

Drug-Induced Gastroesophageal Reflux Disease

Background

Gastroesophageal reflux disease (GERD) is a commonly encountered condition in primary care. Medications may induce or aggravate GERD symptoms via two mechanisms: lower esophageal sphincter (LES) relaxation and slowing of GI transit. Some medications known to relax the lower esophageal sphincter include calcium channel blockers, nitrates, benzodiazepines, theophylline, and inhaled beta-agonists. Drugs with anticholinergic properties may cause GERD by both relaxing the LES and slowing GI motility.¹⁻⁴

Key Points

- ◆ **Both non-dihydropyridine (e.g. diltiazem, verapamil) and dihydropyridine (e.g. amlodipine, nifedipine) calcium channel blockers can relax the LES.**
- ◆ **Other drug classes known to decrease the lower esophageal sphincter tone include:**
 - Beta-agonists**
 - Nitrates**
 - Theophylline**
 - Benzodiazepines**
 - Anticholinergics (tricyclic antidepressants, antihistamines, urinary incontinence drugs)**
- ◆ **The risk of GERD likely increases with the number of GERD-inducing medications a patient is taking.**
- ◆ **Alternatives exist for many indications in which calcium channel blockers are used.**
- ◆ **Not all medications suspected of causing GERD can be safely discontinued or substituted. These patients may need pharmacologic treatment for their GERD symptoms with anti-reflux medications.**

Cases of GERD that may be drug-induced often resolve upon discontinuation of the offending agent. However, it is important to recognize the benefit of continuing the agent may outweigh the risk in some cases. While undesirable as a general rule, for patients who may be experiencing drug-induced GERD and cannot discontinue the suspected drug offender, pharmacologic treatment with an H₂ receptor antagonist or proton-pump inhibitor may be indicated. Clinicians should be aware of the potential long-term risks associated with acid suppressants use only when indicated at the lowest effective dose for the shortest duration possible to control symptoms, as there may be risks associated with long-term use of acid suppressants, including vitamin B₁₂ deficiency, impaired calcium absorption leading to fractures, and upper respiratory infections.⁵⁻⁷

Calcium Channel Blockers

Calcium channel blockers are a commonly used class of medications known to induce GERD and are broadly divided into two categories known as non-dihydropyridines (diltiazem and verapamil) and dihydropyridines (amlodipine, felodipine, nifedipine, etc). Both subclasses relax the lower esophageal sphincter by inhibiting the influx of calcium into smooth muscle cells. Although many potentially GERD-inducing drug classes have few, if any, clinically acceptable substitutes or equivalents (i.e. inhaled beta-agonists, nitrates), the calcium-channel blockers are a group of drugs for which alternatives do exist. The following table summarizes some of these alternatives and when they may be considered.

Calcium Channel Blocker Alternatives By Indication		
Indication	Possible Alternative(s)	Comments
Hypertension	Thiazide diuretic, ACEI, ARB, BB, AA	CCB rarely recommended first-line, best reserved for add-on therapy or after other medications have failed
Chronic Stable Angina	BB, long-acting nitrates	BB or long-acting nitrates preferred before adding or switching to CCB
Prinzmetal's (vasospastic) Angina	Long-acting nitrates	Long-acting nitrates preferred before adding or switching to CCB; some clinicians consider CCB agents of first choice due to fewer adverse effects and dosing frequency
Silent Ischemia	BB	BB preferred; CCB less effective
Atrial Fibrillation	BB, digoxin	BB or digoxin preferred before adding or switching to non-dihydropyridine CCB
Migraine Prophylaxis	BB, topiramate	BB and topiramate preferred over CCB or amitriptyline

ACEI = ACE inhibitor ARB = angiotensin receptor blocker
 BB = beta blocker AA = aldosterone antagonist
 CCB = calcium channel blocker

References

1. Ishikawa H, Iwakiri K, Sugiura T, et al. Effect of nifedipine administration (10 mg) on esophageal acid exposure time. *J Gastroenterol* 2000;35(1):43-6.
2. Rushnak MJ, Leevy CM. Effect of diazepam on the lower esophageal sphincter. A double-blind controlled study. *Am J Gastroenterol* 1980;73(2):127-30.
3. Berquist WE, Rachelefsky GS, Kadden M, et al. Effect of theophylline on gastroesophageal reflux in normal adults. *J Allergy Clin Immunol* 1981;67(5):407-11.
4. Crowell MD, Zayat EN, Lacy BE, et al. The effects of an inhaled beta(2)-adrenergic agonist on lower esophageal function: A dose-response study. *Chest* 2001;120(4):1184-9.
5. Force RW, Meeker, AD, Cady PS, et al. Ambulatory care increased vitamin B12 requirement associated with chronic acid suppression therapy. *Ann Pharmacother.* 2003;37(4):490-3.
6. Yang YX, Lewis JD, Epstein S, Metz DC. Long-term proton pump inhibitor therapy and risk of hip fracture. *JAMA* 2006;296(24):2947-53.
7. Laheij RJ, Sturkenboom MC, Hassing RJ, et al. Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs. *JAMA* 2004;292(16):1955-60.