The psychopharmacology of agitation: consensus statement of the American association for emergency psychiatry project BETA psychopharmacology workgroup.

Wilson MP, Pepper D, Currier GW, Holloman GH, Feifel D. The psychopharmacology of agitation: consensus statement of the American association for emergency psychiatry project BETA psychopharmacology workgroup. *West J Emerg Med.* 2012; 13:26-34.

Hannah Hays, MD[*]
Heath A. Jolliff, DO, FACEP, FAAEM[*]
Marcel J. Casavant, MD, FACEP, FACMT[†]

[*]*The Ohio State University Wexner Medical Center, Columbus, Ohio*
[†]*The Ohio State University College of Medicine, Columbus, Ohio*

Address for Correspondence: Hannah Hays, MD, The Ohio State University Wexner Medical Center, 410 W. 10th Ave., Columbus, OH 43210. Email: hannah.hays@osumc.edu.

Conflicts of Interest: By the *West*JEM article submission agreement, all authors are required to disclose all affiliations, funding sources and financial or management relationships that could be perceived as potential sources of bias. The authors disclosed none.

To the Editor:

We were excited to read the article by Michael Wilson et al[1] in the March 2012 issue of the *Western Journal of Emergency Medicine* regarding pharmacologic strategies for the management of agitated patients in the emergency setting. This article highlights several important points including the optimal management of stimulant-induced agitation and the feasibility of and reasons for differentiating acute alcohol intoxication from withdrawal, as optimal pharmacologic interventions for each might vary.

While the authors correctly highlight the importance of preferential use of benzodiazepines to calm patients intoxicated with most recreational drugs, we believe that the use of benzodiazepines as first line treatment for agitation should be extended to include that from acute overdose of other agents.

Because many common medications taken in acute overdose, such as cyclic antidepressants, SSRIs, diphenhydramine and other over-the-counter medications have toxicity profiles that include anticholinergic, proconvulsant, hyperthermic, and cardiotoxic (QTc prolongation) properties, which overlap with antipsychotics, we recommend benzodiazepines as first, second and third line for agitation in these instances to avoid contributing to these potentially life threatening adverse effects. Further, benzodiazepines raise the seizure threshold and promote conditions that precipitate heat dissipation.[2,3] If, after liberal use of benzodiazepines, the patient still displays agitation necessitating further pharmacologic intervention, we then use antipsychotics with caution. We found the reported maximum daily dose of lorazepam in the Table[1] to be dangerously low.

We were glad to see the emphasis on patient and staff safety, given the increasing awareness of the excited delirium syndrome, thought to be due to a multifactorial interaction of delirium and agitation often secondary to stimulant intoxication, leading to hyperthermia, profound acidemia and sometimes death.[4-7] We regret that the authors left out a discussion of the increasing use of the dissociative agent ketamine for rapid control of dangerous behavior in this subset of patients. Although no controlled trials exist regarding its use in agitated patients, several case reports show rapid, satisfactory results without significant respiratory and cardiovascular adverse effects.[5,8] Potential adverse effects of ketamine, although uncommon, include hypertension, emergence phenomena, increased oral secretions and laryngospasm.[7,10]

REFERENCES

1. Wilson MP, Pepper D, Currier GW, et al. The psychopharmacology of agitation: consensus statement of the American association for emergency psychiatry project BETA psychopharmacology workgroup. *West J Emerg Med.* 2012; 13:26-34.
2. Zhengnian D, White PF. Anesthesia for electroconvulsive therapy. *Anesthes Analg.* 2002; 94:1351-1364.
3. Schep LJ, Slaughter RJ, Beasley DMG. The clinical toxicology of methamphetamine. *Clin Tox.* 2010; 48:675-694.
4. DeBard ML, Adler J, Bozeman W, et al. White paper report on excited delirium syndrome. ACEP Web site. Available at: http://ccpicd.com/Documents/Excited%20Delirium%20Task%20Force.pdf. Last accessed April 24, 2012.
5. Roberts JR, Geeting GK. Intramuscular ketamine for the rapid tranquilization of the uncontrollable, violent, and dangerous adult patient. *J Trauma.* 2001; 51:1008-1010.
6. Bunai Y, Kayoko A, Wei-Ziong J, et al. Fatal hyperthermia associated with excited delirium during an arrest. *Legal Medicine.* 2008; 10:306-309.
7. Vike GM, Debard ML, Chan TC, et al. Excited delirium syndrome (EXDS): defining based on a review of the literature. *J Emerg Med.* 2011; [epub ahead of print].
8. Cong ML, Gynther B, Hunter, E, et al. Ketamine sedation for patients with acute agitation and psychiatric illness requiring aeromedical retrieval. *Emerg Med J.* 2012; 29:335-337.
9. Strayer RJ, Nelson LS. Adverse events associated with ketamine for procedural sedation in adults. *Amer J Emerg Med.* 2007; 26:985-1028.
10. Burnett AM, Watters BJ, Barringer KW, et al. Laryngospasm and hypoxia after intramuscular administration of ketamine to a patient in excited delirium. *Prehosp Emerg Care.* 2012

In reply:

We appreciate the thoughtful comments by Drs. Hays, Jolliff and Casavant regarding the consensus guidelines we authored for the pharmacologic management of agitated patients in the emergency setting.[1] They disagree with the fact that these guidelines do not recommend benzodiazepines as

first line treatments in all cases of agitation associated with substance intoxication because many compounds taken in acute overdose have a propensity to produce anticholinergic, proconvulsant, hyperthermic, and cardiotoxic (QTc prolongation) effects which overlap with antipsychotics but not benzodiazepines.

Our guidelines divide agitation secondary to intoxication into that which is primarily caused by CNS stimulants and that which is caused primarily by CNS depressants, most notably alcohol. Benzodiazepines are recommended as first line in the guidelines for the former category, while an antipsychotic drug (preferably non-sedating) is recommended for the latter. While we recognize patients displaying agitation in an emergency setting often have more than one substance on board, we believe the division of intoxication-induced agitation into these two categories present clinicians with a conceptual road map for decision making. The overtly alcohol-inebriated, agitated patient is the representative patient we had in mind for the CNS depressant category. Acute alcohol ingestion is not strongly associated with any of the physiological effects that Drs. Hays, Jolliff and Casavant cite. On the other hand, both benzodiazepines and alcohol share a propensity toward respiratory depression and combined they pose an additive or even synergistic potential risk of respiratory depression.[2-4] On this basis we did not recommend benzodiazepines as first line treatment for agitation in a patient whose presentation is highly consistent with alcohol as the primary intoxicant.

We would also like to point out a common misperception, alluded to in the letter by Drs. Hays, Jolliff and Casavant, that antipsychotics produce hyperthermia. While in certain rare situations, excessively high doses of (mostly first generation) antipsychotics can produce NMS, a syndrome associated with hyperthermia, under normal circumstances antipsychotics tend to lower body temperature.[5]

Additionally, we share the interest, expressed by Drs. Hays, Jolliff and Casavant, in ketamine as a potential agent in the treatment of patients described as having "Excited Delirium Syndrome." However, as they note in their letter, despite growing clinical experience and several case reports supporting its use in this putative, specific subgroup of agitated patients, there is, as of yet, a dearth of high quality evidence (i.e. controlled trials) regarding the safety and efficacy of this treatment relative to other established treatments for agitation. There is also no reliable method, as of yet, for identifying patients who may be well suited for ketamine and those for whom it may be contraindicated. For example, patients with untreated psychotic disorders, such as schizophrenia, are considered to represent a substantial portion of the patients who present with "excited delirium."[6] The psychotomimetic nature of ketamine raises the distinct possibility that it may exacerbate the underlying psychosis in these patients. Moreover, recreational ingestion of ketamine and PCP, which is a derivative of ketamine and shares its antagonism of NMDA subtype glutamate receptors, are known to induce an "excited delirium" presentation.[7] In a patient whose agitation is due to ketamine or PCP, administration of ketamine would exacerbate the underlying pharmacological toxicity. For these reasons we felt that clinical knowledge regarding excited delirium syndrome and the use of ketamine in these situations has not, at this time, sufficiently matured to include it among recommended treatments.

David Feifel, MD, PhD[*]
Michael P. Wilson, PhD, MD[*]
David Pepper, MD [†]
Glenn W. Currier, MD, MPH [‡]
Garland Holloman, MD [Ω]
[*]*University of California San Diego, San Diego, CA*
[†]*Hartford Hospital/Institute of Living, Hartford, CT*
[‡]*University of Rochester Medical Center, Rochester, NY*
[Ω]*University of Mississippi Health Care, Jackson, MS*

Address for Correspondence: David Feifel MD, PhD, Department of Psychiatry, University of California San Diego, 9500 Gilman Drive, MC: 0603, La Jolla, CA 92093. Email: dfeifel@ucsd.edu.

Conflicts of Interest: By the *West*JEM article submission agreement, all authors are required to disclose all affiliations, funding sources and financial or management relationships that could be perceived as potential sources of bias. The authors disclosed none.

REFERENCES

1. Wilson MP, Pepper D, Currier GW, et al. The psychopharmacology of agitation: consensus statement of the American association for emergency psychiatry project BETA psychopharmacology workgroup. *West J Emerg Med.* 2012; 13:26-34.
2. Wilson KC, Saukkonen JJ. Acute Respiratory Failure from Abused Substances *J Intensive Care Med.* 2004, 19:183
3. Jedeikin R, Menutti D, Bruderman I, et al. Prolonged respiratory center depression after alcohol and benzodiazepines. *Chest*. 1985, 87(2):262-4.
4. Tanaka E. Toxicological interactions between alcohol and benzodiazepines. *J Toxicol Clin Toxicol*. 2002, 40(1):69-75
5. van Marum RJ, Wegewijs MA, Loonen AJ, et al. Hypothermia following antipsychotic drug use. *Eur J Clin Pharmaco*l. 2007, 63(6):627-31.
6. DeBard ML, Adler J, Bozeman W, et al. White paper report on excited delirium syndrome. ACEP Web site. Available at: http://ccpicd.com/Documents/Excited%20Delirium%20Task%20Force.pdf. Accessed May28, 2012.
7. Baldridge EB, Bessen HA. Phencyclidine. *Emerg Med Clin North Am.* 1990, 8(3):541-50.