Clinical Policy: Critical Issues in the Evaluation and Management of Adult Out-of-Hospital or Emergency Department Patients Presenting With Severe Agitation

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ABSTRACT

This clinical policy from the American College of Emergency Physicians addresses key issues in the evaluation and management of adult out-of-hospital or emergency department patients presenting with severe agitation. A writing subcommittee conducted a systematic review of the literature to derive evidence-based recommendations to answer the following clinical question: Is there a superior parenteral medication or combination of medications for the acute management of adult out-of-hospital or emergency department patients with severe agitation? Evidence was graded, and recommendations were made based on the strength of the available data.

INTRODUCTION

Patients with severe agitation are consistent, high-risk presentations to the emergency department (ED). Such patients typically are suffering from an acute medical emergency, acute intoxication with sympathomimetics or alcohol, or a psychiatric problem.[1-3] In patients where the cause of agitation is known, clinicians can initiate usual treatment for the suspected cause. This policy is intended for the initial treatment of undifferentiated agitation, in which the underlying cause is unknown. Patients with severe agitation may present with altered mental status and increased psychomotor activity, accompanied by a dangerous hyperadrenergic state. It is important to note that the spectrum of severe agitation often represents a critical, life-threatening medical condition that requires urgent treatment, and patients who present in this state have high morbidity and mortality. Patient safety must be paramount in the treatment of these patients. Sedating medications are often required to calm the patient and create a safe environment for the patient and staff. In addition, this facilitates appropriate evaluation and treatment of the patient's serious underlying medical problem.[2] These patients utilize a significant amount of ED resources and carry a risk of harm to medical staff, nearby patients, visitors/family, or the patient themselves.[2-4]

Verbal de-escalation should be considered as first-line management. Following attempts at verbal de-escalation, oral or sublingual medications should be considered in patients where it is safe to administer them.[5] When verbal de-escalation is ineffective and oral/sublingual medications are not feasible, parenteral administration of medications to treat agitation is a safe option for patients and staff.[1] The ideal treatment is an agent with rapid onset, consistent effectiveness, and few to no side effects. Traditionally, to calm ED patients with severe agitation, antipsychotics and benzodiazepines have most often been utilized either in combination or alone. Droperidol has seen a resurgence of use but is not available in all settings. Recently, ketamine has found a role as a rapid sedative for severely agitated patients, but there have been significant concerns regarding its safety profile.

This clinical policy attempts to summarize the current body of literature surrounding the safety and efficacy of agents used for treatment of severe agitation in the ED. It is important to note that this summary includes a number of studies with variability in the routes and doses of medications studied, the choice of medications compared, and the outcomes used to assess adequate sedation or calming. The recommendations that follow are based on summative interpretation of this extremely heterogeneous literature base. As referenced in our discussion on future directions, there is still a need for quality studies that take a standardized approach to further evaluate this question. Additional studies that standardize dosing and compare specific medications head-to-head, alone, and in combination are needed. Additional studies that evaluate the use of sedating medications in the elderly and out-of-hospital settings are needed. The mean and median ages of patients in the studies included in this review are in their 20s to 50s, with some studies explicitly excluding patients aged more than 65 years. These recommendations should be considered as applicable to the patient age range studied. As always, clinicians should use caution administering any sedating agents to older patients. Although our literature search did find some studies evaluating the use of sedating medications in the out-of-hospital setting, none of these studies were of methodologic quality to drive a recommendation for or against the use of any specific agents.

This review includes studies that administered parenteral (intravenous or intramuscular) sedation in severely agitated patients. A summary of the medications discussed in this clinical policy can be found in Table 1. No oral or sublingual administration methods are included, as this clinical policy is geared toward the patient population in which staff would be unable to administer medications through these routes. For the purposes of this policy, severe agitation demonstrates features identified at the extreme of the Richmond Agitation-Sedation Scale for critical care patients or the Altered Mental Status Score.[6,7] These scores are included as a point of reference and are not intended to be an endorsement of a specific scale.

- Richmond Agitation-Sedation Scale score of +4 (overtly combative, violent, immediate danger to staff)

- Altered Mental Status score of 4 (combative, violent, out of control; loud outbursts of speech; agitated facial expression)

METHODOLOGY

This American College of Emergency Physicians (ACEP) clinical policy was developed by emergency physicians with input from medical librarians and a patient safety advocate and is based on a systematic review and critical, descriptive analysis of the medical literature and is reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[8]

Search and Study Selection

This clinical policy is based on a systematic review with critical analysis of the medical literature meeting the inclusion criteria. Searches of PubMed, SCOPUS, Embase, Web of Science, and the Cochrane Database of Systematic Reviews were performed by a librarian. Search terms and strategies were peer reviewed by a second librarian. All searches were limited to human studies published in English. Specific key words/phrases, years used in the searches, dates of searches, and study selection are identified under the critical question. In addition, relevant articles from the bibliographies of included studies and more recent articles identified by committee members and reviewers were included.

Using Covidence (Covidence), 2 subcommittee members independently reviewed the identified abstracts to assess for possible inclusion. Of those identified for potential inclusion, each full-length text was reviewed for eligibility. Those identified as eligible were subsequently abstracted and forwarded to the committee's methodology group (emergency physicians with specific research methodological expertise) for methodological grading using a Class of Evidence framework (Appendix E1, available at http://www.annemergmed.com).

Assessment of Risk of Bias and Determination of Classes of Evidence

Each study identified as eligible by the subcommittee was independently graded by 2 methodologists.

Design 1 represents the strongest possible study design to answer the critical question, which relates to whether the focus was therapeutic, diagnostic, or prognostic, or a meta-analysis. Subsequent design types (ie, Design 2 and Design 3) represent respectively weaker study designs. Articles are then graded on dimensions related to the study's methodological features and execution, including but not limited to randomization processes, blinding, allocation concealment, methods of data collection, outcome measures and their assessment, selection and misclassification biases, sample size, generalizability, data management, analyses, congruence of results and conclusions, and potential for conflicts of interest.

Using a predetermined process that combines the study's design, methodological quality, and applicability to the critical question, 2 methodologists independently assigned a preliminary Class of Evidence grade for each article. Articles with concordant grades from both methodologists received that grade as their final grade. Any discordance in the preliminary grades was adjudicated through discussion, which involved at least 1 additional methodologist, resulting in a final Class of Evidence assignment (ie, Class I, Class II, Class III, or Class X) (Appendix E2, available at http://www.annemergmed.com). Studies identified with significant methodologic limitations and/or ultimately determined to not be applicable to the critical question received a Class of Evidence grade "X" and were not used in formulating recommendations for this policy. However, content in these articles may have been used to formulate the background and to inform expert consensus in the absence of evidence. Classes of Evidence grading may be found in the Evidentiary Table included at the end of this policy.

Translation of Classes of Evidence to Recommendation Levels

Based on the strength of evidence for the critical question, the subcommittee drafted the recommendations and supporting text synthesizing the evidence using the following guidelines:

Level A recommendations. Generally accepted principles for patient care that reflect a high degree of scientific certainty (eg, based on evidence from one or more Class of Evidence I or multiple Class of Evidence II studies that demonstrate consistent effects or estimates).

Level B recommendations. Recommendations for patient care that may identify a particular strategy or range of strategies that reflect moderate scientific certainty (eg, based on evidence from one or more Class of Evidence II studies or multiple Class of Evidence III studies that demonstrate consistent effects or estimates).

Level C recommendations. Recommendations for patient care that are based on evidence from Class of Evidence III studies or, in the absence of adequate published literature, based on expert consensus. In instances where consensus recommendations are made, "consensus" is placed in parentheses at the end of the recommendation.

There are certain circumstances in which the recommendations stemming from a body of evidence should not be rated as highly as the individual studies on which they are based. Factors, such as consistency of results, uncertainty of effect magnitude, and publication bias, among others, might lead to a downgrading of recommendations. When possible, clinically oriented statistics (eg, likelihood ratios, number needed to treat) are presented to help the reader better understand how the results may be applied to the individual patient. This can assist the clinician in applying the recommendations to most patients but allow adjustment when applying to patients with extremes of risk (Appendix E3, available at http://www.annemergmed.com).

Evaluation and Review of Recommendations

Once drafted, the policy was distributed for internal review by members of the entire committee followed by external expert review and an open comment period for all ACEP membership. Comments were received during a 60-day open comment period with notices of the comment period sent electronically to ACEP members, published in *EM Today*, posted on the ACEP website, and sent to pertinent physician and pharmacy organizations. The responses were used to further refine and enhance this clinical policy, although responses do not imply endorsement. Clinical policies are scheduled for revision every 3 years; however, interim reviews are conducted when technology, methodology, or the practice environment changes significantly.

Application of the Policy

This policy is not intended to be a complete manual on the evaluation and management of adult patients with severe agitation but rather a focused examination of a critical question that has particular relevance to the current practice of emergency medicine. Potential benefits and harms of implementing recommendations are briefly summarized within the critical question.

It is the goal of the Clinical Policies Committee to provide evidence-based recommendations when the scientific literature provides sufficient quality information to inform recommendations for the critical question. In accordance with ACEP Resolution 56(21), ACEP clinical policies do not use race-based calculators in the formulation of recommendations. When the medical literature does not contain adequate empirical data to inform the critical question, the members of the Clinical Policies Committee believe that it is equally important to alert emergency physicians to this fact.

This clinical policy is not intended to represent a legal standard of care for emergency physicians. Recommendations offered in this policy are not intended to represent the only diagnostic or management options available to the emergency physician. ACEP recognizes the importance of the individual physician's judgment and patient preferences. This guideline provides clinical strategies for which medical literature exists to inform the critical question addressed in this policy. ACEP funded this clinical policy.

Scope of Application. This guideline is intended for physicians working in EDs.

Inclusion Criteria. This guideline is intended for adults with undifferentiated severe agitation who require immediate sedation to facilitate life-saving medical care.

Exclusion Criteria. This guideline is not intended for pediatric, pregnant or out-of-hospital patients or patients above the age of 65.

CRITICAL QUESTION

Is there a superior parenteral medication or combination of medications for the acute management of adult out-of-hospital or emergency department patients with severe agitation?

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. For more rapid and efficacious treatment of severe agitation in the emergency department, use a combination of droperidol and midazolam or an atypical antipsychotic in combination with midazolam. If a single agent must be administered, use droperidol or an atypical antipsychotic due to the adverse effect profile of midazolam alone.

For efficacious treatment of severe agitation in the emergency department, use the above agents as described or haloperidol alone or in combination with lorazepam.

Level C recommendations. In situations where safety of the patient, bystanders, or staff is a concern, consider ketamine (intravenous or intramuscular) to rapidly treat severe agitation in the ED (Consensus recommendation).

No recommendations for or against the use of specific agents in the out-of-hospital setting can be made at this time (Consensus recommendation).

No recommendation for or against the use of specific agents in patients above the age of 65 years can be made at this time (Consensus recommendation).

Potential Benefit of Implementing the Recommendations:

- Safe, adequate sedation facilitates medical evaluation of the acutely agitated patient.

- Adequate sedation allows avoidance of prolonged physical restraint and/or isolation, both of which are associated with increased morbidity and mortality.
- Safe, adequate sedation improves the safety of staff caring for the patient.
- A combination of droperidol and midazolam maximizes the balance of adequate sedation while minimizing side effects.

Potential Harm of Implementing the Recommendations:

- Use of antipsychotics always carries the inherent risk of extrapyramidal side effects such as a dystonic reaction.
- Use of certain antipsychotics may carry the risk of corrected QT interval (QTc) prolongation and torsades de pointes.
- Use of benzodiazepines carries the risk of oversedation and respiratory depression.

Key words/phrases for literature searches: antipsychotic agents, benzodiazepines, delirium, diazepam, droperidol, emergency department, emergency medical services, emergency medicine, haloperidol, ketamine, ketamine hydrochloride, lorazepam, mania, midazolam, olanzapine, psychomotor agitation, risperidone, ziprasidone, and variations and combinations of the key words/phrases. Searches included June 10, 15, 16, 17, and 18, 2021, and February 1 and 2, 2022.

Study Selection:

Seven hundred thirty-seven articles were identified in the searches. Three hundred two articles were selected from the search results as candidates for further review. After grading for methodological rigor, zero Class I studies, 3 Class II, and 14 Class III studies were included for this critical question (Appendix E4, available at http://www.annemergmed.com).

Antipsychotics, Benzodiazepines, and Combinations

A number of studies have examined a combination of antipsychotics and benzodiazepines for the rapid treatment of agitation in the ED. In particular, droperidol and midazolam in combination appear to result in more rapid sedation and have a more favorable safety profile than other individual medications and combinations of classes. Although droperidol continues to carry a black box warning on QT prolongation, the following review demonstrates an overall favorable safety profile with respect to its use for sedation of agitated patients in the ED.

A Class II, multicenter, randomized, double-blind, placebo-controlled trial by Chan et al[9] found that antipsychotics alone or antipsychotics in combination with midazolam are superior to midazolam alone. Patients were treated with intravenous administration of placebo, droperidol 5 mg, or olanzapine 5 mg. Patients also received intravenous midazolam (2.5 mg if <50 kg or 5 mg if ≥50 kg) with incremental doses up to 20-mg per physician discretion until adequate sedation was achieved. Time to adequate sedation was significantly shorter for both the droperidol (21.3 minutes) and olanzapine (14 minutes) groups versus placebo (67.8 minutes), suggesting that antipsychotics alone or antipsychotics with midazolam are superior to midazolam alone. Whereas the midazolam alone (placebo) group required higher total doses of midazolam to achieve adequate sedation, there was no significant difference in initial midazolam administration compared with the droperidol and olanzapine groups. No differences were reported in adverse events, total length of stay, disposition destination, or QTc prolongation among the 3 groups.[9]

In another Class II, randomized, blinded study, Taylor et al[10] compared the effect of 5-mg intravenous droperidol plus 5-mg intravenous midazolam, 10-mg intravenous droperidol alone, or 10-mg intravenous olanzapine alone in agitated patients. The researchers found that 75% of patients treated with droperidol plus midazolam were adequately sedated at 10 minutes compared with 50% of patients treated with droperidol alone and 49% of patients treated with olanzapine. Whereas there was no significant difference between droperidol and olanzapine, droperidol plus midazolam was superior to either antipsychotic alone.[10]

Although the preponderance of studies found antipsychotics to be the preferred single agent, conflicting evidence occurred in 1 Class II, multicenter, randomized, blinded study by Chan et al,[11] where midazolam alone resulted in faster time to sedation compared with olanzapine or haloperidol. In this study, patients presenting with severe acute agitation were randomized to receive 5 mg of intramuscular midazolam, olanzapine, or haloperidol. Median time to sedation was 8.5 minutes (95% confidence interval [CI] 8.5 to 59.5), 11.5 minutes (95% CI 7.5 to 67), and 23.0 minutes (95% CI 6 to 53.5) for midazolam, olanzapine, and haloperidol, respectively. Both haloperidol and olanzapine were statistically inferior to midazolam as measured by time to sedation. The overall adverse event rate was similar between groups.[11]

A Class III meta-analysis by Korczak et al,[1] which included 7 studies with a total of 1,135 patients, found that combination therapy with antipsychotic and benzodiazepine medications produced more rapid sedation than benzodiazepines alone and required fewer repeat doses. The included studies were not powered to evaluate the frequency of adverse effects.[1]

In a Class III study by Battaglia et al[12] of 98 ED patients presenting with agitation attributed to a psychiatric cause, patients who received a combination of haloperidol and lorazepam had lower agitation scores at 1 hour than those who received lorazepam alone. The agitation scores for patients who received the combination were also lower than for those who received haloperidol alone, but this was not found to be statistically significant.[12] Of note, an additional Class III study by Isbister et al[3] that compared the time to adequate sedation achieved by the administration of 10-mg intramuscular midazolam with 10-mg intramuscular droperidol or a combination of both (5 mg each) found no significant differences between arms.

A Class III study by Thomas et al[13] compared 5-mg intramuscular and intravenous droperidol with 5-mg intramuscular and intravenous haloperidol. Patients who required physical restraint in the ED were randomized to receive droperidol or haloperidol. The route of administration was left to the discretion of the attending physician. The authors found that droperidol administration resulted in significantly lower combativeness at 10 minutes, 15 minutes, and 30 minutes. Overall, there was a significantly faster response to droperidol administration. No significant difference was found with respect to the route of administration and vital signs among the groups at each time interval. Of note, one patient who received haloperidol had a dystonic reaction the following day. No other adverse reactions were observed.[13]

If a single agent is utilized, several studies identify the superiority of antipsychotics over benzodiazepines. A Class III blinded, randomized trial from Australia in 2006 by Knott et al[2] provides evidence for the use of droperidol over midazolam. Patients were treated with either 5-mg intravenous midazolam or 5-mg intravenous droperidol followed by an additional dose every 5 minutes until adequate sedation was achieved. Analysis showed no significant difference in time to sedation. The authors concluded that midazolam and droperidol are equally effective, but the dosing of droperidol may not have been appropriate for comparison. The authors did find that 3 patients managed with midazolam required assisted ventilation compared with 0 in the droperidol group. There were no differences in the proportion of patients with prolonged QT intervals. Given equivalent efficacy, the side effect profile in this study favored droperidol over midazolam.[2]

Another double-blind, randomized trial by Martel et al[6] provided an additional Class III study supporting the use of antipsychotic medications over benzodiazepines. A total of 144 patients with acute agitation were treated with 5-mg intramuscular droperidol, 20-mg intramuscular ziprasidone, or 5-mg intramuscular midazolam. Agitation was measured using a validated scale in 15-minute increments. Significantly fewer patients treated with ziprasidone were adequately sedated at 15 minutes, whereas no difference was observed at 30 minutes. Significantly more patients were recurrently agitated and required rescue medication at 45 minutes in the midazolam group.[6]

A Class III, randomized, open-label trial by Richards et al[14] compared lorazepam (2-mg intravenous if <50 kg or 4-mg intravenous if >50 kg) with droperidol (2.5-mg intravenous if <50 kg or 5-mg intravenous if >50 kg) in an undifferentiated group of agitated ED patients. These patients had sympathomimetic toxicity, psychiatric illness, and alcohol-related agitation. At 5 minutes, the sedation profiles for both groups were similar. However, patients who received droperidol had lower sedation scores at each subsequent time interval, up to 60 minutes, and required fewer rescue medications.[14]

Among antipsychotic medications, droperidol appears to have a more rapid onset, a better safety profile, and requires less repeat dosing. In a recent Class III observational study of 1,257 patients by Cole et al, [15] there was no significant difference between intramuscular olanzapine and intramuscular droperidol with respect to time to sedation. However, patients who received olanzapine in this study were more likely to require additional medications for sedation than those who received droperidol.[15]

Another recent Class III, double-blinded, randomized controlled trial by Martel et al[16] compared 5-mg intramuscular droperidol, 10-mg intramuscular or 20-mg intramuscular ziprasidone, and 2-mg intramuscular lorazepam. Administration of 5-mg droperidol resulted in more patients being sedated at 15 minutes (16 of 25, 64%) than 10 mg of ziprasidone (7 of 28, 25%), 20 mg of ziprasidone (11 of 31, 35%), and 2 mg of lorazepam (9 of 31, 29%). Pairwise comparisons demonstrated that droperidol was more effective than the other medications, 39% (95% CI 3% to 54%) more effective compared with 20 mg of ziprasidone and 33% (95% CI 8% to 58%) more compared with lorazepam. Respiratory depression was also found to occur less often in the droperidol group. There were no cardiac dysrhythmias documented in any treatment group.[16]

An additional Class III single-site randomized, double-blinded study by Nobay et al[17] compared intramuscular midazolam 5 mg, lorazepam 2 mg, and haloperidol 5 mg. Of particular note, interim analysis of this study showed that lorazepam had a significantly longer time to sedation and awakening; thus, it was dropped from the study. The mean time to sedation was 18.3 (±14) minutes for midazolam and 28.3 (±25) minutes for haloperidol.

Compared with haloperidol, midazolam was also found to have a shorter time to arousal by 44.6 minutes (95% CI 9 to 80 minutes).[17]

A Class III study by Klein et al[18] found midazolam alone to work faster than haloperidol, ziprasidone, or olanzapine. This study compared intramuscular administration of haloperidol 5 mg and 10 mg, ziprasidone 20 mg, olanzapine 10 mg, and midazolam 5 mg. Midazolam resulted in a larger proportion of patients adequately sedated at 15 minutes when compared with haloperidol 5 mg (difference 30%; 95% CI 19% to 41%), haloperidol 10 mg (difference 28%; 95% CI 17% to 39%), and ziprasidone (difference 18%; 95% CI 6% to 29%).[18] The effect was less pronounced when comparing midazolam with olanzapine (difference 9%; 95% CI -1% to 20%).[18] The rate of adverse events such as extrapyramidal reaction, hypotension, hypoxemia, and intubation were similar in each group.

To summarize the above studies, the combination of parenteral droperidol and midazolam is likely the most effective option to treat severe agitation. Droperidol appears to be the superior antipsychotic; however, in situations in which droperidol is unavailable, other antipsychotics are effective. Atypical antipsychotics, in particular olanzapine, appear to have a more favorable profile than other available traditional antipsychotics such as haloperidol. Among benzodiazepines, midazolam appears to have a more rapid onset than lorazepam. When a single agent is used, the current body of evidence suggests that antipsychotics are preferred over benzodiazepines, as benzodiazepines may have more adverse side effects and require more rescue medication administration though time to sedation for droperidol, olanzapine, and midazolam are similar.

Ketamine

The N-methyl-D-aspartate receptor antagonist ketamine has been widely used in the ED for pain treatment at doses of 0.1 to 0.3 mg/kg intravenous, for procedural sedation at doses of 1 mg/kg intravenous or 3 to 5 mg/kg intramuscular, and for induction during intubation at a dose of 2 mg/kg intravenous. In the 2010s, the use of ketamine for the management of severe agitation became widespread in out-of-hospital and ED settings, most commonly employing doses similar to those utilized for procedural sedation.[19-35] Ketamine was thought to be an ideal agent for this purpose, given its rapid time to effective sedation: <2 minutes following intravenous administration and 2 to 10 minutes following intramuscular administration.[19-21,23,25-29,33] Compared with antipsychotic or benzodiazepine-based regimens, ketamine appears to provide faster and more reliable management of agitation following a single dose of medication, particularly in cases of intramuscular administration.

However, with increased use for severe agitation, discussion within the medical community has emerged regarding ketamine's safety profile. The use of ketamine to treat agitation carries an appreciable risk of laryngospasm (1% to 4%) and hypersalivation (up to 20%) with an infrequent need for intubation due to these adverse effects.[27-29,33] Reports of respiratory depression following intramuscular ketamine administration to treat agitation range from less than 2% to more than 20%.[21,29,30,33,36,37] Intubation rates vary widely (0% to 62%), although it is likely that patient, treating physician, and departmental factors, along with initial unfamiliarity with use of ketamine for management of agitation, resulted in intubations that may not have been truly reflective of the degree of respiratory distress.[22-24,26,27,29,30,36-41] For example, in a 2016 study by Olives et al,[24] the odds ratio for intubation was 2.57 (95% CI 1.05 to 6.27) during the overnight shift compared with patients presenting during the day shift, and individual physician intubation rates varied from 0% to 100%. Additional concerns regarding labile hemodynamics (either elevated blood pressure/pulse rate or hypotension) and emergence phenomenon have not been found to be clinically meaningful when ketamine is employed to treat severe agitation. Finally, despite widely publicized fatal incidents temporally related to out-of-hospital ketamine administration administered to treat severe agitation, deaths due to ketamine appear to be rare. In a prospectively collected out-of-hospital registry that included 3,795 patients receiving intramuscular/intravenous ketamine with a median dose of 3.7 mg/kg for altered mental status/behavioral reasons, ketamine could not be excluded as the cause of death in only 4 patients.[42]

Unfortunately, the body of literature informing the use of ketamine to treat severe agitation is uniformly flawed. No studies of sufficient quality were identified to inform a recommendation for or against the use of ketamine for this purpose in the out-of-hospital or ED setting. Nevertheless, the rapid time to effective treatment and reliable degree of sedation following intramuscular administration in cases of severe agitation mean that ketamine remains an option in situations where the safety of the patient, bystanders, and staff necessitate a more rapid and reliable treatment of agitation than provided by other therapeutic options. It is possible, but not certain, that this medicine carries with it a higher rate of respiratory compromise compared with alternative agents.[23,26,28,33,34,43] Close observation for potential respiratory and hemodynamic compromise following administration is essential with initiation of

continuous ECG monitoring, pulse oximetry, and continuous waveform capnography as soon as the situation safely allows.

Of note, the evidence surrounding emergency physician use of ketamine for procedural sedation was reviewed in a 2014 clinical policy.[44] Ketamine is widely and safely administered for procedural sedation in EDs, and emergency physicians are already familiar with the drug's desired effects and potential complications. As such, the authors made a consensus recommendation for its use for sedation of agitated patients in the ED.

Other Agents

Whereas the vast majority of the literature has focused on the use of antipsychotics and benzodiazepines for the management of acute agitation in the out-of-hospital and ED settings, other modalities have been studied and may be considered. This brief review is included to frame an understanding of alternatives to the more traditional medications described above.

One Class III study by Asadollahi et al[45] investigated the efficacy of intravenous sodium valproate versus intramuscular haloperidol in the treatment of acute agitation in the ED. This single university hospital double-blind parallel group included agitated adult patients as confirmed by an attending emergency physician or a psychiatrist. Of note, physiologic causes of agitation were excluded. The primary outcome was agitation measured at baseline and 30 minutes after injection using 3 different agitation scales. The valproate study arm (80 patients) received 20 mg/kg intravenous valproate compared with 5-mg intramuscular haloperidol in the second haloperidol study arm (80 patients). No significant difference was found in the sedation scores between valproate and haloperidol arms with regard to decreased levels of agitation. The endpoint change in efficacy measures at 30 minutes after the first injection (intention-to-treat, N=160) was larger for the valproate-treated patients (4.73±1.93) compared with haloperidol-treated patients (5.45±2.09). The authors did note that the haloperidol treatment group had a significantly larger proportion of patients who showed at least one adverse event (37 of 80, 46.2%) than the valproate treatment group (24 of 80, 30%), with intense sedation 30 minutes after intervention representing the most frequent adverse event. Of note, they also found a vomiting and headache incidence of 16.2% (13 of 80) and 11.2% (9 of 80), respectively, in the valproate treatment group compared with none in the haloperidol group. The authors conclude that valproate may be a viable alternative agent for treatment of agitation; however, the side effects of headache, vomiting, and teratogenicity may limit its utility.

Two other Class III studies evaluated supplementing intramuscular haloperidol with additional agents for the treatment of agitation.[46,47] In the first Class III study, Raveendran et al[46] utilized intramuscular promethazine in addition to haloperidol compared with intramuscular olanzapine with the intent that the addition of promethazine will reduce the acute dystonic reactions sometimes seen with haloperidol. In this single-site trial performed in a psychiatric ED in south India, patients with acute agitation were randomized to receive either intramuscular olanzapine or intramuscular haloperidol plus promethazine. Both were equally effective for the primary outcome of tranquillization or sedation at 15 minutes and 4 hours. Additional findings demonstrated that the combination of haloperidol plus promethazine sedated patients more rapidly, and the effects lasted longer. Seventeen percent more patients given olanzapine compared with haloperidol plus promethazine required repeated physician involvement for increased aggression (number needed to treat=6, 95% CI 4 to 13), and additional medications were required to manage aggression over the 4 hours of the study period in 20% more patients who were administered olanzapine than those given haloperidol plus promethazine (number needed to treat=6; 95% CI 3 to 10), 65 of 150 (43%) versus 31 of 150 (21%); relative risk, 2.07; 95% CI 1.43 to 2.97).[45] The authors concluded that both olanzapine and haloperidol plus promethazine provided effective sedation with similar adverse events, but haloperidol plus promethazine resulted in longer sedation over 4 hours without the need for additional sedative agents.

In the second Class III study, the TREC (tranquilização rápida-ensaio clínico [rapid tranquillisation-clinical trial]) Collaborative Group (2003)[47] compared intramuscular midazolam with the combination of intramuscular haloperidol and promethazine. This pragmatic randomized clinical trial enrolled aggressive or agitated patients with mental illness in 3 psychiatric EDs in Brazil. The primary outcome was patient tranquility or sedation at 20 minutes. Numerous secondary outcomes were evaluated: patients tranquil or asleep at later intervals, patients restrained or given extra drugs within 2 hours, and severe adverse events. With regard to the primary outcome, 134 of 151 (89%) of patients given midazolam were tranquil or asleep after 20 minutes compared with 101 of 150 (67%) of patients given haloperidol plus promethazine (relative risk 1.32; 95% CI 1.16 to 1.49). The midazolam study arm continued to demonstrate statistically and clinically significant superiority with 13% tranquil or asleep (relative advantage

Table 1. Summary of medications.*

Name	Class	Dosing	Mean Time to Sedation (Min)	Median Time to Sedation (Min)	Proportion of Patients Sedated at a Time Interval	Other
Droperidol	Antipsychotic	5-mg intramuscular (Cole 2021)[15] 10-mg intravenous (Taylor*)[10] 10-mg intramuscular (Isbister)[3] 5-mg intravenous (Knott)[2] 5-mg intramuscular (Martel 2021)[16]	— — — — —	16 (Cole 2021)[15] 11 (Taylor*)[10] 20 (Isbister)[3] 8 (Knott)[2] —	— 27% (5 min) 55% (10 min) (Taylor*)[10] 16.5% (5 min) (10 min not reported as not significant) (Knott)[2] 64% (15 min) (Martel 2021)[16]	*For the Taylor study,[10] if adequate sedation was not achieved at 5 min, an additional dose of droperidol 5 mg could be administered and repeated in 5 min as needed. Following this, additional, open-label sedation could be administered at the discretion of the treating physician.
Haloperidol	Antipsychotic	5-mg intramuscular (Chan 2021)[11] 5-mg intramuscular (Nobay)[17]	— 28.3 (Nobay)[17]	23 (Chan 2021)[11] —		
Single Agents						
Olanzapine	Atypical antipsychotic	5-mg intramuscular (Chan 2021)[11] 10-mg intravenous (Taylor*)[10] 10-mg intramuscular (Cole 2021)[15]	— — —	11.5 (Chan 2021)[11] 11 (Taylor*)[10] 17.5 (Cole 2021)[15]	— 35% (5 min) 59% (10 min) (Taylor*)[10] —	*For the Taylor study,[10] if adequate sedation was not achieved at 5 min, an additional dose of olanzapine 5 mg could be administered and repeated in 5 min as needed. Following this, additional, open-label sedation could be administered at the discretion of the treating physician.
Ziprasidone	Atypical antipsychotic	10-mg intramuscular (Martel 2021)[16] 20-mg intramuscular (Martel 2021)[16]	— —	— —	25% (Martel 2021)[16] 35% (Martel 2021)[16]	—
Lorazepam	Benzodiazepine	2-mg intramuscular (Martel 2021)[16] 2-mg intramuscular (Nobay*)[17]	— 32.2 (Nobay*)[17]	— —	29% (Martel 2021)[16]	*Nobay[17] dropped lorazepam from the protocol because at interim analysis, lorazepam patients had significantly longer time to sedation and awakening.

Table 1. Continued.

Name	Class	Dosing	Mean Time to Sedation (Min)	Median Time to Sedation (Min)	Proportion of Patients Sedated at a Time Interval	Other
Midazolam	Benzodiazepine	2.5- to 5-mg intravenous (Chan 2013*)[9]	67.8 (Chan 2013)[9]	10 (Chan 2013)[9]	—	*For the 2013 Chan study,[9] midazolam was dosed at 2.5 mg or 5 mg for estimated weights of <50 kg and ≥50 kg, respectively. *For the 2003 TREC Collaborative Study,[47] 124 patients were given 15-mg intramuscular, and 26 were given 7.5-mg intramuscular.
		5-mg intramuscular (Chan 2021)[11]	—	8.5 (Chan 2021)[11]	—	
		10-mg intramuscular (Isbister)[3]	—	24 (Isbister)[3]	—	
		5-mg intravenous (Knott)[2]	—	6.5 (Knott)[2]	44.6% (5 min) (Knott)[2]	
		5-mg intramuscular (Nobay)[17]	18.3 (Nobay)[17]	—		
		7.5- to 15-mg intramuscular (TREC 2003*)[47]	—	—	89% (20 min) (TREC 2003)	
Combinations						
Droperidol+ midazolam	Antipsychotic+ benzodiazepine	5-mg IV droperidol+2.5- to 5-mg IV midazolam boluses (Chan 2013*)[9]	21.3 (Chan 2013)[9]	6 (Chan 2013)[9]	—	*For the 2013 Chan study,[9] midazolam was dosed at 2.5 mg or 5 mg for estimated weights of <50 kg and ≥50 kg, respectively. *For the Taylor study,[10] if adequate sedation was not achieved at 5 min, an additional dose of midazolam 5 mg could be administered and repeated in 5 min as needed. Following this, additional, open-label sedation could be administered at the discretion of the treating physician.
		5-mg IV droperidol+5-mg IV midazolam (Taylor)[10]	—	5 (Taylor)[10]	66% (5 min) 88% (10 min) (Taylor*)[10]	
		5-mg IM droperidol+5-mg IM midazolam (Isbister)[3]	—	25 (Isbister)[3]		
Olanzapine+ midazolam	Atypical antipsychotic+ benzodiazepine	5-mg IV olanzapine+2.5 to 5-mg midazolam boluses (Chan 2013*)[9]	14 (Chan 2013)[9]	5 (Chan 2013)[9]	—	*For the 2013 Chan study,[9] midazolam was dosed at 2.5 mg or 5 mg for estimated weights of <50 kg and ≥50 kg, respectively.

*Ketamine dosing is not included in this table, as none of the ketamine papers assessed for this policy met the quality criteria for inclusion.

1.13; 95% CI 1.01 to 1.26) at 40 minutes. After 1 hour, about 90% of both groups were tranquil or asleep. It is important to note that in the midazolam study arm, 15-mg intramuscular midazolam was predominantly used, which is a higher dose than other studies reviewed. Notable adverse events occurring in each group include one patient given midazolam who had transient respiratory depression and one patient given haloperidol-promethazine who had a grand mal seizure. The authors conclude that both treatments provide effective sedation with midazolam, demonstrating more rapid onset of sedative effects.

Summary

For patients with acute agitation in the ED, a combination of droperidol and midazolam is preferred given the improved time to sedation and side effect profile. If a single agent must be given, droperidol is preferred. If droperidol is not available, use an atypical antipsychotic. In cases where safety calls for the use of ketamine, it must be done in a setting where staff can institute immediate hemodynamic monitoring and advanced airway management when needed.

With respect to special populations, we were unable to make specific recommendations for sedating agents in older patients (more than the age of 65 years) because there was a lack of studies that looked specifically at this patient population. Out-of-hospital studies were included in our literature search; however, none of these studies were determined to be methodologically adequate to inform a specific recommendation, regardless of the agent(s) studied.

Future Research

Available research on the management of severe agitation is impacted by the urgent and dangerous nature of the presenting complaint, degree of mental status changes, and emergent setting of patient presentations. These factors limit the robustness of the literature base and make studies of novel treatment options fraught with difficulty. Furthermore, evidence-based regimens to treat severe agitation typically utilize generic drugs, such as droperidol, midazolam, and ketamine, making pharmaceutical company sponsorship of any trials involving these drugs unlikely. Given these limitations, future impactful trials will likely require governmental or organizational grant funding, standardization of inclusion criteria, meaningful endpoints for treatment of severe agitation, and methods of dealing with informed consent/research ethics in a vulnerable patient population defined by a severe degree of agitation. High quality research should focus on the following:

- Examining the effectiveness of nonpharmaceutical interventions.
- Examining the optimal use of oral and sublingual interventions.
- Determining the efficacy, safety, ideal dosing regimen, and most appropriate situations for the use of ketamine to treat severe agitation.
- Directly comparing the efficacy, safety, and ideal dose of leading options for treatment of severe agitation, such as droperidol (particularly compared directly with haloperidol, and midazolam at lower doses), atypical antipsychotics, midazolam, and ketamine (and combinations thereof).
- Determining the efficacy, safety, ideal dosing regimen, and most appropriate situations for the use of adjunct medications (such as diphenhydramine, prochlorperazine, and others) in combination with other sedating agents.
- Identifying a standardized scale to assess agitation in the ED.
- Identifying out-of-hospital treatments for severe agitation.
- Identifying the safest and most efficacious treatment for acute agitation in older patients.
- Exploring disparities related to race, ethnicity, and language that influence the treatment of severe agitation.

Relevant industry relationships: There were no relevant industry relationships disclosed by the subcommittee members for this topic.

Relevant industry relationships are those relationships with companies associated with products or services that significantly influence the specific aspect of disease addressed in the critical question.

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Appendix E1. Literature classification schema.*

Design/Class	Therapy†	Diagnosis‡	Prognosis§
1	Randomized, controlled trial or meta-analysis of randomized trials	Prospective cohort using a criterion standard or meta-analysis of prospective studies	Population prospective cohort or meta-analysis of prospective studies
2	Nonrandomized trial	Retrospective observational	Retrospective cohort Case control
3	Case series	Case series	Case series

*Some designs (eg, surveys) will not fit this schema and should be assessed individually.
†Objective is to measure therapeutic efficacy comparing interventions.
‡Objective is to determine the sensitivity and specificity of diagnostic tests.
§Objective is to predict outcome, including mortality and morbidity.

Appendix E2. Approach to downgrading strength of evidence.

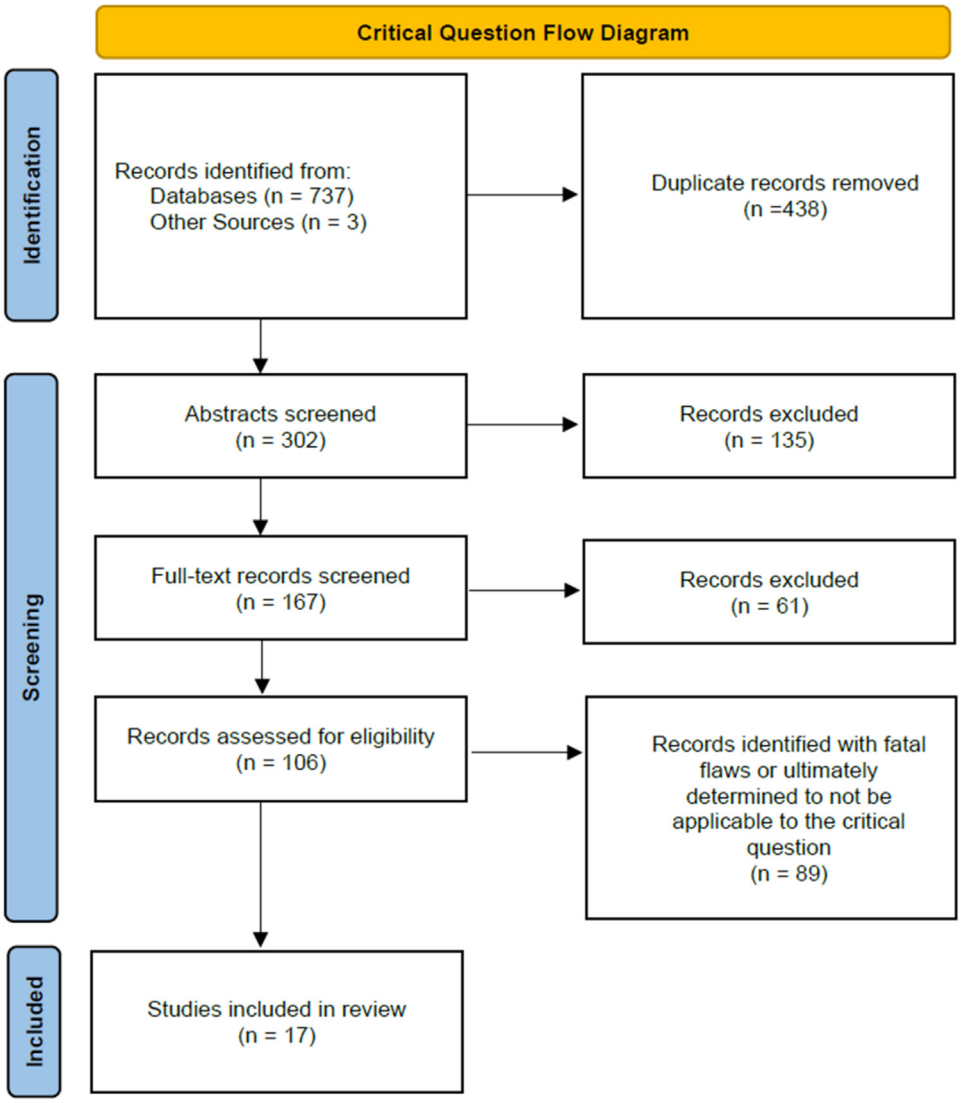
	Design/Class		
Downgrading	**1**	**2**	**3**
None	I	II	III
1 level	II	III	X
2 levels	III	X	X
Fatally flawed	X	X	X

Appendix E3. Likelihood ratios and number needed to treat.*

LR (+)	LR (–)	
1.0	1.0	Does not change pretest probability
1 to 5	0.5 to 1	Minimally changes pretest probability
10	0.1	May be diagnostic if the result is concordant with pretest probability
20	0.05	Usually diagnostic
100	0.01	Almost always diagnostic even in the setting of low or high pretest probability

LR, likelihood ratio.
*Number needed to treat (NNT): number of patients who need to be treated to achieve 1 additional good outcome; NNT = 1/absolute risk reduction×100, where absolute risk reduction is the risk difference between 2 event rates (ie, experimental and control groups).

APPENDIX E4. PREFERRED REPORTING ITEMS FOR SYSTEMATIC REVIEWS AND META-ANALYSES FLOW DIAGRAMS[7].



Evidentiary Table.

Study and Year Published	Class of Evidence	Setting and Study Design	Methods and Outcome Measures	Results	Limitations and Comments
Chan et al (2013)[9]	II	Multicenter, randomized, double-blind, placebo-controlled, double-dummy, clinical trial in 3 large metropolitan EDs	Computerized block randomization to: control (placebo-droperidol, placebo-olanzapine), droperidol group (droperidol 5 mg, placebo-olanzapine), olanzapine group (olanzapine 5 mg, placebo-droperidol); each patient then received IV midazolam 2.5 mg (if <50 kg) or 5 mg (if ≥50 kg), then incremental doses until sedation achieved, up to 20 mg per physician discretion; sedation measured on 6-point scale; primary outcome: time to adequate sedation, proportion adequately sedated at 5 and 10 min; secondary outcomes: need for additional parenteral sedative drugs to achieve adequate initial sedation, need for resedation within 60 min of initial adequate sedation, need for resedation from 60 min after initial adequate sedation until ED discharge, total midazolam dose administered in 60 min following initial adequate sedation, total midazolam dose from 60 min after initial sedation until ED discharge, QTc, length of stay, and adverse events	Time to sedation significantly shorter for droperidol (21.3 min) and olanzapine (14 min) groups vs placebo (67.8 min); differences in medians for times to sedation: control and droperidol 4 min (95% CI 1-6 min), control and olanzapine 5 min (95% CI 1-6 min); survival analysis showed difference in proportion of patients sedated at any point, hazard ratios for droperidol 1.61 (95% CI 1.23-2.11); hazard ratios for olanzapine 1.66 (95% CI 1.27-2.17); no difference in requirement of additional doses to reach adequate sedation, but more in control group needed sedation in the first 60 min and from then until discharge; no significant difference in initial dose of midazolam given, although control did require higher median cumulative dose of midazolam to achieve initial sedation; no difference in adverse events, length of stay, disposition destination or QTc interval	Combination of droperidol plus olanzapine with midazolam appears to be superior; well-executed clinical trial; appears to be some minor imbalances in study groups; possible selection bias

Evidentiary Table (continued).

Study and Year Published	Class of Evidence	Setting and Study Design	Methods and Outcome Measures	Results	Limitations and Comments
Taylor et al (2017)[10]	II	Prospective randomized double-blinded triple-dummy clinical trial of agitated patients in 2 inner-city EDs	Patients aged 18-65 y requiring IV medication for sedation for acute agitation; randomized to droperidol plus midazolam, droperidol alone, or olanzapine; primary outcome included adequate sedation within 10 minutes of first dose of medication	N=361; droperidol plus midazolam: N=120 (118 analyzed) 75% sedated at 10 min; droperidol: N=117 (111 analyzed) 50% sedated at 10 min; olanzapine: N=124 (120 analyzed) 49% sedated at 10 min; difference: 25% (95% CI 12%-38%)	Droperidol plus midazolam was superior to droperidol alone or olanzapine; limited by potential imbalance and lack of generalizability; minimal loss to follow-up or not analyzed
Chan et al (2021)[11]	II	Multicenter, double-blinded, randomized, active-controlled pragmatic trial across 6 public Hong Kong EDs	Patients received 5-mg IM midazolam, olanzapine, or haloperidol; primary outcome was time to achieve adequate sedation at 10, 20, 30, 45 and 60 min; secondary outcomes included proportion of patients receiving additional study drug or other medication to achieve sedation, proportion of patients with QTc interval prolongation, adverse events with study medications, proportion of patients with sedation score of (0) or observed sleep, and ED length of stay	2,423 patients were screened, 206 received study drugs and 167 provided informed consent; 56 patients received midazolam, 54 patients received olanzapine, and 57 patients received haloperidol; median time to sedation estimated by the Kaplan-Meier function was 8.5 (95% CI 8.5-59.5, IQR 8), 11.5 (95% CI 7.5-67.0, IQR 30), and 23 min (95% CI 6.0-53.5, IQR 21) for midazolam, olanzapine, and haloperidol, respectively; at 10 min after the initial dose, 52%, 34%, and 21% were adequately sedated in the midazolam, olanzapine, and haloperidol arms, respectively; significant differences were detected in the Kaplan-Meier curves for midazolam compared with olanzapine (P=.03) and haloperidol (P=.002); overall, the adverse event rate was similar for midazolam, olanzapine, and haloperidol at 4%, 6%, and 5%, respectively	Groups were balanced at baseline; 39 of 206 patients excluded postrandomization and not included in the analysis; study not powered to compare rates of adverse outcomes

Evidentiary Table (continued).

Study and Year Published	Class of Evidence	Setting and Study Design	Methods and Outcome Measures	Results	Limitations and Comments
Korczak et al (2016)[1]	III	Systematic literature review and meta-analysis	Meta-analyses for pairwise comparisons of drug class (benzodiazepine, antipsychotic, or combination) were carried out for each outcome: proportion sedated, need for repeat sedation, and adverse events; analyzed whether a class or combination of drugs (antipsychotics, benzodiazepines or combination) was 1) more effective than another as measured by the proportion of patients sedated within a specific timeframe, and the need for repeat sedation and 2) safer than another as measured by the number and type of reported adverse events; graded final papers with the Jadad Score	7 included articles; proportion sedated at 15-20 min (4 of 7 studies): antipsychotics vs benzodiazepines (3 studies); overall, there was no difference between classes in the proportion of patients sedated at 15 to 20 min (RR=0.88; 95% CI 0.70-1.10; *P*=.25); benzodiazepines vs combination therapy (2 studies), a significantly higher proportion of patients were sedated with combination therapy (RR=1.31; 95% CI 1.15-1.49; *P*<.0001); antipsychotics vs combination therapy (1 study), not analyzed further; need for repeat sedation: (4 studies); antipsychotics vs benzodiazepines, antipsychotics were found to clearly be more effective, as fewer repeat doses needed to be given (RR=0.49; 95% CI 0.36-0.67; *P*<.0001); benzodiazepines vs compared with combination therapy (2 studies), combination therapy requires less repeat sedation than when benzodiazepines were given alone (RR=0.64; 95% CI 0.48 to 0.85; *P*=.002); antipsychotics vs combination (1 study), not analyzed further; adverse events: antipsychotics vs benzodiazepines (6 articles); the overall trend slightly favored antipsychotics (RR=0.85; 95% CI 0.59-1.23; *P*=.38); benzodiazepines vs combination therapy, risk of any adverse event is significantly lower with combination therapy (RR=0.63; 95% CI 0.42-0.97; *P*=.03); respiratory adverse events were the most common in the benzodiazepine group; antipsychotics vs combination therapy (2 studies) with no difference (RR=1.12; 95% CI 0.61-2.04; *P*=.71)	Results support findings from individual/included studies

Evidentiary Table (continued).

Study and Year Published	Class of Evidence	Setting and Study Design	Methods and Outcome Measures	Results	Limitations and Comments
Battaglia et al (1997)[12]	III	Multicenter, prospective, double-blinded trial; ED patients with psychosis and behavioral dyscontrol (agitated, aggressive, destructive, assaultive, or restless behavior) with Brief Psychiatric Rating Scale score ≥5 *Excluded patients with "clinically obvious" alcohol intoxication (defined) and allergic hypersensitivity, central nervous system depression, delirium, neuroleptic malignant syndrome, airway obstruction, severe hypotension or hypertension, acute narrow angle glaucoma, and treatment with a benzodiazepine or neuroleptic in the previous 24 h	Randomized to 2-mg IM lorazepam, 5-mg IM haloperidol or both; outcome measures: assessed hourly on modified Brief Psychiatric Rating Scale, Agitated Behavior Scale, and Clinical Global Impressions scale	98 patients enrolled; all groups had lower scores than baseline at reassessment; Agitated Behavior Scale: patients receiving combination (C) had lower scores at 1 h than those who received lorazepam (L) alone (statistically significant) or haloperidol (H) alone (not statistically significant), C<L P=.014, C<H P=.064, H<L P=.426; Modified Brief Psychiatric Rating Scale: statistically significant at hours 2 and 3; at hour 3: C<L P=.041; C<H P=.016, H<L P=.98; asleep at 3 h: L>H P=.013, C>H P=.026, (if awake at 3 h, more patients in lorazepam and combo groups had improved); adverse events: extrapyramidal syndrome (higher in haloperidol than combo or lorazepam), ataxia, dizziness, dry mouth, speech disorder; no statistically significant difference identified among groups although note extrapyramidal syndrome in 20% of haloperidol vs 6% of combo and 3% of lorazepam	Evaluation and treatment guided by "ED psychiatrist"; psychiatric patients only; at least somewhat differentiated

Evidentiary Table (continued).

Study and Year Published	Class of Evidence	Setting and Study Design	Methods and Outcome Measures	Results	Limitations and Comments
Isbister et al (2010)[3]	III	Blinded RCT in urban ED with 27,000 annual visits in Australia	Blinded RCT of IM droperidol (10 mg), midazolam (10 mg), and droperidol (5 mg)/midazolam (5 mg for acute agitation); primary outcome was the duration of agitation, defined as the time security staff were required; secondary outcomes included time until additional sedation was administered, staff and patient injuries, further episodes of agitation, and drug-related adverse effects	Droperidol (N=33) vs midazolam (N=29) vs combination (N=29); there was no difference in duration of agitation (20 min; IQR 11-37 min) for droperidol, 24 min (IQR 13-35 min) for midazolam, and 25 min (IQR 15-38 min) for the combination; additional sedation was required in 11 droperidol patients (33%, 95% CI 19%-52%), 18 midazolam patients (62%, 95% CI 42%-79%), and 12 (41%, 95% CI 24%-61%) in the combination group; no differences in secondary outcomes	The primary outcome, time security staff was required to be present, was arguably more patient-centered than sedation score (secondary outcome); small sample size resulted in wide confidence intervals for primary outcome (duration of agitation)
Thomas et al (1992)[13]	III	Randomized, double-blind, prospective study, patients requiring physical restraint in a university ED	21 patients received 5-mg haloperidol intramuscular; 26 patients received 5-mg droperidol intramuscular; 12 patients received haloperidol intravenous; 9 patients received 5-mg droperidol intravenous; outcome measure: patients rated on a 5-point combativeness scale and vital signs at 5, 10, 15, 30, and 60 min after medication administration	Significantly more rapid response to IM droperidol than to IM haloperidol (P=.03, ANOVA); IM droperidol decreased combativeness significantly more than IM haloperidol at 10 (P=.006), 15 (P=.01), and 30 (P=.04) min; no significant difference between the drugs when given by the IV route (β at the 5% confidence level, P=.78); no significant difference in vital signs among the groups; 1 patient who received IM haloperidol returned 18 h later with an acute dystonic reaction; no other adverse reactions were noted; the authors concluded that in equal IM doses (5 mg), droperidol results in more rapid control of agitated patients than haloperidol without any increase in undesirable side effects	

Evidentiary Table (continued).

Study and Year Published	Class of Evidence	Setting and Study Design	Methods and Outcome Measures	Results	Limitations and Comments
Knott et al (2006)[2]	III	Double-blind, RCT of IV midazolam vs droperidol in a large Australian university hospital; objective to compare IV midazolam and droperidol for onset of sedation; included patients aged 18-65 y agitated from mental illness, intoxication, or both and required chemical restraint per attending or senior resident; excluded patients with allergy to drug, pregnancy, and reversible causes agitation (hypoglycemia, hypoxia), alcohol intoxication	Intervention: midazolam or droperidol, 5-mg intravenous every, 5 min until sedation; randomization determined by random number tables; if <50 kg, patient received 2.5 mg; if more than the 20 mg in solution, then treating physician chose subsequent therapy; the primary endpoint: time to sedation score ≤2 on 6-point agitation scale (0 asleep, 5 violent and highly aroused, 4 highly aroused, 3 moderately aroused, 2 mildly aroused, 1 settled), median times to sedation, and proportions sedated at 5 and 10 min; secondary endpoints: need for sedation <60 min after adequate sedation, QTc interval on 12-lead ECG, and adverse event rates	74 patients midazolam; 79 patients droperidol; survival analysis: no difference time to sedation (hazard ratio 0.86; 95% CI 0.61-1.23, *P*=.4); median time to sedation: 6.5 min for midazolam (5 mg), 8 min for droperidol (10 mg), difference of 1.5 min, 95% CI 0-4 min; at 5 min, 33 of 74 midazolam patients (44.6%) adequately sedated, 13 of 79 droperidol patients (16.5%) adequately sedated (difference of 28.1%, 95% CI 12.9-43.4%, *P*<.001); at 10 min, 41 of 74 midazolam patients (55.4%) and 42 of 79 droperidol patients (53.2%) (difference of 2.2%, 95% CI 14.9-19.3%, *P*=.91); adverse events: 11 for midazolam and 10 for droperidol; 3 patients needing assisted ventilation and the 1 patient needing intubation were in midazolam cohort; no difference in proportion with long QT; concluded no difference in time of onset of adequate sedation of agitated patients using midazolam or droperidol but patients sedated with midazolam may have increased need for active airway management	Starts as Design 1, but potential for selection bias, not told number eligible not enrolled and they may have preference for pharmacologic treatment; inclusion: "marked agitation" requiring chemical restraint is not standardized and subjective; endpoint time to sedation subjective; number of protocol violations: 17 lost study packs and 11 enrolled; 18 to 65 y; conclusion that "midazolam and droperidol are equally effective sedating agents" is not true because not designed as an equivalence trial

Evidentiary Table (continued).

Study and Year Published	Class of Evidence	Setting and Study Design	Methods and Outcome Measures	Results	Limitations and Comments
Martel et al (2005)[6]	III	Prospective, randomized, double-blind trial; urban ED with annual census of 98,000 patients	Prospective, randomized, double-blind trial of acutely agitated ED patients requiring emergent sedation (convenience sample when researcher available); patients randomized to droperidol 5-mg, ziprasidone 20-mg, or midazolam 5-mg intramuscular at 0, 15, 30, 45, 60, and 120 min and included AMSS, oxygen saturations, and end-tidal carbon dioxide levels were measured	144 patients total (50 droperidol, 46 ziprasidone, 48 midazolam); more patients remained agitated in the ziprasidone group (28 of 46) at 15 min than in the droperidol (20 of 50) and midazolam (15 of 48) groups (P=.01); no difference in number of patients who remained agitated at the 30-min interval (ziprasidone, 14 of 46; droperidol, 6 of 50; midazolam, 11 of 48; P=.08); at 45 min, there were more agitated patients in the midazolam group (14 of 48) than in the droperidol (9 of 50) and ziprasidone (9 of 46) groups (P=.03); rescue medication for sedation was necessary in 38 of 144 patients (droperidol, 5 of 50; ziprasidone, 9 of 46; midazolam, 24 of 48; P<.05); midazolam and droperidol sedated faster than ziprasidone, but all generated equal adequate sedation at 30 min; no cardiac dysrhythmias were identified in any treatment group; respiratory depression that clinically required treatment with supplemental oxygen occurred in 21 of 144 patients (droperidol, 4 of 50; ziprasidone, 7 of 46; midazolam, 10 of 48; P=.20); no patients required endotracheal intubation	Recruitment under waiver of consent unless proxy was available (more representative population than studies requiring consent); unclear training of raters, interrater reliability; some side effects make it obvious which class of medication was administered but unclear how blinding was maintained; safety outcomes are underpowered to detect meaningful differences; older study; CIs not reported for clinical importance determination

Evidentiary Table (continued).

Study and Year Published	Class of Evidence	Setting and Study Design	Methods and Outcome Measures	Results	Limitations and Comments
Richards et al (1998)[14]	III	Prospective open-label randomized trial with agitated patients in an urban ED with annual census of approximately 65,000 patients	Acutely agitated patients were placed on cardiac, blood pressure, and pulse oximetry monitors; excluded patients with readily reversible cause (hypoglycemia, hypoxemia), hypotension, head trauma, anticholinergic toxidrome, pregnancy, among others including allergies); interventions: lorazepam (2-mg intravenous if <50 kg or 4-mg intravenous if >50 kg), droperidol (2.5-mg intravenous if <50 kg or 5-mg intravenous if >50 kg); assessed agitation with a 6-point scale; recorded at 0, 5, 10, 15, 30, and 60 min; repeat dosing at 30 min if agitation score ≥4	259 patients screened; 220 met eligibility criteria; 39 excluded; 18 had missing or incomplete data sheets (protocol violation/loss to follow-up); N=202 seen by 32 attendings; 100 patients received lorazepam and 102 patients received droperidol; agitation was attributed to methamphetamine toxicity in 146 patients (72%), cocaine toxicity in 28 (14%), psychiatric illness in 20 (10%), and ethanol withdrawal in 8 (4%); ethanol intoxication was present in 98 patients (49%); both drugs had similar sedation profiles at 5 min; patients receiving droperidol had significantly lower sedation scores at 10, 15, 30, and 60 min than lorazepam; more repeat doses of lorazepam were given (N=40) than droperidol (N=8) at 30 min	Operated under emergency consent for enrollment; sample more representative; included inebriated/intoxicated patients but excluded head trauma (somewhat representative of typical ED patients presenting in need of sedation); patients seemingly were put on monitors and had IVs placed with blood drawn before sedation, which might have biased selection toward less agitated patients; also excluded those sedated in the field; unblinded study, regardless profiles of the drug's side effects, hinder clinician blinding; agitation scale was validated, but it is not one that is used today nor validated according to modern approaches; CIs and adjustment for multiple comparisons not reported

Evidentiary Table (continued).

Study and Year Published	Class of Evidence	Setting and Study Design	Methods and Outcome Measures	Results	Limitations and Comments
Cole et al (2021)[15]	III	Prospective observational study at an urban Level I trauma center with more than 100,000 annual ED visits	IM droperidol or olanzapine for acute agitation; the treating physician determined the medication and dose; drug shortages made either olanzapine (July-September 2019) or droperidol (November 2019-March 2020) unavailable, creating a natural experiment; the primary outcome was time to adequate sedation, assessed by the AMSS, defined as time to AMSS score <1	1,257 patients (median age 42 y; 73% men); 538 received droperidol (median dose 5 mg) and 719 received olanzapine (median dose 10 mg); the majority of patients (1,086; 86%) had agitation owing to alcohol intoxication; time to adequate sedation was 16 min (IQR 10-30 min) for droperidol and 17.5 min (IQR 10-30 min) for olanzapine; no significant difference between groups in time to sedation; patients receiving olanzapine were more likely to receive additional medications for sedation (droperidol 17%; olanzapine 24%; absolute difference: 8% [95% CI -12%-3%]); no difference between drugs regarding adverse effects except for extrapyramidal adverse effects, which were more common with droperidol (N=6; 1%) than olanzapine (N=11; 0.1%)	Directly applicable study that was a natural experiment due to drug shortages; observational study with minor limitations; dosing was variable based on physician determination and symptoms; unclear how titration was done if at all; selection bias, only included patients who received only IM medications droperidol or olanzapine, although it was customary for some patients to receive other medications in combination; generalizability: study was done in a dedicated alcohol/agitation unit locked and with dedicated teams; missing values for alcohol were assumed to be 0 rather than imputed in the Cox models; propensity score matching might have been useful, though the natural experiment for drug availability likely obviated the need; 3 min difference to sedation for the power calculation seemed arbitrary; sensitivity analyses done with those receiving diphenhydramine in combination and those receiving IV droperidol and olanzapine

Evidentiary Table (continued).

Study and Year Published	Class of Evidence	Setting and Study Design	Methods and Outcome Measures	Results	Limitations and Comments
Martel et al (2021)[16]	III	Randomized, double-blind trial at an urban, academic hospital with an annual ED census of approximately 100,000	Randomized, double-blind trial of ED patients with acute agitation requiring parenteral sedation; patients were randomized to receive 5 mg of droperidol, 10 mg of ziprasidone, 20 mg of ziprasidone, or 2 mg of lorazepam intramuscular; recorded AMSS scores, nasal end-tidal carbon dioxide, and pulse oximetry at 0, 15, 30, 45, 60, 90, and 120 min as well as QTc durations and dysrhythmias; respiratory depression was defined as a change in end-tidal carbon dioxide consistent with respiratory depression or pulse oximetry<90%; the primary outcome was the proportion of patients adequately sedated (AMSS≤0) at 15 min	115 patients; primary outcome: adequate sedation at 15 min, droperidol administration was effective in 16 of 25 (64%) patients compared with 7 of 28 (25%) for 10 mg of ziprasidone, 11 of 31 (35%) for 20 mg of ziprasidone, and 9 of 31 (29%) for lorazepam; pairwise comparisons revealed that droperidol was more effective than the other medications with a 39% (95% CI 3-54%) higher response when compared to 20 mg of ziprasidone and a 33% (95% CI 8-58%) higher response when compared to lorazepam; no significant difference in need of additional rescue sedation; numerically, respiratory depression was lower with droperidol (3 of 25 [12%]) compared to 10 mg of ziprasidone (10 of 28 [36%]), 20 mg of ziprasidone (12 of 31 [39%]), or lorazepam (15 of 31 [48%]); 1 patient receiving 20 mg of ziprasidone required intubation to manage an acute subdural hematoma; no patients had ventricular dysrhythmias; QTc durations were similar in all groups	Droperidol resulted in more rapid sedation than ziprasidone or lorazepam; all were safe

Evidentiary Table (continued).

Study and Year Published	Class of Evidence	Setting and Study Design	Methods and Outcome Measures	Results	Limitations and Comments
Nobay et al (2004)[17]	III	Study design: single-site, urban randomized, prospective, double-blind convenience trial; consent from patient/family; included patients physically threatening to themselves/staff, or severely disruptive; all initially physically restrained; excluded if allergic, hypotensive, >140 beats/min, respiratory rate >40 breaths/min >18, age <18 y, pregnant; outcome: time to sedation, time to arousal	Computer-generated randomization code; research assistant, administering physician, and patient blinded to drug delivered; randomized to IM midazolam 5 mg, lorazepam 2 mg, or haloperidol 5 mg; sedation judged to be adequate if 3 on a 3-point scale that was modified from study by Thomas et al[14] (not validated), 1=violent, 2=decreasing agitation, 3=no agitation; arousal=waking up to verbal commands, able to count backward, and follow simple commands; rescue drugs administered at discretion of treating physician; interim analysis performed; sample size not calculated a priori; corrected for Bonferroni only if $P<.05$	Included 111 severely agitated and violent patients (lorazepam=27, midazolam=42, haloperidol=42); interim analysis after 95 patients showed that lorazepam had a statistically significant longer time to sedation and awakening and was dropped from randomization; mean time to sedation was 18.3 (±14) min for midazolam, 28.3 (±25) min for haloperidol, 32.2 (±20) min for lorazepam; mean difference between midazolam and lorazepam was 13 min (95% CI 5.1-22.8 min) between midazolam and haloperidol was 9.9 min (95% CI 0.5-19 min) time to arousal was 81.9 min for midazolam, 126.5 min for haloperidol, 217.2 min for lorazepam; mean difference in time to awakening: midazolam and lorazepam, 135.3 min (95% CI 89-182 min) midazolam and haloperidol, 44.6 min (95% CI 9-80 min) no difference in vital signs; 1 patient administered haloperidol became hypotensive; another patient was apneic but recovered; study concluded midazolam has significant shorter time to sedation and arousal than lorazepam or haloperidol	Starts as Design 1, but convenience sample, no a priori sample size calculation, interim analysis does not appear to have been planned, stopped lorazepam enrollment halfway through study, used nonvalidated sedation scale and awakening assessment, dosing not weight based, Bonferroni correction only used if $P<.05$

Evidentiary Table (continued).

Study and Year Published	Class of Evidence	Setting and Study Design	Methods and Outcome Measures	Results	Limitations and Comments
Klein et al[18] (2018)	III	Observational study with agitation treatment protocol that was rotated across the study drugs using 3-week blocks; location was a large Level I trauma center, single-center inner-city hospital	Haloperidol 5 mg, ziprasidone 20 mg, olanzapine 10 mg, midazolam 5 mg, and haloperidol 10 mg were administered as part of prespecified medication blocks (all consecutive, and each lasting 3 wks, and each administered intramuscularly); the AMSS was used as the validated agitation scale; the primary outcome was AMSS score at 15 min after medication administration, evaluated as the proportion of patients adequately sedated (defined as AMSS <1); secondary outcomes was median difference in AMSS from baseline at 15 min, rescue medications administered (before and after adequate sedation achieved), time to adequate sedation, and adverse events	Of 3,443 patients screened, 737 patients were enrolled between June and October 2017 (median age 40 y; 72% men); midazolam resulted in a higher proportion of patients adequately sedated at 15 min (AMSS <1) compared with ziprasidone (difference 18%; 95% CI 6%-29%), haloperidol 5 mg (difference 30%; 95% CI 19%-41%), haloperidol 10 mg (difference 28%; 95% CI 17% to 39%), and olanzapine (difference 9%; 95% CI –1% to 20%)	Design; a high proportion of patients were intoxicated from alcohol compared to other studies with large psychiatric diagnosis and/or illicit drug use

Evidentiary Table (continued).

Study and Year Published	Class of Evidence	Setting and Study Design	Methods and Outcome Measures	Results	Limitations and Comments
Asadollahi et al[45] (2015)	III	Randomized, double-blind parallel group trial at a single metropolitan university-affiliated hospital; objective: compare efficacy of valproate vs haloperidol in decreasing agitation in ED; inclusion: agitated adult, classification confirmed by ED attending/ psychiatrist; exclusion: physiologic agitation (hypoxia/hypoglycemia) , systolic blood pressure ≤90 mmHg, pregnancy, breast feeding, liver disease or uncontrolled diabetes, head trauma, neuroleptic malignant syndrome and seizure; informed consent from parent/legal guardian	Outcome was agitation measured at baseline and 30 min after injection on ACES item scale with 9 anchor points where 1=severely agitated, 8=deep sleep, 9=unarousable, and a 1 point difference would be clinically important; the Positive and Negative Syndrome Sale-Excited Component subscale 1 through 7, where 7 is extremely severe agitation); compared differences in baseline with postintervention ACES score within a single patient and between study arms for placebo vs haloperidol vs placebo vs valproate; intended-to-treat analysis	80 patients received 20 mg/kg IV valproate vs 5 mg IM haloperidol; ACES between baseline and 30 min was 4.7 (standard deviation 1.9) for valproate vs 5.5 (standard deviation 2.1) for haloperidol; haloperidol associated with more sedation (36.2% vs 2.5%) and extrapyramidal symptoms (8.7% vs 0%); neither duration of time nor proportion needing restraints differed (85% in valproate vs 76.2% in haloperidol); they conclude that valproate IV is as effective (not an equivalence of noninferiority design)	Starts as Design 1; although we know baseline ACES was −1.6 (standard deviation 0.8) for valproate and 1.8 (standard deviation 0.8) for haloperidol, there was an unknown proportion of severely agitated individuals (as specified in our question or with an ACES score of 1); no incidence rate ratio score assessment postintervention; conclusions not supported by results; not an equivalence or noninferiority trial and claim that valproate did better on the ACES when they report a difference from baseline rather than the final ACES to know how sedated patients were; more difference in ACES the haloperidol arm implies haloperidol resulted in calmer patients but the proportion that started out as severely (ACES=1) agitated remains unclear; limitations do not mention the fact that an IV may be dangerous to place in a severely agitated patient; single-center; only gave 5-mg IM haloperidol, and valproate would need an intravenous; small sample

Evidentiary Table (continued).

Study and Year Published	Class of Evidence	Setting and Study Design	Methods and Outcome Measures	Results	Limitations and Comments
Raveendran et al[46] (2007)	III	Single-site pragmatic RCT; psychiatric ED in Vellore, south India	Adult patients with acute agitation; randomized to either IM olanzapine or IM haloperidol plus promethazine; primary outcomes were the proportion of patients who were "tranquil or asleep" at 15 min and 240 min; secondary outcomes were the proportion of patients who were "tranquil, asleep, restrained, absconding, or clinically improved" at 15, 30, 60, 120, and 240 min; additional medical interventions and adverse effects over 4 h; and compliance with oral drugs and adverse effects over 2 wks	N300, 150 randomized to each group; follow-up data available for 298 (99%); both treatments resulted in similar proportions of people being assessed as "tranquil or asleep" at 15 minutes (131 of 150 (87%) for olanzapine and 136 of 150 (91%) for haloperidol plus promethazine; RR= 0.96 (95% CI 0.34-1.47)); more patients who received olanzapine than those who received haloperidol plus promethazine required additional sedating medications over 4 h (65 of 150 (43%) for olanzapine vs 31 of 150 (21%) for haloperidol plus promethazine; RR=2.07, (95% CI 1.43-2.97)); no serious adverse events were reported	Both medications worked for sedation; researchers did not evaluate possible EKG changes; excellent methodology, including concealed allocation, blinding of outcome assessment; conventional and appropriate statistical methods; minimal loss to follow-up

Evidentiary Table (continued).

Study and Year Published	Class of Evidence	Setting and Study Design	Methods and Outcome Measures	Results	Limitations and Comments
TREC Collaborative Group[47] (2003)	III	Pragmatic RCT; objective to compare IM midazolam or IM haloperidol-promethazine if "aggression/ agitation from psychiatric illness"; included if clinician-determined IM sedation need for agitation/ dangerous; excluded if clinician-determined treatment is risky; clinician-determined dose	Pragmatic RCT in 3 Brazilian psychiatric EDs, convenience sample, randomized by table of random numbers and block size; outcome: tranquil/sedated at 20 min; secondary outcome: patients tranquil/sleep by 40, 60, and 120 min, restrained, needed drugs <2 h, severe adverse events, another episode of agitation/aggression, required additional visits from clinician during first 24 h, antipsychotic load in first 24 h and no discharge in 2 wks	N=301, 151 randomized to midazolam, 150 haloperidol-promethazine; 134 of 151 (89%) midazolam and 101 of 150 (67%) haloperidol-promethazine tranquil/asleep at 20 min, RR=1.32 (95% CI 1.16-1.49); at 40 min, relative risk for tranquility with midazolam was 1.13 (95% CI 1.01-1.26); at 1 h, 90% in both groups tranquil or asleep; 1 adverse event occurred in each (respiratory depression in midazolam; seizure in haloperidol-promethazine); conclude that both agents are effective but midazolam is more rapidly sedating than haloperidol-promethazine	Study begins as Design 1, but convenience sample enrolled at discretion of unblinded clinician; no description of comparability at baseline and unclear validity or reliability of "calm and tranquil" and objective not masked and not generalizable, and dose was at discretion of clinician; midazolam group was more likely to receive 15 mg of midazolam, whereas in the haloperidol group approximately 50% (77) received 5 mg and approximately 50% (71) received 10 mg; substantial dose difference

ACES, Agitation-Calmness Evaluation Scale; *AMSS*, Altered Mental Status Scale; *ANOVA,* analysis of variance; *CI*, confidence interval; *ED*, emergency department; *IM*, intramuscular; *IQR*, interquartile range; *IV*, intravenous; *QTc*, corrected QT interval; *RCT* randomized controlled trial; *RR*, relative risk; *vs*, versus.