Episode Book

EPISODE #6648

What Psilocybin Depression Trials Actually Show

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SYNOPSIS

Compass Pathways has submitted COMP360 to the FDA after two Phase 3 trials hit their primary endpoints, yet the Week 6 advantage over placebo was just 3.6 MADRS points—half of the Week 1 peak. A look at the clinical evidence for psilocybin in treatment-resistant depression unpacks what the COMP005, COMP006, and EPIsoDE trials actually measured, why expectancy and functional unblinding complicate the results, and how much of the effect comes from the drug versus the therapy.

TRANSCRIPT



Corn

The gap between "breakthrough" and "three and a half points" has never been wider.



Herman

It hasn't. And that's the frame for today, because Daniel wants us to walk into that gap.



Corn

His prompt is about psilocybin for depression, and he's very specific about what he doesn't want — he doesn't want the neuroscience tour, the serotonin receptor story, the brain-plasticity narrative. He wants the clinical evidence as it stands right now: what the late-stage trials actually showed, what regulators have done with it, whether the effects last, how much of the result is the drug versus the therapy wrapped around it, and what he calls the honest weaknesses — especially blinding, "when every participant can tell whether they got the real thing."



Herman

Which is the single best phrase in the prompt, because it's exactly right. This is a field where the headline and the data have been living separate lives for about five years now.



Corn

Then let's go look at the data. Starting with what the trials measured — and what they didn't.



Herman

The state of play as of this week: Compass Pathways completed its rolling New Drug Application to the FDA on November ninth, for COMP360, their synthetic psilocybin, in treatment-resistant depression. Over a thousand participants across the Phase 2b and two Phase 3 trials behind it. U.S. launch targeted for the first half of next year, subject to FDA approval and DEA rescheduling.



Corn

Two Phase 3 trials, both hit their primary endpoints. On paper that's a slam dunk.



Herman

On paper. COMP005 reported in June of last year — two hundred fifty-eight participants, single twenty-five milligram dose versus placebo, and at Week 6 the difference on the MADRS, the Montgomery-Åsberg depression scale, was minus three point six points. Statistically robust, p well under zero point zero one. COMP006 reported this February, twenty-five milligrams versus one milligram, minus three point eight points at Week 6.



Corn

Three and a half points on the MADRS. What does a person feel like, three and a half points better?



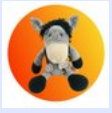
Herman

The minimal clinically important difference on that scale is usually cited around two points. So it's real, it's above the threshold where a patient would notice, and it is nowhere near what the press releases are describing. The Compass CEO, Kabir Nath, in September: COMP360 has "substantial magnitude of effect and sustained durability through one year," a clinical profile "in a league of its own."



Corn

A league of its own, at three point six points. That league has other members.



Herman

Plenty of them.



Corn

Then the spine of the episode is the gap. What did these trials actually prove, and what were they carefully built to avoid proving?



Herman

Start with the shape of COMP005, because the time course is the whole story. The difference between drug and placebo, in MADRS points, at each timepoint: Day 2, minus four point seven. Week 1, minus seven point two. Week 3, minus five point two. Week 6 — the pre-registered primary endpoint — minus three point six.



Corn

The effect peaks at Week 1 and then shrinks toward the endpoint they committed to in advance.



Herman

Half of it evaporates between Week 1 and Week 6. And there are two readings, both honest. One: this is what pre-registration is for — they picked Week 6 before seeing data, and the effect persists at a smaller size, so reporting the shrinking number rather than the flattering Week 1 peak is a point in their favor. That's the charitable reading, and I think it has real force.



Corn

And the uncharitable one.



Herman

The uncharitable one is that Week 1 is peak expectancy. Everyone in the drug arm knows, by Day 2, that they got the drug — you cannot take twenty-five milligrams of psilocybin and wonder. So the Week 1 number is partly pharmacology and partly "I just had the most significant experience of my life, of course I feel better," and some of that glow is still on the Week 6 score, fading.



Corn

Both of those can be true at once.



Herman

Both of them almost certainly are, in some proportion nobody can currently name. COMP006 makes it a bit more interesting, though. Instead of an inert placebo, they compared twenty-five milligrams against one milligram — a real capsule, a real protocol, but a dose that produces almost nothing subjectively. Twenty-five beat one by minus three point eight at Week 6.



Corn

That's their dose-response argument.



Herman

Right, and it does argue that the drug dose contributes something beyond the therapeutic ritual, because the therapy protocol was identical in both arms. But the detail everyone skips: in the twenty-five milligram arm, only thirty-nine percent achieved even a twenty-five percent reduction in symptoms.



Corn

Twenty-five percent. That's the bar for "the drug did something."



Herman

That's a low bar. On MADRS, a twenty-five percent reduction can mean going from "severely depressed" to "still severely depressed." So sixty-one percent of people in the winning arm of a successful Phase 3 didn't clear a modest response threshold.



Corn

I want to pull back to the Phase 2b for one second, because there's a clean piece of side-evidence there. People entering these trials have to come off their existing antidepressants first, and the obvious objection is that some of what you're measuring is withdrawal, or its relief.



Herman

Two hundred thirty-three participants, twenty-five, ten, or one milligram, all with psychological support. A post hoc analysis looked specifically at the people who'd discontinued antidepressants during screening, and they didn't do worse going in, didn't have elevated baseline suicidality, and the discontinuation didn't compromise efficacy or the subjective experience. That's a real objection, and the data answers it. Credit where due.



Corn

Now the pooled picture.



Herman

Menon and colleagues, last year, in Acta Psychiatrica Scandinavica — six randomized trials, about four hundred thirty participants, all psilocybin for major depression. Pooled standardized mean difference at one week: minus zero point seven two. Response relative risk three point four, remission three point seven.



Corn

Minus zero point seven two. For the listener who doesn't live in effect sizes: that's big.



Herman

That's large by psychiatric standards — roughly double what SSRIs produce in their acute-phase trials. And I'd say a careful listener should hear that number and get suspicious, not reassured. When a psychiatric intervention produces double the effect size of the workhorse drug class that's been refined for fifty years, one of the usual explanations is that you're measuring something besides the drug.



Corn

Not an effect that big. Not on the first try.



Herman

Either psilocybin is a unprecedented pharmacological leap — possible, I won't rule it out — or the trials are measuring expectancy, context, and the most elaborate therapeutic ritual ever attached to a pill, and the comparison with SSRI trials, which are thirty minutes and a follow-up appointment, is not apples to apples.



Corn

Which is where the German trial comes in, because it's the one built to answer exactly that.



Herman

EPIsoDE. Mertens and colleagues, published this year in JAMA Psychiatry. Two centers in Germany, a hundred forty-four participants with treatment-resistant depression, and — this is the part that matters — triple-blinded with an active placebo. Nicotinamide, a hundred milligrams. A real pill, a real physiological event, no psychedelic effect. Plus a low-dose arm at five milligrams, which produces some subjective effect but far less than twenty-five. Two doses, six weeks apart, all embedded in seven psychotherapeutic sessions, and the primary endpoint is response before the second dose.



Corn

Nicotinamide is a clever choice. Flushing, a warm feeling — enough that a control participant can believe they got something.



Herman

That's the design intent. It's the field's best attempt at a masked control for a drug that unmasks itself.



Corn

And the result?



Herman

The result is the maddening part. The design is fully documented — the paper, the arms, the endpoints — and I have not been able to get the actual primary numbers. The response-rate comparison between twenty-five milligrams, five milligrams, and nicotinamide. It exists, it's published, and it is the single most important number for the drug-versus-expectancy question in the entire field. I'm not going to guess at it on air.



Corn

So the best-designed trial in psilocybin research is the one we can't quote.



Herman

And the twelve-month follow-up from the same group — that paper exists too, and the numbers in it weren't retrievable either. So I'll name the gap and move on, but it's worth sitting there a second: the field's most rigorous test of whether the trip is doing the work, and the result is behind a wall.



Corn

You've been carrying that grievance since before we started recording.



Herman

I've been carrying it since I found the paper.

L

Larry

This is a public service announcement. Every year, thousands of patients enter clinical trials believing they can tell whether they received the real medicine or the sugar pill, and that belief, that terrible unblinded belief, is quietly eroding the very foundation of the placebo arm. But there is something you can do. Maskwell is the only fully opaque capsule sleeve engineered to make expectancy blinding not just possible but stylish.

L

Larry

Maskwell wraps your treatment in a sleeve so thoroughly unblinded-free that not even the prescribing physician knows which arm the study is in, and with a single Maskwell sleeve you can expect a thirty eight percent reduction in knowing, a durable effect that lasts up to six weeks after the trial ends, and the solemn civic satisfaction of having personally rescued evidence based medicine from itself. Maskwell. Because the only responsible choice, when you cannot tell, is to not tell.



Herman

The Maskwell people again.



Corn

Third week running. Like weather at this point.



Herman

Back to it, though — because the blinding problem isn't just a design quibble, it's measurable, and there's a paper that measures it sideways. Hieronymus and colleagues, last year in JAMA Network Open. Instead of looking at the treatment arms, they looked at the control arms. If psilocybin trials' placebo patients do unusually badly compared with placebo patients in SSRI and esketamine trials — same scale, the MADRS — that tells you something about expectancy, not about the drug.



Corn

The placebo arm as the diagnostic.



Herman

A placebo patient in a psilocybin trial is a person who signed up for a psychedelic experience, believes strongly in it, and spent six hours discovering they didn't get it. That's a different creature from a placebo patient in a sertraline trial who took an ordinary pill and felt nothing in particular. The paper's own framing is that high rates of functional unblinding combined with positive expectations of psychedelic use might bias treatment outcomes.



Corn

So the effect size gets inflated twice over. The drug arm gets the expectancy boost, and the control arm gets the disappointment.



Herman

Both directions of the same error. And Aday and colleagues said it plainly back in twenty twenty-two — expectancy effects and condition masking are critical limitations to the interpretability of the research. That was the careful, diplomatic version. The blunt version is: nobody in a twenty-five milligram arm is blinded, and nobody sitting with them for six hours is either.



Corn

EPIsoDE called itself triple-blind.



Herman

Investigator, participant, rater — all formally blinded, and the ratings were done by people who weren't in the room. That's real, and it's better than everything else out there. But the acute session itself can't be masked. The participant either spends six hours in a profoundly altered state or they don't. The clinician sitting with them either watches that happen or doesn't.



Corn

So the blind survives exactly as long as nobody talks to the participant about what happened to them.



Herman

Which, given that integration sessions are the therapy, is not long.



Corn

Let's turn to the question no trial was designed to answer. Drug versus therapy.



Herman

Every trial we've discussed delivers the psilocybin inside psychotherapy. EPIsoDE: two doses within seven psychotherapeutic sessions. Compass's entire program: dosing with psychological support. Rosenblat and colleagues: preparation and integration sessions around every dose. There is no psilocybin-alone arm, and there is no psychotherapy-alone arm at matched intensity. Not in any of them.



Corn

So the honest answer to Daniel's question — how much is the drug, how much is the therapy —



Herman

Nobody can say. Not "more research needed" as a polite hedge — the trials were not built to separate those, and the answer does not exist in the data anywhere.



Corn

That's the part I find almost admirable. The therapy is so thoroughly confounded with the drug that it's invisible.



Herman

And the one partial handle is COMP006's dose-response. Twenty-five milligrams versus one, same therapy, minus three point eight points. That tells you the dose contributes something beyond the container. It does not tell you the size of the container's contribution, because one milligram isn't zero and the therapy was identical across arms — the design cancels the therapy out rather than measuring it.



Corn

There's a comparison I keep waiting for someone to run. Seven sessions of good psychotherapy, no drug at all, against the full protocol.



Herman

The psychotherapy-alone arm at matched intensity. It's the obvious trial and nobody's running it, and you can guess why — if the therapy alone got you even half of minus three point six, the whole commercial story changes.



Corn

From "a new standard of care" to "expensive adjunct."



Herman

The Rosenblat trial is worth a mention here, because it's the version of the question asked with the weakest possible tool. Thirty participants, complex patients — treatment resistance, suicidality, comorbidity, the people other trials exclude — immediate treatment versus waitlist. Large effect, Hedges' g of one. But a waitlist control for a psychedelic is nearly no control at all: waitlisted patients know they're waiting, and the ones who got the drug know exactly what they got. Still, the safety finding is real — transient adverse events, nothing serious, in a population that usually gets excluded.



Corn

Durability, now. This is where the press releases do their heaviest lifting.



Herman

September ninth this year, Compass put out fifty-two-week data from COMP005 Part C. The headline: an average thirteen-point MADRS reduction from baseline at Week 52 for the twenty-five milligram randomized participants.



Corn

Thirteen points at a year. That sounds spectacular.



Herman

It's designed to. Read the qualifiers. Part C is open-label — everyone knows what they're getting, which is the blinding problem with the safety off. And the thirteen-point figure applies to participants who received an additional dose during the open-label period. This is not evidence that one dose holds for a year. It's evidence that people who got a dose, and then got another one, were doing well a year out — with forty to forty-five percent responders and roughly thirty percent remitters in the six weeks after that second dose. Even Compass's own release calls it "additional benefit from another COMP360 dose."



Corn

So the durable single-dose claim rests on data where everyone knew what they got and most of them got a second dose.



Herman

Both at once.



Corn

We did an episode on exactly this pattern — whether brain changes from therapy or pills persist after you stop — and the rule held there too: the durability claims are always strongest in the designs that can't test durability.



Herman

The Borissova and Rucker review, twenty twenty-four, is the sentence I trust most in this literature. Early evidence suggests single doses with psychological support induce rapid improvement that endures — and the phrase they chose — "for some weeks."



Corn

Some weeks. From the field's own careful reviewers.



Herman

That's the honest unit of durability right now. Some weeks, reliably. A year, in some people, under conditions that can't prove why.



Corn

There's a small cognitive-outcomes study that I think works as a lens for the whole evidence base.



Herman

Johnson and colleagues, twenty twenty-five. Twenty-six adults, post hoc analysis, cognitive testing before and after psilocybin-assisted therapy. Every measure improved significantly over time — all p values under point zero five, and the Trail Making gains survived adjustment for depressive symptoms.



Corn

Sounds great.



Herman

Then they computed reliable change indices — did any individual improve beyond what chance and measurement noise would produce. Between four and twelve and a half percent of participants showed meaningful improvement. And those rates did not significantly exceed chance. The group "improved" because depressed people who feel somewhat better test somewhat better.



Corn

Statistically significant, clinically indistinguishable from noise.



Herman

That's the lens I'd hold over everything we've discussed. When the significance testing is that easy to clear and the individual-level change is that thin, the p value is the least informative number on the page.



Corn

Regulatory, then. Because the last month has been a rollercoaster.



Herman

Australia approved psilocybin for treatment-resistant depression back in twenty twenty-three — first national approval anywhere. In the U.S., psilocybin is still Schedule I, no exceptions, so even an FDA approval requires the DEA to reschedule before anyone can fill a prescription. COMP360 has Breakthrough Therapy designation. In April, the FDA granted it a Commissioner's National Priority Voucher — a program set up under the April executive order, meant to compress review from the usual ten to twelve months down to one or two.



Corn

And then?



Herman

Compass completed the rolling NDA on November ninth. Four days later, Reuters reported the FDA is ending the voucher program entirely.



Corn

Four days.



Herman

Four days after the submission was complete. So Compass filed a full application expecting a compressed review, and the compression mechanism evaporated the same week. Nobody knows yet what that means for the timeline — whether the agency honors



Herman (continued)

something like the original expectation or this falls back to a standard review clock.



Corn

So "first half of next year" is a launch target held together by two things that haven't happened: an approval and a rescheduling.



Herman

Both of which are outside Compass's control. And even if both land, there's the delivery model, which nobody has costed. Seven psychotherapeutic sessions. Two six-hour dosing sessions with two clinicians physically present for each one. That's roughly a working week of trained clinician time per patient, per treatment course, at a minimum.



Corn

No insurer has priced that.



Herman

None that I've seen, and it's not a rounding error — it's possibly the majority of the actual cost. And remember, the therapy component is the bit that's unmeasured. It's unmeasured and it's unbilled and it may be the real barrier between this drug and a single patient.



Corn

We spent the whole episode on whether the drug works, and the access question will be settled by the therapy nobody's counting.



Herman

Which is also the part nobody separated out of the efficacy data.



Corn

Thirteen points on an open-label arm and a CEO calling it a league of its own —



Herman

— he's not lying, exactly. He's describing the trajectory of the company. The data is describing something smaller and slower.



Corn

The bit I can't shake is the shape of that time course. Minus seven at Week 1, minus three point six at Week 6. The drug's best moment is its least informative one, and its most rigorous trial —



Herman

The one we can't quote.



Hilbert

— or you could quote it if you drove the man home, which I did.



Hilbert

My brother-in-law was in one of the early trials, this was a few years back. I was the driver. You sit in a corridor for six hours, then they hand you a man who has just spent the afternoon somewhere else entirely, and you take him home and you stay with him because that's the arrangement. Herman will know the term. Integration, they called it. I called it Tuesday.



Herman

The drive is the part every protocol mentions and nobody studies.



Hilbert

Well I studied it. Two hours he talked, the whole way. Mostly about a dog. A garden hose. A specific afternoon when he was maybe nine. He described the hose in enormous detail, the coiling of it, the green of it. I sat with him the rest of the day as instructed and he never mentioned the dog again.



Corn

Did you ever ask him about it? Later, I mean.



Hilbert

Once. A couple of years after. He said, "I don't remember telling you that." Very flat, the way he says things. I believe he doesn't remember.



Herman

And you've carried that around —



Hilbert

There's a note in my phone from that day. Says "dog, hose, 1990s?" Question mark included. I don't know why I kept it. I don't know what I'd do with it. It's still there, between a plumber's number and a note about windshield wipers.



Herman

That's the durability question in one line, though. The effect on him lasted — he was better for months, I assume.



Hilbert

He was better for a while, and then he wasn't, and then they gave him the second dose, and we did the drive again. The second drive he mostly wanted to talk about the hose.



Corn

The second drive. Same hose.



Hilbert

New dog, he claimed. I didn't press it. I delivered him, Herman, and I left the philosophy to the clinicians. Anyway. You two covered the blinding well enough. The clinician who handed him the capsule knew, my brother-in-law knew within about forty minutes, and I knew by the second roundabout. Four of us, one blind between us.



Corn

Then let's not manufacture a verdict. The open questions are sitting right there. EPIsoDE's primary result — the number that would tell us how much is drug, how much is expectancy — is published somewhere and not in front of us. The twelve-month follow-up numbers likewise. The voucher program died four days after the filing, so the approval clock is a mystery even to Compass. And not one trial in the whole program separates the drug from the therapy.



Herman

And the thing I'd watch isn't the FDA decision at all. It's the first insurer asked to price a treatment course that's two clinicians for six hours, twice, plus seven therapy visits. Whatever number they come back with decides more patients' fates than the MADRS ever did.



Corn

Even that phone note with the question mark on the decade — that's how the memory side of this actually works. You keep the artifact and lose the certainty.



Herman

Well said. Thanks, as ever, to Hilbert Flumingtop for producing the show.



Corn

If you want more of this, try episode twenty-five twenty-seven, Do Brain Changes from Therapy or Pills Actually Last; episode twenty-six oh nine, Mapping the Therapy Family Tree; and episode fourteen, AGI's Crossroads. This has been My Weird Prompts. You can find the archive at my weird prompts dot com.



Herman

We'll be back soon. See you then.

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