Spreading Choosing Wisely® Campaign in Maine: Focus on Reducing Benzodiazepine Use in Patients over 65 Years of Age
Spreading Choosing Wisely in Maine: 2015-17

- Focus on messaging to public in two communities
  - Bath/Brunswick
  - Greater Bangor
- Start conversations in clinical settings
- Foster community awareness to promote quality of care, improve safety, and reduce unnecessary care
Spreading CW in Maine High Priority Focus Areas

- Use of Antibiotics for acute bronchitis in older adults
- Advanced imaging for low back pain
- **Use of benzodiazepines in older adults > 65 years**

Goal: Reduce unnecessary use of tests and treatments to achieve a 20% utilization reduction for the three high priority areas.
### Ten Things Physicians and Patients Should Question

<table>
<thead>
<tr>
<th>Rule</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Don’t recommend percutaneous feeding tubes in patients with advanced dementia; instead offer oral or enteral feeding.</td>
</tr>
<tr>
<td>2</td>
<td>Don’t use antipsychotics as the first choice to treat behavioral and psychological symptoms of dementia.</td>
</tr>
<tr>
<td>3</td>
<td>Avoid using medications other than metformin to achieve hemoglobin A1c&lt;7.5% in most older adults; moderate control is generally better.</td>
</tr>
<tr>
<td>4</td>
<td>Don’t use benzodiazepines or other sedative-hypnotics in older adults as first choice for insomnia, agitation or delirium.</td>
</tr>
<tr>
<td>5</td>
<td>Don’t use antimicrobials to treat bacteriuria in older adults unless specific urinary tract symptoms are present.</td>
</tr>
</tbody>
</table>

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**Falls/Hip Fractures Confusion MVA**
Disclosures

The presenters have nothing to disclose
The Facts

You can’t set her free. But you can help her feel less anxious.

Serax® (oxazepam)

To help you relax and feel better.
“Mother’s Little Helper”

Sweet, refreshing... VALIUM

ALCOHOL

Roughly 9 out of 10 older adults who use benzodiazepines on a long-term basis have their prescriptions written exclusively by primary care physicians or other non-psychiatrists.
IMS Health’s 2011 statistics

Psychotropics ranked by sales:

#1: Xanax
#4: Ativan

Numbers prescribed:

- Xanax: 49 million
- Ativan: 27.6 Million
- Klonopin: 26.9 Million
- Valium: 15 Million

Benzos are the 10th most commonly prescribed therapeutic class...

**BUT, benzos are not first-line therapy for ANY common psychiatric disorder**

30% of nursing home patients receive benzodiazepines. In Maine:
- 677,000 benzodiazepine and 179,000 “z drug” prescriptions were dispensed for greater than 155,000 individuals in 2013.
- Age > 60: increased from 18% in 2011 to 21% in 2014.

Illegitimate Benzo Use

• 7.9% took a benzo *illegitimately* 2011

• 20.4 million over 12: lifetime misuse of a benzo


Diversion

From 2014 federal, state, and local forensic labs:

1. 43,000 oxycodone
2. 40,747 alprazolam
3. 33,132 hydrocodone
4. 15,209 buprenorphine
5. 11,797 clonazepam
6. 5559 methadone
7. 5446 diazepam

- Alprazolam #1, hydrocodone #2, oxycodone #3 in 2006 DEA Office of Diversion Control report
- Alprazolam increased 75% from 2001 to 2005, clonazepam doubled
- Diazepam, alprazolam, morphine and oxycodone had the highest ratios of drugs reported in forensic labs per prescriptions
How do Benzodiazepines Work?

Benzodiazepines potentiate the effects of endogenous GABA, the main inhibitory neurotransmitter.

Alcohol potentiates the effects of endogenous GABA, the main inhibitory neurotransmitter.

Benzo Activity at GABA Receptors

• GABA is the system’s “brake”
• Main inhibitory neurotransmitter
  • 50% of the inhibitory synapses
• Consequences of GABA inhibition includes decreased
  • Excitatory transmission
  • NE, 5HT, ACh, DA
  • Anxiety
  • Alertness
  • Emotional response
  • Endocrine secretion
  • Muscle tone
  • Memory
  • New learning

GABA + benzo = stronger brake
Clinical Uses

reduce
psychic tension

Valium
(diazepam)
Short-Term Uses

- Excessive anxiety
- Muscle relaxation
- Alcohol or benzo withdrawal
- Insomnia
- Acute psychosis

- Acute mania
- Acute agitation
- Sedation for office procedure
- Catatonia
- Seizures and neurological disorders
Continuing a Benzo Beyond Four Weeks

- May result in:
  - Interference with preferred 1st line treatments
  - Loss of effectiveness
  - Tolerance
  - Dependence
  - Withdrawal
  - Persistent adverse effects

The risk of dependence led the Committee on Safety of Medicines and the Royal College of Psychiatrists to recommend that benzodiazepines should be restricted to severe need and that treatment should be at the lowest dose possible and not be continued beyond 4 weeks.

Lader, M. Benzodiazepines revisited—will we ever learn? *Addiction* 2011;106: 2086–2109.

Adverse Effects and Contraindications
• Sedation
• Psychomotor effects
  • Impaired simple repetitive tasks
  • Reduced speed of execution
  • Dose related
  • Persists up to 1 yr after LT use
• Disinhibition
• Psychological dependence
• Addiction

• Respiratory depression
  • Do not use in myasthenia gravis, sleep apnea, bronchitis, or COPD
• Accidents and Injuries
  • 60-80% increase in MVA
  • 7.7 increase in accident with alcohol
  • 50% increase in elderly hip fracture
    • Overall odds ratio 1.7
      • 2.2 ≥80
      • 1.3 <80
• Causes 1800 deaths annually in >80

Lader, M. Benzodiazepines revisited—will we ever learn? Addiction 2011;106: 2086–2109.
Haroutunian HL. Benzodiazepine Dependence/Borderline Personality Disorder. Audio-Digest Psychiatry 2012; 46(9).
Lader, M. Benzodiazepines revisited—will we ever learn? Addiction 2011;106: 2086–2109.
Ashton M. Benzodiazepines: How they work and how to withdraw. 2002.
Issues with Long-Term Benzo Use

**Tolerance**

- Long term use may decrease efficacy of GABA-A receptor
- Hypnotic rapidly
- Anxiolysis slowly
  - But little evidence retain efficacy > 6mos
  - Often continued to suppress withdrawal states which mimic anxiety
  - Dose escalation maintains dependency

**Withdrawal**

- When discontinued, a down regulated inhibitory system is left and a hyper-excitatatory physiologic system results
- Onset varies based on half-life
- Symptoms
  - SEIZURES
  - DELIRIUM
  - ANXIETY
  - INSOMNIA
  - Increased Temp, BP, Pulse, Respirations
  - Tremors, Restlessness, Hyperreflexia
  - Disorientation
  - Psychosis
  - Irritable, agitated

Ashton H. Benzodiazepines: How they work and how to withdraw. 2002.
Cognitive Effects

Inhibits learning
Impairs anterograde memory
Dose related Effects after stopping benzo
Impairment did not fully resolve within 6 months
Increased risk of dementia (controversial)
Majority of studies demonstrate possible relationship between BZD use and dementia
Cannot control for all confounders, NOT cause‐effect relationship
Recall acutely, then unable to recall later

Lader, M. Benzodiazepines revisited—will we ever learn? Addiction 2011;106: 2086–2109.
Haroutunian HL. Benzodiazepine Dependence/Borderline Personality Disorder. Audio-Digest Psychiatry 2012; 419(9).
Drug-related deaths

Benzodiazepines: OR=7.2
Opioid only: OR=3.4
1rx for opioid + BZD: OR = 14.9

Contraindications

- Pregnancy
- Hypoxia and hypoventilation
  - Asthma
  - Sleep apnea
  - COPD
  - CHF
  - Cardiopulmonary diagnosis
- Chronic fatigue
- Somatization disorders
- Depression
- PTSD
- Bipolar disorder
  - EXCEPT for urgent acute mania
- ADHD
- Kleptomania
- Impulse control
- Active substance abuse
  - Especially alcohol
- *Concomitant opioids*
- Fibromyalgia
How to Reduce Benzo Use in Practice
What is the diagnosis and is there an indication?
- “Anxiety” is not a diagnosis; it is a bodily function
- Without anxiety we would not function
- Is this just normal anxiety response to situation?

Have more preferred treatments had adequate trials?
- Rarely in my 20 years of experience

Am I following established guidelines of care?
- Does immediate benefit outweigh the immediate and long-term risk?
- Has education been provided about the risks?
- Has an exit strategy been agreed upon?
• No good evidence supports long-term use for any mental health indication for most people
  • During prescription renewal or medication review, the prescriber should discuss the risks of chronic benzodiazepines and the benefits of discontinuation (on cognition, psychomotor abilities, mood, sleep, and energy level) and advise the patient regarding reduction or discontinuation

In General and Chronic Users

- Taper 10% starting dose every 1 to 2 weeks
- Earlier withdrawal easier to tolerate than later
- Decrease taper amount and lengthen interval for final 25-35% of taper down
  - No more than 5% every 2 to 4 weeks for the last 20%
- Be flexible → may stay put longer, but try not to go backwards
- May take 3-12 months
- Consider adjunctive CBT/SSRI
- Withdrawal symptoms include anxiety and insomnia
- May not feel better until off
- Scheduled doses and frequent follow-up

Resources

Shorter Term


If addicted


If difficult withdrawal

http://www.benzo.org.uk/manual

Lader, M. Withdrawing benzodiazepines in primary care. CNS Drugs 2009;23:19-34.
Life After Benzos

- Most have lower levels of depression/anxiety
- Most patients show improvement in balance
- Most have cognitive function improved at 6 months
- Some long term users have impaired performance on simple repetitive tests for 1y and on tests of attention for several years

Lader, M. Withdrawing benzodiazepines in primary care. CNS Drugs 2009;23:19-34.
<table>
<thead>
<tr>
<th>Generalized Anxiety</th>
<th>Social Anxiety</th>
<th>Panic</th>
<th>PTSD</th>
<th>OCD</th>
</tr>
</thead>
</table>

**BIG PICTURE = CBT or SSRI**
Insomnia

...I can’t believe 9 million Americans take sleeping pills...

I can’t believe the other 300 million don’t!
• Sleeping pills don’t help much so usually significant risk >> minimal benefit
• The “Z” drugs also have comparable risks to the benzodiazepines
• OTC drugs (antihistamines) also have risks

<table>
<thead>
<tr>
<th>Treatment</th>
<th>SOL (min)</th>
<th>WASO (min)</th>
<th>Total Sleep Increase (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non - Drug</td>
<td>−15.7 to −24</td>
<td>−22.5</td>
<td>24.3 to 32</td>
</tr>
<tr>
<td>Benzodiazepine</td>
<td>−4.2 to −16.5</td>
<td>−23.1</td>
<td>39.1 to 61.8</td>
</tr>
<tr>
<td>Other Drug</td>
<td>−18.1</td>
<td>−12.6</td>
<td>28.0</td>
</tr>
</tbody>
</table>

Get a thorough medical examination looking for causes of insomnia including depression

Use non-drug treatments

Advice from Consumer Reports

Tips for better sleep

- Exercise. Physical activity helps people sleep better. But avoid vigorous activity for several hours before bedtime.
- Keep a routine. Try to go to bed and wake up at about the same time every day, even on weekends.
- Try not to eat right before bedtime. Eat three hours or more before going to bed.
- Avoid caffeine after 3 p.m. Some people need to avoid caffeine even earlier.
- Limit alcohol. Alcohol causes sleepiness at first, followed by wakefulness.
- Create the right environment. Keep the bedroom peaceful. And avoid mental excitement before bedtime.
- Avoid bright lights. Watching a bright screen can make you stay awake.
- Control pets. Pets disrupt sleep if they are on and off the bed, taking up space, or wanting to be let out.
- If you don’t fall asleep soon, get out of bed and do something that will make you sleepy, such as reading. Return to bed after you start to feel drowsy.

For additional information, visit healthinaging.org.
Sleep Psychological Therapies

- **Stimulus Control**
  - Go to bed only when sleepy, not asleep in 20 min get up
  - Use bed for sleep and sex only

- **Relaxation Training**
  - Progressive muscle relaxation, guided imagery, or abdominal breathing

- **Cognitive Behavioral Therapy for Insomnia**
  - Seeks to change patient's unrealistic expectations about sleep

- **Sleep Restriction**

- **Paradoxical Intention**
  - Patient is trained to confront fear of staying awake; objective to eliminate anxiety about sleep performance

- **Biofeedback Therapy**
  - Trains patient to control some physiologic variable through visual or auditory feedback. The objective is to reduce somatic arousal

## Clinical Pearls of Treating Insomnia

<table>
<thead>
<tr>
<th>Prescribe the lowest effective dose</th>
<th>Risks of rebound effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescribe for short durations (two to four weeks) and intermittently (duration based on patient's return to an acceptable sleep cycle)</td>
<td>Hypnotics should be discontinued gradually; physician should be alert for adverse effects (especially rebound insomnia) and withdrawal phenomena</td>
</tr>
<tr>
<td>Watch for requests for escalating doses or resistance to tapering or discontinuing</td>
<td>Long term treatment is of un-established efficacy and tolerance probably occurs</td>
</tr>
<tr>
<td>Risk benefit ratio for the benzos becomes adverse for many beyond 2-4 weeks</td>
<td>Avoid if patient has a hx of substance abuse, COPD, myasthenia gravis, respiratory impairment, or acute CVA</td>
</tr>
<tr>
<td>Identify and address behaviors, circumstances, and underlying disorders contributing to insomnia</td>
<td></td>
</tr>
</tbody>
</table>

Alternative Medications for Dementia-Related Agitation (DRA)

Jessica Bates, PharmD
PGY-1 Pharmacist Resident
Penobscot Community Health Care
## Drugs That Cause Falls in the Elderly

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Updated Adjusted OR Estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepines</td>
<td>1.41 (1.20-1.71)</td>
</tr>
<tr>
<td>Neuroleptics &amp; antipsychotics</td>
<td>1.39 (0.94-2.00)</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>1.36 (1.13-1.76)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>0.99 (0.78-1.25)</td>
</tr>
</tbody>
</table>

Antipsychotics are Effective for DRA

- **Conflicting** evidence for the use of antipsychotics
  - May be used for the *acute* treatment of DRA secondary to delirium while the cause of delirium is being determined
  - Risk of stroke outweighs benefits in all other cases

**Mortality rate 1.6-1.7 times higher with antipsychotics than with placebo**


The Benefits of Cholinesterase Inhibitors in DRA are Unclear

- **Cholinesterase inhibitors** (donepezil, galantamine, rivastigmine)
  - Long-term studies have shown improvement in:
    - Hallucinations
    - Apathy
    - Aberrant motor behavior
    - Inappropriate sexual behavior
    - Agitation
  - Demonstrated effects across variety of dementia subtypes
- However, recent randomized controlled trials (12-26 weeks) reported no improvement in DRA
  - Hypothesized that these benefits *evolve gradually* after 3-6 months of treatment

The Benefits of Memantine in DRA are Unclear

- **NMDA-glutamate receptor antagonist** (memantine)
  - Reports have suggested memantine slows progression of disease, improves function, and reduces DRA
  - May delay the need to use antipsychotics
  - 2006 Cochrane review questions statistical significance of these improvements
    - “The average improvement of 2.8 points on the 144-point Neuropsychiatric Inventory may be undetectable by clinicians and caregivers.”

The Benefits of Carbamazepine in DRA are Unclear

**Benefits**
- Reduces dementia-related sexual disinhibition, hostility, and aggression
- Effective in DRA that is refractory to other medications

**Limitations**
- Significant adverse effects
- Pharmacokinetic drug interactions (strong CYP inducer)
  - Not recommended to use with other drugs that are commonly used in the elderly:
    - Apixaban
    - Diltiazem
    - Donepezil
    - Fluoxetine
    - Mirtazapine
    - Olanzapine
    - Quetiapine

Of the antiepileptic drugs, **carbamazepine** is the most studied in the setting of DRA

Medications with Insufficient or Conflicting Evidence

- **Insufficient** evidence for:
  - Beta-blockers
  - Buspirone
  - Estrogen preparations
  - Gabapentin
  - Lithium

- **Conflicting** evidence for the use of:
  - Valproic acid

Antidepressants are clearly effective for depression in patients with DRA

Cochrane review: some evidence to support use of antidepressants in DRA

- One large study was heavily weighted and found a significant outcome change in the Cohen-Mansfield Agitation Inventory (CMAI) scores
- Sertraline and citalopram were associated with a reduction in symptoms of agitation when compared to placebo in two studies
- SSRIs well tolerated compared to placebo

Pipeline Drugs for DRA

- **Dextromethorphan-quinidine (Nuedexta)**
  - Significantly reduced Neuropsychiatric Inventory (NPI) Agitation/Aggression scores compared to placebo
  - Allowed stable dosages of antidepressants, antipsychotics, hypnotics, and anti-dementia medications
  - Adverse effects (dextromethorphan-quinidine > placebo):
    - Falls
    - Diarrhea
    - UTI
    - Serious adverse effects
    - QTc prolongation

Use of Melatonin for Insomnia in Elderly Patients with Dementia

**de Johnge, et al:**
- Melatonin significantly improved sundowning and agitated behavior
  - No effect on sleep quality or daytime functioning

**Riemersma-van der Lek, et al:**
- Night-time melatonin combined with day-time bright light therapy
  - Shortened sleep latency by 8.2 minutes
  - Increased sleep duration by 27 minutes
  - Melatonin alone had a negative impact on affect, but was ameliorated when used in combination with daytime bright-light therapy

*No adverse effects were more common with melatonin compared to placebo*

Reasons to Avoid Anticholinergic Antihistamines

- **Anticholinergic effects:**
  - Red as a beet, dry as a bone, blind as a bat, hot as a hare, mad as a hatter

- **Other effects:**
  - Cognitive impairment
  - Delirium
  - Reduced clearance in the elderly

- **Commonly prescribed anticholinergic antihistamines:**
  - Chlorpheniramine
  - Diphenhydramine
  - Hydroxyzine
Treatment Alternatives to Medications in Elderly Patients with Insomnia, Anxiety, Agitation
The End

- Thanks to our All-Star Integrated Team
  - Videographer Chris Violette
  - Family NP Amy Langley
  - Psych NP Rebecca Casey
  - LCSW Rebecca McElrath
  - LCSW Anne Donovan
  - Dr Julie Lamoreau
  - Dr Jessica Bates
  - Dr Amy Belisle
Supplemental Slides

FDA-labeled indications of antipsychotics
FDA-Labeled Indications

Haloperidol

- Gilles de la Tourette’s syndrome
- Hyperactive behavior after failure to respond to non-antipsychotic medication and psychotherapy
- Problematic behavior in children (severe) after failure to respond to non-antipsychotic medication and psychotherapy
- Schizophrenia

Olanzapine

- Agitation associated with bipolar I disorder or schizophrenia
- Acute mixed or manic episodes or maintenance therapy of bipolar I disorder
- Depressed bipolar I disorder in combination with fluoxetine
- Treatment-resistant major depressive disorder in combination with fluoxetine
- Schizophrenia


Risperidone

- Irritability of autistic disorder
- Bipolar I disorder
- Schizophrenia

Quetiapine

- Monotherapy for acute management of the depressed phase of bipolar disorder
- Maintenance of bipolar disorder in combination with lithium or divalproex
- Adjunct for major depressive disorder
- Acute management of manic bipolar I disorder (adjunct/monotherapy)
- Schizophrenia

Conflicting Evidence for Valproic Acid in DRA

- Many studies have yielded promising results
- **BUT** narrow therapeutic window for treatment of DRA
  - Doses <800 mg/day may not be effective
  - Doses of 1000-1500 mg/day are poorly tolerated
- Recent Cochrane review did not demonstrate benefits in DRA

Evidence for Buspirone for DRA

Case Report: 85 year old male
- Progressive mixed cerebrovascular Alzheimer’s-type dementia
- Initiated buspirone 5 mg b.i.d., titrated to 10 mg b.i.d.
- Family noted more passive and less aggressive behavior, no adverse effects reported
- Benefits over benzodiazepines and antipsychotics:
  - No sedation, no EPS

Case Report: 69 year old female
- Progressive Alzheimer’s disease with constant anxiety, agitation, pacing, and attention-seeking behavior
- Titrated to buspirone 15 mg b.i.d. combined with:
  - Trazodone 300 mg q.d.
  - Citalopram 40 mg q.d.
  - Olanzapine 10 mg h.s.
- Staff reported reduction in episodes of agitation/anxiety by 50%, reduction in need for antipsychotics from t.i.d. to q.d.

The use of Gabapentin in DRA

- One uncontrolled open trial of 12 patients on a mean dose of 900 mg per day for 4 weeks did not show improvement.

- Two case series of 11 patients on 300-1200 mg per day
  - 4 out of 12 patients showed improvement on the Neuropsychiatric Inventory (NPI).

- Two uncontrolled open trials of mean dosage 300 and 980 mg per day showed positive results.

- Several other open trials and case series showed improvement of aggression, anxiety, apathy, wandering, and sleep problems.

- Common side effect: sedation


Evidence to Support the use of Lithium in DRA

- Effective treatment for behavioral disturbances in a wide variety of neuropsychiatric disorders
- Able to optimize tolerability in elderly by targeting lower serum levels with close monitoring
  - 0.2-0.6 mmol/L

Possibly neuroprotective,

**BUT**

may be associated with a higher rate of dementia


Evidence to Support the use of Topiramate in DRA

- One RCT of 48 Alzheimer’s patients on an average daily dose of 44 mg versus risperidone 1.9 mg/day for 8 weeks
  - Improvement in global DRA and agitation
  - No significant difference compared to risperidone
- Case series of 25-150 mg/day showed improvement in agitation
- Topiramate known to cause cognitive deficit in young adults and epileptic patients

Evidence to Support the use of Lamotrigine in DRA

- Two case series using mean dose of 191 mg/day showed improvement in 42 out of 46 demented patients in:
  - Agitation
  - Aggression
- Two other case reports also showed subjective improvement
- One case series of 5 patients on 100-300 mg/day improved manic symptoms
- One uncontrolled trial did not improve behavior, but did improve depressive symptoms
- Common adverse effects: somnolence, rash, tremor

Evidence to Support the use of Oxcarbazepine in DRA

- Better tolerated than carbamazepine
- One RCT of oxcarbazepine for behavioral and psychiatric symptoms of dementia had negative results
  - 103 patients
  - Average 537 mg/day for 8 weeks
  - No impact on aggression or agitation compared to placebo
- Adverse effects: nausea, vomiting, dizziness, drowsiness

Can Anticholinergic Drugs Cause Dementia?

- A 2010 German study showed an increased risk of dementia in patients who used centrally-acting anticholinergic drugs
  - Acetylcholine levels are significantly lower in the Alzheimer brain
    - Hippocampus and cortex
  - Loss of cholinergic activity correlates to Alzheimer’s disease severity
  - Explains why cholinesterase inhibitors are effective at slowing progression of disease
## Other Drugs with Anticholinergic Activity

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Medium or High Activity</th>
<th>Low Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antibiotics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>Ampicillin, cefoxitin, clindamycin, gentamicin, piperacillin, vancomycin</td>
</tr>
<tr>
<td><strong>Antidepressants</strong></td>
<td>Amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline, paroxetine</td>
<td>Bupropion, fluoxetine, fluvoxamine, mirtazapine, sertraline, trazodone</td>
</tr>
<tr>
<td><strong>Antimuscarinics</strong></td>
<td>Darifenacin, oxybutynin, tolterodine</td>
<td></td>
</tr>
<tr>
<td><strong>Anti-Parkinson Agents</strong></td>
<td>Amantadine, benztropine</td>
<td>Bromocriptine, carbidopa/levodopa, entacapone, pramipexole, phenelzine, selegiline</td>
</tr>
<tr>
<td><strong>Antipsychotics</strong></td>
<td>Chlorpromazine, clozapine, fluphenazine, olanzapine, perphenazine, pimozide, quetiapine, thioridazine, thiothixene</td>
<td>Haloperidol, risperidone, ziprasidone</td>
</tr>
<tr>
<td><strong>Antiepileptic Drugs</strong></td>
<td>Carbamazepine, oxcarbazepine</td>
<td>Valproic acid</td>
</tr>
<tr>
<td><strong>Benzodiazepines</strong></td>
<td>-</td>
<td>All benzodiazepines</td>
</tr>
<tr>
<td><strong>Cardiovascular drugs</strong></td>
<td>Disopyramide</td>
<td>Atenolol, captopril, chlorthalidone, digoxin, diltiazem, furosemide, hydralazine, isosorbide, metoprolol, nifedipine, quinidine, triamterene</td>
</tr>
<tr>
<td><strong>Gastrointestinal agents</strong></td>
<td>Atropine, belladonna, cimetidine, dicyclomine, hyoscyamine, loperamide, ranitidine</td>
<td>Famotidine, metoclopramide, nizatidine</td>
</tr>
<tr>
<td><strong>Immunosuppressants</strong></td>
<td>-</td>
<td>Azathioprine, cyclosporine</td>
</tr>
<tr>
<td><strong>Opioids</strong></td>
<td>Meperidine</td>
<td>Codeine, fentanyl, morphine, oxycodone, tramadol</td>
</tr>
<tr>
<td><strong>Respiratory Medications</strong></td>
<td>-</td>
<td>Fluticasone/salmeterol, theophylline</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>-</td>
<td>Colchicine, dipyridamole, scopalamine, warfarin</td>
</tr>
</tbody>
</table>

Table adapted from: [http://prescribersletter.therapeuticresearch.com/](http://prescribersletter.therapeuticresearch.com/)