

TOP TEN TREATMENT UPDATES

FROM THE PAST YEAR

CHRIS AIKEN MD, April 2026

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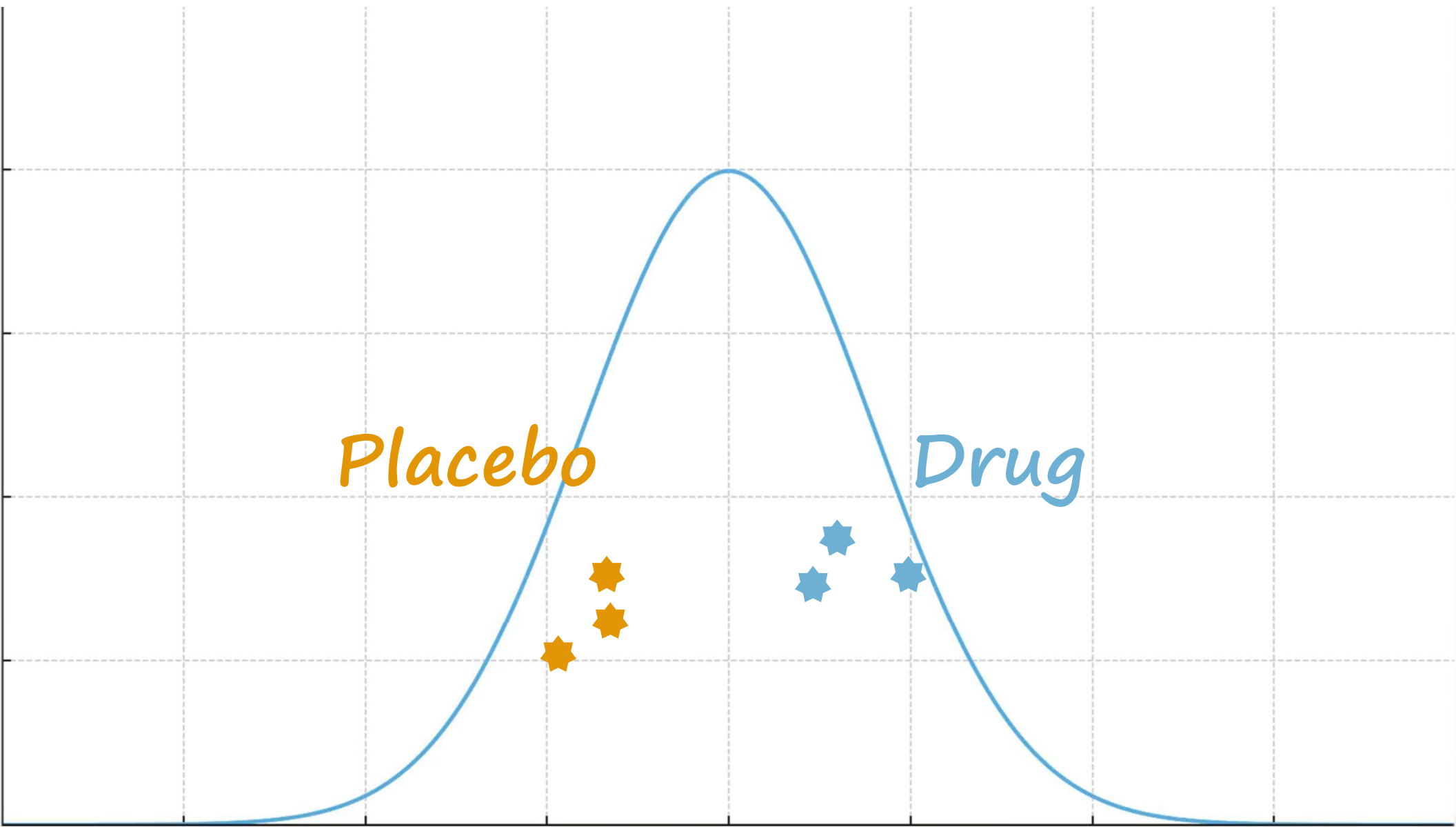
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Placebo



Drug





Placebo

Drug



Placebo controlled?

Double blind?

Size (100-300)?

Drop out rate (<20%)? Intent to treat?

Primary outcome positive?

Other: Enriched sample, randomization not concealed, cross-over trial

Effect size (average = 0.3-0.5) **or NNT?** (average = 5-10)

(Effect size: buspirone 0.2, SSRIs 0.3-0.4, benzos 0.5, amphetamine 0.9)

Replicated?

Backed by basic science?

Randomized Placebo-Controlled Adjunctive Study of an Extract of *Withania somnifera* for Cognitive Dysfunction in Bipolar Disorder



Method: Sixty euthymic subjects with *DSM-IV* bipolar disorder were enrolled in an 8-week, double-blind, placebo-controlled, randomized study of WSE (500 mg/d) as a procognitive agent added adjunctively to the medications being used as maintenance treatment for bipolar disorder. Study enrollment and data analyses were completed between December 2008 and September 2012. Cognitive testing at baseline and 8 weeks assessed primary efficacy outcomes. Psychopathology and adverse events were monitored at scheduled visits.

Results: Fifty-three patients completed the study (WSE, $n = 24$; placebo, $n = 29$), and the 2 groups were matched in terms of demographic, illness, and treatment characteristics. Compared to placebo, WSE provided significant benefits for 3 cognitive tasks: digit span backward ($P = .035$), Flanker neutral response time ($P = .033$), and the social cognition response rating of the Penn Emotional Acuity Test ($P = .045$). The size of the WSE treatment effect for digit span backward was in the medium range (Cohen $d = 0.51$; 95% CI, 0.25–0.77). None of the other cognitive tasks showed significant between-group differences. Mood and anxiety scale scores remained stable, and adverse events were minor.

- ✓ Placebo control
- ✓ Double blind
- ✓ Effect size = medium
- ✓ Replicated (in healthy subjects)
- ✓ Backed by basic science

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✓ Placebo control

✓ Double blind

✗ Size (60)

✗ Drop outs unaccounted (12%)

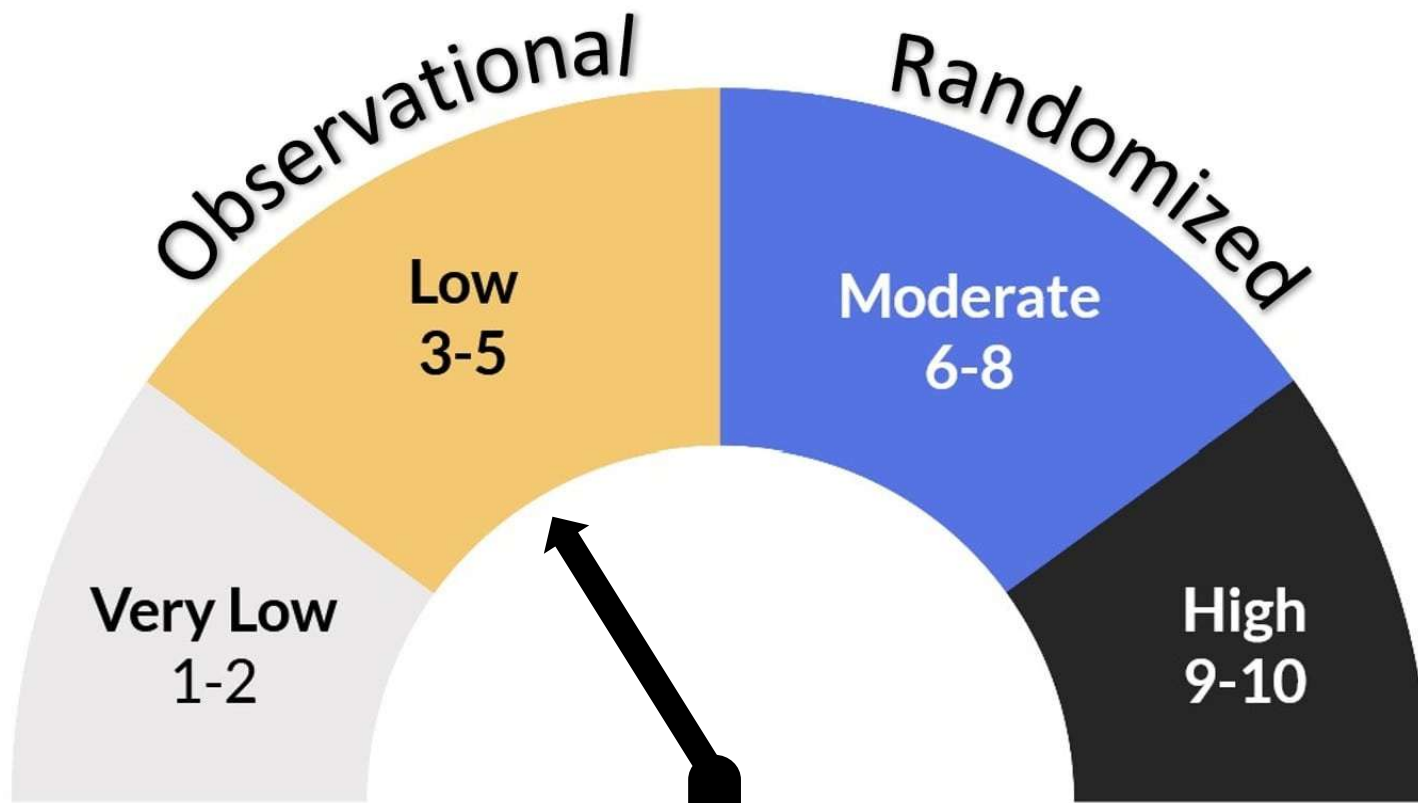
✗ Primary outcome not positive

Bonferroni: divide p cut-off by tests: $0.05/6 = 0.0083$

✓ Effect size = medium

✓ Replicated (in healthy subjects)

✓ Backed by basic science

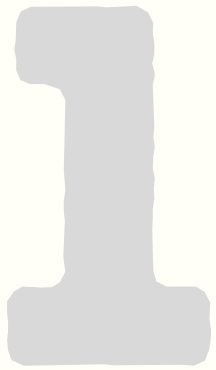


chrisaikenmd.com/ebm



**PRACTICE
CHANGING**



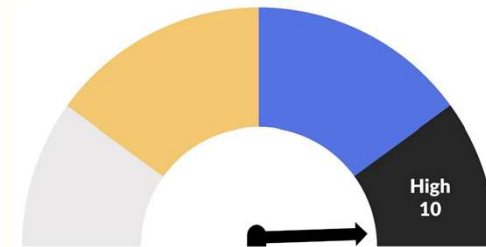


eCOT-AS in Mild TRD

Stimulating cranial nerves at home treated depression after ≥ 1 antidepressant failure

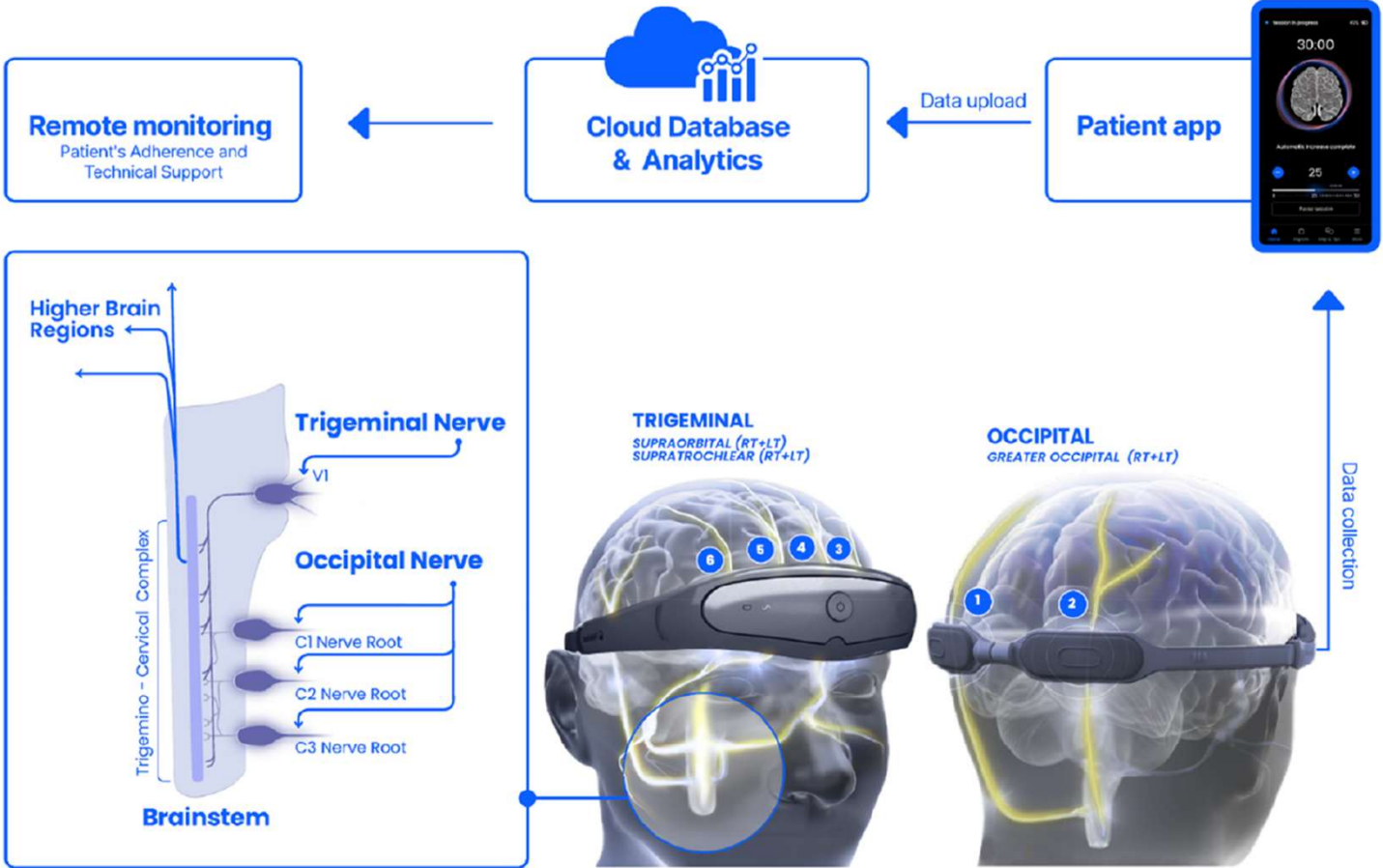
eCOT-AS (ProLivRx) in Mild TRD

Design	Randomized double-blind sham-controlled trial
Size	124
Population	Adult MDD, failed ≥ 1 antidepressant trials (avg 1.8)
Intervention	external Combined Occipital and Trigeminal Afferent Stimulation 40 minutes BID
Duration	8 weeks RCT, another 8 weeks open label
Primary outcome	Change in HDRS17 at 8 weeks
Result	Positive with large effect size (0.7-0.9)
Limitations	Excluded ≥ 1 antidepressant failures
Risks	None
Funding	Industry (<u>Neurolief</u>)

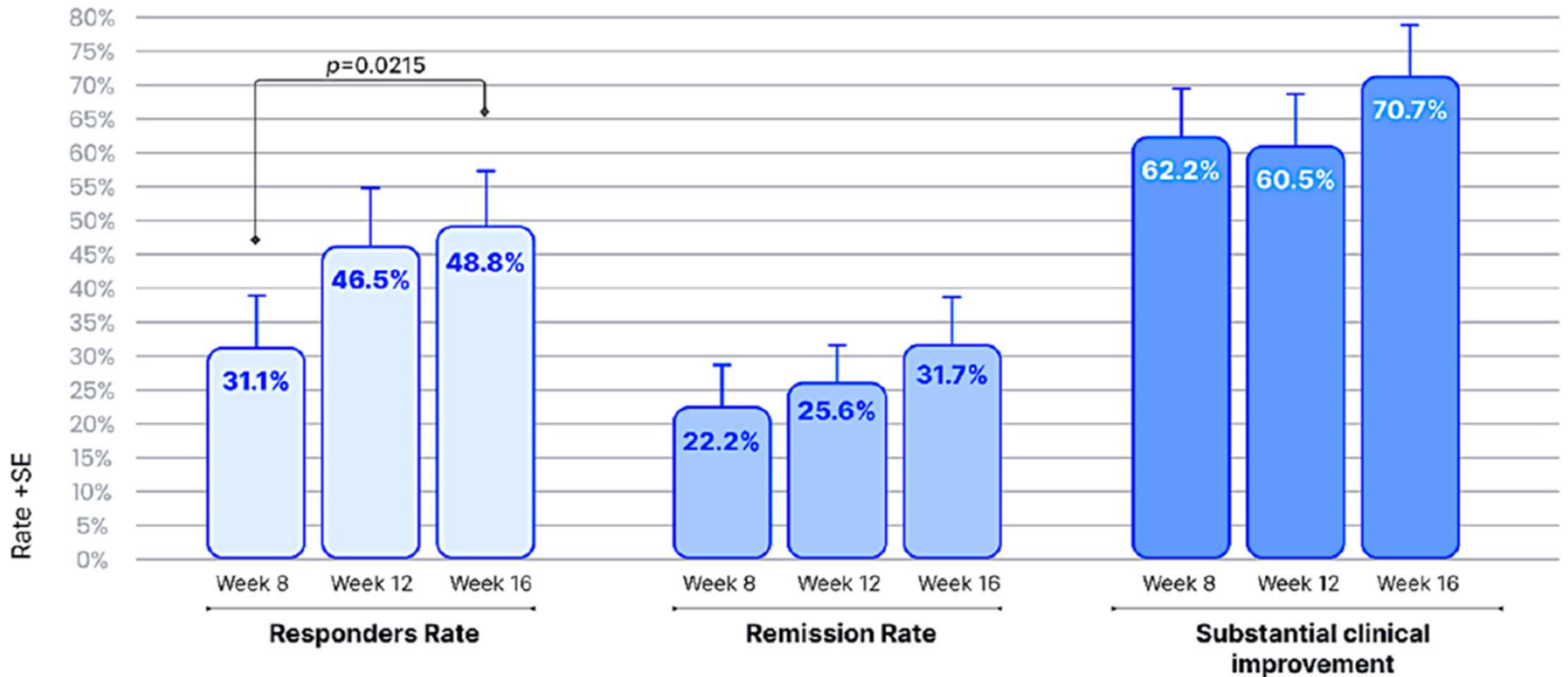


Carpenter LL et al, Brain Stimul
2025;18(5):1695-1704.

eCOT-AS (ProLivRx) modulates cranial nerves



eCOT-AS (ProLivRx) over 8-16 weeks



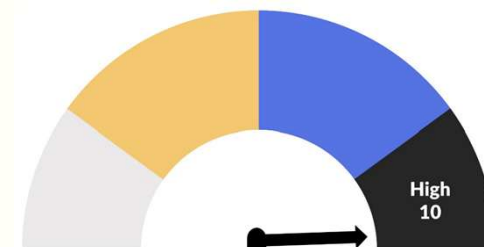
2

Saffron in Subclinical Depression

Low-cost herb effective in its largest trial to date

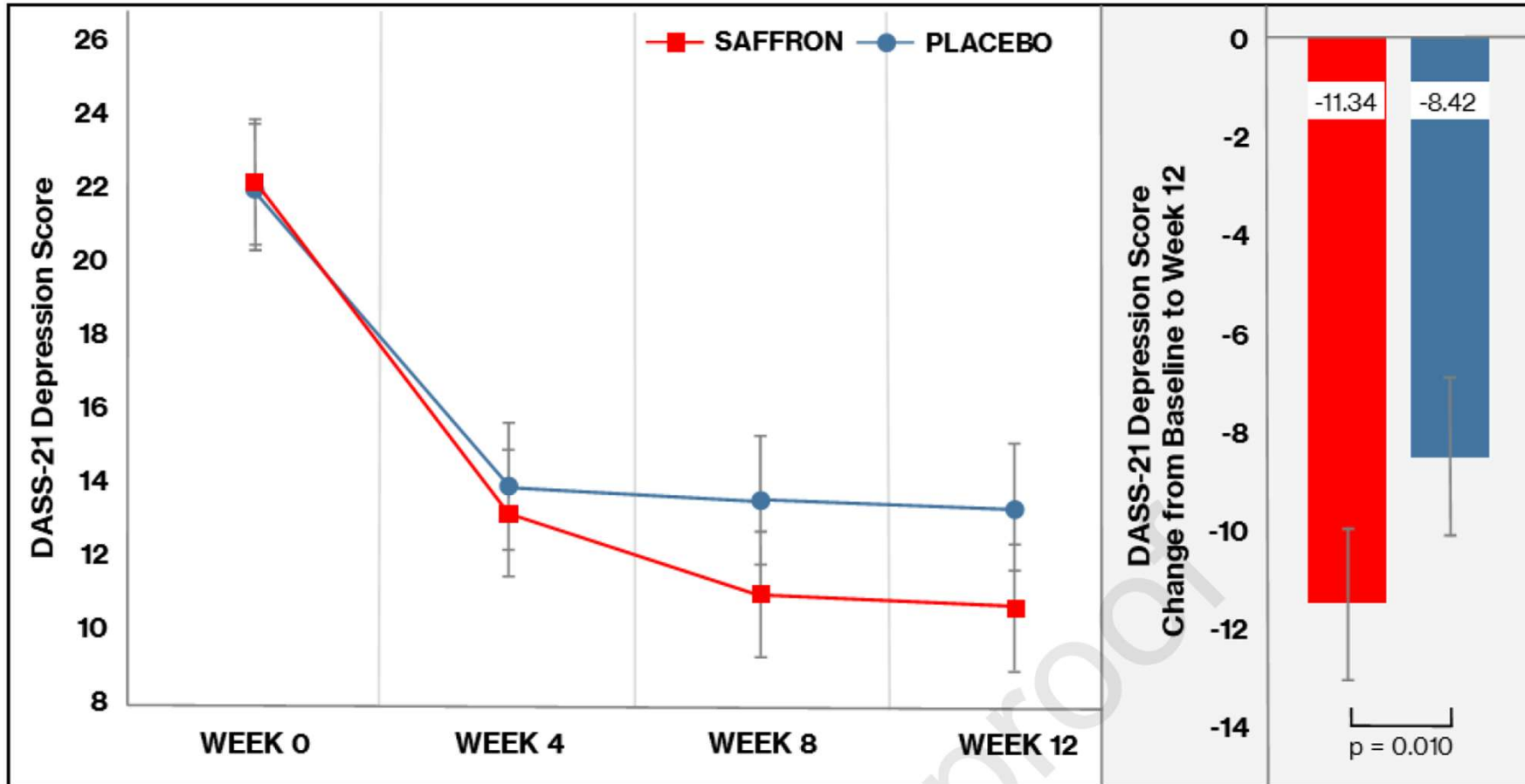
Saffron in Subclinical Depression

Design	Randomized double-blind controlled trial
Size	202 healthy adults with depressive symptoms (not in full episode)
Intervention	Saffron extract 28 mg (Affron brand)
Duration	12 weeks
Primary outcome	Self-report DASS-21 (mix of depressive/stressed symptoms) Blind intact (participants could not tell)
Result	Significant improvement (effect size 0.4)
Limitations	High placebo response in first month Secondary outcomes negative (except insomnia)
Funding	Industry (Pharmactive Biotech Products)



Lopresti AL et al. An Examination into the Effects of a Saffron Extract (Affron) on Mood and General Wellbeing in Adults Experiencing Low Mood: A Randomized, Double-Blind, Placebo-Controlled Trial. J Nutr. 2025:S0022-3166(25)00306-2.

Saffron in Subclinical Depression





800 BCE: Persia

Saffron used for melancholy

Antioxidant

Anti-inflammatory

Increases melatonin

Modulates:

Stress hormones (HPA-axis)

Dopamine

Glutamate

Opioid

Saffron

Randomized trials in psychiatry

- Depression (mild-moderate): 22 RCTs involving 1,620 subjects
- Including adolescents (12-18) and elderly
- Deepens sleep quality in large placebo RCTs
- Improves sexual function in men and women in small trials

- OCD: 2 small trials compared to SSRIs
- ADHD: 2 small trials compared to methylphenidate
- Opioid Use Disorder: 1 small trial (augmented MAT)



Affron
Proprietary extract

chrisaikenmd.com/supplements

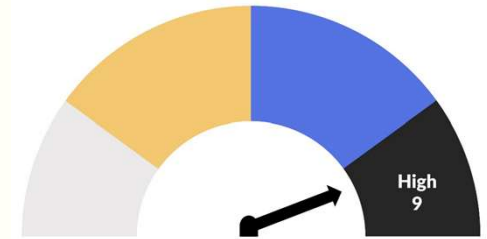
3

Pramipexole in Treatment Resistant Depression

Large effect size sustained over 48 weeks for this dopaminergic D3-selective agonist

Pramipexole Augmentation in TRD

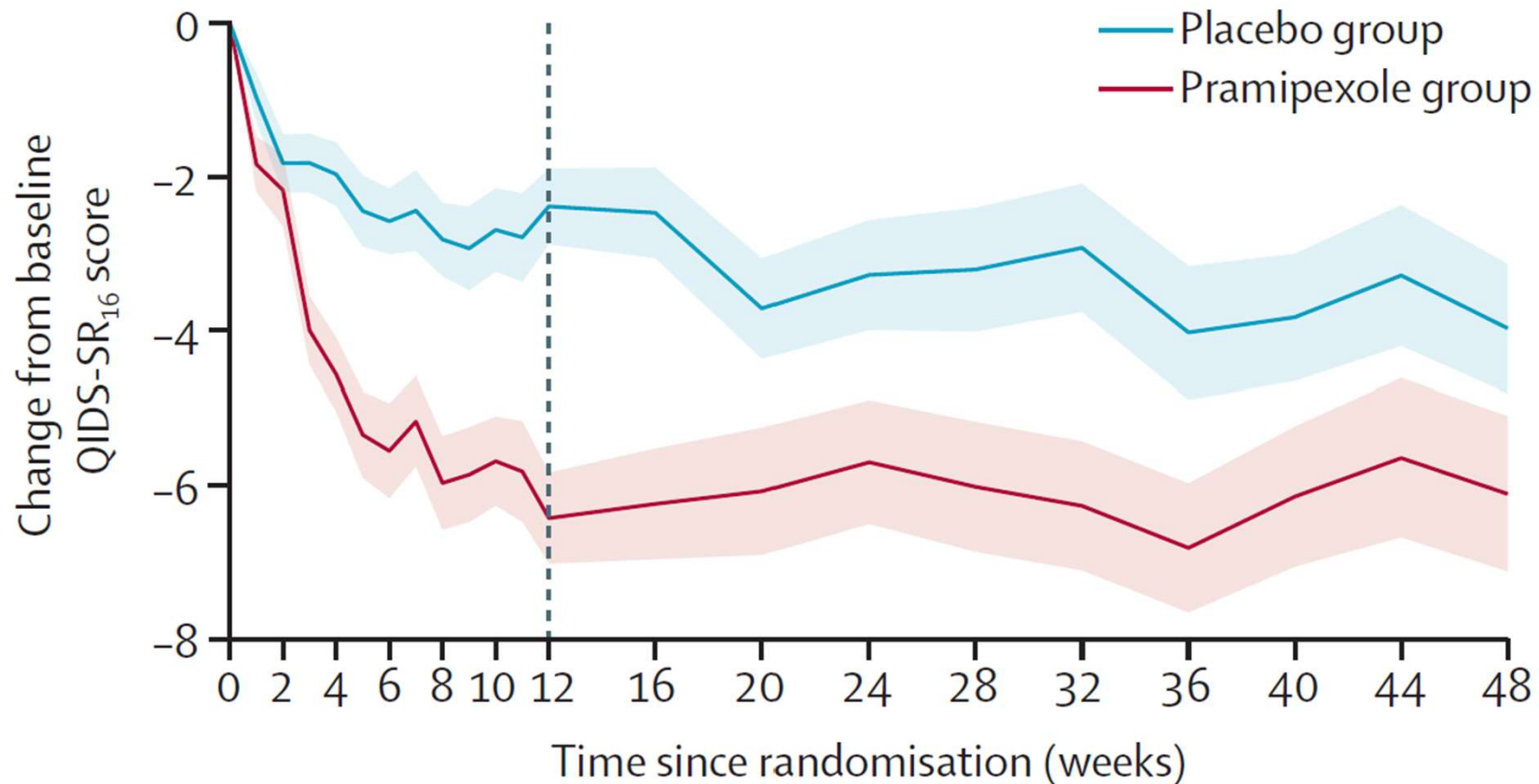
Design	Randomized double-blind placebo-controlled trial
Size	150
Population	Adult MDD, failed ≥ 2 antidepressant trials (avg 3.5) 21% failed augmentation strategies
Intervention	Pramipexole 2.5 mg target (avg 2.3 mg) (start 0.25 mg qhs, raise by 0.25 q3 days)
Duration	48 weeks
Primary outcome	Change in QIDS at 12 weeks
Result	Positive on all measures, large effect size (0.87) at 12 weeks
Limitations	Unblinding (70-77% correct guess)
Risks	Higher dropout due to AEs (20% vs 5%) Somnolence (16%), nausea (26%), orthostasis, impulsivity (3%), psychosis (1%)
Funding	UK government (NIHR)



Functional unblinding

Browning M et al, Pramipexole augmentation for the acute phase of treatment-resistant, unipolar depression: a placebo-controlled, double-blind, randomised trial in the UK. *Lancet Psychiatry*, 2025.

Pramipexole Augmentation in TRD



Pramipexole

Target 1-3 mg hs (average 1.5)

Start 0.125-0.25 mg,
raise by 0.125-0.25mg q3-7 days,
raise faster after 0.75 mg

Large effect in RCTs of unipolar (4) and bipolar (2) depression

Prefer for anhedonia, inflammation, bipolar spectrum, comorbid restless leg syndrome

Tolerability

Nausea, sedation

No weight/sexual/cognitive

Risks

Hedonic dysregulation (approx. 1-3%)

Hallucinations (rare at dose < 2 mg)

Hypotension

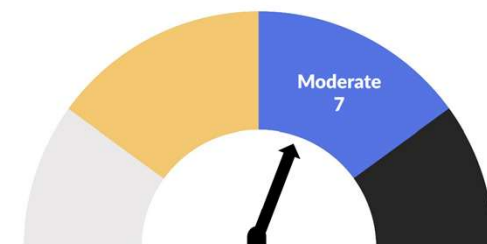
4

Psychodynamic Therapy in Depression

Brief Dynamic Interpersonal Therapy is comparable to CBT but with more lasting effects

Dynamic Interpersonal Therapy in Depression

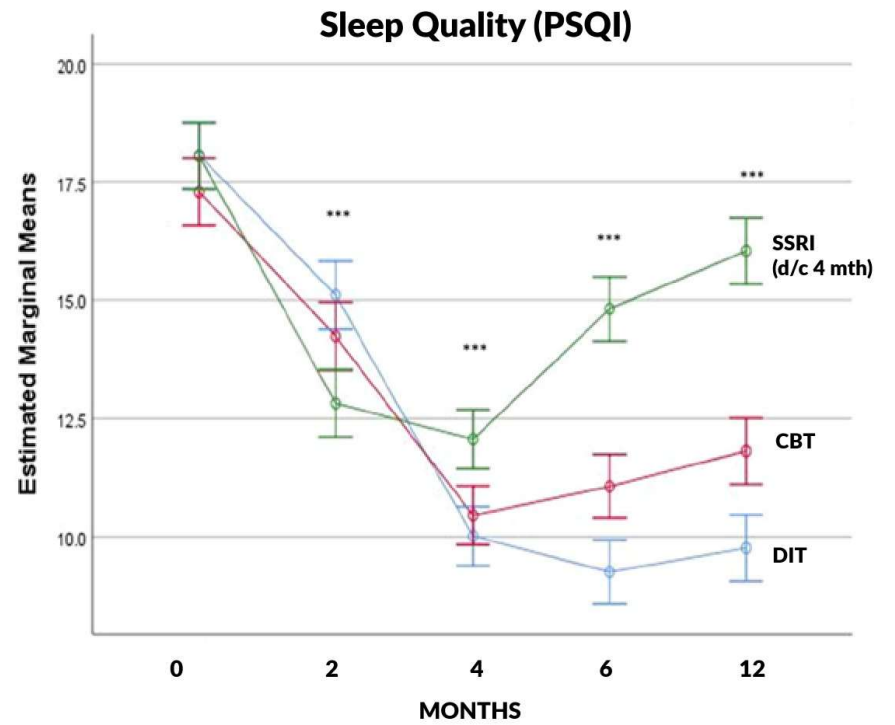
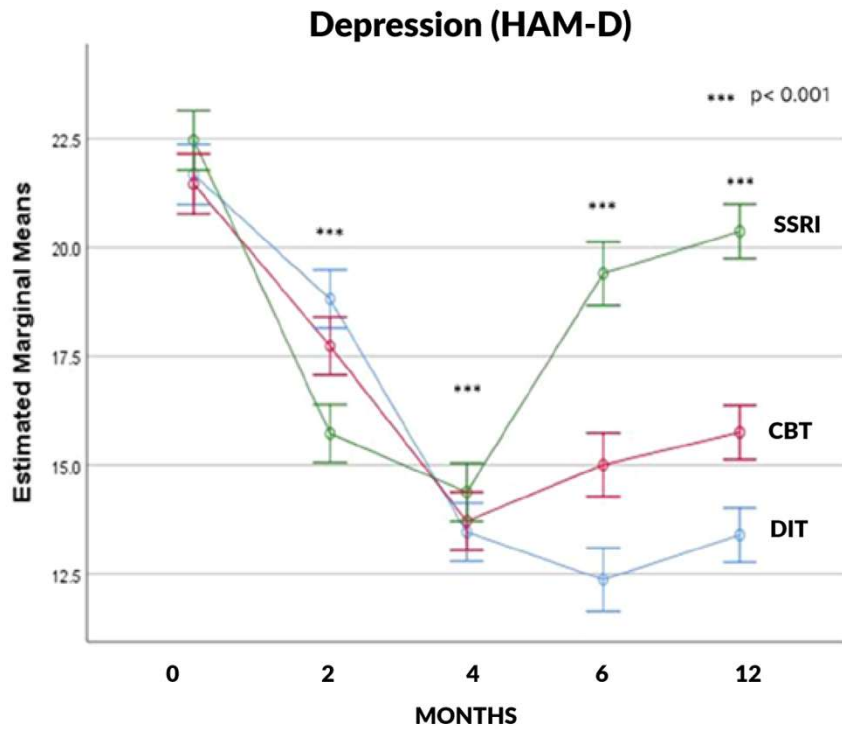
Design	Randomized unblinded comparator trial (no placebo)
Size	240 adults with moderate MDD, in Iran (94% retention at 12 mth)
Intervention	16 weeks of <ul style="list-style-type: none">• Dynamic Interpersonal Therapy (DIT)• CBT• Antidepressant
Duration	16 weeks treatment, 12 months follow-up
Primary outcome	HAM-D 17 (therapist rated)
Result	All equal at 16 weeks, but DIT more sustained at 12 months DIT also superior at 12 mth on secondary measures of <ul style="list-style-type: none">• Sleep quality• Cognition (Stroop test)
Funding	None



No placebo
No blinding

Yari-Renani H, Zare T. Advancing depression treatment: a multi-center randomized controlled trial of dynamic interpersonal therapy versus CBT and pharmacotherapy on symptoms, sleep, and cognition. *Psychiatry Res.* 2025;354:116775.

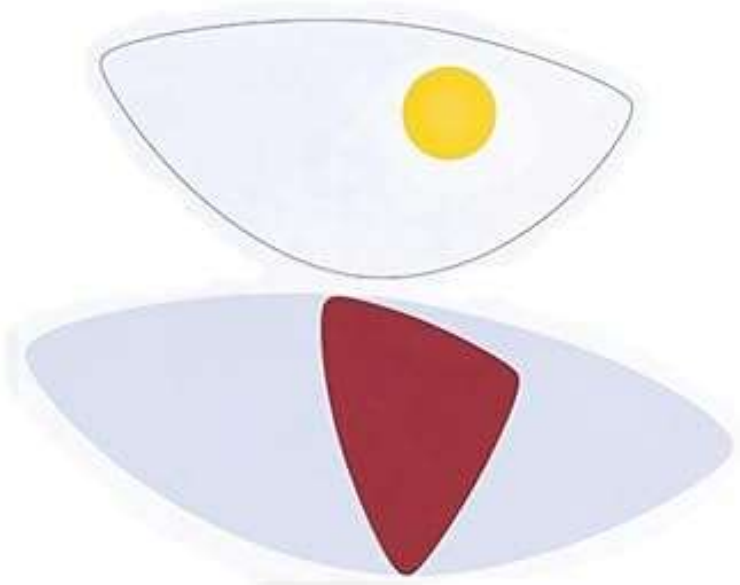
DIT vs CBT vs Antidepressant



alessandra lemma, mary target, & peter fonagy

brief dynamic interpersonal therapy

A CLINICIAN'S GUIDE



OXFORD

Focus on

1. Attachment
2. Relationship patterns
3. Transference
4. Resistance
5. Mentalization

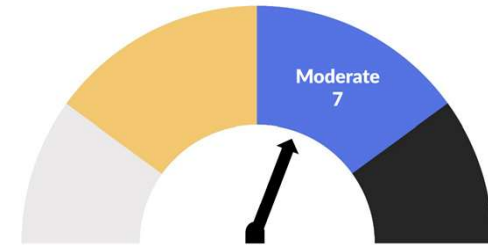
5

GLP-1 Agonists in Alcohol Use

A mix of positive and negative data challenges the hype

Semaglutide in Alcohol Use Disorder

Design	Randomized double-blind, placebo controlled trial
Size	48 with moderate alcohol use disorder, mean BMI 32
Intervention	Semaglutide (0.25 mg/wk x4 wks, 0.5 mg/wk x4 wks, then 1mg/wk)
Duration	9 weeks
Primary outcome	Alcohol self-administration in lab (they could earn money to delay time to drinking)
Result	Reduction in <ul style="list-style-type: none">• Alcohol use in lab (medium to large effect size)• Drinks per day, heavy drinking days, cravings• Cigarettes• Not in average drinks per day or number of drinking days
Funding	Government (National Institute on Alcohol Abuse and Alcoholism)

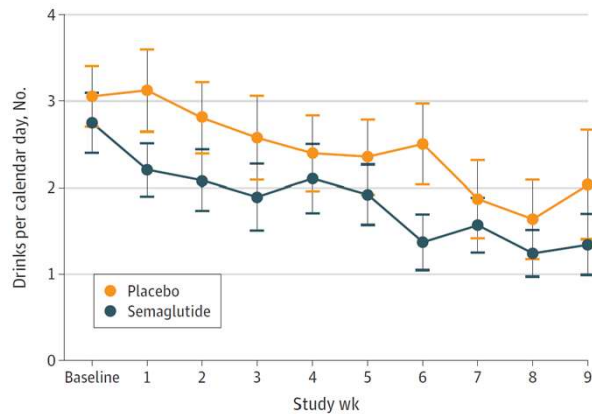


Small Sample
Not treatment-seeking
Not real-world outcome

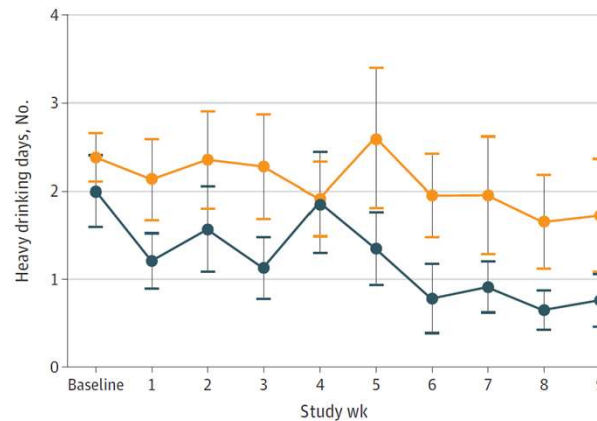
Hendershot CS et al, Once-Weekly Semaglutide in Adults With Alcohol Use Disorder: A Randomized Clinical Trial. JAMA Psychiatry. 2025;82(4):395-405.

Semaglutide in Alcohol Use Disorder? Maybe

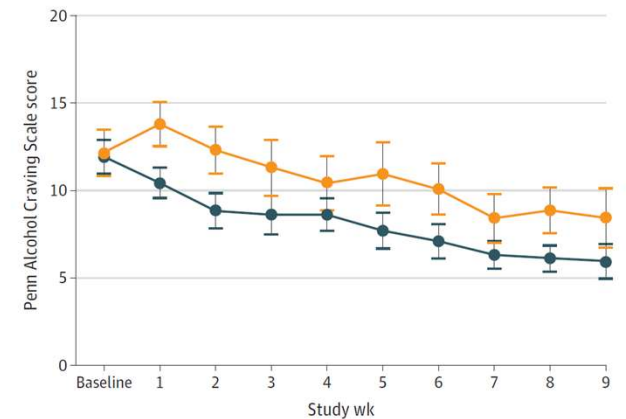
A Changes in drinks per calendar day



C Changes in heavy drinking days



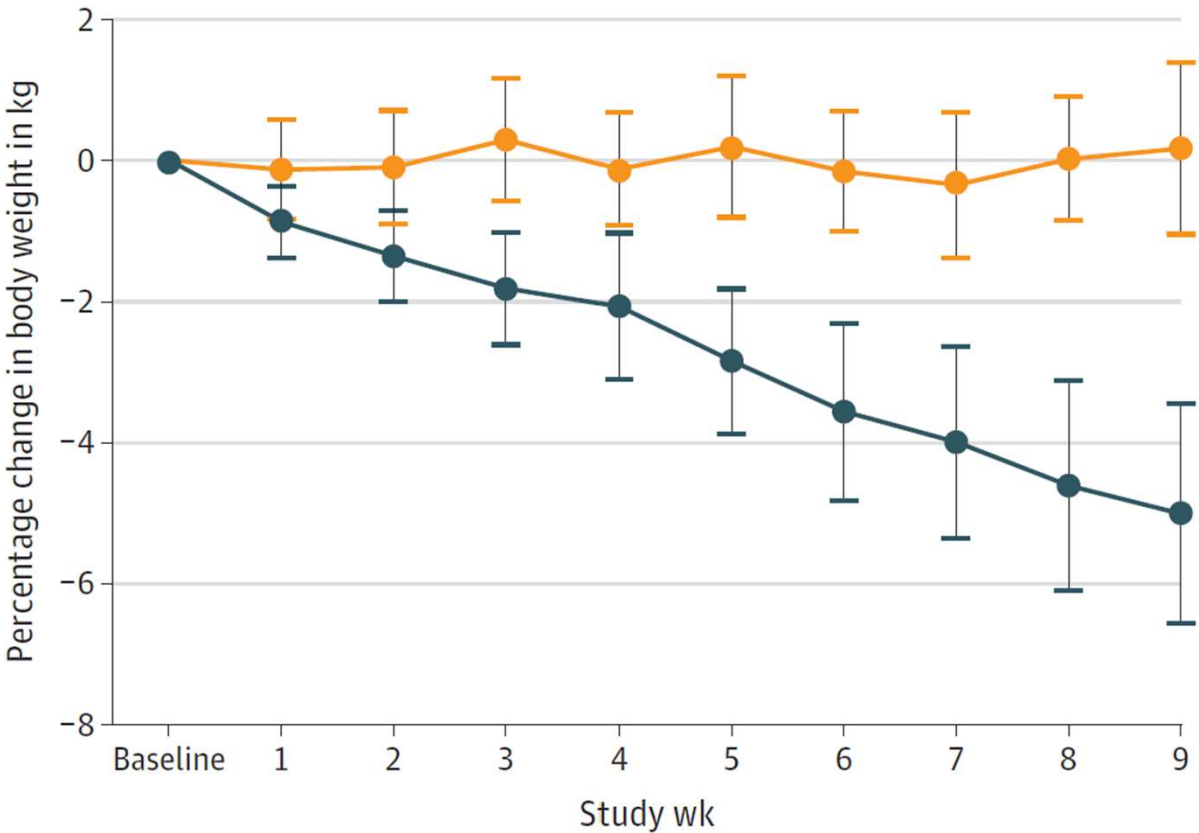
E Changes in alcohol craving assessed by the Penn Alcohol Craving Scale



(3 out of 5 of real-world outcomes positive)

Semaglutide in Weight Loss? Definitely

F Change in body weight



GLP-1 Score Card in Alcohol Use Disorder

Outcome	Med	Grade
Negative	Exenatide	Moderate 8/10
Positive	Semaglutide	Moderate 7/10
Positive	Dulaglutide	Low 5/10 (secondary smoking trial)



Lithium-GLP1 Interaction

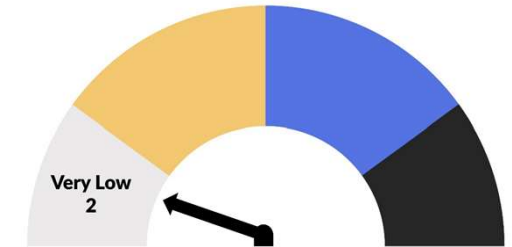
Levels can double with GLP-1s, particularly semaglutide, though unclear how often and who is at risk

Lithium-Semaglutide Interaction

Age	Risk Factors for Toxicity	Weeks to toxicity	Li Level	Cr
41 F	Stage II CKD	1	0.9 → 2.4	0.9 → 1.1
63 M	Stage III CKD, DM, proteinuria	2	0.9 → 1.8	1.6 → 1.3
59 M	10 lb weight loss	6	? → 2.6	? → 2.0
62 M	Stage IIIa CKD, DM, HTN, proteinuria	2-3	1.0 → 1.8	1.4 → 1.3
23 F	Vomiting	"recently"	? → 2.1	? → 1.1
22 M	None (lithium lowered 2100 → 1200 mg while starting semaglutide).	n/a	1.1 → 0.8	1.1 → 1.8

All GLP-1's used for obesity.

One case of toxicity with tirzepatide on Reddit, and *in press* of toxicity after switching from semaglutide to tirzepatide.



Al-Soleiti M et al, J Clin Psychopharmacol. 2025;45(6):613-618; Arriola-Montenegro J et al, J Am Soc Neph, 2025;36(10S); Onggo S et al, J Clin Psychopharmacol 2025;45(4):393-395

When to use GLP-1's for antipsychotic weight

BMI cut off	Population
30	Any patient (FDA indicated)
27.5	South Asian, Chinese, other Asian, Middle Eastern, Hispanic, Black African, or African-Caribbean descent
27	At least one component of metabolic syndrome: Hypertension, dyslipidemia, excess abdominal fat (waist circumference > 102 cm in men or > 88 cm in women), diabetes or borderline diabetes)
24.5	Ethnic background as above with at least one component of metabolic syndrome

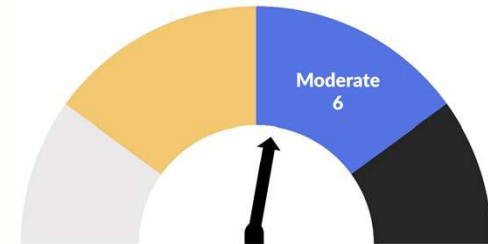
McCutcheon RA, Pillinger T, Varvari I, et al. INTEGRATE: international guidelines for the algorithmic treatment of schizophrenia. *Lancet Psychiatry*. 2025;12(5):384-394.

7 **TRD: Quetiapine vs Lithium**

The antipsychotic took the lead in a one year trial of Treatment Resistant Depression

Quetiapine vs Lithium Augmentation in TRD

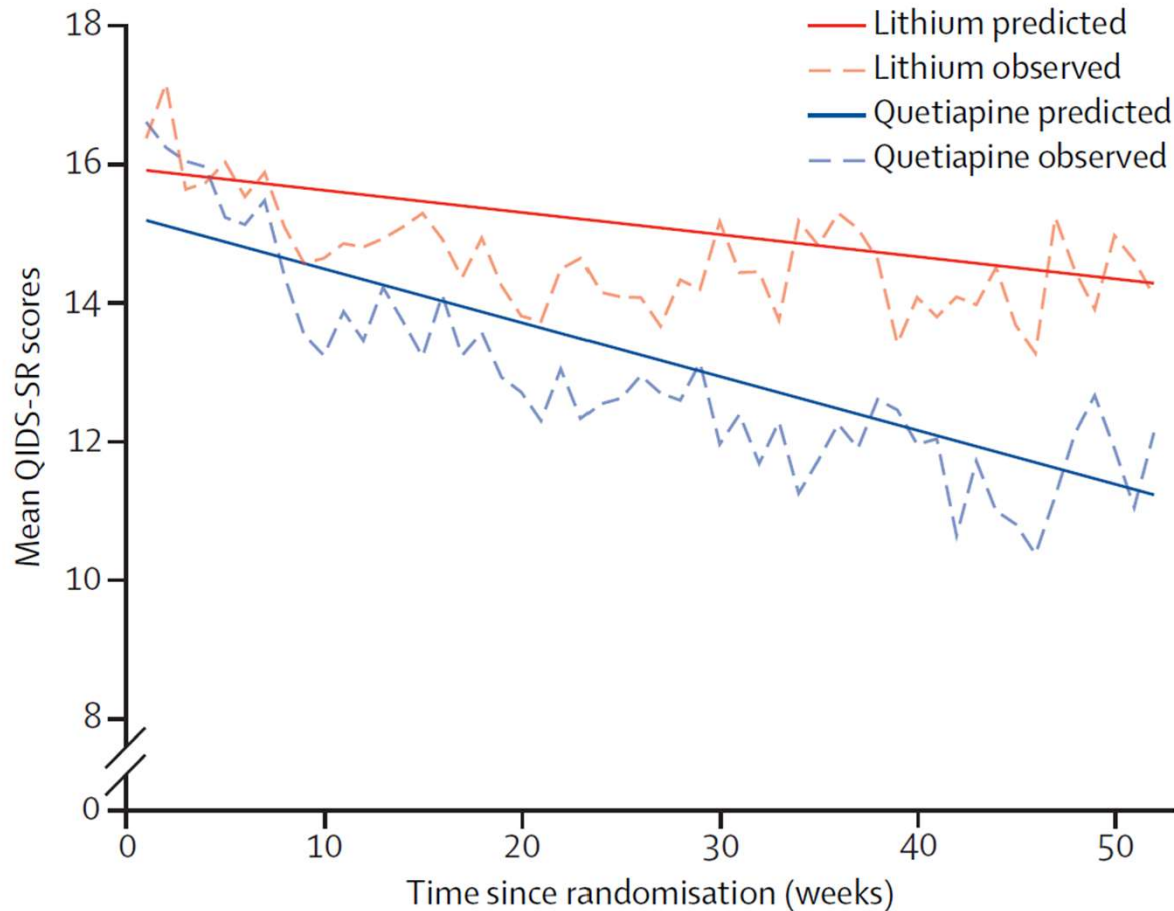
Design	Randomized open-label controlled trial
Size	212 with TRD (60% failed > 2 trials) Mean 42 years
Intervention	Lithium (mean 0.85 mmol/L) Quetiapine (mean 195 mg)
Duration	12 months
Primary outcome	Self-report QIDS and time to discontinuation
Result	Quetiapine = lower depressive burden (p=0.03) Similar time to discontinuation
Limitations	Higher drop out on lithium (40% vs 27%) Not blinded, no placebo
Funding	Government (UK NIH)



No placebo
High drop out
Not blinded

Cleare AJ et al, Clinical and cost-effectiveness of lithium versus quetiapine augmentation for treatment-resistant depression: a pragmatic, open-label, parallel-group, randomised controlled superiority trial in the UK. *Lancet Psychiatry*. 2025;12(4):276-288.

Quetiapine vs Lithium Aug in TRD



Lithium had more drop-outs early on, but quetiapine was superior when analyzing only those who stayed with their med as well as with intent-to-treat population.

In secondary analysis, quetiapine's superior efficacy was limited to patients with high anxiety, even though both meds reduced anxiety at similar rates.

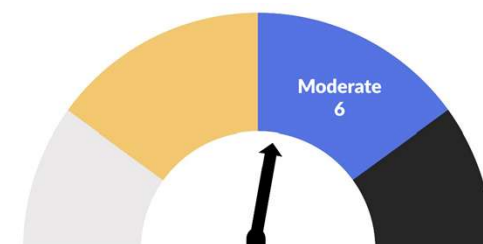


Mentalization Therapy for Antisocial Personality

Challenges “deviancy training” idea that group therapy worsens antisocial by allowing them to learn new antisocial skills from each other

Mentalization Therapy in Antisocial

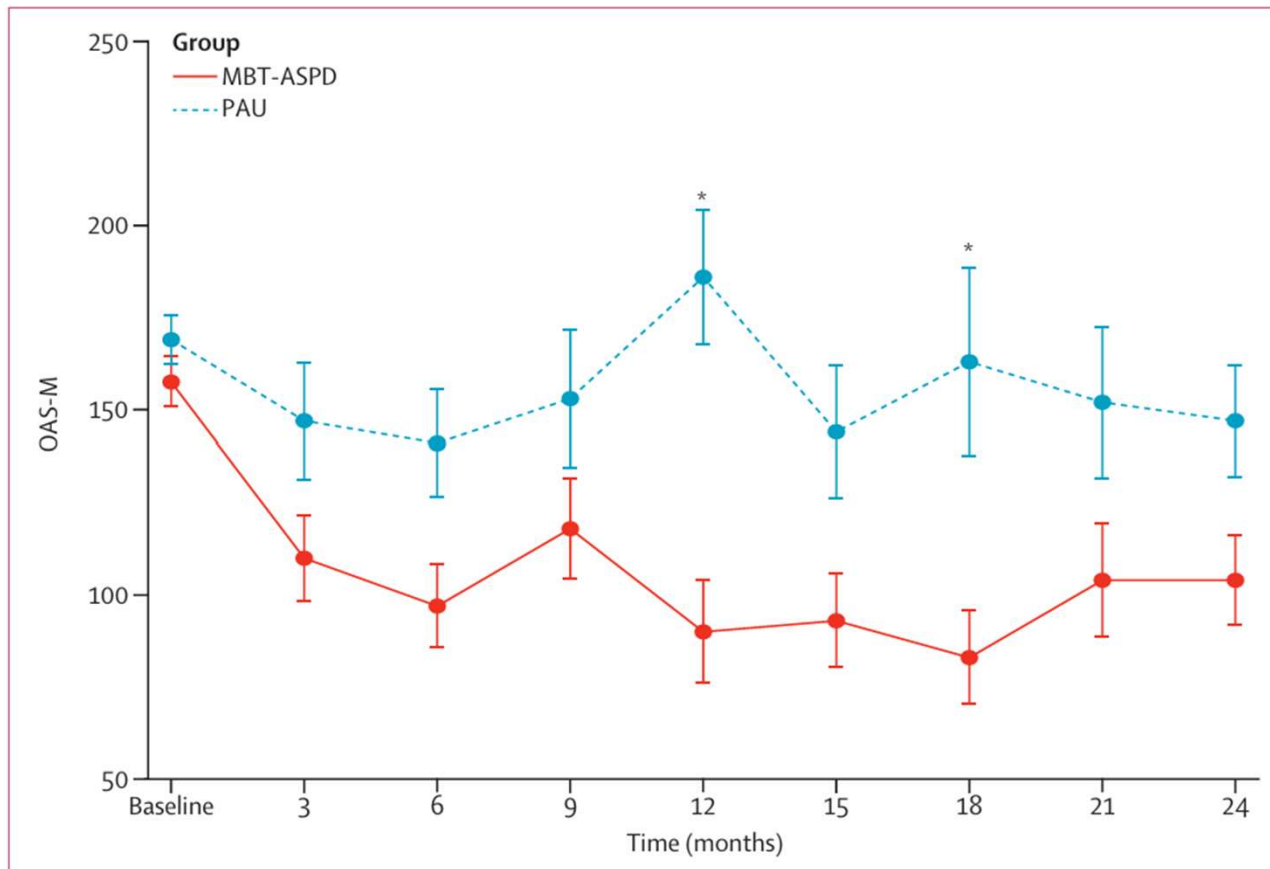
Design	Randomized assessor-masked vs probation as usual
Size	313 men with ASPD who committed recent crime
Intervention	12 months of Mentalisation-based treatment (MBT) tailored for antisocial personality disorder Weekly group (75 min) Monthly individual (50 min)
Duration	12 months treatment, 36 months follow-up
Primary outcome	Aggression at 12 mth (OAS-M)
Result	Reduced aggression (effect size 0.74) Improvements in secondary outcomes: violent behaviors, communication skills, mentalising No change in alcohol use and drug use, self-harm, or suicidal behavior
Funding	National Institute for Health Care Research (UK)



Inactive comparison
Single blind
High drop out
(41-45% @ 1 yr))

Fonagy P, et al. Mentalisation-based treatment for antisocial personality disorder in males convicted of an offence on community probation in England and Wales (Mentalization for Offending Adult Males, MOAM): a multicentre, assessor-blinded, randomised controlled trial. *Lancet Psychiatry*. 2025;12(3):208-219.

Mentalization vs Parole as Usual



Manual

Google "mentalization therapy for antisocial personality manual pdf"

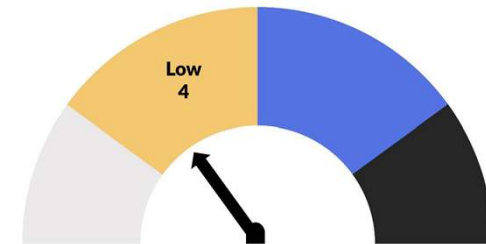
9

Cannabis-Induced Psychosis

1 in 3 developed independent psychosis
1 in 2 developed a 2nd cannabis-psychosis
And antipsychotics prevented both

Cannabis-Induced Psychosis

Design	Prospective cohort study
Size	1,772
Population	Patients with cannabis-induced psychosis diagnosed in Swedish National Patient Database Mean age 27, range 16-64, 84% men No prior history of bipolar or psychotic disorders
Duration	8 years (mean)
Primary outcome	Hospitalization for any psychosis
Result	Hospitalized for 2 nd psychosis: 51% Among hospitalizations, 23% were cannabis-induced 2 nd episode of cannabis-psychosis: 52% Took antipsychotics: 76% Antipsychotic associated with 25% reduction in psychotic hospitalization and 22% reduction in substance use complications (particularly LAIs, clozapine, and oral aripiprazole)
Limitations	Not randomized No information on continued cannabis use (but 70% were re-diagnosed with cannabis use disorder) Duration of antipsychotic use not analyzed
Funding	Government (Swedish Research Council)



Observational
(but large, prospective)

Mustonen A et al. Real-world effectiveness of antipsychotic medication in relapse prevention after cannabis-induced psychosis. Br J Psychiatry. 2025 May 6:1-7.

10 **AI App Screens for TD**

The free app outperformed trained psychiatric clinicians

Tardive Dyskinesia App

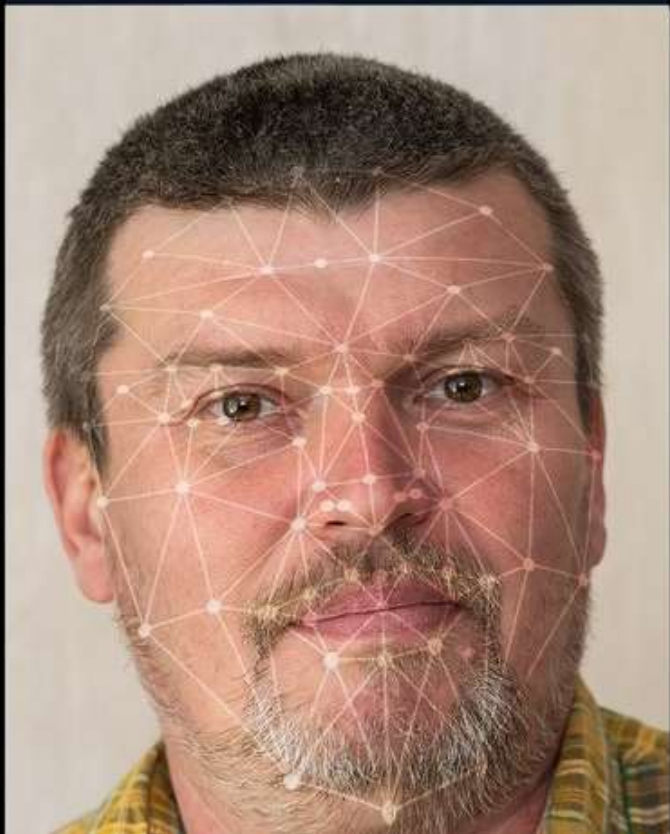
Design	Comparative study
Size	351 recruited from public clinics, taken antipsychotic > 3 <u>months</u> 75% had TD
Intervention	Video based TDScreen app (home and clinic)
Primary outcome	Sensitivity, specificity, area under the curve (AUC) Standard = consensus on AIMS by trained clinicians who watched same app videos
Result	AUC: 0.85 to 0.98 (improved as more training data added) Sensitivity 0.82, Specificity 0.82 App outperformed human raters (on Cohen κ)
Limitations	Did not include leg, trunk, toes 17% of subjects excluded due to poor video quality
Funding	Government (NIMH)

Sterns AA et al, Detecting Tardive Dyskinesia Using Video-Based Artificial Intelligence. J Clin Psychiatry. 2025 May 28;86(3):25m15792.

9:41



Please face the camera for
10 seconds, thank you.



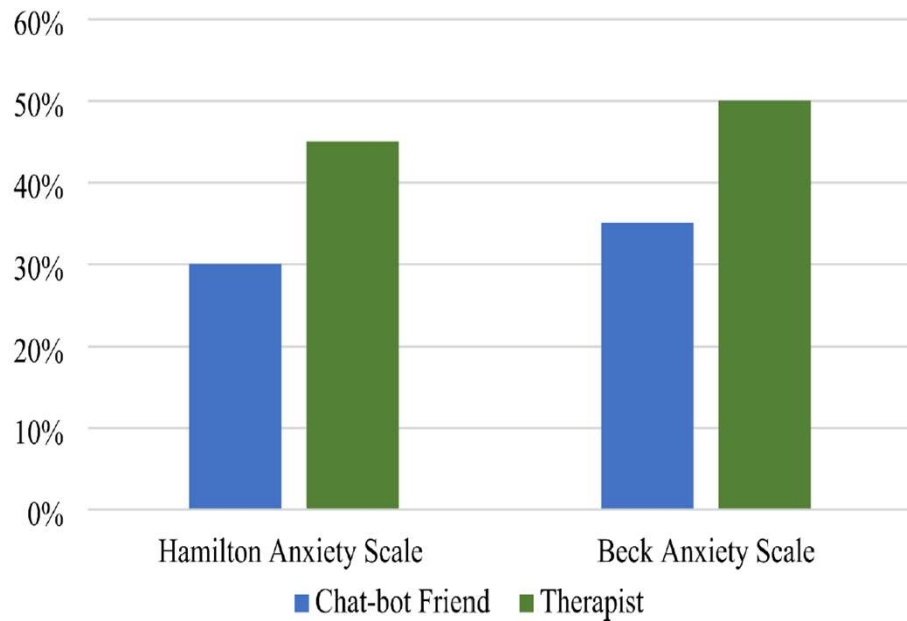
tdscreen.ai



TRENDS



AI Therapy



- 49% of people with psychiatric disorders use Chat-GPT for therapy
- 3 trials found benefit with AI therapy, though human therapist superior
- AI therapy app Woebot closed

Spytska L, BMC Psychol. 025;13(1):175

<https://sentio.org/ai-blog/ai-survey>

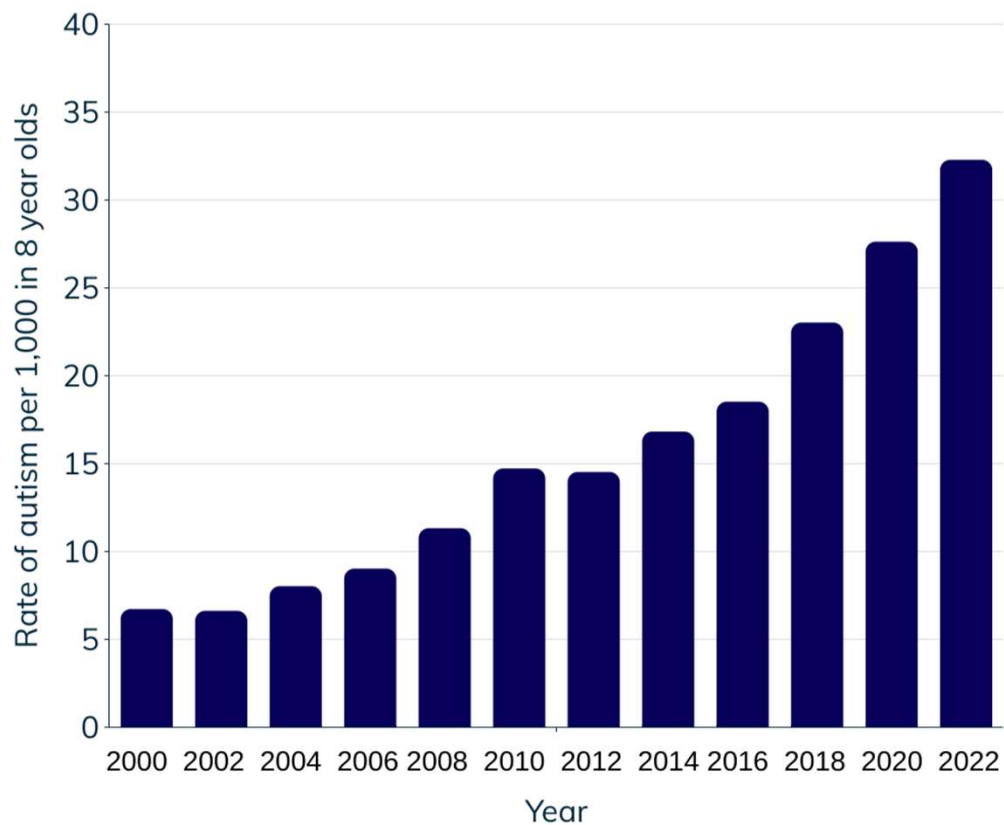
Non-Medical Ketamine & Psilocybin

- Ketamine use rose 37% in NYC nightclubs from 2017-2024
- Recent psilocybin use rose 44% (age 18-29) and 188% (age > 30), 2019-23
- 1 in 8 US adults report lifetime psilocybin use

Accidental Exposures in Children

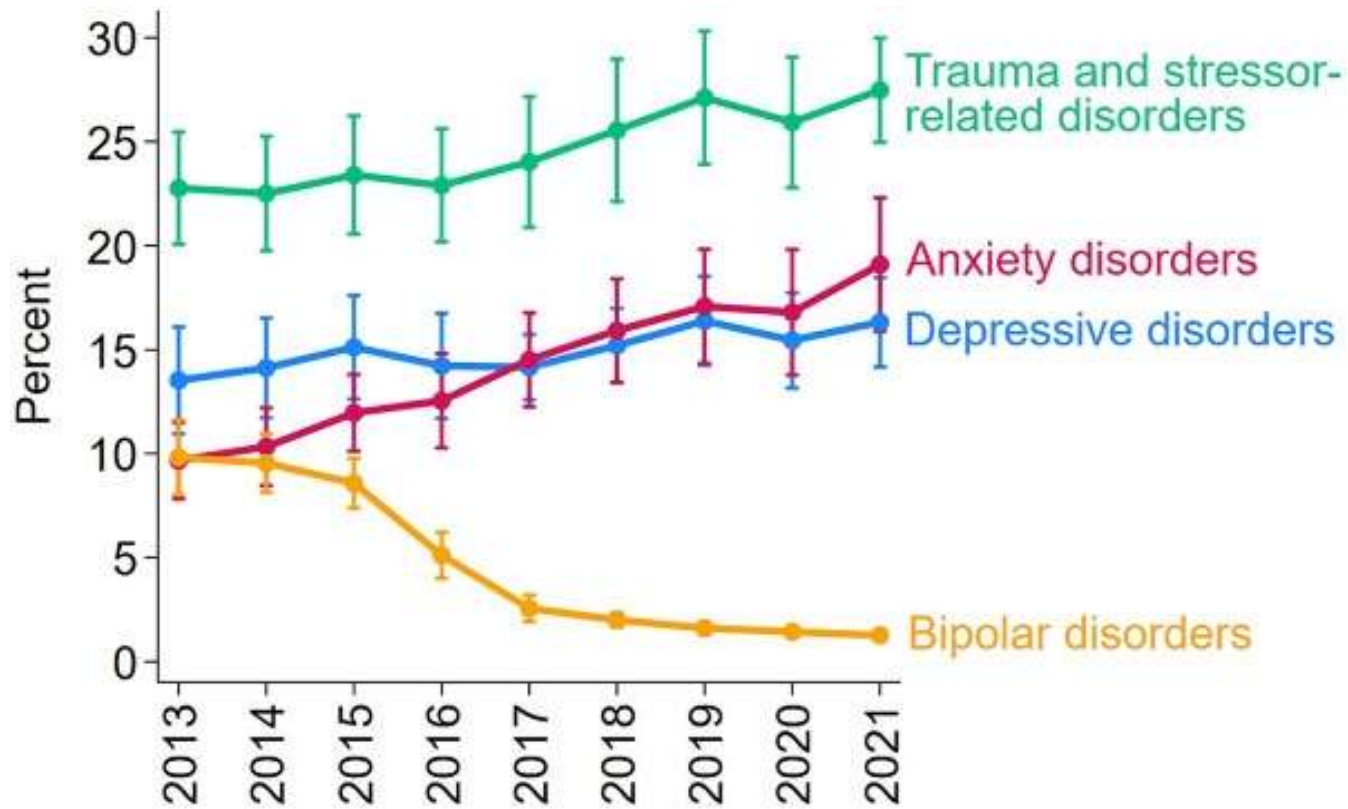
- Accidental cannabis ingestion is rising in children, causing fatigue, nausea, and in worst case respiratory depression and seizures
- Psilocybin poison calls rose 723% in children 2019-2023

Autism Diagnosis in Children



Shaw KA, *CDC Surveillance Summaries*, April 17, 2025, 74(2);1–22
<https://www.cdc.gov/mmwr/volumes/74/ss/ss7402a1.htm>

Bipolar Diagnosis in Children



Mojtabai R, Olfson M. *J Am Acad Child Adolesc Psychiatry*. August 28, 2024.

Antipsychotic Overuse in Non-Whites

- *Schizophrenia*: Blacks and hispanics prescribed...
More older antipsychotics (30-50%)
Less clozapine (55-60%) and newer-but-generic second generations (50%)
- *Mood Disorders*: Black, hispanics, and asians prescribed...
More antipsychotics (30-50%)
Less mood stabilizers (45-63%)

From 224,212 in Mount Sinai Health System EHR



NEWS



Brexpiprazole Rejected in PTSD

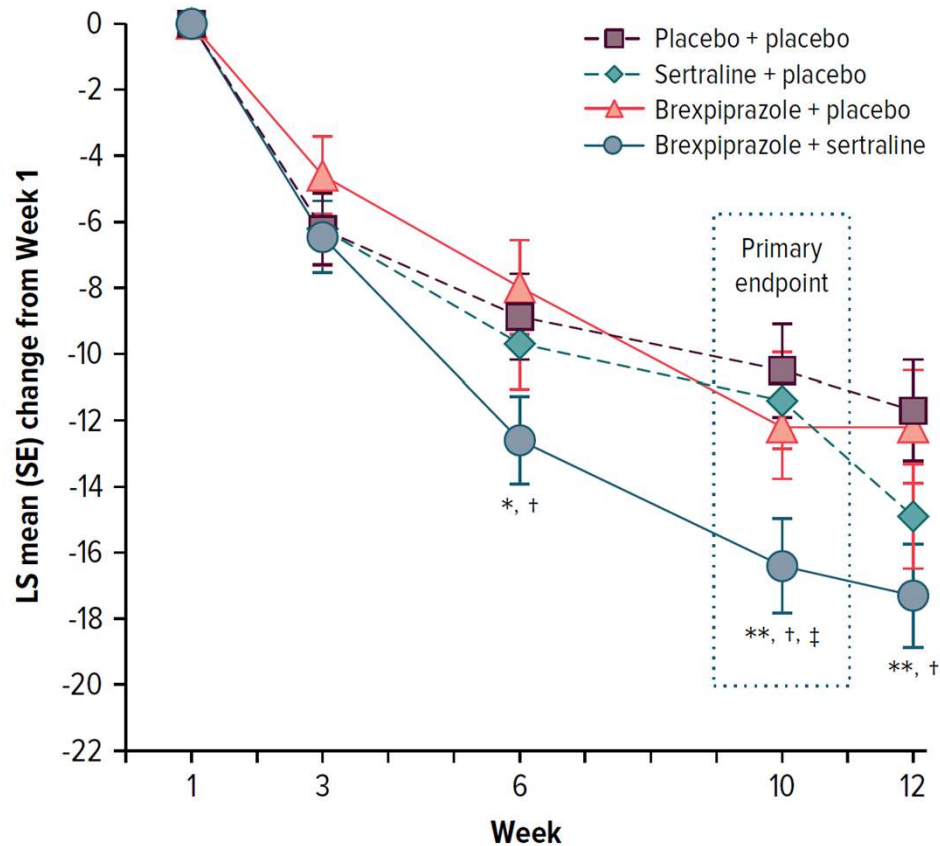
Conflicting results

Trial designs that don't translate well to real-world

-

Brexpiprazole in PTSD (aug / mono) (phase II)

A. CAPS-5 total score (primary endpoint)

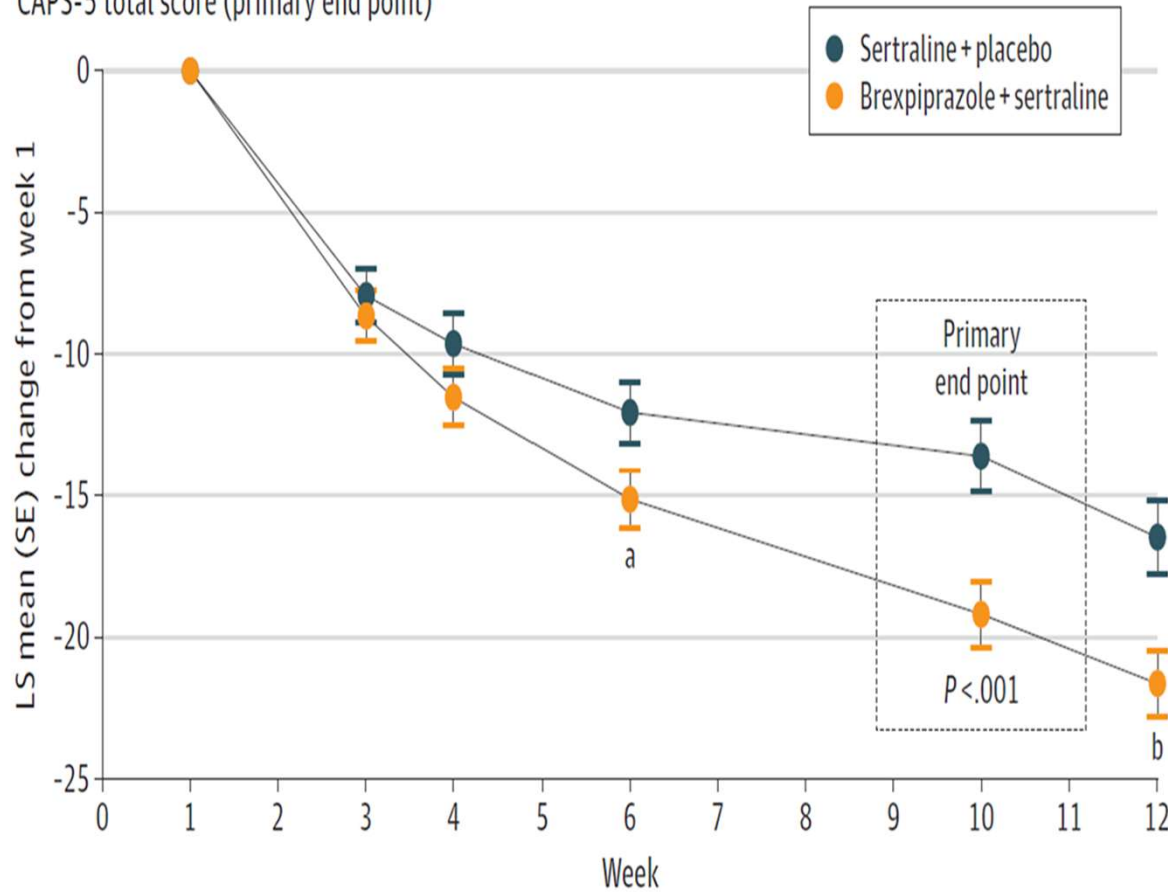


n = 80 per arm
28% drop out

Hobart M et al. Brexpiprazole in Combination With Sertraline and as Monotherapy in Posttraumatic Stress Disorder: A Full-Factorial Randomized Clinical Trial. *J Clin Psychiatry*. 2025;86(1):24m15577.

Brexipiprazole augmentation in PTSD (phase III)

CAPS-5 total score (primary end point)

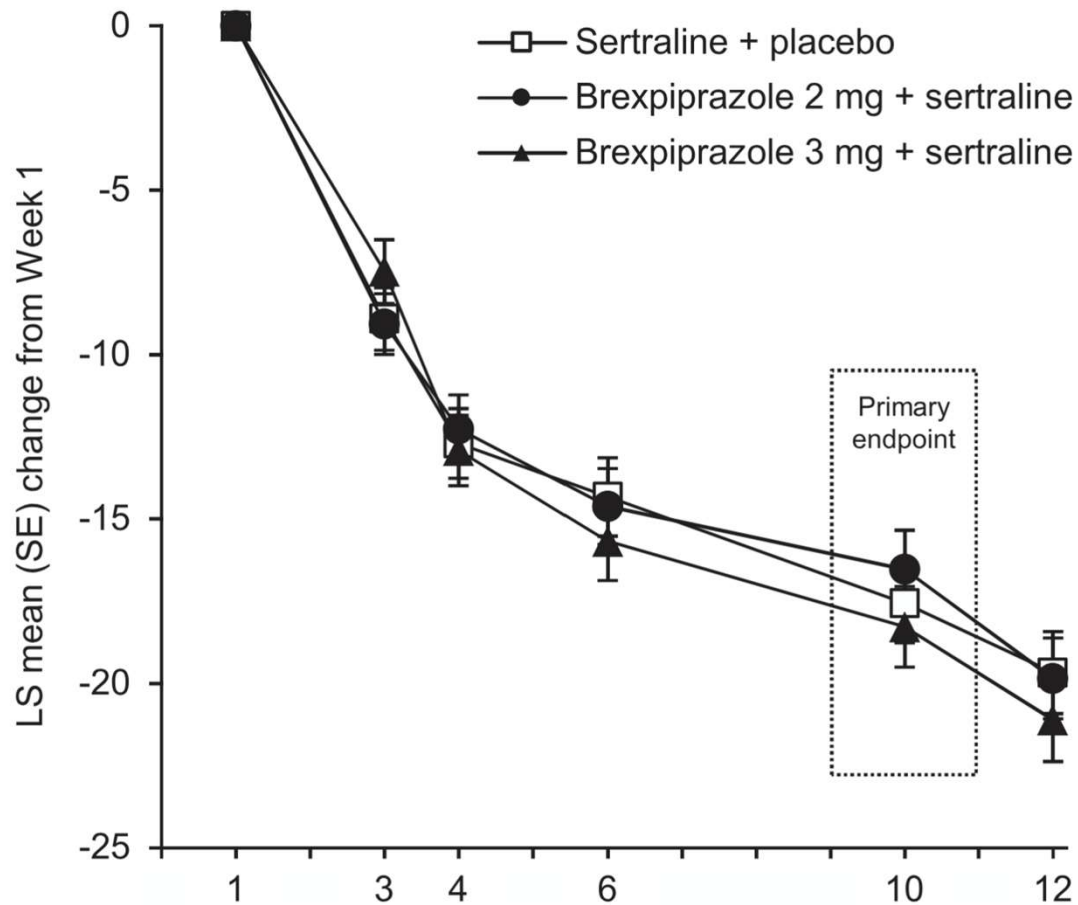


n = 416

40% Drop out

Davis LL, Behl S, Lee D, et al. Brexipiprazole and Sertraline Combination Treatment in Posttraumatic Stress Disorder: A Phase 3 Randomized Clinical Trial. JAMA Psychiatry. 2025;82(3):218-227.

Brexpiprazole augmentation in PTSD (phase III)



n = 553

30% Drop out

Davis LL et al. Fixed-Dose Brexpiprazole and Sertraline Combination Therapy for the Treatment of Posttraumatic Stress Disorder: A Phase 3, Randomized Trial. J Clin Psychopharmacol. 2025;45(6):580-589.

Results do not generalize. Excluded were...

- Depression and comorbidities
- Disability
- Trauma before age 16 (or more than 9 years ago)
- Ongoing trauma
- Limitation of combat-related trauma to 20%
- Placebo-responders

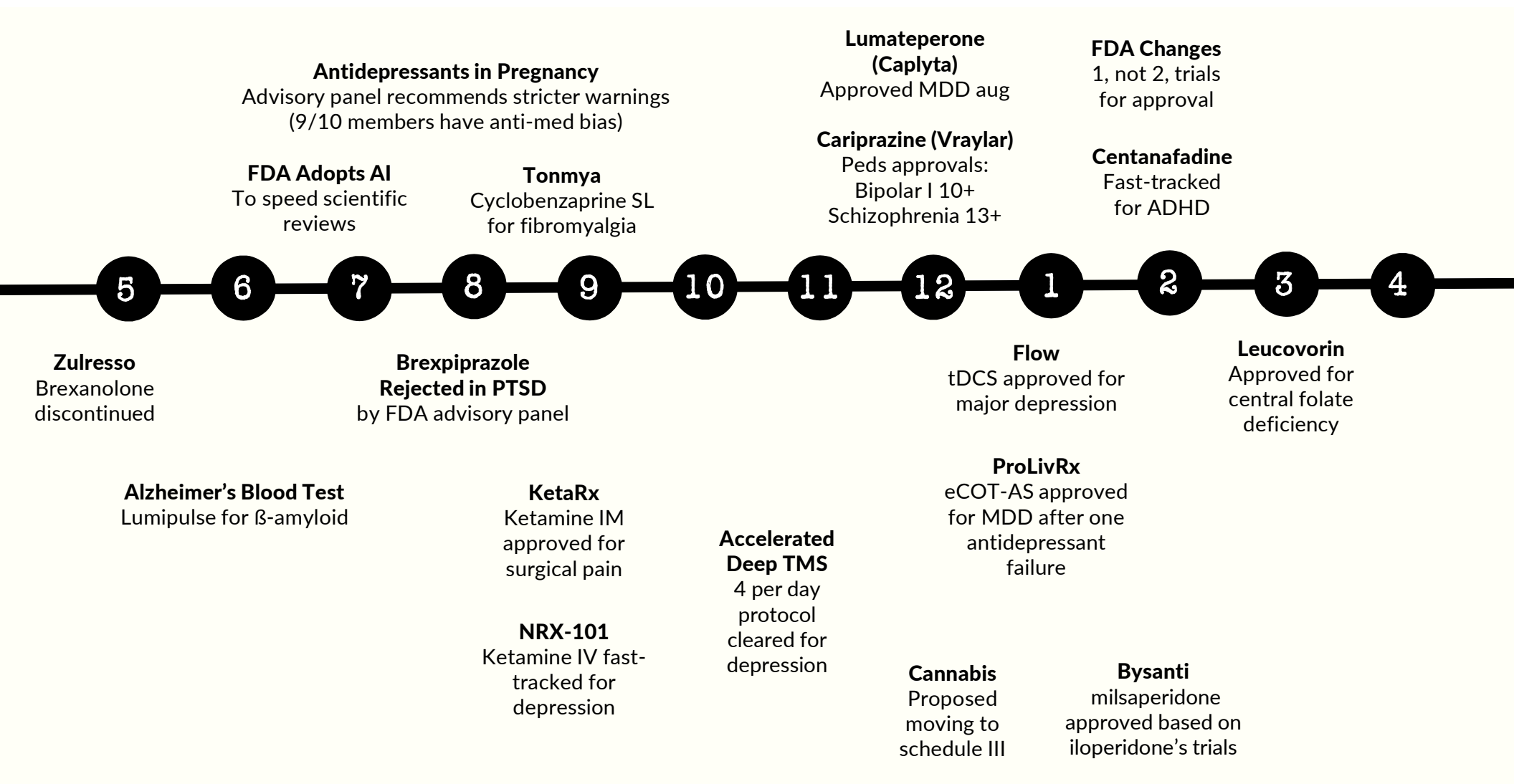
Also most participants treatment-naive

Small Scale Hope

Treatment	Condition	Study
Viloxazine	ADHD (stimulant augmentation) 100-400 mg	RCT n=56, 6-17 yr, open-label PMID: 40014428
Varenicline	Alcohol use disorder	RCT n=384, 4-arm study PMID: 40487775
Levetiracetam	Mania (augmentation) 250 mg qhs	RCT n=65 PMID: 40447146
Prazosin	Depression with trauma history, 0.5-1 mg hs augmentation	RCT n=59 PMID: 39340191
Memantine	Autism (child, normal IQ) social responsiveness 20 mg qd	RCT n=42 PMID: 41032298
Guanfacine	Self-injury and aggression in Prader- Willi, 3-4 mg XR	RCT n=16 PMID: 40395104
Naproxen	OCD (augmentation) 250 mg bid	RCT n=96 PMID: 39354696
SAINT-TMS	Prevention of TRD (100%) given as needed (avg 1 day/month)	Uncontrolled 1 year, n=21 Stimpson K, Brain Stim v18, 1p228-229, 2025
tDCS	Major depression	RCT n=174 (largest to date) PMID: 39433921

Large Scale Failures

Treatment	Failures	Study
Antipsychotics	Suicide in MDD Mortality in MDD (increased 27%)	Large cohort study PMID: 40197402
Semaglutide	Depression and cognition in MDD	RCT (n=72) PMID: 41218611
Semaglutide	Cognition in Alzheimer's	Two large RCTs (Evoke)
Brexipiprazole	Maintenance in MDD (augmentation)	Large 6 mth phase-3 RCT PMID: 39415650
Cobefny	Augmenting antipsychotics in schizophrenia	Phase-3 ARISE RCT n=386 NCT05145413
Pimavanserin	Negative symptoms of schizophrenia Antidepressant augmentation	Phase-3 trial n=484 PMID: 40181715
Ketamine	Inpatient MDD (vs IV midazolam)	RCT n=65 PMID: 41123905
Doxazosin	PTSD	3 small RCTs PMID: 41042258
Vagal Nerve Stimulation	Depression	Large, 12 mth sham RCT PMID: 39706521
Psilocybin	Alcohol use disorder	Small RCT
Microdose LSD	ADHD	Phase-2a RCT, n=53 PMID: 40105807
Orexin antagonist (tebideutorexant)	Depression and anxiety during insomnia	Phase-2a RCT n=222 PMID: 40215570



FDA Updates 5/2025 to 4/2025

Daily updates (@ChrisAikenMD)

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The Carlat Psychiatry Podcast
The Carlat Psychiatry Report

