Piercing the Ketamine Cloud

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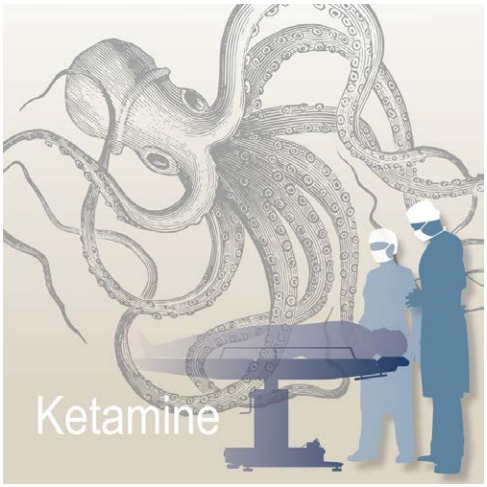
IF ketamine were an animal, it would have to be an octopus: unique, endlessly mutable, potentially dangerous, devilishly complicated to study, and seeming to extend its grasp into every corner of medicine. In the 50 years ketamine has been commercially available in the United States, practitioners and researchers have called it an analgesic, antidepressant, anti-inflammatory agent, dissociative anesthetic, drug of abuse, local anesthetic, neuroprotectant, neurotoxin, psychotomimetic, and therapeutic psychedelic. This (partial!) list makes clear the challenge in trying to harness ketamine for a specific, targeted use in a clinical setting. And yet as these various properties are investigated, we have the unique opportunity to deepen our understanding of how the nervous system works and to develop therapeutics that capitalize on these insights.



"…ketamine analgesia may consist of acute analgesic effects, antihyperalgesic effects, and modulation of opioid-mediated analgesia, each potentially mediated by a different set of peripheral and central nervous system circuits."

In this issue of ANESTHESIOLOGY, Gitlin *et al.*[1] take a novel approach to untangling two of the most well-established properties of ketamine, analgesia and dissociation. For the anesthetic induction of a surgical patient, both effects are desirable. However, in an awake patient being treated for postsurgical or chronic pain, for example, the value of ketamine is in its powerful nonopioid analgesic properties, and dissociation may be a counterproductive side effect. So, are the analgesic and dissociative effects of ketamine separable? Can ketamine be mechanistically split apart, refined, and reconstructed into a more targeted therapy? Or are these two facets of ketamine inextricably linked? Even the first published description of ketamine links the two properties,[2] describing how ketamine produces a "profound analgesia associated with a peculiar state of altered consciousness." However, it is difficult to identify a study that directly compares the dissociative symptoms and analgesic effects using standardized measures and in a standardized experimental pain model.

Gitlin *et al.* fill this gap in the literature by administering a single anesthetic dose of ketamine (2 mg/kg) to a small (n = 15) cohort of healthy adult participants, and analyzed their ratings of both dissociation and pain in response to a standardized noxious stimulus (pneumatic cuff pressure). The authors hypothesized that if dissociation drives analgesia, then a participant's rating of dissociation at various timepoints after ketamine should predict their rating of experimentally induced pain. Framing the question this way allowed the authors to apply a statistical approach related to stepwise multivariate regression, known as backward elimination. In essence, the authors constructed a statistical model to predict pain intensity scores, including factors such as sex, age, time after the ketamine dose, and dissociation score, and algorithmically eliminated each factor until only significantly predictive factors remained. The authors' main finding was that a participant's dissociation score had no predictive value for their pain score, implying that these two processes occur by independent mechanisms. One of the strengths of this study is their use of standardized, validated questionnaires for subjective measures, and a widely used experimental pain stimulus, which the authors note has both nociceptive and neuropathic qualities.

The authors also nest an important experimental manipulation into their timeline, administering a dose of midazolam at 1 h after ketamine. It is common practice to give midazolam with ketamine to prevent a potentially unpleasant dissociative experience. Using a similar statistical approach to the one described above, the authors confirmed

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this clinical intuition, finding that a model that includes midazolam significantly improved the fit for a participant's dissociation scores. While one might expect that midazolam administration would not affect participants' pain scores, the authors did not explicitly test this idea, missing an opportunity to further their claim that dissociation and analgesia are differentially regulated. Nonetheless, the authors' ability to pull out any effect of midazolam demonstrates the power of their experimental approach. A quick look at the highly variable raw data (authors' fig. 2) shows how difficult it might have been to discern an effect of midazolam with a more conventional study design, where, for example, participant groups would be split into midazolam *versus* placebo after ketamine, and mean dissociation scores compared.

This study describes a remarkably simple experiment that provides mechanistic insight into a complex drug effect simply by asking timed questions and applying a well-thought-out statistical modeling approach. One could easily imagine scaling this simple design into larger studies that integrate physiologic monitoring (*e.g.*, electroencephalography), gaining insight into any number of drug effects, potentially unencumbered by the need for planned drug condition groups or even placebo controls. The tradeoff, of course, is that modeling shows associations between variables but does not establish causality, despite the authors' suggestion in their discussion. That next step, establishing causative mechanism in human subjects, is not always easy. For example, the authors point to ketamine antagonism of *N*-methyl-D-aspartate receptors in the frontal cortex as a likely mechanism for the subjective state of dissociation. They support this idea citing human evidence that lamotrigine diminishes ketamine-induced dissociation,[3] reasoning that ketamine antagonism of *N*-methyl-D-aspartate receptors leads to a surge of glutamate release in the frontal cortex in rodents, and lamotrigine blocks both of these effects. Remarkably, the literature also supports a completely different interpretation. Lamotrigine, like ketamine, has an array of molecular targets, and both compounds have affinity for, and opposing activity at, a class of membrane proteins known as hyperpolarization-activated and cyclic nucleotide-gated ion channels. Mouse knockout studies show that forebrain hyperpolarization-activated and cyclic nucleotide-gated channels are necessary for ketamine-induced dissociative-like effects.[4] Pinning the mechanism of ketamine in humans to its interaction with a specific receptor depends greatly on the quality of our pharmacologic tools, which are often imprecise. Furthermore, even a single receptor is capable of multiple activation and signaling states (*e.g.*, biased ligands[5]). Attempting ever-more-refined receptor-level dissection of drug mechanisms may bear diminishing returns. Compounding the difficulty in assigning receptor-based mechanisms to the effects of ketamine, an explosion of recent research shows not only that ketamine binds to numerous receptors and ion channels,[4,6] but also that the enantiomers and metabolites of ketamine have distinct pharmacology and may drive some of the clinical properties of ketamine.[7]

In the face of this complexity, what is the way forward? The authors posit that their current work should inform studies of neural circuits influenced by ketamine, ostensibly to discover new ways to produce nonopioid-based analgesia. Indeed, circuit biology may ultimately have more explanatory power than receptor-based models of physiology. A circuit is a genetically, anatomically, or functionally defined population of neurons that carries information from one brain region to another. Circuits are a basic unit of physiology whose function is frequently conserved across mammalian species. Integrating targeted manipulations of neural circuits into clinical studies with technologies like transcranial magnetic stimulation will undoubtedly grow our understanding of the processes that gives rise to measurable signals (like electroencephalogram), and open new opportunities to probe and treat conditions relevant to perioperative medicine. Finally, future work could build on studies like this one by enhancing the richness of pharmacodynamic measurements incorporated into statistical models. Ketamine is a powerful analgesic, and a large body of research suggests that ketamine analgesia may consist of acute analgesic effects, antihyperalgesic effects, and modulation of opioid-mediated analgesia, each potentially mediated by a different set of peripheral and central nervous system circuits.[8] We have some of the most powerful psychotropic agents in medicine at our disposal in the operating room, and are uniquely situated to understand and develop their full therapeutic potential.

Competing Interests

The author is not supported by, nor maintains any financial interest in, any commercial activity that may be associated with the topic of this article.

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