



THERAPEUTICS INITIATIVE

Evidence Based Drug Therapy

How well do you know your anticholinergic (antimuscarinic) drugs?

Anticholinergic drugs, prescribed for a variety of clinical conditions, are amongst the most frequently used prescription drugs in BC (Table 1). Also referred to as “antimuscarinics,” such drugs specifically block muscarinic receptors for acetylcholine (ACh).¹ Muscarinic ACh receptors are important in the parasympathetic nervous system that governs heart rate, exocrine glands, smooth muscles, as well as brain function. In contrast, nicotinic ACh receptors stimulate contraction of striated muscles. This Letter is intended to remind clinicians of commonly used drugs that have anticholinergic (AC), or technically, antimuscarinic properties, and of their potential adverse effects.

Beneficial and harmful effects of anticholinergic drugs have been known for centuries. In Homer’s *Odyssey*, the nymph pharmacologist Circe utilized central effects of atropinics in the common plant jimson weed (*Datura stramonium*) to cause delusions in the crew of Odysseus. Believing they had been turned into pigs, they could be herded.²

Sometimes a drug is recommended specifically for its anticholinergic potency. Patients using drugs such as benzotropine to counteract the “extrapyramidal” effects of dopamine blockade, or drugs such as oxybutynin to reduce bladder contractility, are relying on deliberate antagonism of muscarinic neurotransmission by ACh.

Many drugs have potential for AC toxicity

Anticholinergic effects are also an unwanted consequence of therapy (Table 2). The number of such drugs is larger than most clinicians realize.³ Lists vary,⁴ and may not in-



clude drugs whose active metabolites are potentially antimuscarinic,⁵ or which often cause typical AC adverse effects such as dry mouth or urinary retention.⁶ People taking antihistamines, antidepressants, antipsychotics, opioids, antimuscarinic inhalers, or many other drugs need to know that blockade of ACh receptors can cause bothersome or even dangerous adverse effects (Table 3).

Subtle and not-so-subtle toxicity

Students often learn the adverse effects of anticholinergics from a mnemonic, e.g.: “Blind as a bat, mad as a hatter, red as a beet, hot as a hare, dry as a bone, the bowel and bladder lose their tone, and the heart runs alone.” This refers to pupillary dilation and impaired lens accommodation, delusions, hallucinations or delirium, flushing, hyperthermia, dry mucosae and skin, gastrointestinal and bladder paralysis, and tachycardia.¹ Shorter mnemonics fail to capture the broad range of anticholinergic toxicity shown in Table 3.

Table 2: Common drug classes with AC properties

Antidepressants: multiple
Antihistamines: found in many over the counter cold remedies and sleep aids, and in dimenhydrinate/Gravol
Antimuscarinic inhalers: all
Antipsychotics: old and new
Antispasmodics: e.g. hyoscine/Buscopan
Bladder drugs: e.g. oxybutynin, tolterodine
Opioids: all

Table 1: Anticholinergics in the Top 100 (BC Data, 2016)

Antidepressants: amitriptyline*, bupropion, citalopram, escitalopram, fluoxetine, mirtazapine, paroxetine, sertraline, venlafaxine
Antipsychotics: aripiprazole, clozapine, olanzapine, quetiapine, risperidone
Drugs for insomnia: trazodone, zopiclone
Drugs for pain: amitriptyline*, cyclobenzaprine

* nortriptyline and other TCAs are similar to amitriptyline



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Drug product monographs and Wikipedia are easily accessible online resources to identify AC toxicity by simple word searches. For example, searching for the word “anticholinergic” in the 2017 revised product monograph for Seroquel XR (quetiapine) yields a discussion of urinary retention observed in patients during post-marketing surveillance.⁵ The monograph also explains that this is probably due to the active metabolite, present in anyone who takes quetiapine. Monographs for all antimuscarinic inhalers specifically warn of potential AC effects.

Long term use linked to dementia

A recent narrative review examined the connection between long-term use of AC drugs and the risk of dementia and identified 4 observational studies of elderly people in France, Germany, and the U.S.⁸ Based on signals from 3 of these 4 studies, the review authors conclude that AC drugs may increase the risk of dementia. They also note signals that people who stop using anticholinergics are at lower risk of dementia than those who continue, and that patients who take higher doses of more potent AC drugs are at greater risk of dementia.

The 4 observational studies were not randomized controlled trials and thus cannot prove that anticholinergic drugs cause dementia. All study authors attempted to correct for potential confounding, but only one study used propensity score matching to minimize confounding. This did not identify a relationship between use of paroxetine and dementia in nursing home residents.^{8,9}

We conclude that there is some reason to be concerned that long-term anticholinergic drug use might increase the subsequent risk of dementia, even though this conclusion needs to be confirmed by longer and more methodologically rigorous studies. Other long-term effects such as increased dental caries are unquestioned.³

References

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2. <https://en.wikipedia.org/wiki/Circe>
3. Nguyen CT, MacEntee ML, Mintzes B, Perry TL. *Information for physicians and pharmacists about drugs that might cause dry mouth: A study of monographs and published literature*. Drugs and Aging 2014; 31(1):55-65. DOI: 10.1007/s40266-013-0141-5
4. Hsu WH, Wen YW, Chen LK, Hsiao FY. *Comparative Associations Between Measures of Anti-cholinergic Burden and Adverse Clinical Outcomes*. Ann Fam Med 2017;15(6):561-9. DOI:10.1370/afm.2131
5. e.g. norquetiapine (desalkylquetiapine); see *Seroquel XR (quetiapine) revised Canadian product monograph 2017*, p. 44-73. <https://www.astrazeneca.ca/content/dam/az-ca/downloads/productinformation/seroquel-xr-product-monograph-en.pdf> (accessed August 28, 2018)

Prescribing Principles

- Before prescribing, consider a patient’s total anticholinergic burden by reviewing all drugs. Inform patients about anticholinergic effects of over the counter drugs (e.g. “Gravol” or “sleep aids” containing diphenhydramine).
- Alert patients and families that using drugs that block cholinergic neurotransmission in the brain can increase the risk of cognitive impairment and may be risky long-term.
- Prescribe anticholinergics only for a clear indication. Document the purpose in the clinical record and on prescription directions (“indication-based prescribing”). This should appear on the medication container label and will facilitate periodic review and deprescribing.
- **Use low doses for the shortest possible time; reassess often for predictable adverse effects** (Table 3). **Ask about subtle manifestations of anticholinergic toxicity** such as impaired cognition, impaired visual accommodation, slurred speech from a dry tongue and mouth, reflux from delayed stomach emptying, or frequent urination due to incomplete voiding. If you suspect dry mouth, see whether a swish of water improves speech.
- If unsure whether antimuscarinic effects may be in play, consult online resources, including drug monographs.

Table 3: Anticholinergic adverse effects

Body system	Potential adverse effects
Brain	Visual/auditory/sensory hallucinations Tremulousness/myoclonic jerking Memory impairment, cognitive impairment e.g. “brain fog”, altered mental status (delirium)
Heart	Tachycardia
Eyes	Dry eyes Difficulty adjusting visual focus (lens accommodation) Sensitivity to bright light (dilated pupils)
GI tract	Impaired stomach emptying/increased esophageal reflux; Constipation
Mouth	Dry mouth/impaired speech articulation Severe tooth decay Difficulty swallowing due to lack of saliva
Skin	Decreased sweating/dry skin
Bladder	Difficulty starting urination/impaired bladder emptying Urinary retention/overflow incontinence

6. e.g. duloxetine (Cymbalta) – see *Cymbalta revised product monograph 2016*. https://pdf.hres.ca/dpd_pm/00035593.pdf (accessed August 28, 2018)
7. <https://en.wikipedia.org/wiki/Toxidrome>
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