DAVID LEVINTHAL: I'm going to be speaking about constipation, and this is a topic that is a very common issue that's seen in primary care. I think everyone here is probably familiar with their approach to constipation. I want to give an overview of the consensus guidelines from a gastroenterology standpoint, and some of the new approaches that have come online over the last several years and the evidence behind them.

So first, before we start talking about constipation, I think it's very important to have a definition of what we're talking about. And as you've seen patients say, when they're dizzy, or other symptoms, these can mean a lot of different things to different patients, so it's really good to clarify with the patient, what do you mean by constipation? So what do patients say when they say, doctor, I'm constipated. Well, there are really several dimensions to the aspect that really needs to be ferreted out.

So there's a frequency definition. Patients will say, well, I don't go every day. Well, actually, physiologically, you don't need to, so that's not enough to say you're constipated. I only go once or twice a week. OK, it starts to sound like constipation to a physician. There's a stool consistency aspect of it. Stools can be hard or lumpy or pellety. Sorry to be graphic right after lunch.

Patient experience of passing a bowel movement can define, or be a hallmark, of constipation. So patient can feel bloated, or have a sense of abdominal pain, or need to strain, or it can be painful to pass, or have an urge to go, but can't go. May even have to digitalize or to assist in defecation. So all those things go along with constipation, but in and of itself may not be sufficient, from a medical standpoint.

So what's out there in clinical trials? Would you believe that there is the stool chart? It's called the Bristol Stool Chart, the United Kingdom Bristol. This chart actually, surprisingly, has a lot of impact and validity in determining if someone is constipated. So if you show a patient this chart and be like, what does your stool look like? And they point to a Type I or Type 2 stool, they're constipated. That actually can vet constipation from a clinical trial standpoint. In fact, that's the study entry criteria for some large studies. The perfect stool is somewhere in between Type 3 to 5, and then diarrhea being Type 6 or 7. So I'm not going to belabor the point with descriptors right now. But needless to say, stool form is a major marker for constipation.

So what is the gastroentrological definition of constipation? Well, actually, it's changed over the years, so in and of itself, it's a moving target. So there are major GI societies that have worked on this for a long time. There's a foundation called the Rome Foundation, which defines functional illnesses and gastroenterologies. For example, irritable bowel syndrome, what is it? They define it. And essentially, there are three major forms of constipation that can't be attributable to some other medical illness or a structural disease. Those are off the table. These are the issues that are basically functional constipation of some form.

So there are basically three different major subtypes, the first of which is chronic idiopathic constipation, sometimes called functional constipation. I'm going to use the abbreviation CIC. I'll just say CIC for the rest of the talk for that issue. Then there's irritable bowel syndrome with a constipation predominance. That's IBSC from here on in. And then there's opiate induced constipation, which essentially is CIC in the context of opiate use, so OIC. So these are defined illnesses that justify drug trials and FDA approval for a certain age, and so it's important to have a definition.

So let's drill down, just briefly, into what we're talking about. So from the Rome criteria for chronic idiopathic constipation has both a frequency definition and kind of an experience in stool form aspect to it. So you need to have fewer than three bowel movements in a week, on average, to justify a diagnosis of CIS. But you also have to have two of the following five aspects, which incorporates some of the things that patients usually talk about, including straining or lumpy or hard stools, sensation of not getting everything out when they go, sensation of a blockage or feeling obstructed, and potentially even digitalization, or splinting, to help them defecate.

So if you have two of those five, and a frequency that's below three or fewer defecations per week, you have CIC. Now, IBS with constipation, or IBS in general, has recently been updated slightly. It used to say abdominal pain or discomfort. The Rome three criteria was changed just recently with Rome four, which came out a few months ago. Now it has to be abdominal pain, per se. So it's recurrent abdominal pain for at least a day a week in a durable way over the past three months, associated with either defecation itself, or a change in stool form, or a frequency. And in the case of IBSC, essentially you have to meet the CIC criteria, but with the abdominal pain aspect.

Then OIC, as I said, was essentially CIC, but in the context of either recent changes in opiate dosing, an increase, or the initiation of opiate therapy in general. OK, so those are the definitions. But sometimes definitions can be semantic, and maybe not even physiologically relevant. And there's been a lot of debate in the GI field whether or not CIC and IBSC represent even different disorders. They likely represent something along the same spectrum, where abdominal pain may be a feature, yes or no. And so there's a lot of debate whether we should just lump these all together and call it constipation with pain, or constipation without pain. There's a lot of literature behind the IBS concept, as opposed to not IBS, and so there's a lot of vested interests in making these distinctions.

But if you look here-- let me get my mouse-- when you take populations and you ask, they meet criteria for IBSC or CIC, do you have gas pain? Do you have abdominal discomfort? Do you have even pain itself? Do you have bloating or stomach cramping? The rates of subjects that endorse those symptoms are very similar between those two populations. And when you look at the presence of hard stools, or the need to strain, incomplete evacuation, or digitalization, those rates are also very similar.

So I think it would be very hard to discriminate these two populations based on the presence or absence of some of these features. And in essence, it may not make that much of a difference, because the general approach is each of these disorders are very similar. In fact, the same medications have FDA indications for both. So I just want to put that as a disclaimer.

So how common is constipation? So we've defined it, but how common is it? It's very common. The population that has IBSC in the adult world is about 4%. IBS in general is about 10% to 15%, a third of which have constipation. That's how you get down to the 4%. The population prevalence of CIC is upwards of 15%. So look around the room and somebody is constipated in this room, by chance, I think. We're all lucky, we don't have constipation.

In those that are age 60 or above, rises to about a third of patients. So there are a lot of reasons why that may be the case. This doesn't differentiate between medication-induced constipation, or other structural issues that may come up. But nevertheless, that's extraordinarily common. So constipation is very, very common.

Now, in those that use chronic opiates, this is usually deemed quote "non-cancer pain" as the setting, but even in the context of cancer, opiate-induced constipation is very common. About 40% of those on chronic opiates suffer from concurrent constipation. So these numbers are extraordinarily high.

And it makes a major impact on patients, not only on their quality of life in their day-to-day life, but also on their work life. There have been some studies showing that, on average, patients with IBSC, or CIC, miss upwards of a day a month from work due to the presence of constipation and the symptoms, and certainly lead to decreased productivity when they do show up at work. So this has a large economic impact beyond just the health care costs associated with managing the disease.

And the health care costs are quite high, and rising. There's been documented about a 200% plus increased cost of constipation-related care in the emergency room alone. There's been some estimates of about $0.7 billion in 2006. That rose to $1.6 billion in 2011, and I suspect that it continues to increase. No one's ever put a great reason why, but I suspect that the prevalence of opiate use may be to blame. Studies I saw did not differentiate the underlying cause of constipation, just merely billing related to constipation. And the costs are likely to rise further now that we have prescription drugs, which I'll talk about today, that are much more expensive than over-the-counter remedies, which were available several years ago. So the care of constipation, the cost of the care, is going up.

And what's the source of this cost? Well, some studies have looked in the Medi-Cal population, or the Medicaid population, in this left-hand slide. Some other ways of looking at data on the right. Physician outpatient costs are really where most of the costs come from. It's less of an inpatient problem, although it does present itself in the inpatient setting, but it's predominantly an office-based issue.

But when you divide the pie, in terms of the source of the costs beyond just the visit itself to the physicians, it's really the procedures and tests that add up quite a bit. There are an extraordinary number of X-rays and CT scans, and other things that usually pop up in this context-- colonoscopies, which I'll talk about. So we can essentially increase the diagnostic yield from less expensive tests, that would make a big difference in the cost, because these are procedures and tests for diagnostic purposes.

So this is a guideline that currently is valid and used by the AGA, the American Gastroenterological Association, one of them the flagship GI societies. This is found on their website. It's been modified over time. And this is really a framework for how I want to go about the talk.

So what do we do with someone that we've identified as having constipation? Well, part of that actually is, importantly, the patient interview in a physical exam, and there may be a role upfront to consider some evaluations to get underlying mechanisms. But ultimately, this paradigm of care goes through a trial of over-the-counter fiber, supplements, or other laxatives, before really getting into much more diagnostic work. And I want to emphasize that this probably would be a relatively cost effective approach for most patients with constipation. You'll see here are some other things which I'll get to as the talk moves on.

So what should one do when you see a constipated patient in a clinic? Have a history and physical is important, and it's really important to determine, are there any alarm symptoms? So the alarm symptom concept really comes out of the IBS literature. IBS was once thought to be a diagnosis of exclusion, and it really isn't. You can make a positive diagnosis for IBS, but it needs to be made in the absence of alarm symptoms. So any of these would justify more work up beyond history and physical, and proceeding down the pathway I suggested.

So is the constipation of new onset? Is it in somebody who's over the age of 50, where they hadn't had constipation all their life? They were very regular and all of the sudden, their bowel pattern has changed. That's a little bit suspicious and unusual. Are there blood in the stool? Are they anemic, which justifies, retroactively, some testing to determine that. Have they had weight loss? And do they have a family history of colon cancer? Those things may change what I'm about to say. So as the talk moves on, I'm going to assume that this is a patient that does not have alarm symptoms.

So part of the evaluation beyond the history and physical would be to say, are there any potential metabolic contributors? Are there any potential drug interactions which could account for the constipation? And then I'll talk a little bit about something called pelvic floor dyssynergia. I don't know if anyone in the audience is familiar with this. It's a major confounding variable in the management of constipation, and it's important to consider.

So what are some common and uncommon medical conditions associated with constipation? So of all people that have constipation, a lot of these are not as common as some other ones. But the metabolic causes of constipation, the predominant ones, are hypercalcemia, hypokalemia, hypomagnesemia. You can see a lot of different drug effects and ways that diuretics that could get you there. Hyperthyroidism comes to mind for probably most people, although I have to say, the literature is not highly supportive of a major yield in testing people with constipation for thyroid disorders. I mean, there's some. It's been estimated in the low single digit percent of finding someone being hypothyroid, given the presenting symptom of constipation. And then diabetes itself can do that as well, so it's worthwhile screening.

There are some other major illnesses which one should consider, but in the right context. So scleroderma and amyloidosis certainly can present with GI symptoms, but those are relatively uncommon disorders. Parkinson's disease, which we'll hear about right after I talk, is actually associated very strongly with constipation. In fact, some people have argued that constipation predates some of the motor dysfunction seen in PD.

So it's good to put that in the back of your mind, but unlikely the case in a 20-year-old with constipation. And then a variety of central nervous system impact, disorders central nervous system impact, can present with constipation. So again, in the right context, it will be obvious if someone had had a stroke or a spinal injury.

I want to put one plug here for immobility. Just movement itself actually has an impact on bowel function through mechanisms that are not fully clear. But if someone broke their leg and was holed up in bed, even if they're not taking opiate medications for pain relief, they will get constipated. Just not moving is sufficient to generate a change in bowel movement pattern. So getting at the person's underlying mobility is important, too. Are they very sedentary?

What are some of the medications associated with constipation? I think most people in the audience are familiar with the idea that anticholinergic drugs can have an impact on GI tract function. So a lot of common medicines, such as diphenhydramine or tricyclic antidepressants can present with constipation. Drugs used for nausea, so serotonin 3 antagonists such as ondansentron, can actually directly impact colonic function and present with constipation. Beta blockers, calcium channel blockers, high doses of calcium supplements, and so on can. There are some anti-psychotics, some pathomimetics, and even progestins, actually, can have an effect, too. So some young women put on a progestin, such as Depo-Provera or others, can actually develop constipation in that context. So those would be medication-induced constipation.

So what should one do to look at some of these? My feeling is that one should really keep it simple. So a CBC basic panel, calcium in a mag, look for hypothyroidism, look for diabetes. That would be it. I think most of the time, that would be more than fine. And if this checks out, moving forward with treatment is very reasonable. You can move forward with the treatment anyway for the constipation, but that would eliminate, I think, medical issues and make it more of an idiopathic-- the CIS, SC, or OIC, depending on the context.

So should one do a colonoscopy? This comes up a lot. I would say no. In the right setting without alarm symptoms, the yield for doing a colonoscopy in the context of constipation is not worth it. It's an expensive test. There's some associated risk. And some studies have looked at the yield of relevant findings. Below here is a plot of the likelihood of finding something very relevant for moving forward with care, and it's actually below chance compared to even a screening colonoscopy. So if someone's constipated, it's a 25-year-old with no other red flags, don't do a colonoscopy. Someone will do the test if it's ordered, but it probably is not the wisest use of resources.

So did we fix their constipation? How do we know if we're successful? That question may seem somewhat obvious, but it's actually not. So what does the FDA say? I'm going to talk about a lot of medications that have been approved for constipation, but it's been a moving target about have we been successful. So in the 1990s, there was a concept of adequate relief. Basically as patients, are you better? Yes or no? And then the percentage of people that said yes or no was deemed the outcome measure. That's changed over time to incorporate a little bit more nuanced view of both a subjective assessment from patients, but also a more objective measure of bowel movement frequency.

As you can see on the slide here, a movement from subjective global assessments to then, in the late 2000s, the FDA endpoints points for these studies in constipation included bowel movement frequency and a severity endpoint. And now, there's a concept of a complete spontaneous bowel movement, meaning, to patients, do you feel like you got everything out? How often does that happen in a week? So that's raising the bar, so to speak, combined with both pain assessments and other subjective assessments.

But the truth is that no matter how you frame it, at least from a pain standpoint, fixing constipation from a frequency standpoint almost always correlates with pain relief. So there's some newer agents that have come out that have touted a specific aspect in pain relief, but that actually does not bear out. So a review that I'm on with a colleague of mine, you can see that as bowel movement frequency increases to the right, pain levels drop. There's some correlation across multiple different studies, including some of the newer agents. So anything that fixes the frequency aspect is likely to help on multiple fronts.

So what's the evidence for pretty common over-the-counter things, like fiber? So a meta analysis that was just recently published showed that fiber does, indeed, work, has a benefit in CIC patients. Who need to use a decent amount, greater than 15 grams of supplementation. So you can show this in this plot here that the aggregate benefit of it favors its use, but I have to say that there is a dose limiting side effect to fiber. If you give enough fiber to anybody, you're going to get bloated and be a little more gassy, and patients don't like that. So while the guidelines do suggest fiber, I think we have to come up with at least something a little bit better than fiber, and to move on through there.

So there are laxatives that are widely available, both stimulant laxatives-- I think most people are familiar with Senna, or bisacodyl products. Really, very little limited evidence, I have to say. There's only one small RCT in using bisacodyl for chronic constipation. I think it's about 40 patients. And it showed an effect, but these are not large trials, and there are no RCTs for Senna. So while the recommendations are generally to use these agents, they are safe and sustainable, the evidence basis for it is actually relatively thin. Osmotic laxatives, such as Peg 3350, which is miraLAX, and maxitrate, or milk of magnesia-- there's some better evidence for those, and I'll show that right now.

So what is the evidence for Peg, basically an osmotic laxative? So there have been several placebo controlled RCTs, relatively short trials, done over the years. And this one was published in 2013, and 139 patients that met the criteria for IBSC. Primary endpoint was the number of spontaneous bowel movements per week, and then some secondary endpoints were some of the associated constipated symptoms of constipation. And these error bars always surprise me that this was a positive trial, but when you actually look at the numbers in the aggregate patients that were on the osmotic laxative, actually had an increase. That's in the blue. Maybe just barely compared to placebo, but there was an increase. So this is one of the pieces of evidence in favor of using polyethylene glycol.

How about for CIC? Well, there was a study in a few more people, 304 patients. It was published several years ago, primary endpoint being at least a 50% or better increase in the number of weeks with greater than three complete spontaneous bowel movements. And this was basically giving patients one standard dose of polyethylene glycol for six months, so a pretty long trial. And this actually had a tremendous impact. Basically half of the patients had had a response compared, to a very low placebo response. So the number needed to treat them, about 2.4. So keep that in mind, 2.4 for polyethylene glycol.

So what do we do with fiber, or OTC laxatives don't work? So I remember I showed you this flow diagram, which I'll go back to in a moment. So I think it's important to talk to patients, are you taking it regularly? A lot of patients will take this as a bailout, so they'll get progressively constipated and then turn to fiber or the laxative. But taking it every day is really a better preventive approach. Are they taking enough of a dose? Polyethylene glycol is very safe. You could take two doses, four doses, six doses. I often say six, and we have to think about something else. But one single dose of polyethylene glycol, as in this study, may not be enough for some people, and it has to be tailored. So it may be worth drilling down on that.

But if that's not successful, then we need to take another look at what's going on with this patient, and that's where we would deem them having an inadequate response. So there's a test called anal rectal manometry that actually looks at some of the mechanisms of anal and rectal function. It's important for the expulsion of stool. And in a sizable number of patients, it's not a propulsion problem, but an expulsion problem. So dyssynergic defecation is important to uncover because their treatment is much different than just laxatives.

So I don't know if any of you have ever seen this, but this is testing we do very often at Presby and I'm involved in. Essentially, about a third of patients that have chronic constipation have some form of dyssynergia. And this is basically a mismatch of the anal contraction pattern, which should-- so in here, being red being contractions, this is the pressure band of the anal canal. There's a probe that's measuring this over time, left to right. Patient is asked to push, simulate a bowel movement, and you can see a relaxation and then a return to baseline after the push. That's normal. Pushing should increase rectal pressure, but decrease the outlet pressure as the barrier.

Now, in dyssynergia, patient will be asked, OK, bear down, as if you're having a bowel movement, yet they're anal canal pressures go up. And this is due to some mismatch of the instructions to the external anal sphincter to actually relax. It actually clamps down. So they are, essentially, anal retentive. That's the classic view. There are other subforms of dyssynergia that are more subtle and I won't go into, but this can be unlearned. This is basically a learned pattern that's maladaptive, and actually can drive constipation in a lot of people.

I don't think it would be cost conscious to do this in everyone presenting with constipation. But if they've failed the standard therapy, it's important to uncover this underlying defect, because it can be treatable with biofeedback. So pelvic floor physiotherapist can do this, and anywhere in the community there is someone capable of doing this with patients. And it's very effective. About 80% of patients improve. So it's important to look at that.

There's another test we do along with the functional test called the balloon expulsion test. So this sounds immensely pleasant, to have a balloon put up into the rectum. It's inflated with a standard volume. Patient then walk waddles over to the toilet and then tries to poop out the balloon, and if it takes you more than a minute, then there's something wrong. So that's kind of a functional test of defecation. So a balloon expulsion test that's positive, along with the correct setting here, really cinches the diagnosis of dyssynergic defecation.

But what if that's normal? So if that's normal, what I just mentioned, and they've had an inadequate response to other things, then I think we have to get into some of the oral medications that are available now for constipation. So there are four currently-- well, actually I should say there are four drugs, three of which are currently FDA approved and available, one of which was FDA approved and pulled from the market several years ago. This is the current armamentarium for non over-the-counter, non-osmotic laxative, non-stimulant laxative class of medication. So these are pills, systemic medications for constipation.

So I'll focus on these three, lubiprostone, which was FDA approved in the mid-2000s; linaclotide, which just came out about four years ago; and then naloxegol, a relatively new agent that's FDA approved for OIC. So what's the evidence for some of these? Before getting into that, I have one caveat that I really want to put forth. The systemic therapies that have been thus far evaluated for IBSC and CIC, as well as OIC, generally are larger trials, are industry sponsored trials, and generally have hundreds, if not a thousand or more, patients. And they have shown statistically significant impacts bowel function, but they're marginal, and marginal compared to placebo, and I think that's important to realize.

These are extremely expensive medications. And the effect sizes seem to be very similar to what is present for the trials that looked at polyethylene glycol. There have been no head to head trials between some of the newer agents and polyethylene glycol. These are all placebo controlled trials. So I think we need to kind of keep that in mind. And these are new, very expensive, and heavily marketed agents, but may not be better than some other over-the counters.

So lubiprostone is a chloride channel activator that promotes chloride-rich secretion in the GI tract. And in preclinical studies, it showed increased motility that would be predicted to be helpful in the IBSC, CIC, and even the OIC population. And indeed, that ended up being the case. So large trials-- I'm going to go a little faster, I'm sorry, on time-- but the IBSC trials came from the mid-2000s, about 1,100 patients here that met an older form of the IBSC criteria. This was looking at satisfactory relief, like I alluded to before, rather than a distinct endpoint in bowel frequency.

And sure enough, there was some impact About 10% of the placebo controlled arm met study criteria, and 16%, 17% met the criteria in the treatment arm. And you can show a statistical effect, but that's a number needed to treat of 12.8. For a very expensive medicine, you would expect one response in treating about 13 patients. Not too impressive. When you look at the response rates over time during the study, even the placebo group goes up pretty well. And there is a difference here. So yes, it has an increased effect compared to placebo, but not much.

There are other studies with the lubiprostone that looked in the CIC population. Primary outcome here was the spontaneous bowel movements per week. And indeed, in the black, this is now a treatment dose. It's a little higher than the previous study I showed. This is the higher dose that's currently available for lubiprostone, 24 micrograms twice daily. This showed a pretty robust increase in the spontaneous bowel movements per week above baseline, but placebo did, too. So just the expectation of receiving some benefit created a decent benefit.

In fact, in the first week, they would not technically be constipated, from a frequency definition. And the final fourth week outcome was just a hair shy of meeting criteria from a frequency standpoint, so don't discount placebo. But there was a difference between the rates and the treatment arm and placebo. So a number needed to treat of about 3.3, close to what I showed you for the polyethylene glycol.

So then there's no linaclotide. linaclotide has a much different mechanism of action. It's a guanylate cyclase C agonist. It's minimally absorbed, so it acts, actually, at the epithelial cell level. And agonizing receptors for the GCC receptor essentially releases cyclic GMP, causes activation of the cystic fibrosis transmembrane receptor, which then leads to chloride activation secretion, and so on. So ultimately, a roundabout way of getting more secretion.

The claim is that cyclic GMP also diffuses out the bottom of the cell and then can impact pain fibers that are supposedly very close by, and that's from the marketing of linaclotide. It has been shown to be fairly useful, and I'll show you some of the data for that. So IBSC and CIC are the current FDA indications. So the two pivotal trials that justified its approval, there's a 12 week study in 420 patients that met a mixed criteria of CIC and IBSC. They focused on complete spontaneous bowel movements. You had to have improvement on 3/4 of all the treatment weeks. And this was a dose finding study that settled out at finding that the 300 microgram dose was generally the best one. So it's kind of a U-curve of 300 being better than 600, but better than placebo. There were impacts on their abdominal pain and the mean change and complete spontaneous bowel movements.

Tony Lembo at Harvard had a huge study that justified the approval for CIC using linaclotide. These were two different doses. It was done in 1,200 patients. Similar endpoints to what I just showed you. And indeed, compared to placebo, there was an increase in the response at the study endpoint that I've mentioned. The numbers needed to treat were not too amazing, 8 and 10, respectively, but there was, statistically, a change.

So what else is there out there? I mentioned lubiprostone, linaclotide. There's a new agent called elobixibat, which is a tongue twister, but I've gotten used to saying it. Elobixibat. This uses yet a different mechanism to treat constipation. It's an ileal bile acid reabsorption inhibitor, so essentially inducing a bile acid choleretic-like diarrheal state. Doesn't sound like it's going to be too awesome from other metabolic reasons, but so be it. That is the mechanism. And in pre-clinical trials, phase II trials, there seems to be some dose responsiveness and the increase in spontaneous bowel movements with this agent. It would basically be mimicking almost a cholecystectomy, postcholecystectomy impact on bowel function. So that's a new agent that, given what's happening in the GI world, probably will come out in the next two years, I think, so then we'll have a fourth agent.

So naloxegol is the one of the specific medicines for OIC. It's a peripherally acting, orally available mu-opiate receptor antagonist. So this is essentially undoing the opiate-induced constipation at the colon level. It does not get into the central nervous system, hence you can have the pain benefits of opiates without the constipation. So now we're treating a side effect of chronic opiate use. There was a sub-q, or IV, form of a similar medication called methylnaltrexone. It's very expensive. There's no orally available agent until naloxegol came along. And in the OIC population, two critical trials that were done identically in different populations showed benefits.

So this is some of the data from that. There was an increase in response rates between placebo and the naloxegol, somewhere in the 40 range, with the number needed to treat in the six to eight range. Again, not too amazing, and this was against placebo. There's now an orally available methylnaltrexone, because they have to keep up with the Joneses, so the company that makes methylnaltrexone is different than naloxegol. And that was just FDA approved July 22nd, so now there are two agents for OIC.

There are a couple of other tricks that a gastroenterologist has, at least in my shoes. Patients have often taken these agents and failed. So then I get to meet them for the first time, and I have to think, what else could I do? What other agents are there to try? And the evidence basis for these approaches is much thinner than what I just mentioned. But in essence, it should work. A procholinergic agent-- such as bethanechol, an old agent that's been around for a long time, or pyridostigmine, Mestinon, which is used for myasthenia gravis and usually well-tolerated-- in theory should promote colonic contractions and promote bowel movement transit time.

Colchicine, which is used for gout, often has diarrhea as a side effect, and that side effect can be used to treat constipation through mechanisms that are not entirely clear, but actually can be quite effective. Misoprostol, an agent that's in the prostaglandin family, actually can also stimulate motility through other mechanisms. So there are a couple of other agents that I don't think in general practice would be used, but are in the armamentarium for bailout approaches.

So in summary, CIC and IBSC are common. They have a significant overlap, and they have a significant impact. To have a cost-effective approach to constipation, we really need to minimize-- we need to get to a diagnosis efficiently, at low cost, hopefully, and really focus on over-the-counter therapies that are available, and then really optimize their use, before getting too far down the diagnostic tree. But don't forget about dyssynergia defecation. It confounds the picture in many cases, and actually dramatically changes the treatment plan.

So in someone who has failed the first line agents, I think it would be reasonable to send someone for an anal rectal manometry test. The most currently widely available, orally available pills for medications for constipation, lubiprostone and linaclotide, have very good evidence. It's high quality evidence. But the effect sizes are very small, and there are no head to head trials with very widely available and also safe approaches, such as Peg 3350. So they may be similar, and I think that trial may never happen, but I'd be very curious what would come from that. So I think maximizing osmotic laxative is a good approach upfront. And stay tuned for elobixibat. I think that's going to come out in the next two years, so there'll be a few more options. OK, thank you.

[APPLAUSE]