

Clinical Policy: Critical Issues in the Diagnosis and Management of the Adult Psychiatric Patient in the Emergency Department

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Approved by the ACEP Board of Directors September 23, 2005

Endorsed by the American Association for Emergency Psychiatry December 1, 2005

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0196-0644/\$-see front matter

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doi:10.1016/j.annemergmed.2005.10.002

[Ann Emerg Med. 2006;47:79-99]

This clinical policy focuses on 4 critical issues concerning the medical assessment and management of emergency department (ED) patients who present with psychiatric symptoms. The subcommittee reviewed the medical literature relevant to the questions posed. The critical questions are as follows:

1. What testing is necessary in order to determine medical stability in alert, cooperative patients with normal vital signs, a noncontributory history and physical examination, and psychiatric symptoms?
2. Do the results of a urine drug screen for drugs of abuse affect management in alert, cooperative patients with normal vital signs, a noncontributory history and physical examination, and a psychiatric complaint?
3. Does an elevated alcohol level preclude the initiation of a psychiatric evaluation in alert, cooperative patients with normal vital signs and a noncontributory history and physical examination?
4. What is the most effective pharmacologic treatment for the acutely agitated patient in the ED?

Recommendations are provided for each question on the basis of the strength of evidence of the literature. Level A recommendations represent patient management principles that reflect a high degree of clinical certainty; Level B recommendations represent patient management principles that reflect moderate clinical certainty; and Level C recommendations represent other patient management strategies that are based on preliminary, inconclusive, or conflicting evidence, or committee consensus. This guideline is intended for physicians working in hospital-based EDs.

INTRODUCTION

Behavioral emergencies from acute psychotic disturbances, manic episodes, major depression, bipolar disorder, and substance abuse are responsible for approximately 6% of all emergency department (ED) visits in the United States.¹ Behavioral abnormalities and psychiatric illness can coexist with or be caused by medical disease.²⁻⁵ Therefore, emergency physicians are frequently required to provide the initial assessment of patients who manifest behavioral abnormalities. Psychiatric consultants request that the emergency physician (1) establish if the patient's symptoms are caused or exacerbated by a medical illness, (2) assess and treat any medical situation that needs acute intervention, and (3) determine if the patient is intoxicated, thereby preventing an accurate psychiatric evaluation. This process has typically been termed "medical clearance" but becomes problematic because the term can imply different things to psychiatrists and emergency physicians and because there is no standard process for providing this "medical clearance."⁶⁻⁹ Focused medical assessment better describes the process in which a medical etiology for the patient's symptoms is excluded and other illness and/or injury in need of acute care is detected and treated. It is important, for example, to determine in the ED if a cognitive disorder such as dementia or

delirium is masquerading as a psychiatric condition (Appendix A). In at least 2 states, organizations of emergency physicians and psychiatrists have together formulated consensus guidelines about what components should be included in the medical assessment of the psychiatric patient in the ED.^{10,11}

Focused laboratory and radiologic testing may need to be obtained to ensure the stability of the patient based on their history and physical examination. Psychiatric facilities often have limited resources to further evaluate and treat acute and even chronic illnesses. Thus, the initial ED assessment is often the only medical evaluation the patient will receive. In addition, some laboratory testing, such as toxicologic screens that reveal substance abuse, may be very useful in treatment planning of psychiatric patients even though they may have no impact on medical stabilization.^{7,12}

A difficult aspect of the focused medical assessment is clearly determining when a patient is not only medically stable but has the cognitive status suitable for the psychiatric interview, which is especially important, given that substance abuse and acute intoxication often confound the patients' behavioral problems. As such, it is unclear what tests need to be performed along with the history and physical examination to establish that the patient is truly stable in preparation for the psychiatric interview.

This clinical policy uses an evidence-based approach to evaluate the literature and make recommendations regarding the medical evaluation of the psychiatric patient and initial pharmacologic therapy of agitated ED patients requiring treatment. Four questions were generated by the committee that were believed to be important for emergency physicians initially providing care in the ED. Except for question 4, which addresses the agitated patient, this clinical policy assumes that the patients being evaluated have normal vital signs and a noncontributory history and physical examination including normal cognitive function. Specifically excluded are patients with abnormal vital signs, delirium, altered cognition, or abnormal physical examination because they often have medical illness that mandates a symptom-based evaluation that is outside the scope of this guideline. Pediatric patients are also excluded.

Recommendations offered in this policy are not intended to represent the only diagnostic and management options that the emergency physician should consider. The American College of Emergency Physicians (ACEP) clearly recognizes the importance of the individual physician's judgment. Rather, this guideline defines for the physician those strategies for which medical literature exists to provide support for answers to the crucial questions addressed in this policy.

This policy evolved from the 1999 ACEP "Clinical Policy for the Initial Approach to Patients Presenting with Altered Mental Status."¹³

METHODOLOGY

This clinical policy was created after careful review and critical analysis of the medical literature. MEDLINE searches for articles published between January 1980 and January 2005 were performed using a combination of key words and their variations,

including “psychiatry,” “medical clearance,” “agitation,” “toxicologic screens,” “drugs of abuse,” “alcohol testing,” and names of individual drugs. Searches were limited to English-language sources. Additional articles were reviewed from the bibliography of articles cited. Subcommittee members also supplied articles from their own knowledge base.

The reasons for developing clinical policies in emergency medicine and the approaches used in their development have been enumerated.¹⁴ This policy is a product of the ACEP clinical policy development process and is based on the existing literature; where literature was not available, consensus of emergency and psychiatric physicians was used. Expert review comments were received from individual emergency physicians and psychiatrists and from members of the American Association for Emergency Psychiatry, American Association of Community Psychiatrists, American Psychiatric Association, and Emergency Nurses Association. Their responses were used to further refine and enhance this policy. Clinical policies are scheduled for revision every 3 years; however, interim reviews are conducted when technology or the practice environment changes significantly.

All publications were graded by at least 2 of the subcommittee members into 1 of 3 categories of strength of evidence. Some articles were downgraded on the basis of a standardized formula that considers the size of study population, methodology, validity of conclusions, and potential sources of bias (Appendix B).

During the review process, all articles were given a baseline “strength of evidence” by the subcommittee members according to the following criteria:

Strength of evidence Class I—Interventional studies including clinical trials, observational studies including prospective cohort studies, aggregate studies including meta-analyses of randomized clinical trials only.

Strength of evidence Class II—Observational studies including retrospective cohort studies, case-controlled studies, aggregate studies including other meta-analyses.

Strength of evidence Class III—Descriptive cross-sectional studies, observational reports including case series and case reports, consensus studies including published panel consensus by acknowledged groups of experts.

Strength of evidence Class I and II articles were then rated on elements subcommittee members believed were most important in creating a quality work. Class I and II articles with significant flaws or design bias were downgraded on the basis of a set formula (Appendix C). Strength of evidence Class III articles were downgraded if they demonstrated significant flaws or bias. Articles downgraded below strength of evidence Class III were given an “X” rating and were not used in formulating recommendations in this policy. An **Evidentiary Table** was constructed and is included in this policy.

Recommendations regarding patient management were then made according to the following criteria:

Level A recommendations. Generally accepted principles for patient management that reflect a high degree of clinical certainty (ie, based on strength of evidence Class I or

overwhelming evidence from strength of evidence Class II studies that directly address all the issues).

Level B recommendations. Recommendations for patient management that may identify a particular strategy or range of management strategies that reflect moderate clinical certainty (ie, based on strength of evidence Class II studies that directly address the issue, decision analysis that directly addresses the issue, or strong consensus of strength of evidence Class III studies).

Level C recommendations. Other strategies for patient management that are based on preliminary, inconclusive, or conflicting evidence, or in the absence of any published literature, based on panel consensus.

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 heterogeneity of results, uncertainty about effect magnitude and consequences, strength of prior beliefs, and publication bias, among others, might lead to such a downgrading of recommendations.

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

Inclusion Criteria. This guideline is intended for adult patients presenting to the ED with psychiatric symptoms.

Exclusion Criteria. This guideline, with the exception of question 4, is not intended for patients with delirium or abnormal vital signs, altered cognition, or abnormal physical examination. Pediatric patients are also excluded.

CRITICAL QUESTIONS

1. What testing is necessary in order to determine medical stability in alert, cooperative patients with normal vital signs, a noncontributory history and physical examination, and psychiatric symptoms?

In patients with acute behavioral emergencies, emergency physicians are frequently asked to perform detailed screening laboratory and radiologic testing to “exclude” medical illnesses that may be causing or contributing to the patient’s acute psychiatric symptoms. Patients with suggestive histories or abnormal vital signs and/or physical examination need to have medical illness specifically excluded during their screening evaluation. Gregory et al⁹ refer to 4 groups that may be high risk in this regard: the elderly, those with substance abuse, patients without a prior psychiatric history, and those with preexisting or new medical complaints. Anfinson and Kathol¹⁵ identified an additional group at risk: those of lower socioeconomic level. They agree, as do others, that patients presenting with new psychiatric symptoms particularly need careful evaluation in the ED for medical illness.^{9,15,16}

Several class III studies have identified the coexistence of medical illness in patients with psychiatric symptoms by using a routine battery of laboratory testing and recommend using this approach.^{2,3,16,17} However, these studies often did not specify what components of the initial history and physical examination were included, who performed the screening, and did not perform all tests on all patients, and the decision about what

constituted an “important” positive was sometimes arbitrary. Hall et al^{2,3} suggested that a routine battery of laboratory testing be completed on all psychiatric patients being hospitalized, including extensive laboratory testing, urinalysis, ECG, and sleep-deprived electroencephalogram because 46% of their patients had medical illness exacerbating the psychiatric illness, and overall, 80% of the patients had a physical illness requiring treatment. They based their observations on 100 patients admitted directly to a state psychiatric hospital but made no mention of whether a medical screening process was done before that admission. Kolman¹⁷ believed that certain screening tests, ECG, chest radiograph, blood urea nitrogen, and serum B₁₂, should be obtained in the psychogeriatric population despite the admittedly low yield. Henneman et al¹⁶ studied a group of patients presenting to the ED with new psychiatric complaints. In their series of 100 patients, there was a medical reason for the patients’ behavior in 63% of the patients. Their conclusion was that most patients with their first psychiatric presentation have a medical illness as the etiology, and require laboratory testing, as well as head computed tomography and cerebrospinal fluid analysis, in addition to a history and physical examination in their medical clearance evaluation. This study included many patients with delirium, and a large number of their patients had alteration of either vital signs (13% had fever and 37% had tachycardia) or cognitive state (60% were disoriented). Furthermore, their recommended tests were not done for every patient. This study, for the most part, is not relevant to the patient population addressed in this guideline.

On the other hand, a preponderance of reports, also class III, concluded that selective testing was the correct strategy.^{12,15,18-22} Dolan and Mushlin¹⁸ demonstrated that extensive, routine laboratory testing is unnecessary. When laboratory testing is done, it should be guided by the patient’s clinical evaluation. They also found false positive laboratory results to be 8 times more frequent than true positives (1.8%) in patients with routine testing. Likewise, Ferguson and Dudleston,¹⁹ in their series of patients, discovered a 17% rate of laboratory test abnormalities, but only 2 results were not predicted by the patients’ history and physical examination; therefore, they concluded that laboratory testing ought to be done selectively based on clinical need.

White and Barraclough²⁰ reported abnormal laboratory values in 10.2% of their patients yet determined that most were clinically insignificant. They had 5 cases of thyroid disease in patients with affective disorder. No routine screening tests were suggested by the authors, except for thyroid functions and urinalysis in women. Anfinson and Kathol¹⁵ reviewed the available literature on laboratory testing of psychiatric patients and also concluded that routine laboratory screening was not indicated and that most of the abnormal results obtained were clinically insignificant.

Tintinalli et al²¹ analyzed the medical records of 298 ED patients with psychiatric complaints. Although there were major documentation failures noted, only 12 patients (4%) required acute medical treatment within 24 hours of psychiatric admission, and in almost all (83%) patients, the history and physical

examination should have identified the problem. Korn et al²² performed a standard panel of tests in ED patients with psychiatric complaints. They analyzed 80 patients (38% of total) with no self-identified medical complaints but a past psychiatric history. Two of these patients had abnormalities in this standard panel of diagnostic tests: 1 a positive pregnancy test and the other, mild leukocytosis that was considered to be clinically insignificant. The authors concluded that routine laboratory testing in patients with no self-identified medical complaint and a past psychiatric history is unnecessary and patients could be directly referred safely for psychiatric evaluation if they have normal history, physical examination, and vital signs.

Additionally, Olshaker et al¹² retrospectively studied 352 adult ED patients with psychiatric chief complaints. By clinical protocol, all patients were asked about alcohol and recreational drug use. Also by protocol, all patients had laboratory analysis, including CBCs, SMA-7, urine and blood toxicologic screens, and blood alcohol testing. The patients correctly self-reported alcohol use 95% of the time and drug use 91% of the time. Nineteen percent of patients (65 of 352) had an acute medical condition. Of these patients, history identified 94% of them (61 of 65), physical examination 51% (33 of 65), and vital signs 17% (11 of 65). Of the 4 patients not identified by history, 2 had abnormal physical examinations, and the remaining 2 had hypokalemia (2.9 and 3.1 mmol/L). These latter 2 patients were the only ones with abnormalities who had normal history, physical examination, and vital signs. The authors conclude that universal laboratory testing and drug screening is of very low yield.

Future Area of Research: Development of the most efficient tools in the emergency setting for the assessment of cognition and behavioral abnormalities.

1. Patient management recommendations: What testing is necessary in order to determine medical stability in alert, cooperative patients with normal vital signs, a noncontributory history and physical examination, and psychiatric symptoms?

Level A recommendations. None specified.

Level B recommendations. In adult ED patients with primary psychiatric complaints, diagnostic evaluation should be directed by the history and physical examination. Routine laboratory testing of all patients is of very low yield and need not be performed as part of the ED assessment.

Level C recommendations. None specified.

2. Do the results of a urine drug screen for drugs of abuse affect management in alert, cooperative patients with normal vital signs, a noncontributory history and physical examination, and a psychiatric complaint?

The role of the urine toxicologic screen for drugs of abuse in the evaluation of ED patients with psychiatric complaints is controversial. A survey in 2001 found that almost half of ED physicians required to obtain a urine toxicologic screen for medical clearance thought it was unnecessary.⁶ Psychiatrists, on

the other hand, may use the results of this screen to help determine the etiology of the patient's symptoms and aid in the patient's disposition and long-term care. Furthermore, the screening results may be required for admission to some facilities.

There are no class I or II studies that directly examined how the urine toxicologic screen affects the medical management of a patient with a psychiatric complaint who is alert and cooperative, with a noncontributory history and physical examination, and normal vital signs. There are several class III studies on which recommendations can be based.

Routine toxicologic screening is not supported by the class III studies concerning this issue. A retrospective observational analysis of 352 patients showed that laboratory studies, including urine toxicologic screens, in patients with isolated psychiatric complaints carried a sensitivity of only 20% for organic etiology of their complaint.¹² Therefore, authors suggest that urine toxicologic screens are not indicated routinely. This conclusion is supported by a class III study by Schiller and colleagues²³ examining how the urine drug screen affects disposition of patients from psychiatric emergency services by psychiatrists. In this prospective series, 392 patients were randomized in a blinded fashion to mandatory urine toxicologic screens versus 'usual care,' which may or may not have entailed a urine toxicologic screen. The authors found no difference between the 2 groups for inpatient or outpatient disposition or hospital length of stay and again concluded that the routine use of urine toxicologic screening is not indicated. Unfortunately, this study did not specify the patient's medical status or thoroughly outline 'usual care.' In a class III study by Eisen et al,²⁴ no justified change in the management plans occurred in 110 patients after the results of a drug of abuse screen became available to the ED clinician. This study did not specify, however, how many of the 110 patients were having a psychiatric evaluation.

Two class III studies advocate obtaining routine urine toxicologic screens, but their data do not seem to support their conclusions in our target population.^{3,16} Hall et al³ reviewed 100 inpatient psychiatric admissions and reported that 46% had an unrecognized medical problem. However, the urine toxicologic screen identified only 1 of these patients, and its effect on patient management was not discussed. Henneman et al¹⁶ prospectively studied 100 consecutive, alert patients presenting with new psychiatric complaints, although many were noted to have fever, abnormal vital signs, or altered mental status. They found 63 patients with an organic etiology for their symptoms. Thirty-seven percent of these patients were found to have an abnormal alcohol level or urine drugs of abuse screen, of which 29% were believed to be significant. Significance was defined as a result leading to the etiology of the original complaint or resulting in admission. Unfortunately, they did not discuss how these tests changed the patient's management, and imply that a positive urine toxicologic screen result is almost always significant, regardless of whether or not the patient was acutely intoxicated.

In 1999, the Massachusetts College of Emergency Physicians and the Massachusetts Psychiatric Society formed a task force that

released consensus recommendations about obtaining toxicologic screens in the ED for drugs of abuse.¹¹ They concluded that drug screens not required for the evaluation of the medically stable psychiatric patient but requested by the receiving service or facility, if done, should not delay the transfer of the patient.

2. Patient management recommendations: Do the results of a urine drug screen for drugs of abuse affect management in alert, cooperative patients with normal vital signs, a non-contributory history and physical examination, and a psychiatric complaint?

Level A recommendations. None specified.

Level B recommendations. None specified.

Level C recommendations.

1. Routine urine toxicologic screens for drugs of abuse in alert, awake, cooperative patients do not affect ED management and need not be performed as part of the ED assessment.
2. Urine toxicologic screens for drugs of abuse obtained in the ED for the use of the receiving psychiatric facility or service should not delay patient evaluation or transfer.

3. Does an elevated alcohol level preclude the initiation of a psychiatric evaluation in alert, cooperative patients with normal vital signs and a noncontributory history and physical examination?

Emergency physicians are asked to see intoxicated patients and determine whether they are medically stable for the psychiatric evaluation. Acute intoxication may impair the ability to conduct a valid psychiatric examination. Alcohol acts as a central nervous system depressant, resulting in poor coordination, sluggish reflexes, and emotional lability, and is often a confounding factor in the evaluation, treatment, and disposition of psychiatric patients. Alcohol intoxication can mimic or alter psychiatric symptoms and delay proper patient disposition.²⁵ Generally, psychiatric facilities will not accept transfers of inebriated patients. Patients impaired by alcohol may not be deemed medically stable. As the blood alcohol concentration decreases, the patient often becomes less impaired, psychiatric symptoms may clear, particularly suicidality, and the need for acute hospitalization is often obviated.²⁶⁻²⁸ There are no evidenced-based data to support a specific blood alcohol concentration at which psychiatric evaluation can accurately commence, nor are there any studies that show that individuals regain adequate decisionmaking capacity when the blood alcohol concentration reaches the legal limit for driving. Cognitive function should be assessed with each patient individually,²⁹ and this should be the basis for initiating the psychiatric interview rather than a predetermined blood alcohol concentration. Furthermore, there is no evidence in the literature to support the practice of delaying the initiation of psychiatric evaluation to obtain a blood alcohol concentration result if the patient is alert, and has appropriate cognition, normal vital signs, and a noncontributory history and physical examination.

3. Patient management recommendations: Does an elevated alcohol level preclude the initiation of a psychiatric evaluation in alert, cooperative patients with normal vital signs and a noncontributory history and physical examination?

Level A recommendations. None specified.

Level B recommendations. None specified.

Level C recommendations.

1. The patient's cognitive abilities, rather than a specific blood alcohol level, should be the basis on which clinicians begin the psychiatric assessment.
2. Consider using a period of observation to determine if psychiatric symptoms resolve as the episode of intoxication resolves.

4. What is the most effective pharmacologic treatment for the acutely agitated patient in the ED?

Agitation characterized by behavioral features such as destructiveness, disorganization, or dysphoria is a frequent finding in ED patients. Such agitated and sometimes violent behavior often poses a serious risk to the patient's health, as well as to the health care providers. Although the focus here will be on the psychopharmacologic management of agitation, clinicians should make every effort to first establish whether the potential for violence can be managed at a verbal or behavioral level before proceeding to management with medications that carry a risk of undesirable side effects.

Benzodiazepines and some antipsychotics have been the pharmacologic agents most used for the control of the agitated patient, and the existing studies have been recently summarized.³⁰⁻³² Most were conducted in patients with a known psychiatric diagnosis, so the results cannot necessarily be extrapolated to the undifferentiated agitated patient in the ED. There are also few fixed dose studies directed at determining the appropriate dose of the various agents, and many of the studies permit repeated administration, further clouding the comparability of different agents and doses.

Caution also needs to be taken in caring for patients agitated because of medical illness so that any reversible causes are identified and treated. In addition, agitation may be a result of drug ingestions or poisonings with anticholinergic or sympathomimetic agents. In this scenario, the antipsychotics, both conventional and atypical, and the medications used to manage extrapyramidal symptoms (EPS) can potentially exacerbate agitation because of their anticholinergic side effects.³⁰

Benzodiazepines

There are no class I studies using benzodiazepines in patients for acute agitation. There are multiple class II studies demonstrating that benzodiazepines are valuable in reducing agitation and are at least as effective as the conventional antipsychotic haloperidol in control of the agitated patient.³³⁻³⁵ All used 2 mg or 4 mg lorazepam compared with 5-mg doses of haloperidol. The class III study by Garza-Trevino et al³⁶ reached similar conclusions. Studies with 2 other benzodiazepines, clonazepam and flunitrazepam, also

demonstrate that benzodiazepine is equivalent to haloperidol in reducing agitation.^{37,38} One class III study reported haloperidol (10 mg) with the addition of promethazine (25 to 50 mg) to have a faster onset of tranquilization than lorazepam (4 mg), but at 4 hours, 96% of subjects in each treatment group were tranquil. The addition of the antihistamine promethazine to control dystonic reactions produced additional sedation.³⁹

The use of midazolam intramuscular (IM) was recently studied in a randomized, prospective, double-blind class II study by Nobay et al⁴⁰ and is the most relevant study of this benzodiazepine in the control of the severely agitated patient. The authors compared IM midazolam (5 mg) to IM lorazepam (2 mg) or IM haloperidol (5 mg). Midazolam had a significantly shorter time to sedation than did lorazepam or haloperidol. The mean time to sedation was 18.3 minutes for midazolam, 28.3 minutes for haloperidol, and 32.2 minutes for lorazepam. The time to arousal (81.9 minutes) in patients given midazolam was also significantly shorter than that of the other therapies.

In addition, several class III studies found midazolam (2.5 to 3 mg IM) to be efficacious in reducing agitation. It produced rapid sedation, within 6 to 8 minutes, in a small series of acutely agitated patients.⁴¹ Midazolam was significantly better than haloperidol in controlling motor agitation in a small study of schizophrenic patients.⁴² A large series reported by the TREC Collaborative group⁴³ found that midazolam (15 mg) was superior to haloperidol (5 mg) plus promethazine (50 mg) in producing rapid sedation at 20- and 40-minute endpoints. At 60 minutes, more than 90% of each group were tranquil or asleep.

A variety of studies has compared the combination of a benzodiazepine with an antipsychotic to either alone. The strongest evidence comes from the large class II ED study by Battaglia et al³⁴ in which the combination of haloperidol (5 mg) and lorazepam (2 mg) was shown to be superior to lorazepam or haloperidol alone for controlling the patients' acute agitation at 1 hour. Side effects did not differ significantly between the treatment groups, although the incidence of EPS in the haloperidol group was 20%, which is 6 times the rate in lorazepam-treated patients. Level III studies by Garza-Trevino et al³⁶ and Bieniek et al⁴⁴ concluded that the combination of haloperidol (5 mg) and lorazepam (4 mg and 2 mg, respectively) was statistically superior in producing more rapid tranquilization than either component medication alone. However, these studies do not use equipotent doses of the single drug when compared to the combination, so definite conclusions await further trials.

Conventional Antipsychotics

Haloperidol has by far the best evidence base among conventional antipsychotics for the treatment of agitation. The recent reviews by Allen³⁰ that categorized 20 double-blind studies since 1973 involving the use of haloperidol and by Yildiz et al³² summarized the randomized trials with haloperidol compared with a benzodiazepine to treat agitation. Most of the studies were done in patients with a known psychiatric diagnosis

that may not extrapolate directly to the undifferentiated combative ED patient. Furthermore, studies comparing medications did not necessarily use equipotent dosages.

In a case series of general ED patients needing sedation, the safety and effectiveness of haloperidol alone was demonstrated by Clinton et al.⁴⁵ The authors treated 136 agitated patients with haloperidol (average dose 8.4 mg) and found that behavior was alleviated in 113 patients with only 3 patients showing no response. Four complications were noted, including 2 cases of dystonia.

Haloperidol compared with benzodiazepines was considered previously. Several studies found little to no additional benefit in sedation after 10 mg of IM haloperidol had been administered to psychotic patients.^{35,37,46}

Droperidol is a butyrophenone structurally related to haloperidol but available only by injection and used primarily in anesthesia for postoperative nausea. Anecdotally, it has received strong support as a calming agent in behavioral emergencies. It was superior to haloperidol in acutely reducing the level of agitation in patients already physically restrained for violent behavior in a class II study comparing IM haloperidol 5 mg to IM droperidol 5 mg.⁴⁷ Agitated patients receiving droperidol (5 mg) required fewer repeat doses than those receiving an equivalent dose of haloperidol.⁴⁸ Richards et al,⁴⁹ a class II study, is the largest prospective, randomized study of undifferentiated agitation using droperidol in an ED setting. The authors compared weight-based doses of IV droperidol to IV lorazepam. Sedation was similar at 5 minutes in the 2 groups, but thereafter, droperidol was significantly better in producing sedation up through 60 minutes. The study showed that patients treated with intravenous droperidol had lower sedation scores, required fewer repeat doses, and had shorter ED lengths of stay. One case of dystonia was reported.

In 2001, the US Food and Drug Administration (FDA) issued a black box warning about droperidol's potential for dysrhythmias, making its subsequent use problematic. However, large patient series have appeared attesting to its safety. Chase and Biros⁵⁰ reviewed their use of droperidol in 2,468 ED patients, with 1,357 receiving it for agitation. Few (6) adverse events occurred, none in patients without serious comorbidities, and none were documented dysrhythmias. No dysrhythmic events were observed in an estimated 12,000 patients treated with droperidol for violence and/or agitation.⁵¹ Some authors have reviewed the existing reports of droperidol toxicity, including all of the material submitted to the FDA on which the ruling was based, and concluded that although droperidol can be associated with prolongation of the QT interval, there is not convincing evidence that the drug causes severe cardiac events.^{52,53}

Atypical Antipsychotics

Atypical antipsychotics are noted for their differing mechanism of action, lower rates of motor side effects, and their efficacy in long-term treatment.^{32,54} Harrigan et al,⁵⁵ in an open-label prospective class II randomized study, compared 4 atypical antipsychotics: olanzapine, ziprasidone, quetiapine, and

risperidone with haloperidol and thioridazine. They concluded that all of the 6 antipsychotics studied, at their maximum recommended daily dosage, prolong the QTc interval at the steady-state peak plasma concentration. None, however, exceeded 500 ms. Thioridazine had the greatest QTc change and olanzapine the least.

Two class II reports showed that ziprasidone IM 20 mg is effective in rapidly and substantially reducing the symptoms of acute agitation in patients with known psychotic disorders, and it is well tolerated.^{56,57} The efficacy of the 10-mg dose is not as great as the 20-mg dose, although it is significantly better than a 2-mg dose. The absence of movement disorders, including extrapyramidal symptoms, dystonia, and hypertonia with ziprasidone 20 mg is noteworthy.⁵⁶ In a class III study, ziprasidone IM was significantly more effective in reducing the symptoms of acute psychosis than haloperidol IM when each was dosed every 4 to 6 hours as needed. Ziprasidone was better tolerated, particularly in the incidence of movement disorders.⁵⁸ In the single report available using atypical antipsychotics in the undifferentiated patients with agitation presenting to a psychiatric ED, Preval et al⁵⁹ found that ziprasidone 20 mg IM decreased agitation scores quickly and equally to conventional therapy (usually haloperidol with lorazepam) and significantly decreased the mean restraint time when compared to a group of historic controls.

Olanzapine IM was compared to haloperidol IM for treatment of acute agitation in schizophrenic patients in 2 class II studies and found to be equivalent in reducing agitation.^{60,61} Wright et al⁶¹ demonstrated that olanzapine decreased the agitated behavior more quickly, as measured at 15 to 45 minutes, although thereafter there was no significant difference in the 2 treatment groups. There was a greater incidence of acute dystonia in the haloperidol group (7%). Meehan et al,^{62,63} in randomized double-blinded fashion, compared IM olanzapine with IM lorazepam in agitated patients with bipolar mania and patients with dementia, respectively. Sedation was equivalent in the dementia patients among treatment groups. In patients with bipolar mania, there was significantly greater reduction in agitation scores shown with olanzapine (10 mg) over lorazepam (2 mg) at 2 hours but equivalent at 24 hours. Breier et al⁶⁰ reported that hypotension occurred in 8 of 185 (4.3%) olanzapine-treated patients and 0 of 40 haloperidol and 0 of 45 placebo-treated patients. There are no published reports of vital sign measurements with IM olanzapine, but an FDA Psychopharmacological Drugs Advisory Committee briefing document cites a prevalence of 11.9% for a 20 mm Hg drop in systolic blood pressure in clinical trial subjects.⁶⁴ Orthostatic vital signs are recommended if repeated administration of olanzapine is contemplated. Concomitant use of IM olanzapine with benzodiazepines has not been studied and is not recommended by the manufacturer.

Currier et al,⁶⁵ in a rater-blinded randomized class II trial, found that oral treatment with risperidone (2 mg) and lorazepam (2 mg) was comparable to IM haloperidol (5 mg)

and lorazepam (2 mg) for short-term treatment of agitated psychosis in patients who accept oral medications. Both treatment groups showed similar improvement in agitation, with similar times to sedation. It is possible that the group receiving intramuscular haloperidol and lorazepam had more severe psychotic agitation.

Future Areas of Research: (1) comparison of parenteral midazolam to lorazepam for the control of acute agitation, (2) role of combination therapy when individual drugs are used in doses equivalent to the combination, and (3) the role of the atypical antipsychotics as parental or oral monotherapy or in combination with a benzodiazepine for rapid control of the agitated ED patient.

4. Patient management recommendations: What is the most effective pharmacologic treatment for the acutely agitated patient in the ED?

Level A recommendations. None specified.

Level B recommendations.

1. Use a benzodiazepine (lorazepam or midazolam) or a conventional antipsychotic (droperidol* or haloperidol) as effective monotherapy for the initial drug treatment of the acutely agitated undifferentiated patient in the ED.
2. If rapid sedation is required, consider droperidol* instead of haloperidol.
3. Use an antipsychotic (typical or atypical) as effective monotherapy for both management of agitation and initial drug therapy for the patient with known psychiatric illness for which antipsychotics are indicated.
4. Use a combination of an oral benzodiazepine (lorazepam) and an oral antipsychotic (risperidone) for agitated but cooperative patients.

Level C recommendations. The combination of a parenteral benzodiazepine and haloperidol may produce more rapid sedation than monotherapy in the acutely agitated psychiatric patient in the ED.

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*Refer to the discussion of droperidol in the text.

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Evidentiary Table.

| Study | Design | Findings | Limitations | Grade |
|------------------------------|---|--|---|--------------|
| Hall et al ² | Case series | 100 consecutive admissions by warrant to a clinical research ward in a psychiatric facility for study; patients excluded if they had a significant drug abuse history or previously diagnosed medical illnesses; 46% found to have medical illnesses directly causing or exacerbating their psychiatric symptoms and an additional 34% had a medical illness requiring treatment; 80% had a previous physical illness requiring intervention | Screening examinations, if any, not specified before admission to the psychiatric facility; how authors determined medical illnesses caused or exacerbated psychiatric symptoms not clear | III |
| Hall et al ³ | Retrospective case series review of prospective data collection | 100 consecutive patients admitted by warrant to state mental health facility; apparently same patient population as author's 1980 article; 46% thought to have medical illness causing or exacerbating psychiatric symptoms; 28% had clearing of psychiatric symptoms with treatment of medical condition; 34% had physical disorder believed to need treatment; surgery prescribed in 8%; 186 medical diseases uncovered in these patients | No previous screening mentioned; psychiatrists, not internists, did medical causation analysis; >1 wk required to obtain all the testing; follow-up not stated; selection bias | III |
| Koran et al ⁵ | Prognostic case series | 289 admitted patients to a public psychiatric hospital screened for physical disorders; history and physical examination by admitting psychiatrist who ordered routine set of laboratory tests; internist analyzed results; 29% with active/important medical disorders, 10% of those were previously unknown but only 1 thought to be causing psychiatric symptoms (hypothyroidism); 14 of 18 abnormal thyroxin tests were false positives; most abnormal lab test results clinically unimportant | Excluded patients admitted through EDs; many patient exclusions - 56% of potential patients enrolled; many discharged before abnormalities were followed | III |
| Broderick et al ⁶ | Anonymous mail survey of 500 emergency physicians | 58% return rate; 35% respondents stated that mandatory testing is required regardless of patient presentation, 16% by ED protocol and 84% by psychiatrist/psychiatric facility; CBC count required in 56%, electrolyte level in 56%, serum alcohol level in 85%, urine toxicologic screen in 86%, serum toxicologic screen in 31%; few respondents believed that any of these tests were necessary | No return from almost 50%; respondent's involvement with psychiatric patients not stated | III |
| Gregory et al ⁹ | Review article | Review of the literature from 1966-2003 about medical screening/clearance of the psychiatric patient; medical history, physical examination, review of symptoms, and test for orientation are high yield, whereas routine laboratory testing is of low yield for clinically significant conditions; 4 higher-risk groups are suggested based on the published data and consensus; a sample protocol for medical screening examinations is presented | Review article; few ED studies included; screening mechanisms and populations studied varied considerably among studies | III |
| MACEP ¹¹ | Consensus report | Massachusetts ACEP in conjunction with Massachusetts Psychiatric Society produced guidelines for the evaluation and treatment of patients with psychiatric complaints | Consensus based | III |

Evidentiary Table (continued).

| Study | Design | Findings | Limitations | Grade |
|-----------------------------------|--|--|---|--------------|
| Olshaker et al ¹² | Retrospective observational analysis | 345 patients with psychiatric complaints screened in an urban ED during a 2-mo period; 19% had an acute medical condition, the most common: lacerations, hyperglycemia, chest pain, hypertension, and bronchitis; history had 94% sensitivity for identifying these conditions; physical examination had 51% sensitivity for identifying the medical condition; vital signs 17% sensitivity; laboratory studies alone 20% sensitivity; self-reporting had 92% sensitivity; specificity was 91% for identifying those with positive drug screen result; 2 laboratory abnormalities were not detected by history and physical examination and both were low potassium levels: 2.9-3.1 mmol/L; history and physical examination picked up the vast majority of physical problems and substance abuse in the psychiatric patient | Follow-up was not done on the patients after screening; patients with new or chronic psychiatric symptoms were not separated | III |
| Anfinson and Kathol ¹⁵ | Review article | Review of studies, both retrospective and prospective, using laboratory and radiologic testing in screening psychiatric patients; most abnormal results can be predicted from a careful history and physical examination; most abnormal results found on routine testing are clinically insignificant and do not affect patient outcome; certain populations appear to benefit from more extensive testing: >65 y of age, those with drug/alcohol histories, those disoriented, or of lower socioeconomic level | Review article; few ED-based studies available | III |
| Henneman et al ¹⁶ | Case controlled, retrospective review of prospectively gathered data | 100 consecutive alert patients, average age 38 y, with new psychiatric symptoms studied; patients excluded: previous psychiatric illness, obvious intoxication, those with overdose, and suicide patient; 63% believed to have an organic etiology for their psychiatric symptoms; medical history significant in 27, physical examination in 6, alcohol/drug screen in 28%, CT in 8%, and lumbar puncture in 3%; 30 patients had toxicologic etiologies for their behavior; of all tests, CBC and PT were the only tests that did not lead to identification of a medical illness | Large number of exclusions; psychiatric symptoms not defined; included many patients with altered mental status (yet still considered alert), confusion, and abnormal vital signs | III |
| Kolman ¹⁷ | Case series | 68 elderly patients with routine testing on admission to psychiatric unit; medical history disclosed 33 with active medical problems; physical examination uncovered 49 with active medical conditions; 1,210 laboratory tests done, 274 abnormal results, only 17 (1.4%) tests led to diagnosis and treatment of a condition not already detected by history and physical examination (13 indicated infection: either urinary tract infection or pulmonary); routine CXR, ECG, BUN, and serum B12 were recommended in psychogeriatric patients | Not ED based; admission criteria not specified; medical examination by psychiatric residents; patient follow-up was 3 mo | III |

Evidentiary Table (continued).

| Study | Design | Findings | Limitations | Grade |
|--------------------------------------|---|--|---|--------------|
| Dolan and Mushlin ¹⁸ | Retrospective case series | Utility of routine admission laboratory tests studied in 250 patients picked at random from a larger group of patients admitted to a private psychiatric facility; laboratory tests ordered by admitting psychiatrist then patient examined by internist; mean number of laboratory tests completed per patient was 27.7; mean percentage of true-positive results are 1.8%, less than 1 test in 50 resulted in clinically meaningful results; false-positive tests 8 times more common than true-positive test; 4% (11) of patients had medical diagnoses made solely on the basis of the laboratory testing, 2 were treated, the other 9 had no follow-up and later discharged without medical illness | Large number of excluded patients; selection bias, all private patients; initial screening before admission to psychiatry facility not described; not all patients had all tests | III |
| Ferguson and Dudleston ¹⁹ | Retrospective case series | 650 newly admitted psychiatric patients (excluding drug and alcohol patients) examined; total of 2,753 laboratory tests ordered, 463 (17%) abnormal results; 38 abnormal thyroid test results, most normal on repeat and only 2 positives not predicted on basis of previous history and physical examination; neither received treatment during hospitalization; of the 63 abnormal test results not predicted, majority were clinically unimportant; selective rather than routine laboratory ordering suggested | No screening before admission stated; psychiatrist did medical evaluation; exclusions not stated | III |
| White and Barraclough ²⁰ | Retrospective case series | 1,000 admissions to a psychiatric facility, 719 separate patients; overall, 8,663 results obtained for screening, 10.2% (887) abnormal results, 73 (0.8%) made important contribution to diagnosis or treatment; 10 thyroid test results abnormal, 5 of these patients thought to have their mental illness related; 2 chest infections in patients believed related to their sustained mania; overall, mental illness attributable to illness detected by laboratory tests was rare; recommended thyroid and urine testing as screening tests | Screening prior to admission not stated; many (40%) patients had no tests done; skill level of admitting physicians not stated; cause and effect between abnormal laboratory result and the patient's mental illness not clear in some | III |
| Tintinalli et al ²¹ | Prognostic retrospective observational series | Record review of the ED records of 298 voluntarily admitted patients to a psychiatric unit; 12 (4%) patients required acute medical treatment, 10 transferred to a medical service within 24 h of admission; ED history and physical examination should have identified >80% of these 12 patients; overall, mental status of 298 patients was not documented at triage in 56% of patients; most common deficiency in the medical examination was the neurologic examination; the term "medically clear" was not documented in the record of 62% of patients; younger patients had 4 times greater chance of a missed medical diagnosis | Retrospective record review; only volunteered admitted patients studied; follow-up not stated; all admitted patients had an internal medical consultation; various residents evaluated the patients; no standard laboratory examination | III |

Evidentiary Table (continued).

| Study | Design | Findings | Limitations | Grade |
|------------------------------|---|--|---|--------------|
| Korn et al ²² | Retrospective observational series | Used standard protocol for evaluating all patients presenting with psychiatric complaints or psychiatric and medically based complaints to an adult ED; 80 (38%) patients with solely psychiatric complaints and with past psychiatric history; this group revealed no abnormal laboratory or radiology results except for 1 positive pregnancy test; 62% presented with a medically based chief complaint or a past medical history in addition to the psychiatric complaint; their initial complaints directly correlated with their need for laboratory and radiographic medical evaluation; those without current medical problems, stable vital signs, and negative physical findings had no need for ancillary testing in the ED | No follow-up of patients made; no follow-up laboratory examination mentioned; patients with psychiatric symptoms not receiving psychiatric consultation were excluded | III |
| Schiller et al ²³ | Prospective cohort with retrospective review | 392 patients at psychiatric ED randomized to mandatory drug testing vs usual care; physicians ordered drug screens based on clinical judgment; 43% tested positive in mandatory group; no difference in disposition or subsequent lengths of stay between groups; 88% of those admitting drug use had positive screen results; clinicians accurate in suspicion of drug use; when not suspecting and patient denies only 10% had positive screens; 80% denying drugs had negative screen; evidence did not support obtaining routine screens | Consent needed, selection bias; significantly more males in mandatory group; vital signs/mental status not mentioned; many patients excluded from the study | III |
| Eisen et al ²⁴ | Prospective population study of physician test ordering and subsequent management changes | ED physicians obtained urine screens for drugs of abuse as deemed necessary for patient management; investigators queried ordering physician with standardized script before learning test results as to anticipated results, disposition, and management plans; results then given to the ordering physician and changes in management, if any, noted; 271 drug screens done in 9 mo, laboratory notified investigators of 160 of these; 50 excluded, 110 total patients studied; only 4 management decisions changed after results known but none believed to be justified on review by independent expert | Providers informed of the study before data collection; not specified which were psychiatric patients; many exclusions; no follow-up mentioned | III |
| Yost ²⁵ | Review article | Review of alcohol intoxication physiology and management of the intoxicated patient | Review article | III |
| Jayaram et al ²⁶ | Retrospective case review | Records of 92 patients who were involuntarily admitted to a county hospital ED were reviewed retrospectively, and 47 (51%) had previous or current drug abuse documented, with PCP the most frequently recorded drug of abuse (39%); approximately 1/2 of the 92 patients were admitted; the reviewers agreed with the disposition decision in 90% of the 92 patients; intoxication on the initial ED evaluation predicted subsequent release from the ED after intoxication resolved | Exclusions not described; disposition criteria not described; medical screening not described; small number | III |

Evidentiary Table (continued).

| Study | Design | Findings | Limitations | Grade |
|---|--|--|--|--------------|
| Breslow et al ²⁷ | Prognostic retrospective case series | 294 consecutive patients presenting to a psychiatric ED tested for acute intoxication and substance abuse; 94 (32%) had acute intoxication, 17% given primary diagnosis of substance abuse/dependence; these patients actually less likely to be admitted but have longer length of stay, more behavior management needs; alcohol most common finding (50%) followed by cocaine and alcohol (17%), then cocaine alone (16%) | Acute intoxication defined as any substance use in past 24 h, regardless of behavior; 1 mo survey, potential bias; some patients were missed in the mo | III |
| Dhossche and Rubinstein ²⁸ | Retrospective case-control record review of patients with or without positive toxicologic screen results | Patient cohort (112 subjects) with positive drug screen for cocaine metabolite plus or minus alcohol compared with similar patients without positive screen results; only 6% of drug screen results known to the clinician at time of examination; alcohol most common screening finding, followed by cocaine; suicidality significantly associated with cocaine in young males; no patient remained suicidal at end of assessment if only alcohol finding on screen | Retrospective review; only 50% had screen done; screen results apparently did not affect disposition, although not detailed; details of drug use not recorded well | III |
| Lavoie ²⁹ | Retrospective case series | Review of security log to determine patients needing security assistance in ED; 314 total (8.6% of total ED population), 281 had complete records; observation in 57%, restraint in 26%; suicidal ideation most common reason for observation | Patients possibly missed by relying on log, selection bias; guidelines for placing in involuntary treatment not stated | III |
| Allen ³⁰ | Review article | Reviewed all the controlled studies of medication treatment of agitation to date since introduction of the neuroleptics; 24 studies met criteria and were reviewed | Review article | III |
| McAllister-Williams and Ferrier ³¹ | Review | Reviewed the past and current options and future trends in treatment of the agitated psychiatric patient from the British perspective; concludes benzodiazepines are the drug of choice until further evaluation of the atypical agents is available | Review article | III |
| Yildiz et al ³² | Review article | Review of studies comparing antipsychotics, benzodiazepines, and combinations, followed by review of efficacy of atypical antipsychotics | Review article | III |
| Salzman et al ³³ | A randomized controlled drug trial, comparing IM lorazepam with IM haloperidol | 30 patients in each drug arm: 2 mg of IM lorazepam vs 5 mg of IM haloperidol; the OAS was used to monitor patients; all patients showed marked reduction in overt aggression and assaultive behavior with either treatment; there was no significant group difference between the decrease in aggression produced by the haloperidol or the lorazepam recipients; side effects were more prevalent among the haloperidol group (11 times more likely) | Additional medications given were not controlled; small sample size; all psychiatric patients; those with positive toxicity screen result excluded | II |

Evidentiary Table (continued).

| Study | Design | Findings | Limitations | Grade |
|-----------------------------------|--|---|---|-------|
| Battaglia et al ³⁴ | A randomized trial comparing lorazepam with haloperidol and with a combination of lorazepam and haloperidol | 98 ED patients entered from 5 sites received lorazepam 2 mg, haloperidol 5 mg, or combination of lorazepam and haloperidol; outcomes measured by BPRS, ABS, and CGI scale; all patients showed significant reduction in ABS from baseline, but combination treatment showed significantly greater decrease in agitation scale when compared to lorazepam at 1 h; combination was superior to haloperidol also, although the decrease was not significantly significant; 20% had side effects (EPS) in the haloperidol group | Redosing was not controlled; multiple evaluators at each site, integrated reliability not addressed; those with alcohol intoxication excluded | II |
| Foster et al ³⁵ | A randomized non-controlled comparison of lorazepam vs haloperidol | Total of 37 patients rated by a BPRS or the CGI Scale; subjects received either 2 mg of lorazepam or 5 mg of haloperidol IM or by mouth; both drugs produced a significant decrease in the agitation scales, with lorazepam having a more rapid decrease in the scores at 1, 2, 3 h from baseline; there were no demonstrated EPS symptoms in 20 patients receiving haloperidol; no difference in administration route noted | IM or PO administration; small number of patients; only psychiatric diagnoses included; variable redoing during the study period; oral concentrates not similar in appearance | II |
| Garza-Trevino et al ³⁶ | Randomized study of 3 treatments: combination of haloperidol 5 mg and lorazepam 4 mg against each individually | 68 patients; 21 given haloperidol 5 mg, 23 given lorazepam 4 mg, and 24 given combination of haloperidol and lorazepam; patients all had a documented psychiatric diagnosis; agitation measured on a 100 mm VAS; all patients scored >50 initially; the combination reduced agitation significantly when compared to either drug alone; fewer repeat doses were also required with the combination arm | Nonpsychiatric patients not included; background characteristics in groups not equal; doses were not equivalent; combination received more medication than either drug alone; agitation scale used not validated | III |
| Chouinard et al ³⁷ | Randomized double-blind drug trial comparing clonazepam and haloperidol | 16 acute agitated psychotic patients received either haloperidol or clonazepam; drugs were administered at 0, ½ h and 1 h intervals, and doses ranged from 5-10 mg of haloperidol and 1-2 mg of clonazepam; patient agitation measured by a TMBSS and a 9-point CGI scale; an IMPS and an ESRS also used; nurses rated a patient on a NOSIE; both medications produced reduction in manic symptoms within 2 h although haloperidol produced results more rapidly than clonazepam at the 1 h endpoint; mean dose of haloperidol was 19.4 mg, and mean dose of clonazepam, 5.4 mg | Small number of patients in each treatment arm; all had psychiatric diagnoses; variable doses of drugs given to patients; groups not equivalent in their past medications; all patients signed voluntary consent; thus, most agitated patients not included | III |
| Dorevitch et al ³⁸ | Randomized study comparing haloperidol vs flunitrazepam in hospitalized psychiatric patients | 28 patients hospitalized with schizophrenia, schizoaffective disorder, or bipolar disorder; received 5 mg of haloperidol vs 1 mg of flunitrazepam; both drugs caused significant reduction in the OAS, however, flunitrazepam achieved maximal reduction with 30 min, whereas haloperidol decreased more gradually; after 30 min, there was no significant difference in the 2 drugs | Flunitrazepam not marketed in United States; doses may not be equipotent; selection method not reported; small number in each treatment group | III |

Evidentiary Table (continued).

| Study | Design | Findings | Limitations | Grade |
|--|---|---|---|--------------|
| Alexander et al ³⁹ | Randomized controlled drug trial | 200 patients received either combination of haloperidol (10 mg) and promethazine (25-50 mg) or lorazepam (4 mg) for agitation; nonblinded assessment for first 2 h, then blinded; equal number of patients (96%) each group tranquil/asleep at 4 h; combination treatment produced more patients tranquil/asleep at 15, 30, 60, and 120 min; number of patients requiring restraint, having further episodes of agitation, needing additional medication, adverse effects, or admission not different between groups | Patients entered at physician discretion; dosing at physician discretion; varying dose of promethazine used; not blinded assessment | III |
| Nobay et al ⁴⁰ | Randomized prospective double-blind study comparing midazolam with lorazepam with haloperidol | Convenience sample of agitated patients medicated with 5 mg of midazolam or 5 mg of haloperidol or 2 mg of lorazepam all given IM; all patients were initially physically restrained to see if behavior improved and if not were entered into the drug study; total of 111 patients were entered; a 3-point combativeness scale was used to measure agitation; data recorded every 15 min; mean time to sedation for lorazepam was 32.2 min, haloperidol 28.3 min, and midazolam 18.3 min; mean time to arousal after initial medications was 217 min for lorazepam, 126 min for haloperidol, and 82 min for midazolam; differences were significant; there was no difference in the percentage of patients requiring rescue medications at 20 min among groups | Convenience sample; combativeness scale had not been validated; drug dosages used may not be equipotent | II |
| Mendoza et al ⁴¹ | Case report | Discussed 3 patients who received 2.5-3 mg of midazolam for acute psychiatric agitation; all patients were rapidly sedated within 6-8 min without any ill affects | Case study | III |
| Wyant et al ⁴² | Nonrandomized drug trial | 3 treatment groups of agitated inpatients: 5 patients each received 10 mg IM haloperidol or 5 mg IM midazolam or 250 mg IM sodium amytal; assessed by a clinical global rating scale; all treatments effective in reducing agitation; amytal and midazolam were significantly more effective than haloperidol in motor agitation, all equivalent in hostility rating | Small numbers; not randomized; schizophrenic patients; redosing not mentioned | III |
| TREC Collaborative Group ⁴³ | Randomized clinical trial comparing midazolam vs haloperidol with promethazine | 301 patients from 3 different psychiatric EDs compared 7.5 or 15 mg of midazolam to 5 or 10 mg haloperidol plus 25 or 50 mg of promethazine; outcomes were tranquil or asleep by 20 min; more patients given midazolam were tranquil or asleep at 40 min, but at 1 h 90% of both groups were tranquil or asleep; twice as many patients given midazolam were asleep at 20 min than those given haloperidol-promethazine; 1 patient in each group with side effects | Nurses did the assessment and not blinded; patients entered at discretion of physician; reasons for patient exclusion not mentioned; doses were not controlled; promethazine may contribute to sedation | III |

Evidentiary Table (continued).

| Study | Design | Findings | Limitations | Grade |
|-----------------------------------|---|--|---|--------------|
| Bieniek et al ⁴⁴ | A randomized double-blinded controlled study of lorazepam vs combination of haloperidol and lorazepam | 20 patients total; 11 patients received lorazepam 2 mg, and 9 patients received a combination of 5 mg haloperidol with 2 mg of lorazepam; improvement in agitation measured by analog scale and OAS at 60 min after injection; combination of haloperidol and lorazepam was superior to lorazepam alone with both agitation scales but not statistically different with a third, CGI scale | Small number of patients; convenience sample | III |
| Clinton et al ⁴⁵ | Case series | 136 patients had haloperidol administered to control behavior in an ED setting; disruptive behavior was decreased within 30 min in 83% of patients; no effect was noted in 2 and suboptimal effect in 15%; 4 (3%) complications were noted, the most serious being an episode of hypertension | Retrospective review of medical record; no inclusion criteria mentioned; measure of agitation not validated | III |
| Baldessarini, et al ⁴⁶ | Review article | Review of the results of 3 randomized, blinded comparisons of 8 doses of parenteral haloperidol from 2.5-41 mg and a placebo in diagnostically mixed agitated psychotic patients; demonstrated dose dependent improvement to a maximum of about 50% within 2-4 h at doses up to 10-15 mg; above 15 mg, there was less improvement and eventual decrease in effect | 2 of the studies used only 2 separate doses; chlorpromazine used for 1 point on the scale; equivalence to haloperidol not clear; not clear if measure of agitation between studies was equal | III |
| Thomas et al ⁴⁷ | Randomized trial comparing haloperidol vs droperidol in agitated patients | 68 ED patients; 21 received 5 mg of haloperidol IM, 26 received 5 mg droperidol IM; 12 administered haloperidol IV and 9 received 5 mg droperidol IV; patients rated on a 5 point combativeness scale; there was a significantly more rapid response to IM droperidol than to IM haloperidol at 5, 15, and 30 but not 60 min; there is no significant difference between the 2 drugs given by IV route although the number of patients was small; 1 patient returned with dystonic reaction; more patients receiving haloperidol required hospital admission | Small number of patients in each arm; combativeness scale not validated; many subjects dropped at 30 min because of persistent agitation and therefore remedicated; equal doses of droperidol and haloperidol may not be equipotent | II |
| Resnick and Burton ⁴⁸ | A randomized drug therapy study of involuntarily hospitalized patients | 27 patients randomized to receive either IM droperidol 5 mg or haloperidol 5 mg; patients followed by changes in BPRS 15 min after injection and at 30 min intervals for 3 h; patients receiving droperidol require fewer injections, at 30 min after treatment 81% of haloperidol treated patients but only 35% of those treated with droperidol required a second injection; droperidol seemed to perform better than haloperidol; only adverse reaction was mild dystonic reaction in a patient in the haloperidol group | Small sample size; not clear if generalizable to an ED; scale scores of the BPRS not reported, only the number of injections used; all psychiatric patients | III |

Evidentiary Table (continued).

| Study | Design | Findings | Limitations | Grade |
|-------------------------------|---|---|--|--------------|
| Richards et al ⁴⁹ | Randomized nonblinded ED drug therapy study comparing lorazepam 4 mg and droperidol 5 mg (dose reduced for less than 50 kg in patients) | Convenience sample of 202 patients entered; validated 6-point sedation scale was used and observations were recorded at 0, 5, 10, 15, 30, and 60 min; total of 32 different physicians were involved in determining level of sedation; there was a significantly faster response to droperidol 5 mg than lorazepam 4 mg at 10, 15, 30, and 60 min; 40 repeat doses of lorazepam were given compared to 8 of droperidol; there was no difference in patients given lorazepam or droperidol in regard to change of pulse, systolic blood pressure, respiratory rate; 1 patient had an acute dystonic reaction to droperidol; 32% had their agitation ultimately attributed to methamphetamine toxicity, 14% to cocaine, 10% to psychiatric illness, and 4% ethanol withdrawal | Treating physicians knew which drug was given; multiple observers of agitation, intraobserver reliability not determined; many excluded patients | II |
| Chase and Biros ⁵⁰ | A retrospective review of droperidol safety in ED use over 1 y | Total of 2,468 patients received droperidol; 2,123 for agitation/anxiety; overall 6 had adverse reactions noted, respiratory depression in 2, seizures in 3, cardiac arrest in 1 with cocaine toxicity 11 h after receiving the droperidol; no prolonged QT on ECG; the great majority of patients who received droperidol in the ED did not experience any adverse events | Retrospective review of patient records | III |
| Shale et al ⁵¹ | Review of literature on droperidol use | More than 12,000 patients received droperidol for agitation without any significant dysrhythmic event in more than 10 y of experience; all doses 5 mg or less | Review; number extrapolated from 3 y of documented use | III |
| Horowitz et al ⁵² | Commentary | Describes the events surrounding the FDA advisory placing a 'black box' warning for droperidol; discussed the evidence, and lack thereof, presented to the FDA to produce the warning | Commentary | III |
| Kao et al ⁵³ | Review article | Literature search of the evidence for droperidol and QT prolongation and the occurrence of torsades de pointes; 3 clinical studies, an abstract, and 7 case reports located implicating droperidol; applied evidence-based principles to the reports and found a dose-dependent relationship between the drug and QT prolongation; however, there was not a clear causal link between therapeutic administration of droperidol and dysrhythmias such as torsades or sudden death | Review article | III |
| Citrome ⁵⁴ | Review article | Newer antipsychotics are often better tolerated than the older neuroleptics; they may be used IM when oral administration is difficult; atypical antipsychotics are generally better tolerated than the older medications | Review article | III |

Evidentiary Table (continued).

| Study | Design | Findings | Limitations | Grade |
|------------------------------|---|--|---|-------|
| Harrigan et al ⁵⁵ | Prospective, open label, randomized parallel-group cohort | 164 stable patients received maximum recommended doses of ziprasidone, olanzapine, quetiapine, risperidone, haloperidol, or thioridazine; study drug administered for at least 3 days after steady state reached, then inhibitors of drug metabolism given; ECG and blood samples obtained at baseline and 3 each day of study; approximately 30 patients completed study with each drug; mean heart rate increased in each group, except haloperidol; QTc increased with all drugs from olanzapine 1.7 ms to thioridazine 30.1 ms; no drug increased QTc >500 ms, with or without metabolic inhibitor | Small numbers in each group; only 1 blood sample measured to assess maximum blood level; number of dropouts | II |
| Daniel et al ⁵⁶ | Prospective, randomized, double-blind study comparing IM ziprasidone 2 mg vs 20 mg | Randomized 79 patients to ziprasidone 2 mg or 20 mg both IM; the mean BARS score showed statistically significant reduction in the 20 mg group at 30 min post-dose compared to the 2-mg dose subjects; no substantial side effects were noted, including EPS, dystonia, or excessive sedation | Study excluded the most hostile/agitated patients because of requirement of written informed consent | II |
| Lesem et al ⁵⁷ | Randomized, double-blinded trial comparing IM ziprasidone 2 mg to 10 mg | 117 patients assigned to receive up to 4 doses every 2 h PRN of 2 mg or 10 mg IM ziprasidone; patients receiving 10 mg IM ziprasidone had a more significant reduction in BARS scores at 15 min after initial dose, demonstrating rapid onset of action as compared to the 2-mg dose | Patients with substance abuse excluded but some positive for cannabinoids or benzodiazepines were admitted at investigator's discretion; written consent needed, selection bias | II |
| Brook et al ⁵⁸ | Randomized, open-label, multicenter, international study comparing IM ziprasidone with IM haloperidol | 132 patients randomly assigned to 3 days of IM ziprasidone or haloperidol; after an initial IM ziprasidone dose of 10 mg, subsequent IM doses of 5-20 mg could be given every 4-6 h followed by oral; haloperidol IM of 2.5-10 mg was given on entry, followed by 2.5-10 mg every 4 to 6 h, followed by oral; the mean reduction in BPRS total, BPRS agitation items, and CGIS scale scores were statistically significantly greater after IM ziprasidone compared with the IM haloperidol group; ziprasidone was also associated with a lower incidence of movement disorders | Excluded extremely agitated patients; questionable generalizability; unknown if equipotent doses | III |
| Preval et al ⁵⁹ | Nonrandomized, nonblinded convenience sample | 110 patients with agitation (17 classified as psychiatric-induced, 10 alcohol-induced, and 28 substance-induced) were treated with 20 mg IM ziprasidone compared to 9 patients given conventional IM therapy, usually haloperidol and lorazepam; both ziprasidone-treated patients and conventionally treated patients had equally decreased agitation scores (BARS) at 15 min; at 120 min, agitation scores of both groups remained decreased as compared to baseline; ziprasidone use decreased the mean time needed for patient restraints compared to a group of like patients treated a month before ziprasidone was introduced | Not randomized or blinded; few control patients; varying dosages of conventional drugs; selection bias | III |

Evidentiary Table (continued).

| Study | Design | Findings | Limitations | Grade |
|-----------------------------|--|---|---|--------------|
| Breier et al ⁶⁰ | Double-blind, randomized, placebo-controlled trial comparing IM olanzapine to IM haloperidol | 270 recently hospitalized, acutely agitated patients with schizophrenia randomized to receive IM olanzapine (2.5, 5, 7.5, or 10 mg), haloperidol (7.5 mg) or placebo; IM olanzapine and haloperidol were both superior to placebo, however, no significant difference noted between IM olanzapine and haloperidol based on the PANSS-EC scores | Signed consent needed; non-ED study | II |
| Wright et al ⁶¹ | Double-blind, randomized, placebo-controlled comparison of IM olanzapine and IM haloperidol | 311 patients were randomly assigned to receive 10 mg IM olanzapine or 7.5 mg IM haloperidol or placebo; there was no significant difference in response rate between patients treated with olanzapine and those treated with haloperidol based on PANSS-EC scores, ABS score, and the ACES score; both olanzapine and haloperidol were superior to placebo | Patients needed to sign informed consent; non-ED study | II |
| Meehan et al ⁶² | Double-blind, randomized, placebo-controlled trial | 201 patients were randomly assigned to receive 1-3 injections of olanzapine (10/10/5), lorazepam (2/2/1) or placebo IM; at 2 h after the first injection, olanzapine-treated patients showed a significantly greater reduction in scores on all agitation scales compared with patients treated with either placebo or lorazepam; at 24 h however, there was no significant difference between olanzapine or lorazepam-treated patients | All patients with bipolar mania; all patients needed signed informed consent to enter | II |
| Meehan et al ⁶³ | Randomized, double-blind, placebo-controlled study | 272 patients were randomly assigned to receive either olanzapine 2.5 mg or 5 mg or lorazepam 1 mg or placebo IM; differences among the 3 active treatment groups on the 3 measures of agitation: PANSS-EC, CMAI, ACES were not significant; however, olanzapine 5 mg dose had a faster onset of action, and both doses were longer lasting than lorazepam; no significant difference seen in EPS or corrected QT interval | All patients with dementia related agitation associated with Alzheimer's disease and/or vascular dementia | II |
| Currier et al ⁶⁵ | A prospective randomized rater-blinded study of both ED and inpatients; group received oral dose of risperidone plus lorazepam or IM dose of haloperidol and lorazepam | 162 patients at 24 sites entered; patients received either an oral dose of 2 mg risperidone plus 2 mg lorazepam or 5 mg haloperidol and 2 mg of lorazepam IM; efficacy measured with a PANSS Scale, CGI Scale, and the OAS; both treatment groups had significant improvements in the agitation cluster score at 30, 60, and 120 min; improvement in the PANSS and the OAS scores was demonstrated in both groups with no between group differences; at 30 min, only 6% of the oral group could not be evaluated because of sleeping, whereas 21% of the IM group could not be evaluated because of sleep; oral dose of risperidone plus lorazepam was as effective as haloperidol plus risperidone administered IM | Only psychiatric patients involved; patients who should not take oral administration were excluded | II |

ABS, Agitated Behavior Scale; ACES, Agitation Calmness Evaluation Scale; BARS, Behavioral Activity Rating Scale; BPRS, Brief Psychiatric Rating Scale; BUN, blood urea nitrogen; CGI, Clinical Global Impressions; CGIS, Clinical Global Impressions Severity; CMAI, Cohen-Mansfield Agitation Inventory; CT, computed tomography; CXR, chest radiograph; EPS, extrapyramidal symptoms; ESRS, extrapyramidal symptom reading scale; FDA, Food and Drug Administration; IM, intramuscular; IMPS, inpatient multidimensional psychiatric scale; IV, intravenous; NOSIE, Nurses Observation Scale for Inpatient Evaluation; OAS, Overt Aggression Scale; PANSS, Positive and Negative Syndrome Scale; PANSS-EC, Positive and Negative Syndrome Scale-Excited Component; PRN, as needed; PT, prothrombin time; TMBSS, Target Manic Behavioral Symptom Scale; VAS, visual analog scale.

Appendix A. Definitions of delirium and dementia

Delirium is a condition of impaired attention, changes in behavior, and clouded sensorium, which follows a waxing and waning course. The delirious patient may be agitated, disoriented, and confused. Importantly, delirium is a disturbance of impaired attention; it is not primarily a disturbance of memory. It is acute or subacute in onset and may be accompanied by a panoply of other symptoms, including neurologic disturbances such as tremor, increased muscle tone, visual hallucinations, and impaired speech.

Dementia is a chronic disturbance of mental function due to diffuse or disseminated disease of the cerebral hemispheres that may affect memory, language, visual-spatial skills, complex cognition, emotion, and personality to varying degrees. Unlike those with delirium, patients with dementia have a clear sensorium and do not present with cyclic patterns of symptoms. Delirium may occur in patients with an underlying dementia, posing a diagnostic challenge.

Meyers J, Stein S. The psychiatric interview in the emergency department. *Emerg Med Clin North Am.* 2000;18:173-183. Printed with permission.

Appendix B. Literature classification schema*

| Design/Class | Therapy [†] | Diagnosis [‡] | Prognosis [§] |
|--------------|--|---|---|
| 1 | Randomized, controlled trial or meta-analyses of randomized trials | Prospective cohort using a criterion standard | Population prospective cohort |
| 2 | Nonrandomized trial | Retrospective observational | Retrospective cohort Case control |
| 3 | Case series Case report Other (eg, consensus, review) | Case series Case report Other (eg, consensus, review) | Case series Case report Other (eg, consensus, review) |

*Some designs (eg, surveys) will not fit this schema and should be assessed individually.

[†]Objective is to measure therapeutic efficacy comparing ≥ 2 interventions.

[‡]Objective is to determine the sensitivity and specificity of diagnostic tests.

[§]Objective is to predict outcome including mortality and morbidity.

Appendix C. Approach to downgrading strength of evidence

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