Racemic Ketamine vs Esketamine in Treatment-Resistant Depression:

The Overlooked Role of Arketamine

To the Editor: We read with great interest Meisner and colleagues' report[1] comparing intravenous (IV) racemic ketamine with intranasal (IN) esketamine in treatment-resistant depression (TRD), showing faster and greater symptom reduction with IV ketamine, consistent with prior meta-analytic evidence.[2] This observation is biologically plausible and, in our view, attributable in part to enantiomer pharmacology.[3] Racemic ketamine comprises equimolar (*R*)-ketamine (arketamine) and (*S*)-ketamine (esketamine). Preclinical work—including that by our group and independent replications—indicates that arketamine confers stronger and longer-lasting antidepressant effects than esketamine despite weaker *N*-methyl-D-aspartate receptor (NMDAR) affinity,[4,5] together with fewer psychotomimetic/dissociative effects and lower abuse liability in rodents and humans.[4,6] The racemate's superiority over IN esketamine therefore likely reflects the pharmacodynamic contribution of the R-enantiomer, which is absent from the IN esketamine.

Side effect patterns further support mechanisms beyond primary NMDAR antagonism. Dissociation after ketamine/esketamine administration does not correlate with antidepressant benefit across multiple clinical studies.[7] Because dissociation is generally attributed to NMDAR blockade, this dissociation–efficacy disconnect implies that additional pathways—such as brain-derived neurotrophic factor (BDNF)-TrkB signaling and downstream synaptogenic cascades—are critical mediators of clinical response.[3,7,8] Notably, arketamine may preferentially engage these plasticity-related pathways, offering a parsimonious explanation for the durability and tolerability signals observed in preclinical models.[3,8]

Real-world pharmacovigilance also supports enantiomer-related differences. WHO VigiBase analyses show higher disproportionality for suicidal ideation with esketamine, whereas ketamine shows lower disproportionality for ideation, suicide attempts, and completed suicide; for attempts and completed suicide, both agents have lower reporting odds than lithium.[9] Although disproportionality cannot prove causation and is susceptible to reporting bias, these signals suggest clinically meaningful differences between racemic ketamine and esketamine. Pharmacokinetics (PKs) likely contribute: IV dosing provides complete, controlled exposure, whereas IN delivery has lower, more variable bioavailability due to mucosal and technique factors—plausibly slowing onset and reducing effect size with IN esketamine. Nonetheless, PK alone does not account for the findings; enantiomer-specific pharmacodynamics remain a compelling explanation.

A recent commentary[10] rightly underscored limitations of retrospective, nonrandomized cohorts and highlighted public-health safeguards, yet it did not address arketamine's role. Emphasizing socioeconomic and regulatory factors without considering enantiomer pharmacology risks obscuring the contribution of arketamine in the racemate. Future comparative-effectiveness studies and randomized trials should prespecify enantiomer-stratified analyses (including IV arketamine), harmonize route and dosing, and rigorously account for socioeconomic variables.

Taken together, Meisner et al[1] highlight the need for well-controlled, prospective comparisons among arketamine, esketamine, and racemic ketamine to disentangle enantiomer-specific effects and optimize TRD care. Given its efficacy and tolerability profile, the clinical development of arketamine appears particularly promising.[3,8] In conclusion, the data by Meisner et al[1] strengthen the case that IV racemic ketamine is more effective than IN esketamine in TRD; convergent preclinical and clinical findings support the hypothesis that arketamine plays a key role in this superiority and that ketamine's antidepressant mechanisms extend beyond simple NMDAR antagonism. A randomized head-to-head trial of arketamine versus esketamine in TRD is warranted.[8]

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