[MUSIC PLAYING]

SPEAKER: Good afternoon, everyone. Thank you for the invitation to speak to you about Functional Dyspepsia and Gastroparesis. These are relatively common problems in the general population. I'm sure you have individuals in your practices that suffer from these issues. And I wanted to give an overview about the current understanding of some of the pathophysiology of these disorders and some practical management considerations. So have a few disclosures, none of which are relevant to this talk. OK.

So as an overview for what I want to try to get through in the next half hour or so is basically talking about the definition of functional dyspepsia and gastroparesis-- how do we diagnose it, talk about some of the pathophysiology as we currently understand it, and really kind of emphasize that the emerging view is that these two disorders, while semantically different, really might have very highly overlapping mechanisms, urging academic argument about whether or not these are actually truly just different disorders or if there's kind of a spectrum, so to speak. So I think the emerging view is that there's really a spectrum of gastric sensory motor dysfunction. And patients can express various degrees of symptoms in that context. Then we'll go over some of the treatment options for these disorders.

So what do patients say? You know, we say the word dyspepsia, that's a medical term. That's a physician term. But patients don't complain of dyspepsia. That's never the chief complaint in their words.

So what they really complain about are a variety of symptoms that really kind of get molded into one kind of global dyspepsia concept. So they can express fullness very easily with a meal. Not a lot of volume, even drinking four or five ounces and just feeling very full, or having a few bites of a meal and feeling full. So early satiety. Or having a meal, but feeling just particularly full for long periods of time after the meal, so even several hours after eating.

So we're used to feeling full after we're satisfied with eating. But we shouldn't feel full for hours. So that discomfortable feeling of fullness is really what patients remark about. They can express bloating sensations in their abdomen, and almost always express some degree of upper abdominal discomfort, or a sense of pain or burning in that area of their abdomen.

And often these symptoms coexist with mentioning nausea or vomiting. And that may be more or less prominent, depending on what subtype of disorder the patient has. They might also describe a loss of appetite. So all of these symptoms really kind of co-exist in a matrix of more or less present in any one person.

So what's the epidemiology of functional dyspepsia-- which I'll designate as FD-- and gastroparesis, which is also phrased as GP. So basically, these are very common disorders. When you look at the general population, the general population of adults, functional dyspepsia surveys for symptoms would identify about 10% to 20% of patients as having functional dyspepsia. That's huge. I mean, in this room, maybe we're all not the average population. But there are some functional dyspeptics, patients that have those symptoms, in this room. So 10% to 20% is quite high.

Gastroparesis might be a lower prevalence, but still a pretty common disorder. You will have many patients in your practice that have gastroparesis. And so 0.2% to 1% is often the estimate in the general population. The gender skews of these disorders-- functional dyspepsia is a little bit more evenly matched between female and male. Maybe a little bit more female than male, but maybe like a 60-40 split, maybe 55-45.

But in gastroparesis, there's actually a very overrepresented female dominant population. I'm not sure if that's generally known. So it's about 3 to 1. Almost every clinical trial in gastroparesis shows that gender split.

So these disorders affect adults of all ages. So this is 18 and up. And it affects children as well. But in the adult population, there's no specific age that would be more prevalent than another.

So something that might surprise you is the idea that delayed gastric emptying, a test that we often send patients for, gastric emptying test, there can be delayed gastric emptying even in those with functional dyspepsia. So about a third of patients that meet the criteria for functional dyspepsia may have modest delay in gastric emptying. And those with gastroparesis by definition have that.

So that might be a perplexing statement to some of you. And I'll get into some of the details about that. There is a movement to raise the bar for how delayed gastric emptying has to be to call it gastroparesis. So it's really a spectrum.

And then the associated conditions with these disorders-- often with functional dyspepsia, patients describe, or have, comorbid anxiety or depression, maybe a history of early life adversity, and kind of other chronic pain disorders. So there's a certain phenotype of someone that has functional dyspepsia. Those with gastroparesis often have diabetes, or Parkinson's, or scleroderma as classic associations. But in over 50% of patients with gastroparesis, we don't know why they have it.

OK. So how do we define functional dyspepsia? So there's Rome IV criteria. This is like the DSM for functional GI disorders. So there's a committee that meets every 10 years and defines what irritable bowel syndrome is, what functional dyspepsia is. And what's emerging is basically a consensus set of factors that need to be present to invoke the diagnosis, functional dyspepsia.

So patients need to have one or more of the defining symptoms that I mentioned before-- postprandial fullness, early satiation, epigastric pain or burning. And they have to have those symptoms in the absence of some structural disease. So this is what used to be called non-ulcer dyspepsia in older literature. So these are patients that almost always will have been sent for an upper endoscopy to look for some causes for the symptoms. And if they don't have ulcers, if they don't have really fulminant gastritis, and if they don't have H pylori positivity, then we deem them functional dyspepsia.

So the symptoms have to be there for at least some period of time before we invoke the diagnosis. It's not just one week of not feeling well. It's at least in the last three months persistent symptoms on a regular basis with some onset at least six months prior. And they have to experience those symptoms at some frequency on a weekly basis. And I'll go into a little bit more detail about that.

So if nausea and vomiting is present, it may warrant the consideration of another disorder. But I'll tell you that patients that have functional dyspepsia often complain of some degree of nausea. It just might not be the dominant symptom.

So functional dyspepsia, in the Rome IV criteria, has been split into two concepts. One is what's called epigastric pain syndrome. This is basically having specifically pain or burning in the epigastric region at least a day a week, and severe enough to impact one's usual activities. So not five minutes of discomfort, but really incapacitating, really getting your day out of whack, and maybe even leaving work-- not being able to eat.

Postprandial distress syndrome, on the other hand, is perhaps more than three days a week of the fullness and early satiation symptoms. Or it could be potentially some discomfort, but it's really not pain-specific. And it's severe enough to prevent finishing a meal.

So these are really ends of a spectrum that creates kind of an imprecise distinction. So it's really a false distinction to say people are in one of these two bins or the other. 61% of people with functional dyspepsia might have this PDS form. 20% or so might have EPS. And then there's a good population that might have both.

So it might be good for epidemiologic studies and mechanistic studies. But in practice, we often just say you have functional dyspepsia. But what I want to really emphasize is that thinking about these distinctions may matter for the choices of therapy that we offer patients. So there might be some room for personalized approaches.

So gastroparesis defined would be basically patients that have dyspepsia, often a PDS dominant form, but almost always with the context of fairly severe nausea and vomiting as well. So someone with gastroparesis may look a little different than a PDS functional dyspepsia patient. And the defining test is basically delayed gastric emptying in the context of no mechanical obstruction.

So again, these patients that have symptoms are going to have an upper endoscopy. And they're not going to find an obstructive mass, or cancer, or anything like that. So they don't have a mechanical obstruction, and they have these symptoms. If a gastric emptying study is ordered and that's significantly delayed, they have gastroparesis. OK.

So as I alluded to, these two disorders are really kind of blurred a bit because they share some common pathophysiologic mechanism. So on the left here is a picture of a typical stomach. I can't really point to the screen very easily. But on the left, if you can imagine where food moves through the stomach as we eat, there's a process called fundic accommodation.

So our stomach is usually in a relatively contracted state when we're fasted. And when we start to eat, the stomach actually actively relaxes to make room for food. And so that process is called gastric, or fundic, accommodation. The fundus of the stomach being the predominant capacitive part of the stomach.

And that actually is under neural regulation. So it's really important that that process happen, because it dictates the pressure that's occurring in the stomach for a given volume of ingestion. And material stays in the stomach for some period of time in the fundus, but it eventually moves through and starts to get mixed in the corpus, or body, of the stomach, and eventually extruded through the antrum into the duodenum. So there's a highly coordinated movement of contraction and relaxation patterns that the stomach does to handle a meal.

On the right is a listing of many different pathophysiologic mechanisms that could affect patients. And I highlight a few that I'm going to focus on in the talk. So one is the idea that some patients are very viscerally hypersensitive.

So the material that goes in the stomach and the amount of mechanical stretch might be felt more actually as painful when it shouldn't be. They might have impaired fundic accommodation, and they may have delayed gastric empty. And I also circle a brain there because brain matters. And all these symptoms are felt ultimately in the brain. And there's an interplay between brain and gut. So these are the kind of basis of what I'm going to talk about.

So can we measure visceral or gastric hypersensitivity? So this is not done clinically. But in research studies of patients that have functional dyspepsia, compared to those that don't, you can actually demonstrate that the relationship between what distension pressure in the fundus it takes to feel discomfort. So if you imagine having a balloon in your stomach blowing up to some threshold, you would feel uncomfortable at some point. And what is that point.

On the left here-- on the y-axis, excuse me-- is the percentage of subjects that report discomfort at a given distension pressure. And you can see the dotted line are basically normal subjects. And there's a left shift toward more sensitivity to report discomfort at lower pressures in those with functional dyspepsia.

So about 35% of functional dyspepsia patients actually show discomfort to distension pressures that wouldn't even remotely be felt as discomfort-- uncomfortable to a normal person. And that's called allodynia. That's the neurophysiologic term of feeling pain to normal non-painful stimuli. So there's clearly some degree of mechanical hypersensitivity in those with functional dyspepsia.

So what would a patient look like that has that mechanism. They might say I have stomach pain within minutes after eating a meal. So anything I eat, it hurts right away. So that might be a clue that they have hypersensitivity.

Can we measure fundic accommodation? Well, we can. So there's another research tool. But these experiments are very important to kind of ferret out some of the underlying mechanisms.

So in these type of experiments, with some minimal distension pressure to keep a balloon at a certain volume-- or excuse me, at a certain pressure-- if the stomach is relaxing, it may take more volume to maintain that pressure. So that's called a barostat. So eating basically causes gastric accommodation. And the volume change on the y-axis here is the impact of gastric accommodation, or fundic accommodation.

So interestingly, in patients that have functional dyspepsia, they have impaired fundic accommodation. And that seems to be independent of their hypersensitivity status. So basically, a solid line here being the control patients, takes less volume to get to the same pressure. So basically, that implies that it's a stiffer stomach, so to speak.

So patients often will report feeling full after swallowing just a few bites of a sandwich because the pressure to cause a change in volume is a very steep curve. So basically, that's a change in compliance, or impaired compliance.

So does that happen just in functional dyspeptic patients, or is it in anybody? So interestingly, even just being anxious. So this is an experiment I love to show. It just shows that even in normal people and all of us, if you meet any of us anxious with some kind of intervention. So this was a study where they showed a kind of anxious face and played a scary audio kind of clip, and they measured the gastric accommodation reflex.

It actually was impaired in those that were in the anxiety kind of exposed condition, anxious enough to have this balloon down your mouth and do the experiment. But compared to the neutral versus anxiety, there was a difference. So who knows what it would have been without the tool down the throat? But neutral versus anxiety makes a difference.

And so I think all of us need to realize that just thinking about eating actually changes our stomach function. And so patients with these disorders may have an impairment in this brain to gut link.

So can we measure gastric emptying? Sure. This is the gastric emptying study that we often send patients for. And so the gold standard is a four-hour study. So if you locally work with a radiology group and you want to make sure they're doing things right, you might get a test back and they say we did it for 90 minutes, and we extrapolated the half time of emptying. Give them a call and say, no, that's not right. That's not the gold standard way of doing a gastric emptying study. It's truly a four-hour test.

And the reason why has to be four hours is that there's often a lag phase where material is in the stomach. So you can kind of see in the first hour, things kind of sit around and then kind of accelerate out of the stomach. So that's a normal kind of curve of how much material is in the stomach at any one time over four hours.

And on the bottom of the slide here is just an example of the scinitigraphic kind of images that you get during a gastric emptying study. All the ingested meals in the stomach at first, and then basically there's a windowing kind of procedure to see how many counts of radioactivity are left in that stomach window over time.

So if you can see on the diagram, what I've shown is basically a dotted line and a solid red line. And the solid red line is at the classic 10% left after four hours. That's kind of the normal/abnormal curve in most standard textbooks and labs. And technically, one could say you have gastroparesis if there's delay of any retention of anything over 10% of material after four hours.

But what I'll tell you is what's emerging is the idea that really more significant delay might be needed to truly invoke the diagnosis of gastroparesis. This isn't really official yet. But I think there's a sense academically that really 20%, 25% retention is needed to be gastroparesis, and that functional dyspepsia patients may have milder delays. So about a third of patients might have that mild form of delay.

And so what do patients say? I just feel like a boulder's sitting in my stomach for hours after a meal. So when you take all the patients that come to your clinic and say I have some kind of dyspepsia, and they don't say dyspepsia, but they fit the bill for dyspeptic symptoms, and you look at some of these mechanisms--

The Mayo Clinic group had done a very large study of over 1,200 patients that fit this category, many of which already had an upper endoscopy. And they did the gastric emptying test, and they did gastric accommodation tests, which are not standard. And they looked at what mechanisms are dominant in that population. And it's really about a quarter for all of these different categories-- patients that have both impaired gastric accommodation and emptying delays, those that have only emptying delays alone, those that have only gastric accommodation delays, and then those that are deemed to have normal gastric emptying and gastric accommodation. And I bet those are the patients that actually have sensitivity issues.

So the reason I went into some detail about that is that the clinical approach to these disorders really comes down to a personalized kind of medicine framework to try to categorize patients that you might see into the PDS-dominant or EPS-dominant, or maybe nausea/vomiting dominant phenotypes and thinking about the mechanisms that may be driving that. So for PDS-dominant problems, there's probably some problem with impaired accommodation, possibly a delay of gastric emptying. Those with EPS-dominant symptoms almost assuredly have some issue with visceral hypersensitivity. And those with nausea and vomiting disorders may have impaired gastric emptying or any one of a number of mechanisms.

But it really dictates what we might offer to patients, because there are a lot of options for therapies. There's not a lot of data to support the use of these. But there are a lot of medicines you could use. And these include brain-targeted therapies, anti-nausea drugs, neuromodulators, fundus-relaxing drugs, gastric prokinetics, and so on.

So I'm going to go through the data now for what to do for these patients. So I think the baseline therapy for anyone with chronic dyspepsia is to think about changing meal patterns. It's a very American pattern to have three large meals a day at distinct times.

And it's tough for patients to kind of switch that pattern. Our whole lives revolve around that type of meal pattern. We have dinner with our family and so on. But trying to eat smaller more frequent meals is really kind of the bedrock.

And that's not just for gastroparesis. That would be for functional dyspepsia as well. And it makes sense. Because if you're eating less at a time, you might be able to accommodate that smaller volume without getting to a threshold of feeling symptoms.

You need to meet nutrient and hydration needs. So spreading that out over smaller bits over the day is a good strategy. So kind of a grazing pattern, rather than large meals.

Decreasing fat content of meals is really important because the fat content of a meal actually dictates gastric emptying rates. And so even in a normal person, if we ate a fatty meal, the rate of gastric emptying is delayed. So there's actually a nutrient sensing mechanism in our stomach, which is fascinating. So it actually programs how the stomach reacts to a given food. So it's not just volume. It's actually what we eat.

Highly fibrous foods present a mechanical challenge. So breaking that down into the stomach, if you have impaired kind of contractile mechanisms, you might not be able to break down the food enough to get through the pyloris. And so food can sit and create a bezoar.

And then turning to nutri, soft or liquid substances might be really needed for those that are struggling to maintain weight. OK. So hopefully, you don't get to that point.

So what are some of the drugs that we can use for these different mechanisms? So for visceral hypersensitivity, we have a few choices. There are a couple of options for fundic accommodation, couple of options for gastric emptying, and options for nausea-dominant symptoms. So let's get into some of the data.

So if someone has visceral sensitivity, they may actually be sensitive to gastric acid itself. So it kind of makes sense to try acid suppression. And that has been tried for many years. And a number of large-- large for the functional GI realm-- clinical trials have been done. And almost 6,000 patients in a meta analysis showed that there's some benefit of acid suppression for those with dyspepsia. So it's worth a try. That might help some patients. The number needed to treat would be somewhere on the order of 1 in 8.

How about neuromodulators? If someone has visceral hypersensitivity, that might actually help. And there was a nice study in functional dyspepsia with nearly 300 patients that were randomized to receive placebo, amitriptyline or escitalopram. And this was published a couple of years ago. And these were functional dyspepsia patients that they basically randomized to those three arms.

But they did some phenotyping of them. So it's very interesting to look at the mainline figures here, that placebo rates are very high. Almost any functional GI trial, a placebo is always about 30% to 40%, which says a lot in and of itself.

So they felt better-- 40%-- just doing nothing entering the trial. But with the amitriptyline, that number was higher. 53% had adequate relief. Just basically, global symptoms were a little bit better.

But not so with the escitalopram. So there's some specific improvement with amitriptyline, which is interesting. We use that a lot for neuropathies in general, and that seemed to help.

And when they splayed out the patients into those that had more EPS-like phenotypes, almost all of that benefit was in the EPS group. Those that had a PDS-like phenotype saw almost no benefit above placebo. So that's another piece of evidence to suggest that a personalized medicine approach might be really feasible for those with dyspepsia.

So what about neuromodulators and gastroparesis? So the interesting thing here is that we know that these patients have delayed gastric emptying. They might have visceral sensitivity.

But it was not known if it would be helpful. So nortriptyline, very similar to amitriptyline-- so a slightly higher dose of nortriptyline compared to the previous trial I showed you-- but it did nothing for the nausea, bloating, or fullness, or early satiety kind of symptoms. So notice that you don't see pain. So these are non-EPS-like symptoms.

So again, it gives some evidence that if we think about postprandial distress versus epigastric pain dominant symptoms, that might be two different phenotypes of the group. And when actually you look back at the previous trial that I showed you and look at the gastric emptying delay in the subgroups, almost all the benefit that was seen was in the normal gastric emptying group. So it seems that neuromodulators don't work very well in those that have a delayed gastric emptying, or PDS-dominant phenotype.

So neuromodulators for dyspepsia-- other ones, other than the TCA class. There was one small trial using gabapentin. I'll tell you academically. My colleagues around the country, we use gabapentin very readily. But there's just not a lot of data. So this is one of the few papers that actually shows some evidence that it can actually help beyond anecdotal evidence.

But this was an open label retrospective cohort study in only 62 functional dyspepsia patients. But basically, these are patients that often had anxiety and depression, 2/3 of them. They had already tried a TCA, or a SSRI, or an SNRI. And there seemed to be some benefit.

So gabapentin may have some added value in a way that's independent of a TCA. And so these are multiple symptoms and scores that were improved in those that had been exposed to gabapentin, relatively low doses. So that might be worth trying.

What about fundus relaxants for dyspepsia? So in those that might have more of a PDS phenotype, where they have the postprandial bloating, early satiety, there was one nice study using buspirone, which is a 5-HT1A agonist, the serotonin 1A receptor agonist. And that happens to be very important for the gastric fundic relaxation mechanism.

So it makes sense that an agonist could help, and indeed it seems to. So when they did the barostat type studies, it seemed to-- buspirone exposed patients restored their fundic accommodation. And there were some dyspepsia severity score improvement, as you can see in the dark black bar on buspirone.

So what about other neuromodulators? So actually, mirtazapine has been looked at in a number of patients with dyspepsia-- small trials. But there's a growing recognition that mirtazapine can be useful for nausea and vomiting. And also dyspepsia writ large, it's often used in functional GI clinics. And this is a small trial, but showed a symptom benefit with those that were randomized to mirtazapine 15 mg at night.

And particularly, this was a challenging population. These were functional dyspepsia patients that were losing weight, so greater than 10% weight loss from their baseline. So very severe symptoms. And actually, the group that was randomized to mirtazapine saw an increase in their body weight. So not only were symptoms improved-- makes sense they were able to eat a little bit better-- they gained weight. So that's some good evidence for mirtazapine.

So what about speeding up gastric emptying? That would make sense to do that for gastroparesis, you would think. But it actually has been tried also for functional dyspepsia. So cisapride is an old agent, but kind of a stand-in for a relatively reliable gastroprokinetic. And there's some evidence to suggest that it does help a subset of patients.

And if you remember that kind of pie diagram I showed you, there is a good subset of people, where gastric emptying alone might be their issue. And so addressing that and matching that with a prokinetic might make some sense. So about 25% of patients do improve.

And that's not the first line approach. But it could be used. And there are other prokinetics, such as erythromycin, that could be also trialed for those with functional dyspepsia.

But I'll tell you, the surprising finding-- and really the last five years has been somewhat of a controversy in the field of gastroparesis-- is that while the defining biomarker for this disorder is a delay in gastric emptying, it actually correlates very poorly with symptom severity at baseline. And improving gastric emptying, even objectively, does not seem to correlate with symptom improvement.

So this paper caused a lot of stir about six years ago when it was published in one of the flagship GI journals. This looks kind of like a mess when you look at the screen here. But there's a very poor correlation between the degree of gastric emptying improvement on the bottom with symptom improvement. It basically fills the entire space of that diagram. So it's not a very nice, tight linear improvement. So some patients may improve. But the aggregate is a very poor correlation.

So what about anti-nausea drugs and approaches? So there are some patients that have a lot of nausea and vomiting, even if they have functional dyspepsia, which would be the patients that don't have any emptying delay. So the standard medications-- basically, antiemetics are the standard therapy. So the big three-- promethazine, prochlorperazine, ondansetron. I think most people are familiar with these agents.

But some other things that could be tried for patients include antihistamines, such as meclizine, especially if someone has vertigo. And anti-cholinergics, like a scopolamine patch, can also be very helpful. And an emerging use is actually mirtazapine, which I mentioned before.

And increasingly, there's an interest in cannabinoids as being really important for helping with nausea and vomiting. And dronabinol actually can be quite effective. It's very hard to get insurance coverage for it. But it can be a really effective anti-nausea agent and appetite stimulant.

And there's a newer agent which many of you may be familiar with called aprepitant, which came out of the chemotherapy associated nausea and vomiting literature, and FDA approved in that context. But there's emerging interest in using aprepitant for nausea-dominant dyspeptic spectrum symptoms.

And lastly, there are complementary medicine approaches, like aromatherapy. I mean, my clinic is trying to open up the whole toolkit. Because patients have often tried a lot of the agents, and we don't have a lot left to try. But aromatherapy actually can work. There's an emerging data that that surprisingly can be effective.

Acupuncture, acupressure can be tried. And herbal remedies, such as ginger, is kind of a classic. It's used in a lot of women that are pregnant and have nausea in that context. And it can actually help a number of people that have nausea-dominant dyspepsia.

What about psychological interventions? I mentioned that there's a high placebo rate in all these clinical trials for dyspepsia. And it's high for a reason. Because what we think and feel and what we expect to happen matters. And surprisingly, these are among the most effective therapies for functional dyspepsia.

So psychologic therapies have a number needed to treat, around two. There are a lack of very high quality trials. But the data that has been published always seems to be very promising. And I think we need to consider that as valid intervention as any medication that we might offer patients. So particularly, those patients that have coexisting anxiety and depression, therapies, like cognitive behavioral therapy, or other psychotherapies, can be effective.

So lastly, I'll leave with the idea that what other interventions are there. I mean, there are some patients that are very severe, have been very drug refractory. And as you can imagine with any chronic stomach disorder, especially in gastroparesis, patients can't maintain their hydration and nutrition needs.

So when nutrition is really dropping off, we're kind of forced to consider how can we keep someone going. And a trial of a nasojejunal tube feeds is often, in my practice, used as a prelude to committing to a feeding tube if we can't fix the issue. We need to have people tolerate some form of enteral nutrition, ideally.

And if they tolerate tube feeds using a nasojejeunal tube, then we can convert over to a venting gastrostomy with a J tube extension, so basically a so-called GJ tube. I never like to do that. I rarely have to turn to that, even in my practice. But that's technically an option. And patients that go on TPN, even more rare.

But there's emerging some devices and other interventions that are really directed toward the pylorus. So this is kind of coming from a perspective where impaired gastric emptying is a problem with pyloric spasm, or pyloric-- just discoordination and essentially paralyzing the pylorus so that it can't contract-- has been thought of as an approach. But that's failed placebo controlled trial. So basically injecting Botox into the pylorus. So that has not held up over time.

Similarly, there are no sham controlled trials for pyloroplasties, or basically incising the muscle of the pylorus, to try to have a drainage procedure. So that can be done surgically or endoscopically in a procedure called G-POEM. And even just cutting the stomach partially out, so a partial gastrectomy, or a Roux-en-Y. No formal studies on that.

And to the right, I'm showing you a meta analysis that we had published about gastric electrical stimulation. So some of you might have heard that there's something people often call a gastric pacer, but it doesn't really pace. It's really more of like a gastric Tens unit. But the basically implanted electrodes that kind of go off at a certain stimulation frequency. And that has been shown to help some patients.

But when you look at the open label trials of gastric electrical stimulation, there was an effect size. But when they blinded patients to whether the thing was on or off, no benefit. So I do not recommend that for my patients.

So in summary, there are many different mechanisms that might be important in functional dyspepsia and gastroparesis. I think there's really a spectrum. And so these disorders are starting to blur, even though we can make the distinction semantically. It's really a spectrum of sensory motor dysfunction.

And I think personalized medicine approaches are feasible if we really listen to what patients are saying and categorize them by what we think the main mechanism might be. Rather than a pure trial and error approach, we might be able to hit the right drug for the right mechanism right away. And there are lots of options. But it's certainly an emerging field.

So thank you for your time. We welcome to take any questions.

[APPLAUSE]