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ORIGINAL RESEARCH

Off-label use of transmucosal ketamine as a rapid-acting antidepressant: a retrospective chart review

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Objective: This study evaluated the effectiveness and safety of subanesthetic doses of ketamine using an off-label, transmucosal administration route in patients with treatment-resistant depression.

Methods: A retrospective chart review was conducted to identify patients who met the inclusion criteria for treatment-resistant major depressive disorder. Seventeen such patients who received subanesthetic doses of ketamine were included. Patient demographics, efficacy (drug refill, clinician notes), side effects, and concurrent medications were assessed.

Results: Benefit from low-dose transmucosal ketamine was noted in 76% of subjects (average age 48 years, 88% female), with a dose duration lasting 7–14 days. No notable side effects were noted. The most common classes of concurrent medications to which ketamine was added were serotonin–norepinephrine reuptake inhibitors (59%), stimulants (47%), folate replacement (47%), and benzodiazepines (47%).

Conclusion: Our results provide preliminary evidence of the effectiveness and safety of low-dose transmucosal ketamine in treatment-resistant patients. A controlled, prospective pilot study is warranted to validate these findings.

Keywords: ketamine, depression, treatment resistance, NMDA receptor, glutamate, mood disorder

Introduction

Major depressive disorder (MDD) is a leading cause of disability worldwide, affecting an estimated 350 million people.[1] Current limitations of pharmaceutical treatments include a delay in therapeutic efficacy of several weeks to months and a lack of efficacy in approximately a third of the patients with MDD.[2,3] Revolutionizing the therapeutic armamentarium for the treatment of depression, the *N*-methyl-D-aspartate (NMDA) receptor antagonist ketamine administered at subanesthetic doses via an intravenous (iv) route can elicit robust, rapid, and sustained antidepressant effects, even in treatment-resistant patients.[4–13] However, the need for iv administration limits the use of ketamine to an inpatient setting, requiring support services and monitoring.[14,15]

To minimize the adverse events associated with iv ketamine, including acute dissociative and psychotomimetic effects and cardiovascular changes,[7,14–16] recent investigations have attempted alternative routes of administration to elicit rapid antidepressant effects.[17–28] Oral administration is the simplest route to implement. However, due to its lower bioavailability compared to iv administration, oral ketamine often requires higher or more frequent dosing.[17–19,24,27] Intramuscular and intranasal administration of ketamine have yielded more promising results with improvement in depression measures in patients with MDD.[20,22] However, injectables are not a preferred administration route for many patients,[28] and concerns surrounding inhaler use with regard to ease of reliable dosing and abuse potential remain.[29]

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A transmucosal route of administration, in which a small amount of liquid ketamine (approximately 1 mL) is absorbed through the oral mucosa rather than swallowed and thus increases bioavailability (17% oral vs 30% sublingual/transbuccal),[30] may prove more effective. We report herein a retrospective chart review of 17 patients with treatment-resistant MDD at a psychiatric clinic in Morgantown, WV, USA who received low-dose ketamine using this alternative route of administration, which is amenable to outpatient use. We examined the effectiveness and tolerability of off-label use of ketamine when administered via the transmucosal route.

Methods

This retrospective chart review was carried out at Chestnut Ridge Center (Morgantown, WV, USA), a comprehensive psychiatric treatment facility, and comprised records of patients with a diagnosis of treatment-resistant MDD who received clinical services as part of the day hospital program under the care of Dr Scott Pollard, between January 2011 and September 2013. The diagnosis of MDD was based on *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition, Text Revision (DSM-IV-TR) criteria,[31] and treatment resistance was defined as "failure to respond to two or more trials of antidepressant monotherapy or failure to respond to four or more trials of different antidepressant therapies", including augmentation, combination therapy, and electroconvulsive therapy.[32] Trials with antidepressant monotherapy were each at least 6 weeks in duration. Augmentation therapies included the addition of an antipsychotic (eg, aripiprazole), lithium, a stimulant (eg, methylphenidate), another class of antidepressant (eg, mirtazapine or bupropion), or L-methylfolate. Typically, patients who were recommended to the day hospital program, which is synonymous with partial hospitalization, were either recently discharged from the inpatient unit or were failing outpatient care. Most participants were long-term patients with significantly persistent mental illness or patients who function in the community, but were at risk for inpatient admission or needed help through a turbulent period. Services provided at the day hospital included medical evaluation and education by an attending psychiatrist and medical staff in the morning, followed by group therapy sessions to help increase the patients' capacity to manage the symptoms of their illness and improve their quality of life. Of the patients with MDD who were seen in the day hospital setting during this period, those who were initiated on the transmucosal ketamine under off-label usage conditions along with treatment-as-usual for MDD were identified through the clinical notes in 18 files. Data were extracted from the medical charts of these 18 patients for demographic and illness variables, concurrent psychotropic medication use, dosing of ketamine, treatment response, and emergent side effects. Patients were classified as "responders" or "nonresponders" on the basis of the clinician's notes in the medical charts and/or drug refill history pulled from the West Virginia Board of Pharmacy Controlled Substance Monitoring Program (WVBOP CSMP) database. For the drug refill history, we classified a patient as a responder if he/she filled the ketamine prescription more than once.

The data from all of the patients in this report have been de-identified. None of the patients were contacted to obtain additional clinical or biological data for the purposes of this manuscript. The Institutional Review Board of West Virginia University (Morgantown, WV, USA) approved the study.

Results

During the study period, 18 patients who were diagnosed with treatment-resistant MDD received transmucosal ketamine; one patient was excluded from the study due to significant changes in medication regimen after initiation of ketamine treatment. The demographic, clinical, and treatment variables of each subject collected from the chart review are detailed in Table 1. The mean age of the patients was 48 years (range 24–66), and 88% were females. Of the 17 subjects included in the study, three had a prior history of substance abuse, though none had active substance abuse disorder at the time ketamine was initiated. Patients were generally administered 0.5 mg/kg to 1 mg/kg of ketamine from a 50 mg/mL vial of ketamine. In an effort to reduce side effects, liquid ketamine was placed on the tongues of the patients and they were instructed to hold it in their mouths for as long as possible. Thus, in contrast to standard oral dosing, where the drug is quickly swallowed, the administration route used in our patients may best be described as transmucosal. Moreover, dosing frequency started at every 14 days (based on the iv ketamine infusion clinical reports)[4,9,10] and was reduced to every 10 or 7 days when it became clear that the patient had loss of benefit prior to the 14 days.

Out of the 17 subjects who were treated with transmucosal ketamine, 13 (76%) were classified as responders and four (24%) as nonresponders. The onset of response was generally noted within 24 hours of taking ketamine. If patients did not respond within 24 hours, they typically received no benefit from taking ketamine. Among the responders, the frequency of dosing was based on the duration of the antidepressant effect, with seven subjects dosed once every 2 weeks, three once every 10 days, and one once every week.

Table 1 Demographic and treatment characteristics of the patient sample on transmucosal KET treatment

Patient ID number/ sex/age (years)	History of substance abuse	Concurrent medications with KET	Date KET first noted in chart	Initial (1st) and most current KET dosing*	Efficacy information noted in chart	Side effects	KET Rx re/filled (pharmacy)	Response: yes or no?
1/F/60	NR	Quetiapine[a] Clonazepam[a] Desvenlafaxine[a] L-methylfolate[a] Propranolol[a]	Mar 2013	NA	NA	No side effects noted	None	No
2/F/66	NR	Lisdexamfetamine Clonazepam Escitalopram Haloperidol L-methylfolate DHA CoQ10	Dec 2011	1st: 0.35 mL by mouth; current: 1 mL by mouth, q1w	NA	No side effects noted	Dec 2011 (0.35 mL); Mar 2012 (q1w); May, Jun, Jul, Nov 2012 (1 mL, q1w); Mar, May, Aug 2013 (1 mL, q1w)	Yes
3/M/38	NR	Tranylcypromine[a] Nortriptyline[a] Venlafaxine Methylphenidate L-methylfolate Mirtazapine Pregabalin	Jun 2012	1st: 1 mg/kg, q2w; discontinued July 2012	Ineffective	No side effects noted	Jun 2012 (q2w)	No
4/F/41	NR	Lisdexamfetamine Propranolol Aripiprazole Citalopram Hydroxyzine Lithium Doxazosin	Sep 2012	1st: 0.5 mg/kg, q2w; discontinued July 2013	NA	No side effects noted	Sep 2012 (0.5 mg/kg, q2w); Dec 2012 (0.5 mg/kg, q10d)	Yes
5/F/44	NR	Doxazosin Hydroxyzine Desvenlafaxine L-methylfolate Fish oil	Aug 2012	Current: 0.5 mg/kg, q10d	Patient reported doing better on Oct 2012	No side effects noted	Aug 2012 (0.5 mg/kg, q2w); Jul 2013 (0.5 mg/kg, q2w)	Yes
6/F/24	NR	Venlafaxine Desvenlafaxine Clonazepam Propranolol	Sep 2012	1st: 0.5 mg/kg, q2w	Patient discharged from day hospital Jul 2013	No side effects noted	Sep 2012 (0.67 mL, q2w)	No
7/F/51	NR	Lamotrigine Hydroxyzine Fluoxetine *N*-acetylcysteine	Jul 2012	Current: 0.5 mg/kg, q10d	Patient reported mood is good since taking ketamine	No side effects noted	Jul 2012; Jun 2013 (0.5 mg/kg, q2w)	Yes

(*Continued*)

Table 1 (*Continued*)

Patient ID number/ sex/age (years)	History of substance abuse	Concurrent medications with KET	Date KET first noted in chart	Initial and most current KET dosing	Efficacy information noted in chart	Side effects	KET Rx re/filled (pharmacy)	Response: yes or no?
8/F/28	NR	Duloxetine Pregabalin Lorazepam Doxazosin	Feb 2012	Discontinued July 2013	Note that ketamine continued to work well, with strong effects the following day in Jul 2012; still benefitting Sep 2012	No side effects noted	None	Yes
9/F/47	NR	Lisdexamfetamine Fluoxetine L-methylfolate	Oct 2012	1st: 0.5 mg/kg, q2w; current: 0.5 mg/kg, q2w	Patient still on ketamine as of Oct 2013	No side effects noted	Oct 2012 (0.5 mg/kg, q2w); Jun 2013 (0.5 mg/kg, q2w)	Yes
10/F/51	NR	Venlafaxine Lorazepam	Jul 2012	1st: 1 mg/kg, q2w; current: 0.5 mg/kg, q2w	Patient reported migraines and mood are better on Aug 2012	Light headaches	Jul 2012 (as directed)	Yes
11/F/42	NR	Lisdexamfetamine Amphetamine/ dextroamphetamine Duloxetine Doxepin L-methylfolate	Aug 2012	1st: 0.5 mg/kg, q2w	Note that there is continued improvement on Oct 2012	No side effects noted	Aug 2012, Feb 2013, Jun 2013 (0.5 mg/kg, q2w)	Yes
12/F/57	NR	Amphetamine/ dextroamphetamine[a] Trazodone[a] Doxepin[a] Bupropion[a]	Jan 2012	NA	Note: patient is doing well on ketamine on Jan 2013	No side effects noted	Jan 2012, Aug 2012, Jan 2013 (q2w)	Yes
13/F/56	Alcohol and other substances	Vilazodone Trazodone Aripiprazole Gabapentin Buspirone L-methylfolate Duloxetine	Feb 2013	1st: 0.5 mg/kg, q2w; current: 0.5 mg/kg, q2w	Note: patient is doing well and mood improved the next day after ketamine treatment	No adverse effects (specified in chart)	Feb, Jul 2013 (0.5 mg/kg, q2w)	Yes
14/M/65	Alcohol	Propranolol Omega-3 fatty acids L-methylfolate *N*-acetylcysteine Hydroxyzine Risperidone Clonazepam Sertraline	Dec 2012	NA	Rx filled, but unclear if he took it because of other health issues (in and out of the hospital a lot within a short time span); Patient underwent 10 ECT treatments starting in Jan 2013 (improved after 6 ECT treatments; but discontinued after 10 treatments due to adverse memory effects) and was interested in taking ketamine as an antidepressant and willing to restart ECT on Mar 2013		Dec 2012 (as directed)	No

16/F/50	NR	Methylphenidate ER Doxazosin Alprazolam Venlafaxine Hydroxyzine Clonazepam	Jan 2013	1st: 0.5 mg/kg, q2w	Patient reported she can feel the difference and can tell when a dose is due	No side effects noted	Jan 2013 (0.5 mg/kg, q2w)	Yes
17/F/63	NR	Duloxetine Galantamine Quetiapine Oxcarbazepine	May 2012	1st: 0.5 mg/kg, q2w; current: 0.5 mg/kg, q2w	Note that patient mood was boosted and is good	No side effects (specified in chart) except for slight dizziness for 5 minutes	May 2012, Jan 2013 (q2w)	Yes
18/F/35	Narcotics	Lorazepam Divalproex sodium Citalopram Lisdexamfetamine Topiramate Inositol	Jan 2013	1st: 50 mg/mL, 0.6 mL	Patient reported that ketamine has helped in augmentation of mood benefit	No side effects noted	None	Yes

Notes: Patient 15 was excluded from the study due to changes in medication regimen after initiation of KET treatment and is intentionally excluded in this table. *Where the initial dose is not noted, it was because the information was not available. [a]Indicates current psychotropic medications taken at the time of data retrieval (October 2013).

Abbreviations: CoQ10, coenzyme Q10; DHA, docosahexaenoic acid; ECT, electroconvulsive therapy; ER, extended-release; F, female; KET, ketamine; M, male; NA, not available; NR, none reported; q1w, once every week; q2w, once every 2 weeks; q10d, once every 10 days; Rx, prescription.

Table 2 Concurrent medications with ketamine

Medication	Subjects taking the drug (%)
SNRI	59%
Stimulant	47%
Folate replacement	47%
Benzodiazepine	47%
SSRI	35%
Antipsychotic	35%
H1-antihistamine	29%
Beta blocker	24%
Alpha blocker	24%
TCA	18%
Neuropathic pain treatment (pregabalin)	12%

Abbreviations: SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

The remaining two responders (#8 and #18) did not have adequate information on maintenance dosing regimens. Of the 13 responders, two (#2 and #4) were based solely on the drug refill history (ie, the prescription was filled more than once but their charts had no note of efficacy). In addition, the clinical notes for two patients (#8 and #12) explicitly stated continued benefits with ketamine 6 months or more after the first ketamine treatment.

Of the four nonresponders (50% females), two had their prescriptions filled once: one had a note of inefficacy in the patient chart, and the other subsequently underwent and responded to ten electroconvulsive therapy treatments approximately 1 month after the prescription was filled. The other two nonresponders had no ketamine refill history and no reports of efficacy in their charts.

Other medications taken concurrently with ketamine included serotonin–norepinephrine reuptake inhibitors (n=10), stimulants (n=8), folate replacement (n=8), benzodiazepines (n=8), selective serotonin reuptake inhibitors (n=6), antipsychotics (n=6), and others (Table 2). Potential drug interactions or adverse effects are summarized in Table 3. Overall, no serious adverse events were noted in any of the subjects initiated on transmucosal ketamine. The two mild

Table 3 Potential drug interactions/adverse effects with ketamine

Medications	Side effects
Clonazepam, lorazepam, pregabalin, nortriptyline, hydroxyzine, doxepin, trazodone	CNS depression
Haloperidol, mirtazapine, tranylcypromine	Additive CNS effects
Propranolol, doxazosin	Hypotension
Lisdexamfetamine, amphetamine/dextroamphetamine	Cardiac effects

Abbreviation: CNS, central nervous system.

side effects reported were transient light headache (n=1) and slight dizziness (n=1).

Discussion

This is an exploratory study in a naturalistic setting of the potential effectiveness and tolerability of transmucosal ketamine in 17 patients with treatment-resistant MDD. The findings in this chart review support previous reports of effectiveness of low-dose ketamine in rapidly alleviating symptoms of MDD, with effects lasting up to 2 weeks. Importantly, in contrast to iv ketamine, the administration of ketamine using the transmucosal route is better tolerated and has minimal psychiatric side effects. All patients were in a partial hospitalization program, wherein they were seen frequently and had adequate nursing support for administration/education and observation with respect to ketamine. There were no adverse effects that would cause clinical concern for attempting to address depressive symptoms quickly in an at-risk, treatment-resistant population who otherwise are often being referred to high levels of care such as acute inpatient hospitalization.

A similar exploratory study has been conducted using low-dose sublingual ketamine in refractory unipolar and bipolar depression, in which patients were instructed to hold approximately 1 mL liquid ketamine in their mouths for 5 minutes and then swallow it.[23] In that report, ketamine also produced rapid and relatively sustained antidepressant effects with only mild and transient light-headedness as a common side effect (no euphoria, psychotic or dissociative symptoms).[23] Moreover, like the exploratory study using sublingual ketamine, the nature of our study provided an opportunity for reviewing treatment response in a "dirty" population that may be more representative of the treatment-resistant psychiatric patient pool, which is not possible with randomized controlled trials. Oftentimes, as in our chart review, the patients have multiple medical and psychiatric comorbidities, including but not limited to prior substance use disorders, chronic pain, attention deficit hyperactivity disorder, borderline personality disorder, and anxiety disorders like posttraumatic stress disorder. With that in mind, it is reassuring that the addition of low-dose ketamine had no serious adverse effects, including no drug–drug interactions or recurrence of substance misuse/abuse. Moreover, though side effects were not systematically monitored, it is important to note that these patients were a part of the day hospital program at the psychiatric center, participating in group therapy sessions often within 1 hour of taking transmucosal ketamine and having adequate medical support during their stay. None of the patients in our study discontinued using ketamine because of adverse events, with only mild, transient side effects noted (headache, dizziness).

This study has many limitations which are inherent to using a retrospective design. These include the lack of randomization and consistent baseline clinical data. Moreover, data for each variable were not available in every chart. As this was not a controlled study and our patient population had taken a number of medications which may affect the antidepressant effects and pharmacokinetics of ketamine, we were also unable to determine whether the positive effects of treatment were due to ketamine alone or a combination of ketamine and other therapies. In addition, no standardized clinical measures were used to evaluate depressive symptoms and adverse effects, including the monitoring of vital signs. Tachycardia and increased blood pressure in particular have been commonly observed following low-dose ketamine injections[14] and should be systematically examined in future studies with transmucosal ketamine. The reliance on the drug refill history of a patient as an indicator of therapeutic efficacy introduces additional concerns that go beyond uncertainties regarding patient compliance and medication adherence. With the drug refill history omitted, however, ten of the 17 patients (ie, 59%) would have been classified as "responders" from clinical notes of efficacy in the charts, which remains a sizeable proportion of the treatment-refractory population. Nevertheless, due to these limitations, a prospective, pilot study is strongly warranted to validate the efficacy of the transmucosal route of ketamine as a viable option for eliciting fast-acting and sustained antidepressant effects, with a side effect profile suitable for use in outpatients. Whether ketamine remains as effective if patients were withdrawn from their routine antidepressants is also of great interest.

Conclusion

This retrospective chart review describes the use of transmucosal ketamine for treatment-resistant depression and suggests that it may be a safe, tolerable, and effective antidepressant in some depressed patients.

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The abstract of this paper was accepted for presentation at the 115th Annual Meeting of the American Association of Colleges of Pharmacy as a poster with interim findings. The poster's abstract was published in the *American Journal of Pharmaceutical Education* (2014;78(5):111; http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4064488/). The actual paper has never been previously published.

Disclosure

Several of the authors (SEP, PJM, RRM) are co-inventors on a US utility patent application (serial number 14/644,608), "Ketamine or dextromethorphan formulations and methods of use". The authors report no other conflicts of interest in this work.

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