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Feifel et al reply to Hays et al regarding 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.

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-intoxicated, 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.

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