TSPP · SATURDAY, NOVEMBER 7, 2026

Peptides and Mental Health

Peptide pharmacology — and why psychiatry can't stay walled inside the barrier of the CNS

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DISCLOSURE

Disclosure & off-label notice

- I have no relevant financial relationships or conflicts of interest to disclose.
- Global Examination Services is Andrew Brylowski, MD, PA — my solo practice. The ~2,800 de-identified disability exams referenced are from that practice; they are my own.
- GLP-1 receptor agonists have NO FDA-approved psychiatric indication. All psychiatric and addiction uses discussed are investigational / off-label.
- BPC-157, Semax, Selank and similar peptides are unapproved — discussed, not recommended.

WHAT YOU'LL LEAVE WITH

I'm going to make you three promises

01 **A new way to think about pharmacokinetics** when the drug is a peptide — and what that means for dosing and monitoring.

02 **How these molecules actually signal** direct and indirect — and the blood–brain-barrier problem that defines the field.

03 **How to tell signal from hype** in the clinical-trial evidence — and why you are allowed to find out for yourself.

The larger claim: psychiatry has to practice medicine again — examine the body, and own the metabolic and endocrine problems our own drugs create. These peptides are the way back in.

WHY WE'RE HERE

The promises and the thesis

THE PROMISE

"By the end of this session you'll think differently about a class of molecules you already prescribe, and you'll know what you can lawfully do to find out what they do."

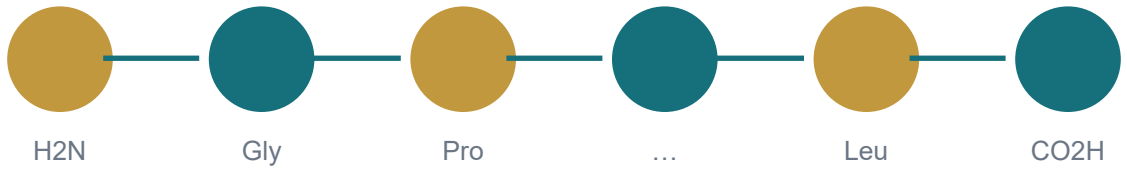
THE THESIS

"Our drugs break metabolism. The approved peptides are psychiatry's way back into the body. The unapproved ones are widely used and barely studied, and that part we can change."

WHAT A PEPTIDE IS

You already prescribe peptide-receptor drugs — directly or as side effects

A peptide is just a short chain of amino acids — the body's own signaling language.



The one you already fight: *the metabolic syndrome your antipsychotics cause is a failure of this same peptide / endocrine system — here's exactly how, next.*

Insulin | **Oxytocin** | **GLP-1 / tirzepatide** | **Vasopressin (ADH)** | **TRH** | **ACTH** | **Glucagon**

Every one of these is a peptide. This isn't a fringe class of molecules — it's most of endocrinology.

Peptide vs protein is a length convention (~under 50 amino acids) — insulin, at 51, is a borderline case; cytokines like IL-6 and CRP are longer “proteins” that still signal.

HOW THE SIDE EFFECT HAPPENS

Endocrine cells have neurotransmitter receptors — like neurons do

A NEURON



has receptors for neurotransmitters. No surprise.

A β-CELL (endocrine)



has the SAME receptors — and answers with a hormone.

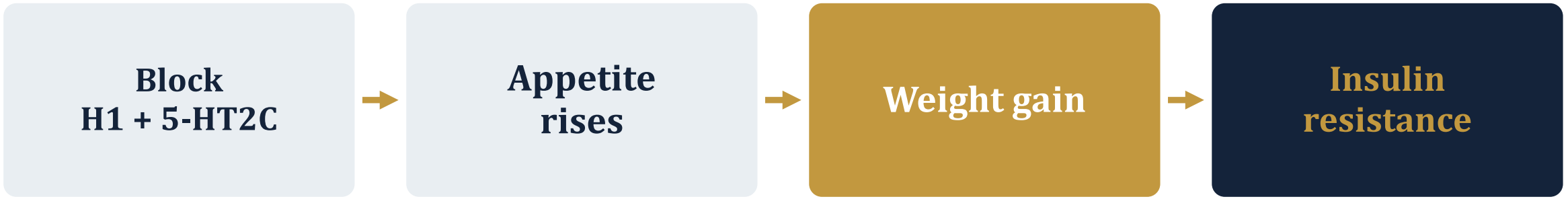
Block one of those receptors with a drug — and the hormone changes. That's the whole bridge.

Route 1 — the direct hit on the β-cell



Weight-independent — the cleanest proposed mechanism: the drug acts on the β-cell itself.

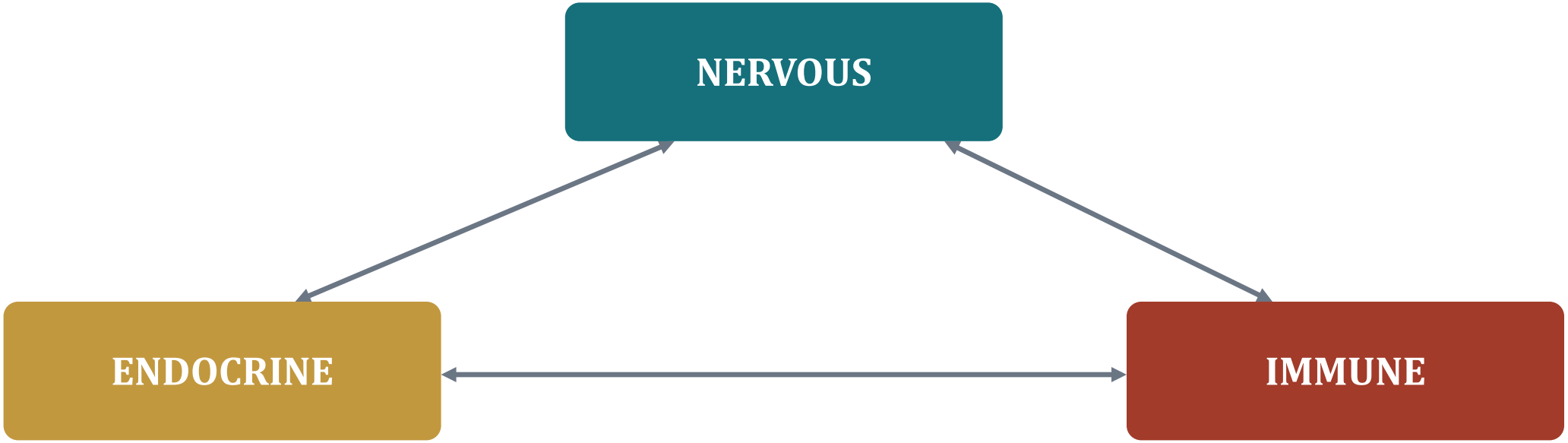
Route 2 — the ordinary overeating cascade



Same cascade as any weight gain — the drug just drives the eating.

The endpoint — insulin & the incretins — is exactly where GLP-1 drugs act.

Not three systems — one signaling web



They share the same ligands and receptors — acetylcholine, monoamines, peptides. A signal in one is read by all three.

THE PAYOFF

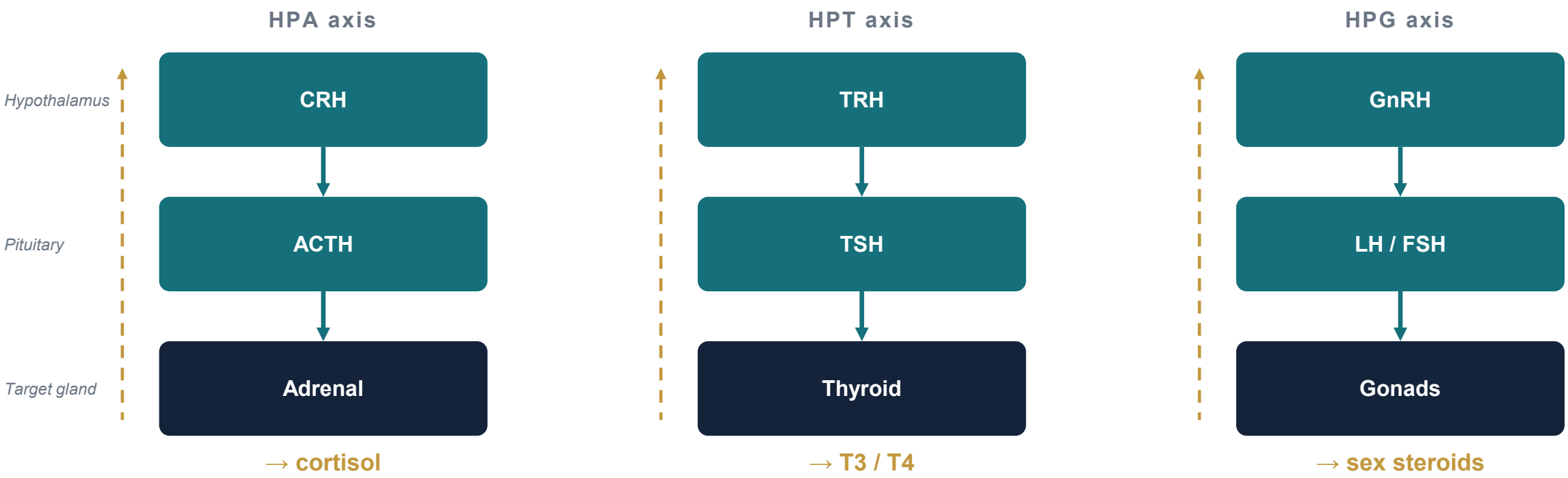
Peptides set the gain — not the signal



Peptides don't send the message — they set how loudly it's read. Reset the gain, and medication, therapy, sleep and exercise all land harder. That's why they belong in psychiatry.

THE AXES YOU ALREADY MANAGE

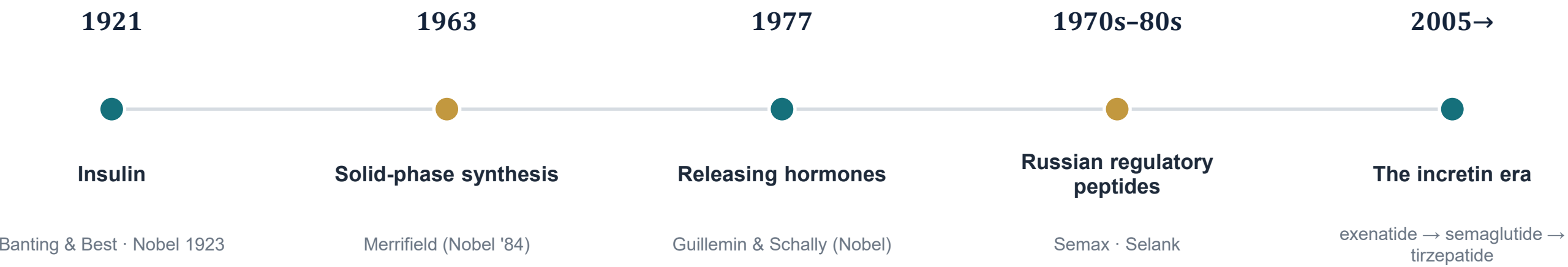
Every one is a peptide axis



Also peptides you already touch: oxytocin & ADH (posterior pituitary) · insulin & glucagon (pancreas) · prolactin — dopamine is its brake, and because TRH also raises prolactin, hypothyroidism can raise it too.

A CENTURY OF DISCOVERY

From a lifesaving extract to a weekly injection



Three Nobel Prizes sit on this timeline. The science is old and deep — the hype is new.

Unthink pharmacokinetics

THE SMALL MOLECULE

Swallowed — crosses membranes

Liver / CYP metabolism

Half-life hours to days

Dose to a steady state

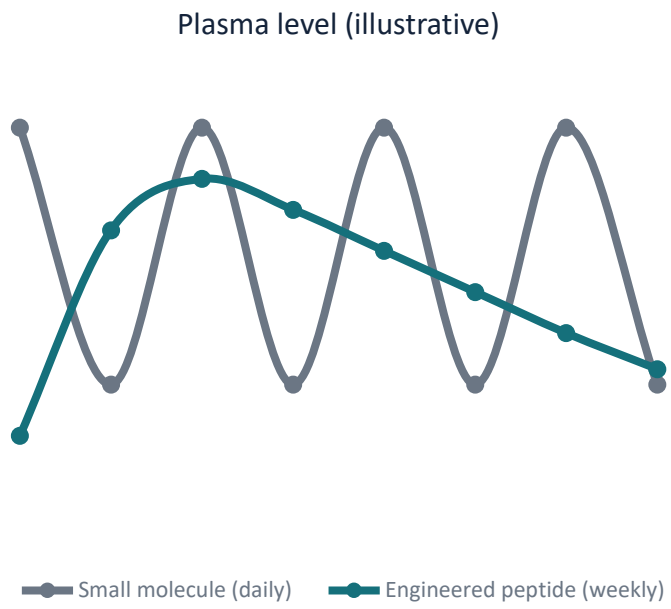
THE PEPTIDE

Injected — mostly destroyed if swallowed (oral semaglutide is the engineered exception)

Chewed up by peptidases

Native half-life: minutes

We ENGINEER the half-life: GLP-1 ~2 min → liraglutide ~13 h → semaglutide ~1 week

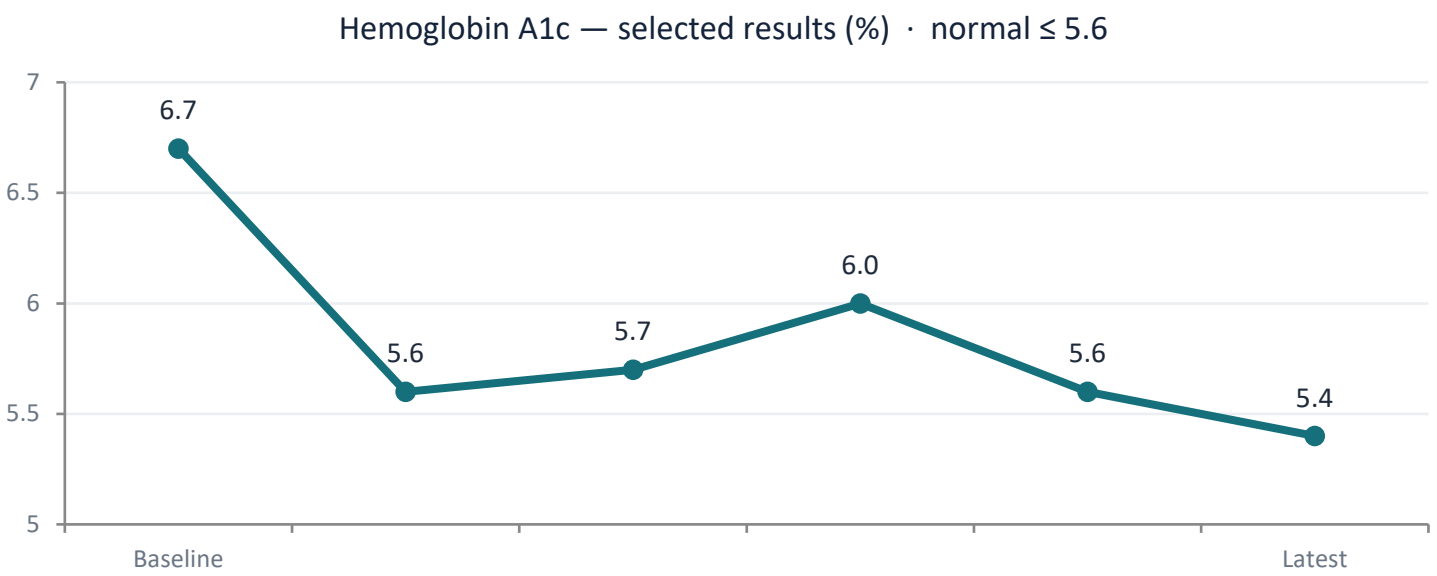


Monitor what the engineering changed: titrate to tolerability (GI), then watch the metabolic panel — HbA1c, lipids, weight — plus injection technique. The follow-up schedule IS the pharmacokinetics.

A PATIENT · USED WITH WRITTEN CONSENT

His own labs tell the story

Stable for over two decades on a simple regimen — then a severe relapse: depressed, suicidal, sleepless, deconditioned. We treated the whole person — cycled medications, started a GLP-1 (tirzepatide, a peptide), repleted a low vitamin D, and got him back outdoors in the sun — and landed back on his original regimen plus low-dose gabapentin. ~70 lb lost; his labs, and his life, followed.



6.0 → 5.4%

HbA1c: High → normal, on a GLP-1

~120 → ~95

Fasting glucose (mg/dL) — back in range

~70 lb

Weight lost (clinical observation)

Say it out loud: n-of-1, several changes at once — not causation. Hard to ignore; almost impossible to study the way we're currently allowed to.

OBJECTIVE 1 · MONITORING

The autonomic trade-off: heart rate up, HRV down

+2–4 bpm

Resting heart rate — modest (most with oral agents, least with tirzepatide)

HRV ↓

Vagal (parasympathetic) withdrawal

SBP ↓ ~3–5

Mostly weight-driven — room to de-prescribe

The mechanism is DUAL (say it this way): partly vagal/parasympathetic withdrawal (shown in humans) and partly a direct sinoatrial-node action — GLP-1 receptors sit on pacemaker cells (large-animal data; HR rises even after full autonomic blockade). It is not simply “sympathetic up.”

Our patient, and the rule: as his weight and clinic BP fell we eased off his antihypertensives (he turned orthostatic — an individual finding, not a class effect) — while his heart rate drifted up. So: check a baseline resting HR before starting, re-titrate BP meds as weight comes off, and watch closely if HR is already >90 or there's autonomic dysfunction.

THE BRAINSTEM HUB

Breathing improves — and why nausea happens

BREATHING — better, not depressed

Fewer respiratory events. SURMOUNT-OSA: AHI down ~20–24/h (~50–60%). ~14–18% fewer respiratory illnesses in RCT meta-analyses (COPD not significant; ~30% only in observational cohorts). Reassure asthma / COPD / OSA patients.

Why: weight loss + anti-inflammatory/airway effects — NOT proven central respiratory drive (that's preclinical).

NAUSEA — ~30–50%, and why

DUAL mechanism: peripheral (delayed gastric emptying, vagal afferents) AND central — the area postrema / chemoreceptor trigger zone has GLP-1 receptors and drives emesis directly. “Primarily local” understates it.

Slow stomach: titrate slowly, eat to early satiety. “Food noise off” = reward blunted to neutral, not aversive (a clinical description, not a mechanism).

One hub explains all of it: the NTS / dorsal vagal complex integrates gut, cardiovascular (baroreflex), and respiratory control in the same patch of medulla — so one peptide touches heart rate, breathing, and nausea at once. That colocalization is the real, well-supported crossover.

THE OTHER PATIENT

Now the patient in the public clinic

That was a patient with resources — written consent, compounded drug, labs, and follow-up.

Most of us, most days, treat the other patient:
poor, seriously mentally ill, obese, with metabolic syndrome — in a public system, on the very antipsychotics, lithium and clozapine that drove the weight on. This is the patient a GLP-1 could help most.

The psychiatric conundrum: in a severely ill patient, an unexplained body sensation can get absorbed into the illness. A side effect becomes a symptom — and the margin for error is thinner. The next four slides are how to use these GLP-1 drugs safely in exactly this patient.

And you are the PHYSICIAN of record. *Don't reflexively hand the metabolic drug off to an overloaded primary-care clinic, and don't subordinate it to the system — if you start it, you monitor it.*

SIDE EFFECTS OR SYMPTOMS?

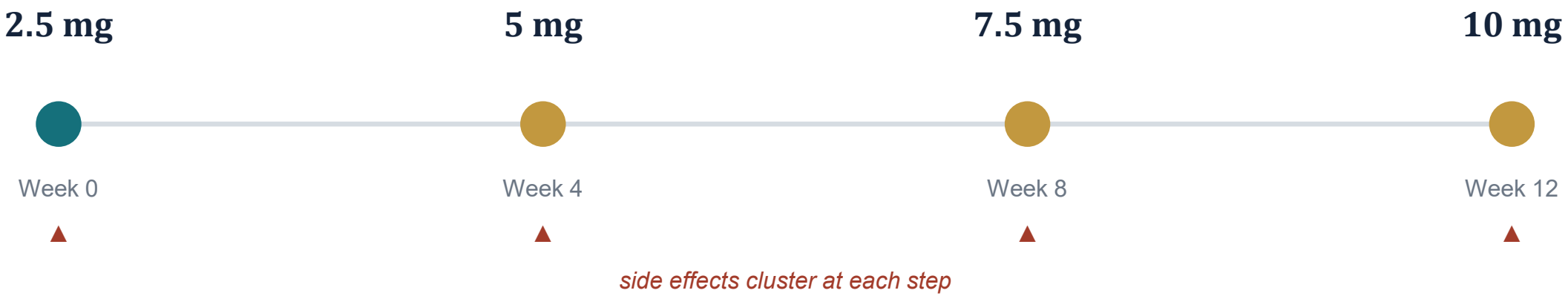
A side effect becomes a symptom

Nausea, vomiting	Read as poisoning. Vomited pills are missed doses — and fluid loss pushes lithium toward toxicity.
Constipation	On clozapine / anticholinergic load, the one common effect that turns dangerous (ileus). Start a bowel regimen on day one.
No appetite	The drug working — or a symptom of depression? Lurasidone (Latuda) needs ~350 kcal, ziprasidone (Geodon) ~500 kcal with food to absorb — skipped meals mean low levels and risk of psychiatric relapse.
Fatigue, flatness	Mistaken for relapse or negative symptoms. Rate drive and pleasure BEFORE starting, so a change can discriminate drug from psychiatric illness (or a combination).
Injection-site reaction	Can become a paranoid focus. Consider giving the weekly shot in the clinic — it defuses that and buys you a weekly look at the patient.

ADHERENCE

Trouble arrives on a schedule

Stomach side effects are the #1 reason people stop tirzepatide (a GLP-1 drug) — and they cluster at each dose step.



1

Starts early, returns at each step — so you can tell the patient in advance when they'll feel bad — and that it ends.

2

See the patient at every step — misattribution happens at the dose increases, not between them.

3

Go slower than the label — four weeks is a minimum. Hold at 2.5 or 5 mg until they've stopped noticing the drug.

SAFETY

Serious events hide behind the illness

Pancreatitis, gallbladder	Pain goes unreported — ask about it. Valproate, alcohol and antipsychotic triglycerides add risk; rapid weight loss drives gallstones.
Dehydration	Vomiting/diarrhea raise the lithium level and can injure the kidney. Check a lithium level AND creatinine at every dose step.
Low blood sugar	With insulin or a sulfonylurea. Confusion, sweating, agitation get treated as decompensation — check a glucose before any PRN.
Ileus on clozapine	Median colonic transit **104 h vs 23 h** on other antipsychotics (olanzapine, risperidone, paliperidone, aripiprazole, others); **80% had hypomotility vs none**. Reported pharmacovigilance: ~37 per 10,000 serious gut complications and ~7 per 10,000 deaths — GI deaths outnumber agranulocytosis deaths. **Check bowel sounds (borborygmi +/−).** On clozapine, **vomiting plus no stool is ileus until proven otherwise**.

Suicidality — the label changed: On Jan 13, 2026 the FDA requested removal of the suicidal-ideation/behavior warning from the weight-loss labels (Saxenda, Wegovy, Zepbound) after reviewing 91 placebo-controlled trials (107,910 patients) and finding no increased risk. But the pivotal trials excluded recent unstable depression and prior suicide attempts, so your own monitoring still matters. · **Boxed warning: thyroid C-cell tumors — avoid with a personal/family history of medullary thyroid cancer or MEN2.**

BEFORE THE FIRST SHOT

Three things to say before the first injection

The discrimination has to happen BEFORE the first shot — to the patient and one family member or caregiver, in plain words.

EXPECTED — and it passes

- **Upset stomach**
- **Less hunger**
- **Tired after a dose increase**

"This is the medicine slowing your stomach. It is not poison, and it is not your illness."

CALL ME

- **Can't keep pills or fluids down**
- **No stool for 3 days**
- **Feel flat for 2 weeks**

Any of these: pick up the phone before the next dose.

EMERGENCY — 911

- **Belly pain that won't stop**
- **Trouble breathing**
- **Swollen face or throat**

Go now. Don't wait to call.

The adherence payoff: weight gain is a leading reason patients quit antipsychotics. Reversing it gives them a reason to stay on BOTH drugs. Set goals they care about beyond the Obvious weight loss. — clothes, stamina, sleep.

THE ROLE

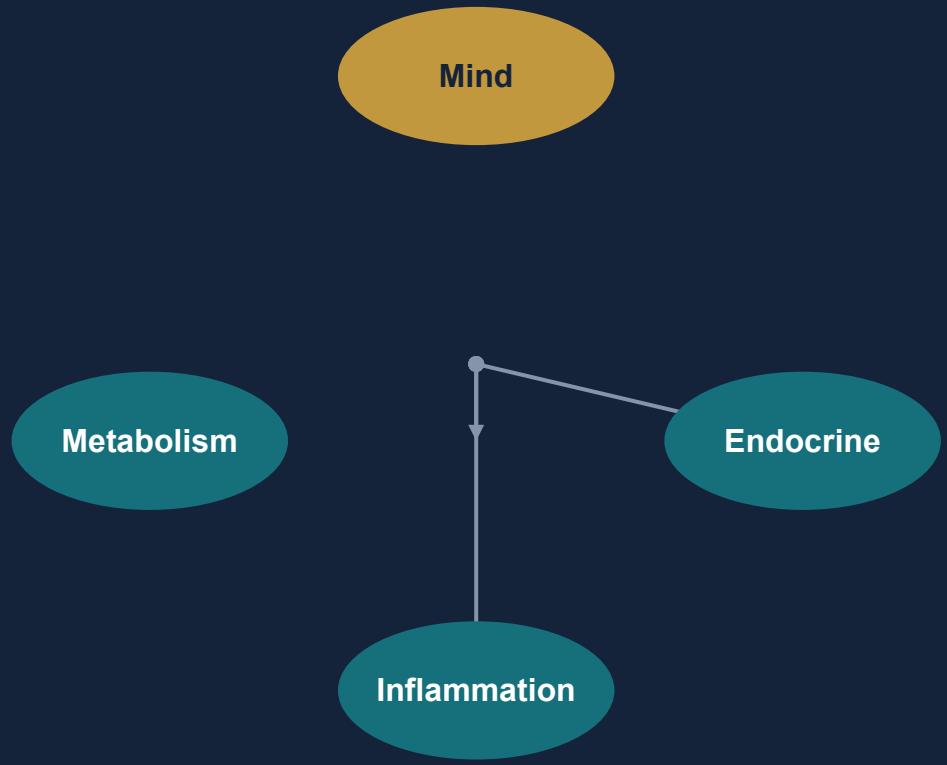
Our drugs break metabolism. Who fixes it?

Antipsychotics and mood stabilizers have effects on weight, glucose, lipids, prolactin. If your prescription caused it, the psycho-endocrine-immune exam is yours too.

The honest part: *doing this well is easier outside a system that won't reimburse the neurologic, endocrine, immunologic, a lot of times the psychiatric work, the GLP-1, or the labs.*

The exam we stopped doing — physical, neurologic, endocrine — is the exam these patients most need.

The thesis: none of these peptides currently are psychiatric drugs — they don't treat the illness. They set the gain, so every tool you already use works better.



WHAT TO ORDER

One blood draw, the whole system

ORDER — the core set

- HbA1c (+ fasting glucose)
- TSH + free T4
- hs-CRP
- 25-OH vitamin D
- CMP + CBC
- Lipids (non-fasting OK)

ADD — if the history points there

- AM cortisol (rule out, not “stress”)
- DHEA-S
- Fasting insulin
- IL-6
- B12 (diet, metformin, neuropathy)

LEAVE OFF the first draw

- ACTH
- Full cytokine panels
- Serum BDNF
- Broad antibody panels
- PM cortisol

One tube = the adjustable input set. A1c, TSH, free T4, hs-CRP, vitamin D, a metabolic panel. It is not a map of CRH or dopamine — pair it with weight, BP, sleep, and the mood time-course. I like to get anti-thyroid antibodies on my first draw, but that's usually a separate test that goes to an outside lab.

OBJECTIVE 2 · SIGNALING

Do GLP-1s even reach the brain?

DIRECT

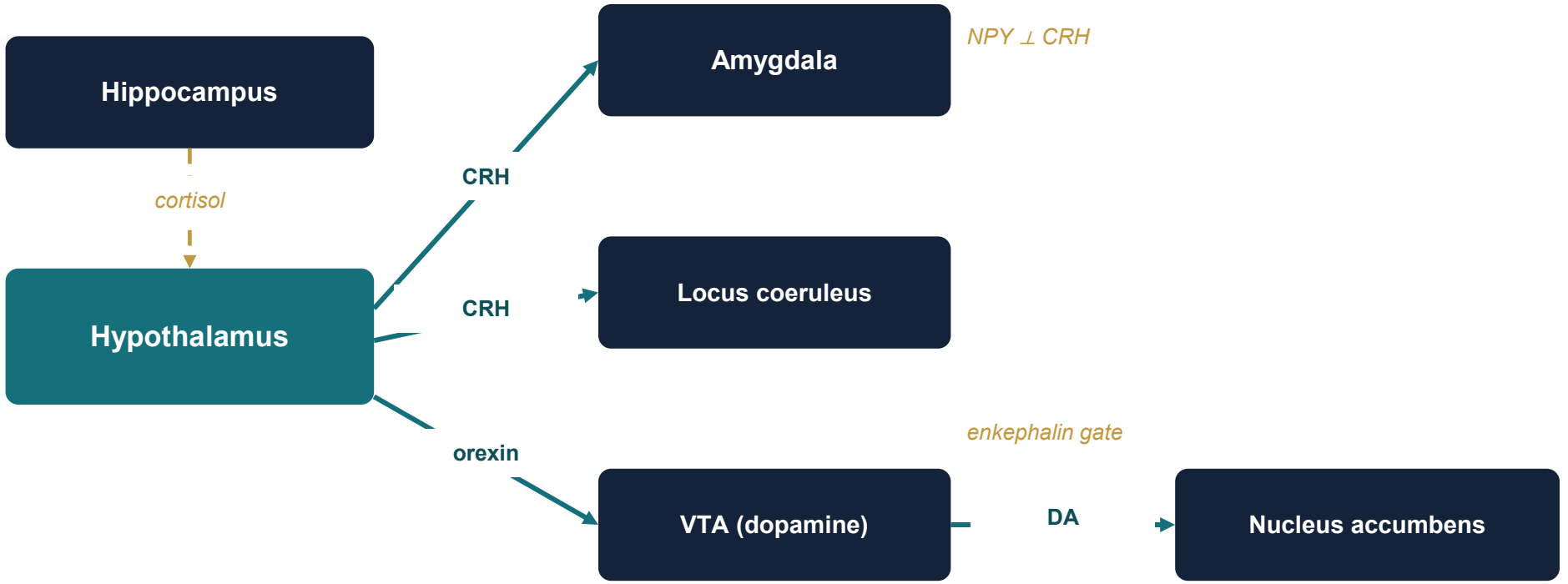
GLP-1 binds its receptor (G-protein-coupled; raises cAMP). A few gateways — area postrema, median eminence, parts of the hypothalamus — sit outside a complete barrier, and drugs reach them unevenly. Much brain GLP-1 is actually made in the brainstem (NTS), not carried in from the gut.

INDIRECT

The body's own GLP-1 signals partly through the vagus; the drugs' effect doesn't depend on it — they act mainly through the brainstem and by changing the metabolic/inflammatory state the brain swims in. The reward (dopamine) effect is mostly indirect.

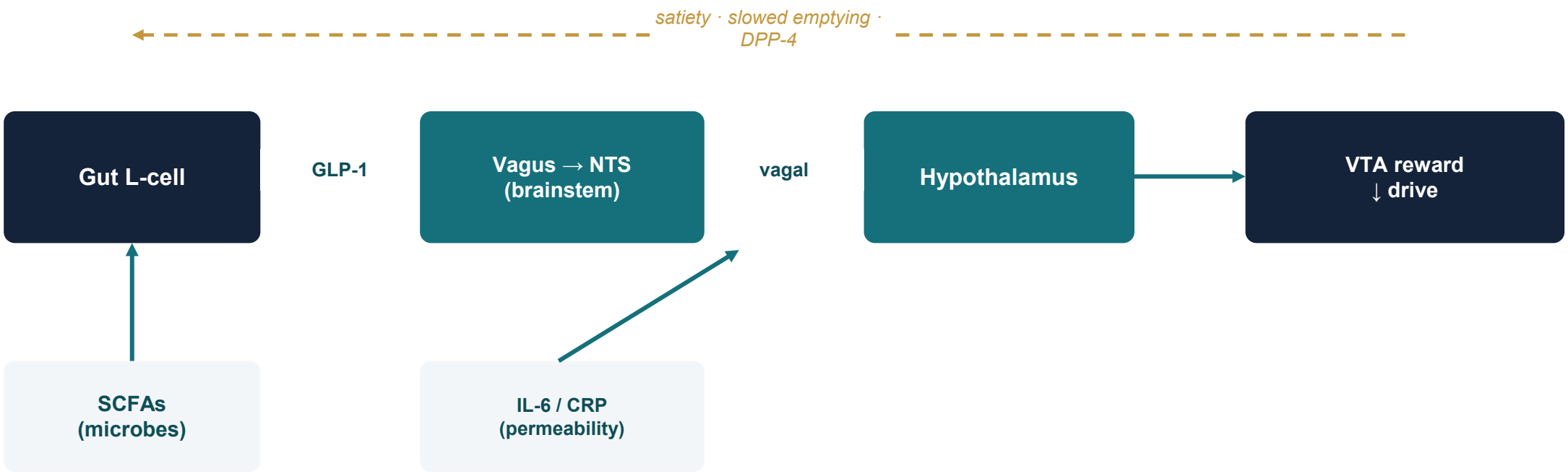
The line to remember: "poor barrier crossing" is not the same as "no CNS effect." The signal can start on the other side of the wall.

Neuropeptides set the GAIN



Neuropeptides don’t replace serotonin, dopamine, or norepinephrine — BUT set the GAIN on those circuits.

The meal becomes peptide (and other) signals to the brain



The gut is a modulator of brain gain — not a second mood center.

Why would a meal change mood?

For most of human history, food was uncertain. The gut hormones that track hunger and fullness also set how hard the brain pushes us to go and get food.

No food: the hunger state

- **Ghrelin rises** from the empty stomach
- **Reward drive goes up** (dopamine)
- **Alert, restless,** motivated to search

Survival value: find food before energy runs out

Food found: the fed state

- **GLP-1, PYY and CCK rise** from the gut
- **Reward drive and craving** turn down
- **Calm and full,** ready to rest and digest

Survival value: stop searching, save energy, digest

GLP-1 drugs send a steady “fed” signal, so the drive to seek food, and for some patients alcohol, eases.

OBJECTIVE 2 · THE BARRIER

The wall that defines the whole field

Pardridge's numbers: about 98% of small molecules and ~100% of large molecules — peptides included — do not cross the blood–brain barrier on their own. Too big, too polar, degraded on arrival.

Intranasal	Nose-to-brain partly bypasses the wall — how the Russian peptides (Semax, Selank) are given.
Transporters	A minority of peptides ride saturable carriers across — small absolute amounts.
Engineering	Shuttles and modifications are the frontier — mostly not here yet.

Myth check: the Pro-Gly-Pro "PGP" tail buys stability — it is not a key to the barrier. Don't let anyone sell it as one.

Peptides act at the barrier's leaky windows, not across it

How peptides reach the brain today

In the blood
GLP-1 drugs circulate widely but are kept out of most brain tissue.

↓

Leaky windows (circumventricular organs)
Area postrema (sits on the NTS), median eminence (next to the arcuate nucleus), subfornical organ. Open capillaries let the peptide reach receptors here.

↓

Neural relay
Those neurons signal on to the hypothalamus, VTA and nucleus accumbens. The peptide stays at the window; the message travels inward.

The frontier: engineered shuttles

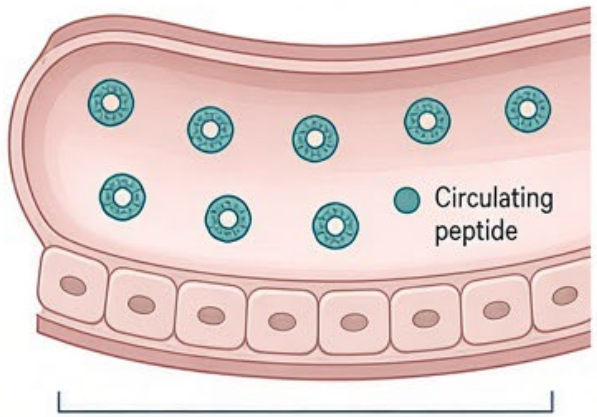
- **Borrow a door.** Fuse the drug to an antibody that binds the transferrin receptor, which already carries iron into the brain.
- **First approval: tividenofusp alfa (Avlayah) — FDA accelerated approval, March 2026, for Hunter syndrome.**
- **Next:** trontinemab, an anti-amyloid antibody on the same shuttle, is in phase 3.
- **Not a shuttle:** semaglutide's fatty-acid chain slows clearance; it does not carry the drug across.
- **Psychiatry:** no mental-health peptide uses a shuttle yet.

Sources: Gabery et al., JCI Insight 2020 (semaglutide brain access in rodents); FDA accelerated approval of tividenofusp alfa, March 2026.

CROSS-SECTION OF THE BLOOD-BRAIN BARRIER

Peptide signal relay at a leaky window (circumventricular organ)

IN THE BLOOD

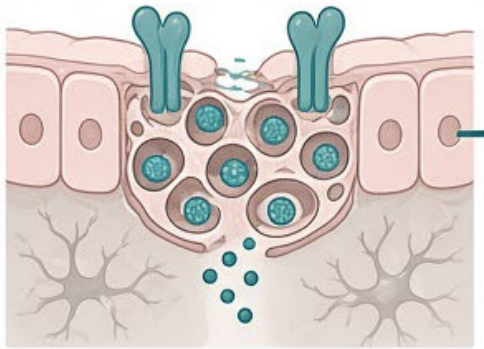


Peptides in the blood are stopped by the tight endothelial barrier.

LEAKY WINDOW

(Circumventricular Organ)

- Area postrema
- Median eminence
- Subfornical organ

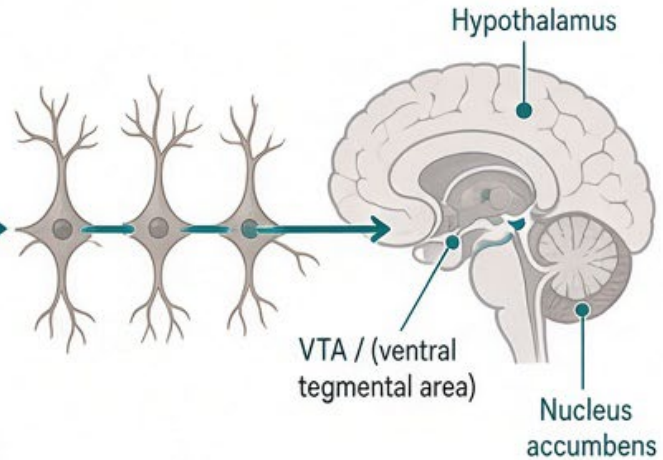


Peptides bind receptors at the leaky window

Signal initiated here.
Peptide does not cross into brain tissue.

NEURONAL SIGNAL RELAY

(Signal travels inward)



Signal is relayed by neurons to deeper brain regions.
Peptide remains at the window.

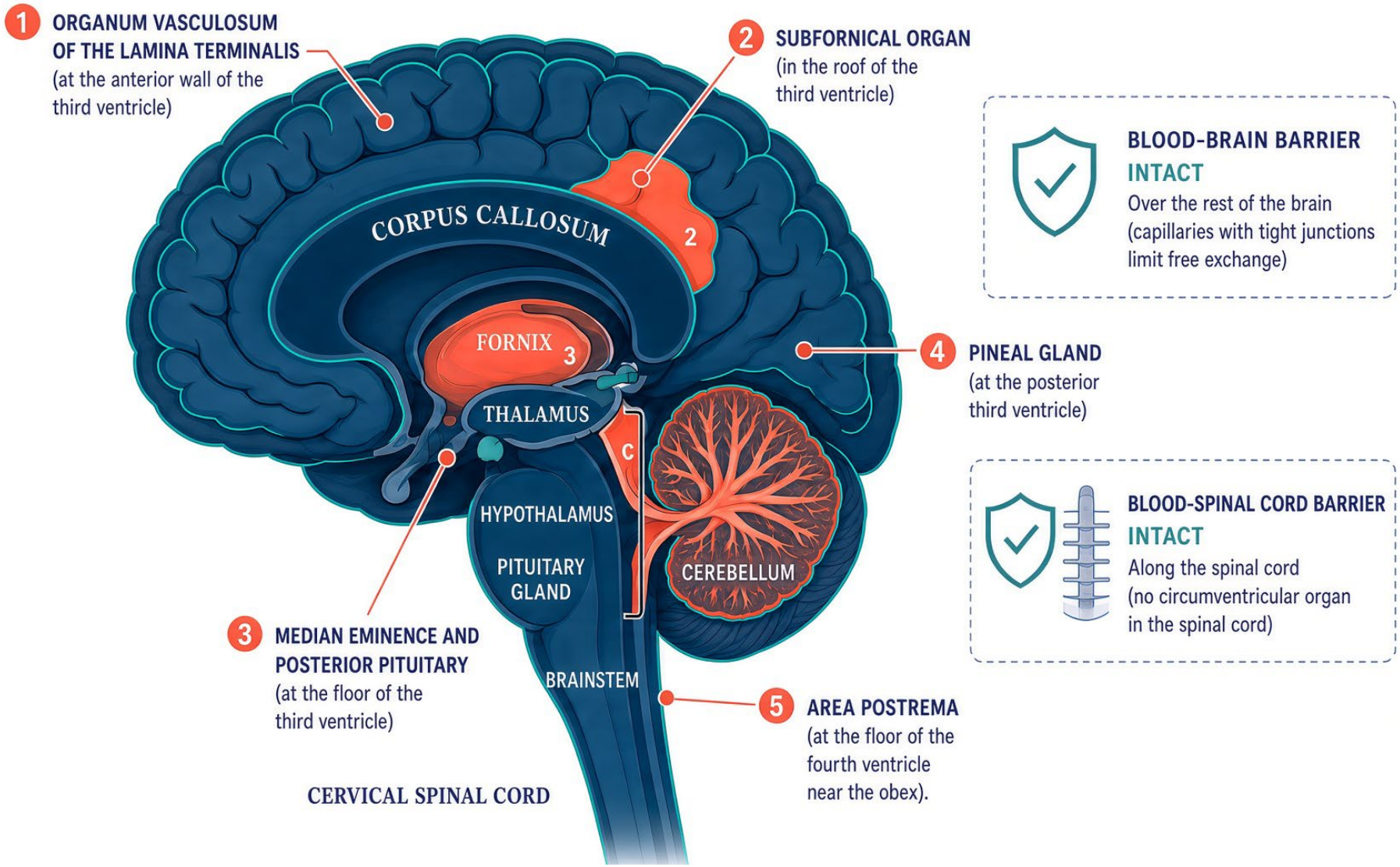


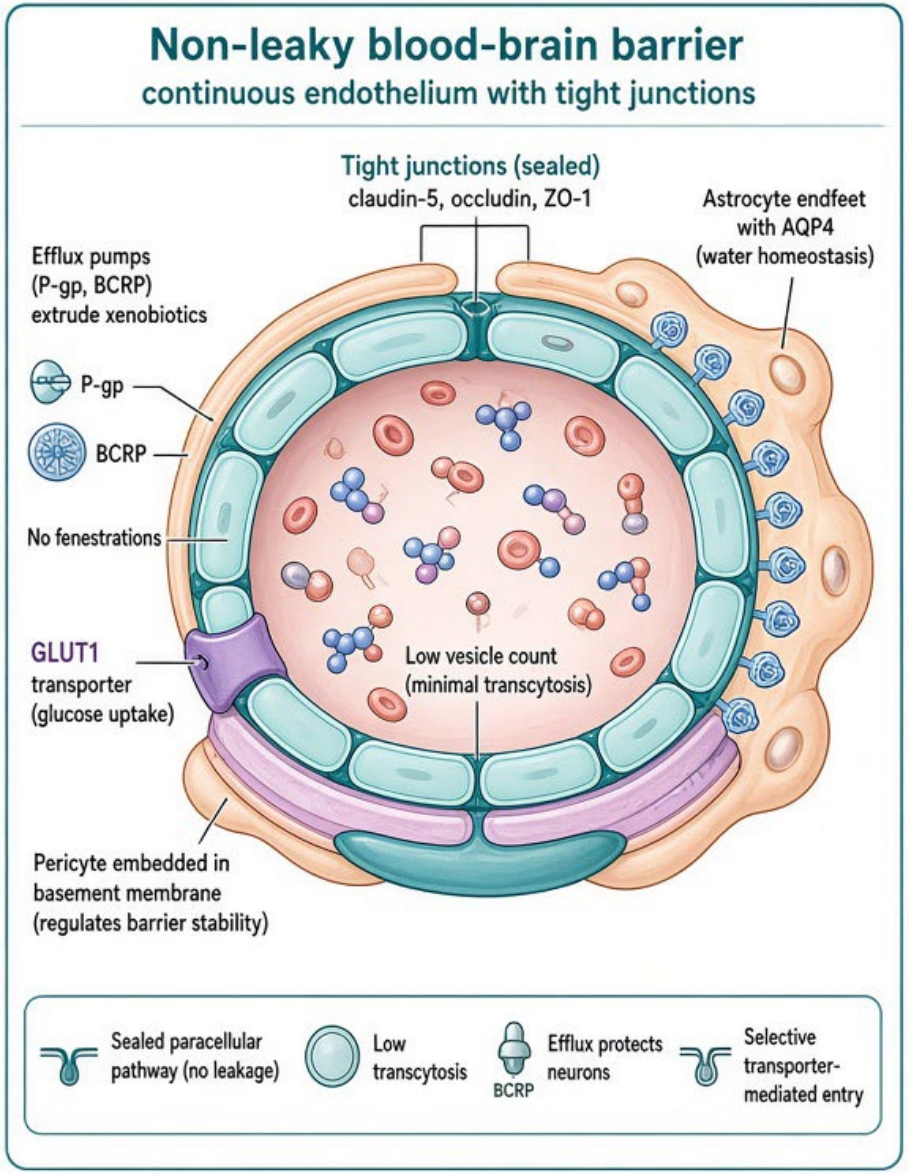
FATTY-ACID CHAIN ON PEPTIDE:
Slows clearance, does not act as a shuttle

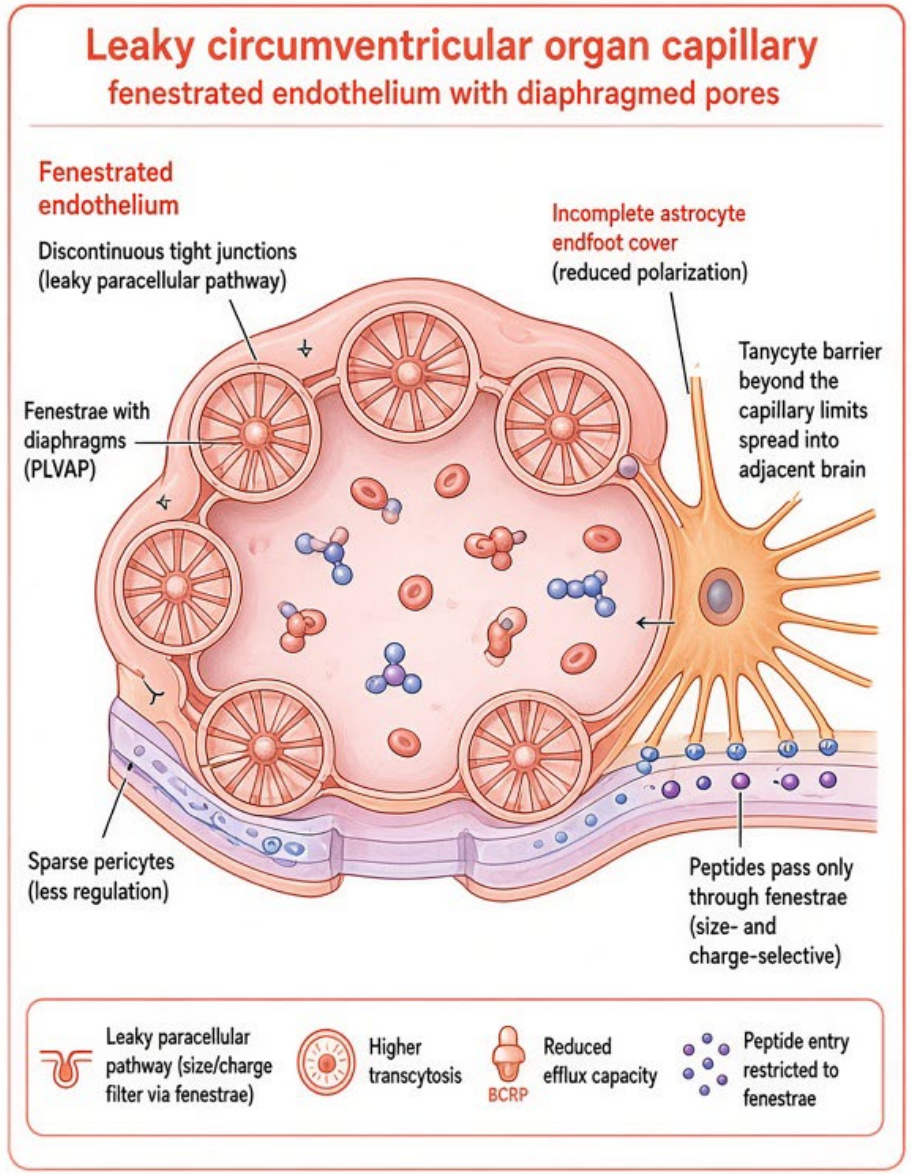
The fatty-acid chain reduces renal clearance and prolongs circulation time.
It does not enable transport across the blood-brain barrier.

BBB = blood-brain barrier | CVO = circumventricular organ

Sagittal section, human brain, leaky BBB areas




Non-leaky blood-brain barrier
continuous endothelium with tight junctions
Tight junctions (sealed)
claudin-5, occludin, ZO-1
Astrocyte endfeet with AQP4 (water homeostasis)
Efflux pumps (P-gp, BCRP) extrude xenobiotics
P-gp
BCRP
No fenestrations
GLUT1 transporter (glucose uptake)
Low vesicle count (minimal transcytosis)
Pericyte embedded in basement membrane (regulates barrier stability)
Sealed paracellular pathway (no leakage)
Low transcytosis
BCRP
Efflux protects neurons
Selective transporter-mediated entry


Leaky circumventricular organ capillary
fenestrated endothelium with diaphragmed pores
Fenestrated endothelium
Discontinuous tight junctions (leaky paracellular pathway)
Incomplete astrocyte endfoot cover (reduced polarization)
Tanycyte barrier beyond the capillary limits spread into adjacent brain
Fenestrae with diaphragms (PLVAP)
Sparse pericytes (less regulation)
Peptides pass only through fenestrae (size- and charge-selective)
Leaky paracellular pathway (size/charge filter via fenestrae)
Higher transcytosis
BCRP
Reduced efflux capacity
Peptide entry restricted to fenestrae

The nose is a second door: it goes around the barrier

How things reach the brain through the nose

In the nose
The olfactory lining in the roof of the nasal cavity sits just below the brain.

↓

Along the nerves
Olfactory nerves pass through the cribriform plate to the olfactory bulb; trigeminal branches run to the brainstem. No brain capillary is crossed.

↓

Into brain and spinal fluid
Within minutes, but under 1% of a dose; most is absorbed into the blood instead.

Who uses the nose? How, why, and where?

- **Approved nasal drugs:** esketamine, butorphanol, naloxone, midazolam enter the blood, then cross the barrier as small molecules; steroid sprays act locally.
- **In trials or sold:** oxytocin, insulin in trials; Semax, Selank sold as drops.
- **COVID-19:** SARS-CoV-2 infects support cells in the olfactory lining, causing loss of smell; entry into the brain this way is debated.
- **Amoeba:** Naegleria fowleri reaches the brain through the cribriform plate, almost always fatally.
- **Herpes simplex:** may reach the brain along olfactory or trigeminal nerves.
- **Limits:** mucus clearance and enzymes destroy most of a nasal dose.

Sources: Lochhead & Thorne, Adv Drug Deliv Rev 2012 (nose-to-brain routes); Brann et al., Sci Adv 2020 (SARS-CoV-2 in olfactory support cells).

“Research use only. Not for human or animal consumption.”

Read that label again. It's on vials people are injecting weekly.

The disclaimer is a legal shield — **for the seller.** It keeps the vendor out of FDA's drug-approval system by denying human use.

It protects you **not at all.** The moment it goes into a person, FDA reads intended use — and a research chemical becomes an unapproved drug with no identity, purity, or sterility guarantee behind it.

OBJECTIVE 3 · BEYOND GLP-1

Beyond GLP-1: a market with no data

GLP-1 drugs went through decades of trials before approval. Dozens of other peptides are now sold online with almost none of that work behind them.

What we know: GLP-1

- **Approved**, backed by large trials
- **Mechanism mapped** from gut to brain
- **Side effects measured** and manageable

What is being sold

- **BPC-157, TB-500** and many others
- **Labeled "research use only,** not for human or animal consumption"
- **Patients buy and inject** them anyway

The catch-22

- **The label lets makers sell** outside FDA's drug rules
- **Asking buyers about injections** would prove intended human use
- **No sponsor, no trial:** clinicians can record, not experiment

Sellers can't ask what happens after injection. Clinicians can record it for an IRB-approved registry.

QUALITY CONTROL

If a patient is going to do this anyway — the red flags

No Certificate of Analysis

no third-party HPLC/MS identity + purity result

No sterility / endotoxin test

no LAL testing — injecting a pyrogen risk

“Research use only” labeling

sold as a chemical, not a medicine

Reconstitution left to the buyer

sterility and dose depend on a layperson

No GMP, unknown origin

overseas bulk, no manufacturing controls

Price too good, claims too big

the two reddest flags, together

OBJECTIVE 3 · EVIDENCE

Signal vs hype: BPC-157 as the test case

Anecdote & marketing — Abundant. Podcasts, forums, influencers.

Human RCTs — None for psychiatric claims, in Western or Russian journals.

Animal / preclinical — Genuinely interesting — tendon, gut, angiogenesis.

My three-question hype test: (1) Is there a receptor and a mechanism? (2) Is there HUMAN evidence, not just animal? (3) Can it even reach the target?

OBJECTIVE 3 · EVIDENCE

GLP-1 drugs now have psychiatric trials; hyped peptides do not

Peptide	Trial	Condition	Status / result
Semaglutide (injected)	Phase 2 RCT, 48 adults, 9 wk	Alcohol use disorder	Less craving, fewer heavy-drinking days; drinking-days unchanged
Semaglutide (oral)	Phase 2 RCT, 50 adults, 8 wk	Alcohol use disorder	Missed craving endpoint; fewer heavy-drinking days
Semaglutide 2.4 mg	RCT, 24 wk, VA (CRAVE)	Alcohol use disorder, veterans	Under way
Semaglutide (oral)	RCT, 72 adults, 16 wk	Depression with overweight	Missed cognition endpoint; better motivation
Oxytocin (nasal)	42 placebo RCTs, meta-analysis	Autism, schizophrenia, addiction	Mixed; largest autism trial negative
ARA-290 (cibinetide)	Phase 2, completed	Sarcoid nerve pain; depression dropped	Phase 2 completed; sponsor closed — no active trials
BPC-157	Phase 2 RCT registered	Hamstring strain	No results; no psychiatric trials

Shaded: GLP-1. Sources: JAMA Psychiatry 2025, 2026; Am J Psychiatry 2026; Neurosci Biobehav Rev 2026; NEJM 2021; IOVS 2017; ClinicalTrials.gov

OBJECTIVE 3 · EVIDENCE

Selank and Semax: Russian trials exist, but small and unreplicated

Selank (anxiety)

- **Approved in Russia** for generalized anxiety and neurasthenia
- **Two small randomized trials,** about 60 patients each
- **Compared with benzodiazepines,** not placebo; similar relief, less sedation
- **One research group,** mostly one Russian journal

Semax (stroke, cognition)

- **Approved in Russia** for stroke and cognitive disorders
- **Largest study: 110 stroke patients;** BDNF and motor scores rose
- **Not randomized,** no placebo arm
- **No trials** for anxiety or depression

Neither has a placebo-controlled trial repeated outside Russia. The problem of negative result studies.

THE LEGAL SPINE

Where you actually stand

THE FEDS (FDA)

- FDA doesn't regulate the practice of medicine.
- But BPC-157 etc. are UNAPPROVED NEW DRUGS — not “off-label.”
- Off Category 2 (April 2026) but not on the 503A compounding list — still not compoundable. A July 2026 panel recommended it; FDA has not acted.
- Enforcement hits sellers & compounders, not prescribers.

THE STATE (TMB)

- Medical Practice Act: standard of care, informed consent, nontherapeutic prescribing.
- Texas CAM rule (22 TAC Ch. 171, Jan 2025): a disclosure-and-consent form.
- Met properly, it documents informed consent — it does not settle the federal question.

THE REALITY

- Not DEA-scheduled — scheduling isn't the issue.
- Risk rises if you source, stock, or sell.
- Compounded tirzepatide now only if NOT “essentially a copy” (FDA flagged the +B12 move).
- Document. Consent. Don't distribute.

Information, not legal advice — confirm specifics with health-law counsel and your carrier before you prescribe.

OBJECTIVE 3 · TEXAS RULE

Texas permits complementary medicine, with signed consent

What the rule allows

- **Alternative:** a diagnosis or treatment most physicians don't consider routine; FDA-approved or not
- **Complementary:** alternative treatment combined with ordinary medicine
- **Condition:** possible benefit must not be unreasonable next to the risk

What the rule requires

- **Before the first dose,** physician and patient read and sign the board's disclosure form
- **Signed form goes in the chart;** no edits except translation or added pages
- **The chart also holds** the usual medical-record items the form lists
- **The rest of the Medical Practice Act** still applies

Sources: 22 Tex. Admin. Code §§171.1–171.2; Texas Medical Board bulletin, Sept 2025.

22 TAC Ch. 171 (eff. Jan 9, 2025) sets a disclosure-and-consent requirement — it governs how, not whether, and doesn't settle the federal question.

THE PARADOX AT THE TOP

Everyone is using them. No one may study them.

On a widely heard podcast (Feb 2026), the HHS Secretary said he has used peptides himself — and wants the FDA to let compounding pharmacies offer them, so people get **“access from ethical suppliers.”**

The incoherence I want you to sit with: the same federal government whose Secretary endorses these molecules keeps them in the category that blocks legitimate study. Maximal use. Minimal knowledge.

MY PRIMARY ARGUMENT

The apparent catch-22

You may treat the patient in front of you.

The moment you systematically prescribe and gather data to LEARN from, you've begun a clinical investigation of an unapproved drug — which needs Formal registration, an IRB etc.



The result: a nationwide uncontrolled experiment is running right now — and the one group apparently forbidden to collect the data is the physicians caring for the subjects.

THE TIE-IN

SI analysis of large data sets works

This morning you heard about AI in psychiatry. Here's what it let us actually do: **we stripped the protected health information out of roughly 2,800 disability exams from my own practice and ran real statistics on them.**

DEFENSIBLE

Observational. De-identified. You administer nothing — you record what's already happening. Find signals, generate hypotheses.

NEEDS IRB / IND

Prospectively giving people an unapproved peptide under a protocol to produce generalizable knowledge. Different animal entirely.

So here's the proposal: a de-identified registry of what patients already report — then design the confirmatory experiments the signals earn — with an IRB determination letter for any publication. That's how residents should be trained to use these tools.

THE TIE-IN · THE LIMITS

AI (SI) drafts fast; licensed experts still decide

Two AI models gave confident, opposite answers to the same questions while I built this talk. Neither carries a license or liability.

Can a clinician run a public website logging patients' peptide use?

My lawyer: a public site — illegal, don't do it.

Grok: legal only if it never sells, links to shops, or gives doses.

Does "research use only" make the sale legal?

Claude, first draft: Yes; it lets reputable makers sell legally.

Grok: No. FDA ignores the label once human use is intended.

Where a skilled human decides

- **Legal exposure:** a health lawyer, not a chatbot
- **Every number and citation:** checked at the source
- **Anatomy:** an AI-drawn brain put the pineal gland in the cortex
- **The clinical call:** the physician signs

AI writes the first draft. A licensed professional still has to sign it.

OBJECTIVE 3 · WHAT'S COMING

What's actually in the pipeline

GLP-1 / incretins	Depression, addiction, neuroprotection	*Human trials underway*
Oxytocin	Social cognition, autism	*Mixed human results*
ARA290 / cibinetide	Innate-repair receptor; neuropathic & inflammatory	*Phase 2 completed; no active trials*
Melanocortins & others	Metabolic, sexual, anti-inflammatory	*Varies by agent*

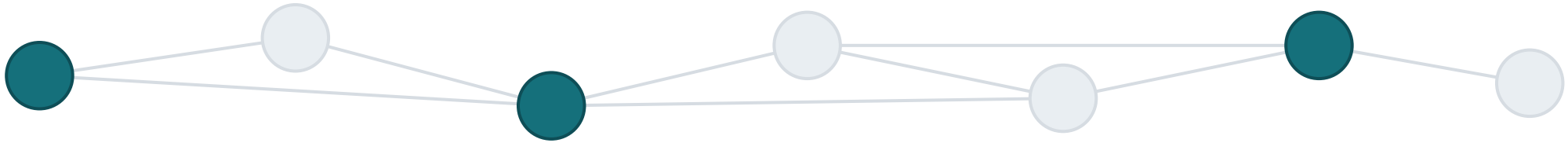
ACCURACY · NAME IT RIGHT

Three drugs, three receptor profiles

Semaglutide	*Wegovy · Ozempic*	**GLP-1 only**
Tirzepatide	*Zepbound · Mounjaro*	**GIP + GLP-1 (NOT GLP-2)**
Retatrutide	*in trials*	**GIP + GLP-1 + glucagon — the "triple"**

Traps: there is no "GLP-3" hormone — it's a nickname for retatrutide's triple action. Proglucagon → glucagon, GLP-1, GLP-2, oxyntomodulin, glicentin. Zepbound is NOT GLP-2; the GLP-2 analog is teduglutide (short-bowel), not a weight drug.

Fast electricity, slow dials



FAST layer — electrical spikes, milliseconds

SLOW layer — peptides set the gain & excitability of the whole field (seconds to minutes)

…which STATE the fast activity settles into (calm · manic · asleep)

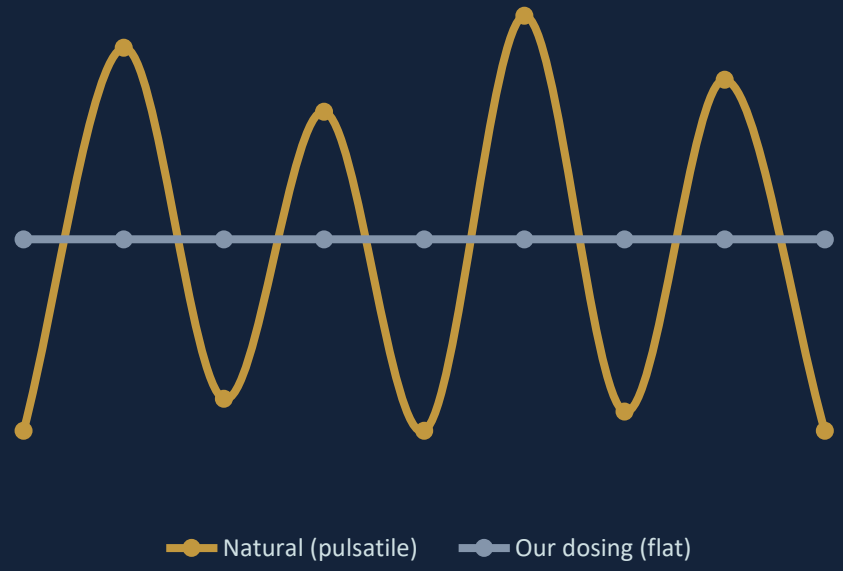
You don't steer each spike — you move the dials that pick the state. State flips are real (sleep, seizure, anesthesia). Driving mania into euthymia with a designed peptide sequence: unproven, not ridiculous.

THE FRONTIER

The brain doesn't do steady-state

Neuropeptide signaling is pulsatile and context-dependent. Our dosing is flat. That gap is the real frontier.

The fantasy worth naming: *a closed-loop implantable pump that releases a neuropeptide on demand. Blocked today by two walls — sensing, and the blood–brain barrier.*



Gut GLP-1 lasts 2 minutes; semaglutide lasts a week

	Native GLP-1 (gut)	Engineered: semaglutide
Released by	Gut L-cells, minutes after a meal	Weekly subcutaneous injection
Half-life	~2 minutes	~1 week (about 165 h)
Cleared by	DPP-4 enzyme, then kidney	Resists DPP-4; albumin binding slows clearance
Reaches blood intact	~10–15% of what is secreted	~89% of the injected dose
Signals mainly via	Vagal nerve endings in gut and portal vein	Receptors in blood, brainstem and hypothalamus
Exposure	Brief, meal-timed pulses	**Continuous, far above physiological levels**

HALF-LIFE, ENGINEERED STEP BY STEP

- **Native GLP-1** ~2 min
  Cut by DPP-4 almost at once
- **Exenatide** ~2.4 h
  Gila monster peptide; resists DPP-4
- **Liraglutide** ~13 h
  Fatty-acid tail binds albumin
- **Semaglutide** ~1 week
  DPP-4-proof swap plus a longer fatty acid

Source: Holst JJ, Physiol Rev 2007; Knudsen LB & Lau J, Front Endocrinol 2019; Ozempic (semaglutide) prescribing information.

WHAT I'M ASKING OF THIS ROOM

Train for this

1

Residency directors

Give residents access to frontier AI models and protect real research time. The grant committee is ready — send us proposals.

2

Every psychiatric patient

A physical, neurologic, and endocrine exam. The systems are one system; you can't read it on a screen.

3

Telemedicine-only

A mistake. You cannot examine a patient you cannot touch. Convenience is not the same as care.

Psychiatry has to expand into the rest of medicine —

as the rest of medicine, and every other kind of "provider," expands into psychiatry.

WHAT I GAVE YOU

Three things to take back to clinic

- A way to think about peptide pharmacokinetics — and what to monitor.
- How these molecules signal, directly and indirectly — and the barrier that defines the field.
- How to separate signal from hype — and exactly how far you're allowed to go in finding out.

Now — where do you think the first signal is hiding?

GLP-1 drugs in addiction: alcohol is the clearest signal

Use disorder	Drug and study	Result
Alcohol	Semaglutide injection, RCT, 48 adults (2025)	Less craving, fewer heavy-drinking days
Alcohol	Oral semaglutide, RCT, 50 adults (2026)	Missed craving goal; fewer heavy-drinking days
Alcohol with obesity	Semaglutide 2.4 mg + CBT, RCT, 108 adults (2026)	−41% on drug vs −26% placebo (~14-pt difference)
Alcohol	Exenatide, RCT (2022)	No overall effect; benefit with obesity
Nicotine	Semaglutide, RCT, 24 smokers (2026)	Less craving; cigarettes per day unchanged
Cocaine	Exenatide, lab study (2021)	No effect
Cannabis	Semaglutide, health-record cohort (2024)	Observational only; RCT registered
Opioids, cocaine	Semaglutide RCTs registered	Under way

Shaded: alcohol. Sources: JAMA Psychiatry 2025; Am J Psychiatry 2026; Lancet 2026; JCI Insight 2022; JAMA Netw Open 2026; Drug Alcohol Depend 2021; Mol Psychiatry 2024; ClinicalTrials.gov

In psychiatry and neurology, GLP-1 gains are metabolic, not the illness

Condition	Drug and study	Result
Schizophrenia, clozapine or olanzapine	Liraglutide, RCT, 103 patients (2017)	Better glucose tolerance; 5.3 kg lost
Schizophrenia, early metabolic change	Semaglutide, RCT, 73 patients (2026)	Lower HbA1c and weight
Schizophrenia on clozapine	Semaglutide, COaST RCT (2026)	13.5% more weight lost; symptoms unchanged
Schizophrenia, antipsychotics	Exenatide, RCT (2017)	No weight difference
Depression with overweight	Oral semaglutide, RCT, 72 adults (2026)	Missed cognition goal; better motivation
Alzheimer's disease	Semaglutide, EVOKE phase 3 (2025)	Did not slow decline
Parkinson's disease	Lixisenatide (2024); exenatide (2025)	Small motor benefit; exenatide none

Shaded: schizophrenia. Sources: JAMA Psychiatry 2017, 2026; Eur Psychiatry 2026; Ishøy 2017; Med 2026; Novo Nordisk 2025; NEJM 2024; Lancet 2025 (expression of concern)

SOURCES

Selected sources

Pharmacology / BBB: Pardridge WM, BBB drug delivery (J Cereb Blood Flow Metab). Banks WA, peptide transport. Merrifield RB, solid-phase synthesis (Nobel 1984). Guillemin & Schally (Nobel 1977).

Regulatory: FDA 503A interim bulk-substances categories (Category 2, Sept 2023). FDA PCAC advisory recommendations, July 23–24, 2026 (non-binding). FDA GLP-1 compounding / “essentially a copy” §503A(b)(1)(D); FDA clarification Apr 1, 2026. 21 CFR 312 (IND); 45 CFR 46 (Common Rule). 22 TAC Ch. 171 (Texas CAM rule, 2025).

Public statements: HHS Secretary interview, Feb 27, 2026 (peptide access).

Fast-moving area: compounding status, any FDA action on the July 2026 recommendations, pipeline trial phases, and current law change month to month — confirm current status.