

A faint background image showing a hand holding several pills of various colors (purple, blue, red, white) against a light, sun-like glow.

To suppress or not to suppress Update on PPI Use

Robert Berger MD FRCPC

NBIMU

April 28, 2017

Disclosures

- Advisory Board
 - AbbVie
 - Lupin
 - Pfizer
- Speakers Panel
 - Takeda
 - Janssen
 - Shire
 - Allergan

CanMEDS Roles

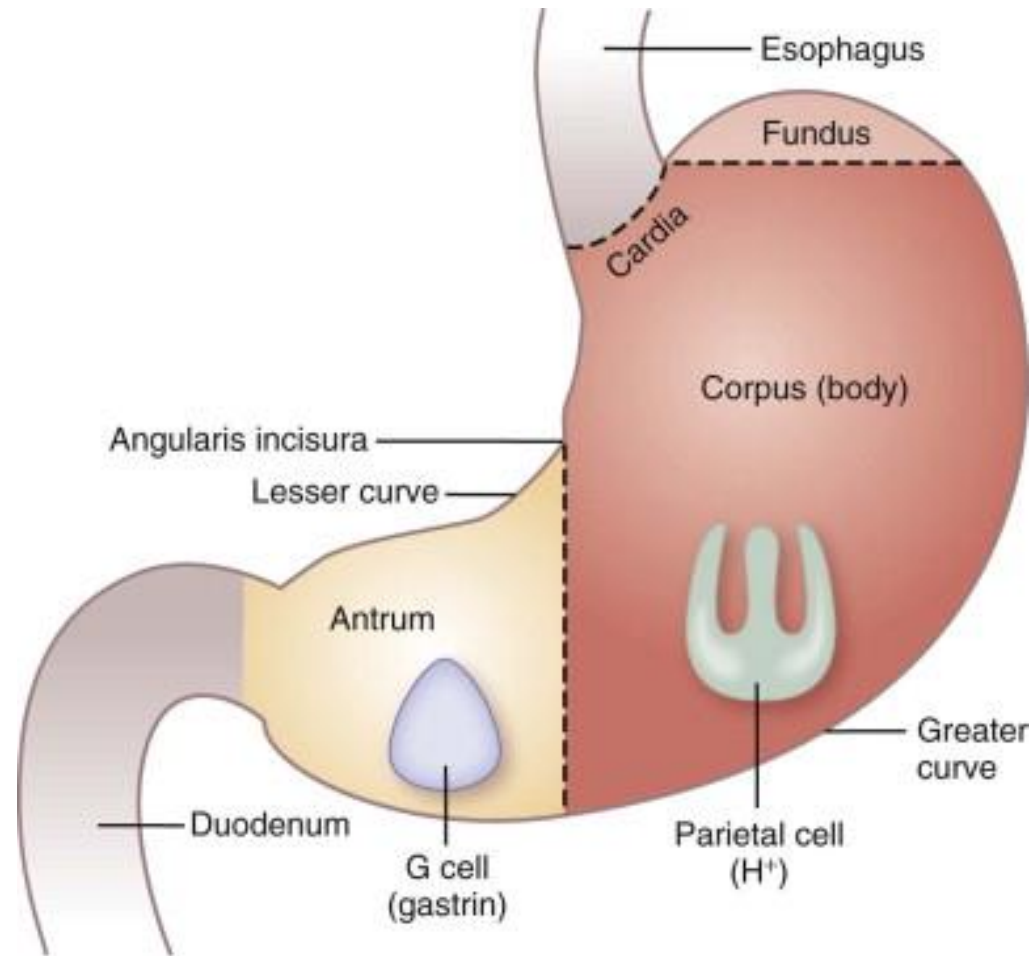
X	Medical Expert (as <i>Medical Experts</i> , physicians integrate all of the CanMEDS Roles, applying medical knowledge, clinical skills, and professional values in their provision of high-quality and safe patient-centered care. <i>Medical Expert</i> is the central physician Role in the CanMEDS Framework and defines the physician's clinical scope of practice.)
X	Communicator (as <i>Communicators</i> , physicians form relationships with patients and their families that facilitate the gathering and sharing of essential information for effective health care.)
	Collaborator (as <i>Collaborators</i> , physicians work effectively with other health care professionals to provide safe, high-quality, patient-centred care.)
	Leader (as <i>Leaders</i> , physicians engage with others to contribute to a vision of a high-quality health care system and take responsibility for the delivery of excellent patient care through their activities as clinicians, administrators, scholars, or teachers.)
X	Health Advocate (as <i>Health Advocates</i> , physicians contribute their expertise and influence as they work with communities or patient populations to improve health. They work with those they serve to determine and understand needs, speak on behalf of others when required, and support the mobilization of resources to effect change.)
X	Scholar (as <i>Scholars</i> , physicians demonstrate a lifelong commitment to excellence in practice through continuous learning and by teaching others, evaluating evidence, and contributing to scholarship.)
	Professional (as <i>Professionals</i> , physicians are committed to the health and well-being of individual patients and society through ethical practice, high personal standards of behaviour, accountability to the profession and society, physician-led regulation, and maintenance of personal health.)

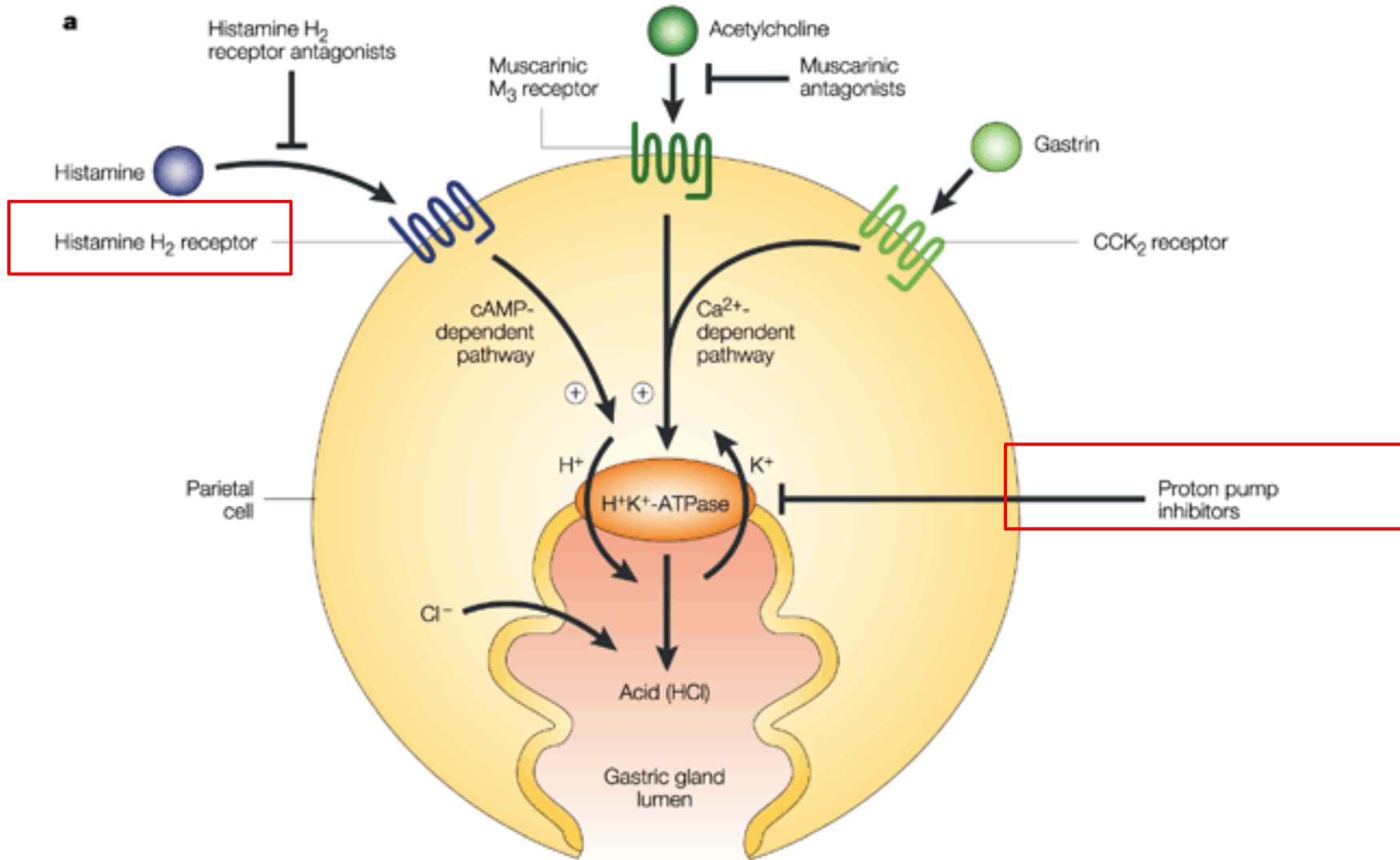
Objectives

- Review the physiology of gastric acid production and the mechanism of action for proton pump inhibitors
- Discuss the relevant literature regarding PPIs for specific indications
- Address controversies and adverse effects associated with long-term use

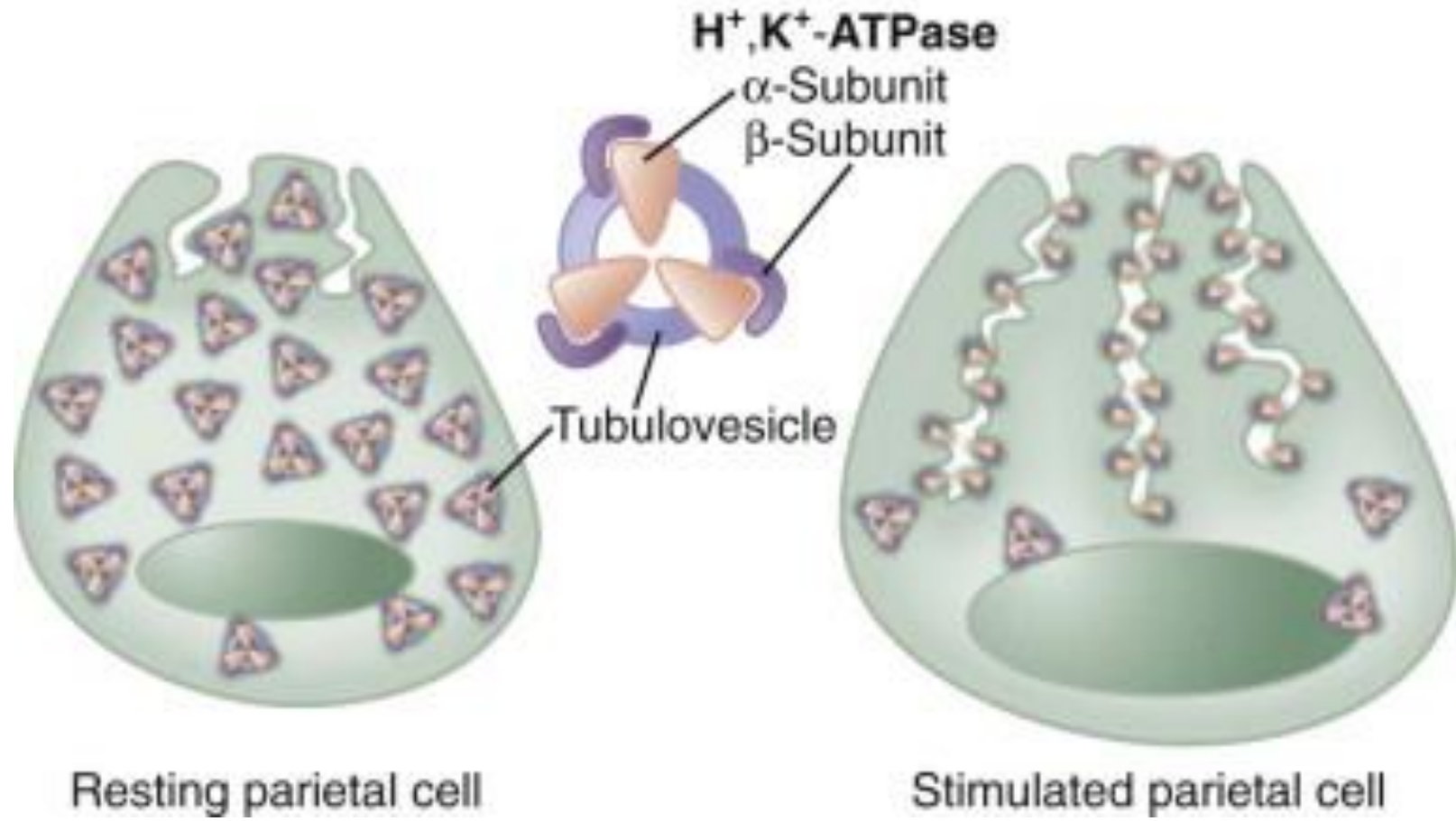
- A 45yo male presents with a 1 year history of heartburn and “indigestion” 3-4 days each week. What is your initial therapy?
 - A. Domperidone
 - B. PPI
 - C. H2RA
 - D. Pepto-bismol
 - E. None of the above

What is the role of HCl?





Mechanism of Action



Trade Name	Generic	Standard dose
Omeprazole	Losec	20mg
Lansoprazole	Prevacid	30mg
Rabeprazole	Pariet	20mg
Pantoprazole	Pantoloc, Tecta	40mg
Esomeprazole	Nexium	40mg
Dexlansoprazole	Dexilant	30, 60mg

Indications for a PPI

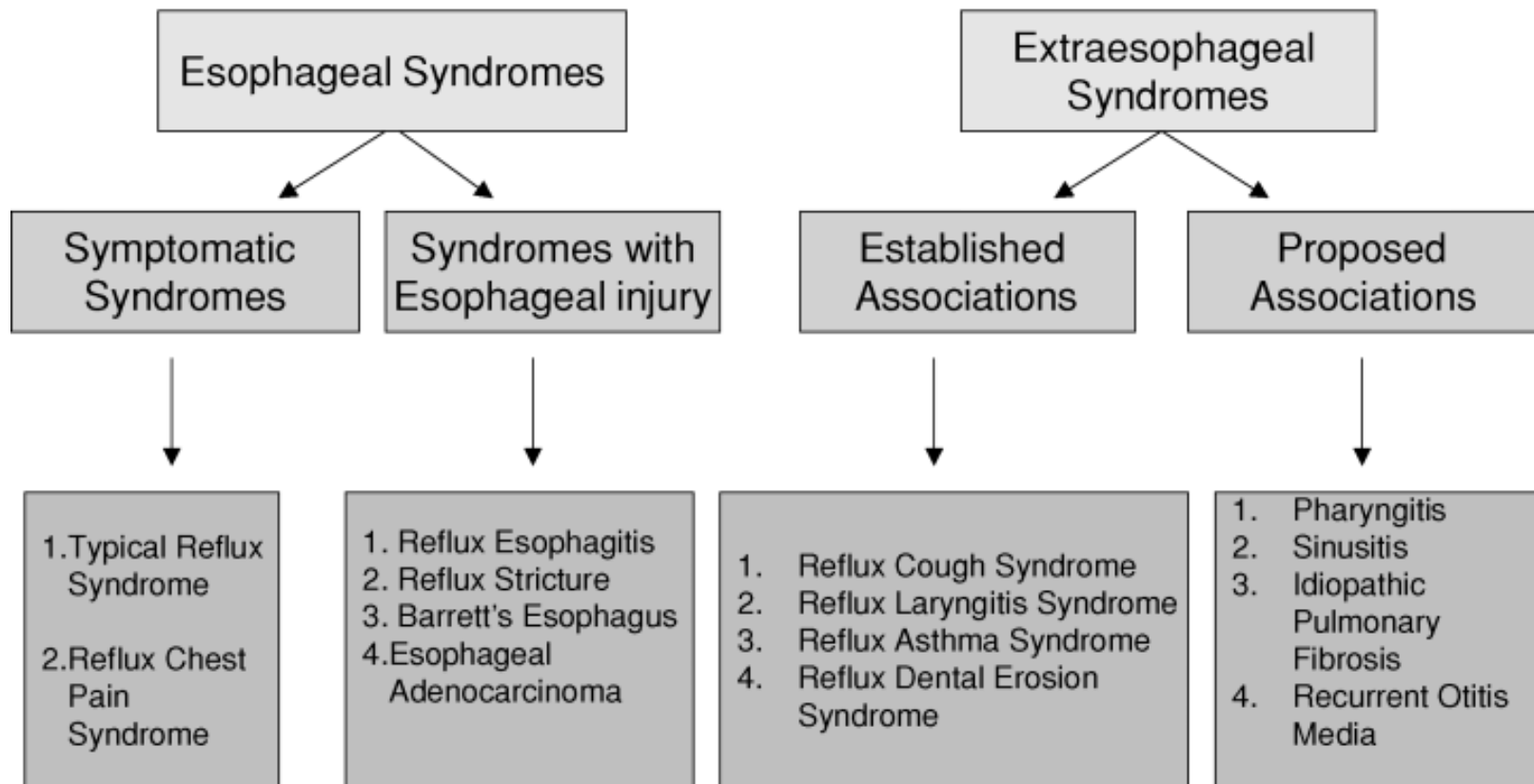
- GERD
- Peptic ulcer disease
- Non-ulcer (functional) dyspepsia
- Acute GI bleeding
- Gastroprotection with NSAIDs and antiplatelet agents
- Treatment of H pylori
- ZES

GERD

- 10-20% of the population
- Heartburn and acid regurgitation are the classic symptoms
- Other symptoms have been attributed to GERD



GERD is a condition which develops when the reflux of gastric content causes troublesome symptoms or complications



PPIs in GERD

- Role in diagnosis if classic symptoms present
- 70-80% symptom relief in erosive GERD
- 84% healing of esophagitis at 8 weeks (52% for H2RA)
- Majority of patients with LA Class B/C esophagitis relapse by 6 months off PPI

Lind et al. APT 1999

Pace et al. APT 2007

Chiba et al. Gastro 1997

- 50-60% symptom relief in non-erosive GERD
- On-demand PPI
 - 83% of patients with NERD achieve symptom remission with on-demand PPI
 - vs 56% on placebo
 - Systematic review shows symptom-free days are similar to continuous therapy

Functional Dyspepsia

Rome IV Criteria

Table 2. Functional Gastrointestinal Disorders: Disorders of Gut–Brain Interaction

A. Esophageal Disorders

- A1. Functional chest pain
- A2. Functional heartburn
- A3. Reflux hypersensitivity

- A4. Globus
 - A5. Functional dysphagia
-

B. Gastroduodenal Disorders

- B1. Functional dyspepsia
 - B1a. Postprandial distress syndrome (PDS)
 - B1b. Epigastric pain syndrome (EPS)
 - B2. Belching disorders
 - B2a. Excessive supragastric belching
 - B2b. Excessive gastric belching
-

- B3. Nausea and vomiting disorders
 - B3a. Chronic nausea vomiting syndrome (CNVS)
 - B3b. Cyclic vomiting syndrome (CVS)
 - B3c. Cannabinoid hyperemesis syndrome (CHS)
 - B4. Rumination syndrome
-

Functional Dyspepsia

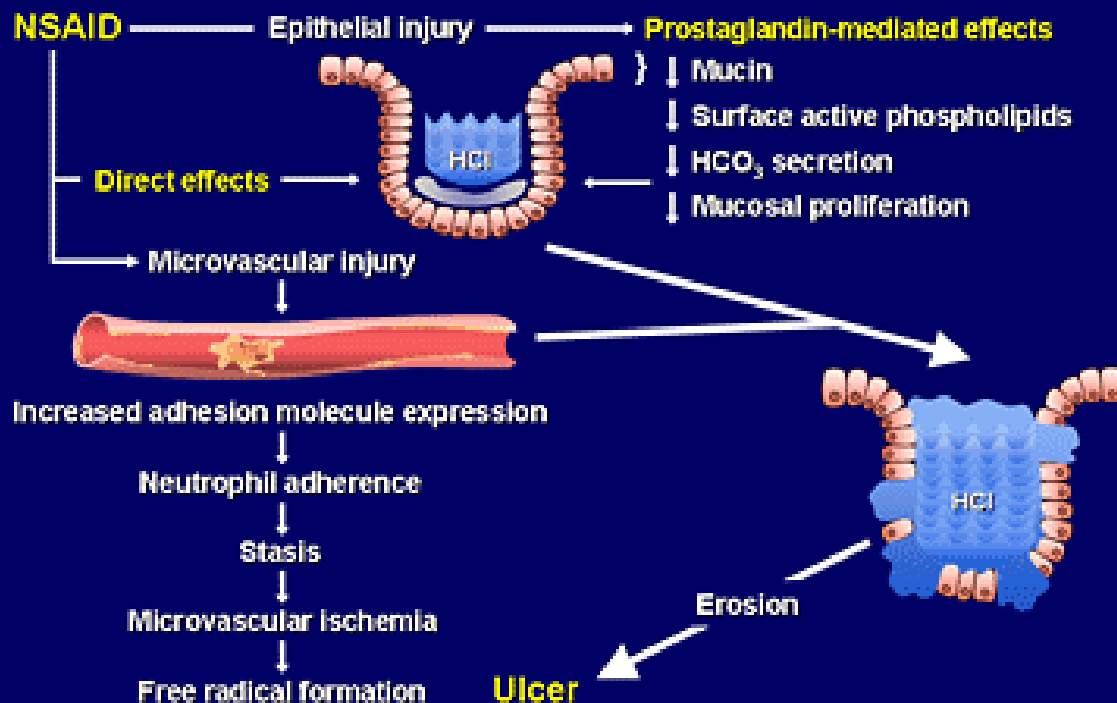
- Up to 20-40% of the population with dyspepsia symptoms
- Treatment options
 - Diet
 - H pylori eradication
 - **Acid suppression**
 - Prokinetics
 - TCA/SSRI
 - CAM

How effective are PPIs in FD?

- 30% of patients have no or minimal symptoms after 2-8 weeks of therapy
- 25% placebo rate
- No benefit to higher doses

NSAIDs and PUD

Mechanisms of NSAID-Related Ulcer Formation



NSAIDs and PUD Risk

- 20-25% of patients on NSAIDs develop PUD
- 2-4% will have significant bleeding
- Risk is increased based on patient characteristics

Increased risk of GI Bleeding

- Age >65
- Higher doses of NSAID
- Short duration of use
- ASA use (2-4x)
- Concurrent corticosteroids or anticoagulation
- Previous PUD or NSAID complications
- ?cardiovascular disease

PPI for PUD Prophylaxis

- Esomeprazole 20, esomeprazole 40, placebo
- 5.3%, 4.7%, 20.4% ulcer rate
 - Age >60
 - h/o PUD past 5 years
 - Scheiman et al. AJG 2006.

Table 1. Patients at increased risk for NSAID GI toxicity

High risk

1. History of a previously complicated ulcer, especially recent
2. Multiple (>2) risk factors

Moderate risk (1–2 risk factors)

1. Age >65 years
2. High dose NSAID therapy
3. A previous history of uncomplicated ulcer
4. Concurrent use of aspirin (including low dose) corticosteroids or anticoagulants

Low risk

1. No risk factors

H. pylori is an independent and additive risk factor and needs to be addressed separately (see text and recommendations).

Table 2. Summary of recommendations for prevention of NSAID-related ulcer complications

	Gastrointestinal risk ^a		
	Low	Moderate	High
Low CV risk	NSAID alone (the least ulcerogenic NSAID at the lowest effective dose)	NSAID+PPI/misoprostol	Alternative therapy if possible or COX-2 inhibitor+PPI/misoprostol
High CV risk ^b (low-dose aspirin required)	Naproxen + PPI/misoprostol	Naproxen + PPI/misoprostol	Avoid NSAIDs or COX-2 inhibitors. Use alternative therapy

^aGastrointestinal risk is stratified into low (no risk factors), moderate (presence of one or two risk factors), and high (multiple risk factors, or previous ulcer complications, or concomitant use of corticosteroids or anticoagulants). ^bHigh CV risk is arbitrarily defined as the requirement for low-dose aspirin for prevention of serious CV events. All patients with a history of ulcers who require NSAIDs should be tested for *H. pylori*, and if the infection is present, eradication therapy should be given.

Acute GI Bleeding

- Mainstay of therapy
- High-dose IV PPI in NVUGIB
 - 55-60% decreased risk of rebleeding
 - 40% decreased need for surgery
 - Up to 43% decreased mortality
- Cost-effective

Leontiadis et al. Gastroenterology 2009.

Laine and McQuaid. Gastroenterol Hepatol 2009.

Indications - Summary

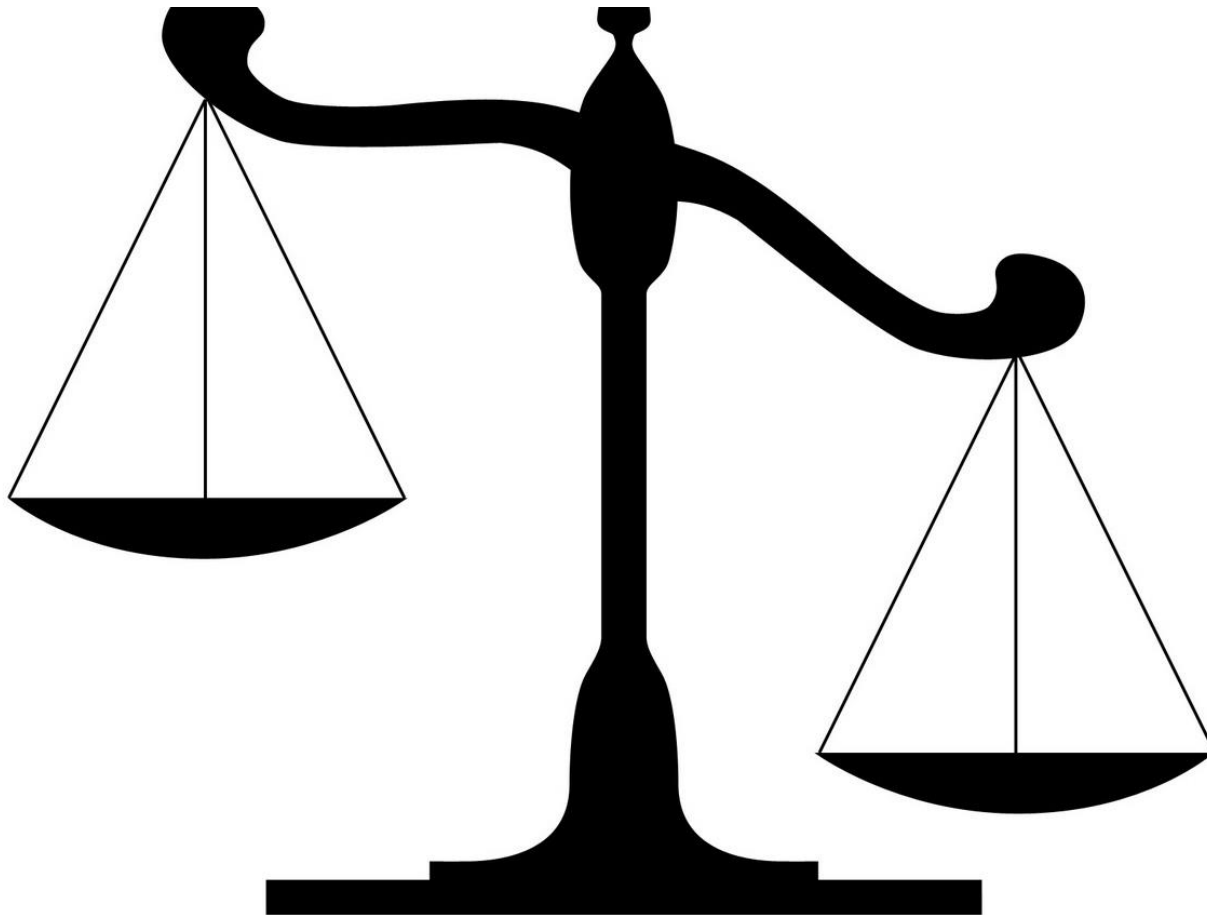
- Good data
 - GERD
 - PUD
 - NSAID ulcer prophylaxis
 - Acute GI bleeding
 - Treatment of H pylori
- Poor/Questionable Data
 - Non-classic GERD symptoms
 - Functional dyspepsia
 - Other

- But, every time I stop the medication, my heartburn comes back...

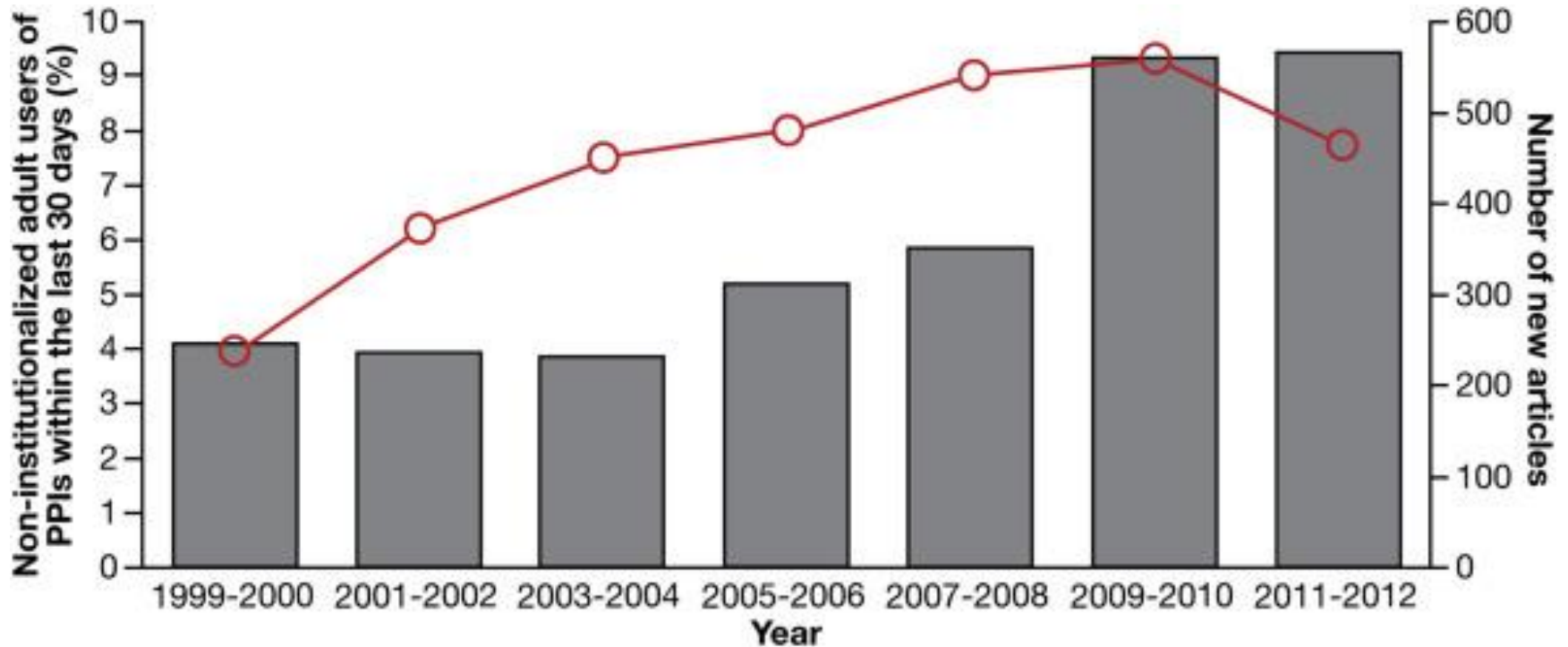
Rebound Hyperacidity with PPI

- 44% of healthy volunteers experience upper GI symptoms after withdrawal of PPI after 8 weeks
 - Reimer et al. Gastroenterology 2009.
- Role in symptomatic patients is not clear

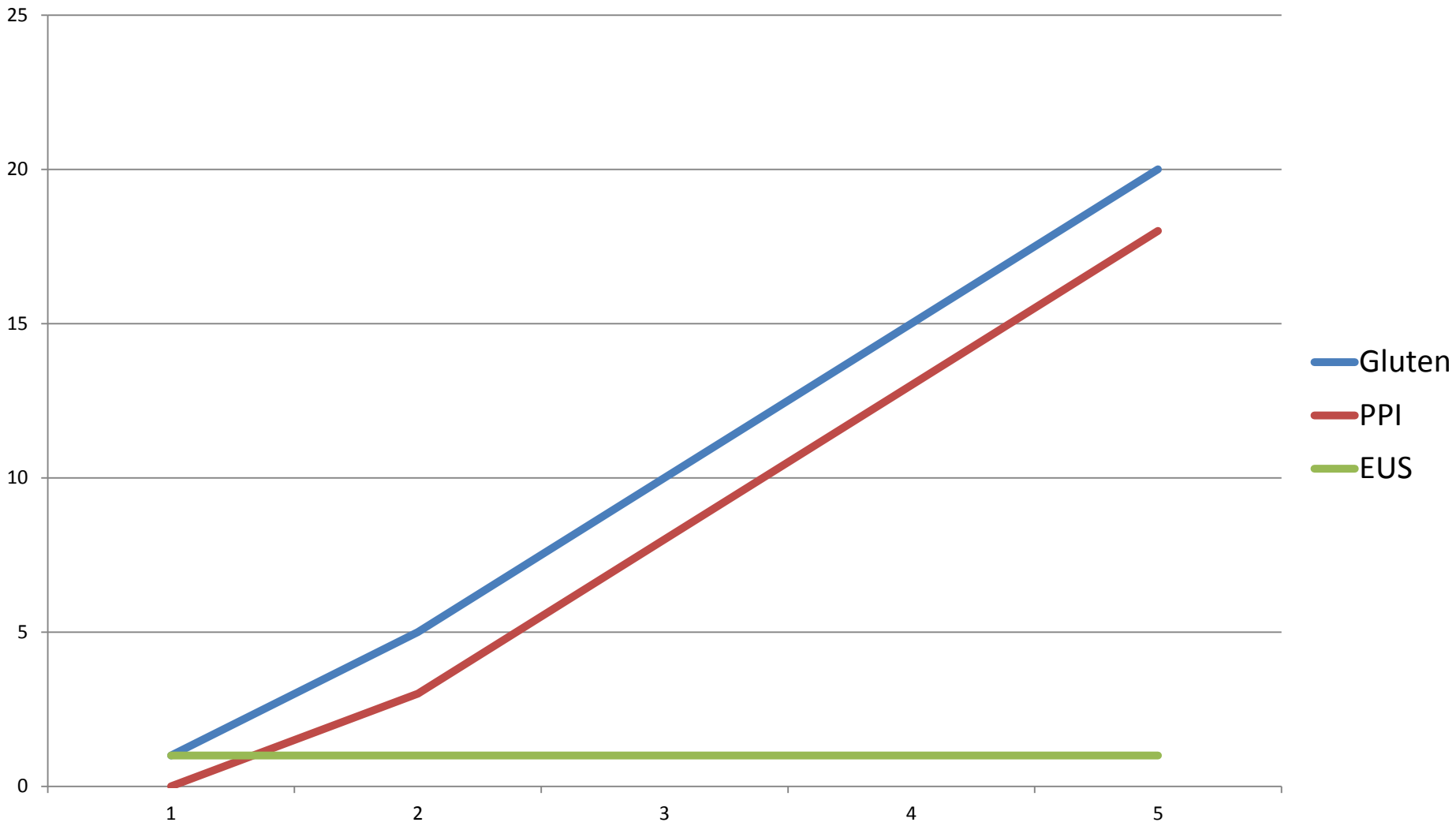
Adverse Effects with PPIs



Publications on AEs



Freedberg et al. Gastroenterology 2017.



Proton-Pump Inhibitor Use and the Risk of First-Time Ischemic Stroke in the General Population: A Nationwide Population-Based Study

Yen-Feng Wang, MD, PhD^{1,2,5}, Yung-Tai Chen, MD^{1,3,5}, Jiing-Chyuan Luo, MD^{1,4}, Tzeng-Ji Chen, MD, PhD¹, Jaw-Ching Wu, MD, PhD^{1,4} and Shuu-Jiun Wang, MD^{1,2}

Potential Adverse Effects

- *C difficile*
- Other enteric infections
- CAP
- Bone disease
- Vitamin/mineral malabsorption
- Drug interactions
 - Clopidogrel
 - Methotrexate
 - HCV therapy
- Diarrhea
- Microscopic colitis
- Hypomagnesemia
- Dementia
- Kidney disease
- Stroke
- SBP in cirrhosis

PPIs and *C difficile*

- Decreased acid may lead to bacterial growth in stomach and proximal SB
- Alteration of gut flora
- Effect on leukocyte activity
- Gastric acid does not kill spores
- Could the vegetative form of *C diff* play a role
 - Decreased gastric acid
 - Increased bile salts

Drug exposure	Pooled OR (95% CI)	I² (heterogeneity)
<i>Studies that reported data on PPI alone, and on H2RA alone (n=15) (3,28,31,35–40,43,45,47,51,57,61)</i>		
PPI alone	2.10 (1.66–2.66)	85
H2RA alone	1.50 (1.23–1.83)	60
<i>Studies that reported data on PPI alone, and on PPI with antibiotics (n=6) (26,32,34,36,61,63)</i>		
PPI alone	1.98 (1.39–2.83)	66
PPI+antibiotic	3.87 (2.28–6.56)	72
<i>Studies that reported data on antibiotic alone, PPI alone, and on PPI with antibiotics (26,34,63)</i>		
Antibiotics alone	1.97 (1.29–3.01)	60
PPI alone	1.82 ((1.50–2.21)	0
PPI+antibiotic	3.44 (2.43–4.87)	16

Population	Estimated incidence	Odds ratio with change in therapy	Change in CDI cases per 1,000 patients	NNT for harm
Unselected hospital admissions without PPI use (51)	16.7/1,000 at 14 days	Add PPIs: 1.93 (1.61–2.31)	+15	67 (48–101)
PPI users admitted to hospital (51)	53/1,000 at 14 days	Switch from PPI to H2RA 0.71 (0.53–0.97)	–15	If 69 (42–668) PPI users switched to H2RA, one case of CDI prevented
PPI users admitted to hospital (51)	53/1,000 at 14 days	Add concomitant antibiotics to PPI 1.96 (1.03–3.70)	+45	22 (9–670)
<i>Impact of adding PPIs according to baseline risk of CDI in different settings</i>				
Hospital admissions with antibiotic use (51)	42/1,000 at 14 days	Add PPIs: 1.93 (1.61–2.31)	+36	28 (21–42)
Hospital admissions with no antibiotic use (51)	5.4/1,000 at 14 days	Add PPIs: 1.93 (1.61–2.31)	+5	202 (144–307)
Community patients (72)	1.2/1,000 per year	Add PPIs: 1.93 (1.61–2.31)	+1	899 (638–1,369)

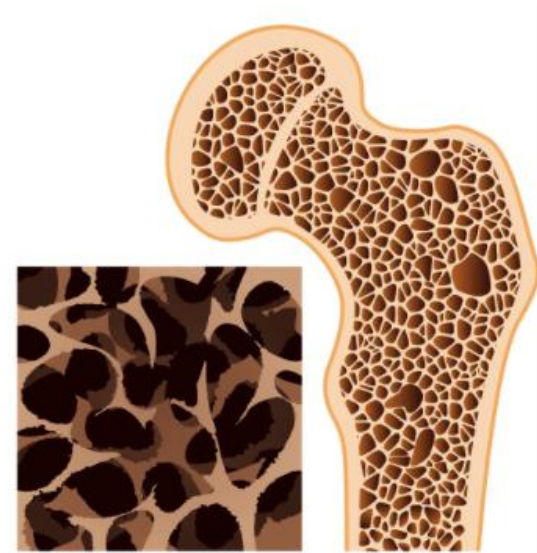
PPIs and C diff

- Meta-analysis of 51 data sets
- Evidence of publication bias and study heterogeneity
- **Pooled OR for PPI and C diff = 1.65**

- CDAD incidence of 48/100,000 patient years
- CDAD at 14 days after hospitalization
 - 42/1000 on Abx
 - 5.4/1000 not on Abx
- **Number needed to harm**
 - **50 for in-patients on Abx**
 - **367 for in-patients not on Abx**
 - **3925 for the general population**

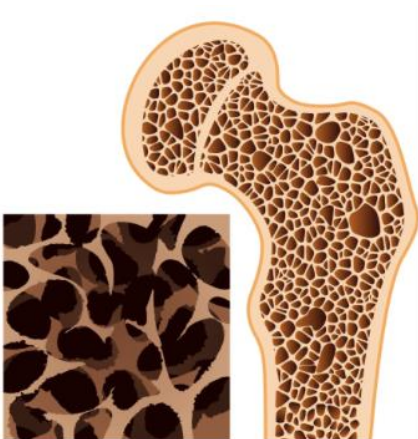
PPIs and the Bone

- What is the effect on calcium absorption?
- Is there an effect on osteoclasts?



PPIs and Bone Health

- No increased risk of osteoporosis identified in a large population-based registry
 - RR 0.84 hip, RR 0.79 vertebrae
- PPIs do not affect calcium absorption or cause osteoporosis



Targownik et al. Gastro 2010.

Leontiadis et al. Curr Treat Opt Gastroenterol 2014.

Risk of Fracture

- Meta-analysis of 223,201 cases of fracture
 - PPI use associated with increased risk of #
 - Vertebral: OR 1.50
 - Hip: OR 1.24
- NNH = 2000
 - Leontiadis et al. Curr Treat Opt Gastroenterol 2014.

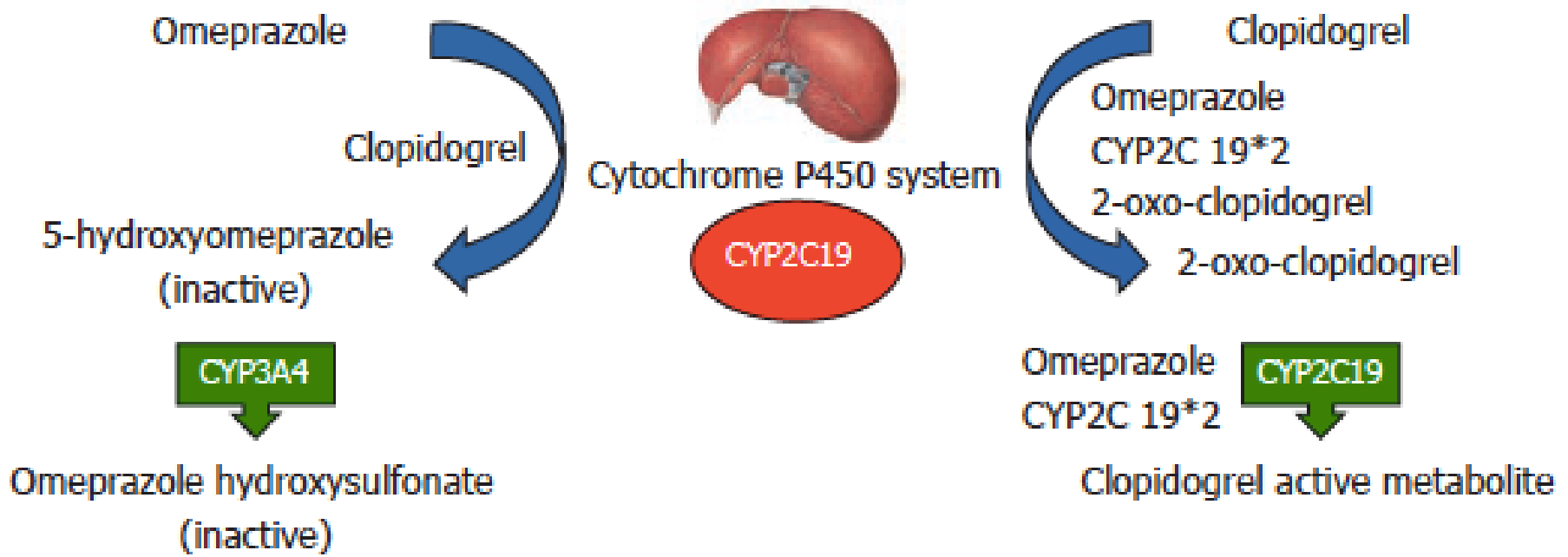
Ngamruengphong et al. Am J Gastroenterol 2011.

Targownik et al. Am J Gastroenterol 2012.

Targownik et al. Gastroenterol 2012.

PPIs and Antiplatelet therapy

- Dual antiplatelet therapy increased the risk of bleeding by 80-95%
- 45% decrease in GI events (bleeding, ulceration, erosions) for omeprazole vs placebo in patients on dual anti-platelet therapy



Is this clinically relevant?

- Observational studies suggested increased risk of CV events (OR 1.25-1.50)
- Several further observational, cohort and post-hoc studies have shown no difference
- RCT of omeprazole vs placebo terminated early (3873/5000 patients enrolled)
 - No difference seen in CV events (HR 0.99)
 - Decreased risk of UGIB (HR 0.34)

Drepper et al. WJG 2012.

Laine et al. Am J Gastroenterol 2010.

- 3 meta-analyses completed showing RR as high as 1.43 for MACE
- RR lower when only high quality studies analyzed or propensity score adjusted studies used (RR 1.15-1.23)
- One meta-analysis showed no difference in events

Kwok et al. Aliment Pharmacol Ther 2010
Siller-Matula et al. J Thromb Haemost 2010
Lima et al. BMC Med 2010

Flavor of the month...

- Dementia
 - ? 1.4x increase in risk in PPI users
 - One RCT showed higher risk of acute cognitive impairment
- Renal impairment
 - 2-3X higher rate of acute kidney injury (AKI)
 - 1.5X increase in CKD

Akter et al. Alzheimer's Research & Therapy 2015.

Batchelor et al. J Gastro and Hepatol 2017.

Gomm et al. JAMA Neuro 2016.

Antoniou et al. CMAJ Open 2015.

Klepser et al. BMC Nephrol 2013.

Lazarus et al. JAMA Intern Med 2016.

Xie et al. J Am Soc Nephrol 2016

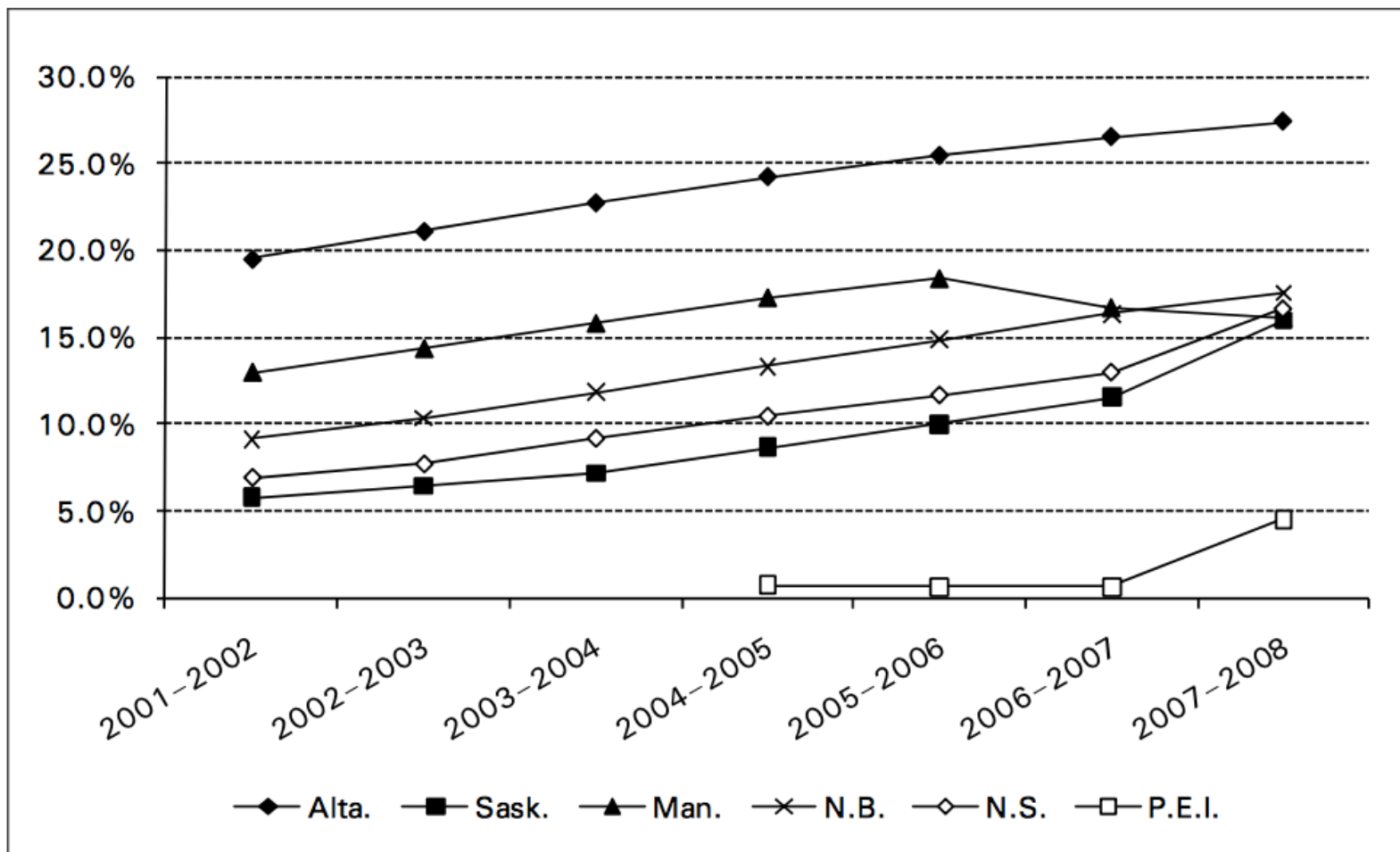
How prevalent is PPI use?

Table 2 Top 10 drug classes by public drug program spending, selected jurisdictions,* 2015

Drug class	Common uses	TPS (\$ millions)	Proportion of TPS (%)	Rate of use (%)	TPS per paid beneficiary (\$)
Tumour necrosis factor alpha inhibitors (anti-TNF drugs)	Rheumatoid arthritis, inflammatory bowel disease, Crohn's disease	717.6	8.2	0.4	18,931.5
Other antivirals[†]	Hepatitis C, HIV	472.2	5.4	0.1	49,559.0
Antineovascularization agents[‡]	Age-related macular degeneration, secondary and diabetic macular edema	432.4	4.9	0.5	9,127.2
HMG-CoA reductase inhibitors (statins)	High cholesterol	257.8	2.9	26.4	131.9
Proton pump inhibitors (PPIs)	Gastroesophageal reflux disease, peptic ulcer disease	253.3	2.9	18.2	174.1



Figure 3 Age–Sex Standardized Rate of PPI Use Among Seniors on Public Drug Programs in Select Provinces,* by Province, 2001–2002 to 2007–2008



PPI Overuse

- Excellent data for use in several indications, but many patients on PPI for “other” reasons
- Naunton et al. J Clin Pharm Ther 2000.
 - Review of 200 inpatients on PPI
 - 39% of patients on PPI for unapproved or questionable indications

PPI Overuse

- Pham et al. Ann Pharma 2006
 - Review of 213 inpatients in Michigan
 - 29% on acid suppression on admission, increasing to 71% on admission (91% PPI)
 - **10% had an appropriate indication**
 - of those without a good indication:
 - 38% for stress-ulcer prophylaxis with steroids
 - 8% with remote PUD
 - 29% without any clear indication

PPI Overuse

- Many patients can discontinue long-term PPI therapy
- Study of 97 patients on PPI for 4 years (excluding h/o esophagitis and PUD)
 - Discontinuation successful in 27% of all patients
 - 48% of those without GERD were off PPI at 1 year

Choosing Wisely Canada



In partnership with the
Canadian Medical Association

1 Don't maintain long term Proton Pump Inhibitor (PPI) therapy for gastrointestinal symptoms without an attempt to stop/reduce PPI at least once per year in most patients.

PPIs are effective drugs for the treatment of gastro-esophageal reflux disease (GERD). Patients should always be prescribed the lowest dose of drug that manages their symptoms. Even though GERD is often a chronic condition, over time the disease may not require acid suppression and it is important that patients do not take drugs that are no longer necessary. For this reason patients should try stopping their acid suppressive therapy at least once per year. Patients with Barrett's esophagus, Los Angeles Grade D esophagitis, and gastrointestinal bleeding would be exempt from this.

Deprescribing PPIs

- What do I do?
- <http://www.open-pharmacy-research.ca/wordpress/wp-content/uploads/ppi-deprescribing-algorithm-cc.pdf>

Conclusions

- PPIs are potent inhibitors of acid production
- There is a defined role in both disease treatment and ulcer prophylaxis
- Use has been extended to numerous indications with minimal supporting data
- Overall excellent side effect profile, but this needs to be balanced with potential adverse effects on a case by case basis

Thank you!

- Questions
- rkberger@dal.ca
- Suggested reading
 - Scarpignato et al. BMC Medicine 2016.
 - Freedberg et al. Gastroenterology 2017.