Commentary

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Does the Opioid System Block or Enhance the Antidepressant Effects of Ketamine?

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Commentary on: Williams NR, Heifets BD, Blasey C, et al. Attenuation of antagonism effects of ketamine by opioid receptor antagonism. *Am J Psychiatry*. 2018;175(12):1205–1215; Yoon G, Petrakis IL, Krystal JH. Association of combined naltrexone and ketamine with depressive symptoms in a case series of patients with depression and alcohol use disorder. *JAMA Psychiatry*. 2019;76(3):337–338.

Despite tremendous growth in the off-label use of racemic ketamine for psychiatric indications and the recent U.S. Food and Drug Administration approval of esketamine nasal spray for treatment-resistant depression (TRD), neural mechanisms underlying the induction and maintenance of ketamine's rapid but transient antidepressant effects remain obscure. Ketamine's initial pharmacological target is not disputed: it acts as a nonselective, noncompetitive N-methyl-D-aspartate receptor (NMDAR) antagonist. Converging preclinical evidence indicates that this NMDAR blockade inhibits (1) Gamma-aminobutyric acid (GABA) interneurons (resulting in enhanced presynaptic release of glutamate and stimulation of postsynaptic α-Amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors), (2) extrasynaptic GluN2B-containing NMDARs (resulting in de-suppression of mTORC1 function), and (3) spontaneous neurotransmission (resulting in inhibition of eukaryotic elongation factor 2 kinase activity).[1] A final common pathway for these effects involves activation of neurotrophic factor signaling pathways, increased synaptic protein synthesis, and dendritic spine formation and restoration of lost spines (''spinogenesis'').[2]

There is considerably less consensus in defining the role of non-NMDAR receptor activity in mediating the rapid (within several hours) and sustained (24 h to 7 days) antidepressant effects observed in numerous clinical trials. Indeed, the sustained antidepressant responses seen in some individuals are particularly puzzling, given the short elimination of half-life of ketamine and its primary metabolite norketamine. Recent preclinical experiments have shown that a different metabolite—hydroxynorketamine [(2R,6R)-HNK]—promotes AMPA-mediated synaptic potentiation via an entirely NMDAR independent pathway.[1] Furthermore, ketamine has significant central antinociceptive effects, with activity at mu-, kappa-, and delta-opioid receptors. Inasmuch as the U.S. continues to face an alarming increase in the number of opioid-related overdose fatalities, some have urged more caution in the use of ketamine (and esketamine) for depression, particularly in the face of recent experimental evidence by Williams et al. that ketamine's antidepressant effects may be mediated by mu-opioid receptor activity.[3]

In this Commentary, we evaluate the evidence presented in Williams' et al. intriguing article as well as counterevidence. The study, a randomized, double-blind, placebo-controlled cross-over study in 12 participants with TRD, showed that pretreatment with the nonselective opioid antagonist naltrexone (50 mg) resulted in marked attenuation of the rapid antidepressant effects of intravenous (IV) ketamine.[3] There were marked differences in depression severity 24 hours and up to three days following the two ketamine infusions, which were administered at the conventional dose of 0.5 mg/kg over 40 min and separated by about 30 days. For the subgroup group of participants who met the prespecified ketamine response criteria ($n = 7$) at the 1 day end point, naltrexone pretreatment of ketamine resulted in a 5.6-point reduction in the 17-item Hamilton Depression Rating Scale (HAM-D), while the placebo pretreatment group had a 22.3-point improvement (effect size $d = 2.5$). Naltrexone pretreatment did not significantly attenuate ketamine-induced dissociative symptoms, although there was an approximate 6-point reduction in mean Clinician-Administered Dissociative States Scale (CADSS). Overall, the between-group efficacy differences were robust, durable (lasting for up to three days, consistent with the known duration of naltrexone on opioid

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receptor function), and were replicated across several depression rating scales. Although carryover effects are always a potential concern in crossover studies, this did not appear to be a factor as there was a sufficiently long washout period between ketamine infusions, and an analysis of only the first randomized infusion prior to crossover revealed similar effects.

However, several methodological limitations hinder the ability to confidently conclude that ketamine acts via an opioid mechanism. Most importantly, the lack of a placebo control arm for the ketamine infusion (which would require additional naltrexone + IV saline and placebo + IV saline treatment arms) impedes the evaluation of the specificity of the naltrexone + ketamine effect. Second, participants may have experienced a nocebo type of response to the naltrexone + ketamine treatment which influenced their subsequent depression ratings. Supporting this view, in the full sample, there was a markedly higher incidence of nausea (7/12 vs 3/12) in the naltrexone group; how many of these seven patients reporting nausea were in the smaller subgroup of ketamine responders is not reported. Indeed, the noxious response to the naltrexone + ketamine combination was cited as a reason for early termination of the study.[3] A third limitation is the lack of a same-day assessment following ketamine administration. A pharmacodynamic marker attributable to ketamine's opioid activity, such as pupillary constriction (miosis), should be discernable during and within several hours of infusion. For example, the mu-agonist fentanyl reliably produces miosis in healthy volunteers, an effect which is completely blocked by 50 mg of naltrexone.[4] To our knowledge, there is no evidence that subanesthetic dose ketamine is similarly associated with miosis.

Recent experimental data in rodents[5] and humans[6] may also contradict this report. The latter report by Yoon et al.[6] describes an open-label study in five recently detoxified veterans with Major depressive disorder (MDD) and alcohol use disorder, in which patients were given a 380 mg of naltrexone injection, followed two to six days later by four weekly infusions of subanesthetic dose ketamine. All five patients met antidepressant response criteria by their fourth dose (Day 21), although one subject did not progress beyond Day 7 and another subject had considerable variability in Montgomery-Åsberg Depression Rating Scale (MADRS) scores. This study is not directly comparable to the Williams et al. report because of differences in study population, ketamine dose frequency, and naltrexone dose but suggests that an individuals' ketamine responsivity is generally preserved in the context of opioid receptor blockade. It is notable that in contrast to the noxious effects observed with oral naltrexone + ketamine, the combination here was well tolerated, likely due to lower peak blood levels of depot naltrexone compared to oral naltrexone.

Finally, it should be acknowledged that naltrexone is an imperfect experimental probe for understanding the specific pharmacological mechanism of *any* drug including ketamine. Naltrexone produces attenuated effects for multiple substances beyond opioids, including alcohol, amphetamine, cocaine, and cannabis. It was recently shown in mice that ketamine's antinociceptive actions are mediated by endogenous cannabinoids and activation of CB_1 cannabinoid receptors.[7] Whether naltrexone modulates other systems linked to ketamine's antidepressant activity awaits further study in humans.

The mechanisms of ketamine's rapid and more persistent antidepressant effects are undoubtedly multifactorial. To assess the relevant contributions of opioid mechanisms, human radioligand Positron emission tomography (PET) studies with mu-opioid tracers should examine ketamine's binding affinity at clinically relevant doses, and clinical studies should rigorously investigate ketamine's impact on endogenous opioid expression. In the meantime, clinicians should continue to employ risk mitigation strategies and appropriate safeguards when treating patients chronically with this unique drug.

Declaration of Conflicting Interests

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References

1. Zanos P, Gould TD. Mechanisms of ketamine action as an antidepressant. *Mol Psychiatry*. 2018; 23(4): 801–811.
2. Moda-Sava RN, Murdock MH, Parekh PK, et al. Sustained rescue of prefrontal circuit dysfunction by antidepressant-induced spine formation. *Science*. 2019; 354(6435): eaat8078.
3. Williams NR, Heifets BD, Blasey C, et al. Attenuation of antagonism effects of ketamine by opioid receptor antagonism. *Am J Psychiatry*. 2018; 175(12): 1205–1215.
4. Rorick-Kehn LM, Witcher JW, Lowe SL, et al. Determining pharmacological selectivity of the kappa opioid receptor

antagonist LY2456302 using pupillometry as a translational biomarker in rat and human. *Int J Neuropsychopharmacology*. 2015; 18(2): 1–11.
5. Zhang K, Hashimoto K. Lack of opioid system in the antidepressant actions of ketamine. *Biol Psychiatry*. 2019; 85: e25–e27.
6. Yoon G, Petrakis IL, Krystal JH. Association of combined naltrexone and ketamine with depressive symptoms in a case series of patients with depression and alcohol use disorder. *JAMA Psychiatry*. 2019; 76(3): 337–338.
7. Pacheco DDF, Romero TRL, Duarte IDG. Ketamine induces central antinociception mediated by endogenous cannabinoids and activation of CB_1 receptors. *Neurosci Lett*. 2019; 699: 140–144.