Choosing antipsychotics for rapid tranquilization in the ER

The patient comes in yelling and screaming and tearing up your emergency room. What's the best pharmacologic approach to achieving control—haloperidol, lorazepam, or a newer antipsychotic? A combination? Oral or IM? CURRENT PSYCHIATRY’s editor-in-chief offers his strategies for calming the patient.

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Ever since psychiatric emergency services got started during the 1960s, emergency treatment of acute psychosis has been a primary rationale for their existence. While most practitioners give up practicing full time in emergency service as quickly as possible after residency, many of us are still working part time, using various techniques of treatment considered rational over the last 50 years.

Which methods are still viable? I’ll start with an historic approach to understanding psychiatric emergency pharmacologic therapy.

Prior to the 1950s, the only way to treat acutely agitated patients was to give them high doses of barbiturates, hoping to put them to sleep and hoping that they would wake up in a better mood. This usually did not work. Patients often woke up from the barbiturates with even more disinhibited behavior.

During the ’50s and ’60s, phenothiazines and related antipsychotics, tricyclic antidepressants and MAO inhibitors, and benzodiazepines were introduced in the United States. Lithium was introduced everywhere in the world except here. During this period of therapeutic optimism, the standard approach to rapid tranquilization was high-potency antipsychotic medication.

From the ’60s on, the doses of antipsychotic medication used for this purpose continued to increase until 1987, when a study by Quitkin et al compared the efficacy of a low dose of fluphenazine equivalent to 2,500 mg of chlorpromazine with a high-dose equivalent to 100,000 mg of chlorpromazine. The lower dose turned out to be just as effective as, and safer than, the higher dose, and subsequent studies, as I will discuss later, have consistently failed to show increased efficacy of antipsychotics in high doses.

The 1970s were generally a disappointing time in psychopharmacology because no really new classes of drugs were introduced. Every few months a new antipsychotic, antidepressant, or anxiolytic came on the market with basically the same effect but with a slightly different side effect profile from those that were already available.

During the 1960s, 1970s, and early 1980s, the main controversy in rapid tranquilization was about whether to use antipsychotics, benzodiazepines, or both. The long period of overhyped, me-too drugs may have discouraged some psychiatrists from adopting the new medications that started to become available in the
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late 1980s.

The 1990s and 2000s have brought more choices of therapeutic agents, particularly the newer antipsychotics.

**What do you call it?**

Over the years, a number of roughly synonymous terms have been used to describe administration of high doses of medication to patients to try to calm them down. These include:

**Rapid neuroleptization and psychotolysis**, which imply making an acute psychosis go away in the emergency room. A pharmaceutical ad that appeared frequently during the 1970s showed a patient acutely agitated in one frame, then in the next leaving the emergency room and shaking hands with his physician. The caption read something like: “John’s remission has started in the emergency room.” In fact, patients will almost never go into remission within a few hours in an emergency setting.

If a patient comes in acutely psychotic with the devil telling him or her to destroy your hospital, and he or she is treated with high doses of antipsychotics, the patient will usually stop tearing up your hospital over that period of treatment. But the patient will generally continue to hear voices, though he or she may describe them as being easier to ignore, not as loud, or less frightening.

**Rapid digitalization**, which was based on the concept that maybe antipsychotics could be dosed as digitalis is, that is, with a high loading dose followed by a lower maintenance dose. Such an approach makes pharmacokinetic—but not pharmacodynamic—sense. Studies such as the one by Quitkin et al, cited earlier, and dozens of others have consistently found that starting patients on high doses of conventional antipsychotic medication does not lead them to respond more rapidly.

**Chemical restraint**, the term most to be avoided. Over the years psychiatrists have labored under a confusing series of guidelines about appropriate use of seclusion and restraint in psychiatry. One of the few consistent decisions about the acutely psychotic patient is that a doctor should use medication rather than restraints. Should the term chemical restraint show up in the chart of a patient who develops, say, neuroleptic malignant syndrome, it would definitely weigh against the treating physician in a professional liability action.

**Rapid tranquilization**, meaning treating patients across several hours with medication to decrease their agitation and hostility. This is the most appropriate, as well as the most modest, of the terms that have been used over the years and is the goal we should be aiming for.

**Which drugs are appropriate?**

Let’s first examine drugs that are definitely not a good idea to use for rapid tranquilization. These include, of course, fluphenazine decanoate and haloperidol decanoate, which are not absorbed rapidly enough to have an effect within the first few days of administration, much less within hours. Chloral hydrate and sodium amytal are not suitable because they represent a general anesthetic approach to rapid tranquilization and offer a narrow approach to therapeutic ranges. Essentially, the same dose necessary to tranquilize patients will also put them to sleep for hours.

Our end point for rapid tranquilization should ordinarily be to calm patients enough so that they can tell us who their case manager is, and the manager can come in and help with treatment planning and disposition. Having patients asleep does not facilitate their disposition.

Low-potency antipsychotics are not a good idea because of the postural hypotensive effect. One of the few professional liability cases we have settled from our emergency room was a patient who overdosed himself on chlorpromazine and fell secondary to postural hypotension, breaking his jaw and leading to our paying for his dental work. IM benzodiazepines other than lorazepam and midazolam are not suitable either because of irregular absorption. Clozapine is not a good idea for a variety of reasons detailed later.

I have never had luck starting patients on lithium from the emergency service. That’s because onset of action takes several days, during which patients generally do not tolerate the side effects and stop their medication.

Appropriate drugs for rapid tranquilization include any of the high-potency antipsychotics or any benzodiazepine. If a benzodiazepine is to be administered IM, only midazolam or lorazepam is appropriate. Any newer antipsychotic, discussed in detail later, is reasonable to consider.
Haloperidol vs. Lorazepam

IM lorazepam and IM haloperidol have approximately equal control of agitation over a period of hours. Both are generally safe, even for medically ill patients, and cause minimal postural hypertension and no major drug interactions. These are positive attributes in the emergency setting, where we frequently cannot get a reliable history from patients.

Haloperidol has the advantage of being specifically for psychosis. We are not going to get patients well a week sooner by starting them on an antipsychotic, as we had hoped when we believed in rapid digitization. But we should get them well 1 day sooner by starting the medication today rather than tomorrow. Haloperidol does, however, have serious extrapyramidal side effects. In an informal poll of our emergency patients who had received rapid tranquilization with haloperidol, 40% believed they were allergic to the drug. None had had anaphylactic reactions, but most had had either dystonic or extremely unpleasant akathetic reactions.

Table 1
CHARACTERISTICS OF NEWER VS. OLDER ANTIPSYCHOTICS

<table>
<thead>
<tr>
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<th>Anticholinergic</th>
<th>Orthostatic hypotension</th>
<th>Extrapyramidal side effects</th>
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<tr>
<td>Conventional (e.g., haloperidol)</td>
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<td>Clozapine</td>
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<td>Ziprasidone</td>
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A frequent mistake by emergency medicine practitioners (as opposed to emergency psychiatric practitioners) is treating akathisia, misdiagnosed as psychotic agitation, with more haloperidol. This tends to make the situation worse rather than better.

Lorazepam can, rarely, cause respiratory depression, whereas haloperidol generally cannot. This serious side effect, however, is extremely rare in young, physically healthy patients. The only cases I worry about are patients with respiratory problems or who are already intoxicated with other sedative hypnotics.

Paradoxical hostility from intoxication and disinhibition in patients treated with lorazepam is not often an issue in young, healthy individuals. For geriatric or pediatric patients, however, and for patients with mental retardation or brain damage, such lorazepam-induced behavior is not infrequent.4

One advantage of lorazepam is that it does not cause akathisia, as does haloperidol. Akathisia itself can be a cause of agitation and is better avoided, if possible.

How much to use

The dose-response curve for the acute treatment of psychotic agitation by haloperidol shows a relatively classic shape. Up to 2 mg, there is really no improvement among young, healthy people. From 2 to 10 or 15 mg, there is a more or less linear dose-response curve. After 10 or 15 mg, patients tend to respond less rather than more well.
These data, combined with data suggesting that unusually high doses or unusually rapidly increased doses of antipsychotics lead to neuroleptic malignant syndrome, suggest that rapid titration to high doses of antipsychotics is not a good idea.

**How to dose**

Not many years ago, the typical protocol for treatment of agitated patients was to start with a low dose of antipsychotic medication and repeat it at 30-minute intervals until the patient was no longer psychotic or else no longer awake.

This approach has generally fallen from favor as it has become clearer that repeated doses do not lead to more rapid response. For medication administered PO, it takes about 1 1/2 to 2 hours for patients to get the full effect. When medicine is administered IM, the onset of action is within 1 to 1 1/2 hours.5

Our emergency service is using less and less IM medication each year because patients generally prefer to take oral forms. With PO administration, patients feel more a part of the treatment and more satisfied with it. Our use of IM antipsychotics has fallen by 75%, accompanied by a dramatic decrease in seclusion and restraint and by a decrease in staff injuries.

IV antipsychotics are another realistic alternative for treating acutely agitated patients because of rapid onset of action. Although it takes 30 to 60 minutes to see a full effect, IV antipsychotics are generally safe.

The bad news is that the patient who I would like to start on IV antipsychotics in the emergency room is at the same time not someone on whom I would like to try to start an IV. In addition, the literature shows a variety of cardiac arrhythmias associated with rapidly administered IV antipsychotics. For these reasons, I use IV antipsychotics only for patients in the medical intensive care unit who already have IV lines started, are on cardiac monitors, and are in an environment that has no tolerance for aberrant behavior.

**Alternative medications**

**Midazolam** is an alternative for treating patients in the emergency service.7 It is marketed as a pre-endoscopy agent and has the advantages of a shorter duration of action than lorazepam while being absorbed well IM.

The disadvantage is that it causes a fairly dense anterograde amnesia, which may be good if the patient is getting an endoscopy procedure but is bad if you hope to say something therapeutic to him or her. The anterograde amnesia also may lead to increased confusion in an already confused patient. There have been cases in which, when the drug has been used for endoscopy procedures, patients have alleged sexual abuse by their physicians during the procedure.

**Droperidol**, marketed as a preanesthetic agent,8 is closely related to haloperidol and is safe and effective when used in the same dosage. It probably has a more rapid onset of action, shorter duration of action, and a lower incidence of extrapyramidal effects than haloperidol. But droperidol has a somewhat higher incidence of postural hypotensive effect than does haloperidol.

A potential problem is that it is not available for PO use. I like to give patients the same medication in the emergency room, if possible, that I am going to be giving them as outpatients. As they come to the emergency room feeling really bad, I can reassure them on discharge that this is the same drug that made them feel better, and that they should keep taking it.

Though droperidol is not specifically labeled for psychiatric indications, I do not let this bother me too much. Of greater concern, the Food and Drug Administration has recently added a black box warning because cases of QT prolongation and/or torsade de pointes arrhythmia have been reported in patients receiving droperidol at or below the recommended doses.

**Valproate loading**

A recent advance in the pharmacologic treatment of acute agitation is sodium valproate loading for patients with acute mania, accomplished by giving 15 mg per kilogram PO, or the equivalent of about 1 gram of
sodium valproate for a young, healthy person. Within the first 24 hours, many patients realize a substantial improvement in their manic symptoms with relatively few side effects. Perhaps 20% will have excessive sedation and 10% excessive tremor or nausea.9

**Newer antipsychotics**

The newer antipsychotic agents offer potential for improved treatment.

**Clozapine**, the first such agent available, has not proven to be useful in the emergency setting because of its extremely high rate of sedation and anticholinergic effects, making it difficult to quickly get up to a therapeutic dose. In addition, the prevalence of serious side effects such as seizures and blood dysplasia has limited its usefulness.

**Risperidone** is the first of the newer antipsychotic agents to prove useful. The lower prevalence of extrapyramidal reactions makes it much more tolerable to patients. Although risperidone was introduced at a recommended standard dosage of 6-8 mg/d, I usually start with 4 mg. I also raise the dosage more rapidly than the package insert suggests, at levels of 2 to 4 mg in young, healthy people and 1 to 2 mg in older or more debilitated individuals.

One study has demonstrated that oral risperidone plus oral lorazepam produces results comparable to IM haloperidol plus IM lorazepam.10 Risperidone is available in an oral concentrate, which is useful for patients who might be at risk for not swallowing their pills.

**Olanzapine** has proven useful in the emergency setting. At least one study has clearly demonstrated such advantages over haloperidol as more rapid onset of action, greater overall improvement, and less use of adjunctive lorazepam11 (Table 1). As with risperidone, most patients need 15 to 20 mg of olanzapine, rather than the 10 mg that was recommended when the drug was introduced. Olanzapine is available in a rapidly dissolving form (Zyprexa Zydis), which is useful for potentially nonswallowing patients. Its pharmacokinetics are essentially similar to the pill form, however, and it should not be regarded as a sublingual preparation.

Olanzapine’s main drawback: it is similar to clozapine in terms of anticholinergic reactions and postural hypertension. If I plan to continue a patient on olanzapine after the emergency service, I will then start with it.

**Ziprasidone** is supported by excellent data for use in the emergency setting12 at doses of 10 to 20 mg.

**Quetiapine** has been used less frequently than the other atypical antipsychotics in the emergency setting but should be similarly effective.

**Two or three drugs at once**

Many emergency facilities now routinely use a “cocktail” for acutely agitated patients. Common versions include haloperidol 5 mg plus lorazepam 2 mg (sometimes referred to as a “B52”); haloperidol 10 mg plus lorazepam 2 mg; or haloperidol 10 mg, lorazepam 2 mg, and cogentin 1 mg.

I do not routinely use these cocktails because they more frequently put the patient to sleep. I prefer to go stepwise, trying not to get patients overly sedated and aiming for a state at which patients are awake and able to help with disposition planning.

Adding cogentin to a cocktail seems particularly irrational; most patients will not need it with a 10 mg dose of haloperidol. The extrapyramidal symptoms are not likely to surface for 8 to 12 hours. If I have given a patient 10 mg of haloperidol and am going to admit him or her to the hospital, I generally will let the patient get cogentin from the ward. But, if I am sending the patient home, I generally prescribe cogentin for several days afterwards, because so many patients think they are allergic to haloperidol.

All of this said, the combination of haloperidol plus lorazepam is safe and effective.13 It has been used in shockingly high doses even in medically compromised patients without mortality or excessive morbidity.
**Making the ER decisions**

*Figure 1* shows what I consider to be a rational decision tree for managing patients who come in yelling and screaming and tearing up your emergency room. First, try talking with the patient. This works most of the time. If this does not work and the patient is directable (meaning that he or she will do what you ask, even for a short time) you can usually get by without physical restraint. The rate of physical restraint in our emergency room is below 10%, down from more than 25% in years past.

If the patient is not directable and poses a serious danger to himself or herself, to staff, or to other patients, physical restraint is a safe and effective procedure when done by staff who know what they are doing. It also is generally well tolerated by the patient. Once patients are semi-cooperative or physically restrained, it is possible to get vital signs and something resembling a physical exam. Every week our emergency service receives patients from our medical emergency side who, once calmed, can be sent back to deal with their serious medical problems.

When the patient has previously been on antipsychotic medication, I generally rapidly tranquilize him or her with an antipsychotic, if possible using the medication the patient had been on before. If the patient is able to take oral medication, my choice is generally risperidone 1 to 4 mg or olanzapine 10 to 15 mg. If the patient is not able to take medication PO, the choice is haloperidol 5-10 mg. If the patient has not responded within a couple of hours, I add lorazepam 2 mg.

*Figure 1*

DEcision TREE FOR RAPID TRANQUILIZATION

Short-acting IM preparations of olanzapine and ziprasidone are scheduled to be released this year. Then haloperidol will likely become obsolete in emergency psychiatry, and we will no longer have patients becoming “allergic” to it.

If a patient has never been on antipsychotic medication, I will consider a benzodiazepine as an alternative. If the patient can take medication by mouth, I go with 2 mg of lorazepam PO; if not, 2 mg IM. Whereas repeated doses of antipsychotics do not appear to make pharmacologic sense, my impression is that repeated doses of benzodiazepines probably do, up to a total dose of about 6 mg of lorazepam. The only time it appears necessary to go higher is in patients who are in sedative hypnotic withdrawal. If a patient calms down enough to tell us clear-cut psychotic symptoms, I can add an antipsychotic to the lorazepam, the same way I add lorazepam to the antipsychotic.

If the patient is frail, elderly, mentally retarded, intoxicated on other sedative hypnotics, or has had a previous bad reaction to benzodiazepines, the antipsychotic approach is preferable.

**Related resources**


**Drug brand names**

- Clozapine • Clozaril
- Droperidol • Inapsine
- Midazolam • Versed
- Olanzapine • Zyprexa
Disclosure

Dr. Hillard reports that he is on the speaker’s bureau of Janssen Pharmaceutica, Pfizer Inc., Eli Lilly and Co., and Wyeth-Ayerst Pharmaceuticals.

References