The Taming of Ketamine—40 Years Later

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The pharmacodynamic effects of ketamine on mood, emotion, and perception were a subject of great discussion and some alarm when this dissociative agent first became clinically available 40 years ago. During recovery, some patients experienced vivid hallucinations, with varied manifestations such as psychedelic colors, suspension in midair or outer space, floating down a kaleidoscope, out-of-body experiences, or seeing faceless persons walking around the bed. To some patients these experiences were frightening or nightmarish, whereas others described them as pleasant, joyful, fascinating, or simply bizarre.1

In a landmark 1973 study titled “The Taming of Ketamine,” Coppel et al2 observed that the coadministration of diazepam reduced the incidence of adult recovery delirium from 15% to 3% and unpleasant dreams from 10% to 0%.2 Thereafter, benzodiazepine prophylaxis has been widely regarded as essential in adults,1 and the characterization of ketamine as a “tiger” that “needs to be tamed” survives to this day.3

The fascinating exception to this observation is children, who only rarely exhibit unpleasant recovery agitation or nightmares.1 Children likely hallucinate just like adults but presumably perceive such events as less disturbing because of their developmental level.1 Two randomized, controlled emergency department (ED) trials have shown no measurable benefit from midazolam prophylaxis in children.4,5 In one of these trials, the treating physicians quantified recovery agitation and found it to be typically trivial (median score 5 of 100).4 Consequently, the predominant ED strategy has been to avoid midazolam prophylaxis but instead reserve this drug for treatment should unpleasant dreams or reactions occur during recovery.6

So if ketamine doesn’t require “taming” in ED children, does it in ED adults? Three case series with disparate definitions of recovery reactions fail to provide an answer. Chudnofsky et al7 administered ketomidal with midazolam to 77 ED adults and observed 5 mild and no serious recovery reactions. Newton and Fitton8 sedated 92 adults with ketamine alone; 12 experienced recovery agitation, for which 7 were treated with midazolam. Vardy et al9 also administered ketamine alone to 85 adults and observed 16 recovery reactions of unclear severity and 1 nightmare.

In this issue of Annals, Sener et al10 report the first adult randomized, controlled, double-blind trial of ketamine with and without midazolam. They found significantly less recovery agitation in subjects receiving midazolam prophylaxis (8% versus 25%). This 17% absolute benefit is similar to that observed in the 2 previous randomized trials of ketamine with and without diazepam11,12 and in the original nonrandomized “taming” trial by Coppel et al.2 Thus, the estimated number needed to benefit is 6, i.e., one would need to administer midazolam 6 times to prevent 1 occurrence of recovery agitation. In their discussion, Sener et al10 describe this effect as clinically important and worthwhile.10

So is this now the definitive and simple answer? Should emergency physicians routinely provide midazolam prophylaxis to adults but not children? Two important caveats must be considered.

First, the earlier randomized trials in children4,5 taught us that ketamine-induced recovery reactions are too complex to simply classify as present or absent. Instead, they exhibit a dramatic spectrum of severity while exhibiting a wide and not necessarily proportionate range of patient agreeability. Vivid dreams or hallucinations need not always be feared or avoided. The primary limitation of the otherwise outstanding trial by Sener et al10 is that recovery agitation was coded as either present or absent. It is possible that many of the included reactions were mild or otherwise below many clinicians’ thresholds of clinical importance. Thus, the number needed to benefit of 6 represents the maximally effective treatment scenario. If one presumes that one fourth or one half of the coded reactions were clinically important and worthwhile,10 then the recalculated number needed to benefit would proportionately erode to a less compelling 8 or 12.

Second, all patients and clinical situations are not otherwise equal. Psychological factors appear to influence the nature and severity of recovery reactions. Patients with psychotic traits or evidence of personality disorders on psychological inventories appear at greater risk, as do those who normally dream frequently, and female patients relative to male patients.1 Some patients might be regarded as particularly high or low risk according to their anxiety level and underlying personality.
Additionally, some clinicians believe that the severity of ketamine-associated recovery reactions can be mitigated with positive psychology and "dream planning." \(^{14,15}\) Although such interventions remain unproven.

Given this compelling evidence from Sener et al., \(^{10}\) many clinicians will choose to “tame” ketamine in adults by routinely coadministering midazolam. Others, according to the caveats above, will just as reasonably elect to individualize such prophylaxis, using a subjective assessment of a given patient’s risk. After all, should their prediction fail and an unpleasant reaction result, it can readily be quelled with midazolam. Regardless of these approaches, the ketamine “tiger” may not be as ferocious as some fear. As observed by Grace, \(^{12}\) the effects of ketamine often appear far more troubling to physicians than to their patients.

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**REFERENCES**


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The editors of *Academic Emergency Medicine* invite you to participate in a one-day consensus conference on “Interventions to Assure Quality in the Crowded Emergency Department.” This conference, funded by the Agency for Healthcare Research and Quality, will be held on June 1, 2011, immediately preceding the Society for Academic Emergency Medicine Annual Meeting in Boston, Massachusetts. In the morning, experts from other disciplines and countries will review strategies they employ to assure quality of care in different settings. In the afternoon, participants will break out into small groups to create the research agenda that will guide the science of identifying and implementing promising interventions that have the potential to safeguard the safety, timeliness, effectiveness, efficiency, equity, and patient-centeredness of emergency care, particularly during crowded periods. Please plan to attend; registration for this conference will begin in December of 2010 at www.saem.org. Further information is available at the journal's Web site, www.aemj.org.