**Correspondence**

Dose- and Exposure-Response to Ketamine in Depression

To the Editor:

We read with interest the recent report on the repeated-dose use of ketamine as a rapidly acting antidepressant in patients with treatment-resistant depression (1). Despite the promising antidepressant responses to this intervention in this and other studies (2–4), several important technical questions about administration of ketamine have not yet been explored (5). These include route of administration, dose–exposure relationship, and exposure– and dose–response information. In this letter, we present a simulation on projected exposures between intramuscular and intravenous (IV) ketamine to establish comparable doses and report preliminary dose–response data in patients with treatment-refractory bipolar II depression.

**Route of Administration and Dose–Exposure Relationship.** Most published reports on ketamine used as an antidepressant are at a dose of .5 mg/kg, given as a slow IV infusion over 40 min. This regimen is described as being based on pilot studies in healthy volunteers (6). An intramuscular (IM) route of administration has the advantage of not requiring an IV infusion pump and facilitates dosing in patients with poor venous access.

We developed a model for IM and IV pharmacokinetic profiles based on published reports for racemic ketamine (7,8). The IV parameter values are as reported in Ihmsen et al. (8), and relative bioavailability of IM ketamine to IV was 93% (7). Our model described similar overall exposures over time based on comparable IM and IV dosing (2-hour area under the concentration-time curve values = 20.9 and 21.7 mg.min/L, respectively); however, peak exposures were higher after IM dosing (Figure 1A). Higher IM or IV ketamine doses would be expected to demonstrate dose-proportional pharmacokinetics (8). We propose that IM ketamine may be an acceptable alternative route of administration for ketamine in patients with refractory depression.

**Exposure–Response Relationship.** There is some suggestion that mood response may be related to the early ketamine exposure profile, given the substantial early improvement in depression ratings by 40 min after the start of the IV infusion (1–4).

Therefore, we hypothesize that early exposure is critical to the therapeutic effect of ketamine, and in this context, the higher peak values after IM ketamine may be beneficial (Figure 1A).

**Dose–Response Relationship.** We have preliminary dose–response data in two female patients with refractory depression, treated with open-label ascending doses of IM ketamine as part of clinical care. An initial dose of .5 mg/kg produced minimal (10%–20%) reductions in Montgomery–Asberg Depression Rating Scale (MADRS) scores. Higher doses (.7 and 1.0 mg/kg IM) produced proportionally greater reductions in MADRS scores, in one case providing scores consistent with remission (< 7; Figure 1B; data are for MADRS ratings 24 hours postinjection). All doses were safe. Reported side effects (principally light-headedness, sedation, disassociative symptoms) were qualitatively similar to those reported after IV administration (1–4). With ascending doses, there was no difference in the time of onset or duration of symptoms; however, subjective assessments of symptom intensity indicated greater intensity with higher ketamine doses. It is important to note that the doses used for antidepressant effects are similar to those used for analgesia (9) and are approximately one tenth of that for anesthesia via IM administration (10) (Figure 1C). Doses reported in the drug abuse literature fall into an intermediate range (11).

On the basis of published clinical rating data and our simulation, it is clear that early exposure to ketamine is important in its therapeutic effects, and this can be achieved even more rapidly with IM dosing. Future studies should concentrate on the early exposure–response profile and its relationship with symptom response.

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None of the authors have any biomedical or financial interests or potential conflicts of interest.

Please also see associated correspondence, doi 10.1016/j.biopsych.2011.02.018.

![Figure 1](https://example.com/figure1.png)

**Figure 1.** (A) Simulation of concentration-time profiles up to 120 min for ketamine .5 mg/kg, after intramuscular (IM; dotted line) or intravenous (IV; solid line) administration. (B) Effects of ascending ketamine doses on Montgomery-Asberg Depression Rating Scale scores in two depressed patients, 24 hours postinjection. (C) Ketamine dose–indication relationship.


doi:10.1016/j.biopsych.2010.11.031