For more than half a century, haloperidol has been used as a first-line medication for psychiatric agitation constituting a “behavioral emergency” when a patient cannot or will not take oral medication. Today, haloperidol is most commonly administered as an IM injection along with an anticholinergic medication to minimize extrapyramidal symptoms (EPS) and a benzodiazepine for additional sedation. The multiple-medication “cocktail” is often referred to by double-entendre nicknames, such as “B-52” or “5250” (ie, haloperidol, 5 mg; lorazepam, 2 mg; and diphenhydramine, 50 mg). In this article, I discuss whether haloperidol, a first-generation antipsychotic (FGA) medication developed in 1958, still deserves to be the IM “gold standard” for managing emergency psychiatric agitation.

Earlier evidence of haloperidol’s efficacy
The initial “discovery” of antipsychotic medications was made in 1951 based on the inadvertent observation that chlorpromazine had the potential to calm surgical patients with autonomic activation. This calming effect, described as “désintéressement” (meaning a kind of “indifference to the world”), resulted in a new class of medications replacing barbiturates and bromides as go-to options to achieve “rapid tranquilization” of psychiatric agitation. Although the ability of antipsychotic medications to gradually reduce positive symptoms, such as delusions and hallucinations, has been attributed to dopamine (D2) antagonism, their more immediate sedating and anti-agitation effects are the result of broader effects as histamine (H1) and alpha-1 adrenergic antagonists.

In the 1970s, haloperidol emerged as a first-line option to manage agitation due to its IM and IV availability, as well as its relative lack
of sedation and orthostasis compared with low-potency D2 antagonists such as chlorpromazine. However, haloperidol was observed to have a significant risk of acute EPS, including dystonic reactions. From the 1970s to the 1990s, numerous prospective clinical trials of haloperidol for the treatment of acute psychotic agitation, including several randomized controlled trials (RCTs) comparing haloperidol to lorazepam, were conducted. The design and outcomes of the haloperidol vs lorazepam RCTs were fairly consistent:

- adult participants with acute agitation and a variety of psychiatric diagnoses, for whom informed consent often was waived due to agitation severity
- randomization to either IM haloperidol, 5 mg, or IM lorazepam, 2 mg, administered every 30 minutes until agitation resolved
- behavioral outcomes measured over several hours using various rating scales, without consistent assessment of EPS
- equivalent efficacy of haloperidol and lorazepam, with symptom resolution usually achieved after 1 to 2 doses (in 30 to 60 minutes), but sometimes longer
- anticholinergic “rescue” allowed for EPS, but not administered prophylactically
- EPS, including dystonia and akathisia, were significantly more frequent with haloperidol compared with lorazepam.

In recognition of the greater risk of EPS with haloperidol compared with lorazepam, and the fact that most study participants were already taking standing doses of antipsychotic medications, some researchers have recommended using benzodiazepines alone as the optimal treatment for agitation. As with studies comparing lorazepam with haloperidol, the results of these RCTs revealed that IM aripiprazole, olanzapine, and ziprasidone were at least as effective as IM haloperidol, with haloperidol having a significantly increased risk of akathisia, dystonia, and other EPS. The greater EPS risk of haloperidol is not surprising given the use of comparison doses up to 10 mg. An updated 2017 Cochrane review of haloperidol for psychosis-induced aggression or agitation concluded that:

- haloperidol is an effective intervention, although the evidence is “weak”
- significant treatment effects may take as long as 1 to 2 hours following multiple IM injections

Newer RCTs tell a different story
With the availability of second-generation antipsychotics (SGAs) in IM formulations, clinical trials over the past 2 decades have focused on comparing SGAs with haloperidol alone as the “gold standard” control for acute agitation. Compared with previous trials of haloperidol vs lorazepam, these clinical trials of SGAs vs haloperidol included:

- Study participants who signed informed consent (and were likely less agitated)
- IM haloperidol doses typically >5 mg (eg, 6.5 to 10 mg).

As with studies comparing lorazepam with haloperidol, the results of these RCTs revealed that IM aripiprazole, olanzapine, and ziprasidone were at least as effective as IM haloperidol, with haloperidol having a significantly increased risk of akathisia, dystonia, and other EPS. The greater EPS risk of haloperidol is not surprising given the use of comparison doses up to 10 mg. An updated 2017 Cochrane review of haloperidol for psychosis-induced aggression or agitation concluded that:

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Clinical Point
Adding lorazepam to haloperidol does not mitigate the risk of extrapyramidal symptoms

Discuss this article at www.facebook.com/MDedgePsychiatry
• in contrast to SGAs, treatment with haloperidol carries a significant risk of EPS
• adding a benzodiazepine “does not have strong evidence of benefit and carries risk of additional harm.”

**Haloperidol’s well-known toxicity**

Haloperidol has been associated with numerous adverse effects:

**Akathisia and other acute EPS.** Treatment with even a single dose of IM haloperidol can result in acute EPS, including dystonia and akathisia. At best, such adverse effects are subjectively troubling and unpleasant; at worst, akathisia can exacerbate and be mistaken for agitation, leading to administration of more medication and the possible development of suicidal or violent behavior. In the studies reviewed above, the overall rate of EPS was as high as 21% after treatment with haloperidol, with parkinsonism occurring in up to 17% of patients, dystonia in up to 11%, and akathisia in up to 10%. However, because specific EPS were assessed inconsistently, and sometimes not at all, the rate of akathisia—arguably the most relevant and counter-therapeutic adverse effect related to agitation—remains unclear.

In another study that specifically assessed for akathisia in patients treated with haloperidol, up to 40% experienced akathisia 6 hours after a single oral dose of 5 mg. Even a single dose of IV prochlorperazine, another dopamine-antagonist routinely used to treat nausea in the emergency department (ED), has been reported to cause akathisia in up to 44% of patients. Such results suggest that when akathisia is carefully assessed, the rate with even brief FGA exposure may approach nearly half of treated patients. Because akathisia is typically dose-related, and considering that many patients receiving IM haloperidol may receive multiple injections in addition to standing doses of oral medications, akathisia may be underrecognized in patients who are agitated, with a much greater risk than is generally presumed.

Although anticholinergic medications or benzodiazepines are often administered as part of a haloperidol “cocktail,” these medications often do not adequately resolve emergent akathisia. No clinical trials of IM haloperidol combined with benztpzine or diphenhydramine have been published, but several studies suggest that combining haloperidol with promethazine—a phenothiazine with strong antihistaminergic and anticholinergic activity, but only weak antidopaminergic activity—can decrease the risk of dystonia relative to haloperidol alone. However, there have also been reports of promethazine causing dystonia. In addition, 1 trial of IM haloperidol, 2.5 mg, combined with promethazine reported that 74% of patients still had at least 1 form of EPS. Because the clinical trials of haloperidol with promethazine did not specifically assess for akathisia, promethazine’s ability to decrease the risk of akathisia remains unknown.

**Cardiotoxicity.** Although low-potency antipsychotic medications such as chlorpromazine are more sedating than haloperidol, the latter is preferred as an IM antipsychotic medication for agitation because of its lower risk of hypotension. In terms of cardiac effects, all antipsychotic medications carry a risk of QTc prolongation, with possible progression to the potentially lethal arrhythmia torsades de pointes as a result of interference with cardiac potassium channels. In 2007, the FDA added a “black-box” warning about this risk for haloperidol, in the wake of a disproportionately high number of reported cases associated with IV administration, sometimes even after a single dose.

Although there is no direct evidence that the cardiac risks associated with IV haloperidol apply to IM administration, epidemiologic studies indicate that oral haloperidol carries an elevated risk of ventricular arrhythmia and sudden cardiac death, with 1 study reporting greater risk compared with other SGAs. Haloperidol, whether administered orally or IM, may therefore be an especially poor choice for patients with agitation who are at risk for arrhythmia, including those with relevant medical comorbidities or delirium.

**Neuronal cell death.** Several lines of research evidence have demonstrated that haloperidol can cause cellular injury or death in neuronal tissue in a dose-dependent
fashion through a variety of mechanisms. By contrast, SGAs have been shown to have neuroprotective effects. While these findings have mostly come from studies conducted in animals or in vitro human tumor cell lines, some researchers have nonetheless called for haloperidol to be banned, noting that if its neurotoxic effects were more widely known, “we would realize what a travesty it is to use [such] a brain-unfriendly drug.”

**Several reasonable alternatives**

Echoing the earlier Cochrane review of haloperidol for psychosis-induced aggression or agitation, a 2017 update concluded, “If no other alternative exists, sole use of intramuscular haloperidol could be life-saving. Where additional drugs are available, sole use of haloperidol for extreme emergency could be considered unethical.”

What then are reasonable alternatives to replace IM haloperidol for agitation? Clinicians should consider the following nonpharmacologic and pharmacologic interventions:

**Nonpharmacologic interventions.** Several behavioral interventions have been demonstrated to be effective for managing acute agitation, including verbal de-escalation, enhanced “programming” on the inpatient units, and the judicious use of seclusion. While such interventions may demand additional staff or resources, they have the potential to lower long-term costs, reduce injuries to patients and staff, and improve the quality of care. The use of IM haloperidol as a form of “chemical restraint” does not represent standard-of-care treatment, and from an ethical perspective, should never be implemented punitively or to compensate for substandard care in the form of inadequate staffing or staff training.

**Benzodiazepines.** Lorazepam offers an attractive alternative to haloperidol without the risk of EPS. However, lorazepam alone may be perceived as less efficacious than a haloperidol “cocktail” because it represents less overall medication. Some evidence has suggested that lorazepam, 4 mg, might be the most appropriate dose, although it has only rarely been studied in clinical trials of acute agitation. Midazolam is another IM benzodiazepine alternative to IM haloperidol that has been shown to achieve more rapid sedation than either haloperidol or lorazepam, although it can cause substantial anterograde amnesia and also has an FDA black-box warning for respiratory depression associated with IV administration.

Respiratory depression is frequently cited as an argument against using lorazepam for agitation, as if the therapeutic window is extremely narrow with ineffectiveness at 2 mg, but potential lethality beyond that dose. In fact, serious respiratory depression with lorazepam is unlikely in the absence of chronic obstructive pulmonary disease (COPD), obstructive sleep apnea, or concomitant alcohol or other sedative use. Case reports have documented therapeutic lorazepam dosing of 2 to 4 mg every 2 hours up to 20 to 30 mg/d in patients with manic agitation. Even in patients with COPD, significant respiratory depression tends not to occur at doses <8 mg. A more evidence-based concern about lorazepam dosing is that 2 mg might be ineffective in patients with established tolerance. For example, one report described a patient in acute alcohol withdrawal who required dosing lorazepam to 1,600 mg within 24 hours. Collectively, these reports suggest that lorazepam has a much wider therapeutic window than is typically perceived, and that dosing with 3 to 4 mg IM is a reasonable option for agitation when 2 mg is likely to be inadequate.

Paradoxical disinhibition is another concern that might prevent benzodiazepines from being used alone as a first-line intervention for emergency treatment of agitation. However, similar to respiratory depression, this adverse event is relatively rare and tends to occur in children and geriatric patients, individuals intoxicated with alcohol or other sedatives, and patients with brain injury, developmental delay, or dementia. Although exacerbation of aggression has not been demonstrated in the RCTs examining benzodiazepines for agitation reviewed above, based on other research, some clinicians have expressed concerns about the potential for benzodiazepines to exacerbate
aggression in patients with impulse control disorders and a history of violent behavior.50

The 2005 Expert Consensus Panel for Behavioral Emergencies51 recommended the use of lorazepam alone over haloperidol for agitation for patients for whom the diagnosis is unknown or includes the following:

- stimulant intoxication
- personality disorder
- comorbid obesity
- comorbid cardiac arrhythmia
- a history of akathisia and other EPS
- a history of amenorrhea/galactorrhea
- a history of seizures.

In surveys, patients have ranked lorazepam as the preferred medication for emergency agitation, whereas haloperidol was ranked as one of the least-preferred options.51,52

Second-generation antipsychotics. The SGAs available in IM formulations, such as aripiprazole, olanzapine, and ziprasidone, have been shown to be at least as effective as haloperidol for the treatment of acute agitation (in 2015, the short-acting injectable formulation of aripiprazole was discontinued in the United States independent of safety or efficacy issues53). A review of RCTs examining IM SGAs for the treatment of agitation concluded that the number needed to treat for response compared with placebo was 5 for aripiprazole, 3 for olanzapine, and 3 for ziprasidone.54 In terms of safety, a meta-analysis of studies examining IM medications for agitation confirmed that the risk of acute EPS, including dystonia, akathisia, and parkinsonism, is significantly lower with SGAs compared with haloperidol.55 An RCT comparing IM ziprasidone with haloperidol found equivalently modest effects on QTc prolongation.56 Therefore, SGAs are an obvious and evidence-based option for replacing haloperidol as a treatment for acute agitation.

Unfortunately, for clinicians hoping to replace haloperidol within a multipledrug treatment regimen, there has been no published controlled trials of SGAs combined with benzodiazepines. Although a short report indicated that aripiprazole and lorazepam are chemically compatible to be combined within a single injection,57 the package insert for aripiprazole warns that "If parenteral benzodiazepine therapy is deemed necessary in addition to ABILIFY injection treatment, patients should be monitored for excessive sedation and for orthostatic hypotension."58 The package insert for olanzapine likewise lists the combination of lorazepam and olanzapine as a drug interaction that can potentiate sedation, and the manufacturer issued specific warnings about parenteral combination.59,60 A single published case of significant hypotension with combined IM olanzapine and lorazepam,60 together with the fact that IM olanzapine can cause hypotension by itself,61 has discouraged the coadministration of these medications. Nonetheless, the combination is used in some emergency settings, with several retrospective studies failing to provide evidence of hypotension or respiratory depression as adverse effects.62-64

Droperidol. Droperidol was formerly a popular choice for managing acute agitation, with evidence from RCTs that droperidol, 5 mg, can improve symptoms significantly faster than either haloperidol, 5 mg, or lorazepam, 2 mg, and is absorbed just as rapidly whether administered IV or IM.65-67 However, a 2001 FDA black-box warning about QTc prolongation included recommendations that a screening electrocardiogram should be obtained before administering droperidol. This action greatly curtailed the use of droperidol, and for some time, it was not marketed or available in the United States.

Over the past decade, however, droperidol has returned to the US market68 and its IV and IM usage has been revitalized for managing patients with agitation within or en route to the ED. Studies have demonstrated droperidol efficacy comparable to midazolam, ziprasidone, or olanzapine, as well as effectiveness as an IV adjunct to midazolam.69-71 In contrast to the FDA black-box warning, retrospective studies and RCTs of both IV and IM droperidol suggest that QTc prolongation and torsades de pointes are rare events that do not occur any more frequently than they do with haloperidol, even at doses >10 mg.72,73 However, in studies involving patients with drug intoxication and treatment with multiple medications, oversedation to the point of needing rescue
intervention was reported. In an emergency setting where these issues are relatively easily managed, such risks may be better tolerated than in psychiatric settings.

With earlier studies examining the use of droperidol in an acute psychiatric setting that reported a more rapid onset of action than haloperidol, a 2016 Cochrane review concluded that there was high-quality evidence to support droperidol’s use for psychosis-induced agitation. However, a 2015 RCT comparing IM droperidol, 10 mg, to haloperidol, 10 mg, found equivalent efficacy and response times (with maximal response occurring within 2 hours) and concluded that droperidol had no advantage over haloperidol. Because none of the clinical trials that evaluated droperidol have included assessments for EPS, its risk of akathisia remains uncertain.

**Ketamine.** In recent years, ketamine has been used to treat acute agitation within or en route to the ED. Preliminary observational studies support ketamine’s efficacy when administered via IV or IM routes, with more rapid symptomatic improvement compared with haloperidol, lorazepam, or midazolam alone. Reported adverse effects of ketamine include dissociation, psychotic exacerbation, and respiratory depression, although 1 small naturalistic study found no evidence of exacerbation of psychotic or other psychiatric symptoms. An ongoing RCT is comparing IM ketamine, 5 mg/kg, to combined IM haloperidol, 5 mg, and midazolam, 5 mg. Although various ketamine formulations are increasingly being used in psychiatry, active psychosis is generally regarded as a contraindication. It is premature to recommend parenteral ketamine administration for agitation within most psychiatric settings until more research on safety has been completed.

**Haloperidol, or something else? Practical considerations**

Consider the following factors when deciding whether to use haloperidol or one of its alternatives:

**Limitations of the evidence.** Modern clinical trials requiring informed consent often do not include the kind of severe agitation that clinicians encounter in acute psychiatric, emergency, or forensic settings. In addition, standard interventions, such as 3-medication haloperidol “cocktails,” have not been evaluated in clinical trials. Clinicians are therefore often in the dark about optimal evidence-based practices.

**Treatment goals.** Psychiatric agitation has many causes, with a range of severity that warrants a commensurate range of responses. Protocols for managing acute agitation should include graded interventions that begin with nonpharmacologic
interventions and voluntary oral medications, and move to involuntary IM medications when necessary.

While treatment guidelines clearly recommend against IM medications as “chemical restraint” with a goal of sedating a patient until he/she is unconscious,3,51 such outcomes are nonetheless often sought by staff who are concerned about the risk of injuries during a behavioral emergency. In such instances, the risks of violence towards patients and staff may outweigh concerns about adverse effects in a risk-benefit analysis. Consequently, clinicians may be prone to “skip over” graded interventions because they assume they “won’t work” in favor of administering involuntary multiple-medication haloperidol “cocktails” despite risks of excess sedation, EPS, and cardiotoxicity. Treatment settings should critically evaluate such biased preferences, with a goal of developing tailored, evidence-based strategies that maximize benefits while minimizing excess sedation and other untoward adverse effects, with an eye towards promoting better overall patient care and reducing length of stay.42,43,80

**Clinical Point**

Evidence indicates that even rapid-acting medications take 15 minutes to several hours to resolve acute agitation.

**Limitations of available medications.** There is no perfect medication for the management of acute agitation. Evidence indicates that pharmacologic options take 15 minutes to several hours to resolve acute agitation, even potentially more rapid-acting medications such as midazolam and droperidol. This is well beyond most clinicians’ desired window for response time in a behavioral emergency. Multiple-medication “cocktails” may be used with the hope of hastening response time, but may not achieve this goal at the expense of increasing the risk of adverse effects and the likelihood that a patient will remain sedated for a prolonged time. In the real world, this often means that by the time a psychiatrist comes to evaluate a patient who has been given emergency medications, the patient cannot be aroused for an interview. Ideally, medications would calm an agitated patient rapidly, without excess or prolonged sedation.80

Less-sedating IM medications for managing acute agitation:

**Second-line interventions**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Pros</th>
<th>Cons</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam</td>
<td>5 to 10 mg</td>
<td>Rapid acting</td>
<td>Respiratory depression</td>
<td>FDA “black-box” warning for IV use</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No EPS</td>
<td>Sedation</td>
<td>Avoid use in children, geriatric patients, those with acute alcohol intoxication, or those with traumatic brain injury</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Anterograde amnesia</td>
<td></td>
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<tr>
<td>Haloperidol</td>
<td>2.5 to 10 mg</td>
<td>Antipsychotic effects</td>
<td>EPS</td>
<td>Up to 40% risk of akathisia from a single dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>QTc prolongation</td>
<td>Concomitant anticholinergic and/or benzodiazepine may be insufficient to prevent EPS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>in vitro neuronal cell death</td>
<td>FDA “black-box” warning for IV use</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Unclear if in vitro toxicity occurs in vivo</td>
</tr>
<tr>
<td>Droperidol</td>
<td>2.5 to 10 mg</td>
<td>Rapid acting</td>
<td>QTc prolongation</td>
<td>FDA “black-box” warning</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>EPS</td>
<td>Akathisia risk not well studied</td>
</tr>
<tr>
<td>Ketamine</td>
<td>3 to 6 mg/kg</td>
<td>Rapid acting</td>
<td>Respiratory depression</td>
<td>Unclear safety of parenteral administration</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Dissociation</td>
<td>Untested in randomized controlled trials</td>
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<td></td>
<td></td>
<td></td>
<td>Possible psychotic symptom exacerbation</td>
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</table>

EPS: extrapyramidal symptoms

Evidence indicates that even rapid-acting medications take 15 minutes to several hours to resolve acute agitation.
SGAs, such as ziprasidone, might have this potential, but can sometimes be perceived as ineffective.

Avoiding akathisia. Akathisia’s potential to worsen and be mistaken for agitation makes it an especially concerning, if underappreciated, adverse effect of haloperidol that is often not adequately assessed in clinical trials or practice. In light of evidence that akathisia can occur in nearly half of patients receiving a single 5 mg-dose of haloperidol, it is difficult to justify the use of this medication for agitation when equally effective options exist with a lower risk of EPS.

While haloperidol-induced akathisia could in theory be mitigated by adding anticholinergic medications or benzodiazepines, previous studies have found that such strategies have limited effectiveness compared to “gold standard” treatment with propranolol.28,81,82 Furthermore, the half-lives of anticholinergic medications, such as benztrpine or diphenhydramine, are significantly shorter than that of a single dose of haloperidol, which can be as long as 37 hours.83 Therefore, akathisia and other EPS could emerge or worsen several hours or even days after receiving an IM haloperidol “cocktail” as the shorter-acting medications wear off. Akathisia is best minimized by avoiding FGAs, such as haloperidol, when treating acute agitation.

Promoting adherence. Although haloperidol is often recommended for acute agitation in patients with schizophrenia or bipolar disorder on the basis that it would treat the underlying condition, many patients who receive IM medications for acute agitation are already prescribed standing doses of oral medication, which increases the risk of cumulative toxicity. In addition, receiving a medication likely to cause acute EPS that is ranked near the bottom of patient preferences may erode the potential for a therapeutic alliance and hamper longer-term antipsychotic medication adherence.

Time for a change
For nearly half a century, haloperidol has been a “gold standard” intervention for IM control in patients with agitation. However, given its potential to produce adverse effects, including a significant risk of akathisia that can worsen agitation, along with the availability of newer pharmacologic options that are at least as effective (Table 1, page 24, and Table 2, page 25), haloperidol should be retired as a first-line medication for the treatment of agitation. Clinicians would benefit from RCTs investigating the safety and efficacy of novel interventions including frequently-used, but untested medication combinations, as well as nonpharmacologic interventions.

References

Bottom Line
Although there is no perfect IM medication to treat acute agitation, haloperidol’s higher risk of adverse effects relative to newer alternatives suggest that it should no longer be considered a first-line intervention.


Time to retire haloperidol?

Clinical Point

RCTs investigating the safety and efficacy of novel interventions to treat acute agitation are critically needed.


