



PHARMACOLOGY

A MODIFIABLE RISK
FACTOR FOR DELIRIUM



Pharmacology - A Modifiable Risk Factor for Delirium

TO BE USED BY



NURSES



PROVIDERS

Medications can cause delirium

Medications can be used inappropriately to treat/manage the symptoms of hyperactive delirium resulting in:

- ✓ Prolonged delirium (hyperactive or hypoactive)
- ✓ Falls
- ✓ Dysphagia
- ✓ Oversedation
- ✓ Prolonged hospital stay and readmission

Potentially Inappropriate Medications (PIMs) known to be deliriogenic in high risk populations

- ✓ Anticholinergics¹
- ✓ Antipsychotics¹
- ✓ Benzodiazepines¹
- ✓ Corticosteroids¹
- ✓ H2 Receptors Antagonists¹
 - Cimetadine
 - Famotidine
 - Nizatidine
- ✓ Benzodiazepine receptor agonist hypnotics (z-drugs)¹
 - Eszopiclone
 - Zaleplon
 - Zolpidem
- ✓ Opioids¹

¹Beers Criteria, 2023, AGS

PPIs²

Benzodiazepines²

NSAIDs²

Non-selective beta blockers²

Tricyclic Antidepressants²

Evidence for deliriogenic PIMs

1. Benzodiazepines are strongly predictive of delirium.³
2. Anticholinergic medications increase the risk of hospitalization for altered mental status.⁴

Anticholinergic medications

- ✓ **Antihistamines** (brompheniramine, chlorpheniramine, ciproheptadine, diphenhydramine, doxylamine, hydroxyzine, meclizine).
- ✓ **Antidepressants** (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline).
- ✓ **Antipsychotic medicines** (chlorpromazine, clozapine, mesoridazine, olanzapine, quetiapine, thioridazine).
- ✓ **Muscle relaxants** (cyclobenzaprine, donatrolene, orphenadrine).
- ✓ **GI medicines** (diphenoxylate, atropine, belladonna, clidinium, chlordiazepoxide, dicyclomine, hyoscyamine, propantheline, prochlorperazine, promethazine, cimetidine, ranitidine).
- ✓ **Antivertigo medicines** (meclizine, scopolamine).
- ✓ **Urinary agents** (flavoxate, oxybutynin, probantheline, tolterodine).
- ✓ **Parkinson's medicines** (benztropine, biperiden, trihexyphenidyl).

See Reference card D in Delirium Delphi Algorithms ["Delirium Algorithm Reference Card D: Drugs with strong anticholinergic effects"](#)

² Stopp Start, 2015, O'Mahony

³ Kawada et al, 2021, PLOS

⁴ Kalisch, Ellett et al, 2014, JAGS

Stopping these classes of medications/substances abruptly can cause delirium

1. Acetylcholinesterase inhibitors
2. Anti-epileptics
3. Antipsychotics
4. Benzodiazepines
5. Alcohol
5. Nicotine
6. Opioids/narcotics
7. Sedative/hypnotics
8. SSRIs
9. Steroids

Can medication prevent delirium? **NO**

- Antipsychotics do not prevent delirium.⁵
- Single dose ketamine intra-operatively does not prevent delirium.⁶
- Use of statin as a protective measure is unclear, more research needed.
- Despite early evidence that ramelteon might prevent delirium, subsequent studies have cast doubt on its delirium preventing effect.^{7,8}
- IV dexmedetomidine has shown promise in preventing delirium among critically ill patients.⁹

Can medication treat/resolve delirium? **NO**

- Antipsychotics do not decrease delirium duration, severity, hospital or ICU LOS.⁵
- Statins do not decrease delirium duration, ICU or hospital LOS or mortality.¹⁰
- Single dose Ketamine intra-operatively does not decrease delirium ICU or hospital LOS or mortality.⁶



⁵ Neufeld et al, 2016, JAGS

⁶ Avidan et al, 2017, Lancet

⁷ Hatta et al, 2014, JAMA Psychiatry

⁸ Dang et al. 2023, J Acad Consult Liaison Psychiatry

⁹ Skrobik et al, 2018, Am J Respir Crit Care Med

¹⁰ Devlin et al, 2018, Society of Critical Care Medicine

What medications may be used to alleviate the neuropsychiatric disturbances of delirium?

- Patients experiencing **extreme distress** due to symptoms of delirium (anxiety, fearfulness, hallucinations, delusions) and may be **harmful to self or others** may benefit from SHORT TERM use of haloperidol or atypical antipsychotics.¹¹
- **Benzodiazepines** are generally **contraindicated** except in terminal delirium, active seizure, alcohol dependence or in those using benzodiazepines regularly.
- Haloperidol, olanzapine and risperidone are **contraindicated** in persons with Parkinson's disease or Lewy body dementia.
- Valproic acid IV or PO 250 mg every 12 hours may be an alternative to antipsychotics. Some evidence of benefit, further research needed.¹²
- Dexmedetomidine IV may benefit patients unable to wean off mechanical ventilation by decreasing agitation.¹³
- **Be sure medications are discontinued after extreme symptoms subside.**



¹¹ Devlin et al, 2018, Society of Critical Care Medicine

¹² Crowley et al, 2018, Crit Care Med

¹³ Reade et al, 2016, JAMA

Summary of the role of medication in delirium

- Potentially inappropriate medications (PIMs) can **cause** delirium.
- **Abrupt withdrawal** of selected medications can cause delirium.
- Current evidence does **not** support the routine use of medications to prevent or treat delirium.
- **Selected patients** with severe neuropsychiatric disturbances of delirium may benefit from short term use of medication, including use of antipsychotics.
- **Nonpharmacological measures** should be tried first and then in combination with medications to decrease distress.
- Studies show conflicting evidence regarding the role of statins and ramelteon in the prevention of delirium.
- High quality randomized, controlled trials needed to explore the benefit of dexmedetomidine and valproic acid in delirium management.

Deprescribing: Reducing or stopping PIMs that may no longer benefit or create harm for the patient

Limitations/Challenges	Strategies
Difficult in acute care	Perform medication review during care transitions
Patient resistance	Provider and pharmacist partnership
Prescribing inertia: auto renew med even if initial indication no longer present	Involve patient: <ul style="list-style-type: none"> • Reach informed decisions • Review medications (continue vs discontinue) • Consider patient preferences, life expectancy • Reduce pill burden • Reduce adverse drug reactions
Medication leapfrog: prescribe med to treat the side effects of another med	

