

[MUSIC PLAYING]

RICHARD SAAD:OK. So I'm going to give an overview to all of you about constipation. And I'm going to start with just a question. So what exactly is constipation? The bottom line is constipation is a lot of different things. And it has, for the most part, some personal specificity.

For some people it's making a trip to the bathroom being a very unfulfilling experience, as this cartoon shows. Or in this case, it may be a trip to the bathroom that's marked by discomfort in some way, again, shown by this picture. And then, finally, it could be an infrequent trip to the bathroom and one that could be a large production of stool when a bowel movement finally occurs.

So the bottom line is there is really no precise definition. And I'll explain that to you as we go on in this talk. But simply stated, constipation can be described as infrequent bowel movements and/or difficulty with the passage of stool during a bowel movement. What I want you to understand, though, is constipation is certainly more than just infrequent bowel movements or the passage of hard stool. And again, it can present in many different ways as I'll point out when we get to the diagnostic criteria that has been most recently developed and published.

So in terms of the symptoms that can be reported with constipation, they can be quite variable. Again, it can be the passage of hard or lumpy stool, decreased frequency of bowel movements, straining during bowel movements, a feeling of incomplete emptying after a bowel movement, a feeling of blockage at the anus, having to use either manual or even digital maneuvers to help with evacuation of the stool, symptoms of bloating or excessive gas buildup-- I'm sure most of you in the audience are dietitians. You probably hear about bloating in just about all of your patients, but in particular the constipated population-- cramping or pain. And that's oftentimes the kind of cramping or pain that comes when a bowel movement hasn't happened for quite some time or there's a need to go and an inability to respond to that urge.

And then, I see this and Bill sees this. And we were just talking about this the other day. Many people can present with constipation and actually have a main complain of diarrhea. And you ask yourself well how can that be? Well these people actually develop an overloaded colon and develop what's called overflow diarrhea. And we were just talking about the importance of an X-ray in establishing that problem for a patient. We even have patients come in-- we see a lot of patients with fecal incontinence in our bowel clinic. And a good majority of them have an overloaded colon. And simply just addressing that problem can help their incontinence.

Interestingly, this is one study about 15 years ago showed that less than half of the patients that were defined as having constipation reported the infrequent bowel movements. So these many other symptoms can predominate over infrequent bowel movements.

So I don't know how many of you have seen this, but I personally carry a laminated copy of this chart in my white coat. I think Bill does, too. But it's really important because you can sit there sometimes and spend 10 minutes trying to get a patient to describe to you what actually they put in the toilet and this simplifies it you show them the card and they can simply point to the type of stool that they produce. There's a picture and also a description of the stool type.

Now in general, the type three, four, or five is what we're aiming for. That's what we would consider normal bowel movements. It's the one and two that are the types of stool forms that would be defined as having constipation. In terms of the constipation subtypes, they can pretty much be divided into that of acute or chronic constipation. And for lack of a better description, the literature sticks with three months as defining acute versus chronic. Now I sometimes will use less than three months time.

But the bottom line is acute constipation is probably far more common than chronic constipation. If you were to interview your patient, you would find out that they periodically have a constipation symptom and they take an over-the-counter laxative sort of on an on-demand basis. But the differentiation between acute and chronic constipation is generally going to be defined as three months. And that's for primarily for research, but we've adopted it for clinical purposes.

And then there's the aspect of dividing primary versus secondary constipation. Primary is what we also will refer to as idiopathic constipation. Whereas, secondary is constipation due to another explanation, Medications being probably at the top of the list. There are numerous medications that contribute to constipation. Narcotics probably being the most commonly prescribed drug, at least in the United States, that contributes to constipation.

But another example of one that's commonly used either by the patient without informing you or for other reasons would be an iron supplement, for instance. Iron can be very constipating. And sometimes you have to ask patients about what they're taking over the counter, not just what they're being prescribed. But again as far as medications go, the whole spectrum is covered-- anti-emetics, anti-hypertensives, drugs for Parkinson's disease, the list goes on and on. But you really have to think about the medications before you conclude that the constipation is due to idiopathic reasons.

Then there are a variety of metabolic disorders-- diabetes, for instance, renal failure. You may see patients with renal disease. And that also can contribute to constipation and it's not always thought of. A variety of endocrine disorders, I mean everyone thinks about thyroid disease although I have to say, that's a pretty rare cause of constipation. But still a variety of endocrine disorders, probably diabetes topping that list.

Neurologic disorders, Parkinson's probably is one that leads the list. I see many patients. I have a geriatric clinic as well and Parkinson's is one of the top co-morbidities that I see in the constipated patients that present to me in that clinic.

Rheumatologist disorders. Scleroderma probably is the prototypic rheumatologic disorder that can contribute to constipation.

And then a variety of psychological disorders-- anorexia, depression alone can cause constipation.

And then, finally, the one that we all worry about-- the structural causes-- which is the reason that oftentimes patients with constipation are sent for a colonoscopy. I will say that the yield of colonoscopy is very low. So we generally only pursue a colonoscopy if that person is of age based on screening criteria or if there may be some other symptoms of concern, for instance blood in the stool or anemia.

So Rome is an international working group. Rome's been close to 40 years, this group of international experts in the field of functional gastrointestinal disorders. Sorry, Bill, I know I'm supposed to get away from the word functional. But this is a group that looks at disorders that don't have a structural or a biomarker to define the condition.

And this international group meets. And about every 10 years they come out with an updated set of clinical criteria that they use to define these conditions. Rome IV, of course, is the fourth iteration. It was published last year. And this is basically the definition of chronic idiopathic constipation that's primarily used for research purposes so that we can get a very well-defined population into our clinical trials. But it works great in the clinical arena as well.

So an individual must have two or more of the following symptoms. And you'll see how variable constipation can be based on this definition. So two or more of these conditions, and they have to be present for about a quarter or more of their defecations. These symptoms can include straining, the passage of that lumpy or hard stool that I showed you, a sensation of incomplete evacuation, a sensation of anal rectal obstruction, use of manual maneuvers, or fewer than three defecations a week. So as you can see with this definition, you don't even have to have infrequent bowel movements to meet the criteria for constipation.

Loose stools have to be rarely occurring, unless there is laxative use causing that loose stool. And there has to be insufficient criteria for IBS. I believe you got your talk yesterday-- several talks yesterday on IBS. And then, finally, again, there's that three month time frame with at least symptoms occurring for six months prior to the diagnosis.

So chronic constipation and IBS also overlap to some degree. And there are many of us in the field who believe that they're probably both the same condition with just a key difference in the abdominal pain. That's not to say people with constipation don't get abdominal pain, because they do, especially when they haven't had a bowel movement for several days or are unable to respond to the urge to have a bowel movement. The difference is somebody with IBS is going to have abdominal pain whether or not you control their constipation. And that's sort of what I use to differentiate IBS from chronic constipation. So if you've controlled their constipation, and they're still having abdominal pain, that's probably somebody with IBS with constipation. And your treatment might be a little bit different for them.

In terms of conceptualizing the types of idiopathic constipation, there isn't simply one type of idiopathic constipation. It can be essentially divided into three types of idiopathic constipation. I'll start on the right. There is slow transit constipation. And this is very objectively defined as a slow colon.

There's also a variety of defecatory disorders. I'm going to spend some time going over what exactly those are, because they play a big role in our tertiary care level of patients. But they can be divided into those that have dyssynergia. Now what dyssynergia is is the uncoordinated muscle activity of the pelvic floor during defecation. They could also have impaired propulsion. So when you have a bowel movement, the abdominal wall has to create a negative pressure. And the rectum itself has to help in evacuating the stool. Now if those abdominal wall muscles aren't working or the rectum isn't working properly, you're going to have problems. And that's also defined as a defecatory disorder.

And then, finally, there's the normal transit constipation, which is the constipation in which there is no defecation disorder or slow transit present.

And in terms of constipation, the majority of people with idiopathic constipation are probably going to have the normal-transit constipation. That's what this study which is a bit dated, but this is what this study showed is about half to maybe 3/4. And this is in the general population of constipation. I think in the tertiary care centers, we see a lot more of dyssynergia than anything else. But you can see dyssynergia, slow transit and even-- I should say dyssynergia and slow transit can coexist and these individuals can have a multitude of explanations for their constipation.

So to talk a little bit more about dyssynergic defecation, this also may be described as pelvic floor dyssynergia. Again, this is the uncoordinated pelvic floor muscle activity that occurs during defecation. And this involves skeletal muscles, which is important, because skeletal muscles are directly controlled by our brain. They're not autonomic muscles. Our brain controls how they work.

Those two muscles that are key in this condition are the puborectalis and the external anal sphincter. And what happens is either there's a poor relaxation or a paradoxical contraction of one or both of these muscles during defecation which prevents the rectum from emptying.

So a little bit of anatomy just to help everyone out with those muscles, so I'm not talking in the abstract. This is a side view of the pelvis. Just to orient you, this is the pubic symphysis here. You've got the bladder here, the uterus, and this is the rectum.

The puborectalis, it's a u-shaped muscle. It's part of the levator ani complex. And it attaches to the pubic symphysis, wraps around the rectum, and reattaches to the pubic symphysis. And in the typical state, it's contracted. And what it's doing is it's cinching closed the lower part of the rectum so that the rectum doesn't empty and you don't have incontinence. During defecation, you have to voluntarily relax that muscle to allow the rectum to straighten and empty.

The other key muscle is the external anal sphincter. This is a diagram in the lithotomy position. Again, here's the levator ani muscles. You've got the internal sphincter and the external sphincter around it. And that sphincter, again, skeletal in type, has to relax voluntarily to allow the anal canal to open and stool to evacuate.

The most common complaint a patient may have with this type of problem is they'll tell you they have really thin stool and that's regardless of taking a laxative. And it's because the stool is coming out through a tiny opening because that muscle's not relaxing.

So normally what happens with anorectal function is the rectum distends when it's full of stool and you get the involuntary relaxation of the internal anal sphincter. Now, again, that's a smooth muscle, so that will operate on its own. Then the rectum starts to contract.

Now if you are near a toilet or you can get to a toilet, you're going to increase intrarectal pressure to allow the evacuation to occur, relax both that external anal sphincter and the puborectalis, and you have your bowel movement. If it's not convenient to have a bowel movement, then you will voluntarily relax the rectum and contract the external anal sphincter as well as the puborectalis. Any problem with this process can either lead to constipation at one end of the spectrum or incontinence in some cases at the other end of the spectrum.

The way we diagnose dyssnergic defecation-- well, Bill will probably agree-- that some of us to do this all the time feel pretty confident in just a digital rectal exam. And that's probably the most important thing a clinician can do at the bedside. So any of you clinicians out there, I pretty much tell our trainees when somebody has an anal rectal problem, you should be doing a rectal exam. There's just no reason not to. You may find exactly what their problem is with that exam.

But in terms of more objective, definition of dyssnergic defecation, we have we have basically three studies-- I should say four-- that we can use to evaluate for this problem. One is the balloon expulsion test. It's the placement of a small balloon in the rectum inflated to about 50 ccs. And the patient is asked to expel that balloon voluntarily on a commode. And they should be able to do that within one minute.

There's also anorectal manometry. This is a small catheter that's placed in the rectum. And it measures muscle strength. And we're able to assess how the muscles respond to simulated defecation.

Electromyography is also available. But that's a little bit more painful, a little bit less available. We don't do that at our center as a general rule.

And then there is a defecography. And that defecography can be done in two ways. We have a barium, use of barium and fluoroscopy. Or it can be done with a magnetic resonance imaging. It's basically sitting on a toilet and being watched while you have a bowel movement. So it can be a bit tough for a patient. But Bill and I have ordered this a lot. And it's a very helpful study. It can also exclude structural problems that may be promoting the constipation symptoms, such as an enterocele or a rectocele, particularly in a woman who's had pelvic surgery and had a hysterectomy. That puts them at risk for these conditions.

So moving on to slow transit constipation, this is also objectively defined as the delayed passage of fecal contents through the colon. And you have to, in this case, first exclude medications because they will slow the colon. And you have to exclude that dyssnergic defecation we talked about as well, because that's also going to look like a slow transit when you do the tests.

We have three tests available, all available at our center. We can do what's called the radiopaque marker study. It's the ingestion of these small, non-digestible markers. And then we get two X-rays, usually days four and seven. And we just count up the markers and their location and that gives us an estimate of colon transit.

There's scintigraphy. It's available at our center, but that uses radiation. It's a bit of a long study, too. And the patient has to come back to be scanned on a couple of occasions.

And then we have the wireless motility capsule. This is a non-digestible capsule about the size of a calcium tablet. It's pretty large. And it travels. Once it's swallowed, it travels to the digestive tract and by the process of it measuring pH and timing when it exits the body, we're able to get calculations, direct calculations, of stomach emptying, small intestinal transit, and colon transit.

So now that we've defined the constipation, I'll move on to medical therapy. I know Kate's going to talk about nutrition after me, so I did not specifically talk about nutrition here. I'm going to leave that for her and I left that out. But I will say before I go into medical therapy here that lifestyle and nutritional approaches should certainly be used first before we get into using medications.

I broke down the medications into those available over-the-counter-- they're obviously easier for patients to get and quite frankly they're used by a patient before they oftentimes see me-- and then those that are available by prescription only. So let me just go over two big misconceptions that I always have to answer for patients, too. The first question they ask me is is the chronic use of laxative therapy harmful to my colon? The answer is no. None of the studies that we've done show that. And some of these studies, they can be 12 weeks, they can be 52 weeks.

And the reason I can tell you this is when you study these patients and you put them on a laxative, yeah, their symptoms get better. Their constipation symptoms improve. And when you take the laxative away and you follow them in that withdrawal period, they don't get worse. They simply, if they don't continue to stay well, they go back to their baseline, but they do not get worse.

The other question I get asked is the use of laxative therapy habit forming? Again, the answer here is no for the same reason. The withdrawal does not result in worsening symptoms.

But the way I try to answer this for them is constipation is a problem. It's like having diabetes. It's like having hypertension. You're not right without some form of therapy to make you better. And that's the way I describe it to them.

So I'm going to go into the drugs and talk-- it's going to be fairly superficial. But I want you to just understand the level of evidence that has led to the use of these drugs and constipation. I shouldn't just say drugs, because the first one are the bulk laxatives. They're not really drugs and nor are probiotics for that matter. But you'll see Grade A, Grade B, and Grade C listed throughout my next set of slides.

Grade A are basically those high, quality randomized controlled trials. Grade B are those lower quality randomized controlled trials. And Grade C are simply nonrandomized trials or observational trials.

So I'm going to start with the bulking agents. Hopefully I don't overlap too much with Kate on this. But the bulking agents are essentially the fiber and the fiber supplements. I'm probably preaching to the choir here, but these are organic polymers. They can either be natural or synthetic. And they're divided into those that are water soluble and water insoluble. Their mechanism of action is to increase the water retention of stool. So this bulks up the stool and ultimately increases stool transit. And we have studies that show that.

So in terms of what's soluble and insoluble, for the most part the fiber that people put in their meals, as a result of what they eat are the insoluble fibers. This is the bran, the flax seed, the rye, and other nondigestible seeds and vegetables. The soluble fibers, the water soluble fibers, are psyllium, which is natural, methylcellulose, also natural, calcium polycarbophil, which is a synthetic, inulin, which I believe is a natural, and then wheat dextrin, which is natural.

So the evidence for these bulking agents, there's nothing that's high quality in terms of randomized controlled trials. And the reviews that have been performed are conflicting. But they do work better for chronic constipation than they do for IBS-C, obviously because of the pain component.

Specifically, psyllium has been studied enough out there to receive a Grade B recommendation. There really isn't any sufficient data for any of the other fiber analogs, although we still use them quite regularly. And I think the wheat dextrin's is a pretty popular one. In terms of their safety and efficacy, as a class, they were given a Grade C recommendation, no randomized trials. But psyllium itself, once again, did get a B recommendation. So it's been the best studied of the fiber, the water soluble bulking agents.

And here's the results of a systematic review. As you can see, most of the trials were done with psyllium. It improved global symptoms, increased the bowel movements per week, normalized evacuation, and also helped with straining during defecation. Ultimately, it was the psyllium found to be more effective than placebo. If anything, it looked like the bran and the rye did a little bit, but only in terms of straining. It didn't do much in terms of increasing stool frequency.

So moving onto the stool softeners. This is probably the most commonly used over-the-counter agent by a patient. These are the most readily available. Ducosate comes in either as Ducosate sodium or Ducosate calcium. I would prefer the Ducosate calcium to the sodium, because they're getting a little bit of calcium. The problem, too though, is calcium can be constipating. And basically how these agents work is they are anionic detergents. They lower the surface tension of the stool. And they allow water to penetrate the stool, adding to the water content of the stool.

The studies out there are very poor. They are basically four randomized controlled trials that were found in the most recent systematic review. Basically gave mixed results. Quite frankly, I only like to use these in my elderly patients, because they're so mild and I'm less apt to give an elderly patient a problem with excessively soft stool that's going to result in unnecessary trips to the bathroom and maybe a fall or something in the night. There's also been one study that looked at its use in the chronically ill. But overall, there just aren't great studies for these agents.

Despite that, they are probably the most popular agents over-the-counter. They've been approved by the FDA for occasional use of constipation. And this is why you'll probably have patients come in and tell you they use it when they have their episodic constipation symptoms.

But they are well-tolerated. They have almost no side effects. And they're pregnancy category A, so they're quite safe in pregnancy, which is why most pregnant woman will be issued their iron supplement and a bottle of Colace with it. I know my wife got those when she was pregnant, so-- but they're also quite inexpensive. But again, I think they have minimal efficacy in chronic constipation. And I pretty much limit them to either very mild constipation or the elderly.

So probiotics, there isn't a dedicated talk on probiotics as far as I know. As far as probiotics, I think the evidence is better for use in diarrhea, but there is some evidence for constipation. Again, I'm probably preaching to the choir here, but probiotics are marketed as dietary supplements. The important characteristic in them being dietary supplements is the FDA has no role in these agents, which means there's no regulation. And the biggest problem with the probiotics is what you think you're buying may not actually be what's in the bottle. And a dead organism is useless as well. So if it says it has an organism in the product, and it's dead, it's not going to reanimate when it gets into your GI tract.

How can these help? Well, a lot of this is still theory, but it's felt that they may accelerate colon transit and maybe increase the bulk bowel motility. As far as the evidence, this latest systematic review found three randomized controlled trials that looked like they did help with some stool frequency and consistency. The specific agents were Bifidobacterium lactis, Lactobacillus casei, and E coli Nissle. And there was one study that actually showed-- this was a crossover study. As you can see, it was very tiny study, 20 patients-- using that Lactobacillus paracasei. And it increased stool frequency as well as improved evacuation.

I think to summarize, if a patient's going to come to you and ask about probiotics, these are probably the four strains that I would recommend. So if they find a product that contains these strains, it may help them with their constipation.

So moving on to osmotic laxatives. Probably the most common osmotic laxative out there now is the polyethylene glycol 3350. Every store has their version now. It's the same product. No matter where you get it, it's the same product. There's also lactulose-- it's only available still by prescription-- magnesium salts and sorbitol.

And the way these osmotic works is they're poorly absorbed. And this is a key thing that I tell patients who are afraid of drugs. This is a drug that's not absorbed. Their body is not absorbing it. It's just traveling through and grabbing water and pulling water into the intestines as it travels through. And that's what it does is it creates an osmotic gradient moving water into the bowels.

Really good evidence, actually, for polyethylene glycol. It's got a Grade A recommendation, so high quality randomized controlled trials. Clearly superior to placebo. This was a total of 10 trials that have been done. Increased the stool frequency by over two bowel movements a week. Also superior to lactulose, increased stool frequency more so than lactulose did.

Lactulose, still though, does well. It gets a Grad A or a B recommendation, depending on what systematic review you look at. Sorbitol and milk of magnesia, I do use milk of magnesia. But there just isn't enough data to say based on trials how safe or effective it is. I will say in my clinical experience, milk of magnesia does work as do other magnesium salts.

In terms of the use of PEG, I would not recommend using more than a single dose a day unless they're under the care of a physician. It is generally well tolerated. Bloating is probably the most common symptom that will be reported with it's use. That bloating is usually worse with lactulose, little bit less so with PEG. And interestingly, milk of magnesia or magnesium causes the least amount of bloating.

And the key with these agents is you have to have adequate water. I can't tell you how many times a patient comes in and tells me that they take two doses of MiraLAX powder and they put it in three or four ounces of water. It's not going to work. You need water for an osmotic agent to work. So I tell them at least 8 ounces and even more per a dose of MiraLAX or polyethylene glycol 3350.

As far as the stimulant laxatives, anthraquinones are probably also very commonly used. Senna in a lot of herbal products, a lot of teas, a lot of over-the-counter agents. Cascara has sort of been not used as often. But these are the anthraquinones.

And then there are the diphenylmethanes, Bisacodyl being the most common one that we use here in the United States. Sodium picosulfate is primarily available in Europe.

So the way these stimulants work is they're activated by bacteria in the colon. And they do three things. They irritate the colon wall causing increased contractility of the colon. They stimulate the sensory nerves that line the colon and they also inhibit water absorption. And this is probably why you get the side effects of these agents that are typically cramping and pain. Those are probably the most common complaints that will limit the use of these drugs. The good thing about these drugs is they're very fast acting. For most patients, they'll work within 12 hours time. So taking one to bed time means they're going to have a bowel movement in the morning.

The evidence is pretty limited. Up until recently-- so essentially the latest systematic review gave them a Grade C recommendation. And this was based on a trial in the elderly and the mentally handicapped. And there was insufficient data to really comment on their effectiveness until recently. And these are the two slides I added, because I realized I should have added these.

There's a four week study done with sodium picosulfate in Europe. This was compared to placebo. And it did show that it was well tolerated and improved bowel frequency over that of placebo. It also improved quality of life. Diarrhea and abdominal pain, once again, were, of course, the most common side effects.

This agent is available in the United States, bisacodyl. This was another study-- this was also done in Europe, though, in the UK. A large randomized controlled study, almost 400 patients compared to placebo. Again, this was a four week trial. So these patients were taking these agents chronically. And you can see the outcome here. It improved complete spontaneous movements, as well as spontaneous movements, global improvement, and quality of life. All were improved over that of placebo.

So to summarize how the stimulant laxatives in constipation, they're very effective rescue agents because of their quick onset. They're traditionally used for acute or occasional constipation. But I will use them in my slow transit constipation patients. I think biscuit's probably one of the best agents you can use in slow transit constipation, because it's going to accelerate the colon.

There's the recent evidence I just showed you supporting both safety and efficacy for chronic use. I don't know if any of you have heard of melanosis coli, but it's a staining of the lining of the colon. It's harmless. The only people that see it are those of us that do colonoscopy. But it's a harmless staining. It will go away. But it's always a cue to us that somebody is taking senna.

There's also-- early on in the literature, there was concern about colon damage from the long-term use of these stimulants. It's remained unproven. It's never left the lab. So in humans. It doesn't happen. But the big thing are the side effects that are going to limit the use, particularly the cramping and abdominal pain, and sometimes nausea, or even diarrhea.

So moving on to the prescription therapies. I broke them down into osmotic, lactulose-- I'm really not going to talk about that, because we already talked about osmotic. Serotonin receptor activators, we do not have presently any of these available in the United States, but they are available in Canada and in Europe and I will show a couple of slides on that. And then I'm going to spend most of the time on our chloride channel activators, because we have three now that are available by prescription for both chronic constipation, and for two of them-- Lubiprostone and Linaclotide for IBS-C.

So serotonin. We all think of serotonin and depression. It's actually found that 95% of the serotonin in our bodies is in the GI tract. And those key serotonin receptors are the 5-HT 1, 2, and 4 subtypes. So we know that serotonin plays a role in gut function. And specifically, 5-HT₄, the type four subtype of serotonin, increases intestinal contractions and also intestinal secretion. We've had a variety of agents that have come and gone. And we have one agent still available and being used readily or frequently both in Europe and Canada, that being Prucalopride. I think there is some movement for it to be possibly coming into testing and maybe even availability in the United States in the next few years.

But Cisapride, Mosapride, Renzapride, these are all agents of the past. They had problems with safety and efficacy. And they've all been removed from the market. And the same happened with Tegaserod, which was a wonderful drug, but there were some concerns about cardiovascular incidence, and it was removed from the market a number of years ago.

So those chloride channel activators, just wanted to give you kind of an understanding of how they work. This is a cartoon that shows a-- this is an enterocyte, a cell that lines the intestinal wall. This is the basal side. So this is the inside of the wall. This is the lumen.

We've got these two types of chloride channels. We have the chloride type two channel. And we have these CFTR, the cystic fibrosis transmembrane regulator channel. And what happens is when these channels are opened by an agent, such as Lubiprostone, Linaclotide, or Plecanatide, chloride ions move into the lumen. And then sodium will move along the ionic gradient and pull water with it between these tight junctions that connect the enterocytes.

So Lubiprostone was the first of the agents to become available. It's a synthetic fatty acid. It's derived from prostaglandin. And it activates those type 2 chloride channels I showed you, again, moving sodium and water along that ionic gradient. It's available in two doses-- 8 and 24 micrograms. And it's been FDA approved for those 18 or older for chronic constipation using the 24 microgram dose. The 8 microgram doses for IBS-C.

You can see a response quite quickly, within one week. And it's been shown to improve stool form, frequency, straining, and abdominal pain. Some issues with its potential use in pregnancy, so it's generally advised that you either avoid it or have a serious conversation with a woman who's going to be pursuing pregnancy. Nausea is probably the most common side effect. There is some abdominal pain and headaches as well.

Linaclotide was the second agent to come around. This is a synthetic peptide. And what it does is it activates guanylate cyclase C receptors. And those, through a series of processes, that will activate that CFTR channel I showed you on that cartoon. There also appears to be some effect on pain reception. And it can reduce pain as well.

It's available now in three strengths. There's the 145 for constipation. The 290 for IBS-C. And the 72 microgram dose just came out to sort of handle the diarrhea problem that this drug has had in terms of a side effect. And it's approved for both men and woman over the age of 18 with chronic constipation in either the 145 or 72, now, microgram dose.

Again, response can be pretty early within one week. Again, similar to Linaclotide, improved stool form and frequency, straining, bloating, and abdominal pain. Again, it's safety in pregnancy is unknown. And the side effect, probably the major side effect, is diarrhea. And we've done a variety of things to try to address the diarrhea, the lower dose, maybe alternate day dosing and so on.

And then, finally, there's Plecanatide. This is the newest kid on the block. This is an analog of uroguanylin. So it's very similar in terms of its mechanism of action. It works on that CFTR. But it's a different compound. And what they have found is that it acts in a pH sensitive manner. And as such, it's felt that it might have a different mechanism of how it works in the gut.

It still appears to reduce pain as well as address constipation. It's available in a single dose right now, three milligram strength. It's taken once daily. And it's FDA approved for adults, both men and women, over 18. Again, it's safety in pregnancy is unknown. And side effects can be either, it's primarily diarrhea, about 6%. So certainly fewer reports of diarrhea here than with maybe the other two agents.

So just some key points with chronic constipation. Just remember constipation is more than just infrequent bowel movements or the passage of hard stool. There are a lot of other symptoms that can define constipation for a patient.

Also, remember to look for those secondary causes, because they're quite common. And they should be excluded before you conclude somebody's constipation is idiopathic. It can be the result of a slow colon and/or impaired pelvic muscle function. So again, if you're getting key symptoms from a patient, such as thin stool or anal blockage, there may be something going on with their muscle function in the pelvic floor.

I always start with over-the-counter therapy first before moving into the more expensive drugs which are absorbed-- to some degree absorbed. And then when you have to use combination laxatives, I always try to use two agents that have different mechanisms of the action. There's really no purpose necessarily of using two agents that work the same way. You're just trying to treat the constipation with the same mechanism of action. So I mix drugs with different mechanisms of action. So for instance PEG and bisacodyl, so that's an osmotic and stimulant laxative.

And that's it. I did OK, huh, on time?

[APPLAUSE]