



The acutely agitated or violent adult: Pharmacologic management

AUTHORS: Malia J Moore, MD, Dana Im, MD, MPP, MPhil

SECTION EDITOR: Korilyn S Zachrisson, MD, MSc

DEPUTY EDITOR: Michael Ganetsky, MD

All topics are updated as new evidence becomes available and our [peer review process](#) is complete.

Literature review current through: **Oct 2025**.

This topic last updated: **Oct 10, 2025**.

INTRODUCTION

Clinicians must be prepared to effectively manage agitated or violent patients to reduce the risk of serious injury to the patient and clinical teams. Medication administration may be necessary for an agitated or violent adult patient who does not respond to verbal de-escalation techniques. Anticipating the need for pharmacologic management early in the clinical course of a patient likely to become agitated may obviate the need for physical restraint.

The selection and administration of calming medications for the agitated adult patient is reviewed here. The following related issues are discussed in separate topics:

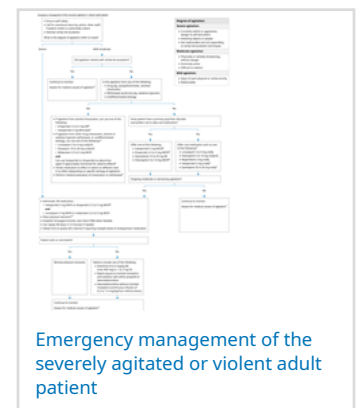
- Evaluation and nonpharmacologic management of the acutely agitated or violent patient (see "[The acutely agitated or violent adult: Overview, assessment, and nonpharmacologic management](#)")
- Management of specific psychiatric ailments (see "[Suicidal ideation and behavior in adults](#)" and "[Psychosis in adults: Epidemiology, clinical manifestations, and diagnostic evaluation](#)")
- Management of neuropsychiatric symptoms of dementia (see "[Management of neuropsychiatric symptoms of dementia](#)")
- Risks of benzodiazepines and antipsychotics during pregnancy (see "[Teratogenicity, pregnancy complications, and postnatal risks of antipsychotics, benzodiazepines, lithium, and neuromodulation](#)")
- Management of poisoned or ethanol-intoxicated patients (see "[General approach to drug poisoning in adults](#)" and "[Ethanol intoxication in adults](#)")

PROPERTIES AND ADMINISTRATION OF CALMING MEDICATIONS

Characteristics of ideal calming medication — The ideal calming medication is rapidly acting, effective regardless of the route of administration, and possesses minimal side effects. Medication classes include benzodiazepines, first-generation (typical) antipsychotics, second-generation (atypical) antipsychotics, dissociative anesthetics (eg, [ketamine](#)), and alpha-2 adrenergic receptor agonists (eg, [dexmedetomidine](#)).

We prefer to use medications with proven efficacy and relative safety as many agitated or violent patients presenting to an emergency department (ED) are not well known to the clinicians providing the initial care. Our approach includes determining the degree of agitation and most likely etiology and is provided below and in the algorithm ([algorithm 1](#)). Our approach is based on the available, albeit limited, evidence and our clinical experience. Available evidence predominantly informs us about young patients (20 to 50 years of age), with many studies excluding patients over age 65. In 2023 the American College of Emergency Physicians updated its clinical policy that discusses pharmacologic treatment for the acutely agitated patient in the ED [1] and in 2012 a workgroup of the American Association for Emergency Psychiatry published recommendations for the management of agitation [2].

We recognize that psychiatrists who are familiar with the patient or are more experienced in the diagnosis and management of particular psychiatric conditions may prefer alternative calming medications that target the underlying symptoms, which is discussed separately. (See "[Bipolar mania and hypomania in adults: Choosing pharmacotherapy](#)", [section on 'Agitation'](#) and "[Schizophrenia in](#)



Algorithm 1 - larger image below

[adults: Maintenance therapy and side effect management](#)", section on [Initial management of acute psychosis](#).)

Special considerations for older adults — In general, for older adults (ie, ≥ 65 years of age), we reduce the initial calming medication dose by half. We generally avoid benzodiazepines in older adults since they can generate paradoxical responses, behavioral disinhibition, and adverse respiratory events [3]. Other considerations include the following:

- Dementia with Lewy bodies (DLB) disease – We avoid antipsychotic medications since they can cause idiosyncratic, life-threatening adverse reactions in patients with DLB. If antipsychotic therapy is required, select agents (eg, [quetiapine](#), [clozapine](#)) can be used in very small doses. (See ["Prognosis and treatment of dementia with Lewy bodies"](#), section on [Antipsychotic drugs](#).)
- Parkinson disease – We avoid first-generation antipsychotics and some second-generation antipsychotics ([risperidone](#), [olanzapine](#)) since they can exacerbate parkinsonism. [Quetiapine](#), [clozapine](#), and [pimavanserin](#) are commonly used in patients with Parkinson disease when pharmacologic treatment of psychotic symptoms is necessary. (See ["Management of nonmotor symptoms in Parkinson disease"](#), section on [Refractory psychotic symptoms](#) and ["Drug-induced parkinsonism"](#), section on [Causative drugs](#).)

Unique aspects of pharmacologic therapy for managing agitation caused by dementia are discussed separately. (See ["Management of neuropsychiatric symptoms of dementia"](#), section on [Severe or refractory symptoms](#).)

Considerations on route of administration — Placing an intravenous (IV) catheter in an agitated patient is potentially difficult and time-consuming. Studies reporting the time required to achieve sedation often do not account for the time needed to establish IV access.

Some patients view injectable (IV or intramuscular) medications as an assault, invoking images of punishment and incarceration rather than therapy and relief [4]. For the agitated but nonviolent patient willing to cooperate with treatment, oral medications can be as effective as a parenteral form [5].

Switching between medication classes — We titrate repeat doses of the calming medication to effect and switch to a different class if there is no effect after the first dose or excessive doses are required. Some patients may have paradoxical reactions and become more agitated after receiving a particular medication. In such cases, no additional agents from this class should be given and only alternative classes used.

APPROACH TO MEDICATION SELECTION

All patients — At all levels of agitation, verbal de-escalation should be attempted and an oral medication offered first (if can be done safely) before moving to involuntary medication administrations and physical restraints. In conjunction with offering oral medications, some clinicians routinely offer intramuscular (IM) or intravenous (IV) medications without physical restraint in case the patient prefers parenteral administration due to familiarity or faster onset. Medication options are discussed immediately below and verbal de-escalation techniques and application of restraints is discussed separately. (See ["The acutely agitated or violent adult: Overview, assessment, and nonpharmacologic management"](#), section on [Initial management](#).)

Severe agitation — This includes a patient who is currently violent or aggressive, danger to self and others, attacking objects or people, or not redirectable and not responding to verbal de-escalation techniques ([algorithm 1](#)). In such a patient or a patient with ongoing agitation following attempted treatment of mild or moderate agitation, we suggest a combination of a rapidly-acting first-generation antipsychotic and a benzodiazepine (eg, [droperidol](#) 2.5 to 5 mg IM/IV and [midazolam](#) 2.5 to 5 mg IM/IV, or [haloperidol](#) 5 mg IM/IV and [lorazepam](#) 2 mg IM/IV). In most cases of undifferentiated agitation, combination therapy provides the optimal balance of rapid onset, efficacy, and minimizing side effects. (See ['Combination benzodiazepine with antipsychotic'](#) below.)

This combination can be repeated in 15 minutes if the patient is not sufficiently calm. However, an electrocardiogram (ECG) should be obtained to assess for prolongation of the QTc interval if the patient is requiring more than one dose of an antipsychotic agent. (See ["Acquired long QT syndrome: Definitions, pathophysiology, and causes"](#), section on [Psychotropic medications](#).)

Considerations in older adults (ie, ≥ 65 years of age), such as reducing the initial dose and avoiding benzodiazepines, are discussed above. (See ['Special considerations for older adults'](#) above.)

In a patient with persistent severe agitation despite multiple doses of an antipsychotic and benzodiazepine, especially if they are struggling against restraints, options include [ketamine](#) (1 to 2 mg/kg IV or 4 to 6 mg/kg IM, maximum dose 400 mg IM), [dexmedetomidine](#) without tracheal intubation (continuous infusion of 0.2 to 1.5 mcg/kg/hour), or rapid sequence tracheal intubation followed by [propofol](#) or dexmedetomidine infusions. If ketamine is administered after or in addition to another sedative or antipsychotic, we suggest reducing the initial dose by 50 percent. (See ['Ketamine'](#) below and ['Dexmedetomidine'](#) below and ["Rapid sequence intubation in adults for emergency medicine and critical care"](#).)

Mild to moderate agitation — This includes a patient who is redirectable or difficult to redirect, has signs of overt physical and/or verbal activity without danger, is physically or verbally threatening, or is extremely active ([algorithm 1](#)).

NOT from drug intoxication or withdrawal

- **Not calm following verbal de-escalation techniques** – We offer oral medications, such as a benzodiazepine (eg, [lorazepam](#) 2 to 4 mg orally) or second-generation antipsychotic (eg, [olanzapine](#) 5 to 10 mg orally/sublingual or [risperidone](#) 2 mg orally). A first-generation antipsychotic (eg, [haloperidol](#) 5 mg orally) is also a reasonable option. In a patient with mild agitation, we offer the lower dose in range provided. [Quetiapine](#) 25 to 50 mg orally is an alternative option in older patients (age ≥65) able to take an oral medication, especially those with dementia or Parkinson disease, although efficacy evidence for acute agitation is limited. (See '[Benzodiazepines](#)' below and '[Second-generation \(atypical\) antipsychotics](#)' below and '[First-generation \(typical\) antipsychotics](#)' below.)
- **Primary psychotic disorder who prefers not to take an oral medication** – We suggest a first-generation antipsychotic (eg, [haloperidol](#) 5 mg IM/IV or [droperidol](#) 2.5 to 5 mg IM/IV), but a second-generation antipsychotic (eg, [ziprasidone](#) 10 to 20 mg IM or [olanzapine](#) 5 to 10 mg IM/IV) is a reasonable option. If we are administering olanzapine IM combined with a parenteral benzodiazepine, we suggest separating these doses by at least 60 minutes given the potential risk of excess sedation and respiratory depression. (See '[First-generation \(typical\) antipsychotics](#)' below and '[Second-generation \(atypical\) antipsychotics](#)' below.)

Drug intoxication, withdrawal, or undifferentiated

- **Agitation from alcohol intoxication** – We suggest a rapidly-acting first-generation antipsychotic (eg, [droperidol](#) 2.5 to 5 mg IM, [haloperidol](#) 5 mg IM/orally). Combining one of these antipsychotic agents with a benzodiazepine is a reasonable alternative, but caution must be taken as benzodiazepines can worsen the respiratory depression caused by ethanol. (See '[First-generation \(typical\) antipsychotics](#)' below and '[Combination benzodiazepine with antipsychotic](#)' below and '[Ethanol intoxication in adults](#)', section on '[Management](#)'.)
- **Agitation from alcohol withdrawal delirium** – We prefer a benzodiazepine, but [phenobarbital](#) 10 mg/kg IV a reasonable alternative. Antipsychotics should generally be avoided for treatment of alcohol withdrawal but may be appropriate in a patient with a coexisting decompensated thought disorder (such as schizophrenia) and any persistent symptoms associated with the withdrawal that have not been definitively treated with a benzodiazepine or phenobarbital. (See '[Management of moderate and severe alcohol withdrawal syndromes](#)', section on '[Treatment of psychomotor agitation](#)'.)
- **Anticholinergic delirium** – A benzodiazepine or [physostigmine](#) (0.5 to 2 mg IV) are reasonable options. Prior to giving physostigmine, obtain an ECG and place the patient on a cardiac monitor. Do not give physostigmine if the patient could have ingested a tricyclic antidepressant or the QRS interval >100 msec. Antipsychotics should be avoided in patients with anticholinergic delirium. (See '[Anticholinergic poisoning](#)', section on '[Agitation, seizures, hyperthermia](#)'.)
- **Agitation from other drug intoxication (eg, sympathomimetic) or sedative-hypnotic withdrawal, or with an undifferentiated etiology of agitation** – We suggest initial treatment with a benzodiazepine (eg, [lorazepam](#) 2 to 4 mg orally/IM/IV, [diazepam](#) 10 to 20 mg orally/IV, or [midazolam](#) 2.5 to 5 mg IM/IV) due to concern for increased risk of adverse effects of antipsychotic agents (eg, prolongation of QTc interval, impaired heat dissipation) in this population. Antipsychotic agents may be used as adjunctive therapy if benzodiazepines do not adequately control agitation. In a patient with undifferentiated agitation, a first-generation antipsychotic is also a reasonable choice if appropriately monitored for adverse effects but should be avoided as monotherapy in a patient with a sedative-hypnotic withdrawal syndrome. (See '[Benzodiazepines](#)' below and '[First-generation \(typical\) antipsychotics](#)' below and '[Methamphetamine: Acute intoxication](#)', section on '[Sedation](#)' and '[Cocaine: Acute intoxication](#)', section on '[Psychomotor agitation](#)' and '[Synthetic cannabinoids: Acute intoxication](#)', section on '[Agitation and psychosis](#)' and '[Acute amphetamine and synthetic cathinone \("bath salt"\) intoxication](#)', section on '[Psychomotor agitation](#)' and '[Benzodiazepine withdrawal](#)', section on '[Initial Management](#)' and '[Gamma hydroxybutyrate \(GHB\) withdrawal and dependence](#)', section on '[Management of acute withdrawal](#)'.)

MEDICATION OPTIONS DISCUSSED ABOVE

Benzodiazepines — Benzodiazepines are especially useful in patients who are agitated from drug intoxication or withdrawal and patients with undifferentiated agitation, but are also effective for acute psychosis [6,7]. In agitated but cooperative patients, benzodiazepines may also be given orally.

- **Lorazepam** – Commonly used for its rapid onset of action, effectiveness, short half-life, and oral, intramuscular (IM), or intravenous (IV) routes of administration [8,9]. Some experts give IV doses as frequently as every 8 to 10 minutes for severely agitated patients, although this could lead to excess sedation since the time to peak central nervous system (CNS) effects can be 30 minutes [10]. The onset of action is slower with IM or oral administration. The duration of effect is six to eight hours.
- **Midazolam** – This is an effective sedative with a more rapid onset than lorazepam but a shorter duration of action (one to two hours) [11]. For IM administration, [midazolam](#) has faster onset compared with [lorazepam](#) and [diazepam](#). In a severely agitated patient, midazolam doses may be repeated every three to five minutes.

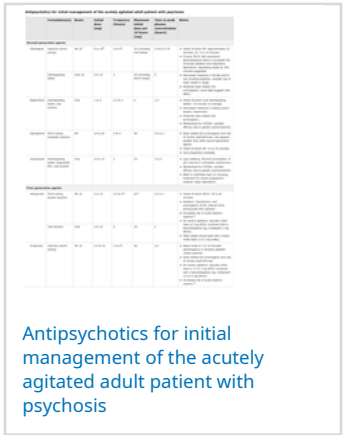
- **Diazepam** – This agent has a rapid onset of action (within minutes) when given IV and is effective orally and IV but has erratic IM absorption [8]. A single IV dose of **diazepam** has a shorter duration of action (one to two hours) compared with an equivalent lorazepam dose [12]. Following multiple diazepam doses, its duration of action is prolonged (>20 hours) due to accumulation and active metabolites and thus, it may be preferable when prolonged agitation is anticipated (eg, alcohol withdrawal). In a severely agitated patient, diazepam IV doses may be repeated every 5 to 10 minutes.

Benzodiazepines may cause excessive somnolence, and less commonly, respiratory depression or paradoxical disinhibition (and repeat dosing may worsen agitation) [13].

The efficacy of benzodiazepines in treating acute agitation has been demonstrated in several trials. In a trial involving 206 acutely agitated emergency department (ED) patients, **midazolam** (5 mg) was found to provide more rapid sedation compared with **olanzapine** (5 mg) or **haloperidol** (5 mg) (median time to sedation 9 versus 12 and 23 minutes, respectively) [14]. In a trial involving 153 acutely agitated ED patients, midazolam (median dose 5 mg) and **droperidol** (median dose 10 mg) were equally effective in achieving sedation within 10 minutes; three patients in the midazolam group temporarily required assisted ventilation, and one required tracheal intubation [15]. In a trial involving 111 ED patients, midazolam (5 mg IM) was found to provide more rapid sedation of severely agitated patients than **lorazepam** (2 mg IM) or haloperidol (5 mg IM); all three agents provided effective sedation, and no differences in hemodynamics or respiratory function were observed [16]. In several studies of agitated ED patients, those treated with midazolam (5 mg IM) achieved more rapid sedation but more often required additional medication for breakthrough symptoms compared with those treated with droperidol (5 mg IM), haloperidol (5 or 10 mg), **ziprasidone** (20 mg), or olanzapine (10 or 20 mg IM) [17-19]. Lorazepam is similarly efficacious and safe compared with midazolam, although the evidence is not as robust [20].

First-generation (typical) antipsychotics — The first-generation (ie, "typical") antipsychotics include the butyrophenones **haloperidol** and **droperidol**, which are effective first-line agents for the sedation of violent and acutely agitated patients ([table 1](#)) [8,21-23].

- **Haloperidol** – This agent can be given IV, IM, or orally, although its IV use is not approved by the United States Food and Drug Administration (FDA). The onset of action of **haloperidol** IV or IM is within 30 to 60 minutes, and the duration of effect can last up to 24 hours [8]. Doses can be repeated every 15 to 30 minutes in patients with severe agitation until the desired level of sedation is achieved. The dose should be decreased by one-half in older patients.
- **Droperidol** – This agent is an analog of haloperidol with a more rapid onset of action (3 to 10 minutes) and shorter duration of effect (of two to four hours) [8,23]. **Droperidol** can be given IM or IV. Multiple randomized trials have demonstrated the effectiveness of droperidol in controlling acute agitation [9,15,17,23-27]. Droperidol may be the most effective antipsychotic available as monotherapy. A pharmacokinetics study found that IM droperidol is rapidly absorbed, obviating the need for IV therapy and preventing risk to health care and security workers during attempts at IV catheter placement [28].



Antipsychotics for initial management of the acutely agitated adult patient with psychosis

Table 1 - larger image below

The first-generation antipsychotics have been extensively studied for the treatment of acute agitation from various etiologies. For example, a trial of 115 ED patients with acute undifferentiated agitation found that 15 minutes after administration, **droperidol** 5 mg IM achieved adequate sedation in 64 percent (16/25) of patients compared with 25 percent (7/28) with **ziprasidone** 10 mg IM, 35 percent (11/31) with ziprasidone 20 mg IM, and 29 percent (9/31) with **lorazepam** 2 mg IM [27]. Respiratory depression was less frequent in patients who received droperidol (12 versus 36-48 percent); QTc intervals were similar for all agents and no ventricular dysrhythmias occurred. A trial of 68 ED patients with acute agitation found that droperidol 5 mg IM more rapidly controlled agitation compared with **haloperidol** 5 mg IM; there was no difference in adverse effects or when haloperidol 5 mg and droperidol 5 mg were given IV [23]. A trial involving 228 patients with acute behavioral disturbance in a psychiatric unit found similar median time to sedation for droperidol (10 mg IM) and haloperidol (10 mg IM) (20 and 25 minutes respectively), but additional sedation was required more often with haloperidol (13 versus 5 percent) [29]. In a retrospective review of 11,787 patients with acute agitation due to alcohol intoxication, droperidol given as monotherapy was associated with a shorter median length of stay in the ED (499 minutes) compared with parental haloperidol (524 minutes) or **olanzapine** (533 minutes) [30].

A low-dose antipsychotic may be helpful for the management of hyperactive delirium, but extensive high-quality trial evidence does not exist to establish the efficacy or safety of any single antipsychotic [31]. The administration and evidence for use in delirium is discussed separately. (See ["Delirium and acute confusional states: Prevention, treatment, and prognosis"](#), section on 'Antipsychotic medications'.)

The adverse effects of first-generation antipsychotics are discussed in detail separately, but the following are often relevant when managing a patient with acute agitation (see ["First-generation antipsychotic medications: Pharmacology, administration, and comparative side effects"](#), section on 'Side effects');

- **QT interval prolongation** – All first-generation antipsychotics possess quinidine-like cardiac effects that can prolong the QT interval and increase risk of dysrhythmias, particularly torsades de pointes. These agents are contraindicated in patients with known QT prolongation, including patients with congenital long QT syndrome. These agents should not be used in a patient with a QTc >500 ms or an increase in QTc $\geq$ 60 ms during treatment. (See "[First-generation antipsychotic medications: Pharmacology, administration, and comparative side effects](#)", section on 'QT interval prolongation and sudden death'.)

First-generation antipsychotics should be administered cautiously to patients with increased risk for QT prolongation, such as concurrently taking other medications known to prolong the QT interval (eg, [methadone](#)), electrolyte disorders (eg, hypokalemia, hypomagnesemia), and those requiring multiple doses of the antipsychotic for agitation control. If feasible, an electrocardiogram (ECG) should be performed prior to administration, but this may be impossible when managing a violent patient. In such cases, an ECG should be obtained once the patient is sufficiently sedated. Depending on the results, the patient should be placed on a cardiac monitor. (See '[Monitoring for adverse effects](#)' below.)

In 2001, the FDA gave [droperidol](#) a "black box" warning because of the risk of QT prolongation [32]. A warning for [haloperidol](#) followed in 2007 [33]. These warnings have generated substantial debate given the drugs' long history of effectiveness and the dearth of substantial clinical evidence demonstrating harm [34-37]. Subsequent studies have raised doubts whether the warning was justified. For example, in a retrospective chart review of 16,546 patient treated with droperidol, the overall incidence of severe dysrhythmia was exceedingly low (0.006 percent); only one patient suffered a cardiac arrest, felt to be unrelated to the medication, and five experienced ventricular dysrhythmias, including one patient with torsades de pointes who had multiple pre-existing risk factors [38]. A multi-center ED study involving 1009 patients who received droperidol (median dose 10 mg) for acute agitation and had an ECG found no episodes of torsades de pointes, and only six patients with QT interval prolongation attributable to droperidol [39].

- **Acute dystonic reactions** — The risk of a dystonic reaction is greatest with high-potency first-generation antipsychotic agents ([table 2](#)). The true incidence following acute administration is unknown but likely relatively low (eg, 1 percent one study) [18]. These reactions are often distressing to the patient and can include sustained muscular spasms (typically in the neck, tongue, or jaw), choreoathetoid movements, opisthotonus, or oculogyric crisis. Treatment is [diphenhydramine](#) 25 to 50 mg IM/IV or [benztropine](#) 1 to 2 mg IM/IV, which is discussed in detail separately. (See "[First-generation \(typical\) antipsychotic medication poisoning](#)", section on 'Acute extrapyramidal syndromes'.)

We suggest to not prophylactically coadminister [diphenhydramine](#) or [benztropine](#) with the IM antipsychotic dose (eg, "B52"). Some experts routinely coadminister diphenhydramine or benztropine as it may decrease the incidence of dystonic reactions, but these reactions are uncommon and the added agent may increase the risk of adverse events. In a retrospective study of 400 patients, the addition of diphenhydramine 50 mg IM to [haloperidol](#) 5 mg/[lorazepam](#) 2 mg IM was associated with a longer ED length of stay (17 versus 14 hours), more frequent use of restraints (43 versus 27 percent), and more patients with hypotensive events (16 versus 4 percent) or oxygen desaturation (3 versus 0 percent) [40].

Second-generation (atypical) antipsychotics — The second-generation (ie, "atypical") antipsychotics effective in treating acute agitation include [olanzapine](#), [risperidone](#), and [ziprasidone](#) ([table 1](#)) [17,18,41-49]. Second-generation antipsychotics are less likely to cause extrapyramidal side effects and sedation compared with first-generation antipsychotics [50,51].

- **Olanzapine** – This agent can be given IM, IV, or orally; IV administration is not approved by the FDA and should be limited to settings where patients can be closely monitored for respiratory depression [52]. The onset of action of [olanzapine](#) IM is 15 to 45 minutes, and the duration of action is up to 24 hours [8]. Excessive sedation is not associated with olanzapine doses up of 10 mg IM [42]. In a patient with mild agitation or increased risk of hypotension, we start with a reduced dose (eg, 5 or 7.5 mg). In a patient who agrees to take an oral medication, the oral disintegrating formulation of olanzapine is rapidly absorbed and may be preferred by the patient compared with the more invasive IM injection [2,53].

We believe combining parenteral [olanzapine](#) (eg, 5 to 10 mg IM/IV) with a benzodiazepine (eg, [lorazepam](#) 2mg IM/IV or [midazolam](#) 5mg IM/IV) is not associated with an increased risk of complications compared with olanzapine alone or other sedative agents. Potential complications can be mitigated with proper monitoring and avoiding coadministration of olanzapine and benzodiazepines in patients with alcohol intoxication or compromised respiratory function, given the higher risk of respiratory depression [54] (see '[Monitoring for adverse effects](#)' below). A postmarketing report described excess sedation and respiratory depression, including 29 fatalities [55]. However, many of the deaths are not attributable to olanzapine as the timing after the last dose of olanzapine was prolonged [56]. Subsequent studies (most retrospective) have found a similar risk of complications [57-62]. Another approach, which is recommended by the European Medicines Agency, is separating doses of parenteral olanzapine and benzodiazepines by at least 60 minutes [63].

- **Risperidone** – This agent is available in an oral and IM extended-release formulation; the latter is not used for control of acute agitation. The time to peak concentration of oral [risperidone](#) is shorter (1.5 hours) compared with other oral second-generation antipsychotics. In a patient who agrees to take an oral medication, risperidone can be combined with [lorazepam](#) instead of using [haloperidol](#) IM combined with [lorazepam](#) [45].

- **Ziprasidone** – This agent is available in oral and IM formulations. [Ziprasidone](#) IM has an onset of action of 15 to 20 minutes and a duration of action of at least four hours [8]. Ziprasidone is associated with a greater prolongation of the QT interval compared with haloperidol, olanzapine, and risperidone [8].
- **Quetiapine** – This agent is widely used to treat psychotic symptoms in patients with Parkinson disease but is generally not used to treat acute agitation in ED patients. It is available only in oral formulations. Some contributors on this topic prefer [quetiapine](#) (eg, 25 to 50 mg) for acute agitation in older adults able to take an oral medication, especially those with dementia or Parkinson disease, which is most applicable in mild to moderate agitation (eg, sundowning). Evidence for management of agitation is mostly based on daily dosing over weeks and not as a single dose [64]. A small study of ED patients with acute agitation with psychosis found that a quetiapine (100 to 200 mg single dose) was associated with improved agitation in 69 percent but also with orthostasis in 40 percent [65].

Studies have demonstrated the effectiveness and safety of second-generation antipsychotics for the treatment of acute agitation. For example, several trials have found that [ziprasidone](#) (10 mg or 20 mg IM) achieved adequate sedation 30 minutes after administration in patients with acute undifferentiated agitation or agitation from a psychotic disorder [17,47,48]. A trial of 162 patients with agitation from active psychosis found that [risperidone](#) 2 mg orally combined with [lorazepam](#) achieved similar degrees of sedation compared with [haloperidol](#) 5 mg IM combined with lorazepam [45].

A trial of 42 patients with acute agitation from psychosis found that [olanzapine](#) IM, olanzapine oral disintegrating tablets, and [risperidone](#) oral solution were as effective as [haloperidol](#) IM [66]. A retrospective review of 15,918 ED patients treated for acute agitation found that those treated with olanzapine (median dose 10 mg IM) were less likely to require subsequent rescue medication compared with those treated with haloperidol (median dose 5 mg); serious adverse events were uncommon (<0.3 percent) and did not differ among treatment groups [41]. A retrospective study of 713 consecutive patients who received olanzapine IV (most either 2.5 or 5 mg) found that a single dose achieved adequate effects in 67 percent [59]. Hypoxia developed in 10 percent, while clinically significant respiratory complications (eg, patient required airway stimulation, repositioning, or tracheal intubation) occurred in 2 percent. Three (out of 15) intubations were deemed either likely or possibly attributable to olanzapine.

The second-generation antipsychotics, especially [ziprasidone](#), can cause QT prolongation [67]. We use similar precautions to those suggested for first-generation antipsychotics. (See 'First-generation (typical) antipsychotics' above and "Second-generation and other antipsychotic medications: Pharmacology, administration, and side effects", section on 'QTc interval prolongation and sudden death'.)

Combination benzodiazepine with antipsychotic — The following combinations of a benzodiazepine with a first-generation antipsychotic have been shown to be effective at treating acute agitation [13,60,68,69]:

- [Midazolam](#) (5 mg IV or IM) and [droperidol](#) (5 mg IV or IM)
- [Lorazepam](#) (2 mg IV or IM) and [haloperidol](#) (5 mg IV or IM)

We reduce the initial dose by half in older adult patients. If additional medication is needed, a reasonable titration approach is to give additional [midazolam](#) every 3 to 5 minutes or [lorazepam](#) every 10 to 20 minutes.

These combinations achieve more rapid sedation than either drug alone and may reduce side effects. A systematic review and meta-analysis (seven ED trials, 1135 patients) found that 15 to 20 minutes following administration, more patients had adequate sedation from combination therapy compared with a benzodiazepine alone (2 trials, 394 patients; 86 versus 65 percent) [70]. Patients receiving combination therapy had fewer adverse events compared with benzodiazepines alone (3 trials, 457 patients; 12 versus 21 percent) but a similar rate of adverse events compared with those receiving an antipsychotic alone. Fewer patients receiving the combination agents required rescue medication [60]. A trial of 349 acutely agitated ED patients compared the combination of [midazolam](#) 5 mg IV plus [droperidol](#) 5 mg IV, droperidol 10 mg IV alone, or [olanzapine](#) 10 mg IV alone [69]. At 10 minutes following the initial dose, approximately 25 percent more patients given combination therapy were adequately sedated compared with the patients treated with either medication alone, while adverse event rates did not differ significantly among groups.

Ketamine — We do not use [ketamine](#) as a first-line agent for the agitated or violent patient in the ED but suggest administering it to a patient with persistent agitation despite multiple doses of an antipsychotic and/or benzodiazepine. Even though this dissociative anesthetic has a good safety profile when used for procedural sedation, we use it with caution and close monitoring since its use for agitation may be associated with increased need for tracheal intubation compared with other agents (depending upon the dose required to achieve adequate sedation) [71-74].

When [ketamine](#) is used to treat acute agitation, the onset of action is approximately one to two minutes with IV administration, but four to five minutes or possibly longer with IM administration. The duration of action is approximately 10 to 20 minutes. A repeat IV or IM dose using a 50 percent reduction in the initial dose may be given after 5 to 10 minutes for IV, and after 10 to 25 minutes for IM treatment.

Adverse effects may include hypertension and tachycardia (usually mild and transient), laryngospasm (uncommon), emergence reactions, and vomiting and may be more common with rapid IV administration. Although respiratory complications are uncommon, clinicians must be

prepared to manage airway obstruction. (See "[Ketamine poisoning](#)", [section on 'Airway and breathing support'](#).)

[Ketamine](#) should be avoided in patients with schizophrenia since it can cause an exacerbation of psychiatric symptoms [75]. We also avoid using it in patients who may not tolerate an increase in heart rate or blood pressure (eg, older adults, known or risk for cardiac disease). The properties of ketamine and its use for anesthesia and procedural sedation in adults are reviewed separately. (See "[General anesthesia: Intravenous induction agents](#)", [section on 'Ketamine'](#) and "[Procedural sedation in adults in the emergency department: Medication selection, dosing, and discharge criteria](#)", [section on 'Ketamine'](#).)

The use of [ketamine](#) by emergency medical personnel to manage the acutely agitated and violent patient in the prehospital setting has been described, although studies have been small with varied methodology [76-82]. Evidence suggests that ketamine can provide more rapid sedation than benzodiazepines and [haloperidol](#) but is associated with more tracheal intubation and complications [80,83,84]. A systematic review and meta-analysis (18 studies, 650 patients) found that ketamine provided rapid sedation (mean time seven minutes) for patients with undifferentiated agitation [85]. Adverse events included tracheal intubation (31 percent), hypertension (12 percent), vomiting (5 percent), emergence reactions (four percent), transient hypoxia (two percent), and laryngospasm (one percent). Compared with ketamine administered in the ED, ketamine administered by ground transport emergency medical personnel was associated with an increased rate of intubation (40 versus 2 percent). However, a large retrospective study of 3795 patients who received ketamine for agitation in the prehospital setting found low overall associated mortality; only three patients could not have ketamine excluded as the cause of death [86].

A randomized trial of 80 acutely agitated patients compared [ketamine](#) 5 mg/kg IM with combination therapy of [haloperidol](#) 5 mg and [midazolam](#) 5 mg IM [87]. Even though the median time to sedation was shorter with ketamine (5.8 versus 14.7 minutes, difference 8.8 minutes, 95% CI 3-14.5), serious adverse events were also more common (12.5 versus 5 percent). No patients required tracheal intubation, but one patient in each group required supplemental oxygen and one patient who developed laryngospasm from ketamine required airway repositioning on two occasions. An open-label trial of 93 acutely agitated patients found that compared with combination therapy with haloperidol and [lorazepam](#) IM/IV, ketamine (mostly given IM) was more likely to achieve adequate sedation by five minutes (22 versus 0 percent) and by 15 minutes (66 versus 7 percent) [88]. Patients who received ketamine had transient tachycardia and hypertension but did not experience serious adverse effects.

[Ketamine](#) combined with [haloperidol](#) has also been studied for the management of delirium with agitation. In a trial with 140 patients, haloperidol 2.5 mg IV plus ketamine 0.5 mg/kg (maximum 75 mg) IV, compared with haloperidol 2.5 mg IV plus [midazolam](#) 0.05 mg/kg IV (maximum 3 mg), more rapidly controlled agitation and decreased use of physical restraints [89]. Patients receiving ketamine had fewer adverse events overall, of which most were emergence reactions, compared with the midazolam group who experienced greater hemodynamic changes and hypoventilation. Patients were older (mean 53 years), potentially limiting the generalizability of these findings.

Dexmedetomidine

- **Sublingual formulation** – We believe there is insufficient evidence and clinical experience to recommend the sublingual formulation of [dexmedetomidine](#) as a first-line agent for treatment of agitation in the ED. Dexmedetomidine, an alpha-2 adrenergic receptor agonist, is a commonly used IV sedative in mechanically ventilated patients. (See "[Sedative-analgesia in ventilated adults: Medication properties, dose regimens, and adverse effects](#)", [section on 'Dexmedetomidine'](#).)

A [dexmedetomidine](#) sublingual formulation received approval in April 2022 in the United States for the acute treatment of agitation associated with schizophrenia and bipolar disorder in adults. Approval was based on two trials that included patients with mild to moderate agitation associated with bipolar disorder or schizophrenia/schizoaffective disorder, most treated in clinical research units, that demonstrated efficacy of sublingual dexmedetomidine in improving agitation scores [90,91]. These results cannot be generalized to ED use since the trial patients were sufficiently calm that they were able to provide informed consent and place the dexmedetomidine film under tongues themselves; it is unclear how many of the patients, if any, were actually cared for in the ED setting. Also, the comparator was placebo rather than an active control. However, emergency clinicians should be aware that dexmedetomidine sublingual film is now available for use in the agitated but cooperative patient. (See "[Bipolar mania and hypomania in adults: Choosing pharmacotherapy](#)", [section on 'Agitation'](#) and "[Psychosis in adults: Initial management](#)", [section on 'Additional patient-specific considerations'](#).)

- **Continuous infusion without tracheal intubation** – Some contributors on this topic use [dexmedetomidine](#) infusion for refractory agitation in spontaneously breathing patients, but other contributors only use it for mechanically ventilated patients. In spontaneously breathing patients, it is administered as a continuous infusion of 0.2 to 1.5 mcg/kg/hour. It should be used cautiously in the ED with continuous pulse oximetry, end-tidal capnography, and cardiac monitoring. We do not administer a bolus since it is associated with an increased risk of hypotension and bradycardia. Evidence is extrapolated from its use for procedural sedation and in the management of delirium in the intensive care unit (ICU). A study of 132 spontaneously breathing ICU patients with hyperactive delirium found that, compared with [haloperidol](#) alone, the addition of dexmedetomidine infusion to haloperidol was associated with a higher percentage of time with satisfactory sedation (93 versus 59 percent) [92]. No patients treated with dexmedetomidine developed excessive sedation, and the incidence of bradycardia or hypotension was similar between both treatments. A poison center retrospective study included 70 spontaneously breathing patients treated with dexmedetomidine as

an adjunct for agitation; 89 percent exhibited clinical improvement in agitation while 6 percent (4 patients) were intubated due to refractory agitation or hypoxia after aspiration [93].

CONSIDERATIONS WHEN PATIENT CALM

Monitoring for adverse effects — Serious adverse events are uncommon following appropriate administration of calming medications and adequate monitoring. In general, a calm patient who is not sedated does not need monitoring, and some patients may decline monitoring or the equipment may pose a risk (eg, use in self-harm attempt). Patients who subsequently deteriorate frequently suffer from an unrecognized infection or drug overdose.

We place patients on continuous pulse oximetry if they exhibit signs of oversedation (eg, airway obstruction, oxygen desaturation) or have risk factors for adverse events from parenteral calming medications, which include age >65, alcohol intoxication, and receiving multiple parenteral sedative medications within 60 minutes [94-97]. We also place patients receiving sedative medications while in physical restraints on continuous pulse oximetry since they are unable to reposition themselves. (See "[The acutely agitated or violent adult: Overview, assessment, and nonpharmacologic management](#)", section on 'Monitoring and care of a physically restrained patient'.)

We establish intravenous (IV) access in most patients who receive calming medication, especially if their presentation warrants additional medical evaluation. Patients who require repeated doses of medications or have risk factors for adverse events should also have IV access established.

We place a patient on a cardiac monitor if an electrocardiogram (ECG), if performed, shows prolongation of the QT interval (>460 msec or ≥60 msec prolongation during treatment). An ECG should be performed if the patient has received multiple doses of an antipsychotic medication or has any risk factors for a pre-existing prolonged QT interval. (See "[Acquired long QT syndrome: Definitions, pathophysiology, and causes](#)" and "[First-generation antipsychotic medications: Pharmacology, administration, and comparative side effects](#)", section on 'QT interval prolongation and sudden death'.)

A patient who is receiving [ketamine](#) or a [dexmedetomidine](#) infusion requires continuous cardiac, pulse oximeter, and capnography monitoring.

Evaluation for medical etiology — Medical cause of agitation can include hypoglycemia, hypoxia, intoxication, withdrawal, intracranial lesions, infection, and others. Checking a fingerstick blood glucose when feasible is required in any patient with delirium, altered mental status, or severe agitation. The evaluation for a medical etiology is discussed separately. (See "[The acutely agitated or violent adult: Overview, assessment, and nonpharmacologic management](#)", section on 'Medical evaluation when patient calm'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "[Society guideline links: Adult with altered mental status in the emergency department](#)" and "[Society guideline links: Treatment of acute poisoning caused by recreational drug or alcohol use](#)".)

SUMMARY AND RECOMMENDATIONS

- **Characteristics of ideal calming medications** – The ideal calming medication is rapidly acting, effective regardless of the route of administration, and possesses minimal side effects. (See '[Characteristics of ideal calming medication](#)' above.)
- **Special considerations for older adults** – In general, for adults ≥65 years of age, we reduce the initial calming medication dose by half and avoid benzodiazepines. In patients with dementia with Lewy bodies disease or Parkinson disease, we avoid first-generation antipsychotics and some second-generation antipsychotics; select agents (eg, [quetiapine](#), [clozapine](#)) can be used in small doses if pharmacologic treatment of psychotic symptoms is necessary. (See '[Special considerations for older adults](#)' above.)
- **Approach** – A treatment algorithm outlining our approach to determining the degree of agitation and choice of calming agent is provided ([algorithm 1](#)). At all levels of agitation, verbal de-escalation should be attempted and an oral medication offered first (if can be done safely) before moving to involuntary medication administrations and physical restraints. (See '[Approach to medication selection](#)' above.)
- **Patient with severe agitation** – For a severely agitated or violent patient requiring immediate sedation, we suggest a combination of a rapidly-acting first-generation antipsychotic and a benzodiazepine rather than monotherapy (**Grade 2B**). Options include [droperidol](#) 2.5 to 5 mg IM/IV and [midazolam](#) 2.5 to 5 mg intramuscularly or intravenously (IM/IV) or [haloperidol](#) 5 mg IM/IV and [lorazepam](#) 2 mg IM/IV. This combination can be repeated in 15 minutes if the patient is not sufficiently calm. (See '[Severe agitation](#)' above and '[Combination benzodiazepine with antipsychotic](#)' above.)

In a patient with persistent agitation despite multiple doses of an antipsychotic and benzodiazepine, especially if they are struggling against restraints, options include [ketamine](#) (1 to 2 mg/kg IV or 4 to 6 mg/kg IM, maximum dose 400 mg IM), [dexmedetomidine](#) without tracheal intubation (continuous infusion of 0.2 to 1.5 mcg/kg/hour), or rapid sequence tracheal intubation followed by [propofol](#) or dexmedetomidine infusions. Agitation treated with ketamine has been associated with an increased rate of tracheal intubation. (See '[Ketamine](#)' above and '[Dexmedetomidine](#)' above.)

• **Patient with mild to moderate agitation NOT from drug intoxication or withdrawal**

- In a patient who is not calm following verbal de-escalation techniques, we offer oral medications, such as a benzodiazepine (eg, [lorazepam](#) 2 to 4 mg orally) or second-generation antipsychotic (eg, [olanzapine](#) 5 to 10 mg orally/sublingual or [risperidone](#) 2 mg orally). A first-generation antipsychotic (eg, [haloperidol](#) 5 mg orally) is also a reasonable option. [Quetiapine](#) 25 to 50 mg orally is an option in older patients (age ≥65), especially with dementia or Parkinson disease. (See '[Mild to moderate agitation](#)' above.)
- In a patient with a known psychotic disorder who prefers not to take an oral medication, we suggest treatment with a first-generation antipsychotic rather than a second-generation antipsychotic or a benzodiazepine (**Grade 2C**). [Haloperidol](#) 5 mg IM/IV or [droperidol](#) 2.5 to 5 mg IM/IV are commonly used, but a second-generation antipsychotic (eg, [ziprasidone](#) 10 to 20 mg IM or [olanzapine](#) 5 to 10 mg IM/IV) is a reasonable option. (See '[First-generation \(typical\) antipsychotics](#)' above and '[Second-generation \(atypical\) antipsychotics](#)' above.)

• **Patient with mild to moderate agitation from drug intoxication or withdrawal, or an undifferentiated etiology of agitation**

- In a patient with agitation from alcohol intoxication, we suggest a rapidly-acting first-generation antipsychotic (eg, [droperidol](#) 2.5 to 5 mg IM/IV, [haloperidol](#) 5 mg IM/IV) rather than a second-generation antipsychotic, a benzodiazepine, or a combination antipsychotic/benzodiazepine (**Grade 2C**). (See '[Drug intoxication, withdrawal, or undifferentiated](#)' above and '[First-generation \(typical\) antipsychotics](#)' above.)
- A patient with agitation from anticholinergic delirium can be treated with a benzodiazepine or [physostigmine](#) (0.5 to 2 mg IV). The evidence is discussed separately. (See '[Anticholinergic poisoning](#)', section on '[Antidotal therapy with physostigmine for severe toxicity](#)'.)
- A patient with agitation from alcohol withdrawal delirium can be treated with a benzodiazepine, but [phenobarbital](#) 10 mg/kg IV is a reasonable alternative. The evidence is discussed separately. (See '[Management of moderate and severe alcohol withdrawal syndromes](#)', section on '[Treatment of psychomotor agitation](#)'.)
- In a patient with agitation from other drug intoxication or withdrawal, or with an undifferentiated etiology of agitation, we suggest initial treatment with a benzodiazepine (**Grade 2C**), owing to concern for increased risk of adverse effects of antipsychotic agents (eg, prolongation of QTc interval, impaired heat dissipation). Options include [lorazepam](#) 2 to 4 mg orally/IV, [diazepam](#) 10 to 20 mg orally/IV, or [midazolam](#) 2.5 to 5 mg IM/IV. In a patient with undifferentiated agitation, a first-generation antipsychotic is also a reasonable choice if appropriately monitored for adverse effects. (See '[Drug intoxication, withdrawal, or undifferentiated](#)' above and '[Benzodiazepines](#)' above and '[First-generation \(typical\) antipsychotics](#)' above.)
- **Dystonic reactions with first-generation antipsychotics** – We suggest to not prophylactically coadminister an anticholinergic agent with an IM antipsychotic dose (**Grade 2C**). Some experts routinely coadminister [diphenhydramine](#) or [benztropine](#) as it may decrease the incidence of dystonic reactions, but these reactions are uncommon and the additional agent may increase the risk of adverse events. If an acute dystonic reaction occurs, treatment is diphenhydramine 25 to 50 mg IM/IV or benztropine 1 to 2 mg IM/IV. (See '[First-generation \(typical\) antipsychotics](#)' above.)
- **Considerations when patient calm** – We place patients at risk for oversedation from calming medications on continuous pulse oximetry; this includes patients receiving multiple doses of parenteral sedative medications within 60 minutes, those with alcohol intoxication, and older patients (age ≥65). Patients receiving sedative medications while in physical restraints should be placed on continuous pulse oximetry. We perform an electrocardiogram in a patient who has received multiple doses of an antipsychotic medication or has any risk factors for a pre-existing prolonged QT interval. Patients should be evaluated for a medical cause of agitation such as hypoglycemia, hypoxia, intoxication, withdrawal, intracranial lesions, infection, and others. (See '[Considerations when patient calm](#)' above.)

ACKNOWLEDGMENT

The UpToDate editorial staff acknowledges Gregory P Moore, MD, JD, who contributed to earlier versions of this topic review.

Use of UpToDate is subject to the [Terms of Use](#).

REFERENCES

1. American College of Emergency Physicians Clinical Policies Subcommittee (Writing Committee) on Severe Agitation, Thiessen MEW, Godwin SA, et al. Clinical Policy: Critical Issues in the Evaluation and Management of Adult Out-of-Hospital or Emergency Department Patients Presenting With Severe Agitation: Approved by the ACEP Board of Directors, October 6, 2023. *Ann Emerg Med* 2024; 83:e1.
2. Wilson MP, Pepper D, Currier GW, et al. The psychopharmacology of agitation: consensus statement of the american association for emergency psychiatry project Beta psychopharmacology workgroup. *West J Emerg Med* 2012; 13:26.
3. Casey MF, Elder NM, Fenn A, et al. Comparative Safety of Medications for Severe Agitation: A Geriatric Emergency Department Guidelines 2.0 Systematic Review. *J Am Geriatr Soc* 2025; 73:2893.
4. Fitzgerald P. Long-acting antipsychotic medication, restraint and treatment in the management of acute psychosis. *Aust N Z J Psychiatry* 1999; 33:660.
5. Yildiz A, Sachs GS, Turgay A. Pharmacological management of agitation in emergency settings. *Emerg Med J* 2003; 20:339.
6. Citrome L, Volavka J. Violent patients in the emergency setting. *Psychiatr Clin North Am* 1999; 22:789.
7. Foster S, Kessel J, Berman ME, Simpson GM. Efficacy of lorazepam and haloperidol for rapid tranquilization in a psychiatric emergency room setting. *Int Clin Psychopharmacol* 1997; 12:175.
8. Battaglia J. Pharmacological management of acute agitation. *Drugs* 2005; 65:1207.
9. Zeller SL, Rhoades RW. Systematic reviews of assessment measures and pharmacologic treatments for agitation. *Clin Ther* 2010; 32:403.
10. Greenblatt DJ, Ehrenberg BL, Gunderman J, et al. Kinetic and dynamic study of intravenous lorazepam: comparison with intravenous diazepam. *J Pharmacol Exp Ther* 1989; 250:134.
11. Mendoza R, Djenderedjian AH, Adams J, Ananth J. Midazolam in acute psychotic patients with hyperarousal. *J Clin Psychiatry* 1987; 48:291.
12. Weintraub SJ. Diazepam in the Treatment of Moderate to Severe Alcohol Withdrawal. *CNS Drugs* 2017; 31:87.
13. Battaglia J, Moss S, Rush J, et al. Haloperidol, lorazepam, or both for psychotic agitation? A multicenter, prospective, double-blind, emergency department study. *Am J Emerg Med* 1997; 15:335.
14. Chan EW, Lao KSJ, Lam L, et al. Intramuscular midazolam, olanzapine, or haloperidol for the management of acute agitation: A multi-centre, double-blind, randomised clinical trial. *EClinicalMedicine* 2021; 32:100751.
15. Knott JC, Taylor DM, Castle DJ. Randomized clinical trial comparing intravenous midazolam and droperidol for sedation of the acutely agitated patient in the emergency department. *Ann Emerg Med* 2006; 47:61.
16. Nobay F, Simon BC, Levitt MA, Dresden GM. A prospective, double-blind, randomized trial of midazolam versus haloperidol versus lorazepam in the chemical restraint of violent and severely agitated patients. *Acad Emerg Med* 2004; 11:744.
17. Martel M, Sterzinger A, Miner J, et al. Management of acute undifferentiated agitation in the emergency department: a randomized double-blind trial of droperidol, ziprasidone, and midazolam. *Acad Emerg Med* 2005; 12:1167.
18. Klein LR, Driver BE, Miner JR, et al. Intramuscular Midazolam, Olanzapine, Ziprasidone, or Haloperidol for Treating Acute Agitation in the Emergency Department. *Ann Emerg Med* 2018; 72:374.
19. Isenberg DL, Jacobs D. Prehospital Agitation and Sedation Trial (PhAST): A Randomized Control Trial of Intramuscular Haloperidol versus Intramuscular Midazolam for the Sedation of the Agitated or Violent Patient in the Prehospital Environment. *Prehosp Disaster Med* 2015; 30:491.
20. Amore M, D'Andrea M, Fagiolini A. Treatment of Agitation With Lorazepam in Clinical Practice: A Systematic Review. *Front Psychiatry* 2021; 12:628965.
21. Clinton JE, Sterner S, Stelmachers Z, Ruiz E. Haloperidol for sedation of disruptive emergency patients. *Ann Emerg Med* 1987; 16:319.
22. Stotsky BA. Relative efficacy of parenteral haloperidol and thiothixene for the emergency treatment of acutely excited and agitated patients. *Dis Nerv Syst* 1977; 38:967.
23. Thomas H Jr, Schwartz E, Petrilli R. Droperidol versus haloperidol for chemical restraint of agitated and combative patients. *Ann Emerg Med* 1992; 21:407.
24. Richards JR, Derlet RW, Duncan DR. Chemical restraint for the agitated patient in the emergency department: lorazepam versus droperidol. *J Emerg Med* 1998; 16:567.
25. Isbister GK, Calver LA, Page CB, et al. Randomized controlled trial of intramuscular droperidol versus midazolam for violence and acute behavioral disturbance: the DORM study. *Ann Emerg Med* 2010; 56:392.
26. Page CB, Parker LE, Rashford SJ, et al. A Prospective Before and After Study of Droperidol for Prehospital Acute Behavioral Disturbance. *Prehosp Emerg Care* 2018; 22:713.
27. Martel ML, Driver BE, Miner JR, et al. Randomized Double-blind Trial of Intramuscular Droperidol, Ziprasidone, and Lorazepam for Acute Undifferentiated Agitation in the Emergency Department. *Acad Emerg Med* 2021; 28:421.

28. Foo LK, Duffull SB, Calver L, et al. Population pharmacokinetics of intramuscular droperidol in acutely agitated patients. *Br J Clin Pharmacol* 2016; 82:1550.
29. Calver L, Drinkwater V, Gupta R, et al. Droperidol v. haloperidol for sedation of aggressive behaviour in acute mental health: randomised controlled trial. *Br J Psychiatry* 2015; 206:223.
30. Cole JB, Klein LR, Martel ML. Parenteral Antipsychotic Choice and Its Association With Emergency Department Length of Stay for Acute Agitation Secondary to Alcohol Intoxication. *Acad Emerg Med* 2019; 26:79.
31. Seitz DP, Gill SS, van Zyl LT. Antipsychotics in the treatment of delirium: a systematic review. *J Clin Psychiatry* 2007; 68:11.
32. US Food and Drug Administration. www.fda.gov/medwatch/SAFETY/2001/inapsine.htm (Accessed on October 07, 2008).
33. US Food and Drug Administration. Information for healthcare professionals: Haloperidol. www.fda.gov/Cder/drug/InfoSheets/HCP/haloperidol.htm (Accessed on October 16, 2008).
34. Kao LW, Kirk MA, Evers SJ, Rosenfeld SH. Droperidol, QT prolongation, and sudden death: what is the evidence? *Ann Emerg Med* 2003; 41:546.
35. Chase PB, Biros MH. A retrospective review of the use and safety of droperidol in a large, high-risk, inner-city emergency department patient population. *Acad Emerg Med* 2002; 9:1402.
36. Shale JH, Shale CM, Mastin WD. A review of the safety and efficacy of droperidol for the rapid sedation of severely agitated and violent patients. *J Clin Psychiatry* 2003; 64:500.
37. Gaw CM, Cabrera D, Bellolio F, et al. Effectiveness and safety of droperidol in a United States emergency department. *Am J Emerg Med* 2020; 38:1310.
38. Cole JB, Lee SC, Martel ML, et al. The Incidence of QT Prolongation and Torsades des Pointes in Patients Receiving Droperidol in an Urban Emergency Department. *West J Emerg Med* 2020; 21:728.
39. Calver L, Page CB, Downes MA, et al. The Safety and Effectiveness of Droperidol for Sedation of Acute Behavioral Disturbance in the Emergency Department. *Ann Emerg Med* 2015; 66:230.
40. Jeffers T, Darling B, Edwards C, Vadieli N. Efficacy of Combination Haloperidol, Lorazepam, and Diphenhydramine vs. Combination Haloperidol and Lorazepam in the Treatment of Acute Agitation: A Multicenter Retrospective Cohort Study. *J Emerg Med* 2022; 62:516.
41. Klein LR, Driver BE, Horton G, et al. Rescue Sedation When Treating Acute Agitation in the Emergency Department With Intramuscular Antipsychotics. *J Emerg Med* 2019; 56:484.
42. Battaglia J, Lindborg SR, Alaka K, et al. Calming versus sedative effects of intramuscular olanzapine in agitated patients. *Am J Emerg Med* 2003; 21:192.
43. Cole JB, Stang JL, DeVries PA, et al. A Prospective Study of Intramuscular Droperidol or Olanzapine for Acute Agitation in the Emergency Department: A Natural Experiment Owing to Drug Shortages. *Ann Emerg Med* 2021; 78:274.
44. Schneider A, Mullinax S, Hall N, et al. Intramuscular medication for treatment of agitation in the emergency department: A systematic review of controlled trials. *Am J Emerg Med* 2021; 46:193.
45. Currier GW, Chou JC, Feifel D, et al. Acute treatment of psychotic agitation: a randomized comparison of oral treatment with risperidone and lorazepam versus intramuscular treatment with haloperidol and lorazepam. *J Clin Psychiatry* 2004; 65:386.
46. Brook S, Lucey JV, Gunn KP. Intramuscular ziprasidone compared with intramuscular haloperidol in the treatment of acute psychosis. Ziprasidone I.M. Study Group. *J Clin Psychiatry* 2000; 61:933.
47. Lesem MD, Zajecka JM, Swift RH, et al. Intramuscular ziprasidone, 2 mg versus 10 mg, in the short-term management of agitated psychotic patients. *J Clin Psychiatry* 2001; 62:12.
48. Daniel DG, Potkin SG, Reeves KR, et al. Intramuscular (IM) ziprasidone 20 mg is effective in reducing acute agitation associated with psychosis: a double-blind, randomized trial. *Psychopharmacology (Berl)* 2001; 155:128.
49. Currier GW, Simpson GM. Risperidone liquid concentrate and oral lorazepam versus intramuscular haloperidol and intramuscular lorazepam for treatment of psychotic agitation. *J Clin Psychiatry* 2001; 62:153.
50. Allen MH, Currier GW, Carpenter D, et al. The expert consensus guideline series. Treatment of behavioral emergencies 2005. *J Psychiatr Pract* 2005; 11 Suppl 1:5.
51. Marco CA, Vaughan J. Emergency management of agitation in schizophrenia. *Am J Emerg Med* 2005; 23:767.
52. Khorassani F, Saad M. Intravenous Olanzapine for the Management of Agitation: Review of the Literature. *Ann Pharmacother* 2019; 53:853.
53. Montgomery W, Treuer T, Karagianis J, et al. Orally disintegrating olanzapine review: effectiveness, patient preference, adherence, and other properties. *Patient Prefer Adherence* 2012; 6:109.
54. Isbister GK. Droperidol or Olanzapine, Intramuscularly or Intravenously, Monotherapy or Combination Therapy for Sedating Acute Behavioral Disturbance. *Ann Emerg Med* 2017; 69:337.

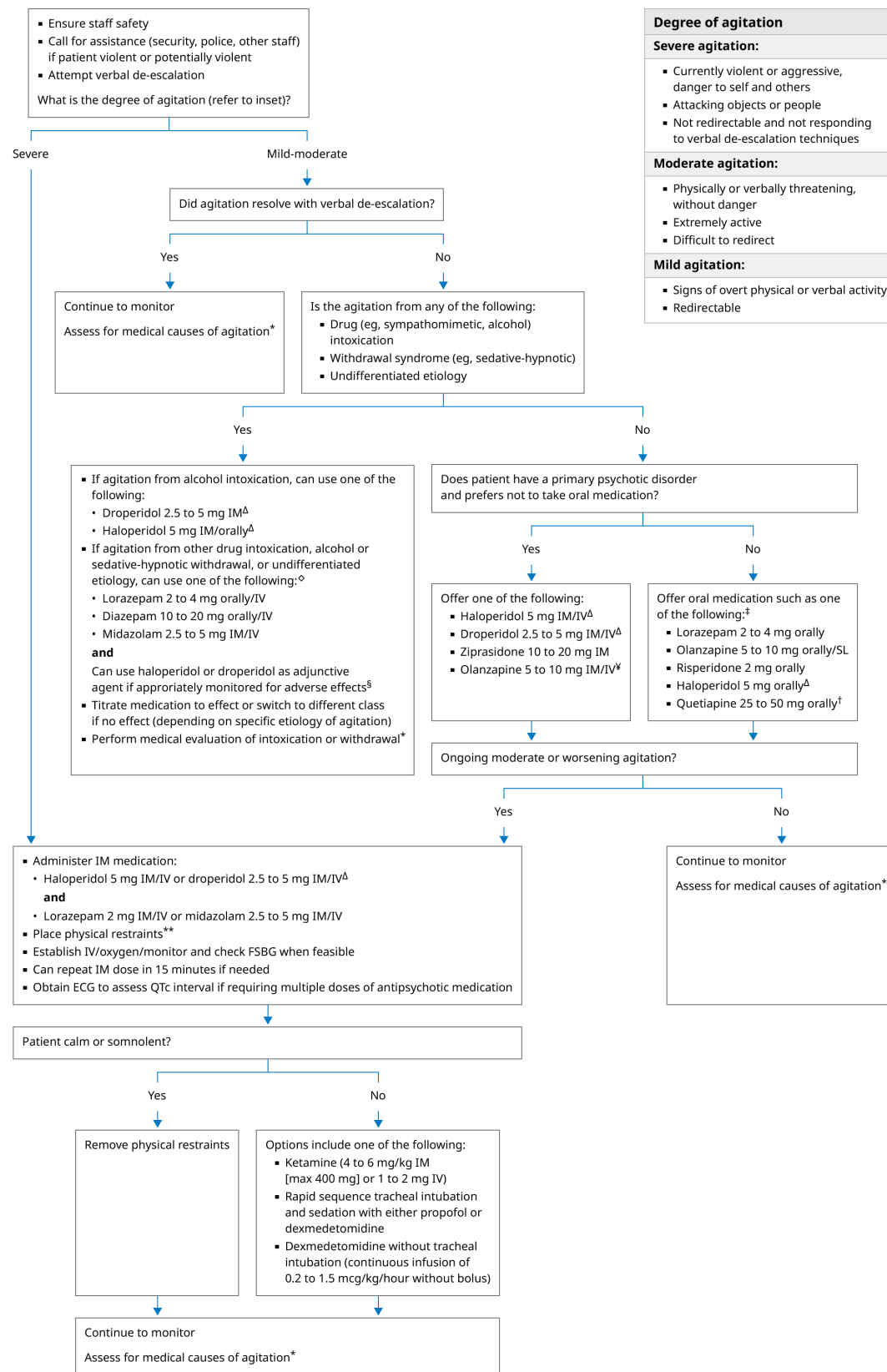
55. Marder SR, Sorsaburu S, Dunayevich E, et al. Case reports of postmarketing adverse event experiences with olanzapine intramuscular treatment in patients with agitation. *J Clin Psychiatry* 2010; 71:433.
56. Hayes BD. When New Data Refute Previous Paradigms: A Commentary on the Olanzapine-Benzodiazepine Interaction. *Ann Emerg Med* 2024; 84:668.
57. Hunt NF, McLaughlin KC, Kovacevic MP, et al. Safety of Intravenous Olanzapine Administration at a Tertiary Academic Medical Center. *Ann Pharmacother* 2021; 55:1127.
58. Cole JB, Moore JC, Dolan BJ, et al. A Prospective Observational Study of Patients Receiving Intravenous and Intramuscular Olanzapine in the Emergency Department. *Ann Emerg Med* 2017; 69:327.
59. Martel ML, Klein LR, Rivard RL, Cole JB. A Large Retrospective Cohort of Patients Receiving Intravenous Olanzapine in the Emergency Department. *Acad Emerg Med* 2016; 23:29.
60. Chan EW, Taylor DM, Knott JC, et al. Intravenous droperidol or olanzapine as an adjunct to midazolam for the acutely agitated patient: a multicenter, randomized, double-blind, placebo-controlled clinical trial. *Ann Emerg Med* 2013; 61:72.
61. Cole JB, Stang JL, Collins JD, et al. Comparing Intubation Rates in Patients Receiving Parenteral Olanzapine With and Without a Parenteral Benzodiazepine in the Emergency Department. *Ann Emerg Med* 2024; 84:658.
62. Bradley K, Feldman EA, Schrader J, et al. Comparing the cardiorespiratory safety of parenteral olanzapine and benzodiazepines to parenteral haloperidol/droperidol and benzodiazepines in emergency department patients. *Am J Emerg Med* 2025; 87:51.
63. European Medicines Agency. ZYPREXA, INN-olanzapine. https://www.ema.europa.eu/en/documents/product-information/zyprexa-epar-product-information_en.pdf (Accessed on June 13, 2023).
64. Mühlbauer V, Möhler R, Dichter MN, et al. Antipsychotics for agitation and psychosis in people with Alzheimer's disease and vascular dementia. *Cochrane Database Syst Rev* 2021; 12:CD013304.
65. Currier GW, Trenton AJ, Walsh PG, van Wijngaarden E. A pilot, open-label safety study of quetiapine for treatment of moderate psychotic agitation in the emergency setting. *J Psychiatr Pract* 2006; 12:223.
66. Hsu WY, Huang SS, Lee BS, Chiu NY. Comparison of intramuscular olanzapine, orally disintegrating olanzapine tablets, oral risperidone solution, and intramuscular haloperidol in the management of acute agitation in an acute care psychiatric ward in Taiwan. *J Clin Psychopharmacol* 2010; 30:230.
67. Glassman AH, Bigger JT Jr. Antipsychotic drugs: prolonged QTc interval, torsade de pointes, and sudden death. *Am J Psychiatry* 2001; 158:1774.
68. Bieniek SA, Ownby RL, Penalver A, Dominguez RA. A double-blind study of lorazepam versus the combination of haloperidol and lorazepam in managing agitation. *Pharmacotherapy* 1998; 18:57.
69. Taylor DM, Yap CY, Knott JC, et al. Midazolam-Droperidol, Droperidol, or Olanzapine for Acute Agitation: A Randomized Clinical Trial. *Ann Emerg Med* 2017; 69:318.
70. Korczak V, Kirby A, Gunja N. Chemical agents for the sedation of agitated patients in the ED: a systematic review. *Am J Emerg Med* 2016; 34:2426.
71. Hopper AB, Vilke GM, Castillo EM, et al. Ketamine use for acute agitation in the emergency department. *J Emerg Med* 2015; 48:712.
72. American College of Emergency Physicians Clinical Policies Subcommittee (Writing Committee) on the Adult Psychiatric Patient, Nazarian DJ, Broder JS, et al. Clinical Policy: Critical Issues in the Diagnosis and Management of the Adult Psychiatric Patient in the Emergency Department. *Ann Emerg Med* 2017; 69:480.
73. Ho JD, Smith SW, Nystrom PC, et al. Successful management of excited delirium syndrome with prehospital ketamine: two case examples. *Prehosp Emerg Care* 2013; 17:274.
74. Isbister GK, Calver LA, Downes MA, Page CB. Ketamine as Rescue Treatment for Difficult-to-Sedate Severe Acute Behavioral Disturbance in the Emergency Department. *Ann Emerg Med* 2016; 67:581.
75. Beck K, Hindley G, Borgan F, et al. Association of Ketamine With Psychiatric Symptoms and Implications for Its Therapeutic Use and for Understanding Schizophrenia: A Systematic Review and Meta-analysis. *JAMA Netw Open* 2020; 3:e204693.
76. Le Cong M, Gynther B, Hunter E, Schuller P. Ketamine sedation for patients with acute agitation and psychiatric illness requiring aeromedical retrieval. *Emerg Med J* 2012; 29:335.
77. Burnett AM, Salzman JG, Griffith KR, et al. The emergency department experience with prehospital ketamine: a case series of 13 patients. *Prehosp Emerg Care* 2012; 16:553.
78. Hick JL, Ho JD. Ketamine chemical restraint to facilitate rescue of a combative "jumper". *Prehosp Emerg Care* 2005; 9:85.
79. Roberts JR, Geeting GK. Intramuscular ketamine for the rapid tranquilization of the uncontrollable, violent, and dangerous adult patient. *J Trauma* 2001; 51:1008.

80. Cole JB, Moore JC, Nystrom PC, et al. A prospective study of ketamine versus haloperidol for severe prehospital agitation. *Clin Toxicol (Phila)* 2016; 54:556.
81. Scheppke KA, Braghiroli J, Shalaby M, Chait R. Prehospital use of i.m. ketamine for sedation of violent and agitated patients. *West J Emerg Med* 2014; 15:736.
82. Muldowney M, Counts CR, Maider MC, et al. A Comparison of Ketamine to Midazolam for the Management of Acute Behavioral Disturbance in the Out-of-Hospital Setting. *Ann Emerg Med* 2025; 85:411.
83. Riddell J, Tran A, Bengiamin R, et al. Ketamine as a first-line treatment for severely agitated emergency department patients. *Am J Emerg Med* 2017; 35:1000.
84. O'Connor L, Rebesco M, Robinson C, et al. Outcomes of Prehospital Chemical Sedation With Ketamine Versus Haloperidol and Benzodiazepine or Physical Restraint Only. *Prehosp Emerg Care* 2019; 23:201.
85. Mankowitz SL, Regenberg P, Kaldan J, Cole JB. Ketamine for Rapid Sedation of Agitated Patients in the Prehospital and Emergency Department Settings: A Systematic Review and Proportional Meta-Analysis. *J Emerg Med* 2018; 55:670.
86. Fernandez AR, Bourn SS, Crowe RP, et al. Out-of-Hospital Ketamine: Indications for Use, Patient Outcomes, and Associated Mortality. *Ann Emerg Med* 2021; 78:123.
87. Barbic D, Andolfatto G, Grunau B, et al. Rapid Agitation Control With Ketamine in the Emergency Department: A Blinded, Randomized Controlled Trial. *Ann Emerg Med* 2021; 78:788.
88. Lin J, Figuerado Y, Montgomery A, et al. Efficacy of ketamine for initial control of acute agitation in the emergency department: A randomized study. *Am J Emerg Med* 2021; 44:306.
89. Aghili M, AkhavanHejazi H, Naderpour Z, et al. Haloperidol-Midazolam vs. Haloperidol-Ketamine in Controlling the Agitation of Delirious Patients; a Randomized Clinical Trial. *Arch Acad Emerg Med* 2023; 11:e61.
90. Preskorn SH, Zeller S, Citrome L, et al. Effect of Sublingual Dexmedetomidine vs Placebo on Acute Agitation Associated With Bipolar Disorder: A Randomized Clinical Trial. *JAMA* 2022; 327:727.
91. Citrome L, Preskorn SH, Lauriello J, et al. Sublingual Dexmedetomidine for the Treatment of Acute Agitation in Adults With Schizophrenia or Schizoaffective Disorder: A Randomized Placebo-Controlled Trial. *J Clin Psychiatry* 2022; 83.
92. Carrasco G, Baeza N, Cabré L, et al. Dexmedetomidine for the Treatment of Hyperactive Delirium Refractory to Haloperidol in Nonintubated ICU Patients: A Nonrandomized Controlled Trial. *Crit Care Med* 2016; 44:1295.
93. Kershner E, Tobarran N, Chambers A, et al. Clinical characteristics and outcomes using dexmedetomidine in nonintubated patients: A poison center observational study. *Am J Health Syst Pharm* 2023; 80:526.
94. Yap CYL, Taylor DM, Kong DCM, et al. Risk Factors for Sedation-related Events During Acute Agitation Management in the Emergency Department. *Acad Emerg Med* 2019; 26:1135.
95. Wilson MP, MacDonald K, Vilke GM, Feifel D. Potential complications of combining intramuscular olanzapine with benzodiazepines in emergency department patients. *J Emerg Med* 2012; 43:889.
96. Wilson MP, MacDonald K, Vilke GM, et al. Intramuscular ziprasidone: influence of alcohol and benzodiazepines on vital signs in the emergency setting. *J Emerg Med* 2013; 45:901.
97. Wilson MP, MacDonald K, Vilke GM, Feifel D. A comparison of the safety of olanzapine and haloperidol in combination with benzodiazepines in emergency department patients with acute agitation. *J Emerg Med* 2012; 43:790.

Topic 141626 Version 8.0

GRAPHICS

Algorithm 1: Emergency management of the severely agitated or violent adult patient



In older adults (≥65 years of age), we generally avoid benzodiazepines since they can generate paradoxical response and behavioral disinhibition. In patients with Lewy bodies disease or Parkinson disease, we avoid first-generation antipsychotics and some second-generation antipsychotics; select agents (eg, quetiapine, clozapine) can be used in small doses if pharmacologic treatment of psychotic symptoms is necessary.

ECG: electrocardiogram; FSBG: fingerstick blood glucose; IM: intramuscular; IV: intravenous; SL: sublingually; TCA: tricyclic antidepressant.

* Medical cause of agitation can include hypoglycemia, hypoxia, intoxication, withdrawal, intracranial lesions, infection, and others. Check FSBG when feasible. Establish IV access depending on patient condition and potential for medical etiology.

¶ Symptoms of sympathomimetic intoxication or sedative-hypnotic withdrawal include diaphoresis, mydriasis, tachycardia, hyperthermia. Symptoms of anticholinergic delirium include mydriasis, dry axilla/lips, tachycardia, mumbling speech, partially redirectable.

Δ In an older adult (≥65 years of age), reduce the initial antipsychotic dose by half.

◇ If concern for anticholinergic delirium, can administer physostigmine 0.5 to 2 mg IV after obtaining ECG and placing patient on cardiac monitor. Do not give physostigmine if possibility of TCA overdose or QRS interval > 100 msec. Refer to UpToDate content on anticholinergic poisoning. If concern for alcohol withdrawal delirium, can administer phenobarbital 10 mg/kg IV instead of a benzodiazepine. Refer to UpToDate content on treatment of moderate-severe alcohol withdrawal.

§ Do not use antipsychotic agents if concern for anticholinergic delirium. Antipsychotic agents can prolong QTc interval and impair heat dissipation.

¥ There is a potential risk of excess sedation and respiratory depression from co-administering olanzapine IV/IM and a parenteral benzodiazepine. If both are needed, we suggest separating these doses by at least 60 minutes.

‡ If patient has mild agitation, start with lower dose in the range provided.

† Quetiapine may be a preferable option in patients with dementia with Lewy bodies disease or Parkinson disease.

** Refer to UpToDate content for suggestions on how to apply restraints (eg, do not place patient in prone position).

Graphic 61852 Version 14.0

Table 1: Antipsychotics for initial management of the acutely agitated adult patient with psychosis

	Formulation(s)	Route	Initial dose (mg)	Frequency (hours)	Maximum initial dose per 24 hours (mg)	Time to peak plasma concentration (hours)	Notes
Second-generation agents							
Olanzapine	Injection (short-acting)	IM, IV*	5 to 10 [¶]	2 to 4 ^Δ	30 (including oral doses)	0.25 to 0.75	- Onset of action IM: Approximately 15 minutes; IV: 5 to 10 minutes. - If given IM/IV with parenteral benzodiazepine there is increased risk of excess sedation and respiratory depression; separating doses by ≥60 minutes suggested. - Decreased clearance in female and/or non-smoking patients; consider use of lower doses in range. - Moderate dose related QTc prolongation; some data suggest mild effect.
	Disintegrating tablet	Oral, SL	5 to 10	2	20 (including IM/IV doses)	5	
Risperidone	Disintegrating tablet, oral solution	Oral	1 to 2	0.5 to 2	6	1.5	- Onset of action (oral disintegrating tablet): 70 minutes on average. - Decreased clearance in kidney and/or hepatic impairment. - Moderate dose related QTc prolongation. - Metabolized by CYP2D6; variable efficacy due to genetic polymorphisms.
Ziprasidone	Short-acting mesylate injection	IM	10 to 20	2 to 4	40	0.5 to 1	- Dose related QTc prolongation and risk of cardiac dysrhythmias; risk appears greater than other second-generation agents. - Onset of action IM: 15 to 20 minutes. - Oral preparation available.
Aripiprazole	Disintegrating tablet, dispersible film, oral solution	Oral	10 to 15	2	30	3 to 5	- Less sedating. Minimal prolongation of QTc interval or orthostatic hypotension. - Metabolized by CYP2D6; variable efficacy due to genetic polymorphisms. - Refer to UpToDate topic on choosing treatment for severe postpartum unipolar major depression.
First-generation agents							
Haloperidol	Short-acting lactate injection	IM, IV	2 to 10	0.5 to 2 ^Δ	20 [◇]	0.5 to 1	- Onset of action IM/IV: 30 to 60 minutes. - Sedation, hypotension, and prolongation of QTc interval more pronounced with injection. - Increased risk of acute dystonic reaction.[§] - For severe agitation, typically initial dose is 5 mg IM/IV combined with a benzodiazepine (eg, lorazepam 2 mg IM/IV). - Older adults should start with a lower initial dose (1 to 2 mg orally).
	Oral solution	Oral	2 to 10	6	30	2	
Droperidol	Injection (short-acting)	IM, IV	2.5 to 10	2 to 4 ^Δ	40	0.5	Rapid onset of 3 to 10 minutes advantageous in severely agitated violent patients.

						▪ Dose related QTc prolongation and risk of cardiac dysrhythmias. ▪ For severe agitation, typically initial dose is 2.5 to 5 mg IM/IV combined with a benzodiazepine (eg, midazolam 2.5 to 5 mg IM/IV). ▪ Increased risk of acute dystonic reaction.[§]
--	--	--	--	--	--	--

- The approach to pharmacologic treatment of the acutely agitated patient, including specific medication choices and combinations depending upon presentation (eg, toxic ingestion, withdrawal syndrome, or known psychiatric history) is provided in the accompanying topic reviews and in an algorithm.
- Antipsychotics should be avoided in patients with anticholinergic delirium or acute alcohol withdrawal; refer to UpToDate topic. Dose reduction by one-half is needed for older adults, debilitated patients, and if used in combination with other sedation.
- Refer to accompanying text for discussion of electrocardiograph and other monitoring for agents known to cause prolongation of the QTc interval.
- Antipsychotics (eg, aripiprazole, risperidone, haloperidol) are metabolized to varying degrees by CYP450 2D6, 3A4, and/or substrates of P-glycoprotein. Drug interactions and additive QTc prolongation effects can be assessed by use of the [drug interactions program](#) included within UpToDate.

IM: intramuscular; IV: intravenous; SL: sublingual.

* IV administration of olanzapine should be limited to settings where patient can be closely monitored for respiratory depression and excessive sedation.

¶ If olanzapine is administered IV, limit total dose to 10 mg per episode (ie, if initial dose was <10 mg, may repeat with additional dose after ≥10 minutes up to 10 mg total).

Δ It may be necessary to repeat initial dose or fraction thereof after 15 to 20 minutes in patients with severe agitation until desired level of sedation attained.

◇ Selected patients without schizophrenia may need a higher cumulative haloperidol dose (eg, up to 30 mg) during the first 24 hours of treatment to achieve and maintain adequate sedation.

§ Treatment of acute dystonic reactions is diphenhydramine 25 to 50 mg IM/IV or benztropine 1 to 2 mg IM/IV, which is discussed in detail separately.

Table 2: Selected adverse effects of antipsychotic medications for schizophrenia

	Weight gain	Glucose abnormalities	Hyperlipidemia	Akathisia	Parkinsonism	Dystonia	Tardive dyskinesia	Prolactin elevation	Sedation
Second-generation agents									
Aripiprazole	+	+	+	++	+	+	+	0	+
Asenapine	++	++	++	++	+	++	++	++	++
Brexipiprazole [¶]	+	+	++	++	+	+	+	0	++
Cariprazine [¶]	++	+	+	++	+	+	+	+	++
Clozapine ^Δ	+++	+++	+++	+	+	+	+	+	+++
Iloperidone	++	++	+	+	+	+	+	++	++
Lumateperone [¶]	+	+	+	+	+	+	+	0	+
Lurasidone	+	++	++	++	++	++	++	++	++
Olanzapine	+++	+++	+++	++	++	+	+	++	+++
Paliperidone	++	+	++	++	++	++	++	+++	++
Pimavanserin	–	+	+	+	+	+	+	+	+
Quetiapine	++	++	+++	+	+	+	+	+	+++
Risperidone	++	++	+	+++	+++	++	++	+++	++
Ziprasidone	+	+	+	++	+	+	+	++	++
Other antipsychotic medications									
Xanomeline-trospium [¶]	0	0	0	0	0	0	0	0	+
First-generation agents									
Chlorpromazine	++	++	+	++	++	++	+++	+	+++
Fluphenazine	++	+	+	+++	+++	+++	+++	+++	+
Haloperidol	++	+	+	+++	+++	+++	+++	+++	+
Loxapine	+	+	+	++	++	++	++	++	++
Molindone	+	+	+	++	++	++	++	++	++
Perphenazine	++	+	+	++	++	++	++	++	++
Pimozide	+	+	+	+++	+++	++	+++	+++	+
Thioridazine [§]	++	+	+	+	+	+	+	++	+++
Thiothixene	+	+	+	+++	+++	+++	+++	+++	+
Trifluoperazine	++	+	+	++	++	++	++	++	+

Adverse effect rankings, with the exception of the QTc classifications, are consistent with American Psychiatric Association practice guidelines for the treatment of schizophrenia.^[1] The QTc classifications are determined by UpToDate Lexidrug according to US Food & Drug Administration guidance.^[2,4] Other sources may use different classification systems resulting in some agents being classified differently.

ECG: electrocardiogram; IV: intravenous.

* Clinically significant QTc prolongation was not detected in preliminary studies or reported in the manufacturer's labeling.

[¶] Based upon limited experience.

^Δ Clozapine also causes granulocytopenia or agranulocytosis in approximately 1% of patients requiring regular blood cell count monitoring. Clozapine has been associated with excess risk of myocarditis and venous thromboembolic events including fatal pulmonary embolism. These issues are addressed in the UpToDate topic review of guidelines for prescribing clozapine section on adverse effects.

[◇] Available data suggest that iloperidone QTc risk is relatively low (+) at usual therapeutic doses. However, moderate QTc prolongation may occur at high doses and with interacting medications; caution (eg, regular ECG monitoring or avoidance) is warranted, particularly in high-risk patients.

[§] Thioridazine is also associated with dose-dependent retinitis pigmentosa. Refer to UpToDate text.

References:

- Keepers GA, Fochtmann LJ, Anzia JM, et al. The American Psychiatric Association practice guideline for the treatment of patients with schizophrenia. American Psychiatric Association 2020. Available at: <https://www.psychiatry.org/psychiatrists/practice/clinical-practice-guidelines> (Accessed on March 24, 2020).
- UpToDate Lexidrug. More information available at <https://online.lexi.com/>.

3. Lin X, Siafis S, Tian J et al. Antipsychotic-Related Prolactin Changes: A Systematic Review and Dose-Response Meta-analysis. *CNS Drugs*. 2025 Oct;39:937.

4. Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs – Questions and Answers; Guidance for Industry US Food and Drug Administration, June 2017 (revision 2). Available at: <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073161.pdf>.

Graphic 82533 Version 48.0

Contributor Disclosures

Malia J Moore, MD No relevant financial relationship(s) with ineligible companies to disclose. **Dana Im, MD, MPP, MPhil** No relevant financial relationship(s) with ineligible companies to disclose. **Korilyn S Zachrison, MD, MSc** No relevant financial relationship(s) with ineligible companies to disclose. **Michael Ganetsky, MD** No relevant financial relationship(s) with ineligible companies to disclose.

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

[Conflict of interest policy](#)

→