Clinical and Practical **Psychopharmacology**

Ketamine for Depression, 4:
In What Dose, at What Rate, by What Route, for How Long, and at What Frequency?

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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

Background: Ketamine, administered in subanesthetic doses, is an effective off-label treatment for severe and even treatment-refractory depression; however, despite dozens of studies across nearly 2 decades of research, there is no definitive guidance on matters related to core practice issues.

Methods: This article presents a qualitative review and summary about what is known about ketamine dosing, rate of administration, route of administration, duration of treatment, and frequency of sessions.

Results: Ketamine is most commonly administered in the dose of 0.5 mg/kg, but some patients may respond to doses as low as 0.1 mg/kg, and others may require up to 0.75 mg/kg. The ketamine dose is conventionally administered across 40 minutes; however, safety and efficacy have been demonstrated in sessions ranging between 2 and 100 minutes in duration. Bolus administration is safe and effective when the drug is administered intramuscularly or subcutaneously. Whereas the intravenous route is the most commonly employed, safety and efficacy have been described with other routes of administration, as well; these include oral, sublingual, transmucosal, intranasal, intramuscular, and subcutaneous routes. Patients may receive a single session of treatment or a course of treatment during the acute phase, and treatment may rarely be continued for weeks to years to extend and maintain treatment gains in refractory cases. When so extended, the ideal frequency is perhaps best individualized wherein ketamine is dosed a little before the effect of the previous session is expected to wear off.

Conclusions: There is likely to be a complex interaction between ketamine dose, session duration, route of administration, frequency of administration, and related practice. Until definitive studies comparing different doses, rates of administration, routes of administration, and other considerations are conducted, firm recommendations are not possible. From the point of view of clinical practicability, subcutaneous, intranasal, and oral ketamine warrant further study. If domiciliary treatment is considered, the risk of abuse must be kept in mind.

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Introduction

Previous articles in this column summarized issues related to the efficacy, adverse effects, and possible mechanism(s) of action of ketamine in the treatment of depression[1]; suggested indications and contexts for the use of ketamine as an off-label antidepressant[2]; and examined issues related to the choice of ketamine enantiomer vs the use of racemic ketamine.[3] The present article examines issues related to dosing, rate of administration, route of administration, duration of treatment, and frequency of sessions when ketamine is used in subanesthetic doses for the treatment of depression, especially treatment-resistant depression.

What Dose?

Ketamine was administered by the intravenous (IV) route in the doses of 0.1 and 0.5 mg/kg when its psychotomimetic and other effects were formally studied.[4] The first 2 randomized controlled trials (RCTs) of subanesthetic ketamine dosing for depression employed a 0.5 mg/kg IV dose.[5,6] This dose has since remained, perhaps by default, the commonest dose that has been studied in the field. Lower doses have been trialed, such as 0.25 mg/kg with *S*-ketamine[3] and even 0.2 mg/kg with the racemate.[7] Doses such as between 0.1 and 0.5 mg/kg have also been formally studied in small crossover clinical trials.[8,9] In general, antidepressant efficacy of ketamine was demonstrated in all the studies, regardless of dose.

In one uncontrolled, open-label study,[10] 14 patients with treatment-resistant depression (TRD) received ketamine augmentation of ongoing antidepressant pharmacotherapy. Ketamine was administered IV in 45-minute infusion sessions at a frequency of 2 per week; the dose was 0.5 mg/kg for the first 3 sessions and 0.75 mg/kg for the next 3 sessions. In a completer analysis, the response rate was only 7% after the first 3 infusions but 42% after all 6 infusions. The remission rate was 17% after 6 infusions. All but 1 responder relapsed within 2 weeks of the last session. The findings of this study suggest that patients may require multiple ketamine sessions to respond and/or that a higher dose (0.75 mg/kg) may benefit patients who do not respond to the conventional dose (0.5 mg/kg).

Chilukuri et al[11] randomized a heterogeneous group of 27 severely depressed patients to receive ketamine in the dose of 0.5 mg/kg IV, 0.5 mg/kg by the intramuscular (IM) route, or 0.25 mg/kg IM. Within 2 hours of treatment, depression scores dropped by 57%–60% in the 3 groups. These benefits were maintained at a 4-day follow-up. This important single-dose RCT, which showed similar outcomes with 2 different

Clinical Points

- Ketamine is commonly administered intravenously in the dose of 0.5 mg/kg. However, benefits and adverse effects are probably dose-dependent in the range of 0.10–0.75 mg/kg.
- Ketamine may be administered as rapidly as in a bolus dose to as slowly as across 100 minutes. Sessions that are 40 minutes in duration are conventional, especially with intravenous dosing.
- Ketamine is safe and effective when administered by oral, sublingual, transmucosal, intranasal, intravenous, intramuscular, and subcutaneous routes. Bioavailability is best when ketamine is administered parenterally or intranasally. Oral, subcutaneous, and intranasal delivery are perhaps the most practical methods.
- Ketamine sessions can be repeated (if necessary, at higher doses) to elicit response in patients who do not respond. Sessions can be repeated to extend and maintain response in those who do benefit. Repeated sessions at suitably spaced intervals have been described across weeks to years of treatment in refractory cases.

doses of IM ketamine, was limited by the absence of a placebo control group.

In a small (n = 15), double-blind, placebo-controlled, multiple crossover RCT in TRD patients,[9] ketamine was incrementally dosed between 0.1 mg/kg and 0.5 mg/kg with dose escalation by 0.1 mg/kg in sessions separated by at least 1 week. Treatment was delivered by IV (n = 4), IM (n = 5), or subcutaneous (SC; n = 6) routes. Whereas some patients responded at even 0.1 mg/kg, others responded only at higher doses. By the end of the study, 12 patients had met both response and remission criteria at least at 1 time point during the study. The adverse effects of ketamine seemed higher at higher doses. This study confirmed the findings of a similar double-blind crossover study of IV ketamine, conducted by the same group in 4 TRD patients.[8]

In a single-dose multicenter study, Singh et al[12] randomized 30 patients with TRD to *S*-ketamine (0.2 mg/kg or 0.4 mg/kg) or placebo groups. One day later, mean Montgomery-Asberg Depression Rating Scale (MADRS) scores fell by about 17 points in each of the 2 ketamine groups as compared with only 4 points in the placebo group.

Whereas it seems possible that doses lower than 0.5 mg/kg may suffice for at least some patients, until adequately powered dose-ranging safety and efficacy RCTs are conducted, the 0.5 mg/kg dose may remain the default. Higher doses may benefit patients who do not respond in 0.5 mg/kg sessions.

At What Rate?

As with ketamine dosing, because the pioneering studies[4–6] administered ketamine in 40-minute sessions, the 40-minute ketamine session has tended to remain the norm. A reasonable explanation for the slow rate of administration is that a faster rate is more likely to elicit a sedative or anesthetic response. Nonetheless, ketamine has also been administered in 2- to 5-minute IV infusions[7–9] and even as an IM or SC bolus.[9,11] Longer, 100-minute sessions have also been reported with a view to mitigating anesthesia risks and the need for anesthesiological supervision.[13,14] Judging from the results of the studies, these variations in the rate of administration are not accompanied by discernible variations in treatment efficacy or adverse effect profile. However, no head-to-head comparisons of different session durations are available.

Intranasal ketamine has been administered in sessions that are 20–40 minutes in duration.[15,16] There is 1 anecdotal report (n = 2) and 1 pilot RCT (n = 20) of the use of ketamine to successfully "break" TRD with the drug being administered as a continuous infusion in best tolerated doses across 4–5 days.[17,18] In the anecdotal report,[17] the patients had not been previously trialed with ketamine as conventionally delivered. In the pilot RCT,[18] efficacy outcomes in the prolonged infusion treatment arm were no better than those in the single ketamine session treatment arm. Therefore, the case for prolonged ketamine infusion remains unestablished.

By What Route?

The antidepressant effect of ketamine has been most extensively studied with the IV route of administration. However, oral, sublingual, transmucosal, intranasal, SC, and IM routes of administration have also been examined.

Bioavailability. The bioavailability of oral ketamine is low when the drug is swallowed; for example, studies have obtained a value of 8% for *S*-ketamine[19] and 24% for racemic ketamine.[20] The bioavailability improves to about 24%–30% with lozenge or liquid sublingual formulations.[20,21] The bioavailability of intranasal ketamine is nearly complete, with loss occurring only if some of the intranasal spray dribbles down the upper lip or enters the pharynx and is swallowed.[16] The bioavailability of SC, IM, and IV ketamine can be expected to be complete; however, a small study[9] reported that the plasma concentration of ketamine was approximately double when the drug was administered by the IV as compared with the IM or SC routes.

Oral administration. There are case reports of the efficacy of oral ketamine in TRD[22–24] and of benefits with oral ketamine that are sustained with daily dosing.[23,25] Daily oral ketamine (0.5 mg/kg for 4 weeks) attenuated anxiety and depression symptoms in 14 patients receiving hospice care.[26] Oral ketamine (150 mg/d) was superior to diclofenac (150 mg/d) in a 6-week parallel group RCT conducted in 40 patients with mild to moderate depression occurring in the context of chronic pain.[27] The unpleasant taste of the drug can be masked by a flavoring agent.[25]

Sublingual and transmucosal administration. Very low dose (10 mg) ketamine, administered sublingually at a frequency of once in 2–7 days, was found to result in sustained clinical improvement in 20 (77%) of 26 patients with refractory unipolar or bipolar depression.[28] Intraoral, transmucosal ketamine (0.5–1.0 mg/kg) improved outcomes in 76% of 17 patients with refractory depression.[29]

Intranasal administration. There is 1 report of the use of intranasal ketamine to treat depression and to maintain antidepressant response for years.[30] Clark[31] also reported successful outcome with the use of intranasal ketamine in a case of refractory depression. One single-dose crossover RCT in partially drug-resistant depressed patients (n = 18) found that intranasal dosing was superior to control treatment.[15] Intranasal *S*-ketamine has been found effective in RCTs.[32]

Subcutaneous administration. There has been 1 case report of the use of SC ketamine to treat depression and maintain antidepressant response across months.[33] In a double-blind, incrementally dosed crossover study of 6 TRD patients, SC ketamine (0.1–0.5 mg/kg) was associated with a 100% remission rate[9] and with lesser hemodynamic effects than those observed with IM and IV ketamine.

Intramuscular administration. There have been case reports of the successful use of IM ketamine to treat depression.[34,35] There have also been reports of the use of repeated, spaced dosing with IM ketamine to maintain antidepressant benefits,[36,37] with repeated dosing in some instances being continued at 3- to 4-day intervals for months.[38] One double-blind, incrementally dosed crossover study of 5 treatment-refractory depressed patients obtained a 60% remission rate with IM ketamine dosed at 0.1–0.5 mg/kg.[9] One 3-arm, single-dose RCT[11] in 27 severely depressed patients found that ketamine dosed at 0.25 mg/kg IM resulted in a mean reduction of depression ratings by 57%, 2 hours after treatment; this was very similar to the reduction of 59%–60% in patients dosed at 0.5 mg/kg IM and 0.5 mg/kg IV. The benefits were maintained and remained comparable at 4 days. However, the RCT lacked a placebo control group.

General notes on route of administration. Oral ketamine has a bitter taste,[25] SC ketamine can have local irritant effects and may need to be diluted,[39] IM ketamine injections can be painful,[40] and the administration of intranasal ketamine can be bothersome if the duration is stretched across 40 minutes.[16] Ketamine injection sites are best rotated when SC or IM treatments are administered. In this regard, the SC route of administration may be better than the IM route because there is a larger number of sites, across the body, that are suitable for injection.

Plasma levels with IM and SC ketamine are roughly half those with IV ketamine.[9] It is not clear to what extent such differences influence the therapeutic effects of the treatment.

Oral and SC administration are clearly more convenient than IV administration and could open the doors wide for the use of ketamine, where indicated, in everyday clinical care.

For How Long and at What Frequency?

Extended acute phase treatment. Many studies, including the early RCTs,[5,6] found dramatic responses to a single treatment with IV ketamine. However, these and subsequent studies observed that not all patients respond. It is possible that some of the nonresponders may convert to responders if treated in serial sessions. This has been demonstrated in a few small uncontrolled, open-label[10,13] and controlled double-blind[9] trials. A limitation of some of these trials[9,10] is that dose escalation in later ketamine sessions was a confound, and so we do not know whether or not the patients would have responded, as do patients receiving electroconvulsive therapy (ECT), were treatment to have been continued without a change in the treatment parameters.

In this context, a large (n = 67), multicenter RCT conducted in patients with TRD studied patients who received ketamine (0.5 mg/kg) or placebo twice vs thrice a week. After 15 days, mean MADRS scores decreased by about 18 points in each of the 2 ketamine groups but by only 3–6 points in the 2 placebo groups.[41]

An earlier, smaller, nonrandomized, open-label, naturalistic study[42] administered ketamine infusions (0.5 mg/kg) once a week (n = 15) or twice a week (n = 13) to 28 patients with unipolar or bipolar TRD. Although the authors did not formally compare the groups, from the data presented it appeared that the 2 treatment schedules yielded similar though modest antidepressant results.

A course of 6 alternate-day IV ketamine infusions (0.5 mg/kg) was administered to a chronically depressed, antidepressant- and ECT-refractory male; the patient remitted by the end of the ketamine course and remained in remission for 26 days, but relapsed after a further 3 days.[43] A similar course of ketamine administered to an antidepressant-refractory female resulted in remission after the very first ketamine session; this remission was maintained during the ketamine course, and the patient remained well without maintenance medication for 3 months, after which her symptoms gradually returned.[44]

In a small open study conducted in 10 medication-free patients with TRD, a course of ketamine infusions (0.5 mg/kg) was administered thrice a week for 2 weeks. Nine patients met response criteria at the end of the first and sixth sessions; there was a mean MADRS score reduction of 85% at the end of the ketamine course. Patients relapsed 6–45 (mean, 19) days after the course. One patient remained in remission for > 3 months.[45]

In another study of 6 ketamine infusions administered thrice a week to 14 on-medication patients with TRD, only 3 patients responded to the first infusion, and only 1 patient remitted; these statistics improved as the ketamine course progressed, and 11 of 12 patients who completed the course achieved response while 8 attained remission. Six patients relapsed after a mean of 16 days, and the remaining 5 maintained response for at least 4 weeks.[46]

Continuation and maintenance treatment. If patients do respond, what comes next? That could depend on why ketamine had been advised. For example, if the purpose of treatment was to improve antidepressant[47] or ECT[48] outcomes, or if the treatment was administered for emergency reduction of suicidality or for a pressing social context,[2] then continuation of ketamine is unnecessary after the objective has been achieved. However, if there is no continuation and maintenance therapy that will keep the patient well after response and remission, then some thought may need to be given to the intermediate- and even long-term

Table 1. Important Take-Home Messages on Dosing, Rate of Administration, Route of Administration, Duration of Treatment, and Frequency of Sessions When Ketamine Is Used in Subanesthetic Doses for the Treatment of Depression

1. Ketamine is most commonly dosed at 0.5 mg/kg. However, some patients may benefit from doses as low as 0.1 mg/kg. Patients who do not benefit at 0.5 mg/kg may respond at higher doses, such as 0.75 mg/kg. Higher doses may be associated with more adverse effects. These findings notwithstanding, parallel-group studies find no efficacy differences between different ketamine doses.
2. Ketamine is usually dosed across 40 min, especially when the dosing is by the IV route. However, benefits have been described even when infusion sessions are as short as 2 min or as long as 100 min. Ketamine is administered as a bolus when treatment is by the IM or SC route. Tolerability does not appear to be compromised by shorter treatment sessions or by bolus administration. Whereas ketamine has also been administered in best tolerated doses as a continuous infusion across 4–5 days, the case for such prolonged treatment remains unestablished.
3. Ketamine has been found effective when administered by oral, sublingual, transmucosal, intranasal, IV, IM, and SC routes. Whereas IV dosing has been the most extensively studied, intranasal, SC, and oral (despite low bioavailability) dosing are more convenient, but will require better study before they can be recommended over IV dosing.
4. Ketamine dosing can be repeated once in 2–3 days for 4–6 treatment sessions if the initial session elicits inadequate response; later sessions can be dosed at the same level or (preferably) at higher levels.
5. In patients in whom ketamine is required for continuation and maintenance therapy (because no other treatment is effective), sessions are best scheduled at an individualized frequency (typically once in 3–5 days) where each dose is administered a little before the effect of the previous dose wears off.

Abbreviations: IM = intramuscular, IV = intravenous, SC = subcutaneous.

continuation of ketamine. In this context, continuation and maintenance therapy with intranasal, SC, IM, and IV ketamine has been described for periods ranging from months to years.[30,36–38,49,50] However, almost all the literature on treatment periods beyond 1 month is anecdotal in nature.

One study[14] examined the benefits of a fixed course of 4 once-weekly ketamine sessions (0.5 mg/kg IV) as continuation phase treatment in 5 patients who had remitted after acute phase treatment. All 5 patients maintained improvement during the continuation phase. A further 4 weeks later, during which period no more ketamine sessions were scheduled, all 5 patients continued to be classified as responders but only 1 patient maintained remission status.

A general impression obtained from the continuation and maintenance treatment literature is that there is no dosing interval that can be universally recommended; given that the benefits of ketamine wear off after different durations in different patients, it is logical to determine by trial and error the frequency at which ketamine needs to be administered in the individual patient. This could be every 3–4 days in the modal patient. Daily dosing, specifically with oral ketamine, has already been referred to in an earlier section.

When long-term ketamine is considered, especially in domiciliary treatment settings, the risk of abuse needs to be kept in mind and periodically reviewed.[51]

Summary

A snapshot of this article is presented in Table 1. Much of the data are from uncontrolled, open-label studies. Many RCTs lacked placebo control arms. There are few to no RCTs and certainly no definitive RCTs that compare different doses, rates of administration, routes of administration, numbers of sessions, and intersession intervals, and so no definitive recommendations can be made. It is possible that there are interactions between the dose of ketamine that is administered, the duration across which it is administered within a session, the frequency at which ketamine sessions are scheduled, and the total number of ketamine sessions. No RCT so far has specifically examined such interactions for a single route of administration, let alone across routes of administration.

Notes on General Safety Issues

Ketamine is a drug that is associated with risks. However, to put these risks in perspective, readers may note that nurses with no experience with sedation were trained to administer ketamine in sedating doses in an emergency care setting in rural Uganda. There was an adverse event (all minor) rate of 18% in 191 administrations by 6 nurses; this rate was stated to be similar to that reported in resource-rich countries.[52] In this context, Blier et al[49] noted that ketamine as anesthesia is especially useful in conditions in which cardiovascular and respiratory monitoring is unavailable because it does not depress these parameters and because its anesthetic effect is short. Given that ketamine is administered for depression in subanesthetic and nonsedating doses, it is possible that it can be safely administered as ambulatory and domiciliary treatment. Nevertheless, this will require formal safety evaluation before firm conclusions can be drawn.

Future Directions

From a clinical perspective, SC and intranasal ketamine demand further study if only because treatment by these routes is convenient. In fact, with ketamine delivered by the intranasal route, domiciliary treatment may someday become feasible.

Given the mood-related benefits reported with oral ketamine in hospice care[26] and chronic pain,[27] one wonders why this route of administration (with a flavored formulation of the drug) has not been better studied. Many other medicines in psychiatry and medicine also have poor and variable oral bioavailability, and these disadvantages are readily overcome by flexible, individually titrated dosing.

The most important role for ketamine could be for the management of patients with TRD. In such patients, ECT is generally administered as a course of treatment, and there is reasonably well-accepted guidance for ECT treatment parameters, the minimum length of an adequate treatment course, and issues such as treatment to remission vs declaration of plateau in improvement vs nonresponse. One wonders whether treatment parameters can be identified for a course of ketamine that, likewise, seeks to treats patients to remission. In such patients,

future research must also formally examine how best ketamine can be used for continuation and maintenance treatment, after determining whether or not it is indeed safe and effective for this purpose.

It is nice to hope that research would identify patients who might be ketamine responders, but given the poor progress in the identification of response predictors to other treatments in psychiatry, there is no reason to expect that similar studies with ketamine would fare any better.

Concluding Notes

Zhang et al[53] examined print media reports on ketamine treatment for depression, published in the United States and Canada from 2000 to 2015. They found that, during 2008–2015, media reports were significantly more likely to support the use of ketamine for depression and for TRD and were significantly more likely to assert that ketamine is more effective than conventional antidepressants. The enthusiasm for the use of ketamine as an antidepressant has clearly traveled far ahead of the evidence, as several cautionary articles note.[54–58] A great deal of good quality RCT research examining issues related to enantiomer, dose, route of administration, treatment schedule, and other matters discussed in this article, requires to be completed before firm recommendations can be made. Nevertheless, naysayers are reminded that ketamine is no more a heroic or risky treatment than is, say, ECT, clozapine, or, for that matter, a large section of the pharmacopeia.

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