Clinical and Practical **Psychopharmacology**

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

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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

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 up-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. Intravenous and intranasal routes may be monetarily more promising, but the oral route could be of greatest service.

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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[1]; diagnostic and contextual indications for ketamine[2]; benefits and risks of *R*-ketamine vs esketamine vs racemic ketamine[3]; 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[4]; pharmacokinetic and pharmacodynamic interactions between ketamine and other treatments[5]; and the use of ketamine as an emergency intervention in patients at risk of suicide.[6]

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.[7] 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[8] 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[9] and 2006,[10] 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.[8] 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.[4]

Oral Ketamine: Bioavailability

Ketamine has been administered intravenously, intramuscularly, subcutaneously, intranasally, orally, transmucosally, sublingually, and even rectally; that is, by 8

different routes.[4,11] The bioavailability of ketamine varies, depending on the route of administration. Oral ketamine has poor bioavailability.

In an early study conducted in 6 healthy volunteers,[12] only 17% of an oral dose of ketamine was found to have reached the systemic circulation. In a very small study of 3 healthy adult volunteers, the oral bioavailability of ketamine was observed to be approximately 20%.[13] In 6 adults with chronic neuropathic pain, the median oral bioavailability of ketamine was 24% (interquartile range, 17%–27%).[14] The highest value 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[15]; 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.[16]

Confident conclusions cannot be drawn when few patients are studied in 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.[12] 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%.[17] 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.[18] 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[19,20] and pediatric[21,22] patients. The literature has been recently reviewed[23] 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)[24–27]; the benefits with oral ketamine have been shown to sustain with daily dosing.[18,20] In one small study[28] (N = 14), patients receiving hospice care experienced reductions in depression and anxiety during daily dosing with oral ketamine. In these reports, many 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 dysfunction[27] and as high as 3 mg/kg in a suicidal patient[26]; all doses were well tolerated.

In a retrospective chart review, Al Shirawi et al[29] 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 al[30] 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 al[31] 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 al[32] 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 al[33] 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 al[33] 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]

Summary

The oral bioavailability of racemic ketamine is about 20%–25%, as far as can be determined from the limited information available. Little is known about interindividual variation in oral bioavailability. Case reports, uncontrolled studies, and RCTs have all shown that oral ketamine reduces depression and suicidality in moderately to severely depressed patients, suicidal patients, and patients with TRD. Doses in these reports and studies have ranged from as low as 0.25 mg/kg to as high as 7 mg/kg per treatment session. Dosing frequency has varied, with repeated intraday dosing, one-off dosing, daily dosing, thrice-weekly dosing, and less frequent dosing described for periods of up to 3 years. Oral ketamine in the administered doses appears to be reasonably well tolerated with no misuse, abuse, dose escalation, craving, dependence, serious adverse events, or deaths reported.

To sum up, oral ketamine is effective but the benefits are not as pronounced or as sustained as those observed in patients treated with ECT. There have been no studies comparing oral ketamine with IV ketamine or intranasal esketamine, both of which are expensive interventions; such studies are necessary. Dose-ranging studies are required to decide what starting doses and what up-titration strategies might be best for use in different clinical contexts; these dosing strategies will need to factor in possible pharmacokinetic interactions between concurrent medications and ketamine.[5]

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