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Intramuscular Midazolam, Olanzapine, Ziprasidone, or Haloperidol for Treating Acute Agitation

To the Editor:

We congratulate Klein et al[1] on their recent article. It is a valuable addition to the literature on agitation, especially the much-needed head-to-head comparisons of different pharmacologic options. And we agree with the paired editorial that doing any research on agitated individuals is very difficult because of restrictions on informed consent, making the authors' work that much more impressive.

However, we do take issue with some aspects of the study, which seem contrary to established expert consensus guidelines. First is the decision to establish sedation as the primary goal of agitation treatment and identify the agent leading to the most rapid and deepest levels of sedation as the study's recommended treatment option. Although rapid response should be a key goal, heavy sedation to the point at which a patient is unarousable should not be; multiple expert consensus guidelines over the past 15 years[2-4] state that the preferred goal of agitation is calming without oversedation. An oversedated patient cannot be further interviewed, care for himself or herself, or identify symptoms and would typically be unable to receive a psychiatric consultation or be transferred to a psychiatric unit. Oversedation thus can increase psychiatric patient boarding in emergency departments. Meanwhile, a patient merely treated to the point of calmness, even to light sleep that is quickly arousable, can participate in interactive care and have improved options for a safe, prompt disposition.

The study authors favored midazolam because it heavily sedates the patient quickly. Midazolam is reported to move patients from the study's consistent patient baseline score on the Altered Mental Status Scale of 2 (anxious, agitated) to –1 (lethargic) at 15 minutes all the way to –3 (obtunded, needs physical prodding to respond) in just 30 minutes, with a percentage of the 30-minute patients completely unarousable even by physical shaking (level –4). In contrast, olanzapine and ziprasidone have been shown to reduce a patient's level from 2 to 0 (calm, normal alertness) in 15 minutes and to –1 (ziprasidone) and –2 (olanzapine) at 30 minutes, with no patients unarousable or level –4 with either medication at that point.

According to these results, it would appear that ziprasidone and olanzapine produce the desired result of calmness without oversedation at both 15 and 30 minutes, allowing safe extra time for further evaluation and questioning of the patient, and thus would be superior to midazolam in the study.

Another fundament of agitation intervention is to treat the underlying condition. For agitation caused by psychotic illness, olanzapine and ziprasidone will begin treating the underlying condition of psychosis, as well as quelling the agitation. However, midazolam is not an antipsychotic agent and works only as a sedative in these cases. Thus, its use is really only for quieting an individual and delaying the actual treatment, and a patient may arise from the sedation with psychosis as severe as on arrival.

A final point is that successful treatment of agitation is best accomplished by de-escalation techniques combined with voluntary administration of oral medications.[5]

Although we recognize that this study was intended to distinguish between intramuscular options for agitation, we would have appreciated more information on this hospital's efforts to reduce agitation without resorting to coercive measures.

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In reply:

Zeller et al[1] discuss their concern with the use of adequate sedation as "the primary goal of agitation treatment." We strongly believe that adequate sedation is necessary for patient and provider safety and to ensure a comprehensive patient evaluation. Adequate sedation, contrary to Zeller's comment, is *not* the same as oversedation. We at no point encouraged "heavy sedation to the point at which a patient is unarousable." As iterated multiple times, we observed a clinical protocol adopted by our emergency department (ED); the indication for sedation and the desired level of sedation were at the discretion of the treating physicians. We would also like to point out the definition of our primary outcome: an Altered Mental Status Score of 0 or lower. A score of 0 indicates someone who responds readily to his or her name in a normal tone, has normal speech, has a normal facial expression, and has no ptosis. This definition is certainly not that of an oversedated patient. Although many patients did achieve a deeper level of sedation, this was a therapeutic consequence of agitation treatments at these standard doses.

It is inaccurate to suggest that "the study authors favored midazolam." Our data demonstrated that midazolam was superior to haloperidol and ziprasidone but not olanzapine in regard to our primary outcome. Reporting conclusions based on an a priori primary outcome is a fundamental tenet of research design. We went on to present secondary outcome data for all medications at each point to allow the reader to consider what treatment would be ideal for his or her clinical practice; for some, that may be olanzapine or ziprasidone if they prefer antipsychotics, or perhaps even haloperidol if time to sedation is not an important factor.

Zeller et al focused primarily on the agitated psychiatric patient. However, in common with our study cohort, agitation observed in ED patients is usually a result of intoxication rather than acute psychiatric illness.[2-4] If the physician knows with certainty that the patient's agitation is due to psychiatric illness, perhaps an antipsychotic agent *is* the best choice. Unfortunately, more often, the emergency physician does not have the luxury of knowing the cause of agitation at the onset of the encounter. We believe that viewing agitation in the ED as an undifferentiated process is critical. As such, we sought to identify the safest and most effective treatment for the patient whose diagnosis is not known, representing a more realistic ED practice.

We have the utmost respect for our patient population, and communicating with them to attempt to de-escalate is fundamental to our clinical practice. However, the purpose of this study was to describe the effects of various medications once the provider had determined that parenteral sedation was indicated. This encompasses a patient population notably different from those who respond to nonpharmacologic methods or who are willing to receive oral medications. It seems Zeller et al are envisioning a group of agitated patients vastly different from those included in our work.