



## Ketamine for Depression, 5:

### Potential Pharmacokinetic and Pharmacodynamic Drug Interactions

Chittaranjan Andrade, MD



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.

Department of Psychopharmacology, National Institute of Mental Health and Neurosciences, Bangalore, India (candrade@psychiatrist.com).

#### ABSTRACT

Ketamine, administered in subanesthetic doses, is gaining recognition as an off-label treatment for severe and even treatment-refractory depression. This article explores potential pharmacokinetic and pharmacodynamic drug interactions of relevance to the use of ketamine in depression. Sparse evidence suggests that ketamine will not induce clinically significant drug interactions except to the extent that these are predictable by its clinical actions. A small body of literature indicates that drugs that induce cytochrome P450 (CYP)2B6 and CYP3A4 will reduce exposure to ketamine and that drugs that inhibit these enzymes will increase exposure to ketamine. Common genetic polymorphisms of the *CYP2B6* gene may also be associated with variations in the exposure to ketamine. However, the clinical implications of such variations in exposure have not been sufficiently studied. A very small number of reports and studies suggest that concurrent benzodiazepine medication may diminish the antidepressant benefits of ketamine. Likewise, a small body of literature suggests that drugs (such as lamotrigine) that inhibit glutamatergic signaling may reduce the adverse effects of ketamine; however, it is unknown whether these drugs also diminish the antidepressant effect. Data from clinical trials indicate that most conventional antidepressants can probably be combined with ketamine without compromising efficacy or increasing the adverse effect burden.

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#### Introduction

Previous articles in this column considered issues related to the efficacy, adverse effects, and possible mechanism(s) of action of ketamine in the treatment of depression<sup>1</sup>; discussed indications and contexts for the use of ketamine as an off-label antidepressant<sup>2</sup>; evaluated the antidepressant benefits and risks of *R*-ketamine, *S*-ketamine, and racemic ketamine<sup>3</sup>; and reviewed issues related to dosing, rate of administration, route of administration, duration of treatment, and frequency of sessions when ketamine is used in subanesthetic doses to treat depression.<sup>4</sup> The present article examines potential pharmacokinetic and pharmacodynamic interactions when ketamine is used as an off-label treatment for depression.

#### The Effect of Ketamine on Cytochrome P450 (and Other) Metabolic Enzymes and Their Substrates

In vivo studies in a rodent model found that a single dose of ketamine had no effect on cytochrome P450 (CYP)1A, CYP2B/2C, and 2E1 enzymatic activity; however, there was mild (13%) and possibly clinically nonsignificant inhibition of the activity of CYP2D1 and mild to modest (18%–32%) inhibition of CYP3A.<sup>5,6</sup> Ketamine-induced reduction in CYP3A4 activity may involve an inhibition of *CYP3A4* gene expression.<sup>7</sup> Contradicting these findings, in another rodent study, after 14 days of continuous gastric infusion with ketamine 50 mg/kg, induction of the activity of the CYP enzymes 1A2, 2B6, and 3A4 was observed.<sup>8</sup>

Given the contradictory findings, the small magnitude of the inhibition described, the prolonged megadosing required for enzyme induction, the absence of report of enzyme modulation in human studies, and the low doses and brief and infrequent occasions of use, it is unlikely that ketamine would cause clinically significant pharmacokinetic interactions when used in subanesthetic doses for the treatment of depression.

Ketamine is also used off label to treat pain, and depression that arises in the context of pain.<sup>9–11</sup> In this context, it may inhibit the glucuronidation of morphine (in patients who are also receiving this drug for pain management), as suggested by the results of an in vitro study.<sup>12</sup> There is no information available, so far, on whether this interaction is clinically significant.

#### The Effect of Cytochrome P450 Enzyme Modulators on Ketamine Pharmacokinetics

Ketamine undergoes *N*-demethylation to norketamine.<sup>13</sup> In an in vitro study, the CYP2B6, CYP2C9, and CYP3A4 enzymes, in that order, showed the highest metabolic activity for both *R*- and *S*- enantiomers of ketamine.<sup>13,14</sup> However, given the relative content of these P450 isoforms in human liver, CYP3A4 may be the most important enzyme involved in ketamine *N*-demethylation at therapeutic concentrations of the drug.<sup>13</sup>

**Rifampicin.** In a study<sup>15</sup> conducted in 20 healthy human volunteers, rifampicin, which potentially induces CYP3A4 and CYP2B6, reduced the

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- Ketamine is metabolized mainly by cytochrome P450 (CYP)2B6 and CYP3A4. Drugs that induce or inhibit these enzymes will correspondingly reduce or increase the exposure to ketamine.
- Genetic variations in the expression of *CYP2B6* could result in interindividual variation in the pharmacokinetics of ketamine. Thus, depending on these variations, some patients could require lower doses of the drug and others, higher doses.
- The antidepressant action of ketamine may be diminished by concurrent benzodiazepine therapy. Concurrent lamotrigine may reduce the risk of ketamine-induced adverse effects. The effect of concurrent lamotrigine on the antidepressant action of ketamine is not known.
- Most conventional antidepressants can probably be safely administered to patients for whom ketamine is trialed.

area under the curve (AUC) of the plasma concentrations of *S*-ketamine and *S*-norketamine by 10% and 50%, respectively. A compartmental analysis suggested increases of 13% and 200% in the elimination of *S*-ketamine and *S*-norketamine from their respective central compartments.<sup>15</sup>

**Itraconazole and ticlopidine.** Emphasizing the importance of CYP2B6 in the metabolism of ketamine, a placebo-controlled crossover study<sup>16</sup> in 11 healthy volunteers found that the CYP2B6 inhibitor ticlopidine more than doubled the AUC of oral *S*-ketamine (0.2 mg/kg), whereas the CYP3A inhibitor itraconazole, unexpectedly, had no effect.

**Macrolide antibiotics.** In a placebo-controlled crossover randomized controlled trial (RCT) conducted in 10 healthy volunteers, 4 days of pretreatment with clarithromycin was associated with a 3.6-fold increase in the peak concentration (C<sub>max</sub>) of oral *S*-ketamine (0.2 mg/kg) and a 2.6-fold increase in the AUC. Clarithromycin also increased the self-rated drug effect.<sup>17</sup> Logically, erythromycin (but not azithromycin), which also inhibits CYP3A4, could be expected to have a similar effect.

**Grapefruit juice.** Grapefruit juice inhibits CYP3A4 and can thereby increase the bioavailability of substrates of this enzyme by decreasing the metabolism of the substrates in the intestinal lining at the time of absorption as well as by decreasing the metabolism of the substrates in the liver, and elsewhere, after absorption.<sup>18</sup> In a randomized crossover trial in 12 healthy volunteers, 5 days of intake of grapefruit juice (200 mL thrice per day) trebled the AUC of oral *S*-ketamine (0.2 mg/kg), doubled the C<sub>max</sub>, and increased the elimination half-life of the drug by 24%.<sup>19</sup> This interaction could be clinically significant in patients who receive therapeutic ketamine by the oral route.

**St John's wort.** In contrast to grapefruit juice, in another study of 12 healthy volunteers, St John's wort, which induces CYP3A4, reduced the AUC of oral *S*-ketamine (0.3 mg/kg) by 58% and the C<sub>max</sub> by 66%; corresponding figures for *S*-norketamine were reductions by 23% and 18%, respectively.<sup>20</sup>

The studies reviewed in this section suggest the reasonable conclusion that whatever induces CYP3A4 or CYP2B6 will reduce exposure to ketamine and whatever inhibits CYP3A4 or CYP2B6 will increase exposure to ketamine; therefore, appropriate dose adjustments may be necessary so that ketamine remains effective and so that its adverse effects are not increased. This could involve some guesswork because the extent of change of exposure to ketamine in the individual patient cannot be predicted. Therefore, to the extent that such is possible, it would be better to avoid the interaction than to deal with it.

### CYP2B6 Polymorphisms and Ketamine Clearance

As already observed, the CYP2B6 enzyme plays an important role in the metabolism of ketamine. The *CYP2B6* gene is highly polymorphic. As a result, there is considerable interindividual variation in the expression and activity of *CYP2B6*. At least 28 allelic variants and subvariants of *CYP2B6* (\*1B through \*29) have been described, some of which have been shown to influence substrate drug clearance and treatment response.<sup>21</sup>

The *CYP2B6*\*6 allele is the most common polymorphism and is found mostly in African, African-American, and some Asian populations<sup>22</sup>; the frequency ranges from 15% to over 60%, depending on ethnicity.<sup>23</sup> An in vitro study demonstrated that the clearance of both *R*- and *S*-enantiomers of ketamine was increased at least 2-fold and 6-fold with the *CYP2B6*\*1/\*1 wild-type genotype as compared with the *CYP2B6*\*1/\*6 and *CYP2B6*\*6/\*6 genotypes, respectively.<sup>24</sup> In explanation, the *CYP2B6*\*6 allele is associated with reduced *CYP2B6* expression and activity, and homozygosity for this allele is associated with greater reduction in activity.<sup>22</sup> The magnitude of the finding demonstrates the importance of CYP2B6 in ketamine metabolism.<sup>24</sup>

The above notwithstanding, a comparison of volunteers with *CYP2B6*\*1/\*1, \*1/\*6, or \*6/\*6 genotypes (n=10 per group) found no differences between groups in ketamine *N*-demethylation, ketamine enantiomer and metabolite AUC, C<sub>max</sub>, apparent oral clearance, and metabolite formation clearance. There were also no differences between groups in subjective outcomes of alertness, energy level, clumsiness, confusion, anxiety, and nausea.<sup>22</sup> A possible limitation of this study is that ketamine was administered orally in the dose of 0.4 mg/kg; given the low and variable oral bioavailability of the drug, this study may not have been adequately designed and powered to identify behavioral outcome differences between genetic polymorphisms. In this connection, another low dose (100 mg/24 h) study of a ketamine infusion in patients with chronic pain (n=49) found a significant, dose-dependent effect of the \*6 allele on ketamine concentration and clearance.<sup>25</sup>

Whereas these studies do not support firm conclusions, it is reasonable to suppose that persons with the \*6 allele, especially those who are homozygous for this allele, may require lower doses of ketamine than the average patient. This lower-dose requirement may be especially noteworthy in African, African-American, and Asian patients. An

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alternate possibility that needs to be studied is that, in the presence of an inefficient CYP2B6 metabolic pathway, the CYP3A4 pathway will compensate; if so, the clinical impact of the 2B6 genetic variations could be small, and there may be no polymorphism-related variations in dose requirement at all.

### Pharmacodynamic Interactions

Pharmacodynamic interactions with ketamine are largely intuitive and can be predicted based on the known clinical effects of ketamine and the interacting drug. Some special interactions are considered in this section.

**Interactions with drugs acting on glutamatergic neurotransmission.** Ketamine has a large number of biological effects, and its mechanism of antidepressant action is not known; however, it is primarily classified as a noncompetitive *N*-methyl-*D*-aspartate (NMDA) receptor antagonist.<sup>26–29</sup> In this connection, memantine, which is a fast-off, voltage-dependent, noncompetitive NMDA receptor antagonist,<sup>30</sup> may offset some actions of ketamine. For example, memantine reduced ketamine-induced social withdrawal in a rodent model.<sup>31</sup> However, there are no clinical reports on ketamine-memantine interactions, and the interaction, if any, may not be important because it is unlikely that a patient who requires ketamine for depression will also be receiving memantine for any on- or off-label indication.

In low doses, ketamine may increase the release of glutamate.<sup>28</sup> Lamotrigine, which inhibits the release of glutamate,<sup>32,33</sup> may be a part of the prescription of patients with bipolar depression. The interaction between ketamine and lamotrigine is therefore of interest. Lamotrigine appears to antagonize some of the effects of ketamine. There is a report of the failure of ketamine anesthesia in a patient with lamotrigine overdose<sup>34</sup> and a report of the use of lamotrigine to reduce craving for and abuse of ketamine in a patient with ketamine use disorder.<sup>35</sup> Lamotrigine was shown to protect against ketamine- but not amphetamine-induced psychosis in a murine model.<sup>36</sup>

In a randomized, placebo-controlled laboratory study<sup>37</sup> of 16 healthy volunteers, pretreatment with lamotrigine (300 mg) attenuated many effects of intravenous ketamine administered as a bolus (0.26 mg/kg) or by infusion (0.65 mg/kg/h); these effects included perceptual abnormalities, schizophrenia-like positive and negative symptoms, and learning and memory impairment. Interestingly, lamotrigine increased the mood-elevating effect of ketamine; however, this effect was observed only at 5 minutes posttreatment with ketamine, and there was no significant interaction at later assessment points.

Clozapine may indirectly influence glutamatergic neurotransmission through action on glycine transporters.<sup>38</sup> In a double-blind, placebo-controlled study, clozapine was shown to blunt ketamine-induced increase in positive symptoms in 10 antipsychotic-free schizophrenia patients.<sup>39</sup> This, however, does not prove that the action of clozapine was mediated through glutamatergic modulation.

The literature reviewed in this section suggests that drugs that interfere with glutamatergic neurotransmission reduce the adverse effects of ketamine. There is no information on how the antidepressant action of ketamine may be impacted, and so, until the subject is formally studied, prudence may be desirable when combining ketamine with drugs with glutamatergic actions.

**Interactions with benzodiazepines.** At least in a murine model, ketamine does not affect the anticonvulsant and antinociceptive action of benzodiazepines.<sup>40</sup> Benzodiazepines, however, may compromise the antidepressant action of ketamine. Ford et al<sup>41</sup> observed that, in a medication-refractory patient with bipolar depression, ketamine infusions resulted in antidepressant benefits that lasted just 1–3 days; this benefit extended to up to 10–14 days when lorazepam (3.5 mg/d) was discontinued from the list of concurrent medications.

Possible attenuation of ketamine response by concurrent benzodiazepine use was also suggested by Frye et al.<sup>42</sup> In this post hoc analysis of a 2-week trial of ketamine in patients with treatment-refractory depression, concurrent benzodiazepine use did not influence the response and remission rates; however, the mean benzodiazepine dose was observed to have been significantly higher in nonresponders (*n* = 2) relative to responders (*n* = 4) (but not in nonremitters relative to remitters). In another post hoc analysis of data from an RCT of ketamine in refractory depression, Albott et al<sup>43</sup> found that, in comparison with patients not receiving benzodiazepines (*n* = 9), those receiving benzodiazepines (*n* = 4) took longer to respond and remit and relapsed earlier; response and remission rates, however, did not vary as a function of benzodiazepine use.

The ketamine-benzodiazepine interaction may arise from the nonspecific central depressant effect of benzodiazepines, mediated through  $\gamma$ -aminobutyric acid (GABA), or it may result from benzodiazepine-induced suppression of ketamine-related activation of dopamine neurons in the nucleus accumbens and striatum.<sup>44</sup> Albott et al<sup>43</sup> suggested another mechanism: benzodiazepines may dampen the NMDA-mediated inhibitory effect of ketamine on GABA interneurons, thereby dampening ketamine-induced increase in glutamatergic signaling through AMPA receptors.

**Antidepressant drugs.** Many ketamine trials that demonstrated the safety and efficacy of the drug were conducted in patients in whom concurrent antidepressant treatments were continued; this suggests that most conventional antidepressants are perhaps compatible with ketamine therapy.<sup>2</sup>

### Conclusions

Ketamine is unlikely to induce clinically significant drug interactions except to the extent that these are predictable by its clinical actions. Drugs that induce or inhibit CYP2B6 and CYP3A4 may reduce or increase, respectively, the clinical effects of ketamine. Interindividual variations in CYP2B6 activity, related to genetic polymorphisms, may likewise influence the clinical effects of ketamine.



Concurrent benzodiazepine medication may diminish the antidepressant benefits of ketamine; whereas drugs that inhibit glutamatergic signaling may reduce the adverse effects of ketamine, it is unknown whether the antidepressant action is also diminished. It is likely that most conventional antidepressants can be safely combined with ketamine.

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