

Managing acute agitation and aggression in the world of drug shortages

Jennifer Miller, PharmD, BCPP¹

How to cite: Miller J. Managing acute agitation and aggression in the world of drug shortages. *Ment Health Clin* [Internet]. 2021;11(6):334-46. DOI: 10.9740/mhc.2021.11.334.

Submitted for Publication: April 6, 2021; **Accepted for Publication:** June 28, 2021

Abstract

Acute agitation and aggression create safety risks for both patients and staff, often leading to psychiatric emergencies. Quick and appropriate treatment is necessary to achieve safe and effective outcomes. Unfortunately, there are several factors that hinder timely interventions, such as medication shortages and delay in staff preparedness. Ultimately, the goal of managing acute agitation and aggression in the clinical setting is to de-escalate the situation and prevent harm to patients and staff. This article will explore useful interventions in realizing treatment goals for the management of agitation and aggression in adults while navigating limitations faced in practice.

Keywords: agitation, aggression, first-generation antipsychotics, second-generation antipsychotics, benzodiazepines, de-escalation, medication shortage

¹ (Corresponding author) Clinical Psychiatric Pharmacist, Wilkes Barre Veterans Affairs Medical Center, Wilkes Barre, Pennsylvania, jennifer.dress55@gmail.com, ORCID: <https://orcid.org/0000-0002-1010-2970>

Disclosures: I have nothing personal to disclose. Psychopharmacology Pearls are review articles intended to highlight both the evidence base available and/or controversial areas of clinical care for psychiatric and neurologic conditions as well as strategies of clinical decision-making used by expert clinicians. As pearls, articles reflect the views and practice of each author as substantiated with evidence-based facts as well as opinion and experience. Articles are edited by members of the Psychopharmacology Pearls Editorial Board as well as peer reviewed by MHC reviewers. This article was developed as part of the 2021 Psychopharmacology Pearls product for BCPP recertification credit. The course information and testing center is at <https://cpnp.org/459431>.

Introduction

Acute agitation is defined as a state of unease or inner tension with or without excessive motor activity.¹⁻³ The term aggression represents a behavioral expression of severe agitation with the potential to cause harm to self or others.⁴ Agitation and aggression are commonly encountered in the context of mental health care and, when encountered, demand serious attention from staff.

The management of acute agitation and aggression has evolved over the years to prioritize rapid symptom improvement and avoidance of more restrictive interventions such as seclusion or restraints.^{5,6} One barrier that has made treatment planning more difficult over the past 10 years has been drug shortages.⁷ Drug shortages force prescribers to use alternatives they may not be as familiar with. This is especially problematic in the setting of acute agitation and aggression, when timely intervention is paramount.

A clinical case will be used throughout the article to explore treatment options and assist the reader in optimizing treatment despite barriers often faced in practice.

Patient Case Part 1: Identifying Risk

H.N. is a 36-year-old patient with a diagnosis of schizophrenia presenting to the mental health clinic. Motor and verbal hyperactivity are exhibited, and a feeling of nervousness is endorsed. Medication nonuse is reported with self-discontinuation of oral risperidone 6

Take Home Points:

1. Treatment should be chosen through a shared decision-making process while considering agitation severity, agitation etiology, medication availability, route of administration, side effect profile, and patient preference, when possible.
2. De-escalation strategies are considered first-line nonpharmacologic treatment for agitation and aggression and include verbal de-escalation and environment modification.
3. Oral medication options including second-generation antipsychotic monotherapy, benzodiazepine monotherapy, combination of oral risperidone plus lorazepam, or a combination of oral haloperidol with either lorazepam, promethazine, or diphenhydramine are recommended for the treatment of mild to moderate agitation.
4. Parenteral pharmacologic treatment recommended for moderate to severe agitation includes monotherapy with an intramuscular benzodiazepine, intramuscular second-generation antipsychotic, intramuscular droperidol, or combination therapy with intramuscular haloperidol plus benzodiazepine, promethazine, or diphenhydramine.
5. Drug shortages preferentially affect older, generic, parenteral medications. Multiple first-line medications used for the management of acute agitation and aggression fit this description, which makes shortages especially concerning when prompt treatment intervention is critical.

weeks ago. History of alcohol use disorder is endorsed with 1-year period of sobriety until relapse 1 week ago. Alcohol use reported as consuming 6 to 8 beers a day to “numb the voices” with last use yesterday. The patient is hearing voices to “hurt and kill” and states, “I will do it if they don’t leave me alone.” Patient reluctantly agrees to further evaluation in the emergency department (ED) stating, “they better let me go from there.”

Recognizing Acute Agitation and Aggression in Clinical Practice

It is important for clinicians to quickly recognize signs of, and risk factors for, agitation due to the associated high acuity. This allows more time for treatment planning and communication to maximize preparedness. There are multiple evidence-based risk factors that should signal a need to prepare management strategies. Static considerations include a history of violence, younger age, social or occupational dysfunction, prior treatment failure or violation of probation or parole, trauma history, and

diagnosis of serious mental illness, substance use disorder, or personality disorder. Dynamic considerations include violent ideation or intent, lack of insight, impulsivity, active symptoms of serious mental illness, active substance use, failure of treatment or probation or parole conditions, and lack of stable housing, employment, or finances.⁸ Static and dynamic risk factors will be revisited in a patient case to highlight their role in clinical assessment. Finally, staff collaboration is important to identify medical or substance-induced etiologies as this will impact treatment decisions.

There are several validated screening tools used to assess agitation and aggression and improve the reliability of a clinician’s assessment.⁹ These tools are considered structured professional judgement tools comprised of evidence-based factors known to affect agitation risk, frequency, and severity. The more clinically relevant screening tools in acute adult psychiatry populations are reviewed in Table 1.^{8,10-16}

Patient Case Part 2: Importance of Structured Professional Judgement

H.N. is now being transported to the ED. The clinician calls the ED to relay the following information for continuity of care: H.N. is a patient known to the facility and has not been taking medications. H.N. is hearing voices at this time to “hurt and kill” but is cooperative when taking medications as prescribed.

When H.N. presents to the ED, he is taken to a triage room. Motor and verbal hyperactivity are ongoing as well as clenched jaw and fists. After being in the triage room for 30 minutes, H.N. sees the ED doors open, pushes past staff, and elbows a nurse in the face. Staff observe the situation and decide to place the patient in restraints. The doctor orders STAT doses of haloperidol 5 mg and lorazepam 2 mg for IM injection.

In the case above, there were opportunities for a structured assessment of agitation. Prompt recognition of risk is the first step in treatment planning and maximizing safety. H.N. has risk factors such as younger age, diagnosis of schizophrenia with active symptoms, treatment nonadherence, and active substance use. Mental health clinic staff may have accounted for these risk factors by conversing with H.N. and using the Historical, Clinical, and Risk Management-20 Violence Risk Assessment Scheme to assist in predicting aggression risk. H.N. also demonstrated active signs of agitation in the ED including restlessness, tension, and nervousness. ED staff may have assessed the severity of agitation using the Overt Agitation Severity Scale. These screening tools

TABLE 1: Assessment tools for agitation in adult psychiatry^{8,10-16}

Tool ^a	Measures	Scoring	Clinical Pearls
Overt Agitation Severity Scale	12 items separated into 3 categories of movements: Vocalization and movements of face; upper torso and upper extremities; lower extremities	Scored from 0 to 4 based on frequency and severity	<ul style="list-style-type: none"> • Developed for inpatient geropsychiatry • Validated in adult inpatient psychiatry • Useful regardless of agitation etiology • Recommended 15 min observation time and relatively complicated scoring may not be ideal for all emergencies
Behavioral Activity Rating Scale	7 items: Difficult or unable to rouse; asleep, but responds normally; drowsy, appears sedated; quiet and awake; overt activity, calms with redirection; extremely/continuously active, not requiring restraint; violent, requires restraint	Scored from 0 to 7 based on severity	<ul style="list-style-type: none"> • Developed for use in adult inpatients with psychosis • Useful to assess treatment efficacy for agitation • Easy to score
Positive and Negative Syndrome Scale-Excited Component	5 items: Hostility, uncooperativeness, impulsivity, tension, excitability	<ul style="list-style-type: none"> • Scored from 1 to 7 based on presence and severity • Decrease $\geq 40\%$ within 2 hours is considered treatment “response” 	<ul style="list-style-type: none"> • Developed for clinical and research use • Useful in ED setting for acute agitation in psychosis • Useful to assess medication need in patients with agitation and schizophrenia
Brøset Violence Checklist	6 items: Confusion, irritability, boisterousness, physical threats, verbal threats, attacks on objects	<ul style="list-style-type: none"> • Scored 0 for absent and 1 for present • Total score ≥ 2 predicts risk of violence over 24 h 	<ul style="list-style-type: none"> • Developed for adult inpatient psychiatry • Assists in predicting future risk of aggression
Historical, Clinical, and Risk Management-20 Violence Risk Assessment Scheme	20 items: History of violence, young age, relationship instability, employment problems, substance use problems, serious mental illness, psychopathy, early maladjustment, personality disorder, prior supervision failure, lack of insight, negative attitudes, active mental illness symptoms, impulsivity, unresponsive to treatment, unrealistic plans, destabilizing surroundings, lack of support, noncompliance, stress	Scored from 0 to 2 based on frequency	<ul style="list-style-type: none"> • Developed for use in various settings including inpatient psychiatry, forensic and correctional facilities • Assists in predicting future risk of aggression

ED = emergency department.

^aTools included are clinician-rated and have been developed for use in adult psychiatry settings. Of note, there are many additional clinical tools published for assessment of agitation and aggression in various conditions and specific patient populations.

would account for active signs of agitation and high risk of aggression, thereby indicating a need for early intervention and collaboration with H.N. on treatment decisions.

Treatment Options

Treatment options are conceptualized on a spectrum of agitation severity with certain interventions being more

appropriate for mild agitation, such as de-escalation strategies and voluntary medication, while others are reserved for severe agitation and aggression, such as parenteral medication and physical restraints.^{3,17} It is generally understood that signs of mild agitation are visible to the trained eye and prompt intervention should be employed to prevent escalation to more severe agitation. Early signs may be subtle but present during initial patient encounters including restlessness and

TABLE 2: Oral medication options recommended for the management of mild to moderate agitation and aggression in adults¹⁸⁻³⁷

Medication	Recommended Initial Dose Ranges, mg ^a	Considerations for Use
First-Generation Antipsychotics		
Haloperidol ^{18-22,24}	2-10	<ul style="list-style-type: none">• Onset 30 min, peak 2-6 h, half-life of 14-37 h• Accumulation possible with hepatic impairment• Caution with cardiac concerns• EKG recommended• Combination with lorazepam, promethazine, or diphenhydramine recommended to prevent EPS¹⁹⁻²¹• Monotherapy preferred in medically compromised^{18,22}
Second-Generation Antipsychotics		
Aripiprazole ^{20,21,28}	10-15	Peak 3-5 h, half-life 75 h
Asenapine ^{21,29}	10	<ul style="list-style-type: none">• Onset 15 min, peak 30-90 min, half-life 24 h• Only sublingual antipsychotic formulation• Contraindicated in severe hepatic impairment
Risperidone ^{18-22,30}	1-2	<ul style="list-style-type: none">• Onset/peak 1-2 h, half-life 3-20 h• ODT pharmacokinetics similar to traditional oral formulation• Consider dose reduction for renal or hepatic impairment
Quetiapine ^{18,20,21,31}	25-50	Peak 1.5 h, half-life 6 h
Olanzapine ^{18-22,32}	5-10	<ul style="list-style-type: none">• Onset ≤60 min, peak 5-8 h, half-life 30 h• ODT pharmacokinetics similar to oral formulation
Benzodiazepines		
Lorazepam ^{18-22,34}	0.5-2	<ul style="list-style-type: none">• Onset 20-30 min, peak 2 h, half-life 12 h• No clinically significant risk of drug accumulation• Monotherapy recommended for undifferentiated agitation by ACEP, AAEP, and BETA^{18,19,22}• Combination with haloperidol preferred by WFSBP and BAP^{20,21}

AAEP = American Association for Emergency Psychiatry; ACEP = American College of Emergency Physicians; BAP = The British Association for Psychopharmacology; BETA = Best Practices in the Evaluation and Treatment of Agitation; EKG = baseline electrocardiogram; EPS = extrapyramidal symptoms; ODT = orally disintegrating tablet; WFSBP = World Federation of Societies of Biological Psychiatry.

^aDose ranges as per tertiary drug references and medication labels; deviations possible based on patient-specific factors and facility policy.³⁷

intense eye contact and may escalate to overt signs like yelling or clenched fists. De-escalation strategies should be employed based on severity including verbal de-escalation and clearing the environment of safety hazards. Specifically, if a person is exhibiting signs of mild to moderate agitation, the clinician should attempt to ask open-ended questions while creating safe opportunities for the person to express their thoughts. If agitation worsens, the clinician will need to alter their approach to set firm boundaries to re-establish safety. An example would be respectfully directing a patient who is yelling to please lower their voice. It is important to remember that agitation severity fluctuates and thus management strategies should be equally fluid.

Pharmacologic Treatment

Pharmacologic treatment options are based on current understanding of agitation pathophysiology. The main neurochemical considerations include dopamine and

norepinephrine hyperactivity and serotonin and GABA hypoactivity.⁴ As such, antipsychotics and benzodiazepines have emerged as the main evidence-based options. Oral medications are considered first in the treatment of mild to moderate agitation, while severe agitation often requires rapid improvement with parenteral medication to calm the person, assist them in regaining self-control, and quell the risk of harm.¹⁸⁻²³ In rare cases of extremely severe agitation, quick acting parenteral medications have been used for sedation when a less invasive outcome isn't sufficient to prevent harm to self or others. Tables 2 and 3 summarize medication options recommended by existing guidelines and expert consensus.¹⁸⁻³⁷

Antipsychotics

Antipsychotics are the preferred initial treatment choice in the presence of a psychiatric etiology or CNS depressant intoxication. Recommended antipsychotics include halo-

TABLE 3: Parenteral and inhaled medication options recommended for the management of moderate to severe agitation and aggression in adults¹⁸⁻³⁷

Medication	Recommended Initial Dose Ranges, mg ^a	Considerations for Use
First-Generation Antipsychotics		
IM		
Haloperidol ^{18-23,25}	2-10	<ul style="list-style-type: none"> • IM onset 15 min, peak 20-40 min, average duration 2 h • Combination with lorazepam, promethazine, or diphenhydramine preferred to prevent EPS¹⁹⁻²¹ • Caution with cardiac concerns; EKG recommended
Droperidol ^{18-23,26}	5-10	<ul style="list-style-type: none"> • IM onset/peak ≤30 min, duration 2-4 h up to 12 h • Rapid IM absorption • Caution with renal and hepatic impairment • Contraindicated in QTc prolongation; EKG recommended
IV		
Droperidol ^{19-22,26}	2.5-10	<ul style="list-style-type: none"> • IM onset/peak ≤30 min, duration 2-4 h up to 12 h • Contraindicated in QTc prolongation; continuous EKG monitoring recommended • Only used in settings with resuscitation equipment
Haloperidol ^{21,25}	2-10	<ul style="list-style-type: none"> • IV onset 3-20 min; peak 30 min; duration range of 3-24 h • Continuous EKG monitoring recommended • IV route is off-label • Only used in settings with resuscitation equipment
Inhaled		
Loxapine ^{20,21,27}	10	<ul style="list-style-type: none"> • Onset/peak 2 min, duration up to 24 h • Contraindicated in lung disease or concurrent use of inhaled medications
Second-Generation Antipsychotics		
IM		
Olanzapine ^{18-22,32}	5-10	<ul style="list-style-type: none"> • Onset/peak 15-45 min, duration 2 h • Do not combine within 2 h of administration of IM benzodiazepines because of risk of respiratory suppression
Ziprasidone ^{18,19,21,22,33}	10-20	<ul style="list-style-type: none"> • Onset 15-30 min, peak 30-60 min, half-life 2-5 h • Contraindicated in QTc prolongation; EKG recommended
IV		
Olanzapine ^{20,21,32}	5-10	<ul style="list-style-type: none"> • Onset/peak 5-10 min, duration 2 h • IV route is off-label • Only used in setting with resuscitation equipment
Benzodiazepines		
IM		
Lorazepam ^{19-23,35}	0.5-2	<ul style="list-style-type: none"> • Onset 20-30 min, peak ≤3 h, duration 6-8 h • Monotherapy recommended by BAP, ACEP, and NICE^{20,22,23} • Combination with haloperidol preferred by WFSBP and BETA^{19,21}
Midazolam ^{19,21,22,36}	2.5-5	<ul style="list-style-type: none"> • Onset 15 min, peak 30-60 min, half-life 2-6 h • Not recommended in BAP 2018 because of waning efficacy and risk of respiratory depression²⁰
IV		
Lorazepam ^{20,21,35}	1-2	<ul style="list-style-type: none"> • Onset 15-20 min, duration 6-8 h • Only used in settings with resuscitation equipment
Midazolam ^{19-21,36}	2.5-5	<ul style="list-style-type: none"> • Onset seconds to minutes, peak 3-5 min, duration <2 h • Reliable IM absorption but short duration of action resulting in need for repeat dosing • Accumulation possible with renal and hepatic impairment • Only used in settings with resuscitation equipment

ACEP = American College of Emergency Physicians; BAP = The British Association for Psychopharmacology; BETA = Best Practices in the Evaluation and Treatment of Agitation; EPS = extrapyramidal symptoms; EKG = baseline electrocardiogram; NICE = National Institute for Health and Care Excellence; WFSBP = World Federation of Societies of Biological Psychiatry.

^aDose ranges as per tertiary drug references and medication labels; deviations possible based on patient-specific factors and facility policy.³⁷

peridol, droperidol, loxapine, olanzapine, ziprasidone, aripiprazole, asenapine, risperidone, and quetiapine with second-generation antipsychotics (SGAs) preferred to first-generation antipsychotics.¹⁸⁻²³ Chlorpromazine has historically been used for agitation in single oral or IM doses of 25 to 50 mg, repeated at 1 hour if needed and then administered every 4 to 6 hours up to a recommended maximum of 200 mg/d. Its use is limited by lack of primary evidence, IM availability in a glass ampule requiring use of a filter needle, significant risk of hypotension, sedation, decreased seizure threshold, and slow time to effect.^{18,21,37}

Fluphenazine has also been used in IM doses of 1.25 to 5 mg administered every 6 to 8 hours up to a maximum of 10 mg/d because of availability of quick-acting formulations, but the IM formulation is only supplied in multidose vials thus limiting its ability to be stored in certain automated dispensing machines for quick access. Despite possibility of chlorpromazine and fluphenazine availability in times of drug shortages of more evidenced-based options, their use carries feasibility and safety issues and is not supported in guidelines.¹⁸⁻²³

Oral Antipsychotics

There have been few studies evaluating oral antipsychotics for agitation. Existing data are reviewed here. Oral haloperidol has evidence for reducing agitation, but data are limited by small sample size and uncontrolled use of concurrent IM lorazepam.^{20,21,38}

Oral haloperidol was also compared to various oral SGAs, including risperidone, quetiapine, olanzapine, and aripiprazole. Studies³⁹⁻⁴¹ reveal similar efficacy between groups, with more extrapyramidal symptoms (EPS) observed in the haloperidol group. Of note, oral ziprasidone is not recommended because of lack of primary evidence in agitation treatment as well as practicality issues including slow peak effect time of 6 to 8 hours and need to administer with food. As above, aripiprazole is recommended as an evidenced-based option for oral treatment of acute agitation, but, like ziprasidone, clinicians should consider the time to peak effect of 3 to 5 hours.

Alternative formulations including sublingual asenapine, and orally disintegrating tablet formulations of olanzapine and risperidone were also studied. Asenapine is the only sublingual option with support from a small randomized controlled trial showing significant reduction in agitation at 2 hours as compared with placebo.⁴² Finally, data from open label trials^{43,44} supports the efficacy of olanzapine and risperidone orally disintegrating tablet formulations similar to that of traditional oral antipsychotic formulations.

Parenteral Antipsychotics

IM haloperidol has been used for the management of severe agitation since the 1950s. Its efficacy was demonstrated in multiple randomized double-blind studies^{20,21,45-47} with data indicating comparable efficacy to IM lorazepam, IM olanzapine, and IM ziprasidone. However, evidence shows IM haloperidol monotherapy carries a greater risk of EPS compared to IM SGAs, and guidelines recommend combination with a benzodiazepine or promethazine over its use alone.^{20,21,46} Of note, more recent guidance from 2020 recommends the combination of haloperidol with diphenhydramine for the prevention of EPS.⁴⁹

IM droperidol use has fluctuated over the years because of supply issues and a 2001 boxed warning for QTc prolongation.⁴⁸ There is evidence to support comparable efficacy to IM haloperidol but with less need for redosing. However, safety concerns for hypotension were more frequent with droperidol.^{20,49} Droperidol's cardiac safety has been further assessed with data from a large prospective observational study showing 1.3% of participants experienced QTc prolongation but no cases of torsade de pointes were observed. These findings are limited by uncontrolled use of either IM or IV droperidol as well as concurrent QTc prolonging medications.⁵⁰ Finally, a Cochrane review⁵¹ published in 2016 determined parenteral droperidol to be safe and effective in the treatment of acute agitation.

There are 2 SGAs, olanzapine and ziprasidone, with IM formulations indicated for the management of agitation. Ziprasidone was FDA-approved in 2002 with double-blind randomized controlled trial support for use.⁵² Furthermore, IM ziprasidone has been shown to be at least as effective, if not more effective than IM haloperidol in some studies, with similar risk for QTc prolongation but less EPS.⁵³⁻⁵⁶

Olanzapine became available for IM use in 2004 and is supported by data from randomized controlled trials and a meta-analysis concluding it as a safe and effective option with comparable efficacy but less EPS than IM haloperidol.^{3,57} It was also comparable in efficacy to haloperidol/promethazine and haloperidol/benzodiazepine combinations. Data⁵⁸⁻⁶¹ suggest more frequent need for redosing in IM olanzapine groups, which raised concern for respiratory suppression. A 2011 observational study⁶² investigating haloperidol, olanzapine, and ziprasidone revealed similar lengths of stay among these IM formulations.

There are 3 IV antipsychotic options that include droperidol, haloperidol, and olanzapine. However, these medications have been shown to produce a main outcome

of sedation versus calming. IV droperidol appears to have more evidence versus haloperidol, but neither were studied in a well-designed trial and data were not controlled for route of administration.^{51,63,64} IV olanzapine was shown to be effective for sedation in ED settings but with significant risk of adverse respiratory events.^{65,66} In conclusion, IV droperidol and olanzapine are recommended as last-line medication options for severe agitation and aggression requiring rapid sedation. The concerns for cardiac and respiratory safety necessitate electrocardiogram monitoring and use only in settings with resuscitation capacity, resulting in some hospitals restricting droperidol and olanzapine to IM use only.²⁰

Inhaled Antipsychotic

Inhaled loxapine was FDA-approved in 2012 with data^{20,67} showing significant improvement in agitation scores at 20 minutes lasting until 2 hours posttreatment compared to placebo but with greater frequency of side effects including altered taste and throat irritation.

A recent randomized trial⁶⁸ comparing inhaled loxapine to IM aripiprazole concluded that inhaled loxapine resulted in quicker onset of effects. Of note, IM aripiprazole is not available in the United States and these data may not be extrapolated to comparisons with other IM antipsychotic injections because of pharmacokinetic differences. Inhaled loxapine is to be used with a patient's cooperation under Risk Evaluation and Mitigation Strategies guidance, and its use is further limited by high cost. It is contraindicated in certain respiratory conditions and may only be used in settings in which staff monitor patients with chest auscultation every 15 minutes for 1 hour and have a short-acting beta-agonist bronchodilator available for rescue use.²⁷

In conclusion, oral SGAs and haloperidol lorazepam combinations are appropriate noninvasive options for mild to moderate agitation. Unfortunately, as seen in our clinical case, the window of opportunity for offering oral medication to a patient with agitation closes if timely de-escalation strategies are not employed. Therefore, we are left with few options to manage severe agitation outside of invasive medications. If agitation does progress to severe levels with imminent risk of harm, IM olanzapine, ziprasidone or haloperidol lorazepam combinations are reasonable options while weighing risks of hypotension, metabolic complications, QTc prolongation, and EPS.

Benzodiazepines

Benzodiazepine monotherapy is recommended as the initial treatment choice in the presence of stimulant intoxication or unknown etiology.¹⁸ Lorazepam and midazolam have emerged as evidence-based options and have desirable pharmacokinetic properties, including

reliable absorption, rapid onset of action, and minimal accumulation of drug. Although diazepam is used, this practice is not supported by guidelines because of limited evidence, risk of drug accumulation with oral and IM administration, erratic absorption, and likelihood of injection site pain with IM administration.^{20,37}

Overall, there is less evidence to support the use of oral monotherapy with benzodiazepines as compared to oral SGA monotherapy. Recommendations are mainly limited to lorazepam and based on a small study²⁰ that revealed comparable reduction in agitation to haloperidol. Data were not controlled for redosing and route of administration.⁶⁹ Based on available evidence and favorable pharmacologic properties, oral lorazepam monotherapy is regarded as an option for the management of acute agitation and aggression when the risks of an antipsychotic are unacceptable, as is the case in stimulant intoxication.

There have been relatively limited studies published supporting the use of IM benzodiazepines, but data^{20,70} appear more robust for lorazepam and midazolam as compared with other benzodiazepines. Specifically, IM lorazepam revealed a similar reduction in agitation scores as compared to IM haloperidol in 2 randomized controlled trials but redosing was not controlled.^{20,46,69} IM midazolam has shown a quicker onset and shorter duration of action as compared with other IM options including lorazepam, haloperidol, and haloperidol/promethazine combination.^{47,71} However, the short duration of action was highlighted as problematic in a study⁷² that showed more patients in the midazolam group with agitation at 45 minutes posttreatment as compared to ziprasidone and droperidol.

IV benzodiazepine formulations include lorazepam and midazolam and have been used in practice for the main therapeutic effect of sedation as opposed to calming. IV lorazepam monotherapy and IV midazolam monotherapy are considered comparable in effect to IV droperidol, but with more need for redosing in benzodiazepine groups.^{63,73,74} Of note, the midazolam group did experience more frequent respiratory suppression as compared to droperidol.⁷³ Based on this limited data and CNS depressant potential, IV lorazepam and midazolam are reserved for last-line use for rapid sedation in severe agitation and aggression in situations where antipsychotic risks are unacceptable and only in settings with resuscitation capacity.

Medication Combinations

Approximately 25% of patients don't respond to initial treatment.²⁰ Therefore, various combination regimens have been studied. Oral risperidone lorazepam and oral haloperidol lorazepam combinations are considered safe and effective for mild to moderate agitation.^{38,69,75,76} For

moderate to severe agitation, the IM haloperidol lorazepam combination is considered more effective than either drug alone and with less risk of EPS versus haloperidol monotherapy.^{70,77,78} The haloperidol/promethazine combination is also considered more effective than haloperidol alone, but parenteral promethazine use is discouraged because of its irritant-like properties, especially when used intravenously.^{79,80} Benztropine has been used to treat EPS, namely acute dystonia, but guidelines do not recommend this as prophylaxis in combination with haloperidol for the treatment of acute agitation.^{18-23,37} Lastly, IM haloperidol combinations have been largely regarded as comparable to IM olanzapine monotherapy.^{59-61,81} However, a Cochrane review⁵⁸ concluded the haloperidol/promethazine combination resulted in less need for redosing as compared with olanzapine.

As seen in the patient case, H.N.'s agitation progressed to a severe level requiring administration of parenteral medication to reestablish safety. Haloperidol was chosen and administered with lorazepam, which was appropriate to minimize risk of EPS. Other options would have been appropriate as well, such as IM olanzapine or ziprasidone monotherapy.

Other Medications

Two alternative parenteral medications used for sedation in severe agitation include ketamine and dexmedetomidine. IM or IV ketamine is considered to have superior sedation with quicker onset as compared to parenteral haloperidol, midazolam, and lorazepam in prospective observational and retrospective studies.⁸² However, ketamine use carries the risk of tachycardia, hypertension, and need for intubation and is typically restricted to ED or intensive care unit settings in patients with extreme agitation unresponsive to benzodiazepines and/or antipsychotics.^{83,84}

Dexmedetomidine is considered a superior IV option for sedation in medical intensive care unit settings but is not recommended for use in the ED because of significant risk for hypotension.²⁰ Both parenteral ketamine and dexmedetomidine cause rapid sedation versus calming. Because of this, they are rarely recommended for the routine management of acute agitation and aggression, but they are valuable options for severe refractory agitation with imminent risk of harm.²⁰

Patient Case Part 3: Optimizing Treatment

After being medically cleared in the ED and receiving 1 dose of IM haloperidol 5 mg and 2 doses of IM lorazepam 2 mg, H.N. presents to the inpatient acute psychiatry unit

on an involuntary commitment. Staff observe the patient to be sedated with rumination on "the need to get home" but minimal ability to respond to questions regarding circumstances of admission. Vital signs are stable. Current electrocardiogram shows normal sinus rhythm with a QTc of 445. Laboratory values are within normal limits. After review of psychiatric history, the interdisciplinary team notes insufficient efficacy from oral risperidone monotherapy for acute agitation during the last admission. They decide to use oral haloperidol/lorazepam combination for mild to moderate agitation and IM haloperidol/lorazepam combination for severe agitation with aggression. However, they are informed oral and IM haloperidol are unavailable due to drug shortage.

Barriers to Treatment

Drug Shortages

What happens when the medication of choice is unavailable due to a drug shortage?

Drug shortages are defined and cataloged by both the FDA and American Society of Health-System Pharmacists.⁷ According to their databases, many of the drugs used for the management of agitation have recently been the subject of a shortage, including: haloperidol tablets, haloperidol injection, droperidol injection, lorazepam tablets, lorazepam injection, midazolam injection, promethazine injection, dexmedetomidine injection, and ketamine injection. At the time this article was written many of these medications remain affected by shortage.^{85,86}

Drug shortages tend to impact older, generic, and/or parenteral medications. Reasons for this are multifactorial and include production delays, lack of manufacturing capacity, decreased profitability, and manufacturer quality management problems.⁷ Unfortunately, clinicians rely on many older, generic, and/or parenteral medications in the management of acute agitation and aggression, making this especially problematic in these high acuity situations.

Staff Preparedness

Drug shortages impair staff preparedness by forcing the clinician to use alternatives that may be unfamiliar, have increased side effect risk, or inferior efficacy. American Society of Health-System Pharmacists recommends preparing and responding to drug shortages through use of operational and therapeutic assessments.⁷ An operational assessment is used to determine the extent and impact of the shortage by working with the pharmacy and inventory specialists to account for current inventory and expected duration and impact of the shortage. A clinician may also access this information directly through the FDA

or American Society of Health-System Pharmacists databases and receive alerts regarding shortages.^{85,86}

A therapeutic assessment involves prioritizing patient populations for which to allocate available resources.⁷ This would include identifying areas of the facility and patient populations with higher incidence of agitation than others. This may differ depending on the facility, but the ED and inpatient psychiatry units are generally considered high-risk areas.²¹ These areas may benefit from outreach and education about the potential implications of drug shortages.

Therapeutic assessment also involves identifying feasible treatment alternatives. First, staff shouldn't underestimate the usefulness of screening tools and nonpharmacologic intervention. For example, using the Overt Agitation Severity Scale may promptly identify signs of agitation, and the Brøset Violence Checklist may indicate a higher risk for aggression. This can signal the need to prioritize early verbal de-escalation and environment modification. It may even create safe opportunities for therapeutic rapport building and collaborative decision making on medication options prior to escalation. Therefore, proper use of these interventions may prevent escalation to severe agitation, spare the need for parenteral medications, and minimize the impact of drug shortages in practice.

When determining alternative medication options, the clinician should be aware of the evidence for medication efficacy and safety. Overall, guideline and expert consensus consider multiple options effective for mild to moderate agitation as well as moderate to severe. These are included in Tables 2 and 3, respectively. There are also various safety concerns that may make one option more desirable. The route of administration is an important consideration, and facility resources in different areas may limit which medication routes are able to be used. For example, IV administration of olanzapine, haloperidol, droperidol, midazolam, and lorazepam are restricted to use in settings with resuscitation capacity, such as in a person with established IV access for treatment of delirium on a medical floor.

Another important consideration in the management of agitation and aggression includes conserving parenteral medication.⁷ For example, a person requiring IM olanzapine to treat severe agitation should be de-escalated to oral antipsychotic as appropriate. Staff should also be aware of supply shortages, such as sterile water which is necessary for administering certain parenteral medications like olanzapine and ziprasidone. Additionally, parenteral haloperidol combinations with a benzodiazepine or diphenhydramine are frequently used as standard treatment for moderate to severe agitation, but these

medications may be in short supply. It should be noted that the combination of 3 IM drugs such as a first-generation antipsychotic, benzodiazepine, and an antihistamine is not supported by evidence and may even be regarded as wasteful given the drug shortages faced in practice.^{7,18-23}

Finally, the clinician should prepare their next step if a patient has an insufficient response to initial treatment. In general, available guidelines/recommendations^{18,23} suggest redosing with the initial treatment at least once for insufficient response and then adding a benzodiazepine or switching to alternative such as haloperidol, benzodiazepine, promethazine, or diphenhydramine combination if not initially used. Screening tools such as the Positive and Negative Syndrome Scale-Excited Component may assist the clinician in determining need for additional medication. In this way, the assessment becomes more objective, and the unnecessary use of medication may be spared.

In the case of H.N., the inpatient psychiatry team is preparing to discuss a treatment plan, given the above described drug shortage of haloperidol. They scan the interview room for safety risks and means of egress. H.N. presents to the team as awake and alert, and a Behavioural Activity Rating Scale screen reflects calmness with redirection. The team concludes mild to moderate agitation is present with spikes when discussing substance use. They employ verbal de-escalation and reassure H.N. that these nonpharmacologic interventions will be used throughout admission. Finally, they discuss use of oral risperidone/lorazepam combination for mild to moderate agitation. This decision is appropriate given history of insufficient response to oral risperidone monotherapy. Additionally, the use of lorazepam would be limited to the inpatient controlled environment and would not be used long-term to minimize any risk of reinforcing a substance use disorder. This plan may establish safe and effective oral risperidone dosing necessary to achieve stabilization and facilitate transition to long-acting injectable risperidone or paliperidone for improved treatment adherence and future agitation risk mitigation. They make H.N. aware that everyone's safety is of the utmost importance and that IM olanzapine will be used for severe agitation with the availability of seclusion and restraints as a last-line option. They are transparent with H.N. and despite need for frequent redirection and de-escalation, H.N. leaves the room to voluntarily take a dose of oral medication.

Conclusion

The management of agitation and aggression is dynamic. There are many factors that affect treatment success, such as medication shortages and delay in staff prepared-

ness. However, there are ways to overcome these barriers. First, the clinician should acknowledge the risk of agitation in certain settings and patient populations. As awareness increases, clinicians should prioritize prompt screening for agitation, use of nonpharmacologic interventions, and noninvasive pharmacologic options. The clinician should be aware of the evidence-based options and feasibility for use in their facilities. In this way, the clinician conserves time in this high acuity situation, which creates opportunities to provide patient-centered care and optimize safety.

References

- American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Washington: American Psychiatric Association; 2013.
- Roberts J, Gracia Canales A, Blanthorn-Hazell S, Craciun Boldeanu A, Judge D. Characterizing the experience of agitation in patients with bipolar disorder and schizophrenia. *BMC Psychiatry*. 2018;18(1):104. DOI: [10.1186/s12888-018-1673-3](https://doi.org/10.1186/s12888-018-1673-3). PubMed PMID: [29661160](https://pubmed.ncbi.nlm.nih.gov/29661160/).
- Schleifer JJ. Management of acute agitation in psychosis: an evidence-based approach in the USA. *Adv Psychiatr Treat*. 2011; 17(2):91-100. DOI: [10.1192/apt.bp.109.007310](https://doi.org/10.1192/apt.bp.109.007310).
- Meyer JM, Cummings MA, Proctor G, Stahl SM. Psychopharmacology of persistent violence and aggression. *Psychiatr Clin North Am*. 2016;39(4):541-56. DOI: [10.1016/j.psc.2016.07.012](https://doi.org/10.1016/j.psc.2016.07.012). PubMed PMID: [27836150](https://pubmed.ncbi.nlm.nih.gov/27836150/).
- Allen MH, Currier GW. Use of restraints and pharmacotherapy in academic psychiatric emergency services. *Gen Hosp Psychiatry*. 2004;26(1):42-9. DOI: [10.1016/j.genhosppsy.2003.08.002](https://doi.org/10.1016/j.genhosppsy.2003.08.002). PubMed PMID: [14757302](https://pubmed.ncbi.nlm.nih.gov/14757302/).
- Downey LVA, Zun LS, Gonzales SJ. Frequency of alternative to restraints and seclusion and uses of agitation reduction techniques in the emergency department. *Gen Hosp Psychiatry*. 2007;29(6):470-4. DOI: [10.1016/j.genhosppsy.2007.07.006](https://doi.org/10.1016/j.genhosppsy.2007.07.006). PubMed PMID: [18022038](https://pubmed.ncbi.nlm.nih.gov/18022038/).
- Fox ER, McLaughlin MM. ASHP guidelines on managing drug product shortages. *Am J Health Syst Pharm*. 2018;75(21):1742-50. DOI: [10.2146/ajhp180441](https://doi.org/10.2146/ajhp180441). PubMed PMID: [30061155](https://pubmed.ncbi.nlm.nih.gov/30061155/).
- Douglas KS. Version 3 of the historical-clinical-risk management-20 (HCR-20V3): relevance to violence risk assessment and management in forensic conditional release contexts. *Behav Sci Law*. 2014;32(5):557-76. DOI: [10.1002/bsl.2134](https://doi.org/10.1002/bsl.2134). PubMed PMID: [25278316](https://pubmed.ncbi.nlm.nih.gov/25278316/).
- Hart SD, Douglas KS, Guy LS. The structured professional judgment approach to violence risk assessment: origins, nature, and advances. In: *The Wiley handbook on theories, assessment, and treatment of sexual offending* [Internet]. Oxford: John Wiley & Sons Ltd; c2016 [updated 2018 Jan 8; cited 2021 Feb 23]. p. 643-66. Available from: https://www.researchgate.net/publication/318437145_The_structured_professional_judgment_approach_to_violence_risk_assessment_Origins_nature_and_advances#:~:text=The%20Structured%20Professional%20Judgement%20%28SPJ%29%20approach%20is%20an,evidence-based%20guidelines%20to%20systematize%20the%20exercise%20of%20discretion
- Zeller SL, Rhoades RW. Systematic reviews of assessment measures and pharmacologic treatments for agitation. *Clin Ther*. 2010;32(3):403-25. DOI: [10.1016/j.clinthera.2010.03.006](https://doi.org/10.1016/j.clinthera.2010.03.006). PubMed PMID: [20399981](https://pubmed.ncbi.nlm.nih.gov/20399981/).
- Yudofsky SC, Kopecky HJ, Kunik M, Silver JM, Endicott J. The overt agitation severity scale for the objective rating of agitation. *J Neuropsychiatry Clin Neurosci*. 1997;9(4):541-8. DOI: [10.1176/jnp.9.4.541](https://doi.org/10.1176/jnp.9.4.541). PubMed PMID: [9447494](https://pubmed.ncbi.nlm.nih.gov/9447494/).
- Kopecky HJ, Kopecky CR, Yudofsky SC. Reliability and validity of the overt agitation severity scale in adult psychiatric inpatients. *Psychiatr Q*. 1998;69(4):301-23. DOI: [10.1023/a:1022182114925](https://doi.org/10.1023/a:1022182114925). PubMed PMID: [9793109](https://pubmed.ncbi.nlm.nih.gov/9793109/).
- Swift RH, Harrigan EP, Cappelleri JC, Kramer D, Chandler LP. Validation of the behavioural activity rating scale (BARS)TM: a novel measure of activity in agitated patients. *J Psychiatric Res*. 2002;36(2):87-95. DOI: [10.1016/s0022-3956\(01\)00052-8](https://doi.org/10.1016/s0022-3956(01)00052-8). PubMed PMID: [11777497](https://pubmed.ncbi.nlm.nih.gov/11777497/).
- Breier A, Meehan K, Birkett M, David S, Ferchland I, Sutton V, et al. A double-blind, placebo-controlled dose-response comparison of intramuscular olanzapine and haloperidol in the treatment of acute agitation in schizophrenia. *Arch Gen Psychiatry*. 2002;59(5):441-8. DOI: [10.1001/archpsyc.59.5.441](https://doi.org/10.1001/archpsyc.59.5.441). PubMed PMID: [11982448](https://pubmed.ncbi.nlm.nih.gov/11982448/).
- Chaichan W. Evaluation of the use of the positive and negative syndrome scale-excited component as a criterion for administration of p.r.n. medication. *J Psychiatr Pract*. 2008;14(2):105-13. DOI: [10.1097/01.pra.0000314317.79544.b4](https://doi.org/10.1097/01.pra.0000314317.79544.b4). PubMed PMID: [18360196](https://pubmed.ncbi.nlm.nih.gov/18360196/).
- Woods P, Almvik R. The Brøset violence checklist (BVC). *Acta Psychiatr Scand Suppl*. 2002;(412):103-5. DOI: [10.1034/j.1600-0447.106.s412.22.x](https://doi.org/10.1034/j.1600-0447.106.s412.22.x). PubMed PMID: [12072138](https://pubmed.ncbi.nlm.nih.gov/12072138/).
- Vieta E, Garriga M, Cardete L, Bernardo M, Lombraña M, Blanch J, et al. Protocol for the management of psychiatric patients with psychomotor agitation. *BMC Psychiatry*. 2017;17(1):328. DOI: [10.1186/s12888-017-1490-0](https://doi.org/10.1186/s12888-017-1490-0). PubMed PMID: [28886752](https://pubmed.ncbi.nlm.nih.gov/28886752/).
- Allen MH, Currier GW, Carpenter D, Ross RW, Docherty JP. The expert consensus guideline series. Treatment of behavioral emergencies 2005. *J Psychiatr Pract*. 2005;11 Suppl 1:5-108; quiz 110-2. PubMed PMID: [16319571](https://pubmed.ncbi.nlm.nih.gov/16319571/).
- Roppolo LP, Morris DW, Khan F, Downs R, Metzger J, Carder T, et al. Improving the management of acutely agitated patients in the emergency department through implementation of Project BETA (Best Practices in the Evaluation and Treatment of Agitation). *J Am Coll Emerg Physicians Open*. 2020;1(5):898-907. DOI: [10.1002/emp2.12138](https://doi.org/10.1002/emp2.12138). PubMed PMID: [33145538](https://pubmed.ncbi.nlm.nih.gov/33145538/).
- Patel MX, Sethi FN, Barnes TR, Dix R, Dratcu L, Fox B, et al. Joint BAP NAPICU evidence-based consensus guidelines for the clinical management of acute disturbance: de-escalation and rapid tranquilisation. *J Psychopharmacol*. 2018;32(6):601-40. DOI: [10.1177/0269881118776738](https://doi.org/10.1177/0269881118776738). PubMed PMID: [29882463](https://pubmed.ncbi.nlm.nih.gov/29882463/).
- Garriga M, Pacchiarotti I, Kasper S, Zeller SL, Allen MH, Vázquez G, et al. Assessment and management of agitation in psychiatry: expert consensus. *World J Biol Psychiatry*. 2016;17(2):86-128. DOI: [10.3109/15622975.2015.1132007](https://doi.org/10.3109/15622975.2015.1132007). PubMed PMID: [26912127](https://pubmed.ncbi.nlm.nih.gov/26912127/).
- Lukens TW, Wolf SJ, Edlow JA, Shahabuddin S, Allen MH, Currier GW, et al. Clinical policy: critical issues in the diagnosis and management of the adult psychiatric patient in the emergency department. *Ann Emerg Med*. 2006;47(1):79-99. DOI: [10.1016/j.annemergmed.2005.10.002](https://doi.org/10.1016/j.annemergmed.2005.10.002). PubMed PMID: [16387222](https://pubmed.ncbi.nlm.nih.gov/16387222/).
- National Collaborating Centre for Mental Health (UK). Violence and aggression: short-term management in mental health, health and community settings. Updated ed. London: British Psychological Society; 2015. PubMed PMID: [26180871](https://pubmed.ncbi.nlm.nih.gov/26180871/).
- Mylan Pharmaceuticals Inc. Haloperidol tablet. c2005 [updated 2020 July; cited 2021 Feb 23]. In: DailyMed [Internet; about 22 p.]. Bethesda (MD): National Library of Medicine (US). Available from: <https://dailymed.nlm.nih.gov/dailymed/druginfo.cfm?setid=c559bobo-4087-d12a-e718-c18ccb6811e6>
- Janssen Pharmaceuticals, Inc. HALDOL (haloperidol) injection. c2005 [updated 2020 Dec; cited 2021 Feb 23]. In: DailyMed [Internet; about 17 p.]. Bethesda (MD): National Library of Medicine (US). Available from: <https://dailymed.nlm.nih.gov/>

- [dailymed/drugInfo.cfm?setid=27cfe684-7d11-4f37-9c8b-b2bdd6b5348e](https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=27cfe684-7d11-4f37-9c8b-b2bdd6b5348e)
26. American Regent, Inc. Droperidol injection. c2005 [updated 2019 Oct; cited 2021 Feb 23]. In: DailyMed [Internet; about 10 p.]. Bethesda (MD): National Library of Medicine (US). Available from: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=147e033d-d997-4ef6-8bb5-9gba372590b2>
 27. Galen US Incorporated. ADASUVE (loxapine aerosol) powder. c1975 [updated 2019 Sep; cited 2021 Feb 23]. In: DailyMed [Internet; about 33 p.]. Bethesda (MD): National Library of Medicine (US). Available from: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=257148b5-869e-4a06-89ca-8b8686e8e528>
 28. Otsuka America Pharmaceutical, Inc. ABILIFY (aripiprazole) tablet, solution, orally disintegrating tablet, injection. c2002 [updated 2020 Jul; cited 2021 Feb 23]. In: DailyMed [Internet; about 82 p.]. Bethesda (MD): National Library of Medicine (US). Available from: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=co40bd1d-45b7-49f2-93ea-aed7220b30ac>
 29. Allergan, Inc. SAPHRIS (asenapine maleate) tablet. c2009 [updated 2017 Feb; cited 2021 Feb 23]. In: DailyMed [Internet; about 49 p.]. Bethesda (MD): National Library of Medicine (US). Available from: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=f5cd9abb-40e3-4cb5-a1b2-40cda8a1c7e>
 30. Janssen Pharmaceuticals, Inc. RISPERDAL (risperidone) tablet, orally disintegrating tablet, solution. c1993 [updated 2020 Sep; cited 2021 Feb 23]. In: DailyMed [Internet; about 78 p.]. Bethesda (MD): National Library of Medicine (US). Available from: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=7e117c7e-02fc-4343-92a1-230061dfc5e0>
 31. AstraZeneca Pharmaceuticals LP. SEROQUEL (quetiapine fumarate) film coated tablet. c1997 [updated 2020 Sep; cited 2021 Feb 23]. In: DailyMed [Internet; about 66 p.]. Bethesda (MD): National Library of Medicine (US). Available from: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=0584dda8-bc3c-48fe-1a90-79608f78e8a0>
 32. Eli Lilly and Company. ZYPREXA (olanzapine) tablet, orally disintegrating tablet, powder for injection. c1996 [updated 2020 Apr; cited 2021 Feb 23]. In: DailyMed [Internet; about 74 p.]. Bethesda (MD): National Library of Medicine (US). Available from: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=d5051fbc-846b-4946-82df-341fb1216341>
 33. Roerig. GEODON (ziprasidone hydrochloride) capsule, injection. c2001 [updated 2020 Nov; cited 2021 Feb 23]. In: DailyMed [Internet; about 64 p.]. Bethesda (MD): National Library of Medicine (US). Available from: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=8326928a-2cb6-4f7f-9712-03a425a14c37>
 34. Bausch Health US LLC. ATIVAN (lorazepam) tablet. c2013 [updated 2020 Oct; cited 2021 Feb 23]. In: DailyMed [Internet; about 20 p.]. Bethesda (MD): National Library of Medicine (US). Available from: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=89057c93-8155-4040-acec-64e877bd2b4c>
 35. Hikma Pharmaceuticals USA Inc. ATIVAN (lorazepam) injection. c2005 [updated 2021 Feb; cited 2021 Feb 23]. In: DailyMed [Internet; about 35 p.]. Bethesda (MD): National Library of Medicine (US). Available from: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=5fcoe987-61c9-40c4-b0d5-fcea07c8733e>
 36. Heritage Pharmaceuticals. Midazolam hydrochloride injection. c2012 [updated 2017 Oct; cited 2021 Feb 23]. In: DailyMed [Internet; about 31 p.]. Bethesda (MD): National Library of Medicine (US). Available from: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=843cc25e-45ea-4372-ae34-843f805fa869>
 37. Lexicomp Online. LexiDrugs [Internet]. Hudson (OH): Lexi-Comp, Inc; 2020 [cited 2021 Feb 22]. Available from: <https://online.lexi.com/lco/action/home>
 38. Vesper FH, Vesper BD, McMullan JT, Zealberg J, Currier GW. Risperidone versus haloperidol, in combination with lorazepam, in the treatment of acute agitation and psychosis: a pilot, randomized, double-blind, placebo-controlled trial. *J Psychiatr Pract.* 2006;12(2):103-8. DOI: [10.1097/00131746-200603000-00005](https://doi.org/10.1097/00131746-200603000-00005). PubMed PMID: [16728906](https://pubmed.ncbi.nlm.nih.gov/16728906/).
 39. Villari V, Rocca P, Fonzo V, Montemagni C, Pandullo P, Bogetto F. Oral risperidone, olanzapine and quetiapine versus haloperidol in psychotic agitation. *Prog Neuropsychopharmacol Biol Psychiatry.* 2008;32(2):405-13. DOI: [10.1016/j.pnpbp.2007.09.007](https://doi.org/10.1016/j.pnpbp.2007.09.007). PubMed PMID: [17900775](https://pubmed.ncbi.nlm.nih.gov/17900775/).
 40. Kinon BJ, Stauffer VL, Kollack-Walker S, Chen L, Sniadecki J. Olanzapine versus aripiprazole for the treatment of agitation in acutely ill patients with schizophrenia. *J Clin Psychopharmacol.* 2008;28(6):601-7. DOI: [10.1097/JCP.0b013e31818aaf6c](https://doi.org/10.1097/JCP.0b013e31818aaf6c). PubMed PMID: [19011427](https://pubmed.ncbi.nlm.nih.gov/19011427/).
 41. Kinon BJ, Ahl J, Rotelli MD, McMullen E. Efficacy of accelerated dose titration of olanzapine with adjunctive lorazepam to treat acute agitation in schizophrenia. *Am J Emerg Med.* 2004;22(3):181-6. DOI: [10.1016/j.ajem.2004.02.021](https://doi.org/10.1016/j.ajem.2004.02.021). PubMed PMID: [15138953](https://pubmed.ncbi.nlm.nih.gov/15138953/).
 42. Pratts M, Citrome L, Grant W, Leso L, Opler LA. A single-dose, randomized, double-blind, placebo-controlled trial of sublingual asenapine for acute agitation. *Acta Psychiatr Scand.* 2014;130(1):61-8. DOI: [10.1111/acps.12262](https://doi.org/10.1111/acps.12262). PubMed PMID: [24606117](https://pubmed.ncbi.nlm.nih.gov/24606117/).
 43. Hatta K, Kawabata T, Yoshida K, Hamakawa H, Wakejima T, Furuta K, et al. Olanzapine orally disintegrating tablet vs. risperidone oral solution in the treatment of acutely agitated psychotic patients. *Gen Hosp Psychiatry.* 2008;30(4):367-71. DOI: [10.1016/j.genhosppsych.2008.03.004](https://doi.org/10.1016/j.genhosppsych.2008.03.004). PubMed PMID: [18585542](https://pubmed.ncbi.nlm.nih.gov/18585542/).
 44. Normann C, Schmauß M, Bakri N, Gerwe M, Schreiner A. Initial treatment of severe acute psychosis with fast orally disintegrating risperidone tablets. *Pharmacopsychiatry.* 2006;39(6):209-12. DOI: [10.1055/s-2006-950498](https://doi.org/10.1055/s-2006-950498). PubMed PMID: [17124642](https://pubmed.ncbi.nlm.nih.gov/17124642/).
 45. Lenox RH, Newhouse PA, Creelman WL, Whitaker TM. Adjunctive treatment of manic agitation with lorazepam versus haloperidol: a double-blind study. *J Clin Psychiatry.* 1992;53(2):47-52. PubMed PMID: [1541605](https://pubmed.ncbi.nlm.nih.gov/1541605/).
 46. Salzman C, Solomon D, Miyawaki E, Glassman R, Rood L, Flowers E, et al. Parenteral lorazepam versus parenteral haloperidol for the control of psychotic disruptive behavior. *J Clin Psychiatry.* 1991;52(4):177-80. PubMed PMID: [1673123](https://pubmed.ncbi.nlm.nih.gov/1673123/).
 47. 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(7):744-9. DOI: [10.1197/j.aem.2003.06.015](https://doi.org/10.1197/j.aem.2003.06.015). PubMed PMID: [15231461](https://pubmed.ncbi.nlm.nih.gov/15231461/).
 48. Mattson A, Friend K, Brown CS, Cabrera D. Reintegrating droperidol into emergency medicine practice. *Am J Health Syst Pharm.* 2020;77(22):1838-45. DOI: [10.1093/ajhp/zxaa271](https://doi.org/10.1093/ajhp/zxaa271). PubMed PMID: [32839811](https://pubmed.ncbi.nlm.nih.gov/32839811/).
 49. Calver L, Page CB, Downes MA, Chan B, Kinnear F, Wheatley L, et al. The safety and effectiveness of droperidol for sedation of acute behavioral disturbance in the emergency department. *Ann Emerg Med.* 2015;66(3):230-8.e1. DOI: [10.1016/j.annemergmed.2015.03.016](https://doi.org/10.1016/j.annemergmed.2015.03.016). PubMed PMID: [25890395](https://pubmed.ncbi.nlm.nih.gov/25890395/).
 50. Calver L, Drinkwater V, Gupta R, Page CB, Isbister GK. Droperidol v. haloperidol for sedation of aggressive behaviour in acute mental health: randomised controlled trial. *Br J Psychiatry.* 2015;206(3):223-8. DOI: [10.1192/bjp.bp.114.150227](https://doi.org/10.1192/bjp.bp.114.150227). PubMed PMID: [25395689](https://pubmed.ncbi.nlm.nih.gov/25395689/).
 51. Khokhar MA, Rathbone J. Droperidol for psychosis-induced aggression or agitation. *Cochrane Database Syst Rev.* 2016;12(12):CD002830. DOI: [10.1002/14651858.CD002830.pub3](https://doi.org/10.1002/14651858.CD002830.pub3). PubMed PMID: [27976370](https://pubmed.ncbi.nlm.nih.gov/27976370/); PubMed Central PMCID: [PMC6463952](https://pubmed.ncbi.nlm.nih.gov/PMC6463952/).

52. Daniel DG, Potkin SG, Reeves KR, Swift RH, Harrigan EP. Intramuscular (IM) ziprasidone 20 mg is effective in reducing acute agitation associated with psychosis: a double-blind, randomized trial. *Psychopharmacology*. 2001;155(2):128-34. DOI: [10.1007/s002130000658](https://doi.org/10.1007/s002130000658). PubMed PMID: [11401000](https://pubmed.ncbi.nlm.nih.gov/11401000/).
53. 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(12):933-41. DOI: [10.4088/jcp.v61n1208](https://doi.org/10.4088/jcp.v61n1208). PubMed PMID: [11206599](https://pubmed.ncbi.nlm.nih.gov/11206599/).
54. Brook S, Walden J, Benattia I, Siu CO, Romano SJ. Ziprasidone and haloperidol in the treatment of acute exacerbation of schizophrenia and schizoaffective disorder: comparison of intramuscular and oral formulations in a 6-week, randomized, blinded-assessment study. *Psychopharmacology*. 2005;178(4):514-23. DOI: [10.1007/s00213-004-2082-5](https://doi.org/10.1007/s00213-004-2082-5). PubMed PMID: [15650846](https://pubmed.ncbi.nlm.nih.gov/15650846/).
55. Zhang H, Wang G, Zhao J, Xie S, Xu X, Shi J, et al. Intramuscular ziprasidone versus haloperidol for managing agitation in Chinese patients with schizophrenia. *J Clin Psychopharmacol*. 2013;33(2):178-85. DOI: [10.1097/JCP.0b013e3182839612](https://doi.org/10.1097/JCP.0b013e3182839612). PubMed PMID: [23422376](https://pubmed.ncbi.nlm.nih.gov/23422376/).
56. Mautone A, Scarone S. Transition from ziprasidone IM to oral formulation in agitated patients with acute exacerbation of schizophrenia: an open trial. *Pharmacopsychiatry*. 2011;44(5):173-8. DOI: [10.1055/s-0031-1280794](https://doi.org/10.1055/s-0031-1280794). PubMed PMID: [21751127](https://pubmed.ncbi.nlm.nih.gov/21751127/).
57. Kishi T, Matsunaga S, Iwata N. Intramuscular olanzapine for agitated patients: a systematic review and meta-analysis of randomized controlled trials. *J Psychiatr Res*. 2015;68:198-209. DOI: [10.1016/j.jpsychires.2015.07.005](https://doi.org/10.1016/j.jpsychires.2015.07.005). PubMed PMID: [26228420](https://pubmed.ncbi.nlm.nih.gov/26228420/).
58. Huf G, Alexander J, Gandhi P, Allen MH. Haloperidol plus promethazine for psychosis-induced aggression. *Cochrane Database Syst Rev*. 2016;11(11):CD005146. DOI: [10.1002/14651858.CD005146.pub3](https://doi.org/10.1002/14651858.CD005146.pub3). PubMed PMID: [27885664](https://pubmed.ncbi.nlm.nih.gov/27885664/).
59. Raveendran NS, Tharyan P, Alexander J, Adams CE. Rapid tranquilisation in psychiatric emergency settings in India: pragmatic randomised controlled trial of intramuscular olanzapine versus intramuscular haloperidol plus promethazine. *BMJ*. 2007;335(7625):865. DOI: [10.1136/bmj.39341.608519.BE](https://doi.org/10.1136/bmj.39341.608519.BE). PubMed PMID: [17954514](https://pubmed.ncbi.nlm.nih.gov/17954514/).
60. Macdonald K, Wilson MP, Minassian A, Vilke GM, Perez R, Cobb P, et al. A retrospective analysis of intramuscular haloperidol and intramuscular olanzapine in the treatment of agitation in drug- and alcohol-using patients. *Gen Hosp Psychiatry*. 2010;32(4):443-5. DOI: [10.1016/j.genhosppsy.2010.04.005](https://doi.org/10.1016/j.genhosppsy.2010.04.005). PubMed PMID: [20633750](https://pubmed.ncbi.nlm.nih.gov/20633750/).
61. MacDonald K, Wilson M, Minassian A, Vilke GM, Becker O, Tallian K, et al. A naturalistic study of intramuscular haloperidol versus intramuscular olanzapine for the management of acute agitation. *J Clin Psychopharmacol*. 2012;32(3):317-22. DOI: [10.1097/JCP.0b013e318253a2fe](https://doi.org/10.1097/JCP.0b013e318253a2fe). PubMed PMID: [22544013](https://pubmed.ncbi.nlm.nih.gov/22544013/).
62. Leung JG, Benedetti AM, Frazee LA, Myers N. Comparison of short-acting intramuscular antipsychotic medication: impact on length of stay and cost. *Am J Ther*. 2011;18(4):300-4. DOI: [10.1097/MJT.0b013e3181d48320](https://doi.org/10.1097/MJT.0b013e3181d48320). PubMed PMID: [20335789](https://pubmed.ncbi.nlm.nih.gov/20335789/).
63. Richards JR, Derlet RW, Duncan DR. Chemical restraint for the agitated patient in the emergency department: lorazepam versus droperidol. *J Emerg Med*. 1998;16(4):567-73. DOI: [10.1016/s0736-4679\(98\)00045-6](https://doi.org/10.1016/s0736-4679(98)00045-6). PubMed PMID: [9696171](https://pubmed.ncbi.nlm.nih.gov/9696171/).
64. Clinton JE, Sterner S, Stelmachers Z, Ruiz E. Haloperidol for sedation of disruptive emergency patients. *Ann Emerg Med*. 1987;16(3):319-22. DOI: [10.1016/s0196-0644\(87\)80179-8](https://doi.org/10.1016/s0196-0644(87)80179-8). PubMed PMID: [3813167](https://pubmed.ncbi.nlm.nih.gov/3813167/).
65. 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(1):29-35. DOI: [10.1111/acem.12842](https://doi.org/10.1111/acem.12842). PubMed PMID: [26720055](https://pubmed.ncbi.nlm.nih.gov/26720055/).
66. Cole JB, Moore JC, Dolan BJ, O'Brien-Lambert A, Fryza BJ, Miner JR, et al. A prospective observational study of patients receiving intravenous and intramuscular olanzapine in the emergency department. *Ann Emerg Med*. 2017;69(3):327-36.e2. DOI: [10.1016/j.annemergmed.2016.08.008](https://doi.org/10.1016/j.annemergmed.2016.08.008). PubMed PMID: [27823873](https://pubmed.ncbi.nlm.nih.gov/27823873/).
67. Allen MH, Feifel D, Lesem MD, Zimbroff DL, Ross R, Munzar P, et al. Efficacy and safety of lorazepam for inhalation in the treatment of agitation in patients with schizophrenia: a randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry*. 2011;72(10):1313-21. DOI: [10.4088/JCP.10mo6011yel](https://doi.org/10.4088/JCP.10mo6011yel). PubMed PMID: [21294997](https://pubmed.ncbi.nlm.nih.gov/21294997/).
68. San L, Estrada G, Oudovenko N, Montañés F, Dobrovolskaya N, Bukhanovskaya O, et al. PLACID study: a randomized trial comparing the efficacy and safety of inhaled lorazepam versus intramuscular aripiprazole in acutely agitated patients with schizophrenia or bipolar disorder. *Eur Neuropsychopharmacol*. 2018;28(6):710-8. DOI: [10.1016/j.euroneuro.2018.03.010](https://doi.org/10.1016/j.euroneuro.2018.03.010). PubMed PMID: [29724638](https://pubmed.ncbi.nlm.nih.gov/29724638/).
69. 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(3):175-80. DOI: [10.1097/00004850-199705000-00009](https://doi.org/10.1097/00004850-199705000-00009). PubMed PMID: [9248875](https://pubmed.ncbi.nlm.nih.gov/9248875/).
70. Zaman H, Sampson SJ, Beck AL, Sharma T, Clay FJ, Spyridi S, et al. Benzodiazepines for psychosis-induced aggression or agitation. *Cochrane Database Syst Rev*. 2017;12:CD003079. DOI: [10.1002/14651858.CD003079.pub4](https://doi.org/10.1002/14651858.CD003079.pub4). PubMed PMID: [29219171](https://pubmed.ncbi.nlm.nih.gov/29219171/).
71. TREC Collaborative Group. Rapid tranquilisation for agitated patients in emergency psychiatric rooms: a randomised trial of midazolam versus haloperidol plus promethazine. *BMJ*. 2003;327(7417):708-13. DOI: [10.1136/bmj.327.7417.708](https://doi.org/10.1136/bmj.327.7417.708). PubMed PMID: [14512476](https://pubmed.ncbi.nlm.nih.gov/14512476/).
72. Martel M, Sterzinger A, Miner J, Clinton J, Biros M. Management of acute undifferentiated agitation in the emergency department: a randomized double-blind trial of droperidol, ziprasidone, and midazolam. *Acad Emerg Med*. 2005;12(12):1167-72. DOI: [10.1197/j.aem.2005.07.017](https://doi.org/10.1197/j.aem.2005.07.017). PubMed PMID: [16282517](https://pubmed.ncbi.nlm.nih.gov/16282517/).
73. 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(1):61-7. DOI: [10.1016/j.annemergmed.2005.07.003](https://doi.org/10.1016/j.annemergmed.2005.07.003). PubMed PMID: [16387219](https://pubmed.ncbi.nlm.nih.gov/16387219/).
74. Chan EW, Taylor DM, Knott JC, Phillips GA, Castle DJ, Kong DCM. 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(1):72-81. DOI: [10.1016/j.annemergmed.2012.07.118](https://doi.org/10.1016/j.annemergmed.2012.07.118). PubMed PMID: [22981685](https://pubmed.ncbi.nlm.nih.gov/22981685/).
75. 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(3):153-7. DOI: [10.4088/jcp.v62n0303](https://doi.org/10.4088/jcp.v62n0303). PubMed PMID: [11305699](https://pubmed.ncbi.nlm.nih.gov/11305699/).
76. Currier GW, Chou JC, Feifel D, Bossie CA, Turkoz I, Mahmoud RA, 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(3):386-94. PubMed PMID: [15096079](https://pubmed.ncbi.nlm.nih.gov/15096079/).
77. Ostinelli EG, Brooke-Powney MJ, Li X, Adams CE. Haloperidol for psychosis-induced aggression or agitation (rapid tranquilisation). *Cochrane Database Syst Rev*. 2017;7(7):CD009377. DOI: [10.1002/14651858.CD009377.pub3](https://doi.org/10.1002/14651858.CD009377.pub3). PubMed PMID: [28758203](https://pubmed.ncbi.nlm.nih.gov/28758203/).
78. Battaglia J, Moss S, Rush J, Kang J, Mendoza R, Leedom L, et al. Haloperidol, lorazepam, or both for psychotic agitation? A multicenter, prospective, double-blind, emergency department

- study. *Am J Emerg Med.* 1997;15(4):335-40. DOI: [10.1016/s0735-6757\(97\)90119-4](https://doi.org/10.1016/s0735-6757(97)90119-4). PubMed PMID: [9217519](https://pubmed.ncbi.nlm.nih.gov/9217519/).
79. Huf G, Coutinho ESF, Adams CE. Rapid tranquilisation in psychiatric emergency settings in Brazil: pragmatic randomised controlled trial of intramuscular haloperidol versus intramuscular haloperidol plus promethazine. *BMJ.* 2007;335(7625):869. DOI: [10.1136/bmj.39339.448819.AE](https://doi.org/10.1136/bmj.39339.448819.AE). PubMed PMID: [17954515](https://pubmed.ncbi.nlm.nih.gov/17954515/); PubMed Central PMCID: [PMC2043463](https://pubmed.ncbi.nlm.nih.gov/PMC2043463/).
 80. Rich DS. Introducing ISMP's new targeted best practices for 2018-2019 [slideshow]. Horsham (PA): Institute for Safe Medication Practices (ISMP); 2018.
 81. Mantovani C, Labate CM, Sponholz A, de Azevedo Marques JM, Guapo VG, de Simone Brito dos Santos ME, et al. Are low doses of antipsychotics effective in the management of psychomotor agitation? A randomized, rated-blind trial of 4 intramuscular interventions. *J Clin Psychopharmacol.* 2013;33(3):306-12. DOI: [10.1097/JCP.0b013e3182900fd6](https://doi.org/10.1097/JCP.0b013e3182900fd6). PubMed PMID: [23609398](https://pubmed.ncbi.nlm.nih.gov/23609398/).
 82. Riddell J, Tran A, Bengiamin R, Hendey GW, Armenian P. Ketamine as a first-line treatment for severely agitated emergency department patients. *Am J Emerg Med.* 2017;35(7):1000-4. DOI: [10.1016/j.ajem.2017.02.026](https://doi.org/10.1016/j.ajem.2017.02.026). PubMed PMID: [28237385](https://pubmed.ncbi.nlm.nih.gov/28237385/).
 83. Cole JB, Moore JC, Nystrom PC, Orozco BS, Stellpflug SJ, Kornas RL, et al. A prospective study of ketamine versus haloperidol for severe prehospital agitation. *Clin Toxicol (Phila).* 2016;54(7):556-62. DOI: [10.1080/15563650.2016.1177652](https://doi.org/10.1080/15563650.2016.1177652). PubMed PMID: [27102743](https://pubmed.ncbi.nlm.nih.gov/27102743/).
 84. Nazarian DJ, Broder JS, Thiessen MEW, Wilson MP, Zun LS, Brown MD. Clinical policy: critical issues in the diagnosis and management of the adult psychiatric patient in the emergency department. *Ann Emerg Med.* 2017;69(4):480-98. DOI: [10.1016/j.annemergmed.2017.01.036](https://doi.org/10.1016/j.annemergmed.2017.01.036). PubMed PMID: [28335913](https://pubmed.ncbi.nlm.nih.gov/28335913/).
 85. ASHP.org [Internet]. Bethesda (MD): American Society of Health-System Pharmacists; c2021 [cited 2021 Feb 23]. Available from: <https://www.ashp.org/Drug-Shortages/Current-Shortages/Drug-Shortages-List?page=CurrentShortages&loginreturnUrl=SSOCheckOnly>
 86. FDA.gov [Internet]. Silver Spring (MD): FDA; c2021 [updated 2021 Jun 28; cited 2021 Feb 23]. Available from: <https://www.accessdata.fda.gov/scripts/drugshortages/default.cfm>