

Therapeutics Initiative

Better prescribing. Better health.

Reducing prescribing cascades

Case vignette: A 70-year-old woman is diagnosed with COPD, obstructive sleep apnea, left ventricular dysfunction with outflow obstruction, hypertension, prior pulmonary embolism, insomnia, anxiety, depression, mild cognitive impairment, and unexplained laryngitis. She takes 14 prescription drugs and 4 supplements, but would prefer fewer. Her primary care nurse practitioner consults an outpatient clinical pharmacist for a comprehensive medication review.

Heart/blood pressure	COPD
1. spironolactone 25mg/d morning	8. tiotropium 2.5mcg (2 inh) morning
2. diltiazem 180mg/d (ER) morning	9. budesonide 100mcg/formoterol 6mcg (2) bid
3. bisoprolol 2.5mg/d morning	10. salbutamol 100mcg 2 puffs tid prn
4. furosemide 40mg q2d morning	Anxiety/depression/sleep
5. rosuvastatin 10mg/d bedtime	11. venlafaxine 300mg/d morning
Prevent VTE	12. mirtazapine 30mg/d bedtime
6. rivaroxaban 20mg/d evening	13. clonazepam 0.25mg/d bedtime
Suspected acid reflux (no GI bleed)	14. melatonin 3mg/d bedtime
7. pantoprazole 40mg/d morning	15-18. iron, calcium, Vitamin C, Vitamin D

Are prescribing cascades hiding in plain sight?

Once unimaginable, intimidating drug lists are now common.¹ Mitigation may be easier if prescribers and dispensing pharmacists recognize the potential for **"prescribing cascades"**. Coined by 2 geriatricians in 1995,² "a prescribing cascade begins when a drug is prescribed, an adverse drug event occurs that is misinterpreted as a new medical condition, and a subsequent drug is prescribed to treat this drug-induced adverse event."³ Sequelae also include over the counter medicines or medical devices (e.g. cardiac pacemaker insertion).

Potential prescribing cascades in this vignette include:

Drug	Common adverse effect	Possible cascade prescriptions
Diltiazem	Peripheral edema	Furosemide for edema mistaken as volume overload or right heart failure
Tiotropium	Anticholinergic: hoarseness/laryngitis	Pantoprazole to reduce stomach acid (but not reflux)
Budesonide	Corticosteroid: Candidiasis/hoarseness	Pantoprazole
Mirtazapine	Anticholinergic: impaired stomach emptying; hoarseness/laryngitis	Pantoprazole
Venlafaxine	Nausea, "indigestion", gastric upset	Pantoprazole
Venlafaxine	Insomnia, agitation, anxiety	Clonazepam, melatonin, mirtazapine
Venlafaxine	Tachycardia/palpitations	Increased dose of bisoprolol
Pantoprazole	Impairment of iron absorption	Iron supplement
FeSO4	Nausea, indigestion	Pantoprazole



Prescriptions added to counter one or more drug effects could induce falls from oversedation, "mild cognitive disorder" or other long-term anticholinergic (antimuscarinic) effects, or adverse effects of a PPI. Given this woman's interest in deprescribing, the clinical pharmacist also questioned other drugs in her list.

What is known about "prescribing cascades"?

Published studies of prescribing cascades focus on several drug classes.⁴ Those previously identified include some of the 200 drugs most often prescribed to people in BC.

Seven prevalent examples

1. Anticholinergic drugs → cognitive dysfunction → drugs for dementia

Anticholinergics (e.g. tricyclic antidepressants, cyclobenzaprine, mirtazapine, quetiapine, oxybutynin)⁵ block acetylcholinergic neurotransmission in the brain, impairing cognition and memory even in the presence of acetylcholinesterase inhibitors (AChE-I: donepezil, galantamine, rivastigmine).^{6,7} Cognitive decline perceived as a new condition or worsening dementia can lead to new prescriptions or increased doses of AChE-I.^{8,9}



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2. Drugs for dementia ➔ incontinence ➔ anticholinergics

Conversely, AChE-I can cause urinary or fecal incontinence, that may “cascade” to prescription of an anticholinergic. Two studies found increased use of antimuscarinic bladder drugs (e.g. oxybutynin) after prescription of cholinesterase inhibitors for dementia.¹⁰ Bradycardia or syncope (muscarinic) or muscle cramps (nicotinic) are other cholinergic effects that may precipitate new treatments.¹¹⁻¹³

3. Anticholinergics ➔ dyspepsia/reflux (“GERD”) ➔ PPI

Dyspepsia or heartburn due to delayed gastric emptying can be mistaken for spontaneous gastrointestinal reflux, or labeled loosely as “GERD”. This association was suggested as a possible cascade in a study evaluating longstanding (“legacy”) prescriptions of PPIs.¹⁴ In a U.S. study of 248 nursing home residents, the likelihood of receiving a PPI increased with anticholinergic burden.¹⁵ Similarly, a large Nova Scotia cohort study of seniors with dementia suggested that anticholinergics increased PPI dispensing “consistent with a prescribing cascade.”¹⁶

4. Anticholinergics ➔ constipation ➔ laxatives

Drug-induced constipation is well recognized, an association confirmed by a 2021 systematic review.¹⁷ Amongst Italian nursing home residents, tricyclics increased laxative use (OR 2.98, 95% CI 1.31-6.77), as did other antidepressants, especially mirtazapine (OR 1.37, 95%CI 1.09-1.71).¹⁸

5. Calcium channel blockers/gabapentin/pregabalin ➔ edema ➔ diuretics

Dihydropyridine calcium channel blockers (CCB) frequently cause dose-dependent edema, affecting up to 30% of older patients.^{19,20} Two recent cohort studies found that furosemide prescriptions increased in people taking CCBs, compared with other antihypertensives.^{21,22} Reducing or stopping a CCB can be preferable to adding furosemide, given its multiple adverse effects.

Gabapentin and pregabalin also cause dose-dependent peripheral edema. In chronic pain this affects up to 9% of people taking gabapentin, and 10% for pregabalin (up to 4-fold vs placebo).²³⁻²⁵ A large Ontario cohort study from 2011-2019 found increased loop diuretic prescriptions following initiation of gabapentin/pregabalin for new onset low back pain in older adults (HR: 1.44, 95% CI: 1.23, 1.70; absolute risk increase 0.7%).²⁶ Both may be associated with inappropriate diagnosis of heart failure.²⁷

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6. Drug-induced movement disorders ➔ antiparkinsonian drugs

Most antipsychotics, some antidepressants, and the anti-emetics metoclopramide and prochlorperazine block dopamine receptors, or cause movement disorders by other mechanisms. Such adverse events can be mistaken for Parkinson’s disease.²⁸ While a Canadian study found these prescribing cascades unusual,¹⁰ others see more reason for concern. Prescriptions for newer as well as older antipsychotics, antidepressants, and metoclopramide have been associated with increased subsequent prescription of L-DOPA/carbidopa and other anti-Parkinsonian drugs.^{3,28-32}

7. Drug-induced hypertension ➔ antihypertensive drugs

About 15% of American adults (19% of adults with hypertension) take a drug that can raise blood pressure.³³ Antidepressants (8.7% of adults) and prescription NSAIDs (6.5%) were the most frequent potential candidates for an under-recognized prescribing cascade.

Reducing prescribing cascades

Preventing, detecting and reversing prescribing cascades is not easy.³⁴ Researchers cited in this Letter propose a comprehensive approach, while the Canadian Deprescribing Network offers a simpler one for the public.^{4,35,36} Recognizing and intercepting cascades still requires knowledge and expert medication review, including attention to known cascades.³⁷ As a rural medical reviewer of this Letter wrote: *“The problem is largely our mindset of reflexively treating new symptoms with medications, without first thinking of drug-induced side effects in patients already taking many. We need to think more, before taking the easy option of reaching for the prescription pad.”*

Conclusions

- Prescribing cascades cause avoidable polypharmacy and harms.
- Prevent them by careful indication-based prescribing and screening for cascades during medication reviews. Utilize expert pharmacist or medical consultation when available.
- Start by familiarization with cascades involving drugs common in primary care; reduce doses if deprescribing seems too radical.
- Identifying a prescribing cascade is a teachable moment: use it.

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