report focuses on ketamine treatment of TRD using a collaborative and consultative approach between psychiatry and primary care and describes a clinical protocol for ketamine treatment for TRD in this setting.

Introduction

Treatment-resistant depression (TRD) in patients with major depressive disorder (MDD) is defined as an inadequate response to appropriate courses of multiple antidepressants. An estimated 33% to 66% of patients with MDD do not respond to the first antidepressant, and between 15% to 33% of patients do not respond to multiple interventions. TRD is associated with higher annual healthcare costs, lost productivity, and lower quality of life, indicating a substantial clinical, economic, and societal burden of this condition.

Clinical guidelines recommend electroconvulsive therapy (ECT) for treating patients with TRD who do not respond to multiple pharmacological treatment trials. However, factors such as the availability of specialized clinical staff and equipment needed to conduct ECT limit the use of ECT for TRD, especially in rural areas. Clearly, there is an unmet need for efficacious care of TRD in areas without access to ECT.

Ketamine, a N-methyl-D-aspartate receptor antagonist, has been shown to have rapid and sustained antidepressant effect in low, subanesthetic doses in patients with major depression and has emerged as a potential alternative to ECT in patients with TRD. Published cases also report the use of ketamine series to achieve a recovery of depressive symptoms in patients with TRD followed by a maintenance treatment regimen to sustain the recovery. Since multiple modalities for ketamine administration are available, ketamine treatments for TRD could be extended into primary care settings using a collaborative approach between psychiatry and primary care.

Primary care and psychiatry collaboration to treat TRD

There are several important challenges for patients with mental illness in rural areas, challenges that are amplified for patients with TRD:

- Primary care clinicians provide care to a large proportion of these patients.
- The need for mental health services in rural settings is significant.
- Travel distances to receive services (accessibility), shortages of mental health professionals (availability) and the stigma of needing to receive mental care (acceptability) are particularly challenging.

A patient’s story

A 51-year-old woman from a rural community (approximately two hours from a psychiatric hospital) was admitted to a psychiatric unit after having a long his-
Ketamine clinic

The ketamine clinic was established for off-label ketamine use for TRD in the psychiatry department of an urban multispecialty medical center in 2008 and was expanded to rural sites in 2012. The collaborative approach between psychiatrists and primary care clinicians from the rural communities allowed local delivery of care for patients with TRD. Since 2008, 46 TRD patients have been treated with ketamine, 16 (35%) of them residing in rural communities. Twelve of these patients received ketamine treatments locally. Overall, more than 2,800 ketamine treatments have been administered by the ketamine clinic physicians.

In addition to the rural primary care clinic, a rural psychiatric clinic with two psychiatrists and a psychiatric nurse practitioner (about 3.5 hours away from our center) joined the ketamine working group. The ketamine working group has been meeting quarterly via videoconferencing to discuss literature and patient cases. Each meeting includes a review of recent literature pertinent to the use of ketamine for depression, clinical presentations and discussion, observations of care process and case review, maintenance of the ketamine registry, observed side effects, and safety considerations.

When a family practice physician is involved in treating patients with TRD, one of the ketamine-trained psychiatrists reviews the case to confirm treatment resistance and to assure that no other alternative treatments are available. After this assessment, patients are referred to the family medicine clinic for intramuscular ketamine treatments according to the established protocol.

Tools to support collaborative care

The ketamine registry was established to assure consistent and safe care for patients with TRD, with focus on clinical, safety, and patient-reported outcomes and clinicians’ adherence to the established clinical protocol for off-label use of ketamine for TRD. Data elements captured in the ketamine registry include patients’ demographics (unique patient identifier, date of birth, gender), body height and weight at treatment initiation, start and end dates enrolled in ketamine care, components and the total Maudsley Scoring System, 13 BDI score at treatment initiation, personal and family history of chemical dependency, and other psychiatric comorbitides.

The BDI has been imbedded in the electronic health record. BDI scores, vital signs, and other relevant clinical observations are documented electronically during treatment encounters and easily linked with the ketamine registry data to assure longitudinal monitoring and treatment outcomes among patients enrolled in the ketamine collaborative care.

Ketamine treatment protocol

Indications

Exhibit 1 shows the criteria for use of ketamine in patients with TRD adapted in our setting. Patients are required to have had adequate trials of medications from multiple families of antidepressants. The depression must surpass mild mood states and be at the very least in the borderline depressive category for initial assessment as measured by BDI. The Maudsley Staging Method is used to confirm severity of treatment resistance. Patients with Maudsley scores of 11 or greater (corresponding to moderately severe to severe treatment resistance) are likely to have poorer outcomes with traditional treatments. With these criteria, ECT must be completed or refused as an end-point of FDA-approved treatments for TRD. Ketamine can be used after ECT as part of the treatment continuum for TRD.

Contraindications

Literature suggests several contraindications for ketamine treatment. Patients with psychosis should not receive ketamine.
treatments since ketamine is known to cause dissociative effects and sensory disturbances, even in subanesthetic doses.\textsuperscript{14,15} Active chemical dependency could lead to forming erroneous symptoms or psychological dependency to the effects of ketamine.\textsuperscript{16} A severe personality disorder as a primary diagnosis could result in poor adherence to the treatment process.\textsuperscript{17} The adverse effects of subanesthetic ketamine on pregnancy and fetus are unknown since no systematic evaluations in humans have been conducted to date.\textsuperscript{18,19} However, a recent study using an animal model reported that in utero ketamine exposure caused abnormal development of prefrontal cortex in rats.\textsuperscript{20}

**Dosing**

In early cases,\textsuperscript{8,21} we used a dose of 0.5 mg per kg of actual body weight as was suggested by Zarate et al\textsuperscript{22} clinical trial. However, in a patient with high BMI, an initial dose of ketamine based on actual weight led to significant negative emotions with visual and sensory disturbances.\textsuperscript{21} A consultation with an anesthesiologist resulted in using “ideal body weight” (IBW) to determine initial ketamine dose. This approach enables initiation of treatment with a safe dose, achievement of an antidepressant effect and ability to titrate to higher doses (between 0.5 mg/kg to 1.25 mg/kg IBW) when clinically necessary, minimizing potential untoward emotional and sensory effects. This approach also allows standardization of dosing independent of patients’ weight changes and permits consistent assessment of doses and their antidepressant effects.

**Initial treatment series**

The ketamine treatment initiation series can include six to nine treatments (three treatments/week for two to three weeks). Response to treatment, defined as a 50% reduction in the BDI score (reduction in depressive symptoms), is assessed after an initial three treatments. If 50% reduction in symptoms is not achieved, three additional treatments with an increased dose of ketamine are attempted. If little change in depressive symptoms is achieved after the sixth treatment, the dose is increased one more time for three additional treatments. The ketamine treatment is terminated if no benefit is observed after this series of treatments or if the depression worsens.

**Maintenance treatment**

The maintenance regimen begins using the last effective dose for the patient after an initial treatment series that resulted in response to treatment. During maintenance treatment, the dose may be increased up to 1.25 mg/kg IBW. Based on prior observations,\textsuperscript{8,9} the frequency of maintenance therapy may range between once a week to once in four weeks. Most patients receive maintenance therapy every two to three weeks. The duration of maintenance treatment in our ketamine clinic ranged from one to nine years.

Maintenance treatment is important for preventing a relapse into depression. A relapse can be dangerous, triggering greater intensity of suicidal ideation—a profound and severe hopelessness that results after the return of depression following a recovery from a long-term depression. Patients may be less suicidal in the chronic depressive state than after having experienced a good recovery.\textsuperscript{8,21}

**Route of administration**

Ketamine can be administered by intravenous, intramuscular, oral, nasal, sublingual, and rectal routes. However, the bioavailability of ketamine varies considerably between routes of administration: intravenous (100%), intramuscular (93%), nasal (45%), sublingual and rectal (30%), and oral (20%).\textsuperscript{23} Clearly, the variation among the non-parenteral routes of administration could complicate the dosing and consistency of treatment. Moreover, the use of non-parenteral routes could lead to potential safety, diversion, and/or abuse issues.

In 2008, we began using intravenous ketamine as described in the literature\textsuperscript{22,24} and added intramuscular ketamine treatments in 2012 after reports of similar antidepressant benefits using intramuscular route.\textsuperscript{25} Either intravenous or intramuscular routes can be used, depending on the availability for venous access as well as the benefits of one route versus the other. The intravenous route (concentration 10mg/1ml) allows us to pause or stop the treatment in case of discomfort, anxiety, or significant hypertension and to assess the patient’s tolerance to the initial dose of ketamine. The intramuscular ketamine administration (concentration 100mg/1ml) results in a more rapid increase and higher serum ketamine concentration\textsuperscript{25} compared to the intravenous course of ketamine given over a period of 40 minutes. As anticipated, some patients feel overwhelmed due to higher intensity of ketamine effect approximately 5 minutes after the intramuscular injection.

The intramuscular route is the least expensive and least complicated way to provide a parenteral ketamine treatment. The intramuscular route is the only option for initiating and maintaining ketamine treatment in some rural settings without access to the infusion facilities. In addition, intramuscular route may be more acceptable for economic reasons associated with the cost of care. In our experience, it appears that there are no significant differences in the treatment outcomes between intravenous and intramuscular routes of administration and the dose calculation is the same. However, some patients do not tolerate the intensity of the intramuscular injection during the first 15 minutes.\textsuperscript{26}

**Treatment workflow (intravenous ketamine administration)**

Patients scheduled for a ketamine treatment are asked to fast for at least four hours before treatment. Patients with prescribed antihypertensive medications are asked to take their usual dose prior to treatment. IBW is calculated by the pharmacy staff or by using a formula (Exhibit 2).

Intravenous ketamine infusions are conducted over 40 minutes; if tolerated, the time may be reduced to 30 minutes to achieve greater intensity of treatment. During treatment, vital signs and observations (oximetry, blood pressure, heart rate, and behavior) are conducted every 15 minutes. The infusion rate can be reduced.
behaviors, and clearance post-treatment used during intravenous treatments. Some patients report a markedly clearer sensorium after the intramuscular ketamine treatment as compared to the intravenous route. Initially, the gluteal muscle was used for injection sites, however, the clinical response varied considerably, potentially due to greater content of adipose tissue in the muscle. An injection in the deltoid muscle has proven to have more predictable absorption and consistent results.

Safety
Ketamine has been shown to be safe as an anesthetic at doses between 1 and 3 mg/kg. Subanesthetic doses used for treatment of depression have been associated with neurocognitive/sensory disturbances, dissociation, and increases in heart rate and blood pressure. These effects usually dissipate shortly after ketamine administration. Patients with a history of cardiovascular disease require additional monitoring during treatment due to potential increases in blood pressure. Chronic ketamine abusers show signs of cognitive impairment, hepatic involvement, and urinary cystitis. Thus, long-term maintenance therapy with ketamine requires regular monitoring.

A complete blood count, urine drug screen, urinalysis, hepatic profile, and hCG for women of childbearing age and ability are obtained prior to initiation of the treatment and every 90 days thereafter. ECG is ordered if patients have history of a cardiovascular illness. Patients with positive illicit drug screen results are discontinued from further ketamine use until they complete chemical dependency evaluation and can maintain sobriety.

Since ketamine is known to be used as a recreational drug, parenteral routes of administration (intravenous or intramuscular) are preferred for patient safety and therapeutic benefit. Treatment should be administered in a controlled setting under clinical observation for potential side effects known to be associated with ketamine even in low subanesthetic doses. Other modalities of ketamine administration are available, but without close clinical management of dose and frequency of administration, non-parenteral routes could lead to medication misuse or diversion.

Conclusion
A collaborative approach to delivery of specialized care can significantly expand access to care, minimize disease burden and improve patient outcomes. The ketamine clinic was initially established in the psychiatric unit of a regional health care delivery system with a large rural service area and focused on providing off-label ketamine for patients who were not willing to use ECT or for whom ECT was contraindicated. Patients from rural and frontier communities who have TRD experience greater burden of the disease compounded by limited access to treatment options.

The key features of the collaborative care in the regional ketamine clinic included creation of a regional ketamine registry and other tools imbedded in the electronic health record to allow consistent assessment and monitoring of patients receiving ketamine treatment, focus on the up-to-date evidence in all aspects of ketamine use for TRD, cooperation among clinicians in reviewing and following patients with TRD, and access to a consultation with a ketamine trained psychiatrist.

To assure consistent treatment within the collaborative model, all ketamine clinic clinicians have been participating in the ketamine working group. Continuing education, case discussion, and established evidence-based clinical protocol for the use of ketamine for TRD allow provision of much needed treatment option for this patient population regardless of place of residence.

While multiple options for ketamine delivery are available, the treatment in a controlled clinical environment, where dose and frequency of administration can be monitored by clinical staff, is essential for keeping ketamine treatments safe and effective. Parenteral routes of administration used in a clinical setting allowed access to and the benefits of ketamine

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EXHIBIT 2

**Calculating ideal body weight (IBW)**

- Men: IBW = 50 kg + 2.3 kg for each inch of height over 60.
- Women: IBW = 45.5 kg + 2.3 kg for each inch of height over 60.
treatment when no other antidepressant treatment resulted in remission or recovery for patients with TRD. MM

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This work was supported by Essentia Health and research grants from Miller-Dwan and Essentia Health Duluth Clinic Foundations.

REFERENCES


Check out resources from the Office of Medical Cannabis website

- Summary of review articles and reports
- CME opportunities
- Dosages and compositions report
- First year report
- Pain report

On the Office of Medical Cannabis’ website, you will find many resources for your patients. We post summaries of review articles and reports that have been put on regarding cannabis for each approved condition and other CME opportunities. We also have created 3 major reports with the data we have collected since the start of the program, the Dosages and Compositions report, First Year report and the Intractable Pain Patients Expectations report.

Contact resources
1 Call center available to speak over the phone Monday - Friday 8:00am-4:30pm • 651-201-5598
2 Email health.cannabis@state.mn.us
3 Website http://www.health.state.mn.us/topics/cannabis/index.html