Pharmacology of Peptic Ulcer Disease

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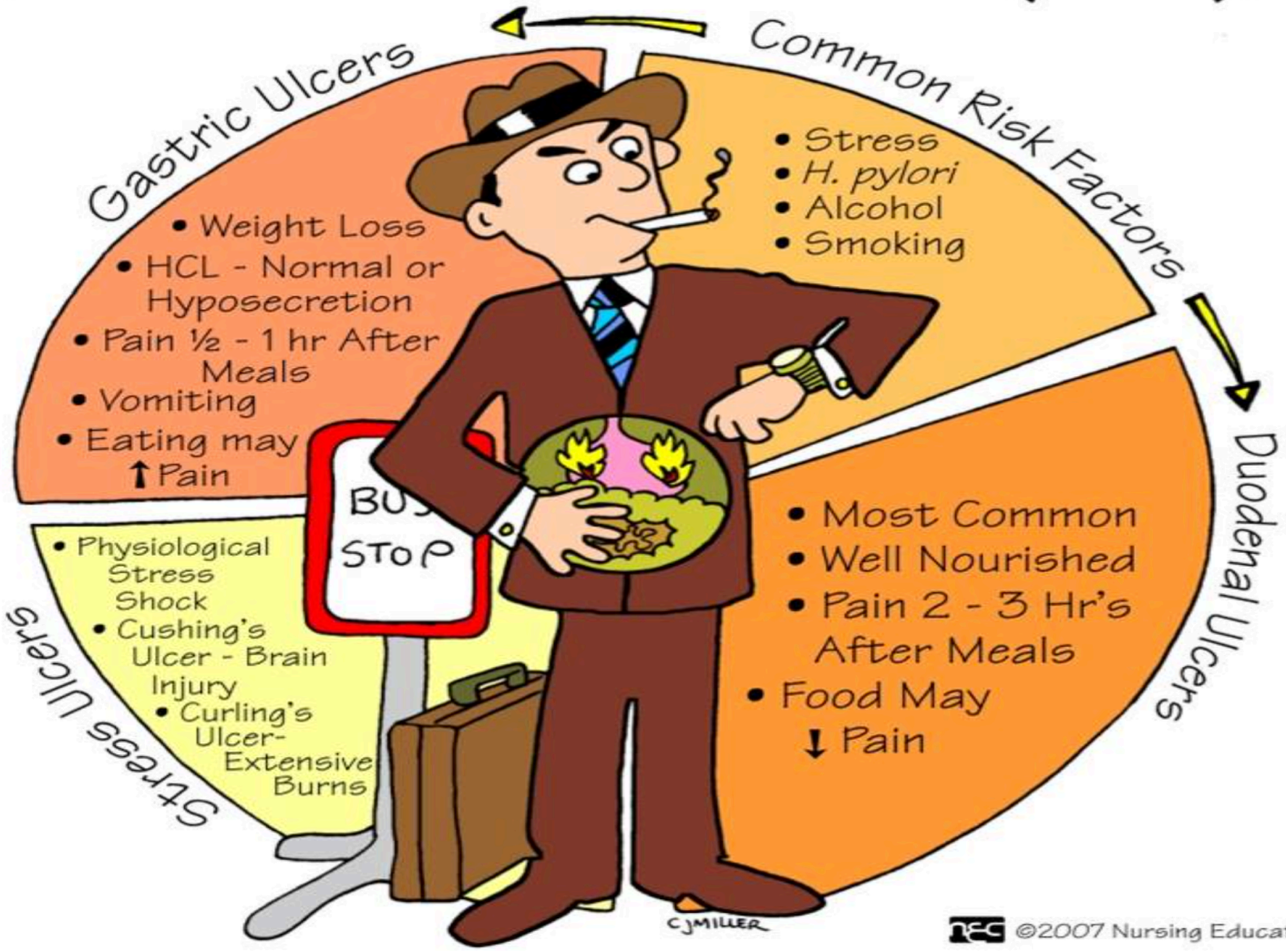
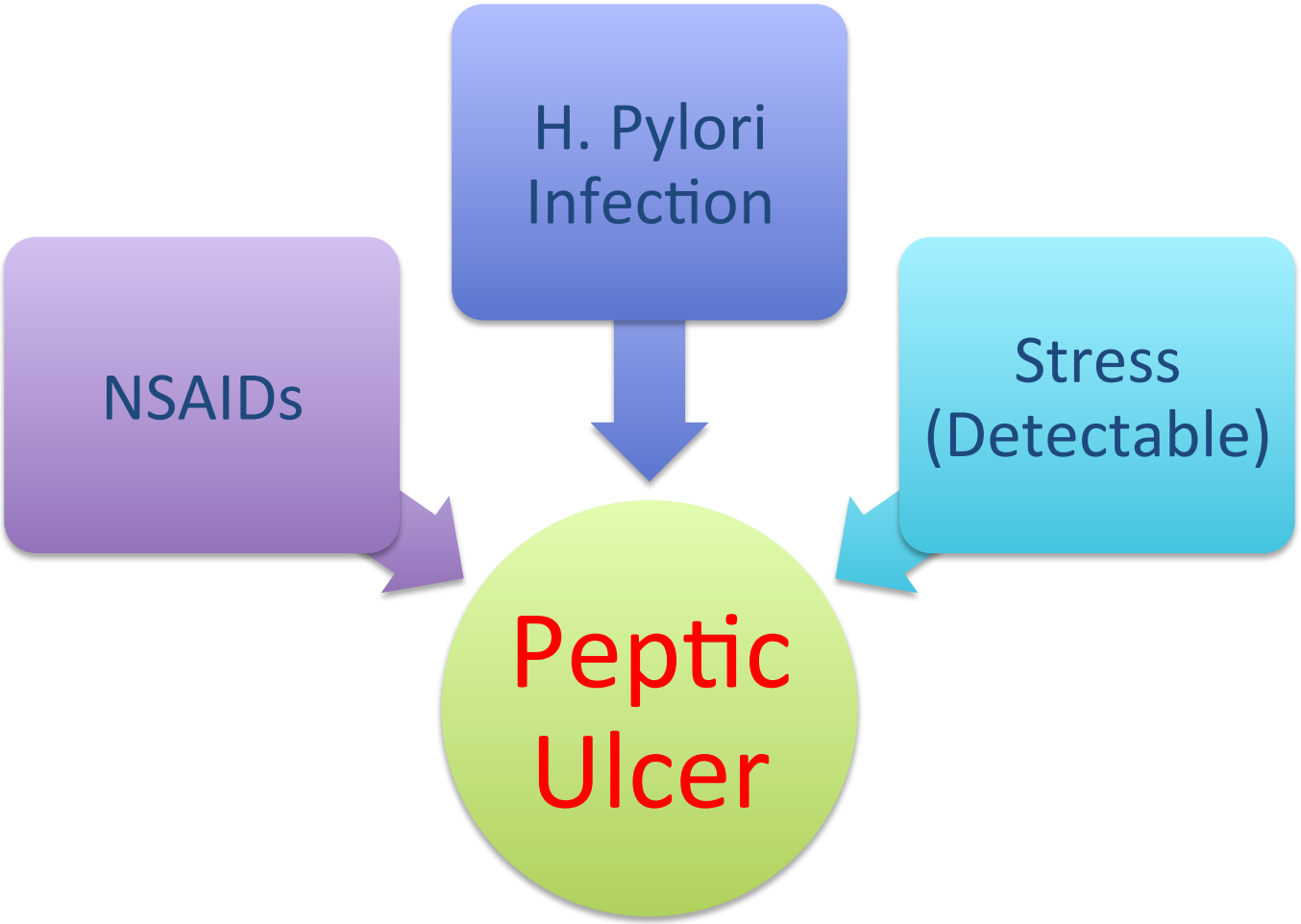
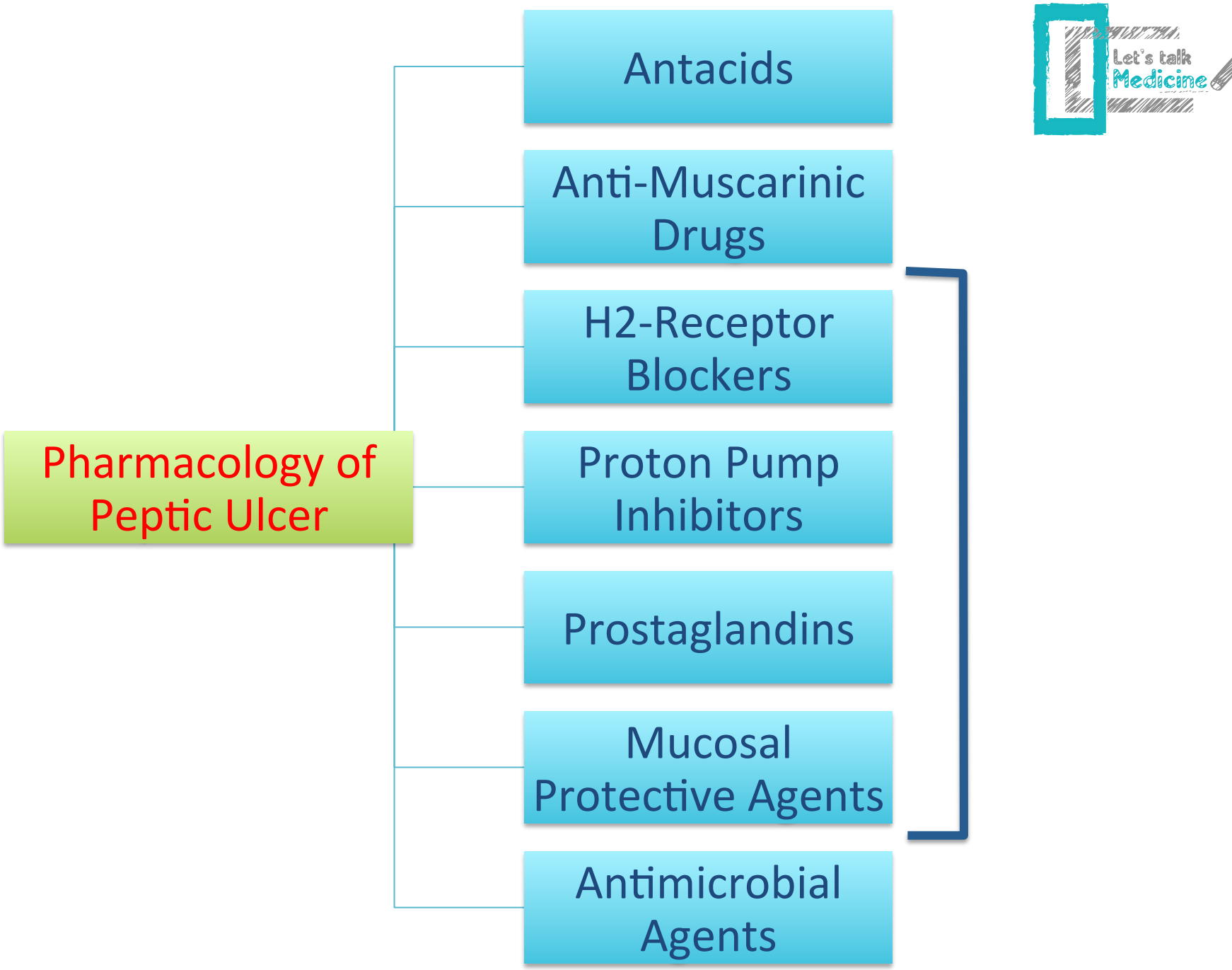
Outline

- General introduction to Peptic Ulcer Disease .
- Drug Classes used in the treatment of Peptic Ulcer Disease.

PEPTIC ULCER DISEASE (PUD)




H. Pylori Infection
NSAIDs
Stress (Detectable)
Peptic Ulcer


Pharmacology of Peptic Ulcer
Antacids
Anti-Muscarinic Drugs
H2-Receptor Blockers
Proton Pump Inhibitors
Prostaglandins
Mucosal Protective Agents
Antimicrobial Agents

Antacids

- They promote the ulcer healing by:
  - Neutralizing the HCl
  - Reducing pepsin formation
- Used for Prompt symptomatic relief of peptic ulcer disease and GERD.
- Types:
  - Systemic: sodium bicarbonate, & calcium carbonate.
  - **Non-systemic: aluminum\magnesium hydroxide**

Antacids cont.

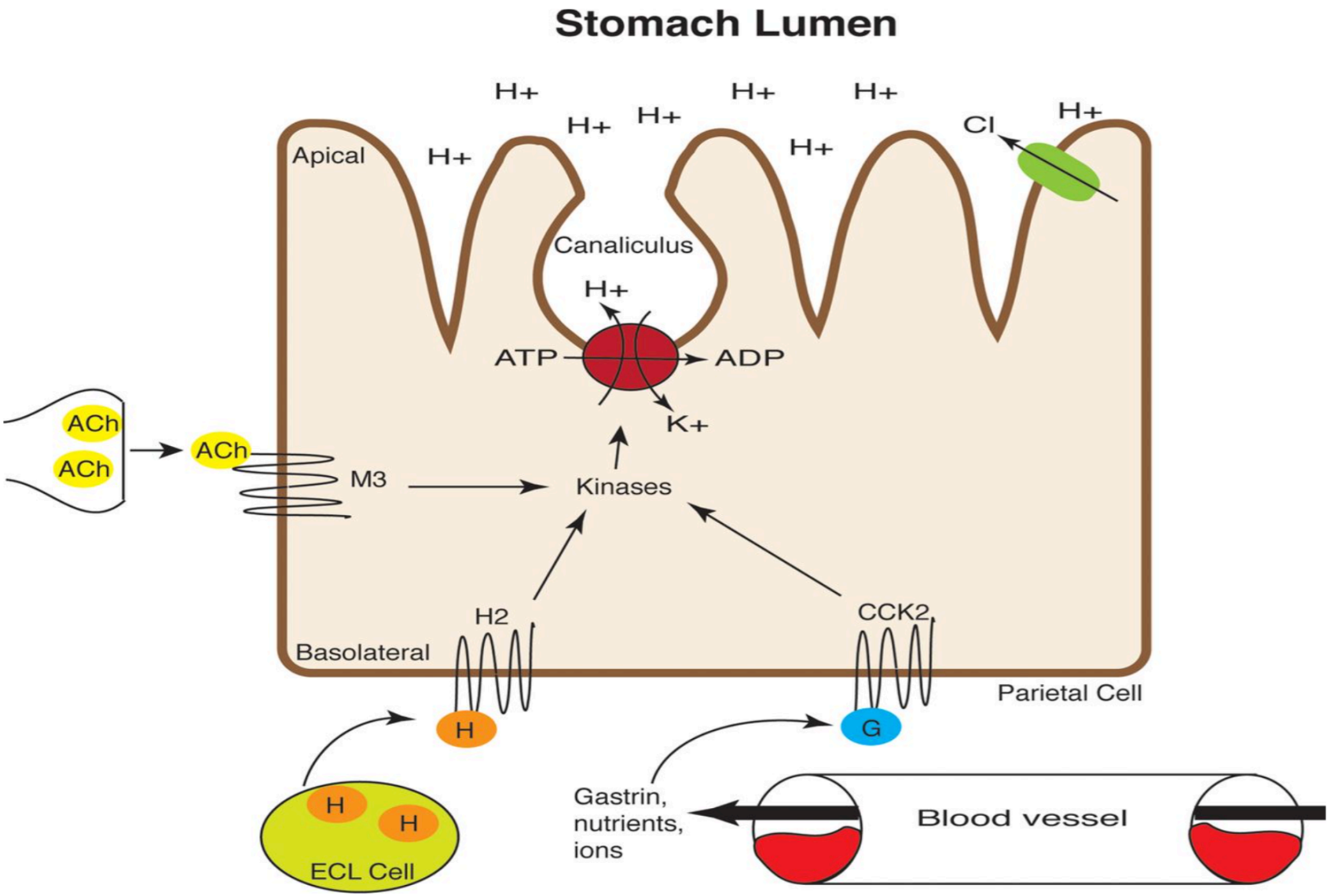
- Side effects S\E:
  - Magnesium Hydroxide → Diarrhea
  - Aluminum Hydroxide → Constipation
  - Hypokalemia

- Many drug-drug interaction and ↓absorption of other drugs:
  - Give other medications 1-2 hrs after
  - Caution with anti-HTNsive, Iron, fluroquinilones

Anti-Muscarinic

- Pirenzepine
- MOA:
  - Selectively blocks M1 muscarinic receptor
  - ⬇Vagal stimulation.
  - Inhibiting the gastric secretions
  - Decrease pepsin secretion
- S\E: dry mouth, blurred vision, tachycardia, photophobia etc.

H2 Receptor Blockers



H2 Receptor Blocker Cont.

- **REVERSIBLE** competitive inhibitor of H2 receptor only (not H1 or H3)

- Drugs: cimetidine, famotidine, ranitidine
- All pass through first pass metabolism

- Inhibition of CYP450 is mostly with Cimetidne & least with famotidine

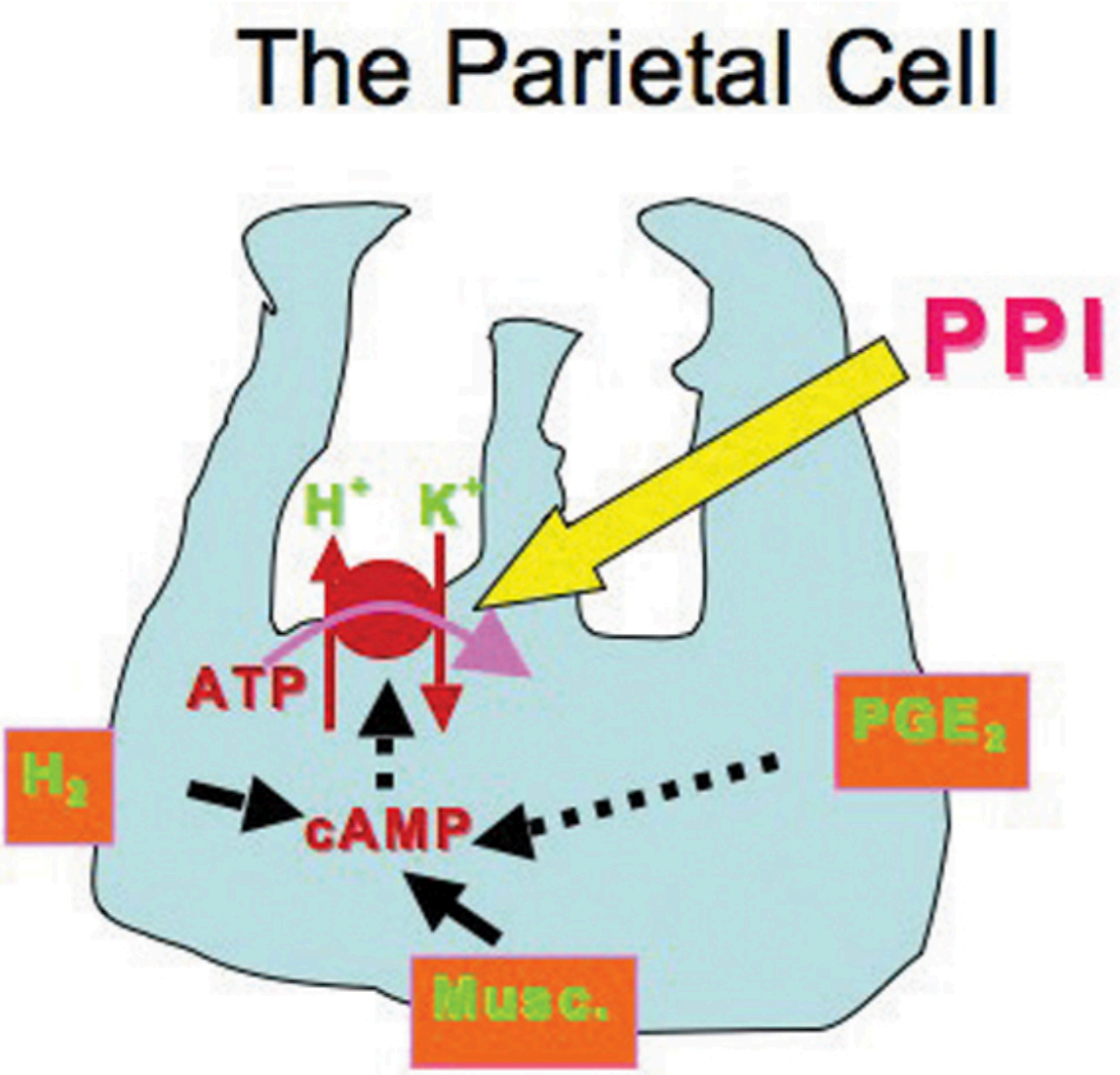
- Famotidine is the most potent
- Effect on ethanol?!

H2 Receptor Blocker Cont.

- Uses:
  - Peptic ulcer, GERD, non-ulcer dyspepsia
  - Prevention of bleeding from stress-related gastritis

- S\E:
  - Headaches, myalgia, diarrhea, confusion, renal impairment in elderly
  - Not used in pregnant women
  - Cimetidine: impotence and gynecomastia or glactorrhea

Proton- Pump Inhibitors



PPIs Cont.

- **Most effective therapy in anti-ulcer therapy**
- **IRREVERSIBLE** inhibition of H+\K+ATPase in the parietal cells
- Dose: mainly once daily
  - Does not need dose adjustment in liver and renal disease

- Drugs: omeprazole, esomeprazole, pantoprazol (IV) etc.

PPIs Cont.

- Avoid long-term use because it ↑ risk of infections
  - C.difficle Psuedomembranous colitis
  - Pneumonia

- All metabolized by CYP450 in the liver

PPIs Cont.

- Omeprazole most potent inhibitor of gastric acid secretion
- Uses: GERD, PUD, Zollinger Ellison Syndrome
- S\E: diarrhea, headache, nausea, weakness

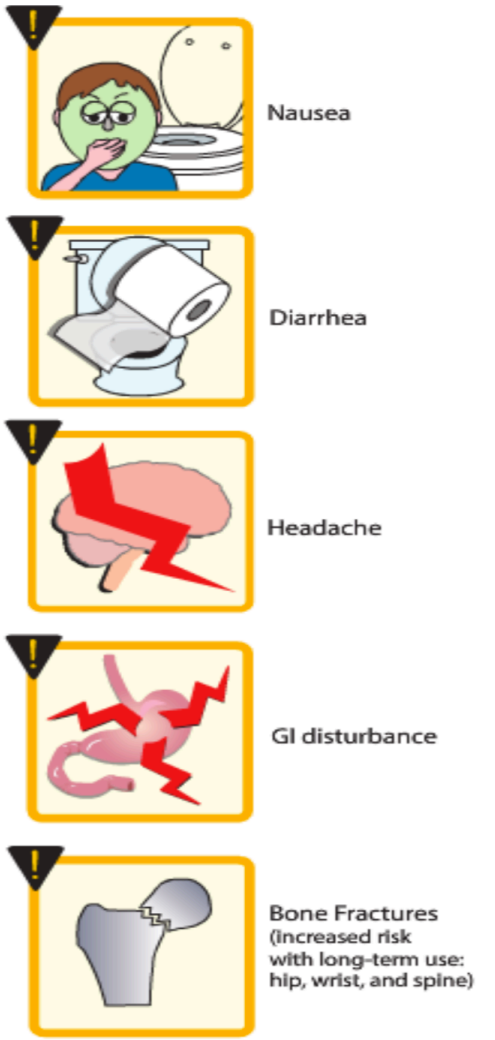


Figure 28.7
Some adverse effects of proton pump therapy.

Prostaglandins

- **Misoprostol**: PGE1 synthetic analogue
- Inhibits the acid secretion and promotes mucus and bicarbonate secretion
- Reduce the incidence of NSAIDs induced ulcers by 50%
- **Protect against NSAIDs PUD**
- Multipledoses
- **Cytoprotective** action!!!

- S\E:
  - Diarrhea and abdominal pain, vomiting and nausea, headache
  - Contraindicated in pregnant women:↑uterine contractions

Mucosal Protective Agents

- Forms:
  - Bismuth Subsalicylate
  - Sucralfate

Sucralfate

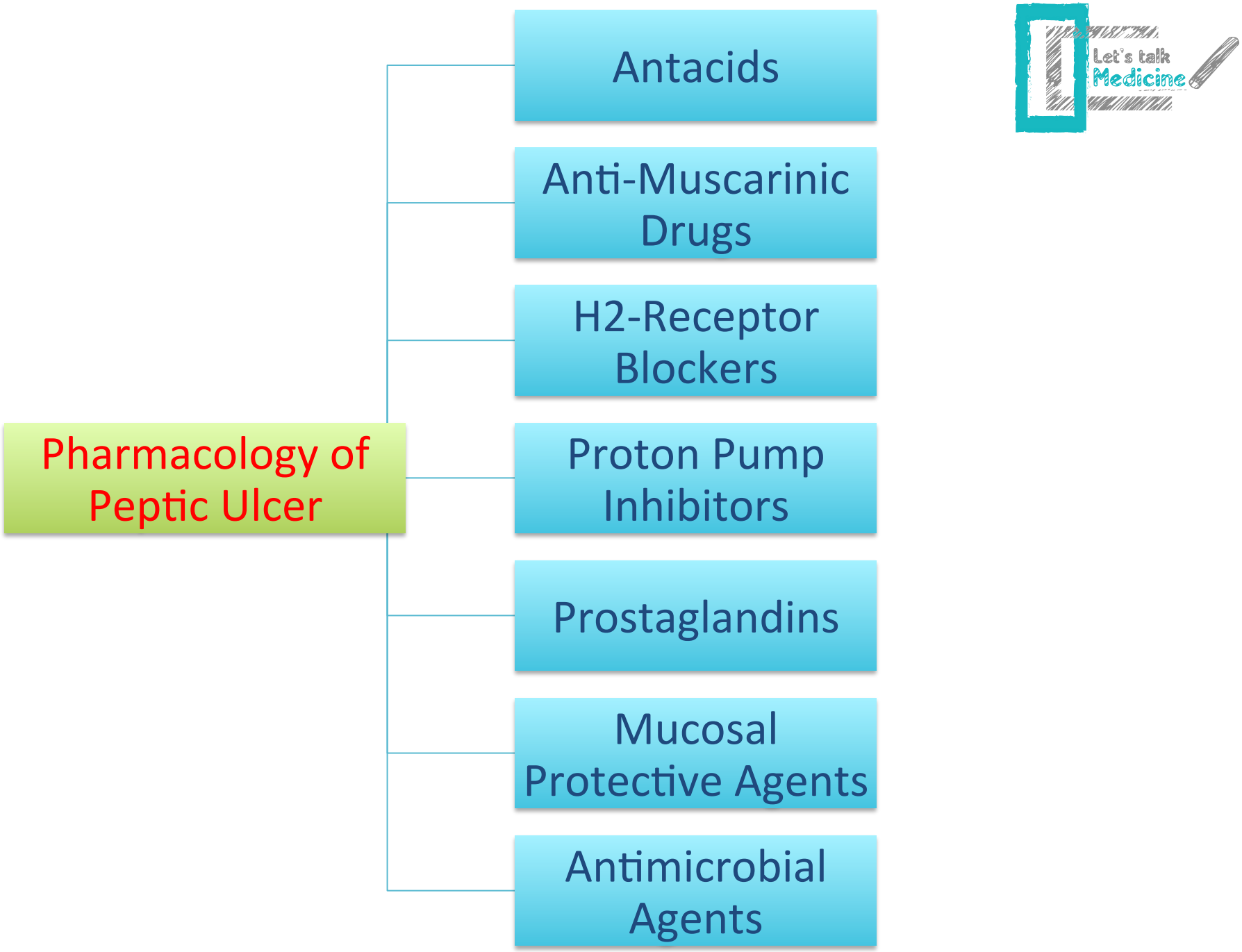
- Salt of sucrose complexed to sulfated aluminum hydroxide
- Forms a gel complex binds to the proteins found in base of the ulcer to form a protective layer
- Stimulates angiogenesis for healing
- Uses: gastritis, stress-ulcer, ↓risks of upper GI bleeding
- S\E:
  - Most common: constipation
  - Headache, flatulence, dry mouth, skin rash
  - Avoid long-term use: ↑risk of nosocomial pneumonia

Bismuth Subsalicylate

- Acts in similar way to Sucralfate
- Inhibits the pepsin activity
- Increase PG production

- **Direct antimicrobial activity against H.pylori**

- S\E:
  - The most common side effects are darkening of the stools and/or tongue
  - Unpleasant taste and severe constipation
  - Contraindicated in any active bleeding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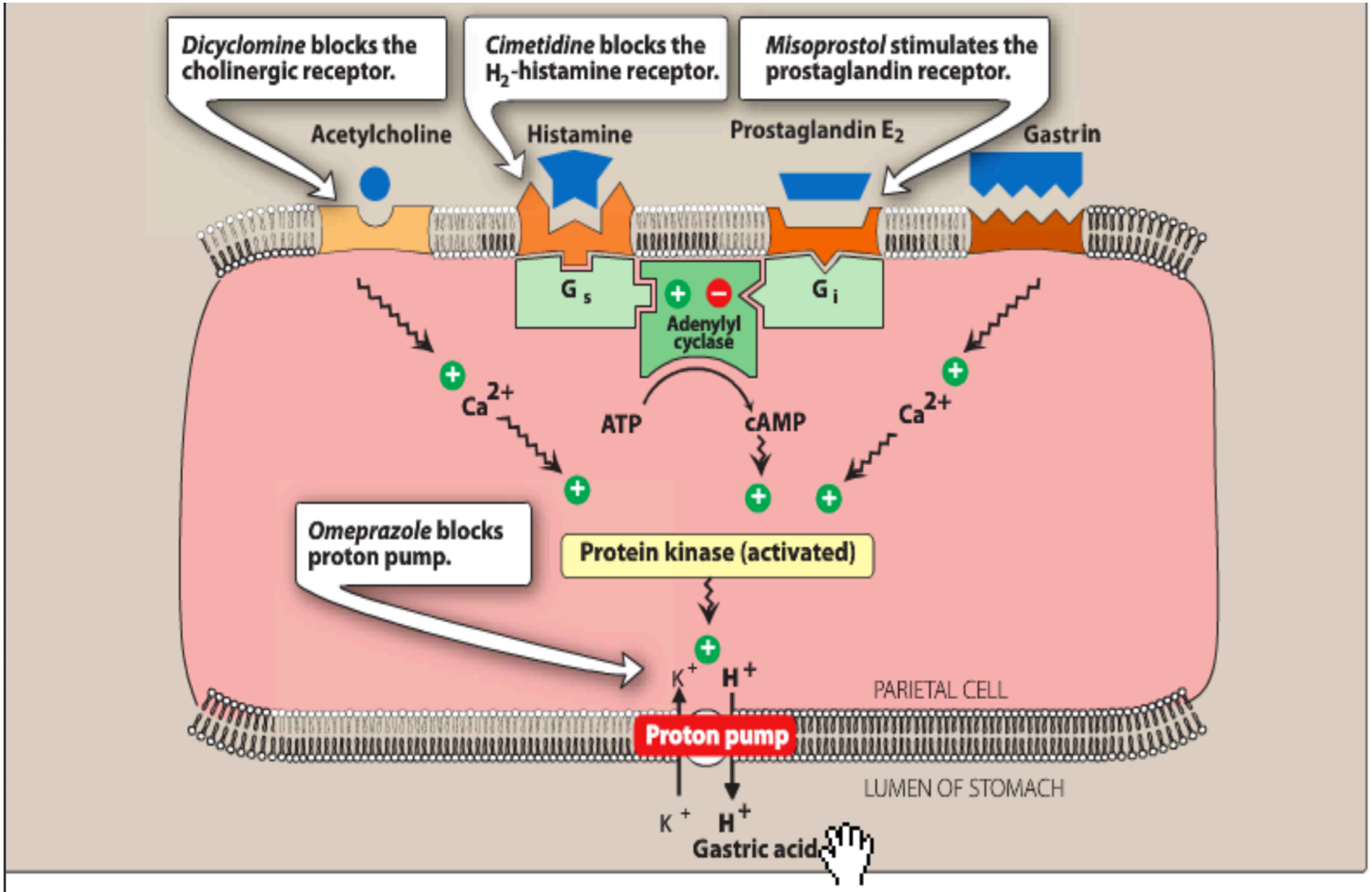

Figure 28.4
Effects of acetylcholine, histamine, prostaglandin E_2, and gastrin on gastric acid secretion by the parietal cells of stomach. G_s and G_i are membrane proteins that mediate the stimulatory or inhibitory effect of receptor coupling to adenylyl cyclase.

Clinical use of agents affecting gastric acidity

- Histamine H_2 receptor antagonists (e.g. **ranitidine**):
  - *peptic ulcer*
  - *reflux oesophagitis.*
- Proton pump inhibitors (e.g. **omeprazole**, **lansoprasole**):
  - *peptic ulcer*
  - *reflux oesophagitis*
  - as one component of therapy for *Helicobacter pylori* infection
  - *Zollinger–Ellison syndrome* (a rare condition caused by gastrin-secreting tumours).
- Antacids (e.g. **magnesium trisilicate**, **aluminium hydroxide**, **alginates**):
  - *dyspepsia*
  - symptomatic relief in *peptic ulcer* or (alginate) *oesophageal reflux*.
- **Bismuth chelate**:
  - as one component of therapy for *H. pylori* infection.

Anti-Microbial Agents

- For PUD associated with H.pylori infection
- **American College of Gastroenterology guidelines and recommendations 2007 include:**

Triple therapy not allergic to penicillin and no macrolide resistance ✓ **First-line Therapy**	**•PPI (esomeprazole) once daily or twice for any other PPI** **•Clarithromycin 500 mg twice daily** **•Amoxicillin 1000 mg twice daily**
Triple therapy, allergic to penicillin ✓ **First-line Therapy**	•PPI (esomeprazole) once daily or twice for any other PPI •Clarithromycin 500 mg twice daily •Metronidazole 500 mg twice daily
Failure of Eradication (Quadruple therapy) can be used for penicillin allergic Ptx. ✓ **Second-line Therapy**	•PPI (esomeprazole) once daily or twice for any other PPI •Bismuth subsalicylate 525 mg four times daily •Metronidazole 250 mg four times daily •Tetracycline 500 mg four times daily
Rescue Therapy ✓ **Third-line Therapy**	•PPI (esomeprazole) once daily or twice for any other PPI •Levofloxacin 250 mg twice daily •Amoxicillin 1000 mg twice daily

General Measures for Antimicrobial Agents

- Duration of therapy 10-14 days
- Eradication rates:
  - 1st -line Therapy ➔➔ 85%
  - 2nd –line Therapy➔➔95%

- **1st line therapy can be used in pregnancy** (low risk especially after 14 weeks of gestation)
  - Treatment can be deferred until after delivery

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