Clinical and Practical **Psychopharmacology**

Ketamine for Depression, 3: Does Chirality Matter?

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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

Ketamine is a racemic mixture of the enantiomers *R*-ketamine and *S*-ketamine (esketamine). *S*-ketamine has greater analgesic and anesthetic effects than *R*-ketamine and is less likely to cause psychotomimetic and other adverse effects. There is therefore an emerging interest favoring the use of *S*-ketamine over racemic ketamine when the drug is used for analgesia or anesthesia. This article examines preclinical and clinical literature on the antidepressant properties of *S*-ketamine. Animal data suggest potential advantages for *R*-ketamine over *S*-ketamine. Case reports, case series, and some small randomized controlled trials suggest that single or repeated intravenous infusions (0.2–0.4 mg/kg) or intranasal administrations (28–84 mg) of *S*-ketamine have antidepressant action in patients with medication-refractory depression and that the observed benefits are similar in magnitude to the antidepressant benefits reported with racemic ketamine. However, there are no direct comparisons between *S*-ketamine and either *R*-ketamine or racemic ketamine in depressed patients; therefore, it is not possible to make an informed choice when considering the enantiomers and the racemate for the indication of depression.

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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] and suggested indications and contexts for the use of ketamine as an off-label antidepressant.[2] The present article examines whether chirality is relevant to the antidepressant action of subanesthetic doses of ketamine.

Terminology

Isomers are chemical substances with the same chemical formula but a different chemical structure, that is, a different arrangement of the atoms in the molecule. This difference usually results in the substances exhibiting different properties. There are 2 important types of isomer: structural isomers and stereoisomers.

Structural isomers are chemical substances that differ in the positions at which atoms or functional groups are connected in the molecule. As an example, the difference may lie in the position at which a halogen atom or a hydroxyl group is attached to a hydrocarbon chain or a benzene ring. Thus, 1-fluoropropane and 2-fluoropropane are structural isomers that differ in the position (indicated by the numeral) at which the fluorine atom substitutes for hydrogen in the propane molecule.

Stereoisomers, in contrast, are isomers that are similar in the positioning of the atoms or functional groups in the molecule; however, they differ in the spatial orientation of the atoms or functional groups around a specific (usually) carbon atom. L and D amino acids are examples of stereoisomers.

Enantiomers are one kind of stereoisomer that exemplify the chiral property of a drug. The *chirality* of a molecule refers to its geometric characteristics that permit or do not permit superimposition of the molecule on its mirror image. When mirror image molecules are not superimposable, chirality is said to be present and the molecules are called enantiomers. Because enantiomers rotate polarized light in opposite directions, they are also called *optical isomers*. Enantiomers of a drug are present in equal proportions in the drug, and the drug is known as a *racemic mixture* of the enantiomers, or as a racemate.

Chirality, which roughly translates to "handedness," is best understood with the help of a rather apt metaphor. Hands are isomers: they have the same formula, comprising 1 palm, 1 thumb, 1 index finger, 1 middle finger, 1 ring finger, and 1 little finger. They are stereoisomers because the named fingers have the same relative positions on the palm. They are enantiomers because the left hand is the mirror image of the right hand and because if the left hand is placed upon the right hand (with palms either both face up or both face down), they do not match; that is, they cannot be superimposed.

With regard to nomenclature, the *d*- and *l*- prefixes are used to designated dextro and levo isomers of amino acids and sugars. Presently, the *R/S* (rectus, right, or clockwise, vs sinister, left, or anticlockwise) system is used to describe the 3-dimensional configuration of the molecule and the *d/l* or +/– (dextrorotatory or positive sign vs

Clinical Points

- Ketamine is a racemic mixture of *R*- and *S*-enantiomers.
- *S*-ketamine has greater analgesic and anesthetic action than *R*-ketamine. *S*-ketamine may carry lower psychotomimetic and other risks than *R*-ketamine.
- Intravenous (0.2–0.4 mg/kg) and intranasal (28–84 mg) *S*-ketamine have both been found effective in patients with treatment-refractory depression; the efficacy has been shown in both single and repeated dosing schedules; however, the size of the evidence base is small.
- No clinical studies in depressed samples have directly compared the ketamine enantiomers with each other or with the racemate.

levorotatory or negative sign) system for optical rotation; that is, the direction in which isomers rotate polarized light. The *R*/*S* and +/– systems are not related, so, for example, an enantiomer can be *R*(+) or *R*(–).

Chirality is common in biological systems and is observed in amino acids, carbohydrates, and lipids. Chirality is even observed in drugs. A drug may have more than 1 chiral center and hence more than 1 pair of enantiomers; paroxetine is one such drug. Neuropsychiatric drugs that are achiral (lacking in chirality) include risperidone, amitriptyline, fluvoxamine, and nefazodone. Those marketed as single enantiomers include L-dopa, levosulpiride, sertraline, paroxetine, escitalopram, eszopiclone, and dexmethylphenidate. Those marketed as racemates include bupropion, reboxetine, fluoxetine, citalopram, venlafaxine, mirtazapine, sulpiride, and zopiclone. Many good reviews provide more detailed discussions on the concepts introduced in this section and on variations in terminology.[3–6]

The Importance of Studying Chirality

There are many reasons why studying chirality can be important. A racemic drug may not necessarily contain the isomers in the ideal therapeutic ratio, the dose-response curves of the isomers may differ, and, most important of all, the isomers may differ in their selectivity and affinity for biological targets, thereby influencing their efficacy and adverse effect profiles. It is even possible that one isomer contributes to the efficacy of the racemate while the other contributes to the adverse effects. Thus, using an enantiomer could reduce the dose of medication that is necessary for a treatment response, make the biological effects more specific, reduce the adverse effects associated with a specific level of benefit, simplify the understanding of the dose-effect relationship, and reduce pharmacokinetic and pharmacodynamic variability between patients. Exceptions do exist, though, and fluoxetine is one drug the safety and efficacy of which are best preserved in the racemate.[5–7]

Ketamine and Chirality

Commercially available ketamine is a 1:1 racemic mixture of *R* and *S* enantiomers.[8] These isomers differ in potency: the *S* isomer is a more potent antagonist at the phencyclidine site on the *N*-methyl-D-aspartate receptor; it is also a more potent agonist at the μ-opioid receptor and a less potent agonist at the sigma receptor.[9,10] From a clinical perspective, the *S* isomer is less psychotomimetic, has greater analgesic and anesthetic action, and results in less drowsiness, lethargy, and cognitive impairment than the *R* isomer.[11,12] There is therefore an emerging interest favoring *S*-ketamine (esketamine) when ketamine is used for anesthesia or analgesia.[12]

Preclinical Studies

Experiments in animal models of depression suggest that *R*-ketamine has longer-lasting antidepressant effects than *S*-ketamine and that *R*-ketamine has antidepressant action even in an animal model that is refractory to standard antidepressants.[13,14] *R*-ketamine is also associated with greater neuroplasticity changes than *S*-ketamine,[15] thereby potentially more effectively correcting the neurohistological correlates of depression and hence more effectively facilitating antidepressant action.[16] However, one study found persistent neuroplasticity and behavioral antidepressant benefits after a single injection of *S*-ketamine in a long-term corticosterone administration rat model of depression.[17]

Plasma levels of D-serine have been suggested as a clinical marker of antidepressant response to ketamine.[18] In this context, an in vitro nerve cell culture study[19] found that *R*-ketamine reduced both intracellular and extracellular D-serine levels whereas *S*-ketamine reduced extracellular D-serine and increased intracellular D-serine; the clinical implication is uncertain.

S-Ketamine for Depression: Case Reports and Case Series

There have been case reports of antidepressant response as well as nonresponse to *S*-ketamine. Paul et al[20] reported a middle-aged woman with treatment-resistant depression who responded to intravenous (iv) *S*-ketamine (0.25 mg/kg) 1–3 days after the infusion; the response faded by 6 days. A male patient, however, responded to neither *S*-ketamine (0.25 mg/kg) nor racemic ketamine (0.5 mg/kg) infusion.[20] Three depressed patients who had not responded to pharmacotherapy, psychotherapy, and electroconvulsive therapy (ECT) improved when repeated *S*-ketamine (iv) infusions were used to augment a course of ECT.[21] Repeated *S*-ketamine (12.5–75 mg) infusions were also used to successfully attenuate the severity of a suicidal crisis in each of 2 treatment-refractory depressed patients receiving tranylcypromine.[22]

Segmiller et al[23] described a series of 6 patients with treatment-refractory unipolar depression; 3 of these patients improved substantially with repeated *S*-ketamine (starting with 0.25 mg/kg) infusions across a month of treatment, administered at a frequency of once to twice a week. In another series of refractory patients treated with *S*-ketamine infusions in a similar protocol, 5 of 6 patients responded after the first session, and the improvement was stabilized in the subsequent sessions.[24]

Interestingly, 2 of 4 nonrefractory depressed patients responded early and then remitted with a 2-week course

of oral *S*-ketamine (1.25 mg/kg/d) augmentation of antidepressant treatment. This dose was chosen because ketamine has an approximately 20% oral bioavailability, and it was assumed that the set dose would be equivalent to a parenteral dose of 0.25 mg/kg.[25]

S-Ketamine for Depression: Clinical Trial Data

In an industry-driven, multicenter, randomized, double-blind, placebo-controlled trial, 30 patients with treatment-resistant depression were randomized to receive a 40-minute iv infusion of *S*-ketamine 0.2 mg/kg, *S*-ketamine 0.4 mg/kg, or placebo. One day later, Montgomery-Asberg Depression Rating Scale scores were observed to improve by about 17 points in each *S*-ketamine group; this figure was a mere 4 points in the placebo group. At the 1-day assessment, about two-thirds of the patients in each ketamine group were classified as responders relative to none in the placebo group. Both doses of *S*-ketamine were superior to placebo at 2- and 3-day posttreatment assessments, as well. The advantage for *S*-ketamine was also observed on global ratings and other clinical measures. Interestingly, the benefits of *S*-ketamine persisted for up to 2 weeks and beyond in some patients. Whereas the two *S*-ketamine doses did not differ on any measure of efficacy, adverse effects appeared to be dose-dependent.[26]

An unpublished randomized controlled trial (RCT) found dose-dependent antidepressant benefits with intranasal *S*-ketamine (28–84 mg) administered twice weekly for 2 weeks; another unpublished RCT also identified an advantage with intranasal *S*-ketamine (84 mg). Patients in both RCTs were also receiving oral antidepressants.[27]

S-Ketamine Anesthesia for ECT in Depression

There is a case report of the use of *S*-ketamine anesthesia in the successful treatment of catatonia using ECT in a patient with dementia and coexisting depression.[28] The contribution of *S*-ketamine to the outcome is unknown; the benefits could have been a result of ECT treatment alone.

There is at least 1 RCT in which *S*-ketamine was examined in the context of ECT. In that study, conducted in 32 medication-refractory patients with severe or psychotic major depressive disorder, whereas *S*-ketamine- (vs placebo)-augmented propofol anesthesia did not improve the speed and magnitude of antidepressant outcomes following a course of ECT, or influence seizure parameters or number of ECTs in the course, it was associated with increased post-ECT disorientation and restlessness.[29]

In a retrospective study of depressed patients who received ECT under *S*-ketamine (n = 31) or etomidate (n = 29) anesthesia, physiologic measures of the ECT seizure were stronger with *S*-ketamine than with etomidate, but the two groups did not differ significantly in efficacy or adverse effect outcomes or in the number of ECT treatments received in their course.[30]

Regardless of enantiomers, the use of low or full doses of ketamine in the ECT anesthesia is at present controversial; there is meta-analytic evidence for early onset of treatment benefits,[31] a controversy over whether the benefits continue to be evident later or at the end of the ECT course,[31,32] and consensus that adverse effects are increased.[21,32]

Summary

A small body of evidence suggests that subanesthetic doses (0.2–0.4 mg/kg iv or 28–84 mg intranasally) of *S*-ketamine have antidepressant action in patients with treatment-resistant depression. No dose-dependent efficacy is evident, at least in the published literature. There are no clinical data that compare *S*-ketamine, *R*-ketamine, and racemic ketamine as antidepressant interventions. Therefore, no guidance can be offered to choose between the enantiomers and the racemate when ketamine is considered for depression. It would be interesting to study whether patients who experience dissociative or other unpleasant adverse effects with racemic ketamine tolerate *S*-ketamine better without compromise in antidepressant benefits.

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