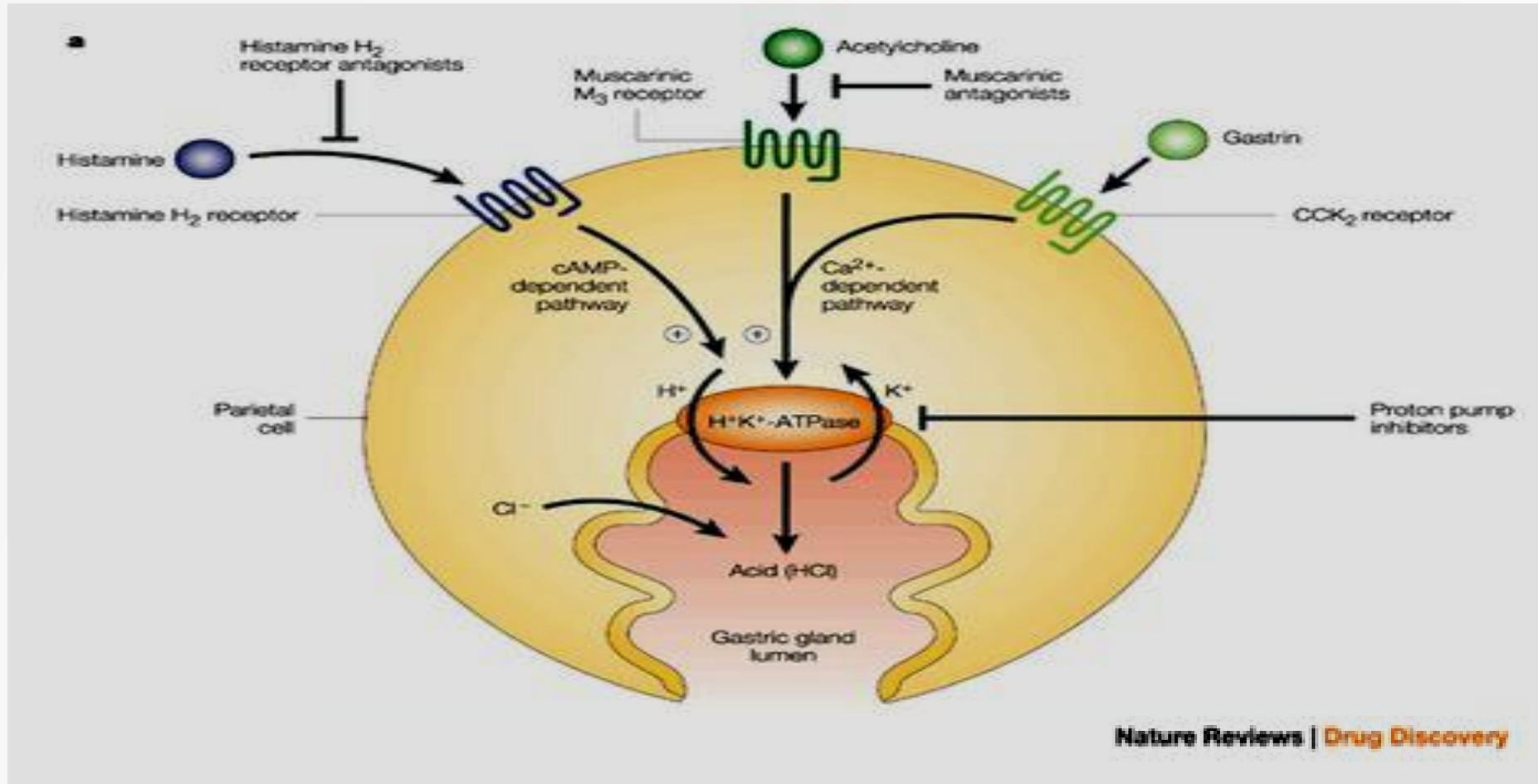


THE EFFECTS OF LONG- TERM PROTON PUMP INHIBITORS USE AND MISUSE

CONTENTS

- Overview
 - Indications
 - Over-prescribed in inappropriate conditions
 - Side effects of long-term PPI use
 - Conclusion
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OVERVIEW



INDICATIONS

- Peptic ulcer disease (6-8 weeks)
 - Gastroesophageal reflux causes complication (2-8 weeks)
 - Zollinger-Ellison syndrome
 - NSAID-associated ulcers (at least 8 weeks)
 - Eradication of *Helicobacter pylori*
- 

OVER-PRESCRIBED IN INAPPROPRIATE CONDITIONS

- Chronic abdominal pain
- Chronic abdominal pain/ peptic ulcer disease treated
- GER with no complications
- GER + prolonged wheezing = causes not found

COMMON SIDE EFFECTS

- Headache
 - Diarrhea
 - Constipation
 - Abdominal pain
 - Flatulence
 - Fever
 - Vomiting
 - Nausea
 - Rash
- 

SIDE EFFECTS OF LONG-TERM USE

Category of adverse effects	Specific adverse effects that have been associated with PPI use
Infections due to hypochlorhydria	<i>Clostridium difficile</i> infection Enteric infections Spontaneous bacterial peritonitis Liver diseases Community-acquired pneumonia
Impaired absorption of nutrients due to hypochlorhydria	Bone fractures Vitamin B12 deficiency Hypomagnesemia Iron deficiency
PPI-induced hypergastrinaemia	Gastric hyperplasia/metaplasia Rebound acid hypersecretion
Other	Kidney disease and acute kidney injury Dementia

* Peter Fentz Hastrup, Wade Thompson, Jens Søndergaard, Dorte Ejg Jarbøl, 2018, Side Effects of Long-Term Proton Pump Inhibitor Use: A Review.

Clostridium difficile infection

REVIEW

Proton pump inhibitors: Risks of long-term use

Leonardo Henry Eusebi,^{*,†} Stefano Rabitti,^{*} Maria Laura Artesiani,^{*} Dania Gelli,^{*} Marco Montagnani,^{*} Rocco Maurizio Zagari^{*} and Franco Bazzoli^{*}

Potential adverse effect	Quality of evidence	Strength of association	Plausible underlying biological mechanism
<i>C. difficile</i> infection	Meta-analysis of observational studies	Weak, OR < 2 ⁶⁻⁸	Reduce gastric acidity may promote bacterial colonization in the GI tract

1. Kwok CS, Arthur AK, Anibueze CI, Singh S, Cavallazzi R, Loke YK. Risk of Clostridium difficile infection with acid suppressing drugs and antibiotics: meta-analysis. Am. J. Gastroenterol. 2012;
2. Janarthanan S, Ditah I, Adler DG, Ehrinpreis MN. Clostridium difficile-associated diarrhea and proton pump inhibitor therapy: a meta-analysis. Am. J. Gastroenterol. 2012;
3. Tleyjeh IM, Bin Abdulhak AA, Riaz M et al. Association between proton pump inhibitor therapy and clostridium difficile infection: a contemporary systematic review and meta-analysis. PLoS One 2012;

Clostridium difficile infection



The screenshot shows the FDA website header with the U.S. Department of Health and Human Services logo and the FDA logo. The main navigation bar includes links for Home, Food, Drugs, Medical Devices, Radiation-Emitting Products, Vaccines, Blood & Biologics, Animal & Veterinary, Cosmetics, and Tobacco Products. A search bar is located in the top right corner. The main content area is titled "Drugs" and features a breadcrumb trail: Home > Drugs > Drug Safety and Availability. A sidebar on the left lists "Drug Safety and Availability" as the active section, with sub-links for "Drug Alerts and Statements", "Medication Guides", and "Drug Safety Communications". The main headline reads: "FDA Drug Safety Communication: Clostridium difficile associated diarrhea can be associated with stomach acid drugs known as proton pump inhibitors (PPIs)".

- FDA: A diagnosis of CDAD should be considered for PPI users with diarrhea that does not improve

Community-acquired pneumonia

Potential adverse effect	Quality of evidence	Strength of association	Plausible underlying biological mechanism
Pneumonia	Meta-analysis of observational studies, case-control studies	Weak, OR < 2 ⁹	Potential micro-aspiration or translocation into the lungs from upper GI bacterial overgrowth

* Lambert AA, Lam JO, Paik JJ, Ugarte-Gil C, Drummond MB, Crowell TA. Risk of community-acquired pneumonia with outpatient proton-pump inhibitor therapy: a systematic review and meta-analysis. PLoS ONE 2015;

* Dublin S, Walker RL, Jackson ML, Nelson JC, Weiss NS, Jackson LA. Use of proton pump inhibitors and H2 blockers and risk of pneumonia in older adults: a population-based case-control study. Pharmacoepidemiol Drug Saf 2010

Bone fractures

Potential adverse effect	Quality of evidence	Strength of association	Plausible underlying biological mechanism
Risk of fracture	Randomized trials, observational studies, systematic review and meta-analysis	Weak, OR < 2 ^{2,3}	Reduced calcium absorption in the duodenum and proximal jejunum as a consequence of achloridria

*Ngamruengphong S, Leontiadis GI, Radhi S, Dentino A, Nugent K. Proton pump inhibitors and risk of fracture: a systematic review and meta-analysis of observational studies. Am J Gastroenterol 2011;

*O'Connell MB, Madden DM, Murray AM, Heaney RP, Kerzner LJ. Effects of proton pump inhibitors on calcium carbonate absorption in women: a randomized crossover trial. Am. J. Med. 2005;

*Targownik LE, Goertzen AL, Luo Y, Leslie WD. Long-term proton pump inhibitor use is not associated with changes in bone strength and structure. Am J Gastroenterol 2017

Hypomagnesaemia

Potential adverse effect	Quality of evidence	Strength of association	Plausible underlying biological mechanism
Hypomagnesaemia	Systematic review and meta-analysis of observational studies	Weak, OR < 2 ⁴	Poorly defined (gastrointestinal malabsorption and renal wasting)

*Park CH, Kim EH, Roh YH, Kim HY, Lee SK. The association between the use of proton pump inhibitors and the risk of hypomagnesemia: a systematic review and meta-analysis. PLoS ONE 2014

*Cheungpasitporn W, Thongprayoon C, Kittanamongkolchai W, Srivali N, Edmonds PJ, Ungprasert P et al. Proton pump inhibitors linked to hypomagnesemia: a systematic review and meta-analysis of observational studies. Ren Fail 2015

Hypomagnesaemia



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Symptoms: spasm (tetany), irregular heartbeat (arrhythmias), and convulsions (seizures),...

Treatment: stopping the PPI.

Vitamin B12 deficiency

Potential adverse effect	Quality of evidence	Strength of association	Plausible underlying biological mechanism
Vitamin B12 deficiency	Observational studies	Weak	Reduced acid-activated proteolytic digestion in the stomach related to reduced absorption

*Lam JR, Schneider JL, Zhao W, Corley DA. Proton pump inhibitor and histamine 2 receptor antagonist use and vitamin B12 deficiency. JAMA 2013

*den Elzen WP, Groeneveld Y, de Ruijter W et al. Long-term use of proton pump inhibitors and vitamin B12 status in elderly individuals. Aliment. Pharmacol. Ther. 2008;

Gastric hyperplasia/metaplasia

Potential adverse effect	Quality of evidence	Strength of association	Plausible underlying biological mechanism
Fundic gland polyps	Observational studies	Consistent	Trophic effect of high gastrin levels on GI mucosa
Gastric cancer	Meta-analysis of observational studies	Uncertain, OR < 2 for gastric cancer, not significant for pre-neoplastic lesion ^{10,11}	Possible synergic effect of PPI treatment and <i>Helicobacter pylori</i> infection
Colon cancer	Observational studies	No clear clinical association	Trophic effect of high gastrin levels on colon cancer cells <i>in vitro</i>

*59 Jalving M, Koornstra JJ, Wesseling J, Boezen HM, De Jong S, Kleibeuker JH. Increased risk of fundic gland polyps during long-term proton pump inhibitor therapy. *Aliment. Pharmacol. Ther.* 2006;

*Tran-Duy A, Spaetgens B, Hoes AW, de Wit NJ, Stehouwer CD. Use of proton pump inhibitors and risks of fundic gland polyps and gastric cancer: systematic review and meta-analysis. *Clin. Gastroenterol. Hepatol.* 2016;

Others

Potential adverse effect	Quality of evidence	Strength of association	Plausible underlying biological mechanism
Dementia	Observational studies	Uncertain	High levels of amyloid- β and deposition of amyloid- β peptides in brains of animal models
Cardiovascular risk	Meta-analysis of observational studies and of RCT	Weak, OR < 2 for mortality and myocardial infarction (not significant when only RCT were included) ⁵	Competitive metabolism effect on cytochrome P450
Renal disease	Observational studies	Modest	Unclear (deposit of PPIs or their metabolites in the kidney's tubulo-interstitium stimulating immune response)

CONCLUSIONS

- PPIs: effective agents for the management of a variety of acid-related disorders.
- For most side effects, the clinical evidence of the adverse effect is often weak and cannot be clearly associated to PPIs use.
- Side effects should not be a reason to withhold PPIs from patients with a **true indication**.

THANK YOU

A decorative graphic on the right side of the slide, consisting of several overlapping, curved shapes in shades of light blue, yellow, and a darker blue.