Episode Book

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Gut-Brain Drugs: Why Old Antidepressants Help Bloating

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SYNOPSIS

A listener wrote in after being prescribed low-dose amitriptyline for bloating and fullness that have followed him since his gallbladder came out seven years ago. It didn't do much — so he came back with three sharp questions: what's the actual mechanism, why are the old tricyclics still the go-to drugs despite their side effects, and is anything new being designed specifically for functional dyspepsia? This episode works through the gut-brain axis, visceral hypersensitivity, gastric accommodation, and the duodenal frontier, and lands on an uncomfortable finding: the drugs that work are the drugs that are messy. We also flag an honest limit — post-cholecystectomy symptoms are not the same as idiopathic functional dyspepsia, and the evidence base is an extrapolation.

TRANSCRIPT



Corn

Okay, so I have read this one three times, and every time I get to the same sentence, and it makes me want to lie down.



Herman

Which sentence?



Corn

"Less than ideal." Daniel describes taking a drug that is famous for making people fat and sleepy to fix a stomach that has been a problem since his gallbladder came out seven years ago, and then he says, and I quote, using these drugs seems less than ideal.



Herman

That's the politest way anyone has ever described a bargain with a pharmacist.



Corn

So here is what he wrote in. He was prescribed low-dose amitriptyline for postprandial fullness and bloating, the stuff that has been with him since the cholecystectomy. It did not do much. Herman, you said on air that you weren't surprised, that the drug looked poorly fitted to the symptoms he described, and that mirtazapine might fit better, though it is notorious for weight gain. Daniel heard all of that and came back with three questions, and they are good ones.



Herman

Go.



Corn

Question one, the mechanism. If postprandial bloating after gallbladder surgery has a credible biochemical explanation behind it, why would a drug that acts on nerves and brain signaling help at all? What is the proposed mechanism? Question two, the pairing problem. The drugs that get used are mostly the old tricyclics, precisely because they are less selective than modern psychiatric drugs, which also means they have a much worse side effect profile. Has anyone mapped specific drugs onto specific manifestations of functional dyspepsia, so the trial and error is less miserable for patients and clinicians? And question three, is anything newer being developed, maybe something designed from the start for functional dyspepsia that avoids the central nervous system entirely?



Herman

That is a full syllabus.



Corn

It is. And the first answer quietly reframes the other two, so let's start there.



Herman

Start with what functional dyspepsia actually is, because the whole conversation hinges on it. It is a disorder of gut-brain interaction. Not a structural disease. You can scope these patients and find nothing. What is wrong is sensation and motility signaling.



Corn

Which means the problem is often not that the gut is failing. It's that the gut is reporting more loudly than it should.



Herman

And it splits into two main subtypes under the Rome criteria. Epigastric pain syndrome, which is pain and burning, and postprandial distress syndrome, which is fullness, early satiation, nausea. Daniel's symptoms sit squarely in the second bucket. Fullness after eating, bloating, the sense that a meal was three sizes too big.



Corn

So when a clinician hands someone a low-dose psychiatric drug for this, what are they actually doing?



Herman

They are using it as a neuromodulator. At a low dose, amitriptyline or mirtazapine is not being used to treat depression or anxiety. There is no claim that Daniel's gut is sad. The dose is below the range where you would expect mood effects, and the target is the signaling between the gut and the central nervous system. The drug is raising a sensory threshold. That is the whole point of the exercise.



Corn

It's a euphemism, though. Neuromodulator is what you call an antidepressant when you want the patient to take it.



Herman

It is partly a marketing term, and partly an honest one. The pharmacology changes with dose. At ten or twenty-five milligrams of amitriptyline, you are mostly hitting receptors other than the serotonin transporter. Anticholinergic effects, histamine, alpha-2. That is a different drug, functionally, from the hundred-milligram version. So the word is defensible. But yes, it exists partly so a gastroenterologist doesn't have to say the word antidepressant to a patient who came in about bloating.



Corn

So mechanism one is visceral hypersensitivity. Explain what that actually means, because I want it concrete.



Herman

It means the gut is perceiving normal events as painful or overwhelming. A normal amount of gas in a normal loop of bowel produces a signal that a healthy gut would filter out, and in functional dyspepsia that signal arrives at full volume. The stretch receptors in the stomach wall fire at a lower threshold. Downstream, in the spinal cord and brainstem, the processing is amplified. So the problem is not the volume of the balloon. It is the sensitivity of the alarm.



Corn

And a tricyclic raises the threshold.



Herman

It dampens the sensory processing along that axis. There's a rat model from last year where they gave amitriptyline and measured what changed. It raised serotonin concentrations in plasma and in gut tissue, it lowered visceral sensitivity, and it altered the expression of the 5-HT2B receptor, phospholipase C beta-2, the IP3 receptor, and a calcium-activated chloride channel called ANO1 down in the gut tissue.



Corn

Say the important part.



Herman

The important part is what it did not do. It did not significantly change gastric or intestinal transit rates. It did not speed anything up. Which means the benefit, in that model, was sensory. It was the alarm being recalibrated. Not the pipes being unblocked.



Corn

That is a very clean finding for a messy topic.



Herman

It is, and it matters for Daniel's question, because it says the drug doesn't need to be a prokinetic to help. It needs to be a volume knob.



Corn

Mechanism two is gastric accommodation. This is the one that hits closest to home for Daniel, isn't it?



Herman

Very much. Accommodation is the stomach's ability to relax and expand when food arrives. A healthy stomach can hold well over a liter of a meal without the pressure inside climbing much, because the fundus relaxes to make room. In postprandial distress syndrome, that relaxation is impaired. The stomach does not give. So a normal meal volume lands in a stomach that is still the size it was before the meal, and the sensation is exactly what Daniel describes. Fullness. Bloating. A meal that was not large feeling like it was enormous.



Corn

So the complaint is real, and it's mechanical, and it's not in his head.



Herman

It's a failure of a reflex. The stomach is supposed to yield, and it doesn't yield.



Corn

Which connects to something we have said before, that the phrase functional gastrointestinal disorder can function as a way to stop investigating.



Herman

And it shouldn't, because there is a mechanism here. Impaired accommodation is measurable. It's a reflex arc, it's vagally mediated, it's a real thing that is not working.



Corn

Mechanism three is the duodenum. This is the newer one.



Herman

The duodenum is the first part of the small intestine, right past the stomach, and it turns out it is not just a pipe. It has a mucosal barrier, it has a resident immune population, it has a microbiome, and in functional dyspepsia there is growing evidence of impaired barrier function, low-grade inflammation, and dysbiosis right there. That is a newer



Herman (continued)

frontier, and it matters for the last part of Daniel's question, because if the problem lives in the duodenal mucosa, the smart drug targets it locally instead of going through the brain.



Corn

You have been very careful with the word duodenum. Say it like you mean it.



Herman

Duodenum.



Corn

Beautiful.



Herman

Can I get to the part Daniel actually asked about?



Corn

Please.



Herman

His framing was that postprandial bloating after gallbladder surgery has a credible biochemical explanation, and he is right. The biochemical story is well supported. The macronutrient most consistently implicated in functional dyspepsia symptoms is fat, and fat triggers symptoms through cholecystokinin pathways. CCK is a chemosensory and mechanosensory signal. It's released in response to fat in the gut, it mediates a whole cascade of digestive responses, and after a cholecystectomy the bile handling and the CCK signaling around a fatty meal are plausibly altered.



Corn

So a fatty meal hits a system that has been rewired, and the rewired system overreacts.



Herman

Right. The gallbladder is a storage tank for bile, and once it is gone, bile delivery is no longer pulsed the way it was. The coordination changes. So yes, there is a credible mechanical and biochemical explanation for why a fatty meal produces trouble in a post-cholecystectomy patient.



Corn

Now the part I actually want to hear you work through. If that explanation is correct, and I am persuaded it is, why would a neuromodulator do anything?



Herman

Because it doesn't have to fix the cause. It has to interrupt the symptom-generation pathway downstream.



Corn

Say that again in a way I can hold.



Herman

Think of it as two separate problems. Problem one is the fat and the CCK and the altered bile physiology. That is real. Problem two is that the gut is now hypersensitive, so the normal postprandial events that follow a meal get amplified into the sensation of fullness and bloating. A neuromodulator does nothing about problem one. The bile physiology is exactly as it was. But it can raise the sensory threshold in problem two, so the same events produce a smaller perceived symptom.



Corn

The fire is still there. You just turn down the smoke alarm.



Herman

And that is a legitimate therapeutic strategy, not a cheat. A lot of medicine works this way. You do not always get to fix the cause.



Corn

I want to be honest about a limit here, though, because it is the kind of thing that gets glossed.



Herman

Go on.



Corn

Daniel's symptoms are post-cholecystectomy. That is not the same thing as idiopathic functional dyspepsia. The evidence base for neuromodulators lives in functional dyspepsia and specifically in the postprandial distress subtype. It does not live in post-cholecystectomy syndrome. So when we say a neuromodulator could help here, we are extrapolating from adjacent populations.



Herman

That's right, and a clinician would reasonably want to look at other post-cholecystectomy contributors first. Bile acid malabsorption is one. Sphincter of Oddi dysfunction is another. Those have their own logic and their own treatments. So the honest statement is: the mechanism is plausible, the extrapolation is reasonable, but it is an extrapolation.



Corn

Which is exactly the ground where trial and error happens. Which brings us to his second question.



Herman

Why the old tricyclics. And the answer is going to sound almost perverse.



Corn

I am ready.



Herman

The tricyclics have the best evidence, and they are the only neuromodulators named in the European, the American, and the Canadian guidelines. That is the state of play. When you look at the review literature, the tricyclics sit at the top and everything else is graded below them as inconclusive.



Corn

But the reason they work is the same reason they hurt.



Herman

Because they are less selective. Amitriptyline and imipramine hit a broad spread of receptors. Anticholinergic, antihistaminergic, alpha-2, and more. The therapeutic benefit in functional dyspepsia appears to come from that breadth, not from serotonin reuptake inhibition on its own. That is the part that surprised me when I first read it.



Corn

Because the obvious modern intuition would be, take the older drug, clean it up, keep the part that works, remove the part that causes side effects. Make an SSRI out of it.



Herman

And that is precisely what does not work. SSRIs and SNRIs have not shown benefit in functional dyspepsia. They have been tried, and they have failed to separate from placebo in the way the tricyclics do. So the field is stuck with the drugs that work being the drugs that make you drowsy, dry, and in some cases put weight on you.



Corn

It's an ugly result. It basically says the mechanism is the mess.



Herman

It says the therapeutic action is spread across multiple receptors, and we do not yet know how to isolate the useful part from the harmful part. So the less selective drug is the effective drug. That is a uncomfortable finding.



Corn

And this is where your mirtazapine suggestion lands. You said on air that it might fit Daniel better.



Herman

Mirtazapine is not a tricyclic. It is a tetracyclic, and its receptor profile is different. It has been studied in functional dyspepsia in patients who did not respond to the standard options. There was a randomized trial of a hundred and twenty patients where mirtazapine was added at fifteen milligrams nightly to standard therapy, and dyspeptic symptoms improved significantly over eight weeks. Symptom scores went from around eleven and a fifth down to around seven and a half. Highly significant. And crucially, the patients in that trial were the ones who had already failed the first-line drugs.



Corn

So it works in the population that has run out of options.



Herman

Which is exactly the population Daniel is in. It also has a specific fit for his symptoms. Mirtazapine is useful for nausea and early satiation, the postprandial distress cluster. It antagonizes the 5-HT3 receptor, which is an anti-nausea mechanism, and it stimulates appetite. So for someone whose complaint is fullness and feeling full too early, it is a coherent choice.



Corn

And the weight gain?



Herman

Real, and quantified. In a pediatric study, eighty-four percent of patients on mirtazapine gained weight, with a mean gain around four kilograms. Undesired weight gain was the most common adverse effect, and there was a significant correlation between the starting dose and how much weight was gained. So when you say notorious, you are not exaggerating.



Corn

It's the same trade as the tricyclics. You are buying symptom relief with a side effect you might not want.



Herman

And in Daniel's case, that trade is worth naming out loud, because he already said the amitriptyline gave him brutal fatigue without helping. So the question is not, do you want a drug with side effects. The question is, which side effect are you willing to accept in exchange for relief.



Corn

Now his second question, the mapping. Has anyone actually done it, or is it all vibes and rechallenge?



Herman

There is a real framework now. A review by Hanna-Jairala, Tack and Drossman develops what they call a symptom-directed approach, and it maps drug classes onto symptom profiles.



Corn

Lay it out.



Herman

For epigastric pain syndrome, the pain and burning subtype, they recommend predominantly central neuromodulators. That means the tricyclics and mirtazapine, the drugs that reduce visceral hypersensitivity centrally. For postprandial distress syndrome, the fullness, early satiation, and nausea subtype, they recommend predominantly peripheral drugs. The prokinetics. Metoclopramide, domperidone, levosulpiride, cinitapride, prucalopride, itopride. Drugs that act on the gut without primarily acting on the brain.



Corn

Hold on. I want this on the record. Daniel's symptoms are postprandial fullness and bloating. That is the second bucket.



Herman

It is.



Corn

So the framework says that for his symptom cluster, the better-matched class is the peripheral prokinetics.



Herman

That is the framework's logic. And it does line up with what I said before, that the amitriptyline looked poorly fitted. If you follow the symptom-directed approach, the mismatch is not a mystery. The drug was chosen from the wrong half of the table.



Corn

Which is a slightly awkward thing for us to be agreeing about on air, because you were the one who said it first.



Herman

I would rather be right than consistent about how surprised I am.



Corn

Do I get to point out the framework has holes in it?



Herman

Please, because it does. First, the authors themselves say that high-quality subtype-specific trials are needed to strengthen the evidence base. So this is a rational clinical framework, not a validated algorithm. It is a reasonable way to choose a drug. It is not a lookup table where you plug in a symptom and get an answer.



Corn

And second?



Herman

Second, the subtypes are messier than the label suggests. When you actually phenotype these patients, about forty percent of the patients classified as epigastric pain syndrome turn out to have postprandial epigastric pain. And half of the postprandial distress patients report postprandial pain. So the clean split we just described does not survive contact with real patients.



Corn

Which means the trial and error Daniel is complaining about is not fully solved. It is reduced, maybe.



Herman

The framework narrows the search space. It doesn't abolish the search.



Corn

Now the third question, which I think is the most interesting one. Is anything better coming? Is there a drug designed from the start for this, that does not touch the brain?



Herman

There is one, and it is called acotiamide. This is the flagship example of a drug developed specifically for postprandial distress syndrome and acting peripherally. It is a prokinetic that works by enhancing acetylcholine release in the gut. It has no meaningful central action. That is the design goal.



Corn

And it works?



Herman

In a Phase Three trial of two hundred and twenty patients, comparing it to mosapride in postprandial distress syndrome, the responder rate for overall treatment effect was ninety-eight percent on acotiamide against a bit over ninety-three percent on mosapride at four weeks. And the secondary endpoints were the elimination of postprandial fullness, upper abdominal bloating, and early satiation. Which is Daniel's exact symptom list, read back to him.



Corn

That responder rate is suspiciously high.



Herman

It is high, and I would treat a ninety-eight percent responder rate with some caution. But the direction of the finding is what matters. A peripheral drug, designed for this condition, hitting the postprandial symptoms directly.



Corn

And where can you get it?



Herman

It is approved in Japan. Availability elsewhere is limited. So the drug that fits the framework beautifully is not sitting on the shelf in most of the world.



Corn

Which is its own kind of answer to Daniel's question. The future exists. It is just not distributed.



Herman

And there is more behind it. The pipeline is moving toward the duodenum. Mucosal barrier repair, low-grade inflammation, microbiota modulation. There is real interest in microbiota-based and immune-modulating strategies, which is a shift away from the central nervous system entirely. And the dietary side is being formalized too, which is a non-drug, non-CNS option.



Corn

Give me the numbers on the diet side.



Herman

A low-FODMAP diet showed seventy-three percent improvement in functional dyspepsia and postprandial distress symptoms over six weeks. And the six-food elimination diet is being studied in the same population. So there are non-pharmacological routes that produce real symptom benefit, and they do not involve a tricyclic at all.



Corn

So the honest summary of the field is two trends. Symptom-directed selection, and peripherally-acting agents. And the evidence base lagging both.



Herman

That is the state of the field. The direction of travel is clear. The evidence has not caught up to the direction of travel. And in the meantime, the guidelines still point at the tricyclics, because they are the only drugs with enough evidence behind them to put in a guideline, messy side effects and all.



Corn

Which is where we should probably hear from the man who has actually watched a prescription get filled.



Hilbert

Daniel is not the first person to take a drug home and find out within a week that the trade was worse than the symptom.



Herman

Go on.



Hilbert

I used to drive a delivery van for a pharmacy in a small town, late eighties, and one of my routes was the retirement flats on the hill. Same thing every month. Little brown bottles, mostly the same four drugs. And there was a cluster of them that always went out with a printed note from the pharmacist in the bag. Ten milligrams. Twenty-five. Never more than that. The note said, take at night, may cause drowsiness, do not drive until you know how it affects you.



Corn

What were they for?



Hilbert

Most of the people on that route were not on them for their nerves. They were on them for their stomachs. That was the whole reason I noticed. The same little bottle, the same note, three different complaints behind it. And the ones who kept coming back for refills were the ones who had worked out their own dose. Not the dose on the label. They would cut the tablet in half, or take it every second night, and they would tell me, because you tell the man with the van, apparently. There was a woman in number fourteen who had decided that half of what the doctor wrote was the right amount, and she had been right about it for a year.



Herman

That is exactly the negotiation the papers do not record.



Hilbert

The label is the starting point. It is not the answer. The people who stayed on the drug were the ones who got enough relief to make the drowsiness worth living with, and found the smallest dose that did it. The ones who came off came off because they could not get the trade to balance. And the pharmacist spent a surprising amount of her day on that balancing act, and none of it showed up in the prescription.



Corn

The dose that works is often below the dose that causes the side effects.



Hilbert

Not always. That is the part people get wrong. Sometimes the two overlap and there is no amount that helps without costing you something. That is when they stop coming in.



Herman

So the trial-and-error process is not just about which drug. It is about finding a dose inside the therapeutic window that happens to fall below the side-effect threshold, and that window is different for every person.



Hilbert

There was a man in the flat below who went through four of them, one in each direction, before he settled. He was very matter-of-fact about it. He said the last one was not better than the first, but he had learned to take it at teatime instead of bedtime, and that made the difference.



Corn

Teatime instead of bedtime changed the verdict.



Hilbert

It did. The drug was the same drug. He moved four hours and it stopped being a problem. Nobody wrote that down anywhere, but he knew it.



Herman

What I take from that is the thing the framework cannot capture. The symptom-directed map tells you which class to reach for. It says nothing about the timing and the dose, which is where a huge amount of the trial and error actually lives.



Corn

And it tells you the search is personal, not algorithmic. The woman at number fourteen was not wrong. She had just solved a different equation than the one on the label.



Herman

Which brings us back to Daniel, and to the actual shape of the problem. His doctors did not fail him. They reached for the drug with the best evidence, and the fit was wrong for his symptom profile, and the side effect landed on him before the benefit did.



Corn

And the alternative you suggested has a real benefit and a real cost, and the cost is weight gain, which is not a trivial thing to weigh.



Herman

No, and it is worth saying clearly that for some patients the weight gain is the dealbreaker, and for others the symptom relief is worth it, and neither of those people is being irrational.



Corn

So here is the open question I keep circling. If the field already knows that postprandial fullness and bloating respond better to peripheral prokinetics than to central tricyclics, why are the tricyclics still the default?



Herman

Inertia is part of it. Cost is part of it. The tricyclics are old, generic, and cheap, and the peripherally-acting options include drugs that are unavailable in most countries or carry their own regulatory history. And the honest answer is the third one. The high-quality subtype-specific trials that would settle the question have not been run, so the guideline cannot move. The evidence base is the bottleneck, not the science.



Corn

But the direction is visible. The duodenum, the microbiota, the peripherally-acting prokinetics. There is a real chance that in ten years the word neuromodulator is a historical curiosity, and nobody is handing out ten milligrams of a tricyclic for a stomach complaint.



Herman

Maybe. The acotiamide trial shows what a purpose-built peripheral drug can do. The limiting factor is not the concept. It is getting the trials done and the drugs distributed.



Corn

And in the meantime, the person who has a stomach that has been a problem for seven years, and a better-matched option with a notorious side effect, and a second option that did nothing but make him tired, is not experiencing a failure of his care. He is experiencing a snapshot of where the science actually is.



Herman

Which is uncomfortable, and honest, and about the best we can say this week.



Corn

Here is the misconception we should kill before we let people go. The most common wrong belief is that these drugs work by treating hidden depression or anxiety, that the stomach problem is really a mood problem and the pill treats the mood.



Herman

The drugs are not treating mood at these doses. They are modulating visceral sensation and accommodation. The amitriptyline raised gut serotonin and lowered visceral sensitivity in that rat model without changing transit speed. It is a sensory drug at that dose, not a psychiatric one. And a second wrong belief worth killing, while we are here, is that the SSRIs would be a cleaner version of the same thing. They have failed in functional dyspepsia. The messy old drugs are the ones that work.



Corn

One thought to leave you with. The thing that made the prescribing work in that pharmacy was not a better drug. It was a person who took the time to find the dose and the hour that fit. That is the part no framework replaces.



Herman

And thanks, as always, to our producer, Hilbert Flumingtop.



Corn

This has been My Weird Prompts, the human-AI collaboration podcast. If you are enjoying the show, leave us a review. It helps other people find us. Email us at show at my weird prompts dot com.



Herman

We will be back soon.