ULCER TREATMENTS – RECEPTOR MEDIATED

The things that cause ulcers are **H. Pylori Infection** and the **Acid Secretion of the Stomach**. H+ and H+ do the damage. So the goal to cure Ulcers is to get rid of the H. Pylori (which is the primary goal, since 100% of duodenal ulcers and 75% of gastric ulcers are associated with H. Pylori) and to reduce the acid. Antibiotics fix the H. Pylori, and then we have a wide range of medications that are used to treat the acid secretion. It’s a bit of a history lesson, but all drugs are still used to treat peptic ulcer disease as well as other symptoms, such as GERD. We begin with a brief review of Gastric Physiology, which is most likely not required for the Tulane exam, but is good for your Board/Shelf review.

**Acetylcholine** binds acetyl choline receptors turning on Calcium, activating a Protein Kinase. This ultimately leads to acid production through a protein pump. Binding = ↑H+ secretion.

**Histamine** activates Gs (stimulatory G protein) which turns on Adenylly Cyclase, ↑cAMP, activating the same Protein Kinase. Binding = ↑H+ secretion

**Gastrin** works in the same manner as acetyl choline, but through a different receptor. So binding of gastrin = ↑H+ secretion.

Binding = ↑H+ secretion, Inhibiting = ↓H+ secretion

**Prostaglandins**, however, activate Gi (inhibitory G protein) which turns off Adenylly Cyclase, turning off cAMP, turning off the protein kinase, decreasing acid secretion.

The binding of prostaglandins = ↓H+ secretion, while its inhibition = ↑H+ secretion.

**The Proton Pump** is the final common pathway of all signals. It secreted hydrogen ion. Block that, and it doesn’t matter what else is going on, acid secretion will decrease.

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**Antiemetic**

- **Cannabinoids**: Dronabinol
- **5HT3-Antagonists**: Ondansetron
- **Anticholinergic**: Scopolamine
- **Prokinetic**: Metoclopramide

**Antidiarrheal**

- **Antimotility**: Diphenoxylate, Loperamide
- **Adsorbents**: Kaolin/Pectin

**Laxatives**

- **Bulk Laxatives**: Methyl Cellulose
- **Cathartics**: Castor Oil
- **Stool Softeners**: Docusate Sodium

**GI Drugs**

- **Ulcer Treatments**
  - **Antibiotics**: Metronidazole
  - **H2 Blockers**:
    - “-tidine”
  - **Prostaglandin**: Misoprostol
  - **PPis**:
    - “prazole”s
  - **Antimuscarinic**: Pirenzipine
  - **Mucosal Protectors**: Sucralfate
  - **Antacids**: Tums, Alka Seltzer

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Ok. You probably already can deduce where we are going. It is important to know some of the nuances of the drugs: how each class works, what the side effects are, and what not to do with them.

**H2-Receptor Antagonists.** Cimetidine (Tagamet), Ranitidine (Zantac), Famotidine (Pepcid). The “-tidine” drugs are H2 histamine receptor antagonists. They are **competitive inhibitors** (which means they require frequent dosing) for the histamine receptor, preventing the binding of histamine to its intended target. Histamine both directly stimulates acid secretion and exacerbates the response to gastrin mediated secretion. These are old drugs, now available **over the counter.** People use them to self-medicate **peptic ulcers, acute stress ulcers,** and **GERD.** Side effects are generally mild. However you must remember that Cimetidine (an older H2 antagonist) is a **P450 inhibitor** and **competes for renal PGP.** This means that when you take Cimetidine the effective dose of other drugs metabolized by P450 or excreted by the kidneys will be increased after Cimetidine than it was before (**reduce dose of drugs** when Cimetidine is added). Cimetidine may also cause **gynecomastia** in men and **galactorrhea** in women. The newer drugs have much fewer side effects.

**Prostaglandins.** Misoprostol. Activation of prostaglandin receptors not only **directly inhibit acid secretion** but they also **stimulate mucus secretion.** That means they turn down the damaging stuff, but turn up the protective stuff. They are particularly useful in patients that have killed their mucosal defense; used to treat **ulcers from NSAID use.** You are essentially replacing the prostaglandins the patients shut down, but keeping it local to the stomach, where it does some good. Misoprostol happens also to be one of the **abortive drugs so pregnant females should not use Misoprostol.**

Proton Pump Inhibitors. Omeprazole (Prilosec), Esomeprazole (Nexium). These are the new guys. They are **noncompetitive inhibitors** (which means they do not require frequent dosing) for the **proton pump** which they **irreversibly inhibit.** They are now the mainstay for treating diseases involving acid secretion: **GERD and Ulcers.** They are also useful in treating diseases where there is an upregulation of receptors we either do not have antagonists for, or for receptors where we have competitive antagonists, such as **Zollinger Ellison Syndrome** (a pancreatic tumor secreting Gastrin).

**Antimuscarinic.** Pirenzipine. This got 0 time in lecture and had a snippet in the drug list. It is commonly used as an **adjunct to H2 Blockers** in cases that are refractory. Messing with acetylcholine is generally a poor decision, so is reserved for only refractory cases.

**ULCER TREATMENTS - ANTIMICROBIALS**

**Antibiotics.** Dr. Beckman said there “many different treatment algorithms.” The two she gave us was **ten days of Metronidazole** (which patients do not tolerated well), or 10 days of **Ampicillin and Clarithromycin.** Basically, what you want to take away is that **antibiotics cure ulcers.**

**ULCER TREATMENTS – NON RECEPTOR MEDIATED**

These are the less sexy drugs that are fairly simple. You have acid in the stomach. Add these to the acid and neutralize the acid. No receptors, no pathways, no backfiring that you have to worry about. But these also come with a price, each with its own unique caveat.
Antacids. Calcium Carbonate (Tums), Magnesium Hydroxide (Alka Seltzer), Aluminum Hydroxide (Rolaids), Sodium Bicarbonate. The bicarbonate and hydroxide parts of these drugs is where the magic is. They dissociate from the mineral and bind to the H+ directly raising the pH. Unfortunately, these are flushed away in the GI tract very quickly, so frequent dosing is required. Aluminum is constipating. Magnesium is a diarrheal. Putting them together, you eliminate the effects. Be careful with the Sodium and Calcium mixtures may go systemic, and may produce a systemic alkalosis.

Mucosal Protective Agents. Sucralfate and Bismuth (Pepto-Bismal). Both of these agents coat the mucosal surface, binding to positively charged proteins at the base of ulcers forming a physical barrier to the acid. Sucralfate causes black stool. Pepto has two beneficial features: it is a heavy metal so it kills H. Pylori and it also has the ability to reduce stool frequency, useful for treating traveler’s diarrhea.

ANTIEMETICS

These are drugs that are generally used to prevent or treat vomiting associated with chemotherapy. They can also be used just to stifle vomiting when it becomes dangerous (like increased cardiac demand during an MI), but there goal is to prevent people from suffering during chemotherapy.

Cannabinoid. Dronabinol. It stimulates cannabinoids receptors in the CNS stimulating appetite, treating anorexia, and reduces nausea and vomiting associated with cancer chemotherapy.

5-HT3 Antagonists. Ondansetron and Granisetron. Selectively inhibits the HT3 Subtype Serotonin Receptor which are present in the vagal nerve terminals and in the chemoreceptor trigger zone. Blocking these reduces nausea and vomiting associated with cancer chemo and surgery.

Anticholinergics. Scopolamine is used as a duralgesic patch for motion sickness

Antihistamines. Dimenhydrinate is also used to treat motion sickness

Prokinetic. Metoclopramide is a dopamine D2 receptor antagonist and a cholinergic agonist. It causes both antiemesis and empties the stomach (so there isn’t anything to throw up). It is used to prevent nausea and vomiting of cancer chemo and prophylactically for surgery.

ANTIDIARRHEAL DRUGS

Antimotility. Diphenoxylate activates presynaptic opioid receptors in the ENS to block ACh release. This decreases peristalsis, and increases transit time (so more water can be absorbed). This is the cheaper version of the two, and, in higher doses, may cause opioid dependence. Loperamide is more expensive but has no potential for addiction.

Adsorbents. Kapectate and Methylcellulose are the classic adsorbent antidiarrheals. They adsorb bacteria, toxins, and fluids, and are therefore useful for acute diarrhea. If given for diarrhea, they may also adsorb medications. In the case of hyperkalemia, Kapectate is used to bind some of the potassium in the GI tract.
LAXATIVES

Nothing was underlined in the drug list and there was no red text in the lecture. I really don’t know what you are supposed to know for these. Old people use Castor Oil to “maintain a regular bowel movement” even if they don’t need them; this and drugs like it are called GI irritants. Docusate Sodium is a stool softener, softening and lubricating stool for easier movements (it is a surfactant). Bulk Laxatives such as methylcellulose are not digested and induce an osmotic draw of water, producing diarrhea or loosening stool.

HERBAL MEDICATIONS

Complementary: used together w/ conventional medicine.
Alternative: used in place of conventional medicine.

Some absolute garbage from the nonmedical community (list of the red about herbal supplements)
Herbal Supplements are:

- Categorized herbal products as foods rather than drugs.
- Herbs do not have to be tested or proven to be safe or to provide specific health benefits.
- Blanket statements such as “improves immune function” or “promotes liver health” are allowed to be made without any scientific evidence.
- A bottle label may claim there is 500 mg of active ingredient (in reality there may be 0 mg or 5000 mg).
- Contamination by heavy metals either maliciously to increase sale weight, or sloppy medicine
- Contamination by digitalis & prescription drugs which is why we spend so much money on prescription
- Only buy drugs that have a USP or NSF certification
  - USP = supplements do not contain harmful levels of any contaminant.
  - NSF = there are no unacceptable levels of contaminants present in the supplement.

Two herbal supplements have been shown to work, lets talk a bit about them.

(1) St. John’s Wart
This is the primary drug of choice for depression in Germany. There was a study that compared St. John’s Wart, Placebo, and Imipramine. By week 4, both Imipramine and St John’s Wart were significantly better than control on a self-reported rating of depression. There was real benefit from St John’s Wart in mild to moderate depression. Side effects were mild and were significantly fewer reported than in Imipramine. Compared to imipramine, then, St John’s Wart is equally effective as TCAs in treating depression with fewer side effects. The active ingredient is unclear, but we think it has something to do with Hyperforin. He really glossed over this stuff, and nothing is in red here, so I wouldn’t worry about active ingredients. HOWEVER, St John’s Wart is a potent inducer of PGP and P450, and as in common antidepressant reactions, Serotonin Syndrome if given together with SSRIs. So, we have to be cautious of people using this drug. It works, it will work for them, but it can really screw up our prescriptions, especially if we don’t know about it.

(2) Saw Palmetto – we aren’t really sure how it works or why it works, but it does have some benefit in benign prostatic hyperplasia.

### Herbals vs. Rx Drugs

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<thead>
<tr>
<th></th>
<th>Rx Drugs</th>
<th>Herbs</th>
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<tbody>
<tr>
<td>Dosage Form</td>
<td>tablet, capsule, etc.</td>
<td>teas, tinctures, tablets</td>
</tr>
<tr>
<td>Purity</td>
<td>Pure</td>
<td>ImpURE</td>
</tr>
<tr>
<td>Mechanism</td>
<td>Usually known</td>
<td>Rarely known</td>
</tr>
<tr>
<td>Efficacy</td>
<td>Proven</td>
<td>Variable</td>
</tr>
<tr>
<td>Regulation</td>
<td>Much</td>
<td>Little</td>
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Lecture Objectives in a Nutshell:

Herbals can be sold without regulation unless proven to be unsafe or harmful (like ephedra).
HEPATIC CLEARANCE

Presystemic Clearance

Go back to the beginning of the year to our first lecture. There are some things that come back to haunt us. **P-glycoprotein** is an extruding type of protein that kicks out anything that happens to get into the enterocyte of the gut. It is the bouncer that stops the 19 year old from getting into the club at the door. There are also **Intestinal Cytochrome P450s** which is the cop in the club that beats the crap out of that 19 year old who snuck passed the bouncer. Still, some 19 year olds get in, as do some drugs.

Both the P-Glycoprotein and the Cytochrome P450 is going to limit the bioavailability of drugs administered orally.

**Extraction Ratio** go to [www.icp.org.nz](http://www.icp.org.nz) for animations.

When you think about how the liver clears drugs, we use the diagram on the following page. There we have both portal vein and artery coming into the liver. You have a certain rate of **blood flow** to the liver that can be affected by changes in cardiovascular dynamics (shock, heart failure). **Blood flow controls how much drug is delivered.** There is the liver itself, where the liver does something to the drug **(metabolism).** On the other end, there is a blood flow away from the liver, supposedly with less drug than went in.

\[
Q = \text{blood flow (ml/min)} \\
C_a = \text{arterial drug conc. ([drug] going in)} \\
C_v = \text{venous drug conc. ([drug] leaving)} \\
Q \times C_a \\
\frac{Q \times E}{\text{ml/min}} \\
\frac{Q \times C_v}{\text{hepatic vein}}
\]

Thus the **extraction ratio** is determined by the **hepatic clearance**, how much drug came out of the blood. We compare the amount of drug in the blood before the liver \((C_a)\) to the amount in the blood after the liver \((C_v)\) an express it as a ratio compared to how much went in overall \((C_a)\).

\[
E = \frac{C_a - C_v}{C_a}
\]

**Drug Categories** fall into 3 categories: **high extraction ratios** \((E>0.7)\), **low extraction ratios** \((E<0.3)\), and **intermediate**. We will focus on the polar opposites today.

Both intestinal /presystemic clearance and hepatic clearance contribute to the bioavailability of an orally delivered drug, whereas hepatic clearance and renal clearance contribute to systemic clearance.
There are three determinants of hepatic clearance. As we just learned, one of them is hepatic blood flow (how much of the drug is brought to the liver). Another component is free drug. If all the drug is in the blood, but all is bound to protein, none of it can get to hepatocytes, so there won’t be any metabolism. There has to be free drug in order to be metabolized. Finally, there is the intrinsic clearance of the liver, termed Ci, which is how much and how hard the liver can work on the drug it has access to.

Don’t memorize this equation, but let’s look at it. It correlates the ability of the liver to clear a drug (hepatic clearance) to the blood flow, the free fraction of the drug, and the intrinsic clearance of the drug by the liver. We can manipulate this equation when we talk about polarities in extraction ratios.

\[
Cl_H = \frac{Q \times f_u \times Ci}{Q + (f_u \times Ci)} \quad Cl_H = \text{hepatic clearance} \\
Q = \text{hepatic blood flow} \\
f_u = \text{fraction of free drug} \\
Ci = \text{intrinsic clearance (ability of hepatocytes to clear drug)}
\]

For drugs with a large extraction ratio, \( Q \ll f_u \times Ci \), so \( Q \) approaches 0, and can be removed from the denominator. Once done, a fraction of \( x \) over \( x \) is equal to 1, so they cancel. What you are left with is only Hepatic Clearance equal to Blood Flow (the math is on the next page).

\[
Cl_H = \frac{f_u \times Ci}{Q + (f_u \times Ci)} \quad Cl_H = Q \times \frac{f_u \times Ci}{f_u \times Ci} \quad Cl_H = Q
\]

Let’s say that again in English: for drugs with a large extraction ratio, clearance depends primarily on hepatic blood flow and is non-restricted by binding to plasma proteins.

So what is the magnitude of these following derangements for drugs with Large Extraction Ratio?

- **First Pass Effect**: Large, most of the drug is cleared on first exposure
- **Effect of Blood Flow on Cl\( H \)**: its large, \( Cl_H = Q \), meaning that shock, CHF, or hypotension will cause a reduced clearance for this drug
- **Half-Life**: short half lives; if you extract them well, they don’t hang around for long
- **Effect of Liver Damage on Bioavailability**: Large impact on bioavailability; if you had cirrhosis, and you killed the filter, the drug gets in and has increased
- **Effect of Enzyme Induction on Cl\( H \)**: small effect on drug. Since it is already highly cleared, inducing enzymes isn’t going to change the metabolism of these drugs; there is little room for improvement.
If we look at drugs with small extraction ratios instead, we see the opposite. Since there is small extraction ratio, the intrinsic clearance is low, and $Q \gg f_u \times Cl_i$.

\[
Cl_H = \frac{Q \times f_u \times Cl_i}{Q + (f_u \times Cl_i)} \quad \rightarrow \quad Cl_H = \frac{Q \times f_u \times Cl_i}{Q} \quad \rightarrow \quad Cl_H = f_u \times Cl_i
\]

Now, **drugs with small extraction ratios** are capacity limited or are restricted by plasma proteins.

- **First Pass Effect**: Small, since most of the drug is not cleared
- **Effect of Blood Flow on Cl_H**: small, $Cl_H = f_u \times Cl_i$, meaning that blood flow doesn’t play a role
- **Half-Life**: long half lives; if you extract them poorly, they will hang around
- **Effect of Liver Damage on Bioavailability**: Small; if you had cirrhosis, and you killed the filter, but the filter doesn’t work very well anyway, there won’t be much change.
- **Effect of Enzyme Induction on Cl_H**: large. Since it is poorly cleared, inducing enzymes is going to change the metabolism of these drugs; there is a lot of room for improvement.
- **Effect of changes in protein binding**: large; in cirrhosis, albumin is lost, and there is less to be bound to, so the free drug is greater, and an increase in hepatic clearance.

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**Drugs with a large extraction ratio** are vulnerable to changes in **blood flow** and not to changes in enzyme induction or protein concentrations.

**Drugs with a small extraction ratio** are vulnerable to changes in **protein concentrations** and **enzyme induction** but not from blood flow.