How safe are PPIs, and when should I get my patients off of them?

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Objectives

- Review appropriate indications for PPIs and recommended treatment durations
- Present most convincing medical literature evaluating long-term safety of PPIs
- Discuss strategies for deprescribing PPIs for patients who no longer require therapy
- Introduce best practices for long-term PPI use

Financial disclosures

- No disclosures to report

Question#1

- Which of the following is the most appropriate duration of PPI treatment for uncomplicated peptic ulcer disease?

Question#1

- A. 2-4 weeks
- B. 6-8 weeks
- C. 8-12 weeks
- D. Greater than 1 year
- E. None, treatment is not indicated

Question#1

- **B. 6-8 weeks**

Question#2

- Which of the following is the most appropriate duration of PPI treatment for functional (non-ulcer) dyspepsia?

Question#2

- A. 2-4 weeks
- B. 6-8 weeks
- C. 8-12 weeks
- D. Greater than 1 year
- E. None, treatment is not indicated

Question#2

- **A. 2-4 weeks**

Question#3

- Which of the following is the most appropriate duration of PPI treatment for reflux esophagitis?

Question#3

- A. 2-4 weeks
- B. 6-8 weeks
- C. 8-12 weeks
- D. Greater than 1 year
- E. None, treatment is not indicated

Question#3

- **C. 8-12 weeks**

Question#4

- Which of the following is NOT an indication for long-term (ie. greater than 1 year) PPI use?

Question#4

- A. Patients with uncomplicated GERD who respond to short-term therapy
- B. Patients with Barrett's esophagus and symptomatic GERD
- C. Patients with recurrent PUD despite negative work-up for secondary causes
- D. Patients at high risk for ulcer-related bleeding from NSAIDs who continue to take NSAIDs
- E. All of the above are indications for long-term PPI use

Question#4

- **A. Patients with uncomplicated GERD who respond to short-term therapy**

Question#5

- Which of the following is NOT an indication for high dose (ie. BID dosing) of PPI?

Question#5

- A. Persistent/severe esophagitis
- B. Complicated/refractory PUD
- C. Known hypersecretory states such as Zollinger-Ellison syndrome (ZES)
- D. Functional dyspepsia not responding to once daily PPI
- E. Abnormal pH test already on once daily PPI

Question#5

- **D. Functional dyspepsia not responding to once daily PPI**

Outline

- Background
- Mechanism of action
- Dosing and administration
- Indications
- Adverse reactions
- Deprescribing
- Best practice recommendations

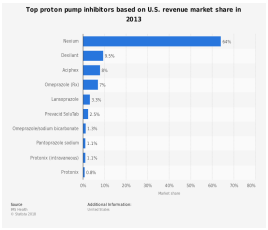
Background

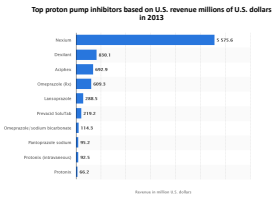
- Proton pump inhibitors (PPIs) were first introduced in 1980s
- Represent major breakthrough in mgmt of acid-related disease
- Now among most widely prescribed drugs, second to only statins
- In 2013, over $8.4 billion spent in US and over $13 billion worldwide
- 8–10% of adults were prescribed a PPI in past 30 days
- 13% of adults use PPI at least twice weekly
- People over 60 years of age 3.5 times more likely to use PPIs

Available PPI formulations

- Omeprazole (Prilosec) (1988)
- Pantoprazole (Protonix) (1994)
- Lansoprazole (Prevacid) (1995)
- Rabeprazole (Aciphex) (1999)
- Esomeprazole (Nexium) (2001)
- Lanso/naprox (NepraPAC) (2003)
- Ome/Na bicarb (Zegerid) (2004)
- Dexlansoprazole (Dexilant) (2009)
- Eso/ibuprofen (Vimovo) (2010)

Available PPI formulations





Mechanism of action

- Gastric acid produced by gastric H+/K+ ATPase (proton pump)
  - kills ingested microorganisms
  - limits bacterial growth in stomach
  - prevents intestinal infections such as C difficile
  - facilitates digestion of protein and absorption of iron, calcium, and B12
  - allows absorption of basic drugs including metoprolol and allopurinol
- Regulation of acid secretion relies on:
  - Gastrin (stimulated by food)
  - Acetylcholine (stimulated by vagus nerve)
  - Histamine (stimulated by gastrin and acetylcholine)

Mechanism of action

- Acid can also have caustic effects on the lining of the gastrointestinal mucosa causing symptoms and injury including esophagitis and ulcers
- Normal gastroduodenal mucosa protects itself from harmful effects of acid through various defensive and healing mechanisms including:
  - Mucus
  - Prostaglandin
  - Bicarbonate secretion
- When these mechanisms fail acid related injury can occur
- Medications can help to neutralize acid or suppress acid production

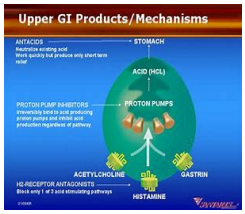
Mechanism of action

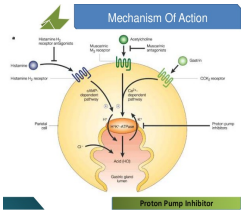
- Acid-suppressing medications include:
  - Antacids such as sodium bicarbonate, magnesium or aluminum hydroxide, calcium carbonate, and bismuth subsalicylate
  - Histamine type 2 (H_2) blockers
  - Proton pump inhibitors (PPI)
- These medications
  - control various different upper GI symptoms including GERD and dyspepsia
  - prevent ulcers from forming in setting of non-steroidals and h pylori infection
  - allow healing of existing ulcers in the esophagus, stomach, and duodenum

Mechanism of action

- Antacids generally work by simple neutralization of acid
- H_2 blockers bind to parietal cell H_2 receptors, blocking histamine released by ECL cells
- PPIs irreversibly bind to and block active proton pumps in the gastric oxyntic mucosa, inhibiting acid production from all pathways
  - Results in profound reduction in basal and stimulated gastric acid output, maintaining intragastric pH at high levels
  - Allows for consistent prevention and healing of esophagitis and peptic ulcer disease and more rapid control of symptoms

Mechanism of action





Dosing and administration

- Most PPIs are encapsulated or enterically coated (EC) to protect the medication against degradation by gastric acid
- Opening capsule may leave granules vulnerable to degradation, premature activation in presence of acid, and decreased efficacy
- All EC PPIs can be administered via NG tubes, while omeprazole and lansoprazole are also effectively administered via G-tube
- For pts with J-tubes, only omeprazole has been found to be effective
- Pantoprazole, esomeprazole, and lansoprazole available as liquid/IV

Dosing and administration

Drug	Dosages (mg)	Capsule or tablet	Liquid or suspension	IV	Generic	OTC
Omeprazole	10, 20, 40	Capsule	No	Yes	Yes	Yes
Pantoprazole	20, 40	Tablet	Yes	Yes	Yes	No
Lansoprazole	15, 30	Capsule	Yes	Yes	Yes	Yes
Rabeprazole	20	Tablet	No	No	Yes	No
Esomeprazole	20, 40	Capsule	Yes	Yes	Yes	Yes
Dexlansoprazole	30, 60	Capsule	No	No	No	No

Equivalent dosing of various PPIs

Omeprazole 20mg
Pantoprazole 40mg

Lansoprazole 15mg
Rabeprazole 20mg

Esomeprazole 20mg
Dexlansoprazole 30mg

Dosing and administration

- PPIs work best on empty stomach, at least 30 minutes before a meal
- Half-life of PPIs is 60–90 min, but acid inhibition lasts up to 24 hrs
- Single dose of PPI does not inhibit all active pumps
- Acid secretion inhibited with subsequent PPI doses, up to 5-7 days
- Steady-state inhibition achieved more rapidly with twice daily dosing
- Alternate PPIs can be considered due to cost or intolerance
- **No evidence that one PPI is more effective than another**

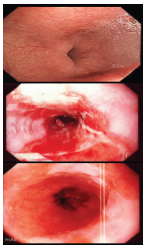
FDA-approved indications

- Treatment of gastroesophageal reflux disease (GERD)
- Healing of erosive esophagitis (EE)
- Maintenance of healed EE
- Risk reduction for gastric ulcer (GU) associated with nonsteroidal anti-inflammatory drugs (NSAIDs)
- Short-term treatment and maintenance of duodenal ulcers (DUs)
- Helicobacter pylori (*H. pylori*) eradication to reduce risk of DU recurrence, in combination with antibiotics
- Pathological hypersecretory conditions, including ZES

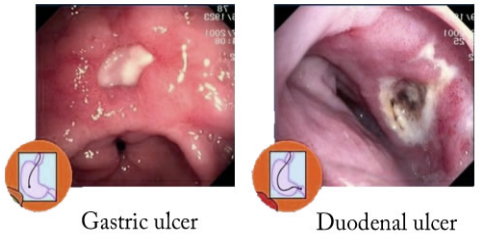
FDA-approved indications

Indication	Omeprazole	Pantoprazole	Lansoprazole	Rabeprazole	Esomeprazole	Dexlansoprazole
GERD						
Nonerosive reflux disease	Yes	No	Yes	Yes	Yes	Yes
Erosive esophagitis-healing	Yes	Yes	Yes	Yes	Yes	Yes
Erosive esophagitis-maintenance	Yes	Yes	Yes	Yes	Yes	Yes
Peptic Ulcer Disease						
Gastric ulcer-healing	Yes	No	Yes	No	No	No
NSAID induced ulcer-healing	No	No	Yes	No	No	No
NSAID induced ulcer-prophylaxis	No	No	Yes	No	Yes	No
Duodenal ulcer-healing	Yes	No	Yes	Yes	No	No
Duodenal ulcer-maintenance	No	No	Yes	No	No	No
Treatment of *H. pylori*						
Dual therapy	Yes	No	Yes	No	No	No
Triple therapy	Yes	No	Yes	Yes	Yes	No
Zollinger-Ellison syndrome	Yes	Yes	Yes	Yes	Yes	No

Erosive esophagitis and Barrett's esophagus



Peptic ulcer disease



Gastric ulcer Duodenal ulcer

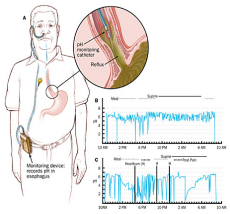
Indications for long-term PPI therapy

- Definite indications
  - Treatment of recurrent erosive esophagitis for prevention of relapse
  - Prevention of progression of Barrett's esophagus in symptomatic patients
  - Treatment of PPI-responsive esophageal eosinophilia
  - Prevention of PUD and its complications in chronic NSAID users
  - Treatment of recurrent PUD after negative work-up for secondary causes
- Not indicated
  - Endoscopy-negative reflux disease (NERD) responding to short-term therapy
  - Symptoms due to LPR/atypical manifestations of GERD
  - Functional (non-ulcer) dyspepsia

Indications for BID or higher dosing

- Definite indications
  - Persistent/severe esophagitis
  - Abnormal pH test already on once daily PPI
  - Symptoms due to LPR/atypical manifestations of GERD
  - Complicated/refractory peptic ulcer disease (PUD)
  - Known hypersecretory states such as Zollinger-Ellison syndrome (ZES)
- Not indicated
  - Uncomplicated GERD
  - Simple PUD
  - Functional dyspepsia not responding to once daily PPI

pH monitoring



pH monitoring

- Kleiman and others retrospectively reviewed type of symptoms and duration of PPI for 100 pts who later underwent pH monitoring
  - In a cost effectiveness study, they subtracted cost of unnecessary PPIs from cost of pH monitoring in pts with normal pH
  - Cost model showed pH monitoring after 8-week PPI trial would have saved from $1966 to $7285 per patient over 10 yrs
  - Authors concluded that early referral for pH monitoring saves $6600 per patient over 10 yrs
  - Cutting down unnecessary PPI use not only helps decrease costs but may also decrease potential risks of long-term exposure

Adverse reactions

- PPIs are generally well tolerated; acute reactions occur only 1-3%
  - Headaches, dizziness
  - Abdominal pain, nausea, vomiting
  - Flatulence, diarrhea
- Drug-drug interactions have been reported with certain PPIs
- Most PPIs are pregnancy category B (omeprazole is category C), but there are no recommendations for use in breast-feeding
- Over last 20 years, a large number of articles have been published regarding safety of long-term use, leading to several FDA notifications

Potential long-term safety considerations

- AIN
- CKD
- Dementia
- **Osteoporosis/bone fractures**
- Acute MI
- **Interaction with clopidogrel**
- SBBO
- ***C. difficile*-associated diarrhea**
- Other enteric infections
- Microscopic colitis
- Colon cancer
- SBP/mortality in cirrhosis
- Pneumonia/URI
- Iron and vitamin B12 deficiency
- **Hypomagnesemia**
- Mortality after PEG insertion
- Gastric carcinoid tumors/polyps
- Interaction with methotrexate

Proposed mechanisms for PPI complications

- Less gastric acid production results in hypergastrinemia and changes in environment of stomach and lower bowel
  - May result in immunosuppression with overgrowth of gastric bacteria and altered intestinal normal flora
  - May affect how Fe, Ca, and minerals like B12 are absorbed
  - May also affect how other drugs are metabolized and absorbed
  - May lead to trophic changes of the stomach and colon
- Direct metabolic interaction with hepatic cytochrome p450, especially omeprazole which is a p450 inducer

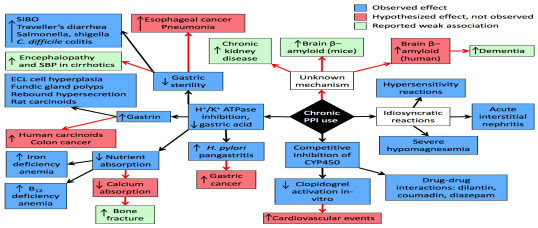
Proposed mechanisms for PPI complications

• Kidney	Recurrent AIN
• Brain	a) Decreased gastric acidity leading to B12 def b) Beta-amyloid deposition
• Bone	a) Decreased gastric acidity leading to Ca and B12 def b) Hypergastrinemia leading to hyperparathyroidism
• Heart	a) CYP450/CYP2C19 induction inhibiting clopidogrel activation b) Increased asymmetric dimethylarginine (ADMA) leading to reduced endothelial nitric oxide resulting in thrombosis
• Colon	a) Decreased gastric acidity altering normal intestinal flora b) Trophic effect of hypergastrinemia on colonocytes

Proposed mechanisms for PPI complications

- Liver — a) Decreased gastric acidity altering gut microbiota; b) Decreased gastric acidity leading to B12 deficiency
- Lungs — a) Decreased gastric acidity leading to overgrowth of gastric bacteria; b) Antineutrophilic effect of PPIs
- Muscle — CYP3A4 enzyme inhibition
- Blood — Decreased gastric acidity leading to Fe and B12 def
- Stomach — a) Decreased gastric acidity leading to overgrowth of gastric bacteria; b) Acid suppression induced parietal cell hyperplasia

Proposed mechanisms for PPI complications



FDA drug safety communications

- **11/17/09: Update to the labeling of clopidogrel bisulfate to alert healthcare professionals about a drug interaction with omeprazole**
- **5/25/10: Possible increased risk of fractures of the hip, wrist, and spine with the use of proton pump inhibitors**
- **3/2/11: Low magnesium levels can be associated with long-term use of proton pump inhibitor drugs**
- **2/8/12: Clostridium difficile associated diarrhea can be associated with stomach acid drugs known as proton pump inhibitors**

Interaction with clopidogrel

- Some data suggest decreased activation of clopidogrel in omeprazole users
- Both drugs share hepatic CYP450 and CYP2C19 metabolism
- 2012 nonrandomized subgroup analysis of PLATO trial
  - Use of PPI was associated with higher rate of CV events in those taking either clopidogrel or ticagrelor
- 2015 meta-analysis of six observational studies evaluating composite outcome of death, MI, or CVA with various different PPIs:
  - pantoprazole (HR 1.38, 95% CI 1.12-1.70)
  - lansoprazole (HR 1.29, 95% CI 1.09-1.52)
  - esomeprazole (HR 1.27, 95% CI 1.02-1.58)
  - omeprazole (HR 1.16, 95% CI 0.93-1.44)

Interaction with clopidogrel

- Only large scale RCT comparing omeprazole to placebo in clopidogrel users (COGENT trial) published in NEJM in 2010
  - NO significant difference in CV events when two were combined (HR 0.99; 95% CI 0.68-1.44)
  - Significant reduction in gastrointestinal events (HR 0.34; 95% CI 0.18-0.63)
- Subsequent systematic review of published data concluded that adverse effect of PPI use with clopidogrel cannot be substantiated
- Risks and benefits of clopidogrel and concomitant PPI therapy need to be individualized based on indication for PPI use
- **Prophylactic PPI should be considered for pts taking clopidogrel who have high risk of PUD (similar to daily ASA users)**

Fracture risk

- Long-term PPI use has been associated with risk of osteoporosis and decreased bone mineral density (BMD), with 35% risk of fractures
- Calcium serves an important role in bone health and formation as key component of hydroxyapatite, which is main element of bone
- PPI-induced fractures may occur because some dietary calcium absorption is dependent upon acidic environment in GI tract
  - Hypochlorhydria reduces absorption of water insoluble calcium (eg. calcium carbonate), which can be overcome by consuming a meal
  - Absorption of water-soluble calcium salts (eg. calcium citrate) or calcium in dairy are not impacted by PPI-induced hypochlorhydria
- This reduction in calcium absorption can augment osteoclastic activity, increasing bone loss and further reducing BMD

Fracture risk

- Some early studies with omeprazole showed that fractional absorption of calcium was reduced in postmenopausal women
- Large prospective cohort study from 2010 Arch Intern Med
  - PPI associated with increased risk of vertebral (HR 1.47, 95% CI 1.18-1.82), wrist, and total fractures
- In a 2011 analysis, concurrent use of PPIs and alendronate was associated with loss of protection against fracture (39 versus 19%)
- 2011 Am J Med meta-analyses of 11 case-control and cohort studies
  - RR of hip, spine, and any-site fractures was 1.30, 1.56, and 1.16, with PPI use
  - Risk was highest in long-term users (>1 year) of high-dose PPI therapy

Fracture risk

- These studies did demonstrate association between long-term PPI use and risk of fractures but contained numerous confounders
- In one analysis from 2012, fracture risk in PPI users was confined to pts with at least one other risk factor:
  - current or former smokers
  - sedentary lifestyle
  - use of certain medications (e.g., HCTZ, HRT, CS)
- Targownik et al. found in 2012 that pts using PPIs were older (66.3 vs. 60.9 years; *P* <.001) with a higher BMI (28.3 vs. 26.9; *P* <.001)

Fracture risk

- Another large prospective cohort study from 2012 showed chronic PPI use over 10 years not associated with accelerated BMD decline
- Other studies have similarly found no decrease in BMD in PPI users
- Although association between PPI use and bone fracture is plausible, causality not yet established
- **In March 2011, FDA concluded that OTC PPI products do not warrant label changes to include warnings of fracture risk**
- **2013 ACG guidelines on GERD state that existing osteoporosis is not a contraindication to PPI therapy, unless other risk factors exist**

Low serum magnesium levels

- All PPIs are associated with decreased Mg absorption
- Mechanism for reduced absorption may be inhibition of transient receptor potential melastatin-6 (TRPM6) and TRPM7 channels
- Hypomagnesemia occurred in approximately 1% of pts taking PPIs according to the FDA's Adverse Reporting System
- Mean time is 5.5 yrs, but cases have been reported within 1 yr
- 2015 meta-analysis of 9 observational studies with 109,798 pts
  - PPI use had RR 1.43 (95% CI, 1.08-1.88) for low Mg

Low serum magnesium levels

- Symptoms include palpitations, tetany, convulsions, and weakness
- Clinical manifestations include neuromuscular excitability (tremor, tetany, seizures) and hypotension
- Severe PPI-induced hypomagnesemia has also been associated with arrhythmias due to QT interval prolongation and torsades de pointes
- It is potentially fatal
- Pts who present with clinically significant hypomagnesemia may require Mg replacement and discontinuation of PPI therapy
- Hypomagnesemia generally resolves after discontinuation but recurs soon after PPI is re-challenged

Low serum magnesium levels

- Hypomagnesemia is more common in older pts taking a PPI (mean age 64.4 yrs) and pts with renal failure
- Concurrent use of medications that decrease Mg also increases risk of significant hypomagnesemia
- Danziger et al. reported that pts who take a PPI with a diuretic have nearly 55% greater risk of hypomagnesemia than with PPI alone
- **FDA suggests obtaining Mg levels prior to initiation of therapy and periodically thereafter although AGA advises against routine testing**

Association with *C. difficile*

- PPI use has also been associated with increased risk of initial and recurrent *C. difficile* infection (CDI)
- Gastric acid is a defense mechanism against enteric bacteria
- Increased gastric pH may allow colonization of opportunistic microbes
- Risk of CDI appears to be greater with PPIs as compared to H2 receptor antagonists and other antacids

Association with *C. difficile*

- 2005 retrospective study
  - Pts taking PPIs had HR of 2.9 (95% CI, 2.4-3.4) for developing *C. difficile*
  - 75% of pts with reported cases of *C. difficile* were over age 65
  - Pts who received PPI during treatment of *C. difficile* were 42% (95% CI, 1.11-1.82) more likely to have recurrent infection after finishing therapy
- 2012 meta-analysis of 29 studies of pts with CDI
  - PPIs increased risk of CDI (pooled OR = 2.15; 95% CI 1.81 – 2.55)
- 2017 meta-analysis of 50 observational studies
  - Also noted that PPI use increased risk of CDI (RR 1.3; 95% CI 1.1-14)

Association with *C. difficile*

- In a 2010 study Linsky et al. determined whether patients with recurrent CDI received a PPI within 14 days of initial infection
  - HR for pts on PPIs during treatment was 1.42 (95% CI 1.11-1.82)
  - For pts over age 80, HR increased to 1.86 (95% CI 1.15-3.01)
- 2017 meta-analysis of 16 studies that included 1525 pts
  - Acid therapy had OR 1.5 (95% CI 1.2-1.9) for recurrent infection
- In adjusted analysis from 9 studies, PPI use was increased even after controlling for age and other conditions (OR 1.4; 95% CI, 1.1-1.8)
- **2013 ACG guidelines on GERD recommend use of PPIs with caution in pts with a risk of *C difficile* infections (CDI)**

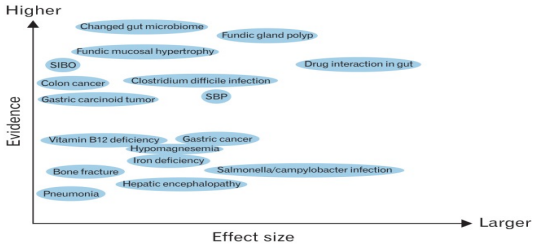
Latest study

- **Safety of Proton Pump Inhibitors Based on a Large, Multi-year, Randomized Trial of Patients Receiving Rivaroxaban or Aspirin**
- Moayyedi, et al. Gastroenterology. In press.
  - Large placebo-controlled RCT, part of the original COMPASS trial
  - 17,598 individuals received pantoprazole or placebo, and were followed for up to 3 years
  - Primary outcome was protection against GI bleeding and secondary outcome was safety analysis
  - Pantoprazole was not associated with any adverse event when used for 3 years, with possible exception of an increased risk of enteric infections
  - Moayyedi reports receiving research funding from Allergan and Takeda

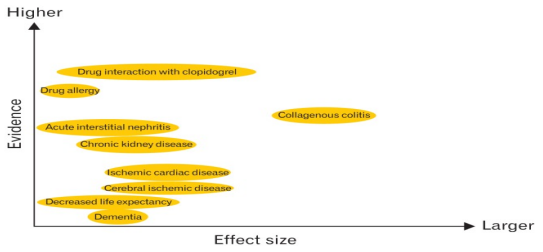
Potential long term safety considerations

Potential Adverse Effect	Relative Risk	Reference for Risk Estimate	Reference for Incidence Estimate	Absolute Excess Risk
Chronic kidney disease	10% to 20% increase	Lazarus et al[88]	Lazarus et al[88]	0.1% to 0.3% per patient/y
Dementia	4% to 80% increase	Haenisch et al[80]	Haenisch et al[80]	.07% to 1.5% per patient/y
Bone fracture	30% to 4-fold increase	Yang et al[27]	Yang et al[27]	0.1% to 0.5% per patient/y
Myocardial infarction	No association in RCTs	---	---	---
SIBO	2-fold to 8-fold increase	Lo et al[91]	None available	Unable to calculate
Enteric infections	2-fold to 6-fold increase	Bavishi et al[24]	Crim et al[92]	.03% to 0.2% per patient/y
SBP	50% to 3-fold increase	Xu et al[93]	Fernandez et al[94]	3% to 16% per patient/y
***C difficile* infection**	No risk to 3-fold increase	Furuya et al[95]	Lessa et al[96]	0% to .09% per patient/y
Pneumonia	No association in RCTs	---	---	---
Micronutrient deficiencies	60% to 70% increase	Lam et al[97]	Bailey et al[98]	0.3% to 0.4% per patient/y
GI malignancies	No association in RCTs	---	---	---
Interaction with clopidogrel	No association in RCTs			

Evidence for Adverse Events Related to Acid Inhibition



Evidence for Adverse Events Unrelated to Acid Inhibition



Keep calm and carry on

- There is currently inadequate evidence to establish causal relationships between PPI therapy and proposed associations
- Safety reviews to date assess evidence as "low" or "very low" quality since data only demonstrates modest association and not causality
- Most reports are retrospective case control studies (cross-sectional) limited by channeling bias and confounding factors
- Only available RCTs have shown no risk of MI, pneumonia, or GI malignancy, and no interaction with clopidogrel
- When used appropriately, benefits of PPIs outweigh risks, but **when used inappropriately, even modest risks become important**

Deprescribing

- If a patient does not have a definite indication for long-term PPI therapy, what strategies can we use to take them off of them?
- Options include:
  - Stepping down to a lower dose or intermittent/on-demand treatment regimen
  - Substituting PPI with less potent form of acid inhibition (ie. H2 blocker)
  - Discontinuing PPIs outright, either suddenly or gradually

Step-down regimens

- Initial goal should be to take patients off high dose PPI therapy if there is no clear indication
- Inadomi et al. prospectively demonstrated that 80% of pts could be stepped down to standard dosing without recurrent symptoms
- Pts already on low dose PPI may be harder to wean off
- There is theoretical risk of rebound acid hypersecretion with sudden discontinuation resulting in symptom recurrence
- This phenomenon was seen in studies by Reimer et al. and Niklasson et al.

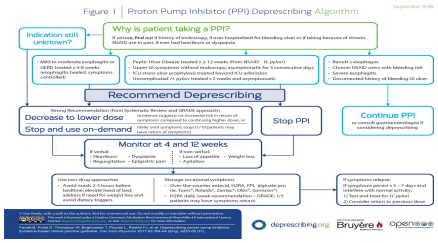
Total discontinuation of PPIs

- Studies by Boghossian et al. and Hansen et al. also suggest loss of symptom control with intermittent dosing or switching to H2 blocker
- For these patients, another option is to taper their PPI gradually, initially decreasing use to every 2 or 3 days
- Inadomi et al. found that 60% of PPI users discontinued over 2 wks were asymptomatic on no or OTC antacids over the following yr

Deprescribing

- Barbara Farrell et al. from University of Ottawa published an evidence-based guideline in *Canadian Family Physician* in 2017
- For adults older than 18 yrs with upper GI symptoms who received PPIs for minimum of 4 weeks and experienced symptom resolution
  - Clinicians should either reduce the daily dose of PPI or stop the drug and switch patient to on-demand PPI use "*strong evidence*"
  - Clinicians may consider stepping down to histamine-2 receptor antagonist therapy "*weak evidence*"

Deprescribing



AGA Best Practices for Long-Term PPI use

- Patients with GERD and acid-related complications should take PPI for short-term healing, maintenance, and long-term symptom control
- Patients with uncomplicated GERD who respond to short-term PPIs should subsequently attempt to stop or reduce them
- Patients with Barrett's esophagus and symptomatic GERD should take a long-term PPI
- Asymptomatic patients with Barrett's esophagus should consider a long-term PPI
- Patients at high risk for ulcer-related bleeding from NSAIDs should take a PPI if they continue to take NSAIDs

AGA Best Practices for Long-Term PPI use

- Specific PPI formulations should not be selected based on risks
- Dose of long-term PPIs should be periodically reevaluated so that lowest effective dose can be prescribed to manage the condition
- Patients who cannot reduce PPIs should consider ambulatory pH/impedance monitoring before committing to lifelong PPIs
- Long-term PPI users should not routinely:
  - screen or monitor bone mineral density, serum creatinine, magnesium, or B12
  - raise their intake of calcium, B12, or magnesium beyond Recommended Dietary Allowance
  - use probiotics to prevent infection

Final thoughts

- After what duration of PPI therapy are patients at risk for complications?
- Are there specific populations at higher risk for these complications?
- Do certain PPI formulations carry higher risk of complications than others?

Summary

- PPIs are highly efficacious acid-suppressing medications that block all three acid-producing pathways
- PPIs work best on an empty stomach, at least 30 minutes before a meal, and require at least 5-7 days to achieve a steady state
- Although probably safe, PPIs should be prescribed only when clinically appropriate, at lowest effective dose for proven indication
- Avoid chronic therapy after a negative work-up, and avoid dose escalation in people unresponsive to initial empiric therapy
- When long term use is needed, use only appropriate maintenance dose and consider on-demand PPIs or drug holidays

Any questions?

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