Mu-Opioid Signaling Engagement as a Candidate Maintenance Mechanism for Prolonging Ketamine's Antisuicidal Effects

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One of the most consequential recent developments in psychiatry is the discovery that subanesthetic ketamine infusions rapidly (within hours) reduce depressive symptoms and suicidal ideation (SI) in individuals with depression, including treatment-resistant depression. However, ketamine's effects are typically not sustained, and, for many, its antisuicidal effects wane within days to weeks. Thus, a fundamental challenge for the field is how to maintain ketamine's effects without indefinitely relying on continuing infusions, particularly in light of ketamine's potential for misuse and its side effect profile.

In this issue, Tucciarone and colleagues (1) directly test the application of a tantalizing bridge to this conceptual gap. The focus of their investigation was whether low-dose sublingual buprenorphine—a partial mu-opioid receptor (MOR) agonist—initiated 48 hours after a single open-label intravenous ketamine infusion, could prolong observed reductions in SI over 4 weeks compared with placebo. Their results suggest that, by engaging the MOR, buprenorphine may represent a viable real-world maintenance strategy to prolong ketamine's rapid antidepressant effects.

Ketamine's antidepressant effects have traditionally been attributed to *N*-methyl-D-aspartate (NMDA) receptor antagonism at synaptic and extrasynaptic sites. However, mounting evidence suggests that opioid receptor signaling also plays a necessary role in translating this glutamatergic pathway-driven plasticity into behavioral outcomes (2, 3). From the outset, it should be noted that ketamine is not an opioid in the classic pharmacological sense, although it does bind and activate mu- and kappa-opioid receptors in vitro (4); nevertheless, its clinically relevant actions appear functionally intertwined with MOR signaling (5). This conceptual distinction is critical. The question is not whether ketamine directly activates the MOR at therapeutic doses but rather whether MOR engagement is necessary downstream of NMDA blockade—or perhaps in parallel and synergistically with it (6)—in order for ketamine to exert its antidepressant and antisuicidal effects.

Recent reverse-translational evidence strengthens this hypothesis. First, two clinical trials found that the oral opioid receptor antagonist naltrexone diminished ketamine's antidepressant effects (7, 8), although it is important to note that naltrexone also has affinity for delta- and kappa-opioid receptors. Another preclinical study subsequently demonstrated that both racemic (*R*,*S*)-ketamine and the more selective NMDA antagonist fluoroethylnormemantine (FENM) both required MOR activation to prevent stress-induced maladaptive behaviors (9). Although FENM exhibits negligible MOR agonism in cell signaling assays, its pro-resilience behavioral effects were abolished by the long-acting MOR antagonist methocinnamox (9). Collectively, these findings strongly support an indirect mechanism whereby NMDA receptor antagonism triggers endogenous opioid release that subsequently activates MORs.

The clinical implication is exciting and clear—MOR modulation may extend ketamine's antisuicidal signal beyond its acute window of effects, thus providing more accessible treatment options.

Under this framework, Tucciarone and colleagues' clinical trial can be conceptualized as a stabilization model. That is, ketamine may initiate rapid changes—which may include transient increases in endogenous opioid signaling—while buprenorphine sustains MOR tone during the postinfusion period.

Buprenorphine's pharmacology may be uniquely suited to this role. As a high-affinity partial MOR agonist and kappa-opioid receptor antagonist, buprenorphine can stabilize MOR engagement (and perhaps signaling) while limiting full agonist-like respiratory and euphoric effects. In this trial, participants with major depressive disorder or bipolar II disorder who had clinically significant SI (Scale for Suicidal Ideation [SSI] score ≥6) received a single standard 0.5 mg/kg intravenous ketamine infusion. Forty-eight hours later, they were randomized to sublingual buprenorphine (0.2–0.8 mg/day) or placebo for 4 weeks under double-blind

conditions in a flexible-dosing design. Patients were able to self-administer buprenorphine at home, a nice demonstration of applicability to real-world clinical settings. Importantly, buprenorphine demonstrated no major safety concerns; although it is a Schedule III substance in the United States, it is widely used as a safe outpatient treatment option for opioid and other substance-related disorders as well as for chronic pain. As expected, ketamine infusion decreased SSI scores by day 3, when the blinded intervention began. By day 31, both randomized treatment groups had lower SSI scores, but the buprenorphine group showed significantly greater improvement, with a mean change in SSI score of −11.6 compared with −6.3 in the placebo group (Glass delta=0.76, $p<0.001$). Overall severity of depressive symptoms did not differ significantly between groups at day 31.

This distinction between sustained improvement in SI without corresponding improvement in global depressive symptoms underscores a key mechanistic point of major importance to the field: Ketamine's antisuicidal effects may not be fully attributable to its antidepressant actions. The clinical implication is exciting and clear—MOR modulation may extend ketamine's antisuicidal signal beyond its acute window of effects, thus providing more accessible treatment options.

The mechanistic implications, however, are more complex. Collectively, the findings suggest a two-stage model: an initiation phase in which NMDA receptor antagonism induces rapid synaptic, extrasynaptic, and circuit-level plasticity (perhaps accompanied by endogenous opioid signaling), followed by a stabilization or maintenance phase in which MOR engagement is required to consolidate behavioral changes and sustain antisuicidal effects. Notably, this model positions MOR signaling as permissive rather than primary with regard to its effects on ketamine's mechanism of action, and necessary but not sufficient for expressing at least some behavioral effects, a hypothesis that should be the focus of future work.

Another crucial question is whether the distinction between improved SI and improved depressive symptoms—an observation seen across experimental contexts—is an epiphenomenal bug or a mechanistic feature. As noted above, the authors found no significant between-group differences in overall severity of depressive symptoms at day 31, recalling a mechanistic question: Why might SI respond differently than overall depression severity? In a similar experimental framework, Chen and colleagues tested D-cycloserine as a maintenance intervention for patients with treatment-resistant depression who responded to ketamine; using item 3 (the individual item for suicide) of the Hamilton Depression Rating Scale (HAM-D), they observed antisuicidal effects but no group differences in depression scores (10). One explanation may be that MOR availability in key brain areas may preferentially stabilize the cognitive-affective circuits that underlie SI rather than those that underlie other depressive symptoms, but further studies are needed to answer this critical question. Moreover, preclinical data suggest that MOR blockade prevents the stress-resilience effects of NMDA antagonists even when some electrophysiological correlates persist (9). This difference suggests that MOR signaling may act as a behavioral gate necessary for translating synaptic plasticity into durable changes in stress responsivity. Such a model could explain why SI trajectories may diverge from global depression scales following opioid modulation.

Importantly, Tucciarone and colleagues highlight a few limitations that can guide future studies. First, roughly one-third of participants in the placebo arm maintained response at 1 month following the single ketamine infusion, which is somewhat higher than in other repeat-dose or continuation trials. Potential explanations include expectancy effects associated with open-label ketamine administration, demographic and clinical characteristics (e.g., exclusion of borderline personality disorder), or other methodological differences. Second, another important limitation is the open-label nature of the ketamine phase of the study; without a placebo-controlled ketamine arm, additive versus synergistic effects of the ketamine–buprenorphine sequence cannot be fully disentangled. A third limitation concerns functional unblinding; 66% of participants in the buprenorphine arm correctly guessed their assignment, compared with 32% in the placebo group. Although side effects were generally mild, perceptible treatment effects could have influenced expectancy. Future multisite trials incorporating double-blind ketamine phases and active comparators would strengthen causal inference. Relatedly, blinding efficiency was assessed only at day 45, and participants may have deduced whether they were on an active treatment or not if their symptoms had worsened in the 2 weeks since concluding the study.

Crucially, the opioid stabilization hypothesis is testable. Positron emission tomography (PET) radioligands such as [^{11}C]carfentanil and [^{11}C]diprenorphine can assess in vivo MOR availability (11). Incorporating PET endpoints into maintenance trials could clarify key mechanistic questions by implicating specific brain areas, testing for transient reductions in MOR availability through endogenous opioid release, and assessing how potential sex differences may influence MOR-mediated maintenance effects. The latter is an important consideration because sex-specific opioid sensitivity has been observed in both preclinical and imaging studies (5, 9). Stratified analyses may therefore be critical for understanding individual variability in maintenance response.

Several methodological clarifications would also strengthen future studies. First, it would be important to establish whether SI is stable across multiple prerandomization assessments, given that instability could inflate apparent changes via regression to the mean; this information would also help describe the clinical demographics more fully. Second, reporting trajectories for the SI items from the Montgomery-Åsberg Depression Rating Scale (MADRS) and the HAM-D alongside the SSI would help determine whether effects generalize across measures or are scale-specific.

Broadly, the trial by Tucciarone and colleagues advances the field by demonstrating that, by engaging the MOR signaling pathway as a novel mechanism, low-dose buprenorphine has clear potential to extend reductions in

SI after ketamine infusion; this finding aligns with converging preclinical and clinical evidence that MOR activation is necessary for the behavioral/symptomatic efficacy of NMDA antagonists (7, 9). In this context, the opioid system may not be the primary gas pedal of ketamine's rapid antidepressant actions. It may, however, be the transmission, converting transient synaptic perturbations into sustained behavioral changes. If confirmed in larger multisite trials with mechanistic biomarkers, opioid stabilization after ketamine treatment could redefine maintenance strategies in acute to chronic suicidality. New strategies for targeted MOR engagement may provide a more approachable, more precise, and potentially safer bridge to prolonging ketamine's effects and move us one step closer to understanding the neurobiology of suicidality.

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Dr. Kvarta holds and receives royalties from a patent for the use of negative modulators of GABA receptors containing α5 subunits as rapid-acting antidepressants, with rights assigned to the University of Maryland, Baltimore. Dr. Zarate is listed as a co-inventor on a patent for the use of ketamine in major depression and suicidal ideation; as a co-inventor on a patent for the use of (2*R*,6*R*)-hydroxynorketamine, (*S*)-dehydronorketamine, and other stereoisomeric dehydroxylated and hydroxylated metabolites of (*R*,*S*)-ketamine in the treatment of depression and neuropathic pain; and as a co-inventor on a patent application for the use of (2*R*,6*R*)-hydroxynorketamine and (2*S*,6*S*)-hydroxynorketamine in the treatment of depression, anxiety, anhedonia, suicidal ideation, and posttraumatic stress disorder; he has assigned his patent rights to the U.S. government but will share a percentage of any royalties that may be received by the government.

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