Oral Ketamine for Depression, 1: Pharmacologic Considerations and Clinical Evidence

Chittaranjan Andrade, MD

ABSTRACT
Clinical evidence is accumulating to support the use of ketamine as a powerful, quick-acting intervention for depression. Ketamine has been administered by oral, sublingual, transmucosal, intravenous, intramuscular, subcutaneous, intranasal, and even rectal routes. Whereas intravenous ketamine is the best studied approach, common sense dictates that oral ketamine is the most practical. The bioavailability of oral ketamine and interindividual variations thereof have been poorly studied; possibly only 20%–25% of an oral dose reaches the bloodstream. This is not necessarily a limitation because, as with other drugs that have poor oral bioavailability, compensation is possible by administering an appropriately higher dose, and interindividual variations can be addressed through individualized dose titration. A quarter-century of experience supports the use of oral ketamine for treating acute and chronic pain in children and adults. Case reports, case series, chart reviews, and 3 recent randomized controlled trials (RCTs) show that oral ketamine is effective in treating severe depression, depression with suicidal ideation, and treatment-resistant depression; that oral ketamine, used as an augmentation agent, improves outcomes in patients receiving a conventional antidepressant; and that oral ketamine reduces depression in patients with chronic pain. Doses of oral ketamine have ranged from 0.25 to 7 mg/kg and from 50 mg per occasion to 300 mg per occasion in multiple daily dosing, daily dosing, and intermittent dosing schedules. Oral ketamine was well tolerated in all studies; dropout and reasons for dropout were similar in ketamine and control arms in the 3 RCTs. These findings suggest that if ketamine is to find a place as an off-label treatment for depression and suicidality in mainstream psychiatry, researchers should study the safety, efficacy, and optimization of oral ketamine.

Ketamine has gained visibility as a unique, powerful, rapid-acting, off-label treatment for depression. Earlier articles in this series summarized issues related to the efficacy, adverse effects, and mechanisms of action of ketamine as an off-label treatment for depression; diagnostic and contextual indications for ketamine; benefits and risks of R-ketamine vs esketamine vs racemic ketamine; treatment considerations, such as dosing, route of administration of the drug, rate of administration of the drug during a session, frequency of treatment sessions, and duration of ketamine therapy; pharmacokinetic and pharmacodynamic interactions between ketamine and other treatments; and the use of ketamine as an emergency intervention in patients at risk of suicide.

Ketamine is most commonly administered in 30- to 40-minute sessions by the intravenous (IV) route. This is inconvenient and expensive and is a barrier to the use of the drug in mainstream psychiatry, especially in emergency contexts. Recent evidence suggests that the administration of the drug by the oral route may be safe and effective. This evidence is examined from the perspectives of pharmacologic feasibility, safety, and efficacy of oral ketamine as an off-label intervention in depressed patients.

Route of Administration: Historical Background
In 1994, a pioneering study by Krystal et al examined the dose-dependent effects of ketamine on perceptual, cognitive, behavioral, neuroendocrine, and physiologic outcomes in 19 healthy volunteers. Ketamine was administered in 2 doses: 0.1 mg/kg and 0.5 mg/kg. Subjects were dosed by the IV route across 40 minutes; IV dosing was preferred perhaps because ketamine is conventionally administered by this route in anesthesiologic practice and also, perhaps, to obtain accurate control over dosing. Ketamine was observed to produce dose-dependent effects across a range of studied outcomes.

In 2000 and 2006, small but pathbreaking studies on the use of ketamine to treat depression employed the same route (IV) and manner of administration (infused across 40 minutes) in the higher dose (0.5 mg/kg) described by Krystal et al. Whereas other doses and routes of administration have been explored, 0.5 mg/kg IV infusions have been used in most of the subsequent studies as an apparently follow-the-leader approach to treatment.

Oral Ketamine: Bioavailability
Ketamine has been administered intravenously, intramuscularly, subcutaneously, intranasally, orally, transmucosally, sublingually, and even rectally; that is, by 8
A sample of 20 children, aged 1–8 years, who had received ketamine for oral bioavailability was 45%, but this was obtained in a very small study of 3 healthy adult volunteers, the oral bioavailability of ketamine was observed to be approximately 20%. In 6 adults with chronic neuropathic pain, the median oral bioavailability of ketamine was 24% (interquartile range, 17%–27%). The highest value observed for oral bioavailability was 45%, but this was obtained in a sample of 20 children, aged 1–8 years, who had received ketamine for procedures related to burns management; the findings may not generalize well to depressed but otherwise reasonably healthy adults. In a small study of 11 healthy volunteers, the oral bioavailability of esketamine was found to be very low, at 8%, with 11% interindividual variability.

Confident conclusions cannot be drawn when few patients are studied in a few studies. At best, therefore, one might surmise that the oral bioavailability of racemic ketamine is about 20%–25%. The interindividual variability in this bioavailability remains to be defined.

**Oral Ketamine Dosing: Theoretical Considerations**

As already stated, when ketamine is used as an off-label treatment for depression, it is most commonly administered IV in the dose of 0.5 mg/kg. So, if the oral bioavailability is reckoned at 20%–25%, one needs to multiply 0.5 mg/kg by a factor of 4–5 to achieve equivalent dosing by the oral route. In other words, the target oral dose could be 2.0–2.5 mg/kg. This works out to a dose of 120–150 mg for a 60-kg individual.

The poor bioavailability of oral ketamine could be a result of poor absorption or of metabolism of the drug as it passes through the intestinal lining and the liver. The latter is a more likely explanation because levels of norketamine, the active metabolite of ketamine, are high after oral administration of the drug. After correction for dose, the area under the norketamine concentration-time curve is similar to that of IV ketamine, indicating that oral ketamine is probably completely absorbed. Therefore, an assumption in multiplying the IV dose of ketamine by a factor of 4–5 (to get the equivalent oral dose) is that norketamine levels do not matter. We do not know whether or not this is true for efficacy and tolerability in the context of norketamine levels and depression. Clinical data are therefore necessary to determine the appropriate oral dose.

**Oral Ketamine Dosing: Practical Considerations**

Most treatments in medicine and psychiatry are administered orally. Logically, therefore, administering ketamine by the oral route would be far more convenient than administering it by the IV route, or by any other route, for that matter. Oral administration is a less expensive option than parenteral administration. Oral administration, though off-label, would also be less expensive than intranasal esketamine, an intervention that was recently approved by the US Food and Drug Administration. Oral administration would be an easy expedient for the emergency care of a suicidal patient and for domiciliary treatment, should this prove necessary. Finally, oral administration could make ketamine treatment more widely available, should this emerge as a justified end.

There are 2 problems associated with the oral administration of ketamine. One is the poor oral bioavailability of the drug. The other is its unpleasant taste. Neither problem is large. Consider that psychiatrists are familiar with drugs that have poor oral bioavailability; that of lurasidone, for example, is just 9%–19%. The solution to poor oral bioavailability is simple; all that one needs to do is to compensate by administering a dose that is high enough to be clinically effective. In research, safe and effective oral doses can be discovered through dose-ranging and flexible-dosing studies, and in clinical practice, by up-titration to effective and well-tolerated doses.

It is critically important to note here that what is necessary is to identify the oral dose that is associated with clinical efficacy, and not the oral dose that is equivalent to 0.5 mg/kg IV. This will mean that, because of interindividual variations in oral bioavailability, the therapeutic oral dose will be a range and not a single value as is 0.5 mg/kg. Interindividual variability in drug absorption is not a problem; consider that psychiatrists are quite familiar with individualizing dosing by titrating oral drugs to efficacy and tolerability across the spectrum of psychiatric disorders.

Ketamine has a taste that patients recognize as unpleasant but, in the experience of this author, are unable to satisfactorily describe. Again in the experience of this author, spanning 18 months specifically with oral ketamine, no patient has refused the treatment because of the taste of the drug. Be that as it may, some physicians prefer to administer the drug using a flavoring agent as a mask. Other physicians, however, may regard the unpleasant taste more as an opportunity than as a limitation because in many parts of the world, patients associate unpleasant-tasting medicines with efficacy. This, in other words, is the recruitment of placebo mechanisms to boost psychopharmacologic response or, in more politically correct terms, a way of harnessing nonspecific factors in psychopharmacology for the patient’s welfare.

Oral ketamine has been used for the management of acute and chronic pain for at least a quarter of a century in both adult and pediatric patients. The literature has been recently reviewed and is not reexamined here.

**Oral Ketamine for Depression: Uncontrolled Studies**

Case reports and small case series have described the successful use of oral ketamine to treat severe depression, depression associated with suicidal intent, and treatment-resistant depression (TRD); the benefits with oral ketamine have been shown to sustain with daily dosing.

In one small study, (N = 14), patients receiving hospice care experienced reductions in depression and anxiety during daily dosing with oral ketamine. In these reports, patients had multiple medical comorbidities, some...
serious, and many patients were receiving polypharmacy
with psychotropic and other medications. Most patients
were dosed at 0.5 mg/kg, and most outcomes were favorable.
Dosing per occasion, however, was as low as 0.25 mg/kg,
thrice a day, in a patient with TRD and liver dysfunction27
and as high as 3 mg/kg in a suicidal patient26; all doses were
well tolerated.

In a retrospective chart review, Al Shirawi et al29
described a series of 22 patients with TRD, all of whom had
received repeated dosing with oral ketamine. Dosing had
been up-titrated from 50 mg/d in the first treatment session
to up to a maximum of 300 mg/d, depending on benefits
and adverse effects. During dose discovery, patients were
-treated every 3 days for a minimum of 4 weeks, depending
on tolerability. The mean dose of ketamine was 222 mg
per treatment occasion; 6 patients reached the maximum
dose of 300 mg per occasion. Domiciliary treatment was
permitted after the initial dose. The authors reported that
only 4 patients had at least 50% improvement in depression
ratings, and a further 3 patients, between 20% and 50%
 improvement. In these 7 patients (32% of the sample),
documentation of continued efficacy extended from
between 15 weeks to 2 years. One patient had transient
visual hallucinations; adverse effects were otherwise mild
and brief.

In another retrospective chart review, Hartberg et
al30 described 37 patients with TRD, many of whom had
comorbid posttraumatic stress disorder or severe anxiety
symptoms. All patients had received repeated dosing with
oral ketamine for up to 3 years. The dose of ketamine
was up-titrated across several sessions from 0.5 mg/kg
to whatever dose resulted in a noticeable psychotropic
or systemic effect, such as a heady feeling or a change in
blood pressure. Final doses ranged from 0.5 to 7.0 mg/kg.
The illness course after initiating ketamine was compared
across a matching period with the illness course before
initiating ketamine. Ketamine treatment was associated
with a very substantial reduction in the number of days
of hospitalization and a very substantial reduction in the
number of hospital admissions; for example, there were
171 admissions pre-ketamine but only 65 admissions after
ketamine initiation. Whereas the mean dose of ketamine
was 3 mg/kg at the end of the dose discovery phase, it was
2 mg/kg at the study endpoint; this indicated continued
efficacy with no tolerance development or requirement for
dose escalation. Adverse effects were mild and transient;
there were no psychotomimetic events nor were there
serious adverse events.

In these reports and retrospective studies, ketamine was,
in general, administered along with other psychotropic
medications and not as monotherapy.

**Oral Ketamine for Depression: Controlled Studies**

Jafarinia et al31 described a 6-week randomized
controlled trial (RCT) of oral ketamine, dosed in capsules
at 50 mg thrice a day, vs oral diclofenac, also dosed in
capsules at 50 mg thrice a day, in 46 patients with mild to
moderate depression. All patients also had chronic pain
(mild to moderate headache) that was persistent for at least
the past 6 months. Forty patients completed the study. At
the 6-week treatment endpoint, mean depression ratings
in the ketamine patients, relative to those in the diclofenac
patients, were significantly lower by nearly 3 points on
the Hamilton Depression Rating Scale (Cohen d, 0.79).
Ketamine was superior to diclofenac on the Hospital Anxiety
and Depression Scale, as well. Endpoint antidepressant
response (60% vs 15%) and remission (45% vs 10%) rates
were also higher in the ketamine relative to the diclofenac
group. The antidepressant superiority of ketamine was
probably unrelated to reduction in pain severity because
the treatment groups did not differ significantly on pain
outcomes as assessed using a visual analog scale. Ketamine
was generally very well tolerated.

Arabzadeh et al32 described a 6-week RCT of oral
ketamine (25 mg twice a day) vs placebo augmentation of
sertraline (150 mg/d) in 90 patients with at least moderately
severe major depressive disorder. Ketamine and placebo
were administered in capsules. Nine patients did not complete
the study. Antidepressant ratings were significantly lower
in the ketamine group from week 2 onward. The response
rate was greater with ketamine than with placebo (85% vs
58%, respectively). Remission rates, however, did not differ
significantly between groups (22% vs 15%, respectively).
Ketamine was associated with a placebo level of adverse
effects.

In the most recent RCT, Domany et al33 administered
oral ketamine (1 mg/kg) or placebo to 41 patients with
TRD. Treatment was administered as a liquid, with no
masking for taste, thrice a week for 3 weeks; ongoing
psychotropic medications were continued unchanged.
Seven patients dropped out of treatment. Ketamine was
substantially superior to placebo. At treatment endpoint,
mean Montgomery-Asberg Depression Rating Scale scores
dropped from 33.4 to 20.7 in the ketamine group and from
30.0 to 27.5 in the placebo group. Response (32% vs 6%)
and remission (27% vs 0%) rates were also higher with ketamine
than with placebo. Adverse effects known to occur with
ketamine, such as dizziness, drowsiness, and euphoria, were
observed in a few ketamine patients and were mild and
transient.

In all 3 RCTs, dropout and reasons for dropout were
similar between ketamine and control groups. In all 3
RCTs, ketamine was self-administered by patients at
home; there was no evidence that the drug was misused.
All 3 RCTs suffered from the same major limitation: no
outcome data were available for the post-treatment weeks.
Whereas Domany et al33 did state that treatment gains
were maintained in the week after the study ended, no data
were presented to support the claim. The reason why this
limitation is important is that, unlike treatment gains with a
course of electroconvulsive therapy (ECT), treatment gains
with single or repeated ketamine dosing have, so far, not been
demonstrated to persist with maintenance pharmacotherapy
with conventional antidepressants.1,4
It is illegal to post this copyrighted PDF on any website.

You are prohibited from making this PDF publicly available.

For reprints or permissions, contact permissions@psychiatrist.com. © 2019 Copyright Physicians Postgraduate Press, Inc.

e4 PSYCHIATRIST.COM

J Clin Psychiatry 80(2), March/April 2019


