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Victoria Hendrick, MD
Editor-in-Chief

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IN THIS ISSUE

Focus of the Month:
Agitation

Learning Objectives

After reading these articles, you should be able to:

1. Determine effective pharmacologic and nonpharmacologic strategies for the management of agitation in patients with dementia on the inpatient unit.
2. Identify the potential risks associated with prescribing anticholinergic medications.
3. Summarize some of the current research findings on psychiatric treatment.

Medications to Rapidly Treat Psychotic Agitation

Victoria Hendrick, MD. Editor in Chief, The Carlat Hospital Psychiatry Report. *Chief, Inpatient Psychiatry, Olive View UCLA Medical Center. Daniel Carlat, MD. Publisher,* The Carlat Hospital Psychiatry Report.

Dr. Hendrick and Dr. Carlat have disclosed no relevant financial or other interests in any commercial companies pertaining to this educational activity.

Highlights From This Issue

Dr. Eran Metzger updates us on the management of agitation in patients with dementia.

We review the safest and most effective medications for acute psychotic agitation.

Strongly anticholinergic medications are associated with lasting cognitive impairment, argues Dr. Shelly Gray.

If you work in an emergency department (ED) or psychiatric inpatient unit, you've encountered agitated and even violent patients. We can help many patients settle down by listening empathically, validating their emotions, and offering oral medications, but even with our best efforts, these interventions do not always work. Medications help reduce agitation, but which ones are the safest and most effective? In this article we will discuss medication strategies that have reasonable safety and efficacy data for managing acute agitation in ED settings and inpatient psychiatry. *(Editor's note: We will cover verbal de-escalation techniques for agitation in an upcoming issue.)*

What's the cause of the agitation?
Before medicating an agitated patient,

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Q&A With the Expert

Treating Agitation in Patients With Dementia
Eran Metzger, MD

Medical Director of Psychiatry, Hebrew SeniorLife, Boston, MA. Assistant Professor of Psychiatry, Harvard Medical School, Boston, MA.

Dr. Metzger has disclosed no relevant financial or other interests in any commercial companies pertaining to this educational activity.

CHPR: Can you tell us about yourself and your background?
Dr. Metzger: I'm the medical director of psychiatry at Hebrew SeniorLife and an assistant professor of psychiatry at Harvard Medical School. My work also includes training residents and geriatric medicine fellows who rotate through our facility.
CHPR: You participated in the psychopharmacology algorithm project for the management of behavioral and psychological symptoms of dementia (BPSD) and co-authored a publication based on that work (Chen A et al, *Psychiatry Res* 2021;295:113641). Can you give us an overview of BPSD?
Dr. Metzger: We know that 80%–90% of patients who suffer from dementia are likely to experience behavioral and psychological symptoms of dementia, or BPSD. Those symptoms vary; we subdivide them into motor symptoms and verbal symptoms, but they can be disruptive regardless of the category.

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Expert Interview—Treating Agitation in Patients With Dementia

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CHPR: What's in your differential diagnosis for these symptoms?

Dr. Metzger: The primary rule-out is an acute medical change. Even in a person who has had these behaviors before, if we see an acute behavioral change, we first look for a change in the patient's medical condition.

CHPR: And what are your steps for management?

Dr. Metzger: A medical examination is the first part of management. This population, even in supervised settings, is prone to medical changes such as infection and dehydration. Sometimes, treating an acute medical condition alone can resolve the behavioral and psychological symptoms.

CHPR: Right. For example, elderly women with UTIs can get quite agitated, but their behavior often improves once you treat the UTI.

Dr. Metzger: Exactly. UTIs, pneumonia, dehydration, or even exacerbation of a pain syndrome can cause agitation, and just managing the pain can resolve the agitation. When I started working in geriatrics over 20 years ago, one of my mentors stressed the importance of getting a bowel history because of constipation's effects on behavior. I was skeptical that someone's constipation could result in clinical changes in behavior, but now I'm a true believer. We often see dramatic improvements in behavior once we remedy a patient's constipation. In our daily report on each patient, the nursing staff reports whether the patient had a bowel movement that day.

CHPR: We want to look at all possible options to help these patients and not just assume we need to medicate. Are there any other nonmedication approaches we should consider?

Dr. Metzger: Yes. Our preference is always to try nonpharmacologic approaches; in fact, for people in skilled nursing facilities, Medicare requires that we document our attempts at nonpharmacologic approaches before we start medicating our patients. The two approaches with the best evidence are 1) caregiver and staff education and 2) music therapy. Web-based training programs are available, often free of charge, that help staff learn how to identify what need a patient is trying to express and how to respond in a nonconfrontational way even when the patient is agitated.

CHPR: Can you give us the websites for any of these web-based training programs?

Dr. Metzger: Sure. Here are two of them: Alzheimer's Association person-centered dementia care training (www.alz.org/professionals/professional-providers/dementia-care-training-certification) and the Oasis senior care program (www.susanwehrymd.com/oasis).

CHPR: One example that I saw in your paper was trying to avoid using the word "no" and instead saying, for example, "How about we do this instead?"

Dr. Metzger: Yes. When we see acutely unsafe behavior, we want it to stop right away, so our natural reflex is to use words like "no" and "stop." But certain patients, particularly men, can escalate in response to that type of language.

CHPR: How about situations where it seems like you need to use a medication to avoid patients hurting themselves or someone else? What's your medication algorithm?

Dr. Metzger: For emergent agitation, we like to give medication orally if possible, but sometimes that's not feasible or safe. Some people have recommended using orally disintegrating olanzapine for a patient who isn't accepting pills, but I know of at least one case where a nurse tried to place an orally disintegrating tablet under a patient's tongue and had her finger bitten badly. So I don't recommend trying to involuntarily administer orally disintegrating tablets to an agitated patient. For emergent agitation in a patient who isn't taking oral medications, our medication of choice would be intramuscular olanzapine. Intramuscular haloperidol hasn't been studied as well in the older age group, but it's been used in medical settings safely and is our second option. We do know that safety of these medications is dose dependent, and that generally the higher doses are where you start to get into trouble. In most of our older patients, that risk can be avoided if you give the medication a little time to work.

CHPR: What dose range do you use?

Dr. Metzger: For olanzapine, I would start with 2.5–5 mg intramuscularly depending on the body habitus and would give that a half hour or an hour to have effect. I would repeat that up to three times over the course of the day as necessary. For haloperidol, again depending on the patient's body habitus, I would use 0.25–1 mg intramuscularly.

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Expert Interview—Treating Agitation in Patients With Dementia
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CHPR: We sometimes see gabapentin, divalproex, prazosin, and SSRIs used to treat agitation in dementia in geri-psych units. Do you use any of these medications?

Dr. Metzger: Of the medications you mentioned, SSRIs have the strongest evidence to support their use in treating BPSD. The most comprehensive study was the CitAD trial using citalopram up to 30 mg daily (Porsteinsson AP et al, *JAMA* 2014;311(7):682–691). However, I tend to use either escitalopram or sertraline to minimize the risk of QTc prolongation, based on a 2013 FDA advisory (www.tinyurl.com/4zrya7h4). I use SSRIs for nonemergent agitation because the response latency is similar to when they are used to treat depression. Unfortunately, the evidence base for the other agents is comparatively weak. Well-designed controlled studies of divalproex had negative findings, and the use of gabapentin is supported only by case reports. Prazosin has two small positive trials to support its use, and I hope it will be studied more in the future.

CHPR: What about benzodiazepines? Do you worry about using them in elderly patients?

Dr. Metzger: We worry *a lot* about benzodiazepines because of their effects on coordination, gait, and cognition. One scenario where I've found them to be helpful is in nonambulatory patients who consistently become agitated during caregiving (eg, bathing) despite nonpharmacologic strategies. I've found that lorazepam 0.25 mg about 30 minutes beforehand can make the activity safer for both the patient and the caregiver.

CHPR: You refer to nonemergent agitation situations as urgent in your paper. Tell us what you mean by that.

Dr. Metzger: These are situations where a behavior does not immediately place someone at risk, but the behavior really can't be supported for much longer. The patient might be combative with others, or they might frequently do things that jeopardize their safety, or perhaps they are at greater risk of falling due to psychomotor agitation. So, we don't have to provide calming within the hour, but we also don't have several weeks to wait; we're talking more along the lines of several days at most.

CHPR: What medications do you recommend in these cases?

Dr. Metzger: We again would want to start with oral medications, and the antipsychotics in order of preference would be aripiprazole, followed by risperidone. We favor aripiprazole since it's less likely to cause extrapyramidal symptoms. I want to emphasize that there are *no* FDA-approved medications for behavioral and psychological symptoms of dementia. I mean no medications from any class—antipsychotics or otherwise. The antipsychotic pimavanserin is FDA approved for psychosis in Parkinson's disease only. Canada has approved risperidone for short-term use in psychosis and aggression, while both Britain and Australia have approved risperidone for behavioral and psychological symptoms of dementia.

"I want to emphasize that there are no medications from any class—antipsychotics or otherwise—that are FDA approved for behavioral and psychological symptoms of dementia. The antipsychotic pimavanserin is FDA approved for psychosis in Parkinson's disease only. Canada has approved risperidone for short-term use in psychosis and aggression, while both Britain and Australia have approved risperidone for behavioral and psychological symptoms of dementia."

Eran Metzger, MD

CHPR: It's too bad we don't have more options, especially since antipsychotic meds have a black box warning on top of not being FDA approved.

Dr. Metzger: Exactly. The black box warning was based on a retrospective review of a number of studies that showed an increase in the incidence of cerebrovascular adverse events, but also a statistically significant increase in mortality among patients with dementia who were prescribed these medications. The risk is highest early in treatment, and the hazard ratio across many studies is around 1.55. That sounds like a lot, but looking at the absolute numbers, the difference in 30-day mortality rate in nursing home patients goes up 1.2 actual percentage points. Or if you're looking at a 180-day study, the absolute risk rises from around 2.9% to about 4.4% (Gill SS et al, *Ann Intern Med* 2007;146(11):775–786). When we present this information to families, our experience is that they will accept that amount of increased risk in exchange for the possibility of improved quality of life and improved safety, because agitation can place patients at serious risk of physical harm.

CHPR: I'm assuming confounding by indication has been taken into account, right? People who are the most agitated might also be the most medically ill.

Dr. Metzger: That's an excellent point—studies do try to control for that confounding, but I am not convinced that we've been able to design ones that can do that. Unfortunately, the patients who have the most severe symptoms are the ones most likely to get treatment, and there's a possibility that those severe symptoms are markers for worsened illness and increased mortality associated with that illness.

CHPR: What are your thoughts about minimizing the anticholinergic load that patients are exposed to, considering that anticholinergic medications can exacerbate confusion and agitation?

Dr. Metzger: When we encounter a patient with new or worsened agitation, we review the medication list to make sure there's not a correlation between the mental status changes and the addition of a new medication, such as one with anticholinergic side effects. An example that comes to mind for male patients is oxybutynin (Ditropan), which is prescribed by our urology colleagues to address urinary frequency. We also see some older patients coming in on tricyclic antidepressants

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for neuropathic pain or insomnia, so we want to carefully remove those medications, particularly if they're linked with a deterioration in mental status.

CHPR: What about patients with Parkinson's or Lewy body dementia? What specific treatment considerations should we keep in mind?

Dr. Metzger: The main concern is exacerbating extrapyramidal symptoms. Although the studies of quetiapine's efficacy have been very disappointing, it is one of the most popular antipsychotics for behavioral and psychological symptoms of dementia. Clinicians might feel falsely reassured that quetiapine is safe since it has fewer extrapyramidal side effects, but in addition to having questionable efficacy, it has several worrisome adverse effects—including sedation, which places elderly patients at risk for falls as well as aspiration during mealtimes. Also, quetiapine produces more orthostatic hypotension than most other second-generation antipsychotics, and that further increases the risk of falls.

CHPR: What medication would you use instead?

Dr. Metzger: This is a situation where I might first give pimavanserin a try. Because it is still under patent protection as Nuplazid, depending on a patient's Medicare D plan, cost may be prohibitive. In my limited experience, it is relatively easy to titrate, seems to be well tolerated, and can be effective in curbing BPSD. An alternative would be clozapine, though that can present some of the same adverse effects of sedation and postural hypotension as quetiapine.

CHPR: And what about cholinesterase inhibitors?

Dr. Metzger: That was a controversial topic between the co-authors of our paper. Cholinesterase inhibitors and memantine have only modest effects on behavior but are relatively safe to administer, and some patients do show behavioral improvements that are lost if we stop the medication. So, you may see some benefits among patients with Alzheimer's, but it's difficult to predict who specifically will benefit. Also, these medications are no longer as prohibitively expensive as when they first came out.

CHPR: What do you watch for when you have patients on these agents?

Dr. Metzger: Mainly anorexia and weight loss. These are the most common reasons we discontinue cholinesterase inhibitors.

CHPR: And how do you manage sundowning? We sometimes see elderly patients who seem fine during the day but become agitated in the evening.

Dr. Metzger: We've used the term sundowning for decades and are no closer to understanding what this syndrome represents. One theory is that it's related to dysregulation of circadian rhythms. Another is that it represents a reaction to what's going on in the inpatient milieu, like a change in shift where there's more commotion and patients are reacting to that. We might try a medication like trazodone because that gets the patient ready for bedtime—something like 25 mg late in the afternoon is enough to calm the patient down and get them ready to go to sleep. But my first choice is melatonin at bedtime.

CHPR: Melatonin levels decline with age, so it makes sense to try it as a first choice for elderly patients.

Dr. Metzger: We also know from a Cochrane Collaboration review that bedtime melatonin can have positive effects over the course of the following day, and that would support a circadian explanation for sundowning (Jansen SL et al, *Cochrane Database of Systematic Reviews* 2006;(1):CD003802).

CHPR: Are you familiar with dexmedetomidine? The FDA granted breakthrough therapy designation to an oral form of this drug for dementia-related agitation.

Dr. Metzger: Yes, dexmedetomidine has been used for years as an IV sedative and has recently been studied as a sublingual film for agitation associated with dementia. A recent small unpublished Phase 1 study of this alpha-2a adrenergic receptor agonist, conducted among assisted-living patients with dementia, showed improvements in scores of three instruments used to measure agitation with no significant adverse events. A larger study is currently underway, and we'll have to see.

CHPR: Thank you for your time, Dr. Metzger.

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Medications to Rapidly Treat Psychotic Agitation

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try to determine the cause. In this article we will focus on agitation caused by a primary psychiatric condition—usually schizophrenia, schizoaffective disorder, or a manic episode of bipolar disorder.

With most of our agitated patients, a primary psychiatric origin is clear from the history. The main differentials to consider are substance-induced agitation, whether intoxication or withdrawal, and delirium/dementia. If a patient is agitated due to alcohol or stimulant intoxication, you can generally follow the medication guidelines in this article, but beware of benzodiazepines, which can have a synergistic effect with alcohol. If the issue is withdrawal, management is more complicated, and we recommend reading "Managing Substance-Related Agitation" in *CATR* May/June 2019 for education on the options. We will cover delirium and dementia in a forthcoming issue.

Oral or IM meds?

Once you've determined that the agitation is psychiatric in origin, you will next have to decide between using oral or IM meds to ease the behavior. While IM medications in general have more reliable bioavailability and a faster onset of action than oral meds, there is a lot of variability in how quickly these options work to quell agitation. In fact, one small

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study of 42 patients found that two special oral formulations (Zyprexa Zydis and risperidone liquid solution) worked just as quickly as IM haloperidol for agitated psychotic patients (Hsu WY et al, *J Clin Psychopharmacol* 2010;30(3):230–234).

Aside from issues of bioavailability, there is the practical issue of whether the patient will accept an oral medication. When patients are about to injure staff or damage hospital property, time is of the essence, and attempting to convince such patients to take a pill is a time-consuming and often futile process. Furthermore, assuming patients do agree to oral administration, it is difficult to ascertain that they have actually swallowed the pill.

There are no clear answers to the oral vs IM conundrum, and each clinical situation requires its own analysis. Generally speaking, the higher the risk for violence, the more likely you and your staff are going to choose IM meds. Be careful not to assume based on a patient's appearance that they'll require IM meds; even the most highly agitated patients might be willing to accept an oral medication. And administering IM meds can backfire: Patients may perceive them as aggressive acts, potentially escalating the risk for patient and staff injury.

Pills vs ODTs?

Orally disintegrating tablets (ODTs) are designed to dissolve on the tongue. These formulations have been on the market for years, but they recently became more popular in psychiatry with the development of a new tablet compression technology called Zydis, which produces pills that dissolve in the mouth within three seconds.

Zyprexa Zydis has achieved something of a niche in the treatment of agitated and psychotic patients in EDs and inpatient settings. But is its onset of action really any faster than regular Zyprexa? One pharmacokinetic study of 11 healthy people found that Zydis appeared in the bloodstream on average 10 minutes after ingestion, as opposed to 30 minutes for standard Zyprexa tablets. The study also found that the average time to peak concentration was 3.5 hours for Zydis and 4.4 hours for the tablets (Markowitz JS et al, *J Clin Pharmacol* 2006;46(2):164–171).

The bottom line is that ODT formulations (Zyprexa Zydis, aripiprazole ODT, risperidone ODT) are likely faster acting than standard tablets. For patients willing to take a pill, Zyprexa Zydis is a good choice for more rapid control of agitation, and it has the advantage of being difficult to cheek because it dissolves almost instantaneously.

Choosing Medications for Acute Psychotic Agitation

Oral Agents	*First line* Haloperidol 5–10 mg with lorazepam 1–2 mg every four hours, up to four doses
	Second line Lorazepam 2 mg every two hours (max daily dose 10 mg) Olanzapine ODT 5–10 mg every four hours (max daily dose 30 mg) Risperidone ODT 2 mg with lorazepam 2 mg every four hours, up to four doses Haloperidol 5–10 mg with diphenhydramine 25–50 mg, or benztropine 1–2 mg, every four hours, up to four doses (with or without lorazepam 2 mg) Chlorpromazine 25–100 mg every four hours
	Third line Aripiprazole ODT 15 mg every two hours (max daily dose 30 mg) Quetiapine 100–300 mg every four hours (max daily dose 800 mg)
IM Agents	*First line* Haloperidol 5–10 mg with lorazepam 1–2 mg every four hours, up to four doses
	Second line Lorazepam 2 mg every two hours (max daily dose 10 mg) Olanzapine 5–10 mg every two hours (max daily dose 30 mg) Haloperidol 5–10 mg plus diphenhydramine or promethazine 25–50 mg, or benztropine 1–2 mg, every four hours, up to four doses (with or without lorazepam 2 mg) Chlorpromazine 25–100 mg every four hours
	Third line Droperidol 5–10 mg, one-time dose Ziprasidone 10–20 mg every 2–4 hours (maximum 40 mg daily)

With all that said, which medications are most effective in treating agitation? Let's run down the list.

Antipsychotics

Haloperidol (Haldol) and the haloperidol cocktails

Haloperidol has long been the gold standard for treating agitation. No other drug has been found to be more effective than haloperidol, and most studies of other agents use haloperidol as the comparison. Haloperidol has its disadvantages, including side effects like dystonia and Parkinsonism, but given its long track record (since 1967), we still consider it the first-line agent for agitation. However, we never prescribe haloperidol alone because in these circumstances the rate of dystonia is close to 50%—and one review considers the use of haloperidol alone to be unethical due to the high rate of EPS (Ostinelli EG et al, *Cochrane Database Syst Rev* 2017;7(7):CD009377).

That brings us to the haloperidol cocktail and its variants. The typical agitation cocktail is haloperidol 5–10 mg/lorazepam 1–2 mg/diphenhydramine 50 mg (or benztropine 1–2 mg), given either IM or orally. The commonsense rationale behind the cocktail is as follows: Haloperidol targets both psychosis and agitation; lorazepam adds a second mechanism to target agitation; and diphenhydramine prevents a dystonic reaction from the haloperidol and adds a sedating effect. Yet no studies have compared this three-medication combination with other options. Furthermore, it's an open question whether anticholinergic agents like diphenhydramine are really necessary. A recent meta-analysis showed that benzodiazepines might suffice to prevent EPS: Rates of dystonia and EPS were 3% and 5%, respectively, for haloperidol plus lorazepam, vs 0% (dystonia) and 0%–84% (EPS) for haloperidol plus the antihistamine promethazine (Bak M et al, *Eur Psychiatry* 2019;57:78–100). Many guidelines recommend using a combination of haloperidol plus anticholinergic *or* haloperidol plus benzodiazepine, but not all three agents combined (Wilson MP et al, *West*

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J Emerg Med 2012;13(1):26–34). An advantage of haloperidol plus lorazepam is that these meds can be administered in one syringe. When diphenhydramine or benztropine are mixed with haloperidol, a precipitate forms within minutes, leading most hospital pharmacies to recommend separate syringes.

Olanzapine (Zyprexa)
Olanzapine is an effective option whether given orally (especially in its ODT form, Zyprexa Zydis) or IM. We like it because it has a low incidence of dystonia and we can safely use it as monotherapy. A four-way comparison of IM agents found that olanzapine was equally effective as the haloperidol/midazolam combination, and that both options were more effective than either ziprasidone or haloperidol plus promethazine (Mantovani C et al, *J Clin Psychopharmacol* 2013;33(3):306–312). Highly agitated patients may not respond to maximal doses of IM Zyprexa, in which case a benzodiazepine can be added, but with caution *(Editor's note: See the callout box below).*

IM Olanzapine Plus Benzodiazepines: Safe or Unsafe?

If you have ever tried to electronically prescribe IM olanzapine with an IM/IV/subcutaneous benzodiazepine, you have probably received an interaction alert warning about the potential for excessive sedation and cardiorespiratory depression. Is this warning justified? Let's look at the data.

The Eli Lilly warning followed reports of 160 adverse events, including 29 fatalities, linked to IM olanzapine/IM benzodiazepine combinations from January 2004 to September 2005 (Marder SR et al, *J Clin Psychiatry* 2010;71(4):433–441). Looking closely at these cases, it is unclear that this medication combination actually caused the fatalities. Many of them occurred days after the olanzapine injection (n = 12) or involved patients with serious medical illnesses or suicide attempts (n = 14), either of which may have been the actual cause of death.

In addition, subsequent controlled trials appear to show that IV and IM olanzapine are safe when combined with benzodiazepines. A double-blind, randomized controlled study that compared IV olanzapine 5 mg combined with IV midazolam 2.5–5 mg (n = 109) to IV midazolam alone (n = 115) found that the olanzapine/midazolam combination produced more rapid sedation than midazolam alone and was safe and well tolerated (Chan EW et al, *Ann Emerg Med* 2013;61(1):72–81). Another study of hospital patients (n = 91) who received IM olanzapine (5–10 mg) plus IM lorazepam (1–2 mg) reported no serious adverse events, even among patients who received both medications within a five-minute interval (Williams AM, *Ment Health Clin* 2018;8(5):208–213). Lastly, in a study that looked at 96 patients who received IM haloperidol (n = 71) or IM olanzapine (n = 25) along with a benzodiazepine, 5% of the patients in the haloperidol plus benzodiazepine group experienced hypotension, while none of the patients in the olanzapine plus benzodiazepine group had this side effect. Also, none experienced decreased oxygen saturation, except for patients who had positive alcohol breathalyzer tests or were visibly intoxicated. The authors concluded that olanzapine plus benzodiazepine is no riskier than haloperidol plus benzodiazepine, provided patients have not ingested significant amounts of alcohol (Wilson MP et al, *J Emerg Med* 2012;43(5):790–797).

Should we separate the administration of these meds by some time interval? The FDA does not give a clear directive on this point, unlike the European Medicines Agency, which recommends separating olanzapine and benzodiazepines by at least one hour.

The olanzapine + benzodiazepines combination is probably safe for most agitated patients who are otherwise healthy—though it is not our first choice, given the clinical controversies. This combination is best avoided in patients with compromised respiratory function (eg, COPD) or who are intoxicated with alcohol.

Risperidone (Risperdal)
For oral use, we like risperidone ODT (Risperdal M-Tab) because, despite its high potency, it has a lower risk for dystonia than haloperidol. While risperidone can be used alone, a study combining it with lorazepam found that the combination was as effective as haloperidol plus lorazepam (Currier GW et al, *J Clin Psychiatry* 2004;65(3):386–394). No studies have evaluated risperidone alone vs risperidone plus lorazepam, but in our experience, the combination of risperidone plus lorazepam is more effective.

Ziprasidone (Geodon)
IM ziprasidone appears less effective than IM olanzapine or the IM haloperidol/benzo combination (Mantovani et al, 2013). Ziprasidone was the least effective at reducing scores on the Positive and Negative Syndrome Scale Excited Component (PANSS-EC) in a meta-analysis of randomized controlled trials that examined various pharmacologic treatments for acute agitation (Bak et al, 2019). A concern with ziprasidone is that it increases the risk of QTc prolongation in patients with other risks for QTc prolongation.

Aripiprazole (Abilify)
Aripiprazole is no longer available in the short-acting IM version as it was withdrawn by the manufacturer due to poor sales. Drawbacks include the potential to be activating and a lower efficacy rate compared to other second-generation agents for managing agitation (Wilson et al, 2012).

Chlorpromazine (Thorazine)
Chlorpromazine, the first antipsychotic to be developed, has a long track record of use for agitation, especially in its IM form. This medication's main advantage is a low EPS risk. Its drawbacks include a QTc prolongation similar to haloperidol's, potential orthostatic dizziness, and a lowered seizure threshold. While these side effects lead some authorities to discourage its use, in the real world of inpatient psychiatry we find that many of our agitated patients respond better to Thorazine than any other agent.

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Q&A With the Expert

Anticholinergic Drugs and Risk of Cognitive Impairment and Dementia

Shelly L. Gray, PharmD

Professor and Plein Endowed Director, Plein Center for Geriatric Pharmacy Research, School of Pharmacy, University of Washington, Seattle, WA.

Dr. Gray has disclosed no relevant financial or other interests in any commercial companies pertaining to this educational activity.

CHPR: Can you tell us about your research?

Dr. Gray: My research uses large databases to examine medication safety issues in older adults with the goal of optimizing healthy aging. My focus is on examining medications and risk for dementia, falls, and fractures—the types of outcomes that are not easily addressed in randomized controlled trials.

CHPR: And in your research on medications and risk for dementia, you have found that anticholinergic medications are associated with an increased risk.

Dr. Gray: Exactly. We conducted a study of older adult subjects who did not have a dementia diagnosis at study entry and found that those with higher cumulative exposure to anticholinergic agents were significantly more likely to receive this diagnosis after, on average, seven years (Gray SL et al, *JAMA Intern Med* 2015;175(3):401–407).

CHPR: Have other studies had similar findings?

Dr. Gray: Yes. To give a couple of examples, a case-control study of over 40,000 older adult patients reported that certain classes of anticholinergic medications were strongly associated with higher risk of new-onset dementia (Richardson K et al, *BMJ* 2018;361:k1315). Another study, which looked at nearly 300,000 subjects age 55 and above, found a nearly 50% increased risk of dementia associated with three years of daily use of strong anticholinergic medications (Coupland CAC et al, *JAMA Intern Med* 2019;179(8):1084–1093).

CHPR: How much should these studies worry us? After all, for years we thought benzodiazepines increased the risk for dementia, but new data show they don't seem to increase this risk.

Dr. Gray: Right. The results of recent research using high-quality study designs do not support a link between benzodiazepines and dementia (Espinoza RT, *J Am Med Dir Assoc* 2020;21(2):143–145). There are a lot of issues that can complicate these pharmacoepidemiology studies—and that's true for studies that have examined anticholinergics too.

CHPR: Can you say more on the limitations of pharmacoepidemiology studies?

Dr. Gray: Sure. These studies rely on pharmacy prescription fills, and patients don't always adhere to their prescribed medications. Patients may take over-the-counter meds that aren't included in studies' analyses, and they may inaccurately estimate their alcohol and nicotine use. Protopathic bias is another important concern.

CHPR: What is protopathic bias?

Dr. Gray: It occurs when a drug is used to treat early symptoms of a disease that has not yet been diagnosed. Patients take benzodiazepines and anticholinergics in the years leading up to a dementia diagnosis for treatment of prodromal symptoms such as anxiety and insomnia. If researchers don't take this use into account, their studies will show spurious positive associations.

> **"With cross-sectional studies you cannot determine that the anticholinergics are the reason for poor cognition. There may be other factors related to the use of anticholinergics that explain the poorer performance. Nevertheless, whenever possible, we should use the fewest number of anticholinergics when treating people with schizophrenia to minimize effects on cognition."**
>
> Shelly L. Gray, PharmD

CHPR: When research takes these limitations and biases into account, do studies still show a strong association between anticholinergic drugs and dementia?

Dr. Gray: Yes. We can't 100% rule out that biases are not an issue, but several studies have done a good job addressing these issues.

CHPR: Is the research consistent in finding a link between anticholinergics and cognitive impairment?

Dr. Gray: There are some discrepancies in the research. For example, in a study I mentioned earlier, the risk of cognitive impairment was linked with anticholinergic antidepressant, urological, and antiparkinsonian drugs, but not gastrointestinal medications (Richardson et al, 2018). But as a whole, the literature supports an association.

CHPR: We know that acetylcholine is important for memory and learning, so it's reasonable to worry that medications that reduce cholinergic activity might adversely affect cognition.

Dr. Gray: Right, and the main drugs approved for dementia are cholinesterase inhibitors, which increase levels of acetylcholine.

CHPR: If cognitive impairment is directly linked to anticholinergic medications, is the impairment reversible once these medications are stopped?

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Expert Interview—Anticholinergic Drugs and Risk of Cognitive Impairment and Dementia
Continued from page 7

Dr. Gray: Unfortunately, this question hasn't received a lot of attention. A study of older adults who were followed over four years reported that the risk of cognitive decline was about 1.5–2 times higher for continuous anticholinergic users but not for those who discontinued the medications (Carrière I et al, *Arch Intern Med* 2009;169(14):1317–1324). That's reassuring—but in my study (Gray et al, 2015), we found the dementia risk was similar among people with past heavy use of anticholinergics and people with recent heavy use, suggesting that the risk for dementia with anticholinergic use persists despite discontinuation.

CHPR: It sounds like most research on anticholinergic agents and cognitive impairment has focused on older adults.

Dr. Gray: Yes, since older patients are at greater risk for cognitive decline and are more prone to side effects. However, we also have limited evidence linking anticholinergic exposure with deteriorating cognition in younger patients. More studies with better methods are needed to determine the risks in younger people.

CHPR: And even in subjects younger than age 50. I read a recent study that looked at the relationship between anticholinergic medication exposure and cognitive performance in patients as young as age 18 with schizophrenia or schizoaffective disorder and found that higher anticholinergic burden was significantly associated with worse cognitive performance (Joshi YB et al, *Am J Psych*. Epub ahead of print). What do we do with all this information?

Dr. Gray: This is a good distinction—cognitive performance versus dementia (or cognitive decline). Unlike dementia, it is well known that anticholinergics are associated with lower performance on tests of cognition. Keep in mind, with cross-sectional studies you cannot determine that the anticholinergics are the reason for poor cognition. There may be other factors that explain the poorer performance. Nevertheless, whenever possible, we should use the fewest number of anticholinergics as possible when treating people with schizophrenia to minimize effects on cognition.

CHPR: And we should be particularly mindful of strongly anticholinergic medications, right?

Dr. Gray: Right—medications that score 3 on scales of anticholinergic activity, like the Anticholinergic Cognitive Burden Scale *(Editor's note: See table at right)*.

CHPR: So, if we have a patient on clozapine and we want to add an antidepressant, we might want to stay away from paroxetine. Or if a patient is on oxybutynin for urinary incontinence and we want to initiate an antipsychotic, it's best to choose one that's not on this list, like aripiprazole or risperidone.

Dr. Gray: Exactly. Look at the patient's med list. If an anticholinergic is still the best option for the patient, consider reducing or discontinuing other anticholinergics to keep the overall burden to a minimum.

CHPR: Thank you for your time, Dr. Gray.

Common Examples of Strongly Anticholinergic Medications (Anticholinergic Cognitive Burden Scale Score = 3)

Amitriptyline (Elavil)
Benztropine (Cogentin)
Chlorpheniramine (Chlor-Trimeton)
Chlorpromazine (Thorazine)
Clemastine (Tavist)
Clomipramine (Anafranil)
Clozapine (Clozaril)
Desipramine (Norpramin)
Dimenhydrinate (Dramamine)
Diphenhydramine (Benadryl)
Doxepin (Sinequan)
Doxylamine (Unisom)
Hydroxyzine (Atarax, Vistaril)
Imipramine (Tofranil)
Meclizine (Antivert)
Nortriptyline (Pamelor)
Olanzapine (Zyprexa)
Oxybutynin (Ditropan)
Paroxetine (Paxil)
Promethazine (Phenergan)
Quetiapine (Seroquel)
Thioridazine (Mellaril)
Trifluoperazine (Stelazine)
Trihexyphenidyl (Artane)
Trimipramine (Surmontil)

Source: Boustani M et al, Aging Health *2008;4(3):311–320*

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Note From the Editor-in-Chief

One of the most challenging aspects of hospital psychiatry is the management of acute psychotic agitation. Sometimes we have little choice but to administer sedating medications to a combative patient who is putting others at risk of injury. Which medications work most quickly, safely, and effectively? Dr. Carlat and I combed through the literature to name our top choices. You might be surprised that some widely used agents, like olanzapine and ziprasidone, did not make it onto our list.

Agitation in elderly patients with dementia requires a different approach than agitation in young patients. Dr. Eran Metzger describes nonpharmacologic interventions that are highly effective in reducing agitation in patients with behavioral and psychological symptoms of dementia (BPSD).

Lastly, Dr. Shelly Gray urges us to be mindful of medications' anticholinergic properties because of their potential enduring effects on cognitive functioning, particularly for older patients. Also, watch for the cumulative burden of multiple anticholinergic agents.

Sincerely,
Victoria Hendrick, MD

Research Updates IN PSYCHIATRY

PEDOPHILIA

Rapid-Onset Treatment for Pedophilic Disorder

REVIEW OF: Landgren V et al, *JAMA Psychiatry* 2020;77(9):897–905

Pedophilia—the sexual attraction to prepubescent children—has no clearly effective treatment. A common pharmacologic intervention is gonadotropin-releasing hormone (GRH) agonists, which lower testosterone through receptor desensitization. However, by producing an initial flare-up of testosterone, this treatment can increase aggression and libido, which limits intervention through GRH agonists to supervised correctional settings.

A recent study evaluated the efficacy of degarelix (Firmagon) for pedophilia. In contrast to GRH agonists, degarelix is a GRH *antagonist* and decreases testosterone to castration levels within three days without a testosterone flare-up. In a three-year study, researchers randomly assigned 52 men with pedophilic disorder to one of two conditions: degarelix (n = 26) or placebo (n = 26).

Participants in the treatment group received two subcutaneous doses of 120 mg degarelix acetate; those in the placebo group received similar-appearing injections of saline. All participants kept a diary and underwent structured interviews at baseline, two weeks, and 10 weeks. Researchers measured efficacy outcomes across five domains: pedophilic disorder as defined by DSM-5, sexual preoccupation, impaired self-regulation, low empathy, and self-rated risk of offending.

Participants receiving degarelix scored significantly lower than the placebo group in scores of pedophilic disorder and sexual preoccupation. However, there were no group differences in the domains of impaired self-regulation, low empathy, and self-rated risk of offending. Post-hoc analyses revealed that 58% of the degarelix group denied sexual attraction to minors at 10 weeks—much more than the placebo group, at only 12%.

Adverse events of degarelix included transient injection site reactions and hepatobiliary enzyme level elevations. Two participants (8%) in the degarelix group experienced transient suicidal ideation.

CHPR'S TAKE

Men who commit sexual offenses against children generally report struggling with their sexual urges for 10 years before committing a sexual crime (Knack N et al, *Int Rev Psychiatry* 2019;31(2):181–194). Degarelix did not improve self-regulation or empathy or reduce the self-rated risk of offending, but it reduced sexual attraction to minors, worked quickly, and was well tolerated. Given that we have few options to treat pedophilic disorder, this may be a helpful intervention.

—Anne Li, MD. Dr. Li has disclosed no relevant financial or other interests in any commercial companies pertaining to this educational activity.

ECT

Melatonin vs Memantine for ECT-Related Cognitive Impairment

REVIEW OF: Sarraf N et al, *J Clin Neurosci* 2020;74:146–150

Many patients hesitate to accept ECT because of the treatment's adverse effects on cognitive function. Memantine (Namenda)—an NMDA receptor antagonist approved for the treatment of Alzheimer's disease—has been shown to be more effective than placebo in preventing cognitive impairment due to ECT. A new study compares memantine with melatonin in depressed patients undergoing this treatment.

The authors conducted a randomized, double-blind trial to compare the effects of the two medications on patients with major depression who were undergoing ECT. Patients in the two medication groups were similar in demographic characteristics, duration of major depression, and scores on the Mini-Mental Status Examination (MMSE). All patients received right unilateral ECT with similar stimulus intensity, frequency, and duration. Melatonin was chosen as a comparative treatment because a previous study reported that it appeared effective at reducing ECT-induced cognitive impairment (Hamdieh M et al, *Neurol Psych Brain Res* 2017;24:30–34).

A total of 40 patients were randomized to receive either memantine 5 mg/day (n = 20) or melatonin 3 mg/day (n = 20), starting on the day of the first ECT treatment and ending on the day of the sixth treatment. ECT was administered every other day, and the trial lasted 12 days. The researchers administered the MMSE and item 3 of the MMSE—a measurement of immediate recall—a day before the first ECT treatment and again 24 hours after completion of the last ECT treatment.

At the conclusion of ECT, participants receiving memantine scored significantly higher than their baseline scores on both the MMSE and item 3 of the MMSE ($p = 0.04$ and $p = 0.03$, respectively). In contrast, participants' scores in the melatonin group dropped on both measures compared to their baselines (MMSE, $p = 0.3$, and item 3 of the MMSE, $p = 0.02$).

Study subjects tolerated the medications well. A previous placebo-controlled study similarly found that memantine 5 mg/day reduced cognitive impairment following ECT (Abbasinazari M et al, *Asian J Psychiatr* 2015;15:5–9).

CHPR'S TAKE

Patients are often reluctant to accept ECT because of its effects on cognition. By prescribing memantine 5 mg/day, we may be able to forestall those effects and improve ECT's acceptability. While previous research has found that melatonin also helps mitigate ECT-induced cognitive impairment, this study did not, possibly because the melatonin was administered in the morning and may have caused sedation.

—Anne Li, MD.

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EATING DISORDERS

Faster Refeeding of Patients With Anorexia Nervosa Appears Safe

REVIEW OF: Garber AK et al, *JAMA Pediatrics* 2021;175(1):19–27

The standard of care for inpatients with anorexia nervosa (AN) and dangerously low weight is to start low-calorie refeeding (LCR). LCR starts the refeeding process at a very low calorie count (~1200 kcal/day) and progresses slowly. If malnourished patients move too quickly in this process, they may experience refeeding syndrome—potentially fatal shifts in fluids and electrolytes. The disadvantages of LCR include slow rates of weight gain and lengthy, expensive hospitalizations.

Some retrospective studies support the safety and efficacy of higher-calorie refeeding (HCR), but they have generally not included atypical anorexia nervosa (AAN), a new diagnosis describing patients who demonstrate restrictive behaviors and fear of weight gain but whose weight is in the normal range. Medically unstable patients with AAN comprise nearly one-third of patients in inpatient eating disorder programs.

In this multicenter randomized controlled trial, researchers compared LCR with HCR in medically unstable adolescents and young adults with AN or AAN. Exclusion criteria included BMI less than 60% of median BMI, recent hospitalization, pregnancy, chronic illnesses, suicidality, or psychosis. Participants in the HCR group (n = 60) initially consumed 2000 kcal/day, with a daily increase of 200 kcal, and those in the LCR group (n = 51) initially consumed 1400 kcal/day, with an increase of 200 kcal every other day. Measures of medical stability included heart rate, systolic blood pressure, temperature, and weight. Blood draws occurred daily for the first week and then every other day unless increased frequency was necessary.

The study found that the HCR group achieved medical stability significantly faster than the LCR group (p = 0.01) and had hospital stays that were four days shorter. The HCR group gained an additional 0.8 kg compared to the LCR group. However, the proportion of patients achieving medical stability did not differ between groups. The HCR group's shorter hospitalizations resulted in savings of over $19,000 in hospital charges per participant.

The study's findings cannot be generalized to extremely malnourished anorexic patients as they were not included in this study.

CHPR'S TAKE

HCR appears safe and effective both for patients with AN as well as those with AAN. Compared to LCR, HCR stabilizes patients faster, resulting in shorter and less costly hospitalizations.

—Susie Morris, MD. Dr. Morris has disclosed no relevant financial or other interests in any commercial companies pertaining to this educational activity.

DEPRESSION

Can We Treat Depression by Targeting Inflammation?

REVIEW OF: Zazula R et al, *Aust N Z J Psychiatry* 2021;55(8):784–798

Recent data suggest inflammation may play a role in depression, prompting research into the efficacy of minocycline—a tetracycline antibiotic with anti-inflammatory effects—as an augmentation agent in the treatment of major depressive disorder (MDD).

This study was a pooled data analysis from two multisite, double-blinded, placebo-controlled trials of minocycline 200 mg/day taken over 12 weeks. Participants were healthy adults who had a diagnosis of non-treatment-resistant, moderate-to-severe MDD and had already been receiving treatment for depression for the prior 2–6 weeks. Treatments included antidepressants (86%–89%), antipsychotics (29%–30%), and benzodiazepines (36%–40%).

Patients (n = 112) who were randomized to adjunctive minocycline (n = 57) were twice as likely as those on placebo (n = 55) to show a response to treatment, defined as a reduction in the Hamilton Rating Scale for Depression (HAM-D) score > 50%. They were also twice as likely to experience remission, defined as a HAM-D score < 7. Specifically, 57% of the minocycline group showed a response to treatment and 32% achieved remission. In comparison, 23% of the placebo group responded to treatment and 11% experienced remission.

Rates of adverse effects were comparable in the minocycline and placebo groups. Interestingly, the best responders were participants who used pain medications, had a longer duration of illness, and were older.

Minocycline is affordable, readily available, and has a low likelihood of producing antibiotic resistance (Husain MI et al, *J Psychopharmacol* 2017;31(9):1166–1175). Be cautious when prescribing to women of reproductive age: Minocycline reduces the efficacy of hormonal contraceptives and should not be used during pregnancy (category D).

CHPR'S TAKE

Consider adding minocycline to your list of augmentation strategies for the treatment of major depression. It's a safe and well-tolerated treatment that might be particularly effective for depressed patients with pain and longer duration of illness.

—Christina Guest, MD. Dr. Guest has disclosed no relevant financial or other interests in any commercial companies pertaining to this educational activity.

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CME Post-Test

To earn CME or CE credit, log on to www.TheCarlatReport.com with your username and password to take the post-test. You must answer 75% of the questions correctly to earn credit. You will be given two attempts to pass the test. Tests must be completed within a year from each issue's publication date. The Carlat CME Institute is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. The Carlat CME Institute is also approved by the American Psychological Association to sponsor continuing education for psychologists. Carlat CME Institute maintains responsibility for this program and its content. The Carlat CME Institute designates this enduring material educational activity for a maximum of two (2) *AMA PRA Category 1 Credits*™ or 2 CE credits for psychologists. Physicians or psychologists should claim credit commensurate only with the extent of their participation in the activity.

For those seeking ABPN Self-Assessment (MOC) credit, a pre- and post-test must be taken online at http://thecarlatcmeinstitute.com/self-assessment/

This page is intended as a study guide. Please complete the test online at www.TheCarlatReport.com. Learning Objectives (LO) are listed on page 1.

1. Which two nonpharmacologic interventions have the best efficacy evidence for reducing agitation in patients with dementia (LO #1)?
   [ ] a. Meditation and Reiki
   [ ] b. Education and music therapy
   [ ] c. Music therapy and meditation
   [ ] d. Relaxation therapy and yoga
2. A study found that daily use of anticholinergic medications increased the risk for dementia within three years by close to (LO #2):
   [ ] a. 10%
   [ ] b. 25%
   [ ] c. 35%
   [ ] d. 50%
3. In a 2020 study that compared degarelix with placebo, results showed that (LO #3):
   [ ] a. Scores for impaired self-regulation decreased
   [ ] b. Scores for empathy increased
   [ ] c. Scores for sexual preoccupation decreased
   [ ] d. Scores for risk of offending decreased
4. What are some of the limitations of using quetiapine for patients with Parkinson's or Lewy body dementia (LO #1)?
   [ ] a. It can exacerbate extrapyramidal symptoms
   [ ] b. It can be addictive and can worsen insomnia
   [ ] c. It can produce sedation and orthostatic hypotension
   [ ] d. It requires frequent blood draws
5. In a 2020 study, what dosage of memantine was found to have a beneficial effect on ECT-related cognitive impairment (LO #3)?
   [ ] a. 1.5 mg/day
   [ ] b. 5 mg/day
   [ ] c. 7 mg/day
   [ ] d. 10 mg/day
6. In a meta-analysis by Wilson and colleagues, what were the rates of extrapyramidal symptoms in patients given haloperidol plus lorazepam (LO #1)?
   [ ] a. 3%
   [ ] b. 5%
   [ ] c. 25%
   [ ] d. 84%
7. In order to keep the Anticholinergic Cognitive Burden Scale score low, which psychotropic would be your first choice (LO #2)?
   [ ] a. Benztropine
   [ ] b. Risperidone
   [ ] c. Clozapine
   [ ] d. Chlorpromazine
8. What is the average time to peak concentration of Zyprexa Zydis (LO #1)?
   [ ] a. 2.5 hours
   [ ] b. 3.5 hours
   [ ] c. 4.4 hours
   [ ] d. 4.5 hours

Medications to Rapidly Treat Psychotic Agitation

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Droperidol (Inapsine)

Droperidol was a reasonable second-line option in the past, but its use was discontinued due to concern that it causes QTc prolongation. However, recent studies have found that its QTc prolongation is no greater than that caused by other antipsychotic medications (Khokar MA et al, *Cochrane Database Syst Rev* 2016;12:CD002830). A recent randomized controlled study found that IM droperidol was more effective than IM lorazepam or IM ziprasidone, with less respiratory depression (Martel ML et al, *Acad Emerg Med* 2021;28(4):421–434). Another advantage of droperidol is that its onset of efficacy is fast, within 5–10 minutes; in comparison, haloperidol typically takes about 20–30 minutes to demonstrate an effect. We expect that droperidol will make a comeback, but the FDA's black box warning (which still has not been revised) will probably limit its use.

Quetiapine (Seroquel)

There are no RCT data on oral quetiapine for agitation, except for one study showing quetiapine 200 mg/day was effective for agitation due to dementia (Zhong KX et al, *Curr Alzheimer Res* 2007;4(1):81–93). Quetiapine's high rate of orthostatic hypotension makes it less than ideal when working in the ED, as patients are often volume depleted (Wilson et al, 2012). We monitor blood pressure closely when we prescribe it for our elderly patients. In our experience, at doses of 100–300 mg, quetiapine is helpful in reducing agitation among patients who are willing to take oral medications. Some patients will ask for quetiapine specifically because it has helped them calm down in the past, and it is reasonable to honor such requests.

Benzodiazepines

Benzodiazepine monotherapy for agitation is highly effective. Studies from the 1990s show that IM lorazepam is equivalent to IM haloperidol or IM haloperidol plus benztropine (Battaglia J et al, *Am J Emerg Med* 1997;15(4):335–340). Lorazepam is the most commonly used benzo for agitation because it rarely causes hypoxia, even when combined with haloperidol or risperidone. Midazolam IM is

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Medications to Rapidly Treat Psychotic Agitation

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faster acting but is best avoided in psychiatric units as it has a short half-life—patients may require multiple doses, placing them at risk for respiratory suppression.

Other agents

Promethazine (Phenergan)
While promethazine has been used to counter extrapyramidal symptoms from haloperidol, we believe diphenhydramine or benztropine are better choices. Promethazine has antidopaminergic properties and has been linked with neuroleptic malignant syndrome (Mendhekar DN and Andrade CR, *Aust N Z J Psychiatry* 2005;39(4):310).

Hydroxyzine (Atarax), diphenhydramine (Benadryl)
These anticholinergic agents are sometimes administered orally for mild agitation. However, no controlled studies have examined their efficacy. Since they are sedating and relatively safe, we see no reason not to use these for mild levels of agitation. However, be aware that they will exacerbate anticholinergic and cardiac conduction side effects when used in combination with antipsychotic medications.

CHPR VERDICT: The Haldol cocktail is still number one for agitation, but in its "skinnier" version—Haldol and Ativan minus the Benadryl.