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Focus on Anticholinergic Burden

By Allen Lefkovitz

Various classes of medications have been associated with a negative impact on cognition including benzodiazepines (e.g., lorazepam), non-benzodiazepine sedative hypnotics (e.g., zolpidem), and antipsychotics (e.g., haloperidol). However, another category of medications frequently associated with drug-induced cognitive effects, especially in older adults, are those with anticholinergic properties. A 2020 study estimated that up to 73% of older adults use one or more anticholinergic medications. From the earliest versions of the Beers Criteria®, several anticholinergic medications have been recognized as significant contributors to potentially avoidable adverse and harmful effects in older adults. Commonly observed side effects associated with anticholinergic medications include:

Blurred vision	**Confusion**	**Constipation**
Delirium	**Dizziness and Falls** *(due to orthostatic hypotension)*	**Dry mouth and/or eyes**
Drowsiness	**Heart rhythm changes**	**Urinary retention**

Anticholinergic medications that can permeate the blood brain barrier of the central nervous system (CNS) have been demonstrated in numerous studies to impact concentration, memory, processing speed, language, and the ability to carry out everyday movements, gestures, and the customary use of objects. Long-term anticholinergic exposure in middle age has been increasingly associated with risk of cognitive decline and cognitive impairment later in life. Their use can be extremely detrimental in older adults, especially those who already are diagnosed with dementia, as these medications have been associated with increased risk of hospitalizations, fractures, and death.

Within their 2021 Choosing Wisely® recommendations, the American Society of Consultant Pharmacists (ASCP), includes not prescribing “highly anticholinergic medications in older adults without first considering safer alternatives or non-drug measures.” In addition to pointing out their adverse effects, ASCP states that anticholinergics have been associated with an increased risk of dementia and that their use can be “especially problematic for people with existing cognitive impairment.”

Approaches to reducing the negative consequences of anticholinergic medications include:

1. early identification of adverse effects and changes in cognitive function
2. minimizing or discontinuing the use of anticholinergic medications, and
3. switching to alternative agents with either no or low anticholinergic activity.

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Several risk-stratification scales have been developed and validated to measure the cumulative anticholinergic burden of medications. Some of the more commonly discussed tools include the following:

- Anticholinergic Cognitive Burden Scale (ACB)
- Anticholinergic Drug Scale (ADS)
- Anticholinergic Risk Scale (ARS)
- Drug Burden Index (DBI)

Various online calculators are also available including:

- Anticholinergic Burden Calculator (http://www.anticholinergicscales.es/)
- ACB calculator (http://www.acbcalc.com/)

It should be noted that scores methods of determining risk vary and are not necessarily interchangeable between scales. As such, a 2021 study entitled "Concordance among 10 different anticholinergic burden scales in at-risk older populations" concluded that "Great care should be taken when assessing anticholinergic drug exposure using existing scales because of the wide variability among them."

Table 7 of the 2019 Beers Criteria® defines an extensive list of "Drugs With Strong Anticholinergic Properties". Select medications from that list, along with potential alternatives are outlined below.

Table - Medications with Strong Anticholinergic Properties*

Class	Medication	Potential Alternatives and Important Considerations
Antidepressants	amitriptyline nortriptyline	**For depression:** citalopram, sertraline, duloxetine, bupropion **For neuropathic pain:** duloxetine, gabapentin, pregabalin, topical capsaicin or lidocaine
	paroxetine	Alternative SSRI (e.g., citalopram, sertraline)
Antiemetics	prochlorperazine promethazine	Serotonin (5-HT3) receptor antagonists (e.g., ondansetron)
Antimuscarinics for Urinary Incontinence	oxybutynin tolterodine	Manage fluid intake; timed toileting; mirabegron or vibegron If cannot use alternatives, consider oral agents with potentially lower CNS penetration (e.g., darifenacin, trospium) or topical products
Antiparkinsonian Agents	benztropine trihexyphenidyl	Carbidopa/levodopa, dopamine agonist (e.g., ropinirole)
Antipsychotics	chlorpromazine clozapine olanzapine	If nonpharmacological approaches are inadequate, and the individual is a danger to themselves or others, consider use of a non-anticholinergic antipsychotic at the lowest effective dose for shortest duration possible
Antispasmodics	dicyclomine scopolamine	**For irritable bowel syndrome (IBS) with diarrhea:** rifaximin **For IBS with constipation:** linaclotide, lubiprostone If unable to use alternatives, use at the lowest effective dose for shortest duration possible
First Generation Antihistamines	diphenhydramine hydroxyzine	**For seasonal allergies:** Second generation antihistamine (e.g., loratadine), intranasal steroid (e.g., fluticasone) **For sleep:** practice good sleep hygiene; assess for uncontrolled pain
Muscle Relaxants	cyclobenzaprine orphenadrine	Address acute mild or moderate pain with an appropriate analgesic; massage; physical therapy; superficial heat therapy; tizanidine

* not all-inclusive; the final choice of therapy is a decision that should be made by the prescriber based on the individual patient characteristics and the clinical situation

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Beyond these strongly anticholinergic medications, other commonly used medications that may contribute to the overall anticholinergic burden include: atenolol, carbamazepine, digoxin, furosemide, metoprolol, mirtazapine, prednisone, risperidone, trazodone, venlafaxine, and warfarin.

Although use of anticholinergic drugs remains prevalent among older adults, the burden caused by using one or more of these medications may be potentially alleviated by an interdisciplinary evaluation of each individual's medication profile.

New Generic Medications

By Allen Lefkovitz

Generic Name	Brand Name	Date Generic Available
Glycopyrrolate 1 mg/5 mL Oral Solution	Cuvposa® Oral Solution	1/7/22
Dexlansoprazole 30 mg and 60 mg DR Capsule	Dexilant™ Capsule	1/6/22
Naloxone 4 mg/0.1 mL Nasal Spray	Narcan® Nasal Spray	12/22/21
Adapalene/Benzoyl Peroxide 0.3%/2.5% Gel	Epiduo® Forte Gel	12/3/21
Atropine Sulfate 1% Ophthalmic Drops	Isopto® Atropine Ophthalmic Solution	12/3/21
Everolimus 1 mg Tablet	Zortress® Tablet	11/22/21
Semglee (insulin glargine-yfgn)* 100 units/mL Vial or Pen	Lantus® Vial or Pen	11/19/21

* Semglee (insulin glargine-yfgn) is technically not a generic medication, but is the first "interchangeable biosimilar product" approved by the US Food and Drug Administration and may be substituted for Lantus at the pharmacy-level without the intervention of the prescribing healthcare provider, subject to state pharmacy laws

Leqvio® Injection

Brand Name (Generic Name)	Leqvio® [Leck-vee-oh] (inclisiran) [IN-kli-SIR-an]
How Supplied	284 mg/1.5 mL (189 mg/mL) in a single-dose prefilled syringe
Therapeutic Class	Small interfering RNA (siRNA) directed to PCSK9 (proprotein convertase subtilisin kexin type 9) mRNA
Approved Indication	Adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD), who require additional lowering of low-density lipoprotein cholesterol (LDL-C)
Usual Dosing	284 mg administered as a single subcutaneous injection (into the abdomen, upper arm, or thigh) initially, again at 3 months, and then every 6 months.
Select Drug Interactions	Leqvio is not expected to cause drug-drug interactions or to be affected by inhibitors or inducers of cytochrome P450 enzymes or transporters.
Most Common Side Effects	Injection site reaction, arthralgia, urinary tract infection, diarrhea, bronchitis, pain in extremity, and dyspnea
Miscellaneous	The effect of Leqvio on cardiovascular morbidity and mortality has not been determined.
Website	Leqvio.com