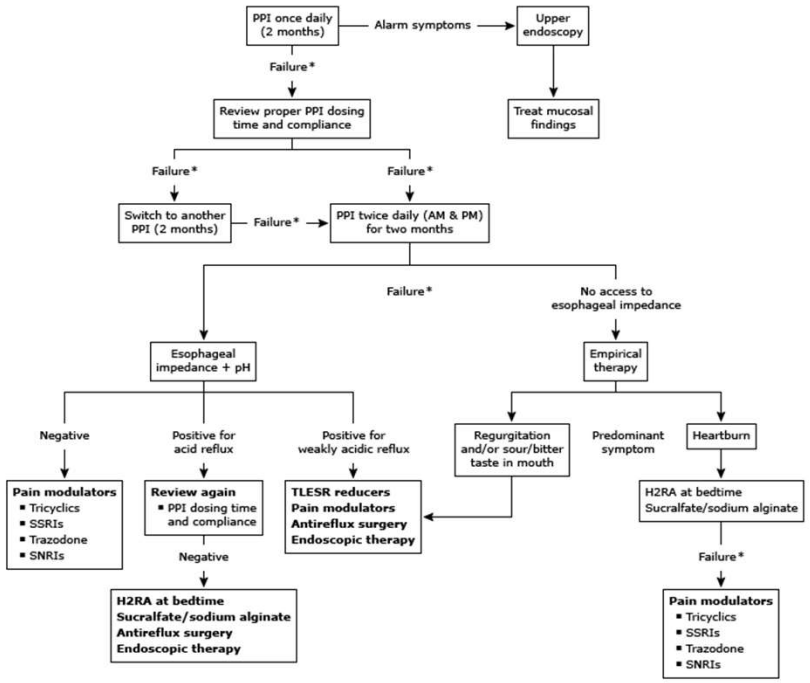
Management algorithm of GERD patient who failed PPI once daily



Management algorithm of gastroesophageal reflux disease (GERD) patient who failed PPI once daily (complete or partial*).

PPI: proton pump inhibitor; SSRIs: selective serotonin reuptake inhibitors; SNRIs: serotonin-norepinephrine reuptake inhibitors; TLESR: transient lower esophageal sphincter relaxation; H2RA: histamine 2 receptor antagonist.

* Partial or incomplete relief of symptoms.

Original figure modified for this publication. Hershcovici T, Fass R. An algorithm for diagnosis and treatment of refractory GERD. Best Pract Res Clin Gastroenterol 2010; 24:923. Illustration used with the permission of Elsevier Inc. All rights reserved.

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TREATMENT

Lifestyle modification

Pharmacological therapy

Endoscopic therapy

Surgical therapy

Individualized plan for lifestyle changes to manage reflux-like symptoms

Healthy eating	Night-time behaviors	Exercise	Medications
☐ Add in fruits or vegetables at each meal (avoid citrus).	☐ Finish eating approximately 3 hours before lying down.	☐ Accumulate 20 to 30 minutes of physical activity on most days of the week such as walking, swimming, dancing, exercise classes, or cleaning.	☐ _____
☐ Use plant-based fats over animal fats.	☐ Wear loose clothing to reduce pressure around the belly.	☐ Add in 2 days of strength and flexibility training such as weight training, yoga, Pilates, etc.	☐ _____
☐ Opt for whole grains such as whole wheat, brown rice, oats, teff, millet, quinoa.	☐ Practice deep breathing or other stress reduction techniques before sleep.	☐ Incorporate activity into lifestyle. If you track steps, aim for >7000 to 10,000 steps on most days (5 to 8 km).	☐ _____
☐ Swap out animal proteins for plant-based options, eg, lentils, pulses, seeds, nuts, and legumes.	☐ Avoid alcohol before bed.		☐ _____
☐ Serve smaller portion sizes to help you reduce meal volume.	☐ Elevate head of bed when sleeping, ideally using a wedge pillow or by adjusting mattress or head of bed.		☐ _____
☐ Use smaller plates and utensils to feel satisfied with smaller amounts.	☐ Lie on left side to minimize reflux.		
☐ Choose water or tea over high-sugar drinks.			
☐ Eliminate carbonated beverages and caffeine if they trigger symptoms.			
☐ Enjoy small desserts a few days in a week or substitute with fruit to finish a meal.			
☐ Limit alcohol.			
☐ Schedule meals to avoid grazing.			

Common triggers and modulators of reflux-like symptoms*

Category	Trigger or modulator
Eating behaviors	▪ Eating too fast ▪ Large portions ▪ Eating past satiety ▪ Eating too close to bedtime
Dietary factors	▪ Fatty/fried foods ▪ Spicy foods (capsaicin) ▪ Excess alcohol ▪ Excess coffee ▪ Carbonated beverages ▪ Patient-specific trigger foods
Lifestyle	▪ Weight gain ▪ Tight garments ▪ Belts ▪ Tobacco use ▪ Excessive exercise
Medications	▪ Anti-inflammatory medicines ▪ Antihypertensives ▪ Erectile dysfunction medicines
Emotional or behavioral factors	▪ High-stress environment ▪ Hypervigilance

* In most instances, only some of these factors are pertinent to an individual patient. Clinicians should assess for specific triggers and individualize recommendations to avoid guidance that is overly restrictive or overwhelming.

PHARMACOLOGICAL THERAPY

- PPI therapy
- H2 Antagonist
- Sucralfate
- Alginates
- Baclofen
- Domperidone
- *Vanoprazan – Potassium competitive acid blocker

PPI THERAPY

- Proton pump inhibitors (PPIs) are the most effective treatment for GERD, but lifestyle modifications are also recommended for all patients.
- They bind irreversibly to the hydrogen-potassium ATPase in the parietal cells of the stomach to prevent acid secretion.
- **All PPIs are equally effective** in suppressing acid when given at equivalent doses so they can be used interchangeably.
- Treat uncomplicated GERD with a once-daily PPI 30 to 60 minutes prior to a meal for 4 to 8 weeks.
- If treatment is effective, you'll want to try to reduce or stop the medication after the 4- to 8-week period.

TABLE 2

Potency of PPIs, based on omeprazole equivalents[17]

Medication at lowest available dose, mg	Omeprazole equivalent, mg	Relative potency
Rabeprazole, 20	36	Most potent
Esomeprazole, 20	32	
Omeprazole, 20	20	
Lansoprazole, 15	13.5	
Pantoprazole, 20	4.5	Least potent

PPIs, proton pump inhibitors.

Adapted from Graham DY, Tansel A. *Clin Gastroenterol Hepatol*. 2018.[17]

PPI AND DRUG INTERACTIONS

Reduced Absorption (Acid-Dependent): Medications that require low pH to dissolve have reduced efficacy. This includes antifungals (ketoconazole, itraconazole), antivirals (atazanavir), tyrosine kinase inhibitors (erlotinib, dasatinib), and oral iron.

Metabolism Inhibition (CYP450 System): PPIs (especially omeprazole, esomeprazole) inhibit the CYP2C19 enzyme, affecting drugs like:

- **Clopidogrel (Plavix):** Reduced effectiveness.
- **Diazepam (Valium):** Increased sedation.
- **Phenytoin:** Toxicity risks.
- **Warfarin:** Altered anticoagulation levels.

- **Other Interactions:**
  - **Methotrexate:** Increased toxicity risk.
  - **Digoxin:** Increased absorption.
  - **Mycophenolate:** Reduced efficacy.

Recommendations for Management

Timing: Administer pH-dependent drugs (e.g., antifungals) at least 2 hours before or after a PPI.

PPI Selection: Rabeprazole or pantoprazole may have lower potential for metabolic drug interactions compared to others.

Clinical Monitoring: Monitor drug levels closely, especially when starting or stopping a PPI with narrow therapeutic index drugs.

Use Caution: Avoid long-tem PPI use unless necessary

S.No	Serious side effects	Probable mechanism(s) of pathogenesis
1	Renal problems (AIN, AKI, CKD, ESRD)	Deposit of PPIs or their metabolites in tubulo-interstitium may induce cell-mediated immune response causing interstitial inflammatory infiltrate and AIN that may result in CKD and ESRD via AKI and interstitial fibrosis and tubular atrophy[15]
2	Cardiovascular risks (MACE, MI, stroke)	Elevated plasma asymmetric dimethylarginine (ADMA) levels causing inhibition of vascular nitric oxide generation by inhibiting nitric oxide synthase enzyme, decreased vitamin C and vitamin B12 levels, hypomagnesemia and hypocalcemia-related arrythmia, and endothelial dysfunction[42]
3	Fractures	More insoluble state of calcium and diminished absorption of calcium due to suppressed acid secretion-associated hypochlorhydria and hypergastrinemia[63]
4	Infections (*C.difficile* infection, CAP, COVID-19)	Hypochlorhydria-associated diminished protective effect, suppressed immune system, and small intestinal bacterial overgrowth due to suppressed gastric acid secretion[75]
5	Micronutrient deficiencies (hypomagnesemia, anemia, vitamin B12 deficiency, hypocalcemia, hypokalemia)	Impaired intestinal absorption of magnesium via decreased solubility of magnesium in intestinal lumen, altered expression and activity of key transporter proteins, and dysbiosis of gut microbiome[84]
6	Hypergastrinemia	Hypochlorhydria or achlorhydria induced by PPIs-associated gastric acid suppression, stimulates G cells in the gastric antrum to release gastrin resulting in hypergastrinemia[94]
7	Cancer (gastric cancer, pancreatic cancer, colorectal cancer, hepatic cancer)	Potent acid suppression by PPIs may ensue in gastric cancer via worsening gastric atrophy, hypergastrinemia, ECL hyperplasia, and bacterial overgrowth[99]
8	Hepatic encephalopathy	Unknown
9	Dementia	Unknown

Maideen NMP. Adverse Effects Associated with Long-Term Use of Proton Pump Inhibitors. Chonnam Med J. 2023 May;59(2):115-127. doi: 10.4068/cmj.2023.59.2.115. Epub 2023 May 25. PMID: 37303818; PMCID: PMC10248387.

GASTRODUODENAL

Association of Proton Pump Inhibitor Use With Incident Dementia and Cognitive Decline in Older Adults: A Prospective Cohort Study

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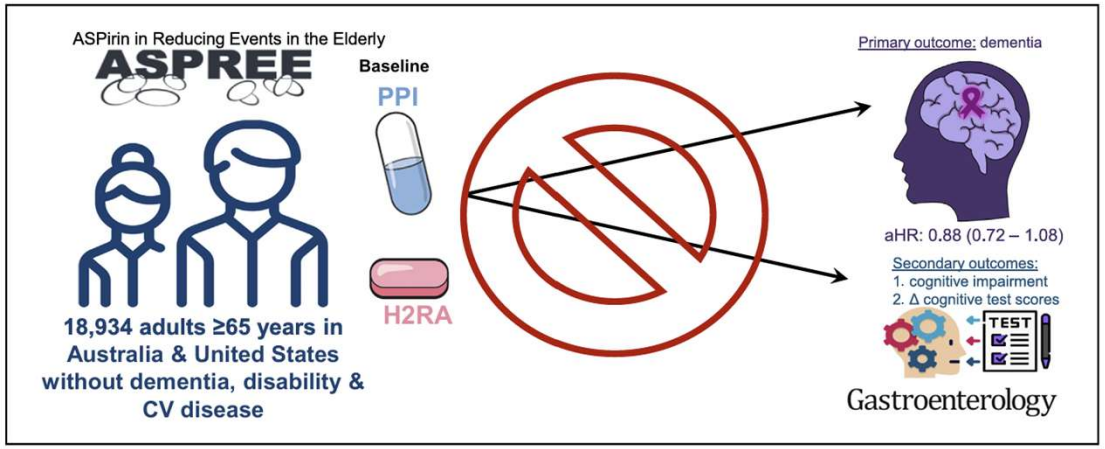

KEY FINDINGS FROM THE ASPREE ANALYSIS REGARDING PPIS AND DEMENTIA:

No Increased Risk: Researchers found no association between baseline or ongoing PPI use and incident dementia.

Cognitive Function: There was no decline in cognitive test scores associated with PPI use over time.

Study Rigor: The study utilized comprehensive in-person cognitive assessments and prospectively collected medication data, offering more robust evidence than previous studies.

No Association with H2RAs: Similarly, no association was found between the use of H2RAs (like ranitidine or famotidine) and cognitive decline.

Conclusion: The findings suggest that PPIs do not accelerate cognitive decline or trigger dementia in older, community-dwelling adults.

H2 ANTAGONIST

- Block histamine (H2) receptors on gastric parietal cells, inhibiting acid production.
- Highly effective for mild, intermittent heartburn (over 70% effective), but less effective (40-60%) for healing severe erosive esophagitis compared to Proton Pump Inhibitors (PPIs)
- They can be taken before meals or at bedtime to reduce overnight acid reflux.
- Side Effects: Headache, dizziness, diarrhea, and constipation.
- **Tachyphylaxis:** The effectiveness of H2 blockers may diminish after just a few days of consistent use.
- Most common used drug is Famotidine

Tougas G, Armstrong D. Efficacy of H2 receptor antagonists in the treatment of gastroesophageal reflux disease and its symptoms. Can J Gastroenterol. 1997 Sep;11 Suppl B:51B-54B. PMID: 9347179.