Welcome to What’s New in GERD Therapy: A Case-Based Approach.

This activity is presented and accredited by Creative Educational Concepts, Inc. Educational support for this activity has been provided by AstraZeneca Pharmaceuticals, LP.

After viewing the presentation you will have the opportunity to submit a posttest and evaluation in order to receive continuing education credit.
Your faculty for this presentation will be Drs. Brien Neudeck and Lynda Welage.

Dr. Brien Neudeck is an assistant professor of Pharmacy and Pharmaceutical sciences at the University of Tennessee College of Pharmacy. Dr. Neudeck is the principal investigator on several research projects and has received funding from the US Department of Agriculture, the National Foundation for Infectious Diseases, the American College of Clinical Pharmacy and the pharmaceutical industry. He has published papers in peer-reviewed journals and is a member of the American College of Clinical Pharmacy, the American Association of Pharmaceutical Scientists, the American Gastro-enterological Association and the American Society for Microbiology.
Dr. Lynda Welage is a Professor of Clinical Sciences, and Associate Dean for Academic Affairs at the University of Michigan College of Pharmacy. For the past 18 years her research program has focused on alterations in gastrointestinal physiology and drug absorption during critical illness. Recent efforts have focused on evaluating the impact of acute inflammation on intestinal transport processes and drug absorption. She has published extensively in the area of critical care and the pharmacotherapeutics of gastrointestinal diseases. Dr. Welage has been an active participant in local, state and national pharmacy and medical organizations, and is a fellow of the American College of Clinical Pharmacy.
The learning objectives for this program are to review the physiology, risks, treatment strategies, and expected outcomes of GERD in all populations. Identify patients on NSAID therapy who may be at risk for serious GI complications so that therapy to prevent adverse events and improve patient outcomes will be considered. According to the guidelines and recent peer reviewed literature, assess the benefits of both pharmacological and non-pharmacological therapies for patients with GERD in order to develop a monitoring plan to ensure the most effective therapy for each patient is being utilized.
Learning Objectives

• Propose strategies for developing optimal therapeutic treatment plans to help patients with asthma minimize symptoms of GERD and prevent exacerbations of their asthma.

• Evaluate the impact of severe nocturnal GERD on patients’ sleep and monitor for appropriate therapy in order to improve patient quality of life and minimize other health risks.

• Summarize the role of proton pump inhibitors (PPIs) in the pediatric population to achieve the best outcome.

As well as, propose strategies for developing optimal therapeutic treatment plans to help patients with asthma minimize symptoms of GERD and prevent exacerbations of their asthma. Evaluate the impact of severe nocturnal GERD on patients’ sleep and monitor for appropriate therapy in order to improve patient quality of life and minimize other health risks. And finally summarize the role of proton pump inhibitors (PPIs) in the pediatric population to achieve the best outcome.
Section 1
Gastroesophageal Reflux Disease (GERD)

Lynda S. Welage, PharmD, FCCP
Professor and Associate Dean for Academic Affairs
College of Pharmacy
University of Michigan
Ann Arbor, Michigan

Now Dr. Lynda S. Welage from the University of Michigan will discuss Gastroesophageal Reflux Disease otherwise known as GERD.
Our first case is a patient with Gastroesophageal Reflux Disease. Because this is a continuing education program I would like to point out our biographical sketches as well as our disclosures are in your handout, my disclosures are indicated there. And if we start with the case the MR is a 40 year old male who complains of a burning in his chest that moves up towards his throat, sort of as he is adjusting his tie there. His past medical history is significant for hypertension. He is treated with amlodipine and atorvastatin.
Case Continued

• Ht: 6'0", Wt: 70 kg
• Social History:
  – Drinks scotch 2-3 x per week
  – Smokes 1-1.5 PPD x 20 yrs; has tried unsuccessfully to quit smoking several times
• He has had occasional heartburn in the past, especially following “over-eating.”
• He thinks that this seems different; he has been eating healthy and exercising.
• MR is not sure if this is heartburn as it occurs sometimes “out of the blue” (midmorning, late night, afternoon).
• He hopes this is “just heartburn”, but worries it might be more serious.

Now he is a 6 foot 70 kilogram individual who drinks scotch about 2-3 times per week. He smokes 1 to 1½ packs per day for 20 years and he indicates he has tried several times to quit but he is been unsuccessful and he notes that he has occasionally had heartburn but particularly in the past that’s usually related to over-eating. And he doesn’t really understand it now and that’s why he’s come in and this seems different. He has been eating healthy, he is exercising. His only bad habit according to him is he still smokes. So he is not sure really if this is heartburn because it occurs all the time it seems, like it occurs sometimes in the mid-morning, sometimes in the afternoon, sometimes even late at night. He really hopes this is just heartburn but he worries it might be something more serious.
Gastroesophageal Reflux Disease

GERD - ACG “Clinical” Definition:

- Chronic symptoms or mucosal damage produced by the abnormal reflux of gastric contents into the esophagus

Heartburn

- The most common symptom of GERD
- Retrosternal chest pain radiating upward toward the throat


Well heartburn is the most common symptom of Gastroesophageal Reflux Disease. And we often think of it as clinicians as the retrosternal chest pain or burning, radiating up towards the throat. But it’s important to recognize many patients present with different definitions or symptoms in descriptions of heartburn. It maybe a fullness in the mid chest. It maybe pain sort of radiating up or in a particular spot. So this definition is very general and you need to ask patients about their different symptoms. Gastroesophageal Reflux Disease according to the American Clinical Gastroenterology Association clinical definition is chronic symptoms or mucosal damage produced by the abnormal reflux of gastric contents into the esophagus. Now the practical definition of GERD or practical clinical definition I would say he is a patient who has heartburn that classic symptom two or more days a week.
Well, Gastroesophageal Reflux Disease and heartburn is extremely prevalent in our economically developed countries, with 44% of Americans indicating in a Gallup Survey that they have heartburn at least monthly. 20% indicate that they have it on a weekly basis, and 7% indicating they have heartburn daily.
It's important to recognize that many patients have heartburn or Gastroesophageal Reflux Disease but they may not seek medical attention. We refer to this as the GERD iceberg to illustrate that patients with persistent symptoms or complications often seek medical attention, frequently a gastroenterologist. Even patients with frequent heartburn may see a physician or a pharmacist. But it's the patient with occasional mild heartburn that doesn't usually seek therapy and the clinician they see is actually the pharmacist, so the pharmacist is the person that sees everyone, okay. And he is actually the target healthcare provider in many ways for managing and evaluating Gastroesophageal Reflux Disease and deciding whether or not they need to seek medical or physician’s attention or they could self treat.
What risk factors does MR have for GERD?

1. Smoking
2. Obesity
3. Amlodipine/atorvastatin
4. 1 and 3
5. 1, 2, and 3

What risk factors does MR have for Gastroesophageal Reflux Disease? 1. Smoking
2. Obesity 3. His amlodipine/atorvastatin therapy 4. #1 and #3 5. #1, #2, and #3
What risk factors does MR have for GERD?

1. Smoking
2. Obesity
3. Amlodipine/atorvastatin
4. 1 and 3
5. 1, 2, and 3

I want to point out he was 6 feet and 70 kilograms, so he wasn’t obese but if we move onto the next slide.
## Risk Factors for GERD

### Physical
- Obesity
- Delayed gastric emptying
- Pregnancy
- Systemic sclerosis
- Hiatal hernia
- Recumbency

### Behavioral
- Smoking
- Alcohol use
- Taking medications such as calcium channel blockers, nitrates, or theophylline
- Consuming large meals (especially before bedtime)
- Eating certain foods such as chocolate, coffee, peppermint, or fatty foods

We do see that actually all three factors, obesity as well as the smoking and certain medications particularly calcium channel blockers are risk factors for Gastroesophageal Reflux Disease. He only had two of them, smoking and his calcium channel blocker. Other risk factors include delayed gastric emptying, and some studies estimate that up to 60% of patients with Gastroesophageal Reflux Disease have some form of delayed gastric emptying due to diabetes or other motility disorders. Pregnancy, sclerosis because it affects the lower esophageal sphincter, hiatal hernia may also impair the lower esophageal sphincter. Recumbency, laying down we will talk a lot about when we talk about our case with night time heartburn and how that contributes to the development of Gastroesophageal Reflux Disease. Behavioral factors that you might be able to do something about, hopefully and quit smoking cut his alcoholic use, change those medications that may lower esophageal sphincter tone such as get him off of his calcium channel blockers, avoid nitrates or theophylline, avoid consuming large meals particularly before bedtime and avoid eating certain foods - coffee, chocolate, peppermint which may affect that lower esophageal sphincter tone or fatty foods which may in fact delay gastric emptying. All of these would be risk factors for Gastroesophageal Reflux Disease and if we think about the pathophysiology we can see how they tie in.
One of the primary pathophysiologic features is the loss of lower esophageal sphincter pressure of the LES. Now most patients don't have totally abnormal LES pressures. They have transient relaxations in this sphincter so sporadic transient relaxation that allows the gastric contents, acid and pepsin to move from the stomach up into the esophagus. This becomes more common obviously when you have an increase in gastric pressure due to high gastric volume or delayed gastric emptying, pylorus obstruction, obesity or in pregnancy. Another contributing factor is how quickly the material can be cleared from the esophagus so reduced esophageal motility contributes to the pathophysiology of GERD because it delays esophageal clearance. All of these factors come to play in GERD pathophysiology.
Which of the following would be appropriate approach to initial diagnosis of MR’s pain?

1. Upper GI series  
2. Endoscopy  
3. Empiric trial of PPI  
4. Gastric pH monitoring

Which of the following however would be appropriate as the initial approach to diagnosed MR’s pain? Would you use:

1. An upper GI series  
2. Endoscopy  
3. An empiric trial of Proton Pump Inhibitor  
4. Gastric pH monitoring
Which of the following would be appropriate approach to initial diagnosis of MR’s pain?

1. Upper GI series
2. Endoscopy
3. Empiric trial of PPI
4. Gastric pH monitoring

Answer 3
Diagnosing GERD

- No gold standard diagnostic test for uncomplicated GERD
- Initial diagnosis obtained via clinical symptoms and confirmed via empiric PPI treatment
- Endoscopy:
  - Reserved for patients with alarm symptoms or disease complications
  - To screen for Barrett’s esophagus in patients with long-standing GERD
- pH Monitoring: patients not responsive to medical or surgical treatment


And there is no gold standard diagnostic test for moving on for Gastroesophageal Reflux Disease but I would agree that the initial diagnosis is usually based on clinical symptoms and confirmed with empiric proton pump inhibitor therapy in the majority of patients. Now there are some exceptions. Endoscopy is reserved for patients who have alarm symptoms or complications of Gastroesophageal Reflux Disease. It’s also used as a screening procedure for Barrett’s esophagus and it should be done in patients who have long standing Gastroesophageal Reflux Disease. pH monitoring on the other hand is used less frequently but it does have a role particularly for patients who are unresponsive to medical or surgical treatment. And you are trying to see if they in fact have acid being reflux into their esophagus and so it’s doing esophageal pH monitoring.
The clinical presentation of GERD is outlined in this slide and as I already mentioned the hallmark symptom is clearly heartburn. But patients often complain of acid regurgitation and we are seeing more and more patients with the super esophageal or what we sometimes call atypical symptoms of Gastroesophageal Reflux Disease. These include laryngitis, asthma which we will talk more about later, chronic cough, aspiration pneumonia, chest pain and dental erosions.
Which of the following would be considered alarm symptoms which warrant immediate referral to a physician?

1. Regurgitation
2. Chronic cough
3. Laryngitis
4. Dysphagia

Which of the following would be considered alarm symptoms of Gastroesophageal Reflux Disease or alarm symptoms that would warn immediate referral to a physician? So if you saw these you would immediately send the patient to see a clinician:

1. Regurgitation
2. Chronic cough
3. Laryngitis
4. Dysphagia
Which of the following would be considered alarm symptoms which warrant immediate referral to a physician?

1. Regurgitation
2. Chronic cough
3. Laryngitis
4. Dysphagia

Answer 4
If we move on to the next slide we see that there are several alarm symptoms one of which is dysphagia. Others include weight loss, choking, chest pain or bleeding. Any patient presenting with any of these symptoms, alarm symptoms, should be immediately referred to a physician. These symptoms may reflect something more severe. The classic being chest pain maybe hard to distinguish whether it’s heartburn or is it angina or someone having a myocardial infarction and so the patient may not be able to distinguish and they might want to think it’s heartburn so it’s important to keep this in mind and question specifically what are the symptoms they are having.
Some people say well it’s just a little heartburn, Gastroesophageal Reflux Disease isn't a big thing, and I hope since you hear today you don't feel that way. But it’s important to recognize it is a big deal. It impacts people’s quality of life. It’s a common disease and it has a negative impact on their quality of life. And that shown here I mean as you can see in blue Gastroesophageal Reflux Disease has a general wellbeing score. So this is a measure of quality of life it’s similar to patients with duodenal ulcer disease and angina in less than things like menopause, heart failure or hypertension. These people don't have good qualities of life and we will talk more about that a little later.
Our goals of therapy first and foremost from a patient’s perspective is relieve those symptoms, get rid of that heartburn or those atypical symptoms. Second heal the esophageal mucosa if in fact they have erosions not all patients have erosive disease. Prevent complications and then maintain symptom control because it’s a long time disease. It waxes in veins.
Lifestyle Changes

- Should be initiated and continued throughout course of GERD therapy; however changes alone unlikely to control symptoms.
  - Weight loss
  - Avoidance of recumbency for 3 hours postprandially
  - Diet modification (smaller, more frequent meals)
  - Avoidance of certain foods (chocolate, peppermint, coffee, and perhaps onions and garlic)
  - Cessation of smoking
  - Discontinuance of drugs that decrease LES pressure (e.g., calcium channel blockers, anticholinergic agents, theophylline)
  - Elevation of the head of the bed


The first line of therapy is often thought to be lifestyle changes and there is numerous lifestyle changes as outlined here including weight loss and it doesn’t have to be a substantial amount of weight to lose and it doesn’t even have to be in a person that’s obese. It can be in the range of 3 to 5 pounds and a person will see a difference usually in their frequency of heartburn. But it won’t be a big difference. You want to instruct them to avoid being recumbent, three hours postprandial, modify their diets if they can’t eat smaller meals more frequently, avoid those trigger foods, try and quit smoking, discontinue drugs which may contribute to the disease and elevate the height of the bed six inches on blocks. Now although we recommend these and these are baseline we recommend them to everyone, it’s important to recognize there is little evidence randomized control clinical trials that say these work. These modifications alone are unlikely to control symptoms.
The most appropriate therapeutic option for MR at this point would be…

1. Antacids prn
2. Low dose H2RA
3. Famotidine/antacid combination product
4. PPI

But everybody gets these and then we think about drug therapy and so the most appropriate therapeutic option for MR at this point would be which of the following:

1. Antacid prn
2. Low dose H2-receptor antagonist
3. Famotidine/antacid combination product
4. Proton Pump Inhibitor
And this is the American Gastroenterology Association consensus recommendations their treatment flowchart and I want to walk through it a little slowly. But we have a patient with symptoms. What do we ask him what do we do? First we have to ask are these alarm symptoms, if yes it’s going to dictate a whole path down the right side of the slide. We are also going to ask have these symptoms been occurring for a long time, greater than four weeks. If they are alarm symptoms or greater than four weeks of having symptoms they should see a physician. If it’s instead classic symptoms which are episodic and haven’t been in existence for greater than four weeks we would recommend an OTC product. If that controls their symptoms you would maintain therapy. If that doesn’t control the symptoms you would refer him to a physician or try an empiric trial of a Proton Pump Inhibitor, if you had not done so already. And so this approach sort of gets you to ask the questions and to guide you in what therapy you are going to take.
It’s important to recognize all of our therapies are anti-reducing acids, okay, whether we neutralize it or we inhibit it in some manner they are all based on getting right to the acid in the esophagus even though we are getting rid of it in the stomach and that’s based on the study shown here in which the duration that Esophageal pH is less than four correlates with healing as you can see. So patients who had long acid exposure times had poor healing.
Therapeutic Options for GERD

- **OTC** *(control of episodic or breakthrough symptoms)*
  - Antacids
  - Antacid/H2RA combination famotidine/Mg hydroxide, calcium carbonate
  - H2RAs
  - PPI: omeprazole
- **Rx**
  - H2RA
  - PPI
    - Delayed release PPI: OME, ESO, LAN, PAN, RAB
    - Immediate release PPI: OME

Our therapeutic options for Gastroesophageal Reflux Disease include the OTC which I would label as control of episodic or breakthrough symptoms and then we have the prescription therapies, the H2-receptor antagonist as well as Proton Pump Inhibitors and we have numerous out there on the market.
Advantages/Disadvantages of Antacids

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid relief of symptoms</td>
<td>Not 100% efficacious</td>
</tr>
<tr>
<td>No food effect</td>
<td>Not effective for healing</td>
</tr>
<tr>
<td>“All shapes and sizes”</td>
<td>Multiple doses required</td>
</tr>
<tr>
<td>Can be used for breakthrough*</td>
<td>Potential for DDI</td>
</tr>
<tr>
<td></td>
<td>Constipation/Diarrhea</td>
</tr>
</tbody>
</table>

We just walk through quickly. I think you know all these and I want to get on to the other cases. The advantages and disadvantages of antacids are outlined in this slide. They provide rapid relief is the big thing and you can carry them in your pockets, you can have liquids if you prefer, come in all shapes and sizes. The disadvantage is they are not a 100% effective, they are not effective for healing and you have to take a lot of them, multiple doses are required which can lead to adverse side effects or drug interactions.
H₂-Receptor Antagonists and the H₂RA/Antacid Combination

<table>
<thead>
<tr>
<th><strong>Advantages</strong></th>
<th><strong>Disadvantages</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Longer duration of symptom relief</td>
<td>• Only 60%-70% effective</td>
</tr>
<tr>
<td>• Prevention of postprandial symptoms</td>
<td>• Role in EE?</td>
</tr>
<tr>
<td>• Safe</td>
<td>• Cost</td>
</tr>
<tr>
<td>• Can be used for breakthrough*</td>
<td>• Tolerance</td>
</tr>
</tbody>
</table>

If we talk about the H₂-receptor antagonist or the combination products you get longer symptom relief and they can be used nicely to prevent postprandial symptoms. Take it before you are going to have that big meal. They are safe and they can be used for breakthrough. The disadvantage is, the big one in my mind, the bottom one and that’s tolerance develops. These aren’t good agents to take day in and day out everyday on a regular basis. Within about a week of therapy you will lose the effect and so these should be used intermittently due to that development of tolerance.
Now we are all familiar with Proton Pump Inhibitors, they are the most potent inhibitors of acid secretion. They are all administered as inactive pro-drugs which remain inactive until they enter the parietal cell which is highly acetic and they get protonated and converted to the active moiety and then that active moiety binds to and inhibits active proton pumps and it’s important to keep this in mind because Proton Pump Inhibitors only inhibit active pumps until we want to think of that in our dosing strategies when would there likely be active pumps and we will talk a little bit about that more.
In terms of their efficacy they have been shown superior over and over again to H2-receptor antagonist. This is a metanalysis done by Chiba and colleagues with over 7000 patients and you can see that the percentage of Esophagitis healed is dramatically higher with the Proton Pump Inhibitors, over 80% as compared to the H2 receptor antagonist, which were only about 50% or placebo at 12 weeks of therapy. Well what about the different Proton Pump Inhibitors? How do they stack up? And I could go through and show lots of different studies looking at esophageal pH, looking at gastric pH, looking at symptom control, looking at healing for each of them and you will see different results somewhat depending on individual studies.
What I thought was more important today was to step back and look at the big picture. So what I did was take several other trials and say if I graph them out how do they stack up, and this slide shows two things. First that going from four weeks to eight weeks you increase your efficacy of your Proton Pump Inhibitor from about 80% up to 90% to 95% of patients being healed. Second all of the Proton Pump Inhibitors are highly effective in healing Erosive Esophagitis.
If MR presents with continued burning in his chest in 4 weeks, despite being given a PPI, you would...

1. Ask when/how he is taking his PPI
2. Refer him to a gastroenterologist
3. Tell him to double his PPI dose
4. Tell him to keep taking it for 6 more weeks to see if it works

And we put MR on a Proton Pump Inhibitor but then he came back four weeks later and so when he came back four weeks later he complained of continued burning in his chest despite his Proton Pump Inhibitor and you can fill in which one you put him on. Now what are you going to do?

1. Ask him when and how he is taking his Proton Pump Inhibitor
2. Refer him to a gastroenterologist
3. Tell him to double his dose
4. Tell him to keep taking it for six more weeks and see if that works
If MR presents with continued burning in his chest in 4 weeks, despite being given a PPI, you would...

1. Ask when/how he is taking his PPI
2. Refer him to a gastroenterologist
3. Tell him to double his PPI dose
4. Tell him to keep taking it for 6 more weeks to see if it works

In this case I think either of those are appropriate answers. I think it’s very important to recognize that about 30% of patients may not respond to the Proton Pump Inhibitor.
Things to Consider for “PPI Failures”

- Are they taking it?
- When are they taking it?
- How are they taking it?
  - with food?
- Pharmacokinetic/dynamic principles

And if we look at that lack of response or PPI failure as it’s come to be known in the literature it often relates to one of two things, either compliance and how they are taking it or the situation that they have functional dyspepsia or functional heartburn so maybe it’s not related to the acid and if we look at things we would ask him, we would want to consider in this particular situation are they taking the drug? When are they taking the drug? How are they taking it? Are they taking it with food or not? It should be taken usually 30 to 60 minutes before the first meal of the day – breakfast, and that’s because when you break a fast with a meal you will turn on the most Proton Pumps which will then be active which you can in turn inhibit with your Proton Pump Inhibitor and so you are going to base their therapy on the Pharmacokinetic and Pharmacodynamic principles. That all being said and I think pharmacists hopefully know all that. There was a recent study that indicated, looked at patients who came to a gastroenterologist for refractory or PPI failure. That had all been started on a Proton Pump Inhibitor and 54% of them were dosed incorrectly when the gastroenterologist said is their first question how did you take your Proton Pump Inhibitor? 54% took it wrong, indicating we are not getting the message to the patient and probably the reason they had to go to the gastroenterologist, a simple fix.
The Approach to Maintenance in Gastroesophageal Reflux Disease

- GERD is a chronic condition
- Many patients with moderate or severe GERD will require maintenance therapy
- H₂RAs may be effective in some patients, although most will require long-term PPIs
- The regimen needed to initially manage symptoms is often the regimen needed to maintain remission of symptoms
- Short courses (at least 2 to 4 weeks) of intermittent therapy may be an option for some patients

It’s important to recognize that I already alluded to Gastroesophageal Reflux Disease is a long term disease. It’s a chronic condition. Many patients with moderate or severe GERD will require maintenance therapy and there is a lot of controversy in the literature do you step off your Proton Pump Inhibitor therapy and then restart it intermittently as needed? Do you step down to an H₂ receptor antagonist? And that will be effective in some patients but it’s important to recognize the regimen needed initially to manage the symptoms is usually the regimen that is needed to maintain that symptom relief.
GERD Maintenance Therapy: Efficacy of Lansoprazole vs. Placebo

- 170 patients with healing of GERD after 8 weeks assigned to receive 1yr of:
  - Lansoprazole 15 mg (n=59),
  - Lansoprazole 30 mg (n=56),
  - Placebo (n=55)


I didn’t include all the studies of the different Proton Pump Inhibitors in terms of maintenance therapy. I used this as just illustrative. They have all been shown effective in maintaining symptom control and healing and this is studied with lansoprazole 15 or 30 mg versus placebo and as you can see that both in terms of healing as well in terms of symptom relief it was superior than placebo.
Indications for Surgery

• Reasonable alternative for patients with moderate to severe GERD
• Patient responds to medical therapy but suffers frequent and bothersome recurrence or is unwilling to live with the limitations imposed by medical therapy
• Young patient who needs medical therapy indefinitely
• Patient refractory to medical therapy
• Cost (lifelong PPI therapy vs. surgery)"

In the rare patient the issue of surgery may come up. It is a reasonable alternative for patients with moderate to severe Gastroesophageal Reflux Disease in patients who respond to medical therapy but suffers from frequent bothersome reoccurrences or is unwilling to live with the limitations imposed by medical therapy, they just don’t want to continue the drug therapy or in a very young patient who may need medical therapy indefinitely or is refractory to therapy. We have numerous surgical options available particularly laproscopically, Nissen, Stretta, etc., but one has to balance the risks of that surgery and cost against the cost of lifelong Proton Pump Inhibitor therapy or intermittent lifelong Proton Pump Inhibitor therapy.
Thank You

You have completed Section 1.
Now Dr. Brien Neudeck from the University of Tennessee will discuss the prevention of NSAID induced ulcers.
Prescription NSAID Use

- More than 111 million NSAID/COX-2 prescriptions were written in 2004
  - 45% for COX-2 selective inhibitors
  - $6.6 billion in annual drug costs
- 70% of people aged ≥65 years take NSAIDs at least weekly
  - 60% of these patients take aspirin
  - 34% take NSAIDs daily


If we look at the first bullet point, we will see that in 2004 so only two years ago there were over a 111 million prescriptions written for NSAIDs including the COX-2 inhibitors and this resulted in almost $7 billion in drug cost. Now granted because of the withdrawal of certain COX-2 inhibitors from the market and a decline in prescription NSAID use these numbers probably are not as accurate in 2006 as they were in 2004. However, just the fact that a 111 million prescriptions were written gives us a pretty good idea in terms of magnitude of the number of patients that take these drugs. Now if we look to a certain subset of these patients that take these drugs, the elderly, so if you look at patients who are over 65 years of age we see some interesting findings. One is that 70% of those patients need to take an NSAID at least weekly and 34% of them take an NSAID daily. Now we are all very familiar with the cardio protective effects of the aspirin for primary and secondary prevention of thromboembolic complications and so compared to say 30 years ago we have a significantly more elderly individuals who have significant cardiac risk of taking daily aspirin and so in this study 60% of people over 65 years of age were taking daily aspirin. So the slide tells us two important things, one is the fact that millions of Americans are taking NSAIDs routinely and then the elderly which is a subset of the population that is certainly growing has multiple reasons to take these drugs and many of them are taking them on a daily basis.
Widely due to the fact that the elderly have multiple reasons for taking NSAID use here we see several on the slide, it’s been estimated that the arthritides are very common in the elderly population and in fact over half of all office visits of the elderly who have these diagnoses whether it be osteoarthritis or rheumatoid arthritis taking NSAID for control of pain and inflammation. Back pain is certainly more common in the elderly, however I know I speak for Dr. Welage and myself that younger individuals can have back pain and routinely take NSAIDs and there are other reasons as well. There are more reasons are non-arthritis musculoskeletal disorders and so we have a population that’s growing and they are taking NSAIDs fairly routinely. Now I mentioned that osteoarthritis and rheumatoid arthritis are common in the elderly but I think it’s important for us to step back and recognize that it’s not just in the elderly population. Unfortunately the incidence of arthritis is growing rapidly in this country.
Arthritis

• The prevalence of arthritis in the US is increasing
  – In 1990, arthritis affected 37.9 million patients
  – By 2020, the prevalence is expected to increase 57% to 59.4 million patients

• Approximately 2 million patients with rheumatoid arthritis use NSAIDs for symptom relief

• With the increased prevalence of arthritis, it is likely that chronic NSAID use will increase

If we go back about say a decade and a half we see that arthritis affected about 38 million people. If we jumped forward in time about by the same number of years a decade and a half we will see that the prevalence of arthritis is expected to increase by 57% so that it’s estimated that almost 60 million Americans will have arthritis. And since we have already established that NSAIDs are routinely prescribed for those patients, here we have a situation where a large number of individuals are currently taking NSAIDs chronically and most certainly in lieu of some other drug class being developed in that timeframe for certainly be taking these on a chronic basis in the future as well.
With Chronic Use Comes Toxicity

Three Categories of GI Side Effects Associated with NSAID Use

1. Mucosal lesions as seen on endoscopy
   - Erosions in 40-60%
   - Ulcers in 15-30%
2. Serious GI complications
3. Gastrointestinal symptoms
   - Heartburn, nausea, dyspepsia, vomiting, and abdominal pain


And again as I referred to my opening slide as we learned in pharmacy school NSAIDs are great drugs but with chronic use we start to pick up some toxicities. There are a variety of toxicities that affect the GI track with respect to the NSAIDs. If we skip down to point number three we know that what I referred to as the non specific gastrointestinal symptoms are actually quite common in the general population and it’s my argument that they are probably under reported. And certainly NSAID use has been linked to dyspepsia, heartburn, abdominal pain and vomiting can also occur. And I am sure these are problematic for the patient but what we really worry about more globally speaking is the top two. So if we do an endoscopy unfortunately we see that in about 40% to 60% of patients who require a chronic NSAID they will have some sort of superficial lesion which is listed in the illustration here. Even more troubling is that fact that on endoscopy we find that anywhere from 15% to 30% and the two number probably we are on 20-22% of patients taking chronic NSAIDs will develop an ulcer so this is particular worrisome. Probably the worst case scenario in the patient taking chronic NSAID is the fact that they have developed a serious GI complication. So this would be a perforation. GI bleed that brings him into the hospital and once they hit the hospital with the GI bleed we know that their morbidity and mortality sky rocket and so these are concerns. These are the reasons why we have asked the question can we do something to maybe minimize the toxicity.
Upper GI Tract Ulcers Due to NSAIDs

- Of patients who take NSAIDs chronically, up to 20% may develop an ulcer
- Symptoms are not a reliable indicator of the presence or absence of ulcers


So if we refer back to a statistics on the last slide and we say that about 20% develop an ulcer we also are troubled with a fact that unfortunately we can’t just look at a patient and say you have symptoms now we need to worry about you. Unfortunately like a lot of things related to GERD symptoms aren’t an accurate predictor of problems or complications. In fact it’s very common for patients to present with the GI bleed to the hospital and never had any sort of symptom other than those that occurred on the day of hospitalization and so let’s look at some of the issues related to potentially solving or at least minimizing this problem.
Ester is a 65-year-old retiree, has a history of osteoarthritis, migraines, and mild coronary artery disease.

After the withdrawal of rofecoxib from the market, she now takes daily ibuprofen and cardioprotective aspirin.

So this is our first case Ester, she is a 65 year old retiree, she has got a history of osteoarthritis, migraines. She does have mild coronary artery disease. After the withdrawal of her COX-2 inhibitor she switched to daily ibuprofen and cardioprotective aspirin.
So my first question is what risk factors do you think Ester has for GI complications. Does she have an increased risk because she has osteoarthritis? Does she have an increased risk because she takes an NSAID daily? Is her age a factor the fact that she is over 65? Is it a combination of these, so osteoarthritis or daily NSAID use, the combination of those two or lastly the fact that she takes a daily NSAID and her age is an issue.
What risk factors does Ester have for GI complications?

1. Osteoarthritis
2. Daily NSAID use
3. Age
4. Osteoarthritis and daily NSAID use
5. Daily NSAID use and age

The fact that she takes an NSAID daily and age is a major risk factor for GI complication.
Potential Risk Factors for Serious Upper GI Complications with NSAID Use

- History of ulcer or GI complications
- Multiple NSAIDs (including aspirin)
- High dose NSAIDs
- Concomitant anticoagulant use
- Concomitant steroid use
- Age \( \geq 60 \) years
- Major illness (e.g. heart disease)

And so if you look to the next slide we see that these are in fact risk factors for having GI complication and I would actually argue that she may have multiple risk factors if we dug even deeper. So we see that patients requiring chronic NSAIDs if they have a history of ulcer or GI complication we unfortunately know that this places him at increased risk for developing one in the future and so this is certainly a population that we need to be wary of. Multiple NSAIDs again which is similar to Ester she takes ibuprofen and cardioprotective aspirin so the fact that more and more people are combining these because of the known cardiac benefits of aspirin plus the fact that they have some other comorbidity that requires a daily NSAID use this segment of the population is certainly increasing and you can see from the slide it's a risk factor for a serious GI complication. On high dose as we will see in a moment the NSAIDs with respect to the GI toxicity have a dose dependent affect so the higher the dose the more likelihood of toxicity. If the patient is taking concomitant steroids or anticoagulants that certainly raises a risk as well. Age as you appropriately identified as risk factor and in major illness in terms of comorbidity certainly plays a role as well.
Daily Aspirin Dose and Admission for Ulcer Bleeding

<table>
<thead>
<tr>
<th>Aspirin Dose</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>75 mg</td>
<td>2.3 (1.2-4.4)</td>
</tr>
<tr>
<td>150 mg</td>
<td>3.2 (1.7-6.5)</td>
</tr>
<tr>
<td>300 mg</td>
<td>3.9 (2.5-6.3)</td>
</tr>
</tbody>
</table>

- Risk of GI complications is dose-dependent and is the same regardless of use of plain, buffered, or enteric-coated aspirin


This slide depicts what I was referring to with respect to the dose dependency with respect to GI toxicity of the NSAIDs. This was taken from a number of studies and as you see with a relatively low dose of 75 mg you still have about twice the likelihood of being admitted for a bleeding ulcer due to that NSAID, and as you increase the dose you see that the risk increases dramatically. Now unfortunately it doesn’t appear that using an enteric-coated or a buffer product helps us out in this regard. Now those products maybe beneficial for improving sort of the local NSAID induced symptoms, so dyspepsia, abdominal pain and those sort of things. But as we will see in a moment many of the adverse effects to the GI track that the NSAIDs produce are due to their systemic effects and so using enteric-coated product is not necessarily going to help in that regard.
And this slide depicts a two important things in my opinion, one it sort of reinforces the fact that we see a dose dependent toxicity with respect to aspirin as we go up. But also the fact and this is especially pertinent for our case in what we are looking at Ester and the fact that when we add aspirin to other non-selective, non-steroidal anti-inflammatory drugs the risk of being admitted for a bleeding ulcer rises dramatically.
Pathophysiology of NSAID Damage

So before we talk about some potential options that we can use in these patients, how do these things occur. So let’s look at the pathophysiology.
Well I think again if you remember back to pharmacology we know that the non-steroidal anti-inflammatory drugs inhibit the cyclooxygenase enzymes and so there are two that are expressed in the body COX-1 and COX-2. If you look over here on the left hand side of the illustration we know that COX-1 enzyme is expressed under normal levels in most tissues in the body. And so it’s expression leads the formation of Prostaglandins and these Prostaglandins are very important for the barrier function of the gastric mucosa and we will go into more in that in a moment. We know from the cardiac side that activation of COX-1 influences the formation of thromboxane which then affects platelet activities so this is why people take cardio-selective aspirin. Now on the right hand side of the slide you see that the COX-2 pathway and it too produces Prostaglandins and these Prostaglandins are believed to be important for inflammation, pain and fever. And so when we look at our traditional non-selective NSAIDs we see that they inhibit both pathways whereas the COX-2 Inhibitors are more recent addition to the market they only are believed to only inhibit the COX-2 pathway.
Pathogenesis of NSAID-induced Ulcers

So we saw on the last side slide that the formation of Prostaglandins is very important for the COX-1 and COX-2 pathway. When we inhibit that COX-1 pathway we lose or we diminish those beneficial Prostaglandins and those Prostaglandins are very important for maintaining the mucosal barrier to acid. As Dr. Welage pointed out there is a lot of acid in the stomach, I mean the pH of the stomach is somewhere between 0.8 and 1.2 and so that mucosa has to have certain things in place in order to prevent the back diffusion or we all have perforated stomachs. So when you inhibit those Prostaglandins with an NSAID you decrease mucin secretion that’s an effective barrier. The Prostaglandins are also important for stimulating bicarb which is important buffer as well as mucosal blood flow which is important for the defense against acid. You will also see on this illustration that there are direct effects but these systemic effects are what we really worry about.
What are potential management options to reduce Ester’s risk of GI complications?

1. Switch her to clopidogrel
2. Discontinue NSAID
3. Consider preventive therapy
4. Do nothing, she will be fine

So if we get back to Ester and we certainly identified that the fact that she is at increased risk for GI complication what things can we do to potentially reduce her risk. Should we switch her to clopidogrel? Should we discontinue her NSAID? Should we consider preventive therapy? Or based on what your perception of her risk factors are maybe we should just do nothing, she will be fine.
What are potential management options to reduce Ester’s risk of GI complications?

1. Switch her to clopidogrel
2. Discontinue NSAID
3. Consider preventive therapy
4. Do nothing, she will be fine
Management Strategies for Patients Requiring Chronic NSAIDs

- Reduce NSAID use or consider alternatives
- Use lowest possible dose
- Take with food or antacid
- Employ NSAIDs with more favorable toxicity profile (COX-2 inhibitor?)
- Consider preventive therapy
  - Misoprostol
  - H2-Receptor Antagonist
  - Proton Pump Inhibitor

So if we look at the list of potential management strategies for patients who require chronic NSAIDs we see that in fact preventive therapy is certainly something that is beneficial and we will get into the data in that in a moment but there are other things as well. As some of you answered it would be nice to reduce or switch to another drug altogether if that doesn’t have the same GI toxicity profile. Again unfortunately that’s not always possible. Use the lowest dose that is certainly an issue that we can address. Keep in mind a lot of these patients when they first come into the physician they are in a lot of pain, they sort of get slammed with an NSAID dose. In some patients it actually maybe possible to back them down a little bit but again that’s only a subset of patients. Take with food or antacid, again this only really applies to limiting the local effects of the NSAIDs and doesn’t do anything really for the systemic effects on Prostaglandins. What about using an NSAID with a more favorable toxicity profile? Certainly the COX-2 inhibitor class was highly touted in this regard. We will talk about some data in that area in a moment but that in theory is a potential option as well. And then summering it up getting back to preventive therapy we essentially have two main options, one a drug that has been around forever and is apostle and then acid suppressive therapy with either an H2 Antagonist or Proton Pump Inhibitor.
So let's go back and visit for a moment the utility of switching to a COX-2 inhibitor. Now there was high hopes for this class when they originally released. We know that lately there is a lot of bad press with respect to their cardiac toxicities several have been withdrawn from the market and so who knows maybe you know the next year this may not be an option as well. But I would like for a moment to go back and address the issue on whether or not these drugs were necessarily safer than the nonselective NSAIDs. These are the results from the CLASS study. This was the study with a Celecoxib. It was published in JAMA, very good results in comparison to diclofenac and ibuprofen. And here we see the percent developing an ulcer while on therapy, and as you see the patients who are on the COX-2 inhibitor had significantly smaller percentage of ulcers developed than patients on the non-selective and this was highly touted, highly publicized.
Now after the JAMA article was published, the FDA posted the entire results from the study and many of you are probably aware of this. If you went to the FDA website and you started poking through all the data, you’d see that they had 12- and 15-month data posted. And when you look out that far, as you see from the slide here, you essentially lose that protective effect in respect to GI toxicity, and there was really no statistical difference with respect to a COX-2 inhibitor and an NSAID drug. There was another trial, the VIGOR trial. Same sort of thing when the data on the FDA website was posted, it didn’t really appear that there was that same beneficial GI toxicity profile as once was hoped. Now this isn’t to say that it doesn’t exist but I think there are certainly data out there that should make us at least question or at least design different studies if we decide to continue with this class on whether or not this effect truly exists.
So let’s talk about preventive therapy. As I said misoprostol has been around forever, it’s relatively cheap. We know it’s prostaglandin analogue and so essentially what we are doing here is we are augmenting that prostaglandin balance so that we can buff up that mucosal barrier and get the positive effects of the prostaglandin’s mucosal defense. Now in addition to being around forever and being relatively cheap, another advantage of this drug is that there are documented studies, many in fact, which show that it’s very useful for preventive gastric and duodenal ulcers. It also reduces NSAID induced complications by up to 40%, which is not insignificant in any regard. However, as we also probably remember from pharmacy school that there are certain drugs to remember what their side-effects were and this is the one that always stood out in my mind, is that we know that in the FDA-approved dose, the 200 mcg four times a day, many patients can’t tolerate it because of the explosive diarrhea and so compliance is an issue.
Pros and Cons of Misoprostol

• Advantages
  – Reduces risk of gastric ulcers
  – Reduces risk of duodenal ulcers
  – Reduces ulcer complications

• Disadvantages
  – Adverse effects (diarrhea)
    • Poor compliance
  – Does not reduce dyspepsia
  – Contraindicated in women of childbearing age

So certainly we can back down to 200 mcg twice a day, you still get a beneficial effect in terms of preventing ulcers a little less but you still get a beneficial effect, but that troubling side-effect of diarrhea can certainly still occur. So the advantage is it’s cost effective, there is a proven track record but because of compliance and remember these patients are going to have to take it for a long periods of time. I think that’s a disadvantage in many patients’ eyes. Furthermore, we know that remember the NSAIDs cause nonspecific effects so dyspepsia, heartburn, etc. Misoprostol hasn’t been shown to be effective for that, so it may prevent the ulcer but it may not prevent any of the nonspecific effects. Lastly, we know that unfortunately there are number of reasons why younger females need chronic NSAID use and because of the prostaglandin aspect it’s contraindicated in women at childbearing age.
What about adding an H2-receptor antagonist to Ester’s regimen?

1. Will be useful
2. Will not be useful

So that leaves us with the acid suppressants and based on what we’ve heard today in your own personal belief, I am curious what do you think about the utility of adding an H2-receptor antagonist to Ester’s regimen? Do you think it will be useful? Or do you think it will not be useful?
What about adding an H2-receptor antagonist to Ester’s regimen?

1. Will be useful
2. Will not be useful

We do have published studies that show that H2 antagonists are effective for treating and healing active ulcer disease, so they may be beneficial in a patient like Ester.
Pros and Cons of H2-Receptor Antagonists

- **Advantages**
  - Alleviate dyspeptic symptoms
  - Treat/heal active ulcer disease

- **Disadvantages**
  - Does not prevent gastric ulcers except a high doses
    - Inferior to PPI class
  - Tolerance
  - False sense of security (low doses)?
  - Inconvenience/cost of NSAID plus another drug

---

We have a number of trials, a meta-analysis that have literally almost tens of thousands of patients that show in terms of healing and preventing ulcer formation, the H2 antagonists class is not as good as some of the other alternatives that we have, sure they were course with respect to acid suppression and for a number of years. But because of that tolerance issue, because of a potency issue in respect to the PPIs, in my mind if we are going to do something for patients and if it's all cost effective, we should at least consider what is the best potential agent that's out there. So when you compare the H2 antagonist to Proton Pump Inhibitors, you may not be able to make that. So we know there are both advantages and disadvantages.
Pros and Cons of Proton Pump Inhibitors

**Advantages**
- Alleviate dyspeptic symptoms
- Prevent endoscopic ulcers
- Treat/heal active ulcer disease

**Disadvantages**
- Prevent GI bleeding?
- Inconvenience and cost of NSAID plus another drug

That leaves us for the Proton Pump Inhibitor class, if you were in that category, obviously as I just alluded to there is no tolerance that develops with the PPI like it does in H2 antagonist. They are the most important acid suppressants we have on the market today, so that’s good. And furthermore, we have a documented history of these drugs with pretty good outcomes - 90% after 8 weeks healing and preventing ulcers. Disadvantages, they haven’t been around as long as the H2 antagonist and so data is still evolving and we will show you some of it in a moment, it looks pretty good but obviously further studies warranted. And much like an H2 antagonist, or even misoprostol, the patient now has to take another drug and they have to pay for another drug, but those are concerns for any preventive therapy.
Prevention of Ulcers in NSAID Users

Omeprazole 20 mg Once Daily vs. Ranitidine 150 mg Twice Daily x 6 Months After Healing of Ulcers, >10 Gastric or Duodenal Erosions

So let's look at some of the PPI data. This was a study published in New England Journal of Medicine in 1998 and they took patients that had documented duodenal or gastric ulcers and they randomized them to either omeprazole 20 mg a day, so relatively low dose we would consider these days or ranitidine 150 mg twice a day. They then had a healing phase of up to 8 weeks and then after the healing phase, they then randomized the patients to the same regimen and then looked at the probability of the ulcer recurrence. And as you see from this slide, the patients who took omeprazole were significantly less likely to develop ulcer recurrence than the H2 antagonist. This is also the case for the healing phase and not surprising like the meta-analysis that Dr. Welage showed, the Proton Pump Inhibitor was more effective.
Prevention of Ulcers in NSAID Users

Omeprazole 20 mg qd vs. Misoprostol 200 µg bid X 6 Months
After Healing of Ulcers, >10 Gastric or Duodenal Erosions

H. pylori positive status associated with significantly greater likelihood of staying in remission.
* P<0.001 vs. placebo; † P<0.001 vs. placebo, misoprostol.

Now in that same issue of the New England Journal of Medicine, Hawkey and colleagues published a similar trial again using patients with documented gastric and duodenal ulcers; this time they randomize them to omeprazole 20 mg a day or misoprostol 20 mg bid 4 times a day. They had the healing phase and then after 8 weeks they went back to a remission phase if you will. And what we see here is the data in terms of preventing ulcer recurrence and again if we look at gastric ulcers, we see that both misoprostol and omeprazole were more effective than placebo in preventing ulcer recurrence. Misoprostol a little better than omeprazole but again keep in mind we are using a relatively low dose of omeprazole. And then with respect to duodenal ulcers, omeprazole again was much better than misoprostol.
Maintenance Therapy with Omeprazole is Superior to Misoprostol in Improving NSAID-Associated GI Symptoms

Improvement assessed using the Gastroduodenal Symptom Rating Scale

- Omeprazole 20 mg od (n=188)
- Misoprostol 200 µg bid (n=193)
- Placebo (n=95)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Omeprazole</th>
<th>Misoprostol</th>
<th>Placebo</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>-0.8</td>
<td>-0.6</td>
<td>0.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Indigestion</td>
<td>-0.8</td>
<td>-1.0</td>
<td>0.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Reflux</td>
<td>0.4</td>
<td>0.2</td>
<td>-0.4</td>
<td>0.003</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0.2</td>
<td>-0.8</td>
<td>0.6</td>
<td>0.003</td>
</tr>
<tr>
<td>Total score</td>
<td>0.6</td>
<td>0.4</td>
<td>0.2</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Also in this trial, they looked at some of those nonspecific GI symptoms that I refer to that can occur with NSAID use and here we see that omeprazole was associated with significantly better outcomes in terms of reflux, diarrhea, abdominal pain and indigestion and so again it just appeared that these drugs can be effective in multiple fronts.

Patients with complicated ulcers while taking low-dose ASA
*H. pylori* treated and ASA restarted at 100 mg/d
Patients then randomized to lansoprazole 30 mg/d or placebo


Omeprazole is not necessarily the only drug that you could use; this is data with lansoprazole and patients who were taking low dose aspirin. Unfortunately many of them developed ulcers and were *H. pylori* positive and so they treated their *H. Pylori* started back on aspirin and then randomized them to either placebo or lansoprazole. And as you see from the illustration, lansoprazole was highly effective in preventing ulcer recurrence.
There is also a positive data out there with pantoprazole as well. So it’s to illustrate the fact that as a class the PPIs appear to be very effective than this. Now the data that I have just shown you really deals with preventing ulcer recurrence, so they have an ulcer on an NSAID and now we want to do something to prevent another one. And so I think a valid question is, well, what happens if someone hasn’t developed an ulcer yet? Can we put them on a preventive therapy to prevent it from happening at all?
And so this was a prospective randomized, double-blind, placebo-control trial. This is published earlier this year in the American Journal of Gastroenterology and this paper actually summarizes two trials. One is the VENUS study, which was done in the country and the PLUTO, which was a more multinational study. But basically they attempted to determine the same thing in that if you had a patient on traditional NSAID or COX-2 Inhibitor, could you prevent an ulcer from occurring if you put them on either as omeprazole 20 mg or 40 mg? And as you see from the probability curve here, the probability of developing an ulcer while on the PPI was significantly less than the placebo arm out to 6 months.
So if we look at the combined or the pooled data with the VENUS and the PLUTO studies and we look at the specific drug classes of the COX-2 Inhibitors or the non-selective NSAIDs. Again we see that the PPI was more effective than placebo in preventing an ulcer from occurring in a first place.
Summary

• NSAIDs increase vulnerability to acid, which can result in gastric ulcers
• Chronic NSAID patients are at risk for gastric ulcer
• Patients considered at increased risk include:
  – Age ≥60 years
  – Prior history of gastric ulcer
• Co-therapy options may be useful for selected patients

NSAIDs are very good drugs but with chronic use, it becomes toxicity. This toxicity increases the longer patient is on it and they are certainly dose dependant. And so if we can identify certain risk factors which predispose our patients to GI toxicities, we might be able to identify a subset of group that would benefit from preventive therapy. And the Proton Pump Inhibitor class may be an effective addition to traditional preventive therapies that we have right now and co-therapy maybe an option for patients like Ester in our case.
Thank You

You have completed Section 2.
Now back to Dr. Lynda Welage with a case study on nighttime GERD.
We are going to specifically talk about nighttime Gastroesophageal Reflux Disease. And in this particular case, we have a patient AN who is a 46-year-old man who presents with symptoms of complaints of daytime sleepiness, falling asleep at work, despite of stimulating job, just can't quite stay awake. His past medical history is significant for hypertension and hypercholesterolemia. He is currently on atorvastatin, hydrochlorothiazide, diltiazem. He is 6 feet tall, 96 kilos. His blood pressure is 140/90 and really we want to rule out whether he has sleep apnea or some other sleep disorder. He is prescribed at this point lifestyle modifications. He is told to cut the caffeine intake, increase your daytime activity and probably most importantly keep a sleep log and ask your spouse to also keep a log of your sleeping pattern.
He returns four weeks later and he adopted the lifestyle modifications, but he is still very sleepy during the day. And I looked at the sleep log and it’s noted to indicate he has severe snoring with frequent nighttime cough, but the patient didn’t report this, it was his wife. I was going to say, could you have taken a picture of my husband and I, because my husband is this patient, but it’s not us. The patient reports he wakes up feeling unrefreshed and some mornings he is kind of hoarse. On further questioning, he indicates “well yeah, occasionally I have some epigastric discomfort radiating towards my throat and spine and when it happens at night, I just wash it down with a Diet Cola at my bedside and then rollover and go back sleep. Occasionally, very rarely, maybe once a month, I have to get up and I try an antacid.” His diagnosis at that time was Gastroesophageal Reflux Disease, particularly nighttime reflux. He didn’t really complain of daytime symptoms.
Is nighttime reflux or nocturnal heartburn common? Is he sort of atypical? (1) It is common or (2) No it is not a common disorder.
Is Nocturnal Heartburn Common?

1. Yes
2. No

It is extremely common. I didn’t want to put the, if you will, question and to say how common is it?
But if we look at two surveys, independent studies, one done by the American Gastroenterological Association looking at a 1000 patients with heartburn and another conducted by Farup looking at over 1200 patients with heartburn. In both cases they ask the question of these patients with heartburn, do you have nighttime heartburn and more than 74%-79% of patients said they had nighttime heartburn. 54%-57% patients indicated they wake up with heartburn. 40% of patients reported that it impacted their ability to work the next day. So it is truly very prevalent.
Nocturnal GERD May Impact...

1. Quality of life
2. Frequency of daytime GERD
3. Productivity
4. 1 and 3
5. 1, 2, and 3

Well what is it impact? Our next question, (1) Does Nocturnal GERD may impact our patient’s quality of life? (2) Frequency of daytime Gastroesophageal Reflux Disease. (3) Productivity. (4) 1 and 3. (5) All of the above, 1, 2, 3?
There has been shown no relationship to nighttime GERD to having daytime symptoms, if you have nighttime GERD, you can have daytime symptoms or you can just have nighttime symptoms. Many people with nighttime GERD have daytime but one doesn’t cause the other and so it doesn’t impact it. So in my mind as we will see on the next few slides in throughout today’s presentation nocturnal GERD impacts specifically quality of the patient’s life as well as their productivity.
Nighttime GERD Reduces Health Status Even More Than Daytime GERD

SF-36=Medical Outcomes Study Short-Form 36 Health Survey

*P<0.001 vs. control group for all scales except “Physical Functioning.” P<0.001 vs. daytime GERD for all scales.


And if we look specifically at quality of life, we can see here that and this is based on the SF-36 scores and we can look at the different domains physical functioning, role limitations, bodily pain general health, vitality, social functioning, emotional health and mental health of the domains in the SF-36. We can see in each case that nighttime GERD sufferers have a poor quality lower scores as compared to individuals with daytime GERD or the control group. And you can actually see in most cases daytime GERD had a poor quality of life, as we talked about earlier, than those with the control group, but nighttime is the worse. It profoundly impacts everything.
Potential contributing factors to AN’s heartburn could include:

1. Obesity
2. Diet caffeine free cola at bedtime
3. Diltiazem therapy
4. 1 and 3
5. 1, 2, and 3

But what are the potential factors contributing to AN’s heartburn in this particular case? (1) Obesity. (2) His Diet Cola at bed time. (3) Diltiazem therapy. (4) 1 and 3. (5) 1, 2, and 3.
Potential contributing factors to AN’s heartburn could include?

1. Obesity
2. Diet caffeine free cola at bedtime
3. Diltiazem therapy
4. 1 and 3
5. 1, 2, and 3

His obesity and he was obese this time. And his Diet Cola at bed time, which I will talk about in a minute and then his diltiazem or Calcium Channel Therapy as we talked about earlier, so you remember what we talked about earlier in terms of risk factors.
But I want to point out a recent study in which they looked at over 15,000 patients with sleep disorders and they were studying cardiac health. And they asked them if they had nighttime GERD or nighttime heartburn and of those patients about 8,000 had nighttime heartburn. And they looked at what risk factors they were in addition to the traditional risk factors and I shared that data with you here. And you can see that factors such as a high body mass index or obesity being a predictor of those individuals with heartburn, the caffeinated beverages, it’s not just the caffeine in his Diet Cola, it’s also the fact that it’s carbonated and carbonated beverages were risk factor. Hypertension, asthma, benzodiazepine usage are also risk factors. And then we see insomnia and snoring and daytime sleepiness being associated with heartburn and I would say they are associated probably not causing the heartburn but more of the opposite that the heartburn impairing the sleep and I will talk more about that.
Why is nocturnal GERD sometimes considered more serious than daytime Gastroesophageal Reflux Disease?  (1) Lack of arousal, the patient doesn’t wake up.  (2) Because the patient’s in the recumbent position.  (3) Diminished esophageal clearance.  (4) All of the above.
Why is nocturnal GERD sometimes considered more serious than daytime GERD?

1. Lack of arousal
2. Recumbent position
3. Diminished esophageal clearance
4. All of the above
If we move on to the next slide, we actually see that in fact all factors do contribute. It's important to recognize when you are lying down in that supine position, you have the absence of gravity. So you don't have the promotion of clearing the esophagus of that reflux say gravity doesn't help you. You also have ineffective esophageal motility or peristalsis occurring at night, less motility occurs at night. You have a reduced salivation at night when you are asleep and so that will also decrease esophageal clearance. And then if you reflux it and you don't wake up that lack of arousal which is quite common, it may sit there longer. And so the net result is the reflux material often migrates more into the esophagus further and you have a prolonged esophageal mucosal contact time due to those delayed and impaired esophageal clearance mechanisms as well as the lack of arousal.
We look at it a little more specifically with esophageal pH monitoring and this is from two patients, and we look at one with the daytime or the upright reflux or GERD patient. You can see that they have several episodes of reflux, where the pH in esophagus dips below 4, but they are very short episodes of reflux. If we look at the nighttime or supine recumbent refluxer, we see a very different pattern. In the day reflux, the esophageal pH stays below 4 very low, about 1 to 2 for almost an hour, so a prolonged contact is going to cause that damage.
### What symptoms suggest AN might have GERD?

1. Sleep disturbance
2. Snoring
3. Hoarseness
4. All of the above

What are the symptoms that suggest AN might have Gastroesophageal Reflux Disease? (1) Sleep disturbance. (2) Snoring. (3) Hoarseness or (4) All of the above.
What symptoms suggest AN might have GERD?

1. Sleep disturbance
2. Snoring
3. Hoarseness
4. All of the above

We will talk more specifically, all of the symptoms listed here as well as others are indicative of potential symptoms of nighttime GERD.
Symptoms reliably reported on by patients

Symptoms masked by ‘sleep,’ resulting in less recall and reporting by patients

Daytime Symptoms
Heartburn
Regurgitation
Wheezing

Nighttime Symptoms
Heartburn (variable)
Sleep disturbance/daytime sleepiness*
Coughing
Wheezing

* Symptom often experienced in daytime hours but results from nighttime reflux.


Moving onto the next slide, I have kind of broken it down schematically and this is very crude because they are overlapping symptoms, into daytime symptoms we can traditionally think of traditional symptoms of heartburn. That was the case that we saw the first time – maybe some regurgitation and maybe some wheezing. Nighttime symptoms patients may have heartburn but in order to have heartburn what do they have to do? They have to wake up and they have to be able to remember it, until you have to arouse to a level of memory, many of us wakeup in night and might have had a dream but you don’t remember it. So in the same case nighttime heartburn is hard to get from a patient when you are questioning them regarding their symptoms because they may not remember that. Nighttime symptoms also include sleep disturbances, daytime sleepiness, coughing or wheezing. The symptoms are often harder to elicit from the patient due to that lack of recall.
Which of the following is not a potential complication of nocturnal GERD?

1. Daytime GERD
2. Esophageal strictures
3. Esophageal adenocarcinoma
4. Nighttime cough

Which of the following, if we talk not about primarily symptoms but if we talk about complications now of Gastroesophageal Reflux Disease, which of the following in not a complication of nocturnal Gastroesophageal Reflux Disease? (1) Daytime GERD. (2) Esophageal strictures. (3) Esophageal carcinoma. (4) Nighttime cough.
Which of the following is not a potential complication of nocturnal GERD?

1. Daytime GERD
2. Esophageal strictures
3. Esophageal adenocarcinoma
4. Nighttime cough

Daytime GERD is not a symptom or complication of nocturnal GERD. And as I indicated before the two are not directly related.
Nocturnal Reflux Increases Risks of GERD Complications

Esophageal Disease Progression

- Erosive esophagitis
- Complicated erosive esophagitis
  - Ulceration
  - Strictures
  - Barrett’s esophagus
- Adenocarcinoma: ~11 times greater among patients experiencing nighttime symptoms at least once a week compared with the general population

The others however are potential complications of nighttime Gastroesophageal Reflux Disease or in fact daytime Gastroesophageal Reflux Disease. Complications include erosive esophagitis, other complications such as ulcerations, strictures, Barrett’s esophagus, adenocarcinoma. But for patients with nighttime Gastroesophageal Reflux Disease, adenocarcinoma is actually 11 times greater among those experiencing nighttime symptoms at least once a week as compared to the general population. We also have complications of respiratory disturbances, asthma, cough, etc., and sleep deprivation that are considered related to nighttime Gastroesophageal Reflux Disease.
We talked specifically about the sleep disturbances in this trial done by Gilason and colleagues and he looked at over 2000 controls, patients who didn’t have any nighttime reflux disease versus those that had nighttime reflux disease. And what you can see here is that the patients with nighttime reflux more commonly had snoring, reported apneic episodes, nightmares, daytime sleepiness as well as involuntary falling asleep as compared to the controlled population. If we look at the respiratory symptoms in our last case, it’s going to specifically focus on asthma in getting to this in more detail.
But if we look at the respiratory symptoms, we again see patients with nighttime reflux as compared to controls more commonly have wheezing, nighttime chest tightness, nighttime breathlessness, asthma as well as cough. So they don’t present in a normal way possibly and they often have different complications and we need to think about that as we try to identify this condition, it actually makes it hard to identify.
Goals of Therapy for Nighttime Reflux

- Prevent, heal esophagitis
- Eliminate recurrence
- Prevent complications
- Eliminate symptoms
- Improve sleep

Once we identify it our goals of therapy to prevent, heal the esophagitis, eliminate recurrence, prevent the complications, get rid of the symptoms and improve their sleep. This is impairing their ability.
If we ask patients what they do about it and this was a survey of those patients with nighttime heartburn and the Gallup’s survey by the AGA specifically asked to these nighttime heartburn surfers, what do you do about it? What medications do you take? And the first thing you can see by this slide is many patients take more than one thing, because the numbers don’t add up to a 100%, they are greater than a 100% here. The second thing you can see is some interesting things where I think we can get involved, 16% of patient said, well, I take a sleeping pill and roll over and go back to sleep. Not got to do anything helpful for that esophagus and in fact may harm it so now they are not going to be aroused and you are going to have that as prolonged esophageal acid contact time. 71% of the patients say they take OTC medications, which we will talk more about and 41% say they take prescription medications.
And if we talk about the therapeutic modalities for nighttime heartburn, lifestyle modifications again are the baseline, we always do those but we know that there isn’t evidence to firmly support their use from randomized controlled trials. Lifestyle modifications here are the same as I talked about before but particularly if they will tolerate it, elevating the head of the bed by 6 inch blocks. Many times they complain that they feel like they are going to slide out or their spouse is going to slide out. Then you have OTC medications and prescription medications. I want to point out, the treatment here is a little different than daytime GERD or that patient we saw the first time. Many of our OTC medications, our antacids and our H-2 receptor antagonists, we are often using them for symptom relief. We have to wake up to take them. So in this case that symptom relief therapy may not be the desired therapy as your primary mode for somebody with nighttime GERD. You want to prevent it from happening, particularly because they may not wakeup every time it happens.
The most appropriate therapeutic option for AN at this point would be…

1. PPI once daily
2. PPI before bedtime
3. PPI 30-60 min before breakfast
4. Any of the above

And so if we talk about using a Proton Pump Inhibitor for this particular patient, what would be the most appropriate therapeutic options? (1) A Proton Pump Inhibitor once daily. (2) Giving it before bedtime. (3) Giving it 30 to 60 minutes before breakfast. (4) Any of the above.
The most appropriate therapeutic option for AN at this point would be...

1. PPI once daily
2. PPI before bedtime
3. PPI 30-60 min before breakfast
4. Any of the above

If we talk about inhibiting the greatest number of active pumps, you want to turn on those pumps and so the correct answer in my mind would be answer (3), giving the Proton Pump Inhibitor 30 to 60 minutes before breakfast before that first meal. Now there is some pH data, not a lot and not a lot of symptom data that I will say with immediate release, omeprazole, which omeprazole with sodium bicarbonate and giving it right before bedtime. The other trials with the Proton Pump Inhibitors would suggest your best option is before breakfast or before dinner and if it was predominantly nighttime symptoms I do know some clinicians do before dinner but most often write 30 to 60 minutes before breakfast and if a second dose is required, split it so that it’s given the other one before dinner.
I’m not going to go through efficacy in terms of symptoms relief in great detail, I want to focus a little bit more on the question, does it help improve their sleep, if we treat their nighttime heartburn and Gastroesophageal Reflux Disease. And there has actually been only two studies looking at this, so we have limited data. This particular trial was a randomized controlled trial with about 220 patients in each of the three groups – placebo, esomeprazole 20 mg, esomeprazole 40 mg. And they looked at patients who had nighttime symptoms of heartburn in order to get into the trial and they gave them these therapies and found that yes in fact their nighttime heartburn was relieved significantly better than placebo, 50.5% with the 20 mg dose and 53.1% of patients with 40 mg dose had their nighttime heartburn relieved. But if we look at their sleep disturbance resolved, we see that 73% of patients indicated their sleep disturbance had resolved. They also did a Pittsburgh Sleep Quality Score and in omeprazole treated patients their sleep quality also improved.
Impact of Sleep Disturbance and PPI Therapy on Work Productivity

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>ESO 20</th>
<th>ESO 40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Degree sleep disturbance affected work productivity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>3.9 ± 2.4</td>
<td>4.0 ± 2.5</td>
<td>4.0 ± 2.7</td>
</tr>
<tr>
<td>Week 4</td>
<td>2.3 ± 2.2</td>
<td>0.9 ± 1.7</td>
<td>1.0 ± 1.5</td>
</tr>
<tr>
<td>Change from BSLN</td>
<td>-1.6 ± 2.6*</td>
<td>-3.1 ± 2.5</td>
<td>-3.0 ± 2.5</td>
</tr>
<tr>
<td>Work hrs lost per week</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>15.8 ± 13.0</td>
<td>16.1 ± 10.7</td>
<td>16.2 ± 12.3</td>
</tr>
<tr>
<td>Week 4</td>
<td>9.6 ± 11.2</td>
<td>3.8 ± 7.3</td>
<td>4.5 ± 7.0</td>
</tr>
<tr>
<td>Work hrs saved</td>
<td>6.2 ± 12.9*</td>
<td>12.3 ± 11.5</td>
<td>11.6 ± 13.3</td>
</tr>
<tr>
<td>Degree sleep disturbance affected regular activities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>4.9 ± 2.6</td>
<td>4.7 ± 2.7</td>
<td>4.8 ± 2.6</td>
</tr>
<tr>
<td>Week 4</td>
<td>2.9 ± 2.7</td>
<td>1.2 ± 2.0</td>
<td>1.6 ± 2.2</td>
</tr>
<tr>
<td>Change from BSLN</td>
<td>-2.0 ± 2.8*</td>
<td>-3.5 ± 2.8</td>
<td>-3.2 ± 3.1</td>
</tr>
</tbody>
</table>

Johnson DA, Orr WC, Crawley JA, et al. Am J Gastroenterol. 2005;100:1914-1922.  *p < 0.05

But does this have any other impact, they asked. And this is a busy slide, it’s looking at the work, productivity, and activity assessment and what we see if we focus specifically on this group in the middle, we see that patients who have nighttime symptoms lose about 16 hours a week of work productivity, that’s at baseline. Now this isn’t because they usually don’t go to work, it’s they go to work and are not necessarily effective, it’s presenteeism versus absenteeism. But they then treated them for 4 weeks and you can see that esomeprazole and 20 mg as well as 40 mg improved their work productivity or saved roughly 11 to 12 hours in work productivity, they’ve restored their productivity. Not quite back fully but made dramatic improvement compared to placebo which was 6 hours saved.
Summary

• Nocturnal heartburn is a common disorder.
• Recumbent position and sleep leads to loss of protective mechanisms thereby enhancing damage.
• Patients with nocturnal GERD may present with atypical symptoms including sleep disturbances, cough, regurgitation and without heartburn.

So in summary nocturnal heartburn is a common disorder, I think we often overlook it. Patients probably often don’t tell us about it because they don’t even realize always it’s heartburn. We have to recognize that the recumbent position and sleep leads to a loss of our protective mechanisms enhancing the damage. Patients with nocturnal Gastroesophageal Reflux Disease frequently present with atypical symptoms of Gastroesophageal Reflux Disease including the sleep disturbances, cough, regurgitation, asthma, which we will talk more about in a minute and without heartburn because they don’t remember they had it, they weren’t arouse to that level.
Summary

- Treatment of nocturnal GERD
  - Make sure patient is following lifestyle modifications, particularly elevating head of bed and avoiding nighttime snacks.
  - Do not use PRN medications (except for occasional symptoms) as they require patient arousal.
  - PPI dose should be taken 30 minutes before first meal of day; if additional therapy needed increase PPI dosing to b.i.d.
  (30 minutes before first meal and evening meal)

The treatment of patient with nocturnal GERD, lifestyle modifications, that’s anybody with Gastroesophageal Reflux Disease, and in my mind and this is a bias, I don’t recommend using PRN medications for the patient with nocturnal GERD except for occasional symptoms or as rescue therapy because they have to wake up and do it. You are already disturbing their sleep in order to implement the therapy and so based on that, I would recommend taking a Proton Pump Inhibitor, the dose should be taken in my mind 30 minutes before the first meal of the day. But if additional doses are needed, in other words you are going to go to b.i.d. therapy it’s before breakfast and before the evening meal.
Follow the Nighttime Symptoms

- After initiating therapy, continue follow-up:
  - Is treatment improving your nighttime symptoms?
  - Are your nighttime symptoms completely gone?
  - If not, which symptoms remain?
  - How are you sleeping?
  - Are you more rested during the day as compared with before treatment?

After you initiate therapy, you want to continue to follow up on these patients and you want to ask, are their nighttime symptoms improved? Are they completely gone? If not, which ones remain? How are you sleeping? By no means is GERD the only disorder that leads to sleep disturbances, but it is a common disorder that can cause this that we need to eliminate. And with that we are going to move on to our last case today and talk about the extraesophageal GERD patient and then we are particularly focusing in on the asthmatic patient.
Thank You

You have completed Section 3.
Now back to Dr. Brien Neudeck with a case study on extraesophageal GERD and its relationship to the asthmatic patient.

In the patient who has nocturnal heartburn or nocturnal Gastroesophageal Reflux Disease rather, they often don't present to us with the hallmark or classic symptom of GERD, which is heartburn. They present with the more atypical symptoms as Dr. Welage alluded to, so essentially if we think about it, these atypical symptoms are essentially extraesophageal manifestations of GERD. And we are going talk about those extraesophageal manifestations and specifically with their relationship to the asthmatic patient. There is a lot of interest right now in the tie between GERD and asthma and the potential for improving outcomes in patients with asthma if we potentially go after their GERD or try to at least diagnose GERD.
Now this slide depicts many of the extraesophageal manifestations of GERD that Dr. Welage has referred to in her earlier presentations. If we look to the left, we see that for ear, nose, and throat – sinusitis, laryngitis. There is lot of literature right now tying Gastroesophageal Reflux Disease to these conditions/symptoms. Hoarseness has been a symptom in many of our cases this morning that too has been tied to reflux. The pulmonary system is what we are going to focus on today, specifically asthma but keep in mind that it doesn’t have to be just asthma it can be chronic cough, even pneumonia. Chest pain as was alluded to earlier, a non-cardiac chest pain has resulted in many people probably coming to the ER thinking they are having a heart attack and when in fact they basically just have a raging case of heartburn. And then there are some nonspecific things that have been tying to reflux halitosis, dental erosions. These are in my mind, the data isn't that strong and I am not sure to necessarily pursue those with the same vigor. But tying anything to GERD is often a difficult task and the reason for that especially with asthma is that both GERD and asthma are very common in the general population, and as I just alluded to, people with GERD and asthma, for the GERD they often don’t present with the classic symptoms but more of these atypical symptoms. And so we as pharmacist I think it need to be vigilant of this and ask them those more specialized questions other than, do you have heartburn and the questions that were covered earlier.
Jim, a 55-year-old man

Referred for evaluation of “difficult-to-manage asthma”

He has been awakening at night frequently with a worsening chronic cough, sore throat, and wheezing.

He has been complaining of difficulty sleeping over the past several months.

So let's look at our case Jim, he is a 55-year-old man. He is referred to you for difficult to manage asthma, he reports to you that he has been awakening at night frequently with a worsening chronic cough, a sore throat and wheezing and he also complains to you that he has had difficult sleeping over the last few months.
• His asthma was diagnosed 2 years ago, and treated with inhaled bronchodilators as needed without major incident.
• Over the past several weeks, his nighttime cough and wheezing have become more frequent to the point where he is waking up 3 or 4 times a week with an attack.
• This is particularly common after a large, late-night meal.

Now he does have a history of asthma and this was diagnosed about 2 years ago. He uses his PRN bronchodilators and up until now he gets pretty good relief. Over the last several weeks however his nighttime cough has increased as his wheezing become more frequent and much to the point so that he is waking up 3 to 4 times a week with an attack. Now when prompting him or when asking him certain questions we find out that this is more common after he eats a large late night meal.
He has long-standing heartburn, 1 or 2 times weekly, always managed with over-the-counter agents, as he has been reluctant to take regular therapy.

The heartburn has been increasing in frequency to the point where it now occurs 2 to 3 times weekly, including episodes at night.

He has history of heartburn and typically it's been only about 1 to 2 times a week and he has been resistant to using prescription therapy. He prefers to just use over the counter PRN therapy. However he does report since his respiratory symptoms have increased in severity, his heartburn has also increased in severity, where right now it occurs 2 to 3 times a week and he does have episodes in night as well.
So for my first question, I am curious what do you think Jim’s asthma exacerbation and chronic cough are due to? Could it be postnasal drip? Could it be #2, which is just that his asthma disease is getting better? Could he have GERD, or is the GERD really the etiology? Dyspepsia, or do you think that, well I don’t have enough information at this time.
Is Jim’s asthma exacerbation and chronic cough due to ______?

1. Postnasal drip
2. Progressing disease (asthma)
3. GERD
4. Dyspepsia
5. Cannot determine without further information

As we get through the case, we may come to the conclusion that it’s GERD. But really this question was meant to demonstrate the fact that when we look at a patient that has extraesophageal manifestations of GERD it’s very difficult often times to say, ah yes the reason why your respiratory symptoms are increasing is because of GERD, and this is because asthma and chronic cough can have a number of triggers.
I think this trial that is summarized in the Venn diagram here nicely illustrates that point. This is a study done few years ago, about 80 people were in it and they reported to their physicians that they had chronic cough. And so intense diagnostic modalities were employed and they found that some patients had GERD, postnasal drip and/or asthma. So as you look at the Venn diagram you see that about 60% of the patients had postnasal drip as cause for their chronic cough, 60% asthma was contributing and about 41% GERD was contributing. But the most important thing with this diagram is the fact that there are areas of overlap here and this is what we face in the clinical arena is that there are areas of overlap and frequently we can't just make a decision based on presentation but we need to employ further diagnostic measures.
If we look at the cases of chronic cough, we do see from the slide that postnasal drip, asthma, and GERD certainly are the most common. There are others that we shouldn’t necessarily discount a chronic bronchitis, bronchiectasis and some other miscellaneous causes. But as you see from the yellow bar on the right hand side of the illustration, if we combine postnasal drip, GERD, and asthma we are going to hit most of the patients. So we can use this information to tailor our decisions where it comes to the next diagnostic decision.
Now asthma and GERD are certainly related in our current case as an adult but there are also evidences that suggest they are linked in children as well. This is a very large retrospective trial that you see on the screen here and children where they present with a variety of pulmonary symptoms, so asthma, pneumonia, sinusitis, and laryngitis. And what they did, they then went back and determine whether or not reflux was present. As you see from the grey bars that the children who had reflux were much more likely to have these pulmonary symptoms and children who didn’t. And so again this tells us that the association between GERD and asthma is not just limited to adults and certainly there is a lot of interest these days in children with asthma into whether or not we can improve their outcomes by going after GERD.


### Association of Nighttime GERD and Respiratory Disturbances

As you see more information that tells us that there is in association between asthma and GERD in some individuals. Here we see patients again to summarize patients with nighttime reflux significantly more likely to have asthma and other respiratory symptoms than patients that did not have nighttime reflux. And so again the questions that we asked, when do you have these symptoms, is very important for identifying the subset of patients that may benefit from our interventions.

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>No Nighttime Reflux (%) (n=2,096)</th>
<th>Nighttime Reflux (%) (n=101)</th>
<th>Adjusted Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wheezing</td>
<td>24/4</td>
<td>47*/13*</td>
<td>2.5 (1.6–3.9) 2.9 (1.5–5.6)</td>
</tr>
<tr>
<td>Nighttime breathlessness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma (physician-diagnosed)</td>
<td>4/9†</td>
<td>2.2 (1.04–4.7)</td>
<td></td>
</tr>
<tr>
<td>Nighttime cough</td>
<td>31/59*</td>
<td></td>
<td>3.0 (1.9–4.9)</td>
</tr>
</tbody>
</table>

*P<0.001; †P<0.05.

CI = confidence interval

So I have talked about symptoms and their relation of GERD and asthma but do we have anything more specific? We do, we can look at ambulatory esophageal pH monitoring, we can look at a number of studies, these were done in the late 80s or early 90s. And what we see from this graph is that the percentage of patients that had an abnormal esophageal pH study ranges anywhere from 34% to 90% so this tells us that again GERD and asthma are quite common in the general population. And that we do have more specific data that suggests reflux occurs in these patients.
Well we have talked that there is an association, how from an anatomy, from a physiology standpoint does this association occur? Well we don't know a 100% but we believe that there are two proposed mechanisms and one is referred to as the reflux theory and the other is refer to as the reflex theory. So if you look on the left hand side of the screen here, the reflux theory rather holds that the reflux of gastric contents into the esophagus is so proximal that those gastric contents are micro-aspirated essentially. And because of their acidic nature they irritate the pulmonary epithelium that cause bronchoconstriction, wheezing and symptoms that we would hold synonymous with asthma. Now the reflex theory is entirely different. Under this theory it's the reflux of gastric contents into the esophagus and because the esophagus and the vagus nerve are so close in terms of anatomical proximity that the vagus nerve is stimulated neural pathways are activated, bronchoconstriction and wheezing then occur. Now it's important to note that just looking at a patient we can't necessarily say, oh you have the reflux mechanism of your asthma exacerbation. It's very difficult to determine which was going on and I would actually argue it's not as important. When we talk about esophageal pH monitoring in a moment we will be able to get some information on the reflux theory but again we can never totally discount the reflex theory.
So we have just been speaking about how GERD can exacerbate asthma. It's important to realize that the relationship between GERD and asthma is more complex than just a one way street. Asthma in fact can exacerbate GERD and this is because if you think about when a patient is experiencing an asthma attack and that wheezing, the shortness of breath that changes intrathoracic pressure, and that drop in intrathoracic pressure certainly can effect lower esophageal sphincter tone, which then predisposes the patient to reflux. And so it is a complex relationship and we all we shouldn't forget that asthma can actually exacerbate GERD.
Now along this line of thinking there are number of things that support this. We know that asthma therapy for example can potentate GERD. One of the examples for potentiators of GERD in Dr. Welage’s slide was drug therapy and theophylline was listed. One can argue that theophylline may or may not be used in much frequency these days but it isn’t important to remember that this is not theophylline that effects lower esophageal sphincter tone. Other things like even inhaled drugs like inhaled bronchodilators can as well and I will show you a slide of that in a moment. Hiatal hernia we know is more common in asthmatics and hiatal hernia as we have talked about previously is an independent risk factor for reflux and so there are number of things that can potentate reflux in this population.
Here are the data that I was referring to with respect to inhaled bronchodilators. This is a study published in CHEST a few years ago and as you see with a pink line as essentially a dose dependent effect the more albuterol was inhaled the greater the changes on lower esophageal sphincter tone, the greater the likelihood that a patient would reflux. Now the patient they didn’t document reflux in this study but they clearly documented that a known risk factor for reflux was altered.
So if we accept the finding that it maybe difficult just to look at Jim and decide what his problem is what would you do in terms of further diagnostic options? Would you recommend him to go see a gastroenterologist, have an endoscopy? Should we have an experiment with ambulatory pH monitoring? Or should we give him a trial of acid suppression? Or maybe we feel based on Jim’s symptoms that all of the above is warranted and we can maybe more definitively go after his cause.
Which of the following are diagnostic options for Jim?

1. Endoscopy
2. Ambulatory pH monitoring
3. Trial of acid suppression
4. All of the above
Diagnostic Options for Patients with Suspected Extraesophageal GERD

- Endoscopy
- Ambulatory monitoring (pH, impedance/pH)
- Therapeutic trial of acid suppression


If we look on the next slide we see that all of those choices are actually appropriate diagnostic modalities for determining the ideology of Jim’s problem. Now I would actually argue and the literature supports this is that the first two endoscopy in ambulatory pH monitoring might want to be reserved to later. First and foremost if you think about it these things are more invasive techniques. Endoscopy they have to go to the GI suite, they get sedated. Big garden hose goes down their throat. Certainly we don’t want to just give that to everyone and we will also talk about the data in terms of the sensitivity of that technique. Ambulatory pH monitoring certainly for diagnosing an Extraesophageal Manifestation of GERD that makes sense, if we do proximal pH monitoring we should be able to pick up on it. Again we will talk about the data behind that but it's similar to endoscopy as an invasive technique. They have to come into the GI suite, generally they are sedated. They then have to go home with a big tube sticking out of their nose. Not real great for social situations and so if we can maybe save those for later that might be a potential option but these are all the modalities that we can employ. Lastly rather a therapy to trial acid suppression, there is data to support that as well.
So let’s walk through some of these diagnostic options. As I said endoscopy is more invasive unfortunately for diagnosing extraesophageal manifestations of GERD it’s not really specific. Less than 40% of your test using endoscopy will be positive in patients with pulmonary symptoms. We have to remember that not everyone with GERD has erosive disease. So the fact that we do an endoscopy and we don’t see any damage doesn’t necessarily mean that they will have abnormal reflux. So based on its relatively low yield we would probably save that to later in our diagnostic algorithm.
pH monitoring in terms of ENT things like laryngitis, sinusitis it's not real sensitive. Only about 50% will be positive. Now in terms of sensitivity it is fairly sensitive in asthma. About 82% of the time you will be able to pick up that Extraesophageal Manifestation of GERD. The problem however lies within the reproducibility of that technique for diagnosing Extraesophageal Manifestations of GERD.
pH Monitoring Reproducibility in Detecting Acid Reflux

- 32 subjects with GERD symptoms
- 11 healthy volunteers, 10 patients with distal esophageal acid reflux, 11 patients with both distal and proximal esophageal acid exposure
- Underwent 24-hour pH monitoring on 2 separate days within 20-day study period

<table>
<thead>
<tr>
<th>Patients</th>
<th>Distal pH Probe</th>
<th>Proximal pH Probe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy controls (n)</td>
<td>73% (11)</td>
<td>91% (11)</td>
</tr>
<tr>
<td>Distal reflux (n)</td>
<td>80% (10)</td>
<td>70% (10)</td>
</tr>
<tr>
<td>Proximal reflux (n)</td>
<td>82% (11)</td>
<td>55% (11)</td>
</tr>
</tbody>
</table>


And this slide illustrates that point. This study took three groups of people or two general groups and then three individual subsets. The two general groups were people who had documented reflux and then those that didn’t, these were the healthy individuals. They then determined in the reflux individuals that some just reflux to the distal part of their esophagus and some were proximal refluxers as well. They then place the pH probes in the distal esophagus and the proximal esophagus and then over series of repeated measurements and days they then determine how sensitive this technique was in terms of picking up abnormal pH readings. So if you look to the first line under the distal and proximal pH probe in healthy individuals you will see that it was highly sensitive for detecting reflux and you say well they are healthy why should they have reflux. We are all reflux to some degree just in some of us it goes on to more of the pathologic condition of GERD. So in those healthy individuals that it could pick it up it was very sensitive, very reproducible. For our distal reflux group it too both proximal and distal probe was very sensitive in picking up that abnormal pH. However, if we look at our proximal reflexers, so those patients that we know reflux of the proximal esophagus and we look at the reproducibility of that proximal pH probe it's actually quite poor, only 55% of the time were they able to pick it up or reproduce that data. So there are probably multiple reasons for this. One is that proximal pH monitoring is relatively new technique and so physicians may not be as familiar with it. But because of this reproducibility issue in my mind it makes sense because it is an invasive technique to maybe save it for those people who fail a trial of acid suppression therapy.
So if we go to acid suppressive therapy or a trial thereof again in this day and age what we are really talking about is the Proton Pump Inhibitor class. H2 antagonists are great drugs. I keep them in my travel kit for meetings when I go out and eat late at night. They are great for treatment of episodic heartburn. They are not as good as the Proton Pump Inhibitors for treatment of reflux related conditions. And since I hope we have already established this morning that the Extraesophageal Manifestations of GERD are actually harder to probably treat than just run with the middle GERD we want to go with an agent that has the best data and in this day and age that’s the Proton Pump Inhibitor class. So what this illustration shows us is how well we can tie GERD to a variety of other disorders or symptoms. So if you look at the base of the pyramid down here with erosive esophagitis you will see that it’s a 100% correlation with GERD. One of the complications of GERD is erosive disease and so the utility of a PPI trial is 0, right it doesn’t make sense to put someone on a trial PPI, we know GERD causes erosive esophagitis so therefore we are just going to treat him. The same thing with non erosive reflux disease, high correlation with reflux that’s why we are just going to treat them with the PPI we are not going to him a trial. However as you move up this pyramid into the ENT manifestations asthma these Extraesophageal Manifestations of GERD we see that the ability to tie it to GERD it becomes much less and this is really where the utility of a trial acid suppressants and in this case PPIs is warranted.
This is a study done back in 1993 published in CHEST and what it took was a group of individuals who are classified as difficult to treat asthmatics, just no matter what they did it didn’t seem to work. And they then designed a very detailed protocol, a step wise protocol, of a variety of interventions which you see on the Y axis here and then to determine how well those interventions were in terms of bumping those people back over into the easy to treat or normal management asthmatic group. As you see from the turquoise bar on the top and then the second black bar on the top of the graph treatment of GERD and inhaled steroids were really the two most popular or the two most effective treatment modalities in terms of improving the outcomes of those asthmatic patients. Everything else didn’t seem to work as well.
So here we have data that seems to suggest treatment of GERD is effective. But there are also data out there that seem to suggest that treating GERD has no effect. These are the results published in 2001 of a Cochrane Systematic Review, so it took a number of trials that looked at the Management of GERD whether a Medical Management, Surgical Management or more Conservative Management style and determine whether or not it had any effect on a variety of outcomes in asthma patients. So peak expiratory flow, use of medications, quality of life issues, need for rescue therapy, etc. Unfortunately for or at least in this trial all of those outcome indicators were not changed with the treatment of GERD and so here we see only one of those outcome indicators listed the peak expiratory flow and as you see from the confidence that arose down here on the bottom really treating GERD had no effect. So it maybe easy to look at this review and say, oh well GERD is not the answer we need to get back to basics and focus on asthma but like with any meta-analysis or any concrete analysis I think it’s important to go back and look at the trials that went into it and even the authors and their discussion will admit there were some limitations to their study. First, many of the trials suffered from design issues. They were underpowered. And so they really weren’t powered to detect the difference in the first place and then how they actually implemented the techniques or problem in terms of study design. For the trials using H2 antagonists we know H2 antagonists are not as good as PPIs for the treatment of GERD so that may have had an issue. In the trials that employed a PPI they weren’t nearly as long as you need to really determine whether or not extraesophageal manifestations of GERD are occurring so that was a limitation. And then lastly many of the trials average the treatment results over the entire study period. And as we know when we are trying to determine the utility of acid suppression for extraesophageal manifestations this tends to minimize the treatment effect and so the authors themselves even in the discussion say, well it’s still relatively early maybe larger more better design trials could be conducted to determine if there is a subset of individuals who would benefit from treating our GERD.
And we are now starting to see these trials actually. This is a trial published in the American Journal of Respiratory and Critical Care Medicine earlier this year. And what this trial attempted to answer was if you had a group of individuals with moderate to severe persistent asthma and you place them on a high dose esomeprazole 40 mg bid, so not the FDA approved dose. And you place them on there for a significant amount of times several months, could you positively impact asthma in this patient population? And so they have patients that had GERD, patients that didn’t have GERD and they also had patients that did report having nighttime respiratory symptoms and patients that did have them. So we had basically four main groups. If you pull out all the data together there is really no significant benefit to adding on esomeprazole compared to placebo and this slide right here depicts that. However if you then do a subset analysis and you say okay in the patients that we know had GERD and/or respiratory symptoms did the drug have an affect? So this slide shows a subset of patients that had GERD but didn’t report having nighttime symptoms. And as you see no real separation of the curves placebo versus esomeprazole as you get out farther in times a day since randomization, maybe some separation of curve but certainly not all that significant.
However, if you took that patients that did have GERD and also reported nighttime respiratory symptoms here we see a significant effect not only early but later. And so what this tells us is that one, we may need to use higher doses of PPIs we are more accustomed to. Two, this trial may not only last a few weeks it may last a few months to really detect a difference. And three, there is probably only a subset of patients who have asthma that may benefit from a trial of acid suppression.
Other PPIs have been employed. This is a trial using lansoprazole in moderate to severe asthma. As you see on the left hand side of screen no overall benefit in terms of asthma symptoms severity. But if you look at number of asthma exacerbations the group that received lansoprazole had significantly fewer and if you look at overall asthma quality of life as which is per a questionnaire, you see again a significant benefit. So again this reinforces the fact that subsets will benefit, others will not.
So where does that leave us? Well as I said a few minutes ago I can’t tell you the answer with respect to the management of extraesophageal manifestations of GERD specifically for that asthmatic patient. What I can do is provide a general algorithm that one could follow in an attempt to determine whether or not reflux is the cause or at least exacerbating asthma in your patient. So again if you take anything away from our presentation I hope it is the fact that we need to be asking patients specific questions, not just do you have heartburn, but specific questions to get out whether or not they have atypical symptoms. And if they do, if there are suggestive symptoms we do an assessment and based on the fact that it’s relative non-invasive consider a high dose trial 8 to 12 weeks maybe even longer depending on your preference of the PPI. If you get symptom resolution that’s great, maybe you can back down to more standard dose of the PPI, if not keep the dose that worked. If you don’t see an improvement this is where in my mind endoscopy and ambulatory pH monitoring play a role. Now there is some debate in the literature whether or not you should pull that person off the PPI before you do endoscopy because if you keep him on the PPI and you look at the literature the diagnostic yield is relatively low. So if you are trying to determine if this patient has reflux pulling him off the PPI probably will give you more information. Then again if it’s positive, if you confirm that reflux is present, increase that PPI dose, give a long duration in terms of your trial and then if you do get symptom resolution determine the lowest effective maintenance dose. If after all this you don’t see any positive results or all your test are negative then I think it’s time to consider other ideologies and we can basically put GERD to rest.
Summary

• Asthma, cough, and laryngitis are frequent extraesophageal symptoms of GERD.
• Diagnosis is often suspected after review of patient history.
• Diagnosis is confirmed by relief of symptoms with trial of acid suppression, after considering asthma and post-nasal drip as possible etiologies.

So in summary hopefully that you have seen the extraesophageal manifestations of GERD are difficult to treat, we certainly don't have the answer. GERD is very common in patients with asthma and there is certainly maybe a subset of patients that may benefit from a trial of acid suppression. And I think we as pharmacists can really play a role in this regard and that when we are interacting with these patients ask them those questions to get it those atypical symptoms to help us guide whether or not acid suppression has a role.
Thank You

You have completed Section 4. Please return to the Main Menu to continue to Post-Test and Evaluation.