

Updates in Behavioral Health: Hot Topics and Articles of Relevance to Primary Care

Thomas W. Heinrich, MD, FACLP

Professor of Psychiatry & Family Medicine
Department of Psychiatry & Behavioral Medicine
Medical College of Wisconsin
Milwaukee, WI
theinric@mcw.edu

 CONTINUING EDUCATION COMPANY

1

Disclosure

I have no financial interests or relationships to disclose.

 CONTINUING EDUCATION COMPANY

2

Thomas Heinrich, MD
Updates in Behavioral Health

Learning Objectives

At the Conclusion of This Activity, Participants Should Be Able to:

- 1 Evaluate recent evidence for the psychiatric uses and safety of GLP-1 receptor agonists and psychedelic therapies, distinguishing supported indications from uncertain or negative findings.
- 2 Apply patient-specific screening and counseling strategies related to GLP-1 receptor agonists and psychedelics, including contraindications, medication, and drug-interactions.
- 3 Appreciate the evidence for and against pharmacogenetic testing and how to interpret the reports.

3

PART 1

GLP-1 Receptor Agonists: A Psychiatric Update

Depression · Addiction · Dementia · Antipsychotic Weight Gain · Safety

4

GLP-1 RECEPTOR AGONISTS**Why This Matters in Primary Care****1 in 8**

US adults take a GLP-1 receptor agonist

5 domains

mood, addiction, dementia, weight, and safety

RCTs

Separate signal from hype

Where we will land:

Depression: no

Alcohol use disorder: promising

Dementia and Parkinson's: no

Antipsychotic weight gain: yes

Liebers D. GLP1-RAs: A Psychiatric Update. Carlat Clinical Update.

5

GLP-1 RECEPTOR AGONISTS**How Could a Weight-Loss Drug Act on the Brain?***Plausible Mechanisms***Reward Circuits**

GLP-1 receptors are present in mesolimbic reward pathways

Anti-Inflammatory and Neurotrophic

Reduced neuroinflammation, amyloid, and tau in animal models

Slowed gastric emptying

Delays the rise in blood alcohol

Weight and metabolic effects

The one mechanism that reliably translated into clinical benefit

Klausen MK, et al. Lancet. 2026;407:1687-1698.

6

GLP-1 RECEPTOR AGONISTS • DEPRESSION

Depression: Sound Rationale, Negative Trials

What Was Tested

- First RCT of semaglutide in major depressive disorder with obesity
- Weight loss occurred as expected
- Mood and executive function did not improve

Across the Medical Trials

- GLP-1RAs improved general well-being
- They did not improve depressive symptoms
- Anecdotal reports of anhedonia and emotional blunting have not appeared in trial data

Bottom line

Weight loss may improve well-being, but it is not an antidepressant.

Hung TH, et al. Hum Psychopharmacol. 2026;41(3):e70041.

7

GLP-1 RECEPTOR AGONISTS • ADDICTION

Addiction: From Media Buzz to Controlled Trials

Observational Data Looked Striking; the First RCTs Were More Modest

Observational Studies

- Lower risk of developing a substance use disorder
- Lower overdose risk among people who already have SUD
- Media reports of decreased cravings multiplied as use took off

Randomized Trials

- Semaglutide (non-treatment-seeking AUD): fewer heavy drinking days, but not fewer drinks per calendar day
- Exenatide (small clinical RCT of AUD): no clinical benefit, though fMRI cue reactivity in reward centers fell

Would a larger trial in treatment-seeking patients show clinically meaningful benefit?

Cai M, et al. BMJ 2026. | Hendershot CS, et al. JAMA Psychiatry 2025.

8

GLP-1 RECEPTOR AGONISTS · ALCOHOL USE DISORDER

Semaglutide for Alcohol Use Disorder*26-Week, Single-Center, Double-Blind, Placebo-Controlled RCT***108**treatment-seeking
adults with moderate-
to-severe AUD plus
obesity**2.4 mg**weekly subcutaneous
semaglutide vs placebo,
titrated over 16 weeks**+ CBT**up to 10 standardized
CBT sessions in both
arms**81%**completed 26 weeks;
intention-to-treat
analysis**Primary endpoint**

- Change in the percentage of heavy drinking days from baseline to week 26

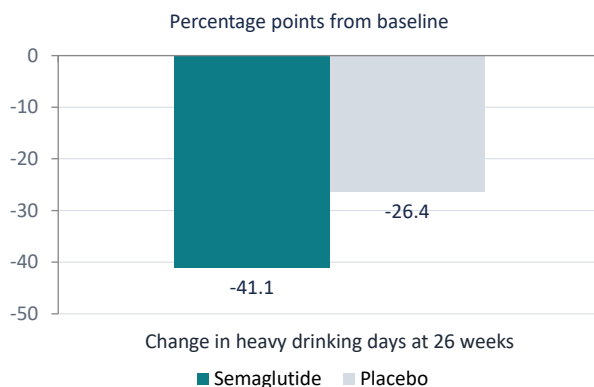
Secondary endpoints

- Total consumption, drinks per drinking day, craving, PETH, LFTs, weight, and BP

Klausen MK, et al. Lancet. 2026;407:1687-1698.

9

GLP-1 RECEPTOR AGONISTS · ALCOHOL USE DISORDER

Result: Fewer Heavy Drinking Days*Both Groups Improved with CBT — Semaglutide Added a Further
14-Percentage-Point Reduction***-13.7 points**estimated treatment difference
(95% CI -22.0 to -5.4; p = 0.0015)**10% more**Days without any alcohol
(p = 0.051)

Klausen MK, et al. Lancet. 2026;407:1687-1698.

10

GLP-1 RECEPTOR AGONISTS · ALCOHOL USE DISORDER

Result: Secondary Outcomes*Self-Report, Peth, Liver Enzymes, and Cardiometabolic Measures All Moved*

Outcome (week 26)	Difference vs placebo	p value
Total alcohol, g per 30 days	−468 g	<0.001
Drinks per drinking day	−1.5	0.005
Alcohol craving (Penn scale)	−3.1 points	0.002
Phosphatidylethanol (PEth)	−0.28 μmol/L	<0.001
γ-glutamyl transferase	−24 U/L	<0.001
Body weight	−9.0 kg (−9%)	<0.001

Klausen MK, et al. Lancet. 2026;407:1687-1698.

11

GLP-1 RECEPTOR AGONISTS · ALCOHOL USE DISORDER

How Big Is the Effect*Number Needed to Treat Compares Favorably with Approved AUD Medications; Adverse Effects Were the Familiar GI Ones***NNT 4.3**

for a 2-level reduction in WHO risk drinking level (95% CI 2.3–30); approved AUD drugs: NNT ≥7

57% vs 7%

nausea with semaglutide vs placebo — transient, mild to moderate; GI effects most common

 $\rho = -0.40$

correlation between weight loss and reduction in heavy drinking days in the semaglutide arm

Caveats before generalizing

- Every participant had comorbid obesity; effect in normal-weight patients with AUD is unknown
- Single center, 26 weeks, 108 participants — durability after stopping is untested
- One serious adverse event on semaglutide (hospital admission); no new safety signals

Klausen MK, et al. Lancet. 2026;407:1687-1698.

12

GLP-1 RECEPTOR AGONISTS · ALCOHOL USE DISORDER

Alcohol Use Disorder: What to Do with This Now

Reasonable Today

- Patient with AUD who meets obesity criteria for a GLP-1RA (BMI ≥ 30 , or ≥ 27 with a weight-related condition)
 - Prescribe for the on-label obesity indication; expect reduced drinking as an added benefit
- Continue evidence-based AUD care
 - Naltrexone, acamprosate, CBT, mutual-help groups

Not Yet Established

- GLP-1RAs as a primary AUD treatment in patients without obesity
- Effects in stimulant or opioid use disorders
 - Trials of are ongoing
- Whether benefit persists after the drug is stopped

Klausen MK, et al. Lancet. 2026;407:1687-1698.

13

GLP-1 RECEPTOR AGONISTS · DEMENTIA

Dementia: Hopes Built on Observational Data

3,808

randomized at 566 sites
in 40 countries

14 mg

oral semaglutide daily
vs placebo, up to 156
weeks

Early AD

amyloid-confirmed MCI
or mild dementia;
mean age 72

CDR-SB

primary endpoint:
change at week 104

The rationale

- Observational cohorts in T2DM demonstrated reduced risk of dementia
- Animal models: less neuroinflammation, amyloid, and tau; preserved blood-brain barrier

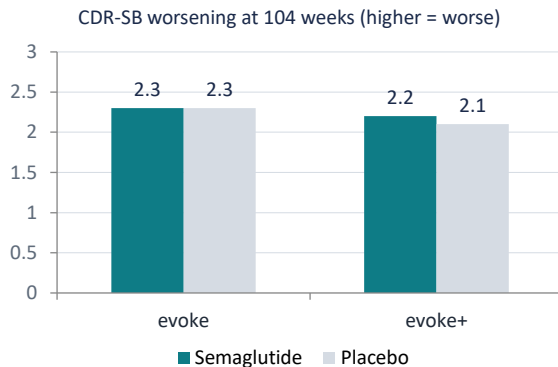
Cummings JL, et al. Lancet. 2026;407:2167-2179.

14

GLP-1 RECEPTOR AGONISTS · DEMENTIA

Dementia: Both Trials Were Negative

*No Slowing of Clinical Progression on Any Global, Cognitive, or Functional Measure;
Both Trials Discontinued*

**Findings**

- Difference: -0.08 ($p = 0.57$) and $+0.10$ ($p = 0.46$); no benefit
- No effect on ADAS-Cog, MMSE, MoCA, function, or behavior
- CSF tau and inflammation markers fell up to 10%; no clinical benefit
- Weight fell 5.8%; nausea 25% vs 7%; no new safety concerns

Cummings JL, et al. Lancet. 2026;407:2167-2179. | Edison P, et al. Nat Med. 2026.

15

GLP-1 RECEPTOR AGONISTS · ANTIPSYCHOTIC WEIGHT GAIN

Antipsychotic Weight Gain

Cardiometabolic Disease Drives the Reduction in Life Expectancy in Schizophrenia

16–20 yr

reduction in life expectancy in schizophrenia, mostly cardiometabolic

Clozapine

the most effective antipsychotic, but the worst for weight and glucose

2–6 kg

typical weight attenuation with metformin, the usual add-on

Two recent randomized trials asked whether semaglutide can weight gain in patients on clozapine or olanzapine; without destabilizing their psychiatric illness

Siskind D, et al. Lancet Psychiatry. 2025;12:493-503. | Sass MR, et al. JAMA Psychiatry. 2026;83(2):128-138.

16

GLP-1 RECEPTOR AGONISTS · ANTIPSYCHOTIC WEIGHT GAIN

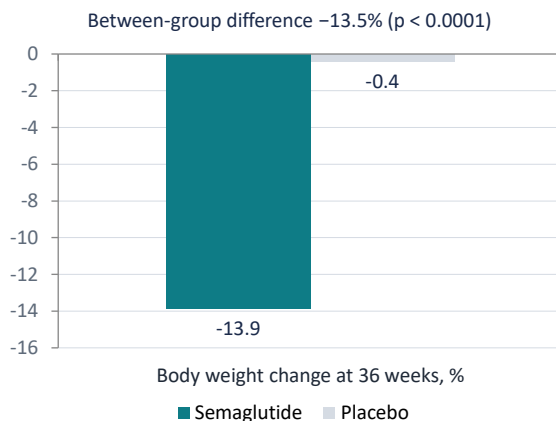
Coast: Semaglutide in Clozapine Treated Schizophrenia*Randomized, Double-blind, Placebo-controlled Trial — Designed with People with Lived Experience***31**adults with
schizophrenia or
schizoaffective
disorder**2.0 mg**weekly semaglutide
vs placebo for 36
weeks**BMI ≥26**on clozapine ≥18
weeks; weight stable
for 3 months**36 wk**primary outcome: %
body weight change**Also measured**

- Clozapine and norclozapine blood concentrations; psychosis symptoms (PANSS); constipation and adverse events
- Recruitment stopped early (target 80) because the study drug became unavailable

Siskind D, et al. Lancet Psychiatry. 2025;12:493-503.

17

GLP-1 RECEPTOR AGONISTS · ANTIPSYCHOTIC WEIGHT GAIN

Coast: Results*The Largest Antipsychotic-Associated Weight Reduction Reported in a Randomized Trial***Findings**

- Two-thirds of semaglutide patients lost ≥10% of body weight
- No change in clozapine or norclozapine concentrations
- No change in PANSS psychosis scores
- No treatment-related serious adverse events; low rates of constipation
- Diarrhea more common with semaglutide; nausea similar

Siskind D, et al. Lancet Psychiatry. 2025;12:493-503.

18

GLP-1 RECEPTOR AGONISTS · ANTIPSYCHOTIC WEIGHT GAIN

Sass Trial: Early Intervention

Multicenter Danish RCT Targeting Patients Before Diabetes Develops

73

randomized; mean
age 35; 65% women;
BMI 36

1 mg

weekly semaglutide
vs placebo for 26
weeks

5.4–7.4%

HbA1c; no
antidiabetic drugs

≤5 years

on clozapine or
olanzapine; age 18–
65

Outcomes

Primary: Change in HbA1c from baseline to week 26

Secondary: Body weight, waist circumference, fat mass, lipids, blood pressure, liver function, psychiatric symptoms (PANSS-6), and safety

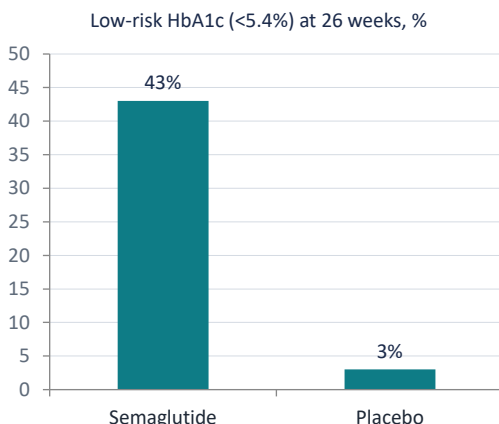
Sass MR, et al. JAMA Psychiatry. 2026;83(2):128-138.

19

GLP-1 RECEPTOR AGONISTS · ANTIPSYCHOTIC WEIGHT GAIN

Sass Trial: Results

Semaglutide Moved Patients Out of the Prediabetic Range Without Affecting Psychiatric Symptoms; NNT 3



Outcome	Difference vs placebo
HbA1c	−0.25% (p < .001)
Body weight	−9.2 kg (≈20 lb)
Waist circumference	−7.0 cm
Fat mass	−6.1 kg
Lipids, BP, liver, PANSS-6	No difference

*GI adverse events common but mild and transient;
psychiatric adverse events similar across groups.*

Sass MR, et al. JAMA Psychiatry. 2026;83(2):128-138.

20

GLP-1 RECEPTOR AGONISTS • SAFETY

Psychiatric Safety

RCTs Across Dementia, Eating Disorders, Mood Disorders, and Schizophrenia Raised No New Psychiatric Safety Concerns

January 2026

FDA removed the suicidality warning from GLP-1RA labeling

No new signals

psychiatric adverse events similar to placebo in the schizophrenia trials

What remains anecdotal

- Reports of anhedonia and emotional blunting; not seen in clinical trials
 - Plausible given GLP-1 receptors in the mesolimbic reward system
 - Ask about loss of pleasure at follow-up in patients with mood disorders

Cummings JL, et al. Lancet. 2026;407:2167-2179.

21

GLP-1 RECEPTOR AGONISTS • SAFETY

Two Practical Warnings

Interactions that Matter When a GLP-1RA Is Started in a Patient on Psychiatric Medication

Lithium toxicity

- Six case reports after starting a GLP-1RA, mostly semaglutide
- Most occurred within the first 2 weeks
- Check a lithium level in that window; counsel on hydration and reduced intake

Slowed gastric motility

- Additive with anticholinergic medications
- Clozapine-related constipation can progress to ileus
- Monitor bowel frequency closely after starting; treat constipation

Liebers D. GLP1-RAs: A Psychiatric Update. Carlat Clinical Update. | Al-Soleiti M, et al. J Clin Psychopharmacol. 2025;45:613-618.

22

GLP-1 RECEPTOR AGONISTS · OPEN QUESTIONS

Other Psychiatric Questions: Still Open

*Areas Where the Evidence Is Mixed or Absent***Binge eating disorder**

Data are mixed; no clear recommendation

Parkinson's Disease

Early phase II trials showed promise, but a larger phase III trial found no improvement in motor symptoms

Psychosis

No change in PANSS scores — neither better nor worse

Other substance use disorders

Trials of more potent GLP-1RAs in amphetamine and opioid use disorders are ongoing

Lieber D. GLP1-RAs: A Psychiatric Update. Carlat Clinical Update.

23

GLP-1 RECEPTOR AGONISTS · SUMMARY

The Verdict: Domain by Domain

Where Controlled Trials Landed as of 2026

Domain	Evidence	Verdict
Antipsychotic weight gain	Two positive RCTs (COaST; Sass): 9–14% weight loss, better HbA1c, no psychiatric destabilization	Use it
Alcohol use disorder	Positive RCT in AUD with obesity: heavy drinking days –14 points, NNT 4.3	Reasonable with obesity
Depression	Negative RCT in MDD with obesity; well-being improved, depression did not	No
Dementia / Parkinson's	Three negative phase 3 AD trials; negative PD phase 3	No
Binge eating disorder	Mixed	Unclear

Lieber D. GLP1-RAs: A Psychiatric Update. Carlat Clinical Update.

24

PART 2

Psychedelic Psychiatry: What Primary Care Needs to Know

Two Drug Classes · Mechanisms · Depression and PTSD Evidence ·
Safety · Counseling

25

PSYCHEDELIC PSYCHIATRY · THE DRUGS

Two Drug Classes

Classic Psychedelics

- Psilocybin, LSD. 5-HT2A agonists producing pronounced alterations in cognition, affect, and perception.
- Session model: eyeshades, music, minimal dialogue, non-directive inner exploration.
- Lead indications: depression, TRD, alcohol and tobacco use disorder, distress in life-threatening illness.

MDMA (Entactogen)

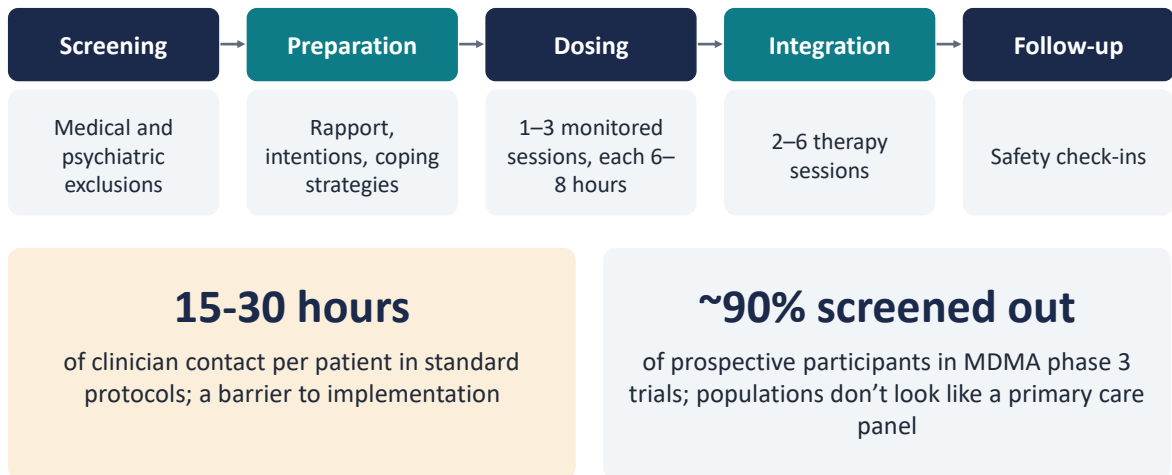
- Releases serotonin, norepinephrine and dopamine
- Less perceptual disruption.
- Session model: active therapeutic dialogue, alternating inner focus and verbal processing.
- Lead indication: PTSD

Jacobs et al., BMJ 2026; McIntyre et al., Am J Psychiatry 2025.

26

PSYCHEDELIC PSYCHIATRY · THE DRUGS

The Delivery Model



Jacobs et al., BMJ 2026; McIntyre et al., Am J Psychiatry 2025.

27

PSYCHEDELIC PSYCHIATRY · MECHANISMS

Is the "Trip" Necessary?

Why This Matters Clinically

- Mechanistic uncertainty is not academic
- Whether the subjective "trip" is essential — or is better understood as a treatment-emergent adverse event — determines whether 6–8 hours of monitoring, specialized facilities, and the risk of hallucinogen persisting perceptual disorder (HPPD) are necessary or avoidable
- Existing controlled data have NOT answered this question

Non-hallucinogenic analogues, that avoid the “trip,” are already in development

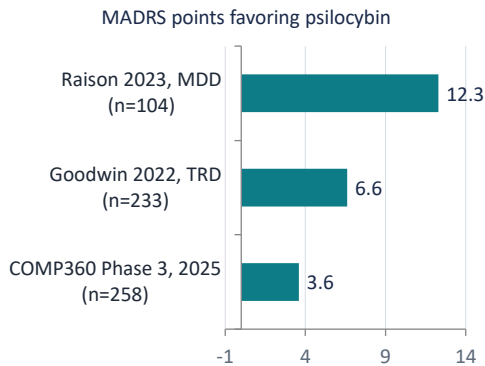
Jacobs et al., BMJ 2026; McIntyre et al., Am J Psychiatry 2025 (see Ly 2018; Moliner 2023; Hesselgrave 2021).

28

PSYCHEDELIC PSYCHIATRY · DEPRESSION

Psilocybin and Depression

As Samples Grow and Blinding Is Tightened, the Effect Estimate Contracts



What Is Solid

- Repeat dosing appears to give cumulative benefit on relapse

What is not solid

- Goodwin 2022: response advantage not sustained at 12 weeks
- Controlled data beyond 12 weeks are lacking for nearly every indication

Raison JAMA 2023; Goodwin NEJM 2022; Carhart-Harris NEJM 2021; Davis JAMA Psychiatry 2021; Jacobs, BMJ 2026.

29

PSYCHEDELIC PSYCHIATRY · PTSD

PTSD and MDMA

Large Effect Size in Two Phase 3 Trials — and an FDA Decision Not to Approve

MAPP1

ES = 0.91

67% vs 32% no longer met PTSD criteria (n=90)

MAPP2

ES = 0.70

remission 46.2% vs 21.4% (n=104)

- Functional unblinding: 94% of MDMA recipients correctly guessed their assignment
- Differential dropout (15.7% placebo vs 1.9% MDMA) suggests nocebo effects in the control arm
- 32% and 46% of participants had prior MDMA experience; recruitment drew heavily from the psychedelic community
- Not blinded, no placebo-controlled data beyond ~2 months

Mitchell Nat Med 2021, 2023; Yang Psychiatry Res 2024; Jacobs, BMJ 2026.

30

PSYCHEDELIC PSYCHIATRY · EMERGING INDICATIONS

Emerging Indications: Addiction and Existential Distress

Promising, but All Include Intensive Psychosocial Treatment

Substance Use Disorders

- Alcohol (n=95): psilocybin + 12 psychotherapy sessions vs diphenhydramine
 - OR 2.84 for confirmed abstinence at 33–36 weeks
 - 90% functional unblinding
- Relapse prevention after withdrawal (n=37)
 - No significant difference vs placebo
- Tobacco (open-label, n=15)
 - 80% abstinence at 6 months
 - Uncontrolled

Distress in Life-Threatening Illness

- Two randomized crossover trials in cancer-related anxiety and depression (n=51; n=31)
 - Large sustained effects at 6 months (Cohen's d 2.98 for depression, 3.40 for anxiety in one trial)
 - At 4.5 years, >60% of surviving participants reported enduring benefit
 - Caveats:
 - Staff correctly guessed assignment for 97%
 - Samples 94% white, 53% postgraduate-educated

Bogenschutz JAMA Psychiatry 2022; Luquiens Addiction 2025; Rieser EClinicalMedicine 2025; Griffiths & Ross J Psychopharmacol 2016; Jacobs, BMJ 2026.

31

PSYCHEDELIC PSYCHIATRY · EMERGING INDICATIONS

Three Structural Gaps

1. Durability

- Controlled data beyond 12 weeks are lacking for most indications
- Relapse rates and retreatment intervals are unknown

2. Equity

- Trial populations are predominantly white, educated, and higher-income
- Generalizability of findings is limited.

3. Economics

- High upfront therapist and facility costs make these more intensive than routine pharmacotherapy.
- Who will pay for it?

Bogenschutz JAMA Psychiatry 2022; Luquiens Addiction 2025; Rieser EClinicalMedicine 2025; Griffiths & Ross J Psychopharmacol 2016; Jacobs, BMJ 2026.

32

PSYCHEDELIC PSYCHIATRY · READING THE EVIDENCE

Four Reasons to Discount the Headlines

None of These Invalidate the Findings — They Set the Width of the Error Bars Around Them

Functional unblinding

- Recipients correctly identified their arm in over 90% of the cases
- Blinding fails almost completely in psychedelic studies

Activated expectancy bias

- Media coverage and "life-changing" testimonials create expectancy that intersects with broken blinding

Medication v. psychotherapy

- No trial has separated drug from psychological support

Durability is unmeasured

- Controlled follow-up rarely extends past 12 weeks.
- Relapse rates and retreatment intervals remain unknown

33

PSYCHEDELIC PSYCHIATRY · SAFETY

Safety: What the Trials Report

Well Tolerated Under Controlled Conditions

Common and Expected

- Psilocybin (6 trials, n=528)
 - Physical: nausea, headache, dizziness, transient BP elevation, anxiety in 4–26%
 - Psychiatric: thought disorder ~5%, paranoia ~2%
- MDMA (3 trials, n=214): hyperhidrosis, chills, mydriasis, nystagmus, blurred vision, reduced appetite

Serious and under-reported

- Suicidal ideation and behavior
- Hallucinogen Persisting Perceptual Disorder (HPPD):
 - ~0.4% of "recreational" users in general populations
- Altered states create vulnerability to boundary violations by providers

Hinkle JAMA Psychiatry 2024; Yerubandi JAMA Netw Open 2024; Colcott Neuropsychopharmacology 2024; Sabé Mol Psychiatry 2025; McIntyre 2025.

34

PSYCHEDELIC PSYCHIATRY · SAFETY

Safety: Whom to Exclude or Refer

Exclude or Refer

- Bipolar I disorder and schizophrenia
- Pre-existing valvular heart disease or pulmonary hypertension
- Pregnancy as teratogenicity risk is uncharacterized
- No pediatric safety or efficacy data exist

Adverse-event reporting is systematically inadequate

- Only 24% of psychedelic studies reporting adverse events used a systematic assessment method
- 56% of non-serious and 31% of serious events on ClinicalTrials.gov never appeared in publications

Hinkle JAMA Psychiatry 2024; Yerubandi JAMA Netw Open 2024; Colcott Neuropsychopharmacology 2024; Sabé Mol Psychiatry 2025; McIntyre 2025.

35

PSYCHEDELIC PSYCHIATRY · INTERACTIONS

Drug–Drug Interactions Worth Knowing

Medication	Evidence	Verdict
SSRIs / SNRIs	Escitalopram pretreatment (n=27) neither compromised psilocybin's effects nor increased adverse effects; an open-label TRD trial with continued SSRIs showed comparable antidepressant response. Subjective effects are often attenuated.	May be continued
Lithium	Retrospective and anecdotal reports link co-use with classic psychedelics to seizures.	Avoid
D2 antagonists	Did not attenuate psilocybin's effects but exacerbated anxiety and thought disturbance; with MDMA, shifts a euphoric profile to a dysphoric one.	Avoid
MAOIs	Combining psychedelics with MAOIs raises the risk of serotonin toxicity and vasopressor effects.	Avoid

Becker Clin Pharmacol Ther 2022; Goodwin Neuropsychopharmacology 2023; Nayak Pharmacopsychiatry 2021; Sarparast Psychopharmacology 2022.

36

PSYCHEDELIC PSYCHIATRY · THE CONVERSATION

The Conversation in Your Exam Room

Questions You Will Actually Be Asked

Q

"Should I Try Microdosing?"

- There is no consensus definition and no controlled evidence for any psychiatric indication
- A study of 109 participants found no benefit over placebo on psychological measures.
- Chronic low-dose 5-HT_{2B} exposure also has the theoretical concern for valvular heart disease

Q

"Can I go to a legal retreat abroad?"

- These agents remain Schedule I.
- Retreats operate outside the structure that produced the trial results.
- If they go anyway... screen for contraindications and drug interactions

Szigeti Elife 2021; Carhart-Harris NEJM 2021; McIntyre et al., Am J Psychiatry 2025; Jacobs et al., BMJ 2026.

37

PSYCHEDELIC PSYCHIATRY · THE CONVERSATION

The Conversation in Your Exam Room (2 of 2)

Questions You Will Actually Be Asked

Q

"Is This Better than My Antidepressant?"

- No! In the only head-to-head trial (n=59), psilocybin did not outperform escitalopram on the primary outcome at 6 weeks.

Szigeti Elife 2021; Carhart-Harris NEJM 2021; McIntyre et al., Am J Psychiatry 2025; Jacobs et al., BMJ 2026.

38

PSYCHEDELIC PSYCHIATRY · TAKE-HOME POINTS

Where This Leaves the Practicing PCP

- 1 The Signal Is Real; the Size Is Unsettled
- 2 Nothing is FDA-approved; nothing is a prescription
- 3 Screen patients for contraindications (medical, psychiatric and polypharmacy)
- 4 Assume harms are under-counted

39

PART 3

Pharmacogenomics and Psychiatry

Two Cases · How Testing Works · Does It Improve Outcomes? · What to Do in Primary Care

40

PART I

A Couple of Cases for Your Consideration

Two Patients with Depression, One Question: Would a Pharmacogenomic Test Change What You Do?

41

PART I • CASE 1

A Case

A 24-Year-Old Woman Complains of Feeling Tired and Sad for the Last Few Months

History and Findings

- Past medical history: obesity, fibromyalgia, and seizure disorder.
- Loss of interest in her usual hobbies; eating more than normal.
- PHQ-9 is 22.
- Denies any history of mood disorder, anxiety, or substance use.
- After examination, you diagnose major depression.

The Question

- This is a first depressive episode with no prior antidepressant trials.
- Would ordering a pharmacogenomic test before the first prescription change your choice, or the outcome?

42

PART I • CASE 2

A (Slightly More Complicated) Case

*A 28-Year-Old Man Reports Feeling Tired and Sad for the past Few Months.
He Was Started on Vortioxetine 8 Weeks Ago*

History and findings

- Past medical history: obesity (BMI 32), hypertension, TBI with possible seizure disorder, and major depression
- Loss of interest, fatigue, poor concentration; no side effects noticed on vortioxetine
- PHQ-9 is 21 today (20 four weeks ago, 22 eight weeks ago)
- Denies mania, anxiety, or substance use
- Family history: younger brother died of "something heart related" at age 22
- As a side note, he reports an "allergy" to SSRIs
- After examination, you diagnose continued depression

43

PART I • CASE 2

The Chart Review: Five Failed Trials

Prior medication	Outcome
Sertraline 100 mg	Did not help
Paroxetine 40 mg	Discontinuation syndrome
Escitalopram 10 mg	Side effects AND did not help
Venlafaxine 75 mg	Side effects AND did not help
Aripiprazole (unknown dose, augmenting sertraline)	Did not help
Vortioxetine (current, 8 weeks)	No response, no side effects

He asks about genetic testing

- Psychiatry is booking out 6 to 7 months.
- He has read that a cheek swab can tell him which antidepressant will work.

44

PART II · HOW PGX WORKS

How Pharmacogenomic Testing Works

From Genome to a Pretty Colored Report: What the Phenotypes Mean and Which Antidepressants Are Affected

45

HOW PGX WORKS

From Genome to a Report

1

Genome

- Each person carries many genetic variants that affect a medication's pharmacokinetics and pharmacodynamics

2

Determination of genetic variations

- Typically a cheek swab or blood sample tested for CYP2D6, CYP2C19, and a handful of other genes

3

Proprietary combinatorial algorithm

- Each company has its own unpublished algorithm
- Two companies given the same DNA can produce different recommendations

4

A report with recommendations on specific drugs

- The output is a color-coded drug table
- Patients read this as a prediction of which drug will work (green)
- However, it is mostly a prediction of drug levels

Baum ML, et al. Am J Psychiatry. 2024;181(7):591-607· Bousman CA, Dunlop BW. Pharmacogenomics J. 2018

46

HOW PGX WORKS

What the Tests Look For

Pharmacokinetic Genes

- Variants in CYP2D6, CYP2C19, CYP3A4 and to a lesser extent CYP2C9, CYP2B6, and CYP1A2, determine how fast a drug is cleared
- The result is expressed as a metabolizer phenotype
 - This is the one part of the report with clear pharmacologic meaning and FDA-label support

Pharmacodynamic Genes

- Variants in genes encoding serotonin receptors (HTR2A), the serotonin transporter (SLC6A4), and others
- These are marketed as predictors of response, but effect sizes are small and inconsistently replicated
- guidelines do not recommend acting on them.

Rosenblat JD, Lee Y, McIntyre RS. J Clin Psychiatry. 2017;78(6):720-729 · Besterman AD, et al. Am J Psychiatry. 2025

47

HOW PGX WORKS

The Four Metabolizer Phenotypes

Poor metabolizer (PM)

Two non-functional alleles
Clearance severely slowed

Intermediate metabolizer (IM)

One reduced-function allele
Clearance moderately slowed

Extensive metabolizer (EM)

Two functional alleles
Standard “normal” clearance

Ultrarapid metabolizer (UM)

Gene duplication or gain-of-function
Clearance increased

Example:

- CYP2D6: Roughly 5–10% of people of European ancestry are poor metabolizers and 1–10% are ultrarapid metabolizer
- Frequencies vary substantially by ancestry

Rosenblat JD, Lee Y, McIntyre RS. J Clin Psychiatry. 2017;78(6):720-729 · Besterman AD, et al. Am J Psychiatry. 2025

48

HOW PGX WORKS

Metabolizer Phenotypes

Phenotype	Clearance	Clinical consequence	Approximate adjustment for a substrate drug
Poor metabolizer	Severely slowed	Higher drug levels; risk of adverse drug reactions and intolerance at standard doses	Lower dose by 30–70%, or choose a drug that uses another pathway
Intermediate metabolizer	Moderately slowed	May or may not raise levels; more susceptible to inhibiting co-medications	Watch carefully; consider a lower starting dose
Extensive (normal) metabolizer	Unchanged	Expected kinetics	Standard dosing
Ultrarapid metabolizer	Accelerated	Lower drug levels; risk of therapeutic failure	Maximum eventual therapeutic dose may increase by 135–180%, or choose an alternative medication

Adapted from Nurnberger J. Genetic testing: what you need to know in 2021. The Carlat Psychiatry Report. 2021;19(6/7)

49

HOW PGX WORKS

Antidepressant Elimination Pathways

Antidepressant	Major pathway	Other pathways	Antidepressant	Major pathway	Other pathways
Citalopram	CYP2C19	CYP3A4, CYP2D6	Duloxetine	CYP1A2	CYP2D6
Escitalopram	CYP2C19	CYP3A4, CYP2D6	Levomilnacipran	Renal	CYP3A4, CYP2C8, CYP2C19, CYP2D6, UGT
Fluoxetine	CYP2D6	CYP2C9, CYP2C19, CYP3A4	Bupropion	CYP2B6	—
Paroxetine	CYP2D6	CYP3A4	Mirtazapine	CYP2D6, CYP3A4	CYP1A2, UGT
Sertraline	CYP2B6	CYP2C19, CYP2C9, CYP3A4, CYP2D6	Vilazodone	CYP3A4	CYP2C19, CYP2D6
Venlafaxine	CYP2D6	CYP3A4	Vortioxetine	CYP2D6	CYP3A4, CYP2C19, CYP2C9, CYP2A6, CYP2C8, CYP2B6
Desvenlafaxine	Renal	UGT, CYP3A4			

Adapted from prescribing information and CPIC guideline tables · Hertz DL, et al. Am J Health Syst Pharm. 2024

50

HOW PGX WORKS**When Testing May Help, and When It Is Less Useful****Situations where a test may add value**

- Multiple failed medication trials
- Significant side effects at normal doses
- Polypharmacy where drug-drug-gene interactions accumulate
- Personal or family history of poor response or adverse reactions to psychotropics
- Medically complex or older patients in whom an avoidable adverse reaction carries higher stakes
- A report the patient already has in their hand (in front of you, demanding answers...)

Besterman AD, et al. Am J Psychiatry. 2025 · Malik S, et al. J Child Adolesc Psychopharmacol. 2024 · Young C, MacDougall D. CADTH Horizon Scan. 2023

51

HOW PGX WORKS**When Testing May Help, and when It Is Less Useful****Where Testing Is Less Useful**

- First-line treatment of mild-to-moderate depression
- To predict overall treatment success: reports are good at flagging drugs likely to reach unusual levels, not at choosing the drug most likely to work.
- As a substitute for a careful medication history, measurement-based follow-up, or psychiatric consultation
- In children and adolescents, where AACAP explicitly recommends against routine use

Besterman AD, et al. Am J Psychiatry. 2025 · Malik S, et al. J Child Adolesc Psychopharmacol. 2024 · Young C, MacDougall D. CADTH Horizon Scan. 2023

52

HOW PGX WORKS

The Promise: What Testing Is Supposed to Improve

Fewer adverse drug reactions

Avoid high levels in poor metabolizers

Fewer drug switches

Skip the drugs that were never going to work at a normal dose

Fewer dose adjustments

Dose where the patient's kinetics say to start

Faster response and remission

Shorten the trial-and-error sequence that defines depression care

How reports are used versus how they are built

- Treatment outcomes depend on both pharmacokinetics and pharmacodynamics, and most PGx clinical support tools report a panel of individual variants across both
- The reports are structured to inform dosing
- They are NOT guides to the probability of clinical response

Karamperis K, et al. Economic evaluation in psychiatric pharmacogenomics: a systematic review. *Pharmacogenomics J.* 2021;21(4):533-541

53

PART III · THE EVIDENCE

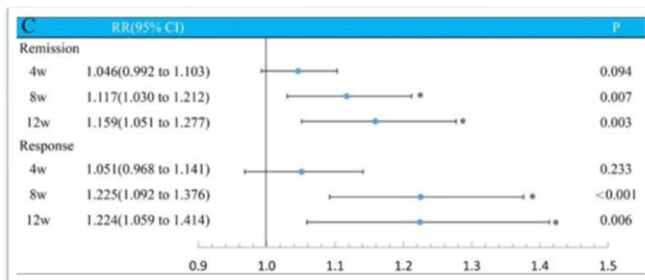
Does Testing Improve Outcomes?

A Single-Center RCT, the Largest Pragmatic Trial, a Meta-Analysis, Concordance Between Tests, and What Professional Organizations Conclude

54

THE EVIDENCE • RANDOMIZED TRIAL

Xu 2024: A Single-Center Trial



Design

- 665 patients with depressive disorder randomized 1:1 to PGx-guided prescribing (n = 333) or clinician-judgment usual care (n = 332)
- Single center in China; **clinicians were not blinded**

Results

- No difference at week 4
- Week 8: remission 24.0% vs 15.1% (P = .007); response 39.3% vs 25.7% (P < .001)
- Week 12: remission 31.0% vs 20.0% (P = .003); response 48.7% vs 37.3% (P = .006)
- Fewer adverse drug reactions in guided group

Xu L, et al. J Affect Disord. 2024;359:117-124.

55

THE EVIDENCE • RANDOMIZED TRIAL

Xu 2024: Adverse Drug Reactions

5

AEs in which the PGx-guided group had significantly fewer events than usual care

12 weeks

duration of follow-up; adverse reactions were a secondary outcome

Unblinded

clinicians knew allocation, and adverse events were clinician-assessed

Domains with lower rates in the guided group

Insomnia
Hypersomnia
Abnormal liver function tests
Abnormal electrocardiogram
Loss of appetite or anorexia

Xu L, et al. J Affect Disord. 2024;359:117-124.

56

THE EVIDENCE • THE LARGEST PRAGMATIC TRIAL

PRIME Care: A Multicenter VA Study

Remission (PHQ-9 ≤ 5)	PGx-guided, n (%)	Usual care, n (%)	OR (95% CI)	P
4 weeks	86 (9.4)	72 (8.0)	1.21 (0.82–1.59)	.27
8 weeks	121 (14.7)	95 (11.3)	1.38 (1.05–1.81)	.02
12 weeks	131 (16.5)	92 (11.2)	1.59 (1.21–2.10)	.001
18 weeks	119 (15.8)	105 (13.6)	1.21 (0.84–1.57)	.14
24 weeks	130 (17.2)	126 (16.0)	1.11 (0.84–1.47)	.45

Design

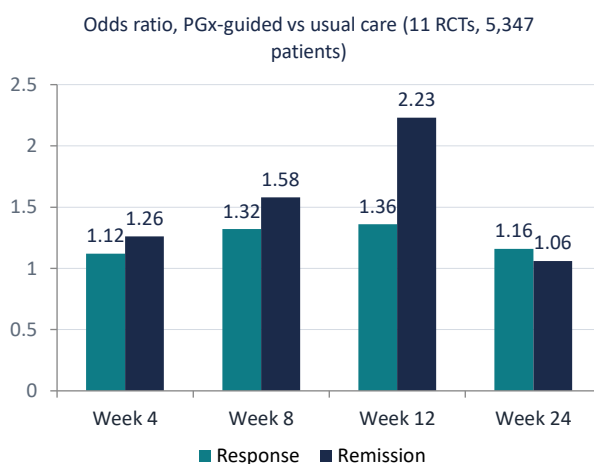
- 1,944 veterans with MDD starting or switching an antidepressant at 22 VA centers; 676 clinicians; open-label; blinded raters.
- Co-primary outcomes: prescriptions with a predicted drug-gene interaction in the first 30 days, and remission over 24 weeks.

Oslin DW, Lynch KG, Shih MC, et al. JAMA. 2022;328(2):151-161

57

THE EVIDENCE • META-ANALYSIS

Wang 2023: A Meta-Analysis



Statistically Significant

- Response: week 8 OR 1.32 (1.15–1.53); week 12 OR 1.36 (1.15–1.62)
- Remission: week 8 OR 1.58 (1.31–1.92); week 12 OR 2.23 (1.23–4.04)

Not significant

- Response: Week 4 OR 1.12, (0.89–1.41); week 24 OR 1.16 (0.96–1.41)
- Remission: Week 4 remission OR 1.26 (0.93–1.72); week 24 OR 1.06 (0.83–1.34)

Wang X, Wang C, Zhang Y, An Z. BMC Psychiatry. 2023;23(1):334

58

THE EVIDENCE • DO THE TESTS AGREE?

Agreement Between Tests

965

medication recommendations
when the same panel of patients'
DNA was run through four PGx
tools

59%

of recommendations concurred
across tools (565 of 965)

41%

of recommendations did not
concur (400 of 965)

Why the tools disagree

- They test different genes and different variants within those genes
- They apply different, proprietary algorithms to translate genotype into a colored recommendation
- The divergence arises primarily in the drug-level recommendation

What that means at the point of care

- The tools are not interchangeable
- Evidence for one product does not transfer to another
- The pharmacokinetic core (CYP2D6 and CYP2C19 phenotype) is the most reproducible content
- The drug ranking is the least reproducible

Bousman CA, Dunlop BW. Pharmacogenomics J. 2018;18(5):613-622

59

THE EVIDENCE • PROFESSIONAL VERDICTS

The American Psychiatric Association

2018 Council on Research Report

- No randomized controlled trial of any PGx clinical support tool had demonstrated efficacy on its primary clinical endpoint
- All studies had serious methodological weaknesses: absent or improper blinding, apparent conflicts of interest, small samples
- **Conclusion: insufficient evidence to support widespread use of combinatorial PGx tools in the treatment of depression.**

2024 Update

11 New Trials and 5 Meta-Analyses

- Three trials (27%) met their primary endpoint
 - All with different tools
 - One open-label and two small single-blind studies.
- Five (45%) found no significant benefit on any primary or secondary outcome
- None was fully blinded; only two attempted to blind the treating clinician
- **Conclusion: the evidence does not support the use of currently available combinatorial PGx tools for treatment selection in depression.**

Baum ML, Widge AS, Carpenter LL, et al.; APA Workgroup on Biomarkers and Novel Treatments. Am J Psychiatry. 2024;181(7):591-607

60

THE EVIDENCE • CLINICAL PRACTICE GUIDELINES

No US Psychiatric Guideline Recommends Testing

Gene–drug pair	Guideline	Testing recommendation
CYP2C19–antidepressants; CYP2D6–antidepressants	VA/DoD: Management of major depressive disorder (2022)	Insufficient evidence to recommend for or against
	AACAP: Clinical use of pharmacogenetic tests in prescribing psychotropic medications for children and adolescents (2020)	Not recommended
CYP2D6–antipsychotics	APA: Practice guideline for the treatment of patients with schizophrenia (2020)	Defers to FDA labeling
	AACAP (2020)	Not recommended
CYP2D6–atomoxetine; CYP2D6–stimulants	AAP: Clinical practice guideline for ADHD in children and adolescents (2019)	Not recommended

Adapted from Hertz DL, Bousman CA, McLeod HL, et al. Am J Health Syst Pharm. 2024;81(16):672-683

61

SUMMARY • BARRIERS AND PRACTICE RECOMMENDATIONS

What to Do with Pharmacogenomic Testing in Primary Care

Uncertain
evidence

Uncertain
generalizability

Inconsistent
guidelines

Education and
equity

Practice recommendations

- Do not order PGx testing before a first standard antidepressant in uncomplicated depression
- Consider testing after two or more failed or poorly tolerated trials, in polypharmacy, or with a family history of poor tolerability
- Set expectations for a modest benefit to the testing with the patient
- Use the CYP phenotypes and match the drug's elimination pathway
- Treat the pretty color-coded drug ranking and pharmacodynamic genes as secondary information
- Never let a report override comorbidity, family history, cost, or the patient's response history

Young C, MacDougall D. CADTH Horizon Scan. 2023 • Baum ML, et al. Am J Psychiatry. 2024 • Hertz DL, et al. Am J Health Syst Pharm. 2024

62

SUMMARY · WHAT EACH CASE TEACHES

Back to the Two Cases

Case 1 — First Episode, No Prior Trials

- Testing is unlikely to change the choice or the outcome.
- Start a first-line agent and follow the PHQ-9.

Case 2 — Long History, Many Failed Trials

- The phenotype explains the history and rules out a few drugs
- The comorbidities and family history rule out others.

In both, the most valuable tool is a good history (medical, family, and medication)

Young C, MacDougall D. CADTH Horizon Scan. 2023 · Baum ML, et al. Am J Psychiatry. 2024 · Hertz DL, et al. Am J Health Syst Pharm. 2024

63

PART 4

Words Matter: Plain Language in the Era of Open Notes

Patient Preferences for Plain-Language Alternatives to Medical Jargon in Clinical Notes

64

PLAIN-LANGUAGE ALTERNATIVES TO MEDICAL JARGON

Your Notes Are Now Patient-Facing Documents

61%

of respondents read their clinician's notes always (39%) or often (22%)

91%

of respondents read them at least sometimes

2016

21st Century Cures Act mandates access to clinical notes

Two kinds of problem language

- Medicalized English: words mean something different, sometimes opposite, in medicine
 - A "negative" test result is good news; "negative" in ordinary usage is not.
- Judgmental jargon: words that read as offensive or critical even though the clinician did not intend them that way

Why it is worth your attention

- Written jargon in notes is linked to patient confusion, dissatisfaction, mistrust, and reluctance to recommend the clinician

Allen KA, Kelly MM, Pitt MB, et al. J Gen Intern Med. 2026.

65

PLAIN-LANGUAGE ALTERNATIVES TO MEDICAL JARGON

Methods

1**Setting and recruitment**

- Survey administered on iPads at the University of Minnesota's Driven to Discover research pavilion at the 2023 Minnesota State Fair
- Eligibility: age 18 or older, English-speaking, no medical or nursing training

2**Participants**

- 276 adults consented and participated
- Mean age 45 years, 56% women, and 67% held a bachelor's degree or higher

3**Instrument**

- Nine clinical scenarios that described a situation
- Participants asked to imagine reading their doctor's note and to choose among traditional documentation, plain-language alternatives, and an open "other" field

4**Analysis**

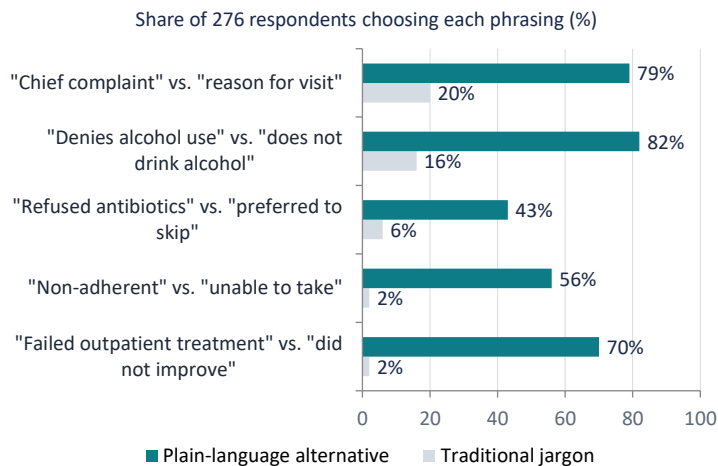
- Descriptive statistics plus inductive and deductive thematic analysis of the free-text comments

Allen KA, Kelly MM, Pitt MB, et al. J Gen Intern Med. 2026.

66

PLAIN-LANGUAGE ALTERNATIVES TO MEDICAL JARGON

Results



Reading the bars

- "Preferred to skip" and "declined" split the antibiotic scenario evenly at 43% each; only 6% chose "refused."
- "Non-compliant" and "non-adherent" were equally disfavored at 2% each.

In their own words

- One respondent said "denies alcohol use" made it feel as though the clinician thought they were lying.
- Another noted that calling a symptom a complaint might keep people from coming in next time.

Allen KA, Kelly MM, Pitt MB, et al. J Gen Intern Med. 2026.

67

PLAIN-LANGUAGE ALTERNATIVES TO MEDICAL JARGON

A Swap List

Framework principle	Commonly used phrase	Preferred alternative
Empathy and affirmation	Chief complaint	Reason for visit or "is here for symptoms of," "the patient presents with"
	Denies	Does not or "reports not using," "has not had"
	Non-adherent / non-compliant	Unable to take due to... or "stopped taking because..."
Clarity and simplicity	Dyspnea	Trouble breathing, difficulty breathing, or shortness of breath
	Strict return precautions	You should return for the following reasons; we discussed reasons to return
	Cheaper	Less expensive; or omit the financial reference entirely
Inclusiveness	Refused	Preferred to skip; declined; chose not to take
	Failed outpatient treatment	Did not improve on oral antibiotics at home; treatment was unsuccessful

Allen KA, Kelly MM, Pitt MB, et al. J Gen Intern Med. 2026.

68

PLAIN-LANGUAGE ALTERNATIVES TO MEDICAL JARGON

Why Patients Chose as They Did: Eight Themes

Clear and thorough

Easy to understand, with the reasoning behind the plan included

Objective and accurate

Just the facts, accurately reflecting the patient's own words

Empathetic and affirming

Respectful, free of judgment, blame, or stigma

Autonomy and agency

Language that emphasizes the patient's right to choose

Direct and concise

Focuses on appropriate content without extraneous information

Financial Neutrality

Do not make assumptions or references to cost concerns or ability to pay

Recognition of patient dependency

Acknowledge considerations when dealing with patients who are dependent on Others (kids)

Maintenance of professional tone

Describes maintaining professional decorum and relationships

Allen KA, Kelly MM, Pitt MB, et al. J Gen Intern Med. 2026. doi:10.1007/s11606-026-10353-2

69

LIMITS AND WHAT TO CHANGE

Limitations to State — and What to Change This Week

Limitations

- Single-site convenience sample at one state fair, entirely in Minnesota, English-speaking only
- Respondents were more educated than the general population
- Hypothetical scenarios are not the same as reading a note about yourself
- No data collected on medical history or disability status

What to Think About

- Read AI-drafted notes with this in mind: ambient documentation tools are trained on historical notes, which are full of exactly this jargon.
- The authors do not argue for eliminating jargon; notes remain how clinicians communicate with each other.
- They argue for recognizing it and substituting where it costs nothing.

Allen KA, Kelly MM, Pitt MB, et al. J Gen Intern Med. 2026. doi:10.1007/s11606-026-10353-2

70

ARS Question #1

A 29-Year-Old Man with Schizophrenia, Stable on Clozapine for 2 Years, Has Gained 15 kg (BMI Now 34) with an HbA1c of 6.1%. Metformin 2 g Daily Produced Only 3 kg of Weight Loss. His Psychiatrist Asks You to Co-Manage His Cardiometabolic Risk. Which Intervention Has the Strongest Recent RCT Support?

- A. Add weekly semaglutide
- B. Add topiramate
- C. Reduce the clozapine dose by 50%
- D. Switch clozapine to aripiprazole



71

ARS Question #2

After a Discussion of the Various Options, the Patient Elects to Trial Semaglutide to Target His Obesity. What Should Receive Particular Attention During Follow-Up?

- A. Development of clozapine toxicity
- B. Bowel frequency and constipation
- C. Emergence of tardive dyskinesia
- D. Reduction in the clozapine concentration



72

ARS Question #3

A 41-Year-Old Woman with Bipolar Disorder, Stable on Lithium 900 mg Daily for Years, Started Semaglutide for Obesity 10 Days Ago. She Now Reports Nausea, Vomiting, a New Coarse Tremor, and Feeling "Foggy." What Is the Most Important Immediate Step?

- A. Check TSH, since lithium causes hyperthyroidism
- B. Diagnose serotonin syndrome and stop all serotonergic drugs
- C. Reassure her that these are common GLP-1RA side effects and will pass
- D. Check a serum lithium level



73

ARS Question #4

A 44-Year-Old Man Tells You He Has Booked a Psilocybin Retreat Abroad Next Month. His Medications Are Sertraline 100 mg, Lithium 600 mg, Atorvastatin, and Metformin. Which Medication Is the Greatest Safety Concern?

- A. Lithium, because co-use with classic psychedelics has been linked to seizures
- B. Atorvastatin, because of additive myopathy risk
- C. None; the combination is safe under retreat supervision
- D. Sertraline, because SSRIs blunt the effect of psychedelics



74

ARS Question #5

A Well-Read Patient Cites the Large Effect Size in an MDMA-Assisted Psychotherapy Trial as Proof That the Medication Alone Is Highly Effective for PTSD. Which Limitation Most Directly Challenges That Conclusion?

- A. Participants could not distinguish MDMA from placebo
- B. Trials separated the medication effect from psychotherapy
- C. Functional unblinding was extensive
- D. The trials followed participants for several years



CONTINUING EDUCATION COMPANY

75

ARS Question #6

A 43-Year-Old Patient With Obesity and Major Depression Asks Whether Semaglutide Could Replace Her Antidepressant Because Losing Weight Might Improve Her Mood. Which Response Best Reflects the Current Evidence?

- A. Semaglutide has established antidepressant efficacy
- B. Semaglutide improves depression only when obesity is present
- C. Weight loss may improve general well-being, but semaglutide has not demonstrated antidepressant effects
- D. Semaglutide should be added routinely to antidepressant treatment as an augmentation strategy



CONTINUING EDUCATION COMPANY

76

ARS Question #7

A Patient Develops Marked Adverse Effects at a Standard Dose of a Medication That Relies Heavily on CYP2D6 for Elimination. Testing Identifies the Patient as a CYP2D6 Poor Metabolizer. Which Explanation and Response Are Most Appropriate?

- A. Accelerated clearance caused a low drug concentration, so the dose should increase
- B. Slowed clearance likely produced a high drug concentration, so a lower dose or an alternative pathway should be considered
- C. The phenotype predicts lack of pharmacodynamic response but provides no dosing information
- D. The result proves that every CYP2D6 substrate will be ineffective



CONTINUING EDUCATION COMPANY

77

ARS Question #8

A Patient Reports That She Does Not Drink Alcohol. Which Documentation Is Most Consistent with Patients' Preferred Plain-Language Alternatives?

- A. Patient denies alcohol use
- B. Patient claims not to drink
- C. Patient reports no alcohol use
- D. Patient's history is negative for alcohol



CONTINUING EDUCATION COMPANY

78

REFERENCES

References — GLP-1 Receptor Agonists

Liebers D. GLP1-RAs: a psychiatric update. *Cariat Clinical Update*.

Pierret ACS, Mizuno Y, Saunders P, Lim E, De Giorgi R, Howes OD, McCutcheon RA, McGowan B, Sen Gupta P, Smith D, Ismail K, Pillinger T. Glucagon-Like Peptide 1 Receptor Agonists and Mental Health: A Systematic Review and Meta-Analysis. *JAMA Psychiatry*. 2025 Jul 1;82(7):643-653.

Hendershot CS, Bremmer MP, Paladino MB, Kostantinis G, Gilmore TA, Sullivan NR, Tow AC, Dermody SS, Prince MA, Jordan R, McKee SA, Fletcher PJ, Claus ED, Klein KR. Once-Weekly Semaglutide in Adults With Alcohol Use Disorder: A Randomized Clinical Trial. *JAMA Psychiatry*. 2025 Apr 1;82(4):395-405.

Hung TH, Chen CR, Hsu CW, Carvalho AF, Stubbs B, Tseng PT, Wang LJ, Lin PY. Efficacy of Glucagon-Like Peptide-1 Receptor Agonists for Psychological Well-Being and Depressive Symptoms: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Hum Psychopharmacol*. 2026 May;41(3):e70041.

Cai M, Choi T, Xie Y, Al-Aly Z. Glucagon-like peptide-1 receptor agonists and risk of substance use disorders among US veterans with type 2 diabetes: cohort study. *BMJ*. 2026 Mar 4;392:e086886

Klausen MK, et al. Semaglutide for alcohol use disorder with comorbid obesity: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2026;407:1687-1698.

Sass MR, et al. Semaglutide in schizophrenia spectrum disorders with early glycemic abnormalities: a randomized clinical trial. *JAMA Psychiatry*. 2026;83(2):128-138.

Siskind D, et al. Semaglutide for clozapine-associated obesity (COaST): a randomised, placebo-controlled trial. *Lancet Psychiatry*. 2025;12:493-503.

Cummings JL, et al. Oral semaglutide in early Alzheimer's disease (evoke and evoke+): two phase 3 trials. *Lancet*. 2026;407:2167-2179.

Edison P, Femminella GD, Ritchie C, Nowell J, Holmes C, Walker Z, Ridha B, Raza S, Livingston NR, Frangou E, Love S, Williams G, Lawrence R, McFarlane B, Archer H, Coulthard E, Underwood BR, Koranteng P, Karim S, Bannister C, Perneckzy R, Prasanna A, Junaid K, McGuinness B, Nilforooshan R, Macharouthu A, Donaldson A, Thacker S, Russell G, Malik N, Mate V, Knight L, Kshemendran S, Holscher C, Mansouri A, Chester-Jones M, Holmes J, Tan T, Williams S, Ashraf A, Brooks DJ, Harrison J, Hinz R, Tadros G, Passmore AP, Ballard C. Liraglutide in mild to moderate Alzheimer's disease: a phase 2b clinical trial. *Nat Med*. 2026 Jan;32(1):353-361.

Al-Soleiti M, Leung JG, Mubaydeen T, Markota M, Abulseoud O, Singh B, Sola CL. Lithium Toxicity and Altered Clearance Following Initiation of Semaglutide in Patients With Bipolar Disorder: A Case Series and Literature Review. *J Clin Psychopharmacol*. 2025 Nov-Dec 01;45(6):613-618.

79

REFERENCES

References — Psychedelic Psychiatry

Jacobs E, Zahid Z, Hinkle J, Nayak S, Yaden DB. Psychedelic medicine: mechanisms, evidence, and translation to practice. *BMJ*. 2026 Feb 23;392:e081723.

McIntyre RS, Kwan ATH, Mansur RB, Oliveira-Maia AJ, Teopiz KM, Maletic V, Suppes T, Stahl SM, Rosenblat JD. Psychedelics for the Treatment of Psychiatric Disorders: Interpreting and Translating Available Evidence and Guidance for Future Research. *Am J Psychiatry*. 2025 Jan 1;182(1):21-32.

80

REFERENCES

References — Pharmacogenomics (1 of 2)

- Baum ML, Widge AS, Carpenter LL, McDonald WM, Cohen BM, Nemeroff CB; APA Workgroup on Biomarkers and Novel Treatments. Pharmacogenomic clinical support tools for the treatment of depression. *Am J Psychiatry*. 2024;181(7):591-607.
- Besterman AD, Alnor MA, Castaño M, et al. Psychiatric genetics in clinical practice: essential knowledge for mental health professionals. *Am J Psychiatry*. 2025:appiajp20240295.
- Bousman CA, Dunlop BW. Genotype, phenotype, and medication recommendation agreement among commercial pharmacogenetic-based decision support tools. *Pharmacogenomics J*. 2018;18(5):613-622.
- Hertz DL, Bousman CA, McLeod HL, et al. Recommendations for pharmacogenetic testing in clinical practice guidelines in the US. *Am J Health Syst Pharm*. 2024;81(16):672-683.
- Iosifescu DV. Pharmacogenomic testing for next-step antidepressant selection: still a work in progress. *JAMA*. 2022;328(2):146-148.
- Karamperis K, Koromina M, Papantoniou P, et al. Economic evaluation in psychiatric pharmacogenomics: a systematic review. *Pharmacogenomics J*. 2021;21(4):533-541.
- Malik S, Verma P, Ruano G, et al. Pharmacogenetics in child and adolescent psychiatry: background and evidence-based clinical applications. *J Child Adolesc Psychopharmacol*. 2024;34(1):4-20.
- Nurnberger J. Genetic testing: what you need to know in 2021. *The Carlat Psychiatry Report*. 2021;19(6/7).

81

REFERENCES

References — Pharmacogenomics (2 of 2) and Open Notes

- Oslin DW, Lynch KG, Shih MC, et al. Effect of pharmacogenomic testing for drug-gene interactions on medication selection and remission of symptoms in major depressive disorder: the PRIME Care randomized clinical trial. *JAMA*. 2022;328(2):151-161.
- Rosenblat JD, Lee Y, McIntyre RS. Does pharmacogenomic testing improve clinical outcomes for major depressive disorder? A systematic review of clinical trials and cost-effectiveness studies. *J Clin Psychiatry*. 2017;78(6):720-729.
- Wang X, Wang C, Zhang Y, An Z. Effect of pharmacogenomics testing guiding on clinical outcomes in major depressive disorder: a systematic review and meta-analysis of RCT. *BMC Psychiatry*. 2023;23(1):334.
- Xu L, Li L, Wang Q, Pan B, Zheng L, Lin Z. Effect of pharmacogenomic testing on the clinical treatment of patients with depressive disorder: a randomized clinical trial. *J Affect Disord*. 2024;359:117-124.
- Young C, MacDougall D. An overview of pharmacogenomic testing for psychiatric disorders: CADTH Horizon Scan. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2023 Jun. Report No.: EH0115.
- Allen KA, Kelly MM, Pitt MB, et al. Patient preferences for plain-language alternatives to medical jargon in clinical notes. *J Gen Intern Med*. 2026. doi:10.1007/s11606-026-10353-2

82