

Ruling out delirium: Therapeutic principles of withdrawing and changing medications

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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,¹ 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.^{1,2} A recently initiated medication is more likely to be a precipitant for delirium; however, long-term medications can con-

tribute to delirium and should be evaluated to determine if they can be discontinued in a patient with symptoms consistent with delirium.¹

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,³ although medications with significant anticholinergic properties have been associated with increased severity of delirium in patients with and without underlying dementia⁴ and are consistently cited as common causes of drug-induced delirium.^{1,2} **Table 1⁵** (page 42) 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



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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- Medications strongly implicated in causing delirium **should be withdrawn or switched.**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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Clinical Point

Taper opioids as quickly and as safely as possible, with a recommended reduction of $\leq 20\%$ per day to prevent withdrawal

Table 1

Medications with significant anticholinergic activity

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

Source: Reference 5

(ie, zolpidem, zaleplon, and eszopiclone) as medications to avoid in patients who have dementia because of adverse CNS effects.⁶ 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

Table 2

Half-lives of commonly used benzodiazepines and opioids

Medication	Elimination half-life
Benzodiazepines	
Diazepam	44 to 48 hours (active metabolite: 100 hours)
Chlordiazepoxide	7 to 28 hours (active metabolite: 14 to 95 hours)
Clonazepam	17 to 60 hours
Temazepam	4 to 18 hours
Lorazepam	Approximately 12 hours
Alprazolam	Approximately 11 hours (16 hours in geriatric patients)
Opioids	
Methadone	9 to 87 hours
Fentanyl (transdermal patch)	20 to 27 hours
Oxycodone	Approximately 4 hours
Hydrocodone	3 to 4 hours
Morphine	2 to 4 hours
Codeine	Approximately 3 hours
Hydromorphone	2 to 3 hours

Source: Lexicomp

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 3

Withdrawal symptoms of deliriogenic medications

Medication class	Withdrawal symptoms
Benzodiazepines	Anxiety Delirium Depressed mood Diaphoresis Insomnia Irritability Nausea Psychomotor agitation Psychosis Seizures Tachycardia Tinnitus Tremor
Opioids	Anxiety/irritability Diaphoresis Diarrhea Joint/muscle pain Lacrimation Nausea Piloerection Pupillary dilation Restlessness Rhinorrhea Sneezing Tremor Vomiting Yawning
Anticholinergics	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

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 $\leq 20\%$ per day to prevent withdrawal symptoms. In general, potentially

Related Resources

- Lader M, Tylee A, Donoghue J. Withdrawing benzodiazepines in primary care. *CNS Drugs*. 2009;23(1):19-34.
- U.S. Department of Veterans Affairs; Department of Defense. Effective treatments for PTSD: helping patients taper from benzodiazepines. www.va.gov/PAINMANAGEMENT/docs/OSI_6_Toolkit_Taper_Benzodiazepines_Clinicians.pdf.
- U.S. Department of Veterans Affairs; Department of Defense. Tapering and discontinuing opioids. www.healthquality.va.gov/guidelines/Pain/cot/OpioidTaperingFactSheet23May2013v1.pdf.

Drug Brand Names

Acetaminophen/codeine • Tylenol No. 3	Hydromorphone • Dilaudid
Alprazolam • Xanax	Hydroxyzine • Atarax, Vistaril
Amitriptyline • Elavil	Hyoscyamine • Levsin
Atropine • AtroPen	Imipramine • Tofranil
Benzotropine • Cogentin	Lorazepam • Ativan
Brompheniramine • J-Tan PD	Meclizine • Antivert
Chlordiazepoxide • Librium	Methadone • Dolophine
Chlorpheniramine • Chlor-Trimeton	Morphine • MS Contin
Chlorpromazine • Thorazine	Nortriptyline • Pamelor
Clemastine • Tavist	Orphenadrine • Norflex
Clomipramine • Anafranil	Oxybutynin • Ditropan
Clonazepam • Klonopin	Oxycodone • Oxycontin, Roxicodone
Clozapine • Clozaril	Promethazine • Phenergan
Darifenacin • Enablex	Propranolol • Pro-Banthene
Desipramine • Norpramin	Protriptyline • Vivactil
Diazepam • Valium	Pyrilamine • Ru-Hist-D
Dicyclomine • Bentyl	Scopolamine • Transderm Scop
Dimenhydrinate • Dramamine	Temazepam • Restoril
Diphenhydramine • Benadryl	Thioridazine • Mellaril
Doxepin • Sinequan	Tolterodine • Detrol
Eszopiclone • Lunesta	Trihexyphenidyl • Artane
Fentanyl (transdermal patch) • Duragesic	Trimipramine • Surmontil
Flavoxate • Urispas	Zaleplon • Sonata
Hydrocodone • Hysingla, Zohydro	Zolpidem • Ambien, Edluar, Intermezzo

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

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

with a longer half-life when tapering and discontinuing benzodiazepines or opioids to provide a smoother withdrawal (*Table 2, page 42*). When ruling out delirium in patients with mild dementia, particularly in a geriatric patient with reduced medication clearance, avoid switching to a longer-acting benzodiazepine or opioid because this could prolong delirium symptoms.

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

1. Inouye SK. Delirium in older persons. *N Engl J Med.* 2006;354(11):1157-1165.
2. Alagiakrishnan K, Wiens CA. An approach to drug induced delirium in the elderly. *Postgrad Med J.* 2004;80(945):388-393.
3. Clegg A, Young JB. Which medications to avoid in people at risk of delirium: a systematic review. *Age Aging.* 2010;40(1):23-29.
4. Han L, McCusker J, Cole M, et al. Use of medications with anticholinergic effect predicts clinical severity of delirium symptoms in older medical inpatients. *Arch Intern Med.* 2001;161(8):1099-1105.
5. Carnahan RM, Lund BC, Perry PJ, et al. The Anticholinergic Drug Scale as a measure of drug-related anticholinergic burden: associations with serum anticholinergic activity. *J Clin Pharmacol.* 2006;46(12):1481-1486.
6. American Geriatrics Society 2015 Beers Criteria Update Expert Panel. American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. *J Am Geriatr Soc.* 2015;63(11):2227-2246.