Ms. M, age 71, was diagnosed with Alzheimer’s disease several months ago and her clinical presentation and Mini-Mental Status Exam score of 22 indicates mild dementia. In addition to chronic medications for hypertension, Ms. M has been taking lorazepam, 1 mg, 3 times daily, for >15 years for unspecified anxiety.

Ms. M becomes more confused at home over the course of a few days, and her daughter brings her to her primary care physician for evaluation. Recognizing that benzodiazepines can contribute to delirium, the physician discontinues lorazepam. Three days later, Ms. M’s confusion worsens, and she develops nausea and a tremor. She is taken to the local emergency department where she is admitted for benzodiazepine withdrawal and diagnosed with a urinary tract infection.

Because dementia is a strong risk factor for developing delirium, withdrawing or changing medications to rule out delirium in patients with mild dementia, such as Ms. M, is a common clinical scenario. Although delirium often is multifactorial, medications are frequent predisposing and precipitating factors and contribute to approximately 12% to 39% of delirium cases. A recently initiated medication is more likely to be a precipitant for delirium; however, long-term medications can contribute to delirium and should be evaluated to determine if they can be discontinued in a patient with symptoms consistent with delirium.

Consider withdrawing or replacing medications that are strongly implicated in causing delirium with another medication for the same indication with a lower potential for precipitating or exacerbating delirium. Benzodiazepines and opioids are medications most clearly associated with an increased risk for delirium, although medications with significant anticholinergic properties have been associated with increased severity of delirium in patients with and without underlying dementia and are consistently cited as common causes of drug-induced delirium. 

Table 1 lists medications that are known to be anticholinergic. The 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults added non-benzodiazepine receptor agonist hypnotics

Practice Points
- Medications strongly implicated in causing delirium should be withdrawn or switched.
- Take into account dosage and duration of treatment, medication half-life, nature of withdrawal symptoms, and care setting when determining how fast to taper a medication.
- More aggressive tapering over 2 or 3 days can be considered for inpatients, while gradual tapering might be necessary to ensure safety in outpatients.

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Disclosure
The author reports no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.
(ie, zolpidem, zaleplon, and eszopiclone) as medications to avoid in patients who have dementia because of adverse CNS effects. These drugs also would be appropriate targets for withdrawal or modification in patients with mild dementia and suspected delirium.

In general, there are no firm rules for how to taper and discontinue potentially deliriogenic medications, as both the need to taper and the best strategy for doing so depends on a number of factors and requires clinical judgement. When determining how quickly to withdraw a potentially offending medication in a patient with suspected delirium, clinicians should consider:

**Dosage and duration of treatment.** Consider tapering and discontinuing benzodiazepines in a patient who is taking more than the minimal scheduled dosages for ≥2 weeks, especially after 8 weeks of scheduled treatment. Consider tapering opioids in a patient taking more than the

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**Table 1**

**Medications with significant anticholinergic activity**

<table>
<thead>
<tr>
<th>Medication class</th>
<th>Markedly anticholinergic medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticholinergics</td>
<td>Atropine, Benztropine, Scopolamine, Trihexyphenidyl, Urinary indications: Darifenacin, Flavoxate, Oxybutynin, Tolterodine, Gastrointestinal: Dicyclomine, Hyoscyamine, Propantheline</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Amitriptyline, Desipramine, Doxepin, Imipramine, Nortriptyline, Protriptyline, Trimipramine</td>
</tr>
<tr>
<td>Antiemetics</td>
<td>Promethazine</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>Brompheniramine, Chlorpheniramine, Clemastine, Clomipramine, Dimenhydrinate, Diphenhydramine, Hydroxyzine, Meclizine, Pyrilamine</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>Chlorpromazine, Clozapine, Thioridazine</td>
</tr>
<tr>
<td>Skeletal muscle relaxants</td>
<td>Orphenadrine</td>
</tr>
</tbody>
</table>

Source: Reference 5

---

**Table 2**

**Half-lives of commonly used benzodiazepines and opioids**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Elimination half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benzodiazepines</strong></td>
<td></td>
</tr>
<tr>
<td>Diazepam</td>
<td>44 to 48 hours (active metabolite: 100 hours)</td>
</tr>
<tr>
<td>Chlordiazepoxide</td>
<td>7 to 28 hours (active metabolite: 14 to 95 hours)</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>17 to 60 hours</td>
</tr>
<tr>
<td>Temazepam</td>
<td>4 to 18 hours</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>Approximately 12 hours</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>Approximately 11 hours (16 hours in geriatric patients)</td>
</tr>
<tr>
<td><strong>Opioids</strong></td>
<td></td>
</tr>
<tr>
<td>Methadone</td>
<td>9 to 87 hours</td>
</tr>
<tr>
<td>Fentanyl (transdermal patch)</td>
<td>20 to 27 hours</td>
</tr>
<tr>
<td>Oxycodeone</td>
<td>Approximately 4 hours</td>
</tr>
<tr>
<td>Hydrocodeone</td>
<td>3 to 4 hours</td>
</tr>
<tr>
<td>Morphine</td>
<td>2 to 4 hours</td>
</tr>
<tr>
<td>Codeine</td>
<td>Approximately 3 hours</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>2 to 3 hours</td>
</tr>
</tbody>
</table>

Source: Lexicomp
minimal scheduled dosage for more than a few days. When attempting to rule out delirium, taper opioids as quickly and as safely possible, with a recommended reduction of ≤20% per day to prevent withdrawal symptoms. In general, potentially deliriogenic medications can be discontinued without tapering if they are taken on a non-daily, as-needed basis.

The half-life of a medication determines both the onset and duration of withdrawal symptoms. Withdrawal occurs earlier when discontinuing medications with short elimination half-lives (usually within 1 to 2 days) and might not emerge until 3 to 8 days after discontinuation for medications with a half-life >24 hours. Many resources suggest switching to an agent

**Table 3**

<table>
<thead>
<tr>
<th>Medication class</th>
<th>Withdrawal symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepines</td>
<td>Anxiety, Delirium, Depressed mood, Diaphoresis, Insomnia, Irritability, Nausea, Psychomotor agitation, Psychosis, Seizures, Tachycardia, Tinnitus, Tremor</td>
</tr>
<tr>
<td>Opioids</td>
<td>Anxiety/irritability, Diaphoresis, Diarrhea, Joint/muscle pain, Lacrimation, Nausea, Piloerection, Pupillary dilation, Restlessness, Rhinorhea, Sneezing, Tremor, Vomiting, Yawning</td>
</tr>
<tr>
<td>Anticholinergics</td>
<td>Agents with anticholinergic effects may be associated with additional withdrawal symptoms depending on the action of the drug at non-muscarinic receptors, but anticipated symptoms of cholinergic rebound include: Agitation, Diarrhea, Headache, Nausea, Restlessness, Sweating, Vomiting</td>
</tr>
</tbody>
</table>

**Related Resources**


**Drug Brand Names**

- Acetaminophen/codeine: Tylenol No. 3
- Alprazolam: Xanax
- Amitriptyline: Elavil
- Atropine: AtroPen
- Benztpine: Cogentin
- Brompheniramine: J-Tan PD
- Chlordiazepoxide: Librium
- Chlorpromazine: Thorazine
- Clemastine: Tavist
- Clomipramine: Anafranil
- Clonazepam: Klonopin
- Clozapine: Clozaril
- Darifenacin:Enablex
- Desipramine: Norpramin
- Diazepam: Valium
- Dicyclomine: Bentyl
- Dimenhydrinate: Dramamine
- Diphenhydramine: Benadryl
- Doxepin: Sinequan
- Etopicon: Lunistra
- Fenotyl (transdermal patch): Duragesic
- Flavoxate: Urispas
- Hydrocodone: Hysingla, Zohydro
- Hydromorphone: Dilaudid
- Hydroxyzine: Atarax, Vistaril
- Hyoscyamine: Levsin
- Impiramine: Tofranil
- Lorazepam: Ativan
- Meclizine: Antvert
- Methadone: Dolophine
- Morphone: MS Contin
- Nortriptlyline: Pamelor
- Orphenadrine: Norflex
- Oxbyutynin: Ditropan
- Oxycodone: Oxycontin, Roxicodone
- Promethazine: Phenergan
- Propantheline: Pro-Banthine
- Prometryline: Vivactil
- Pyrilamine: Ru-Hist-D
- Scopolamine: Transderm Scop
- Temazepam: Restoril
- Thiadamine: Mellaril
- Tolerodine: Detrol
- Trihexyphenidyl: Artane
- Trimipramine: Surmontil
- Zaleplon: Sonata
- Zolpidem: Ambien, Edluar, Intermezzo

**Clinical Point**

Generally, potentially deliriogenic medications can be discontinued without tapering if taken on a non-daily, as-needed basis.
Clinical Point

Because close monitoring is easier during inpatient care, more aggressive tapering over 2 to 3 days generally can be considered.

Nature of withdrawal symptoms. In patients with suspected delirium, tapering over weeks or months—often recommended for sedative-hypnotics and opioids—is not a realistic option; however, stopping the medication abruptly can lead to intolerable withdrawal symptoms (Table 3, page 43). Avoiding withdrawal from benzodiazepines is particularly important because of the potential for severe complications, including seizures and delirium, and possibly death. Withdrawal seizures are especially common with alprazolam because of its short half-life, so additional caution is warranted when tapering and discontinuing this medication. Withdrawal from opioids or anticholinergics generally is not life-threatening, but a brief taper of these medications can be considered, particularly when high dosages have been prescribed, to minimize patient discomfort.

Care setting. When tapering and discontinuing a medication, regularly monitor patients for withdrawal symptoms; slow or temporarily stop the taper if withdrawal symptoms occur. Because close monitoring is easier in an inpatient vs an outpatient care setting, more aggressive tapering over 2 to 3 days generally can be considered, although more gradual tapering might be prudent to ensure safety of outpatients.

References