

LONG -TERM USE OF PPIS: INDICATIONS, BENEFITS AND HARMS

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Objectives

- Identify the conditions supported by AGA/ACG guidelines necessitating long-term use of daily PPIs,
- Recognize which are long-term risks that PPIs have been associated with
- Identify how can inappropriate PPI use be avoided or stopped

Case Presentation

- Mrs. A. is a 65 year old woman presenting to your clinic today for a health maintenance visit and for medications' renewal.
- She has a new insurance plan which refused renewing her medications. A clinical assistant called to inform her that her PPI prescription is not justified and a medical visit is mandatory since her last one was around two years ago.
- *“My PPI is indispensable, it protects my stomach wall from all those pills I have to take everyday, what do I need to justify to the insurance?”* she said.

Case Presentation

- 65 yo female
- PMHx: DM II, HBP since 2007, osteoporosis, bilateral knee OA
- PSHx: Wrist Fracture in 2008, 2 c/s
- ROS: no GI Sx
- Non-smoker
- Rx: PPI, Aspirin, DPP4/Metformin, HCT/ARB, statin, Ca/Vit D, took biphosphonates for 7 years stopped them 2 years ago, paracetamol PRN
- PE
- Health Maintenance work up and labs ordered to monitor her DM and HBP

DO I DE-PRESCRIBE OR
CONTINUE HER PPI?

- How do I justify renewing her PPI prescription?
- For what the PPI was initially prescribed?

Indications of PPIs

Short-term

- Eradication of H.Pylori
- Acute gastritis/duodenitis
- Prophylaxis of gastritis/duodenitis associated with NSAIDs
- Stress ulcer prophylaxis

Long-term

- Gastroesophageal reflux disease and its complications,
- Erosive esophagitis,
- Gastro/Duodenal ulcers,
- Pathologic hypersecretory conditions
- Treatment of gastroduodenitis associated with NSAIDs& if NSAIDs can not be discontinued

Case

- For what the PPI was initially prescribed?

Mrs. A. explains that the PPI was prescribed few years ago for a duration of 8 weeks after taking a course of NSAIDs complicated by severe gastric pain. As she did not want to endure same symptoms again, and her physician prescribes NSAIDs often when her knee pain is severe, she asked him to add the medicine to her chronic meds.

- For what the PPI was initially prescribed?
- If long-term PPI use is considered justified, what should do I take into account before continuing it?

Potential Adverse Effects

- Three main concerns of long-term use of PPIs:
 - **Hypochlorhydria → infections and malabsorption**
 - Hypergastrinemia → gastric carcinoids in rats, different physiology in humans
 - Gastric Atrophy → theoretically increased risk of gastric cancer, one study: confounding factor concomitant infection with H.pylori

Potential Adverse effects

- Clostridium difficile & other enteric infections
- Pneumonia
- Malabsorption: Mg, vit B12, Iron
- Hip fracture and Ca malabsorption
- Drug interactions: clopidogrel, methotrexate
- Kidney disease
- Dementia
- Drug-Induced lupus
- Mortality
- ...

1. Fashner, Julia, and Alfred C. GITU. "Diagnosis and Treatment of Peptic Ulcer Disease and H. pylori Infection." *American family physician* 91.4 (2015).

2. Wolfe, M. "Overview and comparison of the proton pump inhibitors for the treatment of acid-related disorders." *UpToDate*. Waltham, MA: UpToDate (2013).

Clostridium difficile diarrhea

- 3 meta-analyses
 - PPIs vs H2 receptor antagonists
 - ORs 1.7 (1.5-2.5), 2.5 (1.2-5.4)

 - Observational studies
 - Significant heterogeneity
- FDA safety alert,
- consider *C.difficile* infection in PPI users with persistent diarrhea.

Pneumonia

- A meta-analysis of 31 studies
- Patients taking PPIs or H2RAs increased risk of pneumonia OR PPI 1.27 (1.11-1.46) H2RA 1.22 (1.09-1.36)
- Large case control study: increased risk of CAP in patients who started PPI within the previous 48h to 30days.
- Unobserved health characteristics that predispose them to pneumonia

Magnesium absorption

- Due to reduced intestinal absorption
 - FDA issued a safety alert (PPIs prescribed for more than one year)
 - FDA suggests that providers consider obtaining Mg levels prior to starting a PPI if long-term use is expected or PPIs are used in conjunction with other meds associated with hypoMg (digoxin, diuretics...)
- Consider obtaining Mg levels periodically

Hip fracture and Ca Malabsorption

- Meta-analysis that included 11 cohort and case control studies (>1000000 pts) → the risk of hip fracture was increased among PPI users RR 1.3 (1.19-1.43), also there were an increased risk of spine fracture 1.56(1.31-1.85)
 - Nurses' Health Study included post menopausal women (80000). The risk of hip fx with PPI use was 36% higher, however the difference was more pronounced in current and former smokers and no significant increase in hip fracture risk among non smokers who used PPIs. HR 1.6 (0.77-1.46)
- FDA revised safety information about PPIs about a possible increased risk of fractures of the hip, wrist and spine.

Vit B12 and Iron Malabsorption

- Long-term use of omeprazole has been associated with vit B12 malabsorption.
- It is reasonable to assess vit B12 periodically (eg annually)
- Iron: In most cases the decreased absorption does not appear to be of clinical significance.

Interaction with clopidogrel

- The relevance of the data available remains highly controversial regarding clopidogrel-omeprazole.

→ FDA concluded that patients taking clopidogrel should consult their physician if they are taking or considering taking PPIs

Back to the case

- Initially a therapeutic then a prophylactic use
- Asymptomatic
- Hx of wrist fracture and osteoporosis

You decide that her PPI should be de-prescribed and you explain thoroughly your decision to her.

- How do I justify renewing her PPI prescription?
- If long-term PPI use is considered justified, what should do I take into account when continuing it?
- **If unjustified long term use, how am I going to de-prescribe it?**

General guidelines that may be employed when stopping a PPI

- Patients with GERD or dyspepsia are considered for a taper after being asymptomatic for a minimum of 3 months.
- For patients on a moderate to high dose PPI, we cut the dose by 50% every week until the patient is on the lowest dose of the medication. Once on the lowest dose for one week, the patient is instructed to stop the medication.
- Data are limited

- Mrs. A. comes after 14 days complaining of heartburn, she is angry, dissatisfied and is asking you to re-prescribe her PPI.

What did go wrong?

Rebound Gastric acid hypersecretion

- Rebound Gastric acid hypersecretion following the discontinuation of PPIs in patients managed for prolonged periods.
- Many patients relapse
- Reasons are not entirely clear
- Disruption of normal pH-related feedback inhibition of acid secretion that occurs after a meal

In fact...

Data are limited regarding the success of attempts at stopping therapy

- How do I justify renewing her PPI prescription?
- If long-term PPI use is considered justified, what should do I take into account when continuing it?
- If unjustified long term use, how am I going to de-prescribe it?
- **What are the outcomes and success rate at stopping therapy?**

A Cochrane intervention review:

- “Deprescribing versus continuation of chronic proton pump inhibitor use in adults”
- Objective: To determine the effects (benefits and harms) associated with deprescribing long-term PPI therapy in adults, compared to chronic daily use (28 days or greater).
- Comparing at least one deprescribing modality (e.g. stopping PPI or reducing PPI) with a control consisting of no change in continuous daily PPI use
- Outcomes of interest: change in gastrointestinal (GI) symptoms, drug burden/PPI use, cost/resource use, negative and positive drug withdrawal events, and participant satisfaction.

- Trial participants were aged 48 to 57 years, except for one trial that had a mean age of 73 years.
- There was low quality evidence that on-demand use of PPI may increase risk of '**lack of symptom control**' compared with continuous PPI use (risk ratio (RR)1.71, 95% confidence interval (CI) 1.31 to 2.21), thereby favoring continuous PPI use (five trials, n = 1653).
- Patients were also **less satisfied**.
- No data on **Cost**.
- There were insufficient data to make a conclusion regarding long-term benefits and harms of PPI discontinuation, although two trials (one on-demand trial and one abrupt discontinuation trial) reported endoscopic findings in their intervention groups at study end.
- Success rate at one year is 58% year(one cohort study, 71pts)



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- How do I justify renewing her PPI prescription?
- If long-term PPI use is considered justified, what should do I take into account when continuing it?
- If unjustified long term use, how am I going to de-prescribe it?
- What is the success rate at stopping therapy?
- **How to avoid PPIs misuse?**

How to avoid PPIs misuse?

- It is recommended that providers prescribe the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.
- Eradication of H.Pylori (14 days)
- Acute gastritis/duodenitis (4 to 8 weeks/ OTC 14days)
- Prophylaxis of gastritis/duodenitis associated with NSAIDs
- Stress ulcer prophylaxis (ICU days only)
- Start considering discontinuation of PPIs after 6 months of initiation if patient is symptom free

1. Fashner, Julia, and Alfred C. GITU. "Diagnosis and Treatment of Peptic Ulcer Disease and H. pylori Infection." *American family physician* 91.4 (2015).

2. Wolfe, M. "Overview and comparison of the proton pump inhibitors for the treatment of acid-related disorders." *UpToDate*. Waltham, MA: UpToDate (2013).

At the end of the encounter...

- Mrs. A. says
“ You shouldn’t have stopped my PPI”
- You reply
- “ I will re-prescribe your PPI since you had some relapse symptoms. But now you know some adverse events should be monitored and I might try to discontinue it on a later assessment for your own safety.”



In conclusion

- How do I justify renewing PPIs prescription? For what the PPI was initially prescribed?
 - Review indications and check for current GI or GI related symptoms
- If long-term PPI use is considered justified, what should do I take into account when continuing it?
 - Safety and adverse events
- If unjustified long term use, how am I going to de-prescribe it?
 - Taper, stop and monitor relapse symptoms

- What is the success rate at stopping therapy? Any benefits if continued?

→ 58% (one study)

→ Less “lack sense of control” Less Dissatisfaction
(Cochrane review)

- How to avoid PPIs’ misuse?

→ It is recommended that providers prescribe the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

**SUGGESTED
ALGORITHM**

Assessment of long-term use of PPIs
> 6months

Indication Justified for
long-term use



Continue PPI
at a minimal
dose



Monitor adverse
events: vit B12,
Mg, Ca? BMD?
Cl.difficile,
drug-drug
interaction

Indication not justified
Chronic condition resolved
Patient asymptomatic >3
months



Taper and
discontinue



Patient
symptom free



De-prescribing
succeeded

Relapse of
Symptoms

