Impact of midazolam v. saline on effect size estimates in controlled trials of ketamine as a rapid-acting antidepressant

Samuel T. Wilkinson, MD; Cristan Farmer, PhD; Elizabeth Ballard, PhD; Sanjay J. Mathew, MD; Michael F. Grunebaum, MD; James W. Murrough, MD, PhD; Peter Sos, MD, PhD; Gang Wang, MD, PhD; Ralitza Gueorguieva, PhD; Carlos A. Zarate, Jr., MD

Correspondence:
Samuel T. Wilkinson, MD
Yale Depression Research Program, Yale School of Medicine
100 York Street, STE 2J
New Haven, CT 06511 (USA)
E-Mail: samuel.wilkinson@yale.edu

ABSTRACT:

What is the Methodological Question being addressed:
Is midazolam superior to saline in maintaining the integrity of the blind in clinical trials of ketamine as an antidepressant?

Background: Ketamine has emerged as the prototypical rapid-acting antidepressant, yet several issues impede its progress in both research and clinical domains. Among these problems is the integrity of the blind when ketamine is evaluated in randomized controlled trials. Due to the potent psychoactive effects of ketamine, there is concern that both patients and raters may be functionally unblinded when saline is used as the comparator. Midazolam (a benzodiazepine) has been used as an active comparator in an attempt to improve the integrity of the blind. Here, we evaluate the performance of midazolam as an active comparator by examining the effect size of controlled studies of intravenous ketamine using midazolam versus saline.

Methods: In this integrative data analysis (k=9, N=367 patients with mood disorders), clinical outcomes were compared across four groups: ketamine (midazolam-controlled), ketamine (saline-controlled), midazolam, and saline. Ketamine doses ranged from 0.5–0.54 mg/kg and midazolam doses ranged from 0.02–0.045 mg/kg. We compared clinical outcomes at Day 1 post-infusion, using a linear mixed model with a repeated effect of time and a random effect of study. The difference between treatment groups was evaluated with a series of between-group contrasts of improvement from baseline to Day 1.

Results: The 24-hour improvement observed in ketamine (midazolam) (model-estimated mean improvement = 13.6 MADRS points, SE = 1.1) exceeded that in midazolam (mean = 7.0, SE = 0.9) (comparison: $t(185) = 19.94$, $p < .0001$). Similarly, the improvement observed in ketamine (saline) (mean = 12.5, SE = 1.2) exceeded that of saline (mean = 1.6, SE = 0.4) (comparison: $t(96.5) = 80.8$, $p < .0001$). The baseline-to-Day 1 effect size was d=0.7 (95% CI: 0.4–0.9) for ketamine (midazolam) versus midazolam and d = 1.8 (95% CI: 1.4–2.2) for ketamine (saline) versus saline. There was no difference between ketamine arms (p=.51); however, improvement under midazolam exceeded saline ($t_{111}=5.4$, $p<.0001$). Dichotomous outcomes (response rates) showed a similar pattern.

Conclusions: The average effect of ketamine was smaller when compared with midazolam than when compared with saline, which was driven by greater improvement in the midazolam group compared to the saline group. An important limitation is that no trial directly compared midazolam to saline. One interpretation of these results is that midazolam was superior to saline in preserving the integrity of the blind. However, alternative explanations, such as the hypothesis that midazolam has antidepressant effects, cannot be excluded.