Episode Book

EPISODE #5694

Prokinetics When the Emptying Test Is Normal

PUBLISHED	3 October 2026 at 09:33 UTC
DURATION	21:40
LISTEN	myweirdprompts.com/episode/prokinetics-normal-gastric-emptying/
HOSTS	Corn, Herman, Hilbert
SCRIPT MODEL	deepseek-flash
VOICES	chatterbox-regular (chatterbox-local)
PIPELINE	V5.2
BOOK GENERATED	19 October 2026 at 17:39 UTC

SYNOPSIS

Daniel had his gallbladder out seven years ago and has had digestive trouble ever since — visible distension, a sense that food isn't moving, and a gastric emptying study that came back normal. He wants to know whether modern prokinetics are safe for long-term use, and whether they can still be justified when the test is negative. It turns out the answer hinges on something stranger than a drug label: the gap between what a test measures and what a body actually does. This episode walks through the four-hour egg test and its ten-percent threshold, the five distinct ways it can come back clean while something is genuinely wrong, and the twenty twenty-three evidence suggesting prokinetic symptom relief may have nothing to do with speeding up emptying at all.

TRANSCRIPT



Corn

Daniel wrote in this week with a problem I think a lot of people listening are going to recognize, and it sits right on the fault line between what a test says and what a body actually feels. He had his gallbladder out seven years ago. Since then, a whole litany of digestive trouble, and the two worst pieces are visible distension and this strange sense that things just aren't moving after a meal. He tested negative on the egg test for gastroparesis. But he points out that plenty of patients with functional dyspepsia and visible distension test negative too, so he's not sure the negative means much. So he's asking about prokinetics. The classic drugs in that class carry black box labels. Have modern drugs been developed that are safe for long-term use? And in the context of a negative gastric clearance study, is the use of prokinetics still considered, and can it be justified? Then he adds his own sharp observation, that he can feel like things aren't moving properly, but that doesn't necessarily correlate to what's actually happening inside his body.



Herman

There's a lot packed in there, and the last part of it is the part he may not realize is the most important.



Corn

So today we're taking it apart. The test, the label, the drugs, and the gap between all three.



Herman

Let's start with the two labels, because the only thing separating them on paper is the test Daniel already took. Gastroparesis requires two things. Symptoms suggestive of gastric retention, so nausea, vomiting, early satiety, postprandial fullness, bloating, upper abdominal pain. And objective evidence of delayed gastric emptying in the absence of mechanical obstruction. Camilleri's work over the last few years lays this out clearly. You need the symptom picture and you need the number from the study. Both.



Corn

And functional dyspepsia?



Herman

Same symptoms, roughly. Postprandial fullness, early satiation, epigastric pain or burning. Rome criteria. The one thing it does not require is delayed emptying. That's the whole distinction. Take two patients with identical complaints, run the egg test, one retains more than ten percent at four hours, one doesn't, and they end up with different diagnoses and different paperwork.



Corn

Same suffering, different folder.



Herman

Essentially. And the epidemiology makes this concrete. Definite gastroparesis, meaning documented delayed emptying, runs about twenty-one and a half per hundred thousand people. Women outnumber men somewhere between two and four to one. The big US study, eighty-two point six million patients, found type two diabetes the most common cause at just over half, then postsurgical at fifteen percent, medication-induced at about eleven and a half, idiopathic at eleven, type one diabetes at under six.



Corn

Postsurgical being the second biggest bucket.



Herman

Which matters here. Post-cholecystectomy patients show up in a recognized diagnostic category, not a rounding error.



Corn

And the test itself. The number that draws the line.



Herman

Four-hour gastric emptying scintigraphy. Radiolabeled egg-white meal, imaging at intervals, and the threshold is retention greater than ten percent at four hours. The AGA's twenty twenty-five guideline conditionally recommends against two-hour testing and in favor of the full four hours, because a two-hour read misses too much. Severity grading after that is mild at ten to fifteen percent retention, moderate at sixteen to thirty-five, severe above thirty-five.



Corn

So that's the definition. Now here's the problem. The test that separates these two labels is not the body. It's a snapshot. And it can come back clean in at least four distinct ways while something is wrong.



Herman

Four, and they're independent. Any one of them can produce the mismatch. The first is the simplest and the most unsettling, which is that symptoms just don't track with emptying results. Maurer's group in twenty twenty-one said it flatly. Dyspeptic symptoms are not well correlated with gastric emptying results. That's not a hedge, that's the finding.



Corn

Then what did they actually measure?



Herman

Three hundred sixty-three patients. Just under forty-eight percent had delayed solid emptying. But nearly nineteen and a half percent had delayed small-bowel transit. And here's the number that should stop the room. Six point six percent of the patients with normal gastric emptying still had delayed small-bowel transit.



Corn

So the stomach is fine and the problem is further down.



Herman

The delay is downstream of where the test is looking. And those patients, the ones with isolated small-bowel transit delay, scored high on postprandial fullness, stomach fullness, nausea, bloating. The full dyspeptic picture, with a normal stomach-emptying result. If your test only photographs the stomach, you cannot see a slowdown in the small bowel. It's like checking whether a road is clear by looking at one intersection.



Corn

That's mechanism one. The test is aimed at the wrong stretch of pipe for some patients.



Herman

Mechanism two is the snapshot problem, and Lacy's group just published the cleanest demonstration of it. They put patients on a six-day ambulatory wearable patch monitor, reading myoelectric activity continuously, and compared that to the gastric emptying study.



Corn

And?



Herman

The emptying study identified delayed emptying in only eighteen percent. Rapid in twenty-two percent. Normal in sixty percent. But the study results showed no correlation with the multiday myoelectric readings. None. And there was significant day-to-day variability in gastric activity.



Corn

So a single four-hour window on one particular Tuesday.



Herman

Their conclusion, verbatim, is that the study provides only a brief physiologic snapshot that may not accurately reflect daily function. Which is a very polite way of saying the test can be wrong, and not because the lab made a mistake. Because the thing it's photographing changes from day to day.



Corn

That's a rough thing to hear if you're the patient who fasted for it.



Herman

Mechanism three is where it gets interesting. There are multiple pathophysiologic mechanisms that produce the same symptom picture. Camilleri and Jencks laid this out in twenty twenty-five. Symptoms can arise from antroduodenal hypomotility, from pylorospasm, from impaired gastric accommodation, from visceral hypersensitivity. Not just from slow emptying.



Corn

Unpack accommodation, because that's the one people don't know.



Herman

The stomach is not a bag. It's a muscular organ that actively relaxes to receive a meal. That reflex is called accommodation. A normal stomach, when you eat, loosens up to hold the volume without a spike in pressure. If accommodation fails, the stomach stays stiff, and you get distension and fullness and early satiety even though the emptying rate is perfectly normal. The food isn't moving slowly. The container isn't accepting it.



Corn

So you can have a normal emptying number and a stomach that refuses to stretch.



Herman

And the egg test, as usually reported, doesn't tell you about accommodation at all.



Corn

Wait. Usually reported. That phrasing sounds deliberate.



Herman

It is. Mechanism four. Farghaly and colleagues showed this year that fundal accommodation can actually be assessed on the standard emptying images you already took. There's a ratio, fundal-to-total-stomach, and a cutoff of zero point six six nine distinguished normal from abnormal accommodation with seventy percent sensitivity and ninety-two point three percent specificity.



Corn

So the scan that came back negative was sitting there the whole time holding the answer.



Herman

Potentially. The data is in the images. It just isn't routinely extracted and reported. Somebody has to decide to look for it.



Corn

That's a strange kind of failure. Not a missing test, a missing question.



Herman

And then mechanism five, which is really the meta-point. Cangemi, Stephens and Lacy titled a paper in twenty twenty-three, quote, Misdiagnosis of Gastroparesis is Common. Unquote. It goes both directions. People get labeled with gastroparesis who don't have delayed emptying, and people whose emptying is documented get labeled with something else. And the Rome Foundation consensus with Schol in twenty twenty-five reaffirms the requirement. To call it gastroparesis you need documented delayed emptying.



Corn

So the negative test formally excludes gastroparesis. Daniel's label becomes functional dyspepsia.



Herman

By the book, yes. And the symptoms do not care what the label is. They behave identically.



Corn

Here's the thing I keep circling. Daniel said it himself. I can feel like things aren't moving, but that doesn't necessarily correlate to what's actually happening inside my body. He wrote that as a caveat, almost apologetically, like he was conceding his own perception might be unreliable. And the literature says the opposite of what he assumed.



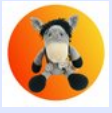
Herman

It says it in both directions. Symptoms don't correlate with emptying. That's Maurer. And in Lacy's data, the test didn't correlate with the actual measured activity either. His sensation is not a less reliable signal than the test. In some ways it's a longer-running one. He has seven years of continuous data on his own body. The scan has four hours.



Corn

The patient is running the better experiment.



Herman

That's not a comfortable thing for a clinician to hear, but the sequencing supports it.



Corn

There's one more piece I want to flag before we get to the drugs. The test meal itself. It's a radiolabeled egg-white meal. The FDA has also approved a carbon-thirteen spirulina breath test as an alternative, and there was a pilot study this year validating a plant-based, allergy-friendly version of the meal.



Herman

Which matters more than it sounds, because if you can't complete the standard test, the alternative is an uninterpretable result, and that quietly narrows who gets diagnosed at all.



Corn

So the test is imperfect. The question is what you do with that fact. And that's where prokinetics come in.



Herman

Agreed. And part one was why the test can be negative. Part two is what to do about it, which is a different argument entirely. Prokinetics are agents that accelerate gastric emptying or improve gastroduodenal coordination, acting on the enteric neuromuscular apparatus. Four main classes. Dopamine D2 antagonists, so metoclopramide and domperidone, which block dopamine-mediated inhibition of gastric motility. Metoclopramide also has some 5-HT3 antagonist and 5-HT4 agonist activity on top of that. Then macrolide motilin agonists, erythromycin being the classic, which stimulate motilin receptors to drive antral contractions. Then 5-HT4 agonists like prucalopride, which enhance acetylcholine release to promote peristalsis. Then ghrelin agonists, relamorelin being the one that's been studied.



Corn

That's a lot of mechanisms pointed at the same symptom list.



Herman

And here's the nuance that reframes the whole question. Goelen and colleagues, in twenty twenty-three, asked a question that sounds almost naive. Do prokinetic agents provide symptom relief through acceleration of gastric emptying? And the paper is framed as an update and revision of the existing evidence. Which is a careful way of saying the assumption may be wrong.



Corn

So the symptom relief might not be coming from the emptying speed at all.



Herman

That's the implication. The benefit may be dissociated from emptying acceleration. It might work through accommodation, through relaxing the pylorus, through visceral pain pathways. Which is exactly why a prokinetic could help someone whose emptying study looks normal. If the drug works on something the test doesn't measure, the test result is irrelevant to the question.



Corn

That's the strongest answer to Daniel's actual question, and it's also the strangest. The drug might be justified precisely because we were wrong about why it worked.



Herman

Now the warnings, because this is where the conversation usually stops. Metoclopramide is the only FDA-approved medication for gastroparesis. In two thousand nine the FDA issued a black box warning for tardive dyskinesia risk with long-term or high-dose use. Tardive dyskinesia is a movement disorder, involuntary movements, and the warning was serious and appropriate at the time.



Corn

Black box on a drug you might take for years is not a small thing. Give me the actual numbers.



Herman

This is where the revision comes in. Historical regulatory and guideline estimates put the risk somewhere between one and ten percent. Rao and Camilleri in twenty ten argued the real risk was likely under one percent. Then Al-Saffar and colleagues in twenty nineteen put it at roughly zero point one percent per thousand patient-years. And they described that as far below the previously estimated one to ten percent. Cangemi and Lacy in twenty twenty-one wrote that the risk of tardive dyskinesia with metoclopramide has likely been significantly overestimated historically.



Corn

So the number in the black box is not the number.



Herman

The warning is real. The risk estimate behind it has been revised downward by roughly an order of magnitude, maybe more, over the last fifteen years. And the risk is not evenly distributed. High-risk groups are elderly women, diabetics, patients with liver or kidney failure, and anyone on concomitant antipsychotics.



Corn

Those are the people you'd think hardest about.



Herman

And when tardive dyskinesia does occur, the movements most often affect the face, sixty percent, and the tongue, forty-five percent. In one older case series, seventy-one percent of the followed patients still had persistent movements six months after stopping the drug. Which is why the caution around long-term use exists at all. It's a low-probability, potentially irreversible harm, and that combination is why it carries a box instead of a footnote.



Corn

Low probability, high permanence. That's the actual shape of the risk.



Herman

Domperidone is the other classic, and it carries cardiac warnings. QT prolongation, sudden cardiac death risk. Which is why the AGA guideline conditionally recommends against it as first-line therapy.



Corn

So that's the old guard. Have the modern drugs arrived?



Herman

The honest answer is progress is real but incremental, and no clean fully safe long-term prokinetic has fully arrived. The AGA guideline in twenty twenty-five, Staller and Parkman and the rest, twelve recommendations. Conditional recommendations for metoclopramide and erythromycin as initial pharmacologic treatment. Conditional recommendations against, as first-line, domperidone, prucalopride, aprepitant, nortriptyline, buspirone, and cannabidiol. And against routine initial use of G-POEM and gastric electrical stimulation, reserving those for refractory cases.



Corn

What's the guideline's own summary line?



Herman

That there are still considerable unmet needs in the treatment of gastroparesis. That's the guideline authors saying it, not a critic.



Corn

Which is a remarkable thing for a guideline to admit.



Herman

Now the pipeline. The most promising class for a modern safe long-term option is the highly selective 5-HT4 agonists. Cangemi and Lacy wrote in twenty twenty-one that the new highly selective 5-HT4 agonists appear safe and may be effective in improving symptoms of gastric emptying. That's the class to watch. Tradipitant is an NK-1 antagonist that went through a Phase three trial in diabetic and idiopathic gastroparesis, but it's primarily anti-nausea rather than prokinetic, so it addresses a different part of the problem. Relamorelin, the ghrelin agonist, has been studied but isn't a mainstream approved option.



Corn

And prucalopride, which is in the class you just called most promising?



Herman

Studied in gastroparesis, Carbone and Andrews both, but the AGA guideline does not endorse it first-line. The class shows promise, that specific agent hasn't earned the endorsement yet. And there's a metoclopramide nasal spray that went through a Phase three trial in women with diabetic gastroparesis, which is a delivery-route innovation rather than a new safety profile.



Corn

Same molecule, different door.



Herman

If you can't swallow or you're nauseated, the route matters. But the risk profile is unchanged.



Corn

Bring it back to Daniel. Negative egg test, real symptoms, seven years in. Is considering a prokinetic defensible?



Herman

Yes, with nuance, and I'd frame it on five grounds. First, the test is imperfect. A snapshot with no correlation to multiday myoelectric activity, and it misses small-bowel transit delay in about nineteen percent of symptomatic patients. A negative result does not prove normal function. Second, symptoms don't equal transit. Maurer and Camilleri both. Third, and this is the one that changes the argument, prokinetics may work through non-emptying mechanisms, which is Goelen's question. Fourth, the formal diagnosis still requires the positive test, so a negative test shifts the label to functional dyspepsia. But functional dyspepsia is treated with overlapping agents, and prokinetics get used in FD.



Corn

And fifth?



Herman

The AGA guideline supports metoclopramide and erythromycin as initial pharmacologic therapy in gastroparesis. And the risk-benefit calculus for a symptomatic patient, using the modern tardive dyskinesia estimate of around zero point one percent per thousand patient-years, can favor a time-limited, monitored trial rather than nothing.



Corn

Which is not the same as saying a negative test means there's no treatment. It's that the label shifts, and the conversation shifts to symptom-targeted therapy.



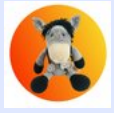
Herman

The negative test doesn't mean nothing is wrong, and it doesn't mean no treatment is possible. It changes what you call it and how you justify what you try next. With attention to risk factors, dose, and duration. The risk factors are the elderly, diabetics, anyone with liver or kidney problems, anyone already on antipsychotics.



Corn

Keep the trial short and watch the face and tongue.



Herman

That's the practical shape of it.



Hilbert

You said four hours on the test. The one I knew about ran two.



Herman

The guideline moved against two-hour testing specifically. The retention threshold only becomes meaningful at four.



Hilbert

I used to drive a machine that did the counting. Radioactive egg, patient on the table, gamma camera above. I'd take the images at one hour, two hours, four. The four-hour frame was the one the physician actually read. The rest were there so he could see the shape of it.



Corn

The two-hour frame existed as context.



Hilbert

Context, and if the patient had to leave early, that's what you had. I remember a woman with diabetes, nine years of vomiting after meals, the study came back clean at four hours. The physician wrote normal gastric emptying and moved on. She was back four months later. Same complaint. She wasn't inventing anything. The number just wasn't where they were looking.



Herman

That matches the transit data almost exactly. If her delay was downstream of the stomach, that clean four-hour read was never going to catch it.



Hilbert

The gamma camera only saw the stomach. There were other studies for the small bowel. They cost their own slot on the schedule, and most of them didn't get ordered.



Corn

The test wasn't wrong, it was aimed.



Hilbert

The equipment did what it said. The order was for the stomach, so we photographed the stomach.



Corn

That's the thing. The gap between what we can measure and what we routinely measure is where patients like Daniel live.



Herman

Which is the right place to leave it. If the test is a snapshot and the body is a movie, what would it take to diagnose the movie? The six-day wearable patch is a start, but it isn't standard. Fundal accommodation can be pulled off the same scan, but usually isn't. Small-bowel transit can be added, and often isn't. Every one of those is a decision somebody makes about what to look at, not a limit of the instruments.



Corn

On the drugs, the honest answer is the promising class is the highly selective 5-HT4 agonists, and they aren't here yet. The guideline's own words are that there are still considerable unmet needs. That's where it actually stands.



Herman

If this episode helped you understand the gap between a test result and a symptom, and why that gap is a real place for people to live, leave a review. It helps other people find the show. Thanks as always to our producer, Hilbert Flumingtop.



Corn

This has been My Weird Prompts. We'll be back soon.