Clinical and Practical **Psychopharmacology**

Oral Ketamine for Depression, 2: Practical Considerations

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Each month in his online column, Dr Andrade considers theoretical and practical ideas in clinical psychopharmacology with a view to update the knowledge and skills of medical practitioners who treat patients with psychiatric conditions.

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ABSTRACT

The oral route of administration is probably the least expensive and most convenient way to administer ketamine in indicated contexts in depressed patients. Because only 20%–25% of orally administered ketamine reaches systemic circulation, oral doses of about 2.0–2.5 mg/kg may need to be administered to achieve equivalence to intravenously administered ketamine. In case reports, case series, standard operating practice in ketamine facilities, and randomized controlled trials, oral ketamine has been administered through weight-based dosing and as fixed doses, and the dosing strategy has been one-size-fits-all or individualized through a dose discovery process. Administered doses have ranged from 0.25 to 7.0 mg/kg in weight-based dosing sessions and from 25 mg to 300 mg in fixed dosing sessions. This article reviews strategies for dosing with oral ketamine, dose discovery procedures, rates of dosing during a session, the frequency of dosing sessions and the duration of treatment, treatment in the clinic vs domiciliary treatment, adverse effects and risks, and safety issues. Finally, this article provides a detailed account of practices and experiences with oral ketamine so that readers may know what to expect when the treatment is orally administered. Whereas oral ketamine appears to be a safe and effective treatment and could make ketamine an accessible and affordable intervention in less privileged medical facilities, readers are warned that the literature on oral ketamine is thin and that there are many areas that need more investigation, especially matters related to pharmacokinetics, physiologic effects, abuse potential and strategies to mitigate illicit use, and adverse effects and efficacy relative to other routes of administration. Until studies of a sufficiently high quality become available, the use of oral ketamine to treat depression must be considered experimental.

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Ketamine, originally approved as an anesthetic drug, is gaining ground as an intervention for patients with treatment-resistant depression (TRD), depression with serious suicidal ideation, and perhaps depression in certain other contexts, as well.[1,2] In March 2019, the US Food and Drug Administration (FDA) approved the use of intranasal esketamine, in conjunction with an oral antidepressant, for patients with TRD. The treatment will be made available only through a restricted distribution system in a Risk Evaluation and Mitigation Strategy program and will need to be administered in a certified medical office where the patient can be monitored for at least 2 hours after dosing.[3]

On the one hand, the FDA approval will make (es)ketamine formally available to patients with TRD; the approval will thus add to the treatment options described for patients with this difficult-to-treat condition. On the other hand, because of the restrictions under which the intervention will be marketed, accessibility could be poor. Affordability is also likely to be a problem. Finally, intranasal (es)ketamine is unlikely to become available, accessible, and/or affordable in other parts of the world in the near future. It is therefore necessary to consider alternatives.

Whereas most of the research on the use of ketamine as an off-label treatment for depression has examined its safety and efficacy as an intravenous (IV) intervention,[1] oral ketamine could be the most convenient, most acceptable, and least expensive form of use, especially in emergency contexts, and contexts in which other options for ketamine administration are not available or feasible. In fact, if the safety and efficacy of oral ketamine can be confirmed, then the contexts for preferring IV or intranasal administration would be few.

A previous article in this column examined pharmacologic considerations and clinical evidence related to the use of oral ketamine as an off-label intervention for depression.[4] This article will consider practical issues, drawing from the published literature on the subject and from the 18-month experience of this author with administering the drug by the oral route. Optimism expressed in this article notwithstanding, readers are invited to note that the off-label use of oral ketamine to treat depression is based on very limited research and requires much more study before confident recommendations can be expressed.

In What Dose Should Oral Ketamine Be Administered?

The bioavailability and pharmacokinetics of oral ketamine have been poorly studied. Oral ketamine is probably well or even completely absorbed; nevertheless, probably as a result of high first-pass metabolism in the intestinal lining and liver, a reasonable estimate is that only about 20%–25% of an oral dose

reaches the circulation. This means that, if the target dose of ketamine is 0.5 mg/kg, as commonly set when ketamine is administered by the IV route, the equivalent oral dose should be about 2.0–2.5 mg/kg, or about 120–150 mg for a 60-kg individual.[4]

Ketamine is metabolized to norketamine. This means that when ketamine is orally administered, blood levels of norketamine will be far higher than they are when ketamine is administered by IV infusion.[4] The antidepressant efficacy and adverse effects (AEs) of norketamine are presently unknown. So, multiplying the IV dose of 0.5 mg/kg by a factor of 4–5 to obtain the equivalent oral dose is not necessarily the right way of determining the target oral dose. Whereas dose-ranging studies will be necessary to identify the range of oral ketamine doses that are safe and effective for clinical practice, in individual patients it is likely that dose discovery will require uptitration to efficacy and AEs, much as is practiced with most psychotropic drugs in most psychiatric disorders.[4]

The existing literature on oral ketamine shows little uniformity in dosing practice. Oral doses have been administered as doses based on body weight or as fixed doses. Weight-based dosing has ranged from a low of 0.25 mg/kg to a high of 7 mg/kg per dosing occasion. Fixed doses have ranged from 25 mg to 300 mg per dosing occasion.[4]

It must be noted that because ketamine is metabolized chiefly in the liver and by cytochrome P450 3A4,[4] patients with liver disease and those receiving medications that induce or inhibit this metabolic enzyme will need appropriate modifications of the ketamine dose; individualized dosing through dose discovery, as discussed below, would be important for such patients.

Does One Size Fit All?

Weight-based dosing and fixed dosing have each been administered in 2 ways: as one size fits all or through a dose discovery process. With regard to weight-based dosing, as examples, Domany et al[5] treated all patients with ketamine in the dose of 1.0 mg/kg, whereas Hartberg et al[6] used a dose discovery process to individualize doses in the very wide range of 0.5 mg/kg to 7.0 mg/kg. With regard to fixed dosing, Arabzadeh et al[7] treated all patients with a fixed dose of 25 mg twice daily, whereas Al Shirawi et al[8] individualized dosing with fixed doses, identified through a dose discovery process, that ranged between 100 mg and 300 mg.

In medicine and psychiatry, dosing is rarely one size fits all. Individualization of ketamine dosing through dose discovery is therefore intuitively appealing. In a chart review of practice and experience with oral ketamine for TRD, conducted in a hospital in Toronto, Canada, Al Shirawi et al[8] reported that dosing began with 50 mg and was uptitrated in 25-mg steps, once in 3 days, until an administered dose resulted in an antidepressant effect on the day after dosing, or until a dose neither resulted in antidepressant benefit nor was tolerated, or until even a ceiling dose of 300 mg failed to elicit improvement. In the latter 2 instances, ketamine was discontinued and the patient was regarded as a nonresponder. Out of a sample of 22 patients, highest doses were 100 mg per dosing occasion in 2 patients, 150 mg in 5 patients, 175 mg in 1 patient, 225 mg in 4 patients, 250 mg in 4 patients, and 300 mg in 6 patients.

In another chart review of experience with oral ketamine for TRD, conducted in a suburban practice at an unnamed location in Australia, Hartberg et al[6] reported that oral dosing began at 0.5 mg/kg and was uptitrated by 20%–50% per session with sessions held twice daily, 3 hours apart, at a maximum frequency of 2 days a week. The target dose was deemed to have been attained if psychotropic effects (such as a "glass of wine" feeling) or systemic effects (such as changes in blood pressure) were detected. Importantly, dose discovery did not mean that no further changes would be made; readjustments were permitted all through the course of therapy. Discovered doses ranged from 0.5 mg/kg to 7.0 mg/kg, with most doses in the 2–3 mg/kg range.

Readers may wish to note that if oral ketamine is being administered as an emergency intervention to a suicidal patient, then it would be best to administer a dose that is sufficiently high as to be effective; individualization through dose discovery is reasonable only when time is not of essence, as in patients with long-standing TRD. A sufficiently high dose could be 2–3 mg/kg, partly because this was the commonest dose discovered by Hartberg et al[6] and partly because this dose approximates the 0.5 mg/kg IV dose multiplied by the oral bioavailability correction factor, as discussed in the previous section.

At What Rate Should Oral Ketamine Be Administered?

The administration of IV ketamine is controlled because the infusion is customarily spread across 30–40 minutes and can be stopped midway should problematic AEs arise. In contrast, once an oral dose is administered, nothing can be done to stop or reverse the administration. Sipping ketamine across a specified period is a possible way to control the rate of administration, and this could blunt the peak in blood levels, thereby reducing AEs associated with peak blood levels.

As far as could be determined from the literature, no author has reported advising patients to sip ketamine. However, as an extreme example of stretching the administration time interval, at least 2 studies[7,9] have reported dividing the dose across the course of a day with individual doses (25–50 mg) so low as to be unlikely to produce a detectable psychotropic effect.

With antidepressant, antipsychotic, and many other drugs in psychiatry, the total dose per day is what defines efficacy; higher peak blood levels contribute to an increased AE burden. However, with certain drugs, such as those used to treat insomnia, peak blood levels drive the onset of therapeutic effect. At present, we do not know whether the defining criterion for the antidepressant efficacy of ketamine is the peak blood level of ketamine that elicits clinically evident changes, the administered dose cumulated per day, or both.

What Are the Optimum Frequency and Duration of Treatment?

Oral ketamine has been administered as a one-off treatment, 2–3 times a day, once daily, thrice a week, and intermittently, as needed; it has been administered in a fixed course for 3–6 weeks and indefinitely for up to 3 years at last report.[4] There is no reason to expect that the frequency and duration of treatment with oral ketamine should be any different from those with other routes of administration. The reader is therefore referred to an earlier article for a discussion on this subject.[10]

Where Can Oral Ketamine Be Administered?

Intranasal esketamine has been licensed by the US FDA for administration in a certified medical office, and the patient is required to be monitored for 2 hours after administration of the drug.[3] Intravenous ketamine must, of necessity, be administered in a clinical setting. The first dose of oral ketamine, at least, is best administered in a medical facility where the patient can be examined before treatment and monitored during and after treatment; given that sedation, cardiostimulation, and emergent psychotic phenomena are all possible outcomes, appropriate facilities must be at hand to deal with these and other contingencies.

Once an appropriate dose is identified for a patient and once the safety and tolerability of this dose are established, it is reasonable to assume that future doses will be similarly tolerated. In this context, self-administration of the drug at home was described in 3 randomized controlled trials (RCTs)[5,7,9] as well as in a chart review.[8] In one of these reports,[8] dose uptitration to a maximum of 300 mg/d was also described to have been permitted by self-administration at home, and dosing was effected at night.

What Are the Adverse Effects and Risks?

The AEs and risks associated with oral ketamine are unlikely to be much different, if at all, from the risks associated with the administration of ketamine by other routes. Possible additional considerations are issues arising from unsupervised domiciliary use and chronic use.

Jafarinia et al[9] described an RCT (n = 46) in which oral ketamine or diclofenac were each administered in the dose of 50 mg thrice a day for 6 weeks. AEs were very few and were closely similar in the 2 groups. Arabzadeh et al[7] described an RCT (n = 90) in which oral ketamine (25 mg twice a day) or placebo were administered for 6 weeks to sertraline-treated patients. Again, AEs were very few and their occurrence was very similar in the 2 groups. Domany et al[5] described an RCT in which ketamine (1 mg/kg) or placebo were administered on alternate days, thrice a week, for 3 weeks. Dizziness and euphoria were each reported by 4 patients; other AEs were very few, occurred in the placebo group as well, and were each reported by just 1 or 2 patients.

In a retrospective case series of TRD patients who took oral ketamine (mean dose, 222 mg; range, 100–300 mg per occasion) at home for up to 2 years, Al Shirawi et al[8] reported that 41% experienced dissociative symptoms that lasted for 30 minutes to 2 hours. Other frequent AEs included dizziness (23%), blurred vision (18%), numbness (14%), sedation (4%), nausea (4%), and insomnia (4%). One patient experienced transient visual hallucinations during the dissociative period but not other psychotic phenomena. Two patients reported transient suicidal ideation. There were no persistent AEs, no urinary complications attributable to ketamine, no cravings for ketamine, no urges for dose escalation or for more frequent drug use, and no misuse of the drug.

In another retrospective case series of TRD patients who took oral ketamine (modal doses, 2–3 mg/kg) for up to 3 years, Hartberg et al[9] reported that the commonest AEs included light-headedness, sedation, and mild dissociative symptoms. About 5%–10% of patients had blood pressure changes, nausea, or headache. All these effects subsided within an hour of dosing; no intervention was necessary. There were no psychotic phenomena or crises of any nature. There were no cases of bladder toxicity. Greater detail, however, was not provided.

Whereas data from RCTs carry greater weight than data from chart reviews, it must be noted that dosing per occasion in the RCTs was lower than that in the chart reviews. This might explain why the chart reviews recorded more AEs.

Safety Issues

Some issues related to safety are worthy of note. Oral ketamine, as dosed for the treatment of depression, will not anesthetize the patient. This is because usual doses of IV ketamine for the induction of anesthesia, as in electroconvulsive therapy practice, lie in the 0.5–2.0 mg/kg range.[11] Given that only a quarter to a fifth of an oral dose (eg, 2–3 mg/kg) of ketamine reaches the bloodstream,[4] and given that oral absorption occurs gradually,[12] meaning that the entire dose does not reach the circulation at the same time, as would be necessary for anesthesia to develop, it is very unlikely that oral ketamine (2–3 mg/kg) would do anything more than briefly sedate the patient.

In this context, readers may note that oral ketamine has even been administered in a dose as high as 6–8 mg/kg, shortly after dosing with an oral benzodiazepine, to effect deep sedation (but not anesthesia) in mentally handicapped children seen in pediatric dental practice.[13] Psychiatrists are quite familiar with sedative-hypnotic, antidepressant, and antipsychotic drugs that effect strong and prolonged sedation, and so transient sedation occasioned by oral ketamine should not be a cause for anxiety. Another way of considering it would be to say that ketamine, administered in what amounts to a subanesthetic dose and by the oral route, is an antidepressant drug and not an anesthetic agent.

A further note of reassurance here is that even when ketamine is administered as anesthesia, it does not cause respiratory and cardiac depression; in fact, this property is the reason why ketamine was considered safe even in patients who were otherwise high risk candidates for anesthesia.[14] Furthermore, one study found ketamine safe for use even in untrained hands.[15] Therefore, subanesthetic dosing with

oral ketamine is likely to be associated with an even higher margin of safety than IV dosing and dosing at anesthetic levels.

Ketamine has a cardiostimulatory effect. In a pooled analysis of 205 IV ketamine sessions in 97 patients, Wan et al[16] found that mean increases in systolic and diastolic blood pressure were about 20 and 13 mm Hg, respectively, and that nearly 30% of patients had had blood pressure readings that exceeded 180 mm Hg systolic and 110 mm Hg diastolic, as well as heart rates that exceeded 110 bpm. All of these changes, however, were transient peak values. Given that similar cardiovascular changes, sustained over longer periods, are observed in persons who perform aerobic and strengthening exercises, there may not be a need for concern about the cardiostimulatory effects of oral ketamine, especially in young and healthy patients. These effects do need to be better characterized in literature, though, if only to provide the necessary reassurances.

Experiences With Oral Ketamine

This author has about 18 months of experience with treating depressed patients with oral ketamine. It could be useful for readers to be aware of how an oral ketamine session might be conducted, and what might happen during the session, because there is little to no published information on the subject.

Risk of suicide is the commonest context for the use of oral ketamine. Involvement or risk of involvement in harmful behaviors associated with depression, such as binge drinking, use of illicit substances, and precipitation of domestic disharmony, is also a considered context. These patients tend to be young and in good physical health, diminishing concerns about ketamine-related health risks. The next most common context is TRD. However, ketamine is also occasionally used for situational indications. One example is the patient who cannot afford to take leave from the workplace; oral ketamine with booster sessions keeps the patient productive until the initiated conventional antidepressant therapy takes effect. Another example is the depressed student who needs to be well enough to attend examinations during the days ahead.

Oral ketamine is always administered in the presence of a competent caregiver who will take responsibility for the patient after the session. There are almost no contraindications for oral ketamine. As an example, a 17-year-old girl with a 5-year history of TRD and with 3 suicide attempts in the past week emerged from intensive care still drowsy and ataxic from the effects of her last drug overdose. Her self-reported suicidal intent was 9 on a scale of 0 to 10. She received oral ketamine, and her suicidal intent dropped by more than 50% during the subsequent days.

In general, a patient who can climb 2 flights of stairs or walk for 15 minutes at a moderate pace can be expected to tolerate the cardiostimulatory effects of ketamine. All treatment is based on risk-benefit evaluations, and so decision-making will need to be individualized in medically compromised patients. Readers may note, however, that as reviewed in an earlier article, many patients treated with oral ketamine had major medical comorbidities and tolerated oral ketamine well.[4]

Oral ketamine is administered in the fixed dose of 150 mg to almost all patients; lower doses appear to be associated with less efficacy or with quicker wearing off of antidepressant benefits, and higher doses are associated with more intrasession AEs. The dose is drawn from vials of ketamine meant for injection in anesthesia. The usual concentration is 50 mg/mL, so a 150 mg dose amounts to just 3 mL. This volume is syringed into a glass containing 30–50 mL of water.

If the patient is receiving ketamine for the first time, s/he is instructed to sip the solution across 10–15 minutes. Sipping is also advised if the patient is on an empty stomach. One reason is that oral ketamine can produce dose-dependent nausea and vomiting, and these are more likely when the patient is fasting. The other reason is that dissociative and other AEs of ketamine can be more pronounced if the patient is fasting. These observations require confirmation in studies that examine the pharmacokinetics of oral ketamine taken with and without food.

The patient is also provided guidance and reassurance along the following lines.

> The medicine may taste a bit nasty. Never mind; good medicines seldom taste good! You probably won't feel anything for the first 15 minutes, while you are sipping the medicine. During the next 15 minutes, however, you may experience strange symptoms. For example, you are likely to feel unreal, or you may feel as though you are floating. If you stand, you are very likely to feel unsteady; you may also experience dizziness. You may feel nauseous and may want to throw up; this is uncommon. You could even have stranger effects such as seeing double, or, as a very unlikely possibility, you might experience visions, that is, seeing things that are not really there. Don't worry, these will last only a short while. Please note that I actually want you to have at least some of these effects because this is how I can know that you have received a biologically significant dose of the drug.
>
> In the third 15 minutes, you are likely to feel sleepy. If so, I encourage you to sleep on the couch. By the fourth 15 minutes, you are likely to awaken on your own. Within minutes of awakening, you are likely to feel fresh and steady on your feet. Once I am confident that you have fully recovered, which is likely to be 60–75 minutes after you began sipping the ketamine, you can leave.
>
> Some patients experience rapid heartbeat during a ketamine session. Some patients feel anxious. Some patients feel temporarily worse and may even cry. These are all transient phenomena.
>
> Your depression and suicidal thoughts are likely to be less intense after the ketamine session. However, it usually takes a full day for the benefits to peak. Note that the benefits of ketamine tend to wear off after anywhere between 3 and 10

days or thereabouts. So the treatment only buys you some time; it is not a permanent solution. However, if you feel better after receiving ketamine, you will be less at risk of harming yourself, and you will be able to work better. Ketamine will also keep you going until your medicines or other treatments begin to act. Now, please ask whatever questions you might wish to ask.

Other Practical Notes

Ketamine is usually administered as an add-on to other necessary psychotropic medications. If a patient tolerated oral ketamine well in the first session, in future sessions the dose can be consumed across a shorter time span, or even gulped down straightaway. Perhaps tolerance develops to the AEs of ketamine. It is also possible that nocebo or expectancy effects drive the greater AEs characteristic of the first session.

Patient experiences with oral ketamine do not necessarily breed true. A patient who has been able to well tolerate several sessions of ketamine may unexpectedly experience nausea or even prominent neurologic, dissociative, or psychotic AEs in a session despite the session being identical in all ways to the previous ones. A patient who has absolutely no discernible response to a 150-mg oral dose may have pronounced AEs when the dose is raised to 200 mg in the next session.

Psychotic AEs are very rare with the fixed oral dose of 150 mg, sipped across 10–15 minutes, and may occur once in about 50–100 treatment sessions if the dose is gulped down on a fasting stomach. Psychotic phenomena are limited to visual and auditory hallucinations and may be accompanied by synesthesia. The patient is seldom distressed by the experiences, especially if the caregiver and physician soothe and reassure the patient. There is no need to intervene medically; the phenomena subside on their own in 15–45 minutes.

Of interest, this author had one young patient who, about 30–45 minutes after sipping her ketamine, developed what appeared to be a full-blown acute psychotic episode characterized by shouting, screaming, rolling eyes, thrashing about, and showing no meaningful contact with reality. This continued for about 2 hours and subsided only when she was told that an "antidote" to ketamine would be administered. She displayed many symptoms over subsequent days, consistent with the diagnosis of a dissociative disorder, all of which disappeared with psychological intervention. So a psychotomimetic response to ketamine may not necessarily be a psychotic reaction to the drug. One wonders to what extent dissociative and other AEs may be induced by suggestion during the process of consenting and educating the patient about the treatment.

Parting Notes and Caveats

Oral ketamine has the potential to become a simple and inexpensive treatment option for physicians who require access to the intervention for the better care of their patients, especially in parts of the world that have less privileged access to medical care. However, readers are reminded that oral ketamine is an emphatically off-label intervention for depression; it is supported by far less research than is available on IV or intranasal ketamine for the same indication. Readers are also reminded that, even more importantly, and even in the experience of this author, ketamine is usually only a temporary expedient in specific contexts within the diagnosis of depression; it is hardly ever a solution to the complexities of depression. This warning is intended to discourage the overenthusiastic off-label use of the treatment before regulatory guidance or support becomes available. Finally, readers are advised to adhere to the local guidelines and regulations that govern their practice and be aware of the abuse potential of ketamine as its use becomes increasingly common.

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