WHY YOU SHOULD NOT BE PUMPED ABOUT PPIS?

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NOTHING TO DISCLOSURE

OBJECTIVES:

1. Evaluate recent literature/recommendations regarding the associated risks of Proton Pump Inhibitors (PPIs)
2. Discuss strategies pharmacists can use to decrease risks of PPIs
Outline

**Introduction/Establishing a Need**
- PPIs available and how they work
- Uses and prescribing

**Safety Concerns-FDA**
- Infections
- Malabsorption
- Drug-drug interactions

**Safety Concerns-Update and Recent Studies**
- Dementia
- Kidney disease

**Discontinuing PPIs**
- Rebound acid hypersecretion
- Tapering

Case/Q&A

**PPIS ARE OVERPRESCRIBED AND BETWEEN 53% AND 69% OF PPI PRESCRIPTIONS WERE FOUND TO BE FOR INAPPROPRIATE INDICATIONS.**

**Appropriate For Short-term Use**

**GERD**
- Initial 8 week course
- For patients that require more long-term therapy, recommend a trial of a lower dose, on-demand therapy, or intermittent therapy to minimize exposure.

**Gastric and duodenal ulcers**
- FDA-approved regimens typically last 4-8 weeks

**Stress ulcer prophylaxis**
- Reserve for certain high risk ICU patients (i.e. mechanical ventilation >48hr)

**H. Pylori**
Potential Long-term Uses

- Refractory GERD
- Erosive esophagitis
- Zollinger-Ellison Syndrome
- NSAID-induced ulcers
- Chronic anticoagulation after a GI bleed
- Barrett’s esophagus

FDA REGARDING THE ASSOCIATED EFFECTS OF PPIS BASED ON OBSERVATIONAL STUDIES

<table>
<thead>
<tr>
<th>FDA Drug Safety Communication</th>
<th>Release Date</th>
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<tbody>
<tr>
<td>PPIs may be associated with an increased risk of Clostridium difficile–associated diarrhea (CDAD)</td>
<td>2/8/2012</td>
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<td>PPI drugs may cause low serum magnesium levels (hypomagnesemia), if taken for prolonged periods of time (in most cases, longer than one year)</td>
<td>3/2/2011</td>
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<td>Possible increased risk of fractures of the hip, wrist, and spine with high doses or long-term use of proton pump inhibitors</td>
<td>5/25/2010</td>
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NO EVIDENCE THAT PPIS INCREASE RISK OF:

- COLON CANCER
- CARDIAC EVENTS
DRUG-DRUG INTERACTIONS

Clopidogrel + esomeprazole, omeprazole → platelet activity 20-40%

- Due to PPIs inhibit cytochrome P450 (CYP2C19)
- Mixed evidence/recommendations:
  - GERD guidelines by the American College of Gastroenterology: PPIs + clopidogrel is okay
  - American College of Cardiology and the American Heart Association: Just use alternative, H2RA
  - Pantoprazole may be preferred given the lower potential to inhibit CYP2C19

NEWER SAFETY CONCERNS WITH PPIS

DEMENTIA
&
KIDNEY FAILURE

PPIS AND DEMENTIA: POSSIBLE MECHANISM

Vit B12 deficiency → Amyloid beta peptide → Dementia
GERMAN STUDY ON AGING, COGNITION AND DEMENTIA IN PRIMARY CARE PATIENTS (AgeCoDe)

2,911 primary care patients 75 years of age or older, the use of PPI medication had a significantly increased risk of any dementia [Hazard ratio (HR) 1.38, 95% confidence interval (CI) 1.04–1.83] and Alzheimer’s disease (HR 1.44, 95%)

PROSPECTIVE COHORT STUDY PUBLISHED BY GOMM, ET.AL.

2,950 patients receiving regular PPI use (mean [SD] age, 83.8 [5.4] years; 77.9% female) had a significantly increased risk of incident dementia versus the patients not receiving PPIs (HR, 1.44 [95% CI, 1.36-1.52]; P < .001).

Strength:
• Data extracted from largest German health insurer (~50% elderly)

Limitation:
• Not able to control for as many variables and confounders such as amyloid deposition.
• PPI use may also be linked to the factors that play a role in risk of dementia; for example, obesity, alcohol consumption, and poorer health and education.

ATHEROSCLEROSIS RISK IN COMMUNITIES (ARIC) COHORT

10,483 patients followed for a median of 13.9 years. 56 incident CKD events among the 322 baseline PPI users (14.2 per 1,000 person years), and 1,382 events among 10,160 baseline nonusers (10.7 per 1,000 person-years) with similar results after adjusting for confounding variables (HR, 1.50; 95%CI, 1.14-1.98; P = .003).

GEISENGER HEALTH SYSTEM COHORT

248,751 patients followed for a median of 6 years. 1,021 incident CKD events among 16,900 baseline PPI users (20.1 per 1,000 person-years) and 28,226 events among 231,851 baseline nonusers (18.3 per 1,000 person-years). Also found that 2x/day PPI use (adj HR, 1.46; 95% CI, 1.28-1.67) was associated with a higher risk compared to 1x/day use (adj HR, 1.15; 95% CI, 1.08-1.21).

*Additional trials needed to establish a causal relationship.
PROTON PUMP INHIBITOR USE AND THE RISK OF INCIDENT CHRONIC KIDNEY DISEASE

PPIs were independently associated with a 20% to 50% higher risk of incident CKD, after adjusting for several potential confounding variables.

Use of H2RAs was not independently associated with CKD.

Additional trials needed to establish a causal relationship.

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<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P Value</th>
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<tbody>
<tr>
<td>PPI users</td>
<td>1.31</td>
<td>1.01-1.71</td>
<td>0.13</td>
</tr>
<tr>
<td>H2RA users</td>
<td>1.21</td>
<td>0.95-1.56</td>
<td>0.15</td>
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*SHORT TERM (<2MTHS) USE OR LOW DOSES*

- STOP IT/
- DISCONTINUE

*LONG TERM USE OR HIGH DOSES*

- REBOUND HYPERSECRETION
TAPER

- Dose
- Extend dosing interval to every other day and possibly every third day for a week or longer
- Recommend antacids or H2RAs as needed for breakthrough symptoms after PPI discontinuation.

DON’T FORGET ABOUT NON-PHARM EDUCATION FOR GERD OR HEARTBURN
• Don’t eat two to three hours before bedtime
• Raise the head of the bed six inches
• Stay at a normal weight and quit smoking
• Avoid foods that seem to make it worse

Also Great Opportunity During Transitions of Care!
CASE:
OP is a 68 yo female
- PMH significant for HTN and CHF
- discharged last month from the hospital in ICU for pneumonia and HF exacerbation.
- Meds before hospitalization:
  - lisinopril 10mg daily
  - carvedilol 25mg BID
- Meds after hospitalization:
  - continued on lisinopril and carvedilol
  - furosemide 40mg BID, new
  - omeprazole 40mg every morning, new
Pt is asking you, his pharmacist, today for a refill on his omeprazole or how to purchase this medication over-the-counter?

IN SUMMARY
- While PPIs are used to effectively treat a variety of GI disorders there have been studies showing associated increase risk of certain infections, hypomagnesium, fractures, Vit B12 deficiency and most recently, dementia and kidney disease.
- Inappropriate PPI use should be discontinued but rebound hypersecretion can be common with symptoms that can last for months.
- Helpful to taper patients off PPIs by first reducing the dose and then dosing every other day for a week or longer.
- Patients can use H2RAs for breakthrough symptoms for GERD as needed.
PHARMACISTS:
Preventing Inappropriate Use/Overprescribing Educating On Safety Concerns & Non-pharm Evaluating Use For DC Or Taper

REFERENCES:


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