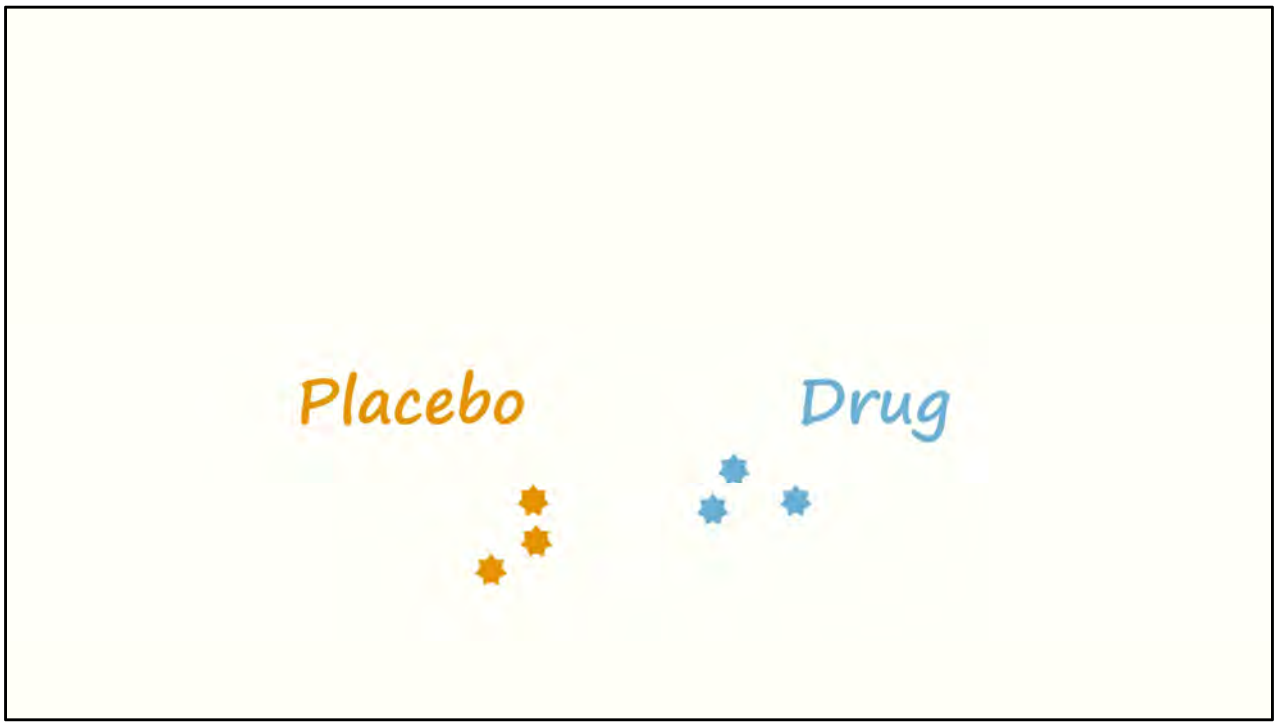
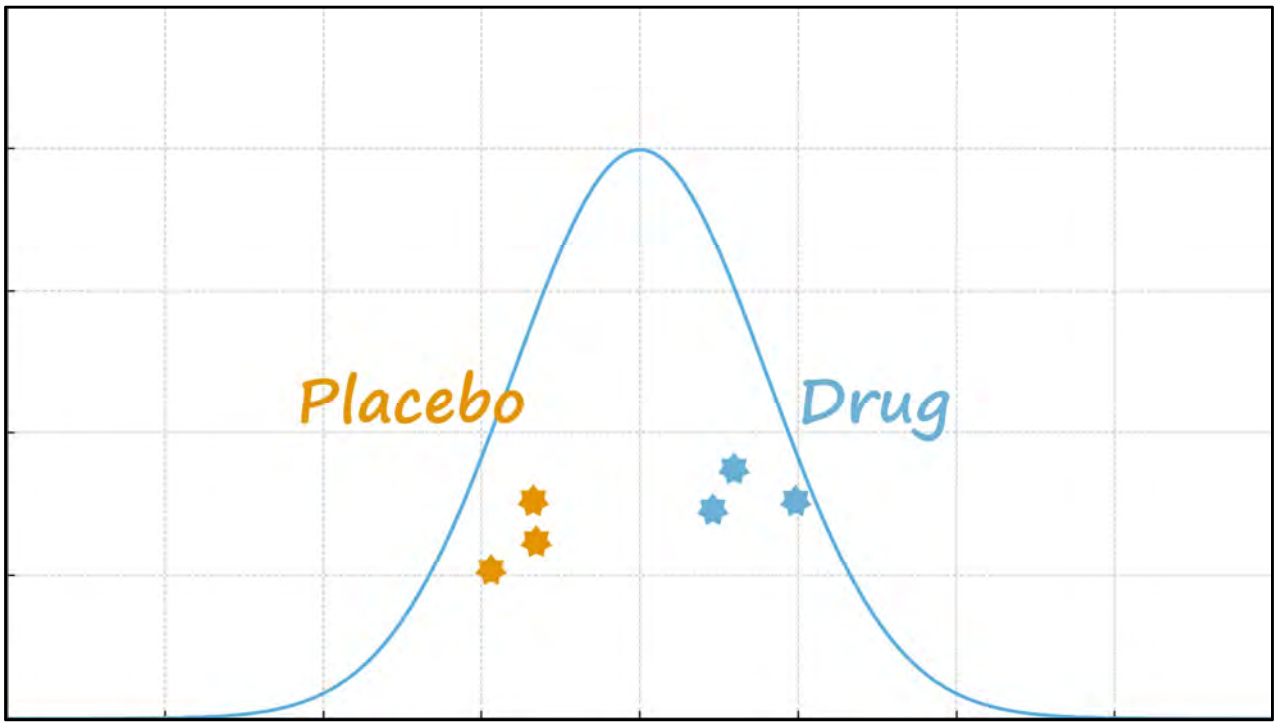
TOP TEN TREATMENT UPDATES

FROM THE PAST YEAR

CHRIS AIKEN MD, September 2026
Editor-in-chief, Carlat Report Director, Psych Partners
Assit Prof, NYU; Instructor, WFU School of Med

No conflicts related to content


Placebo
Drug

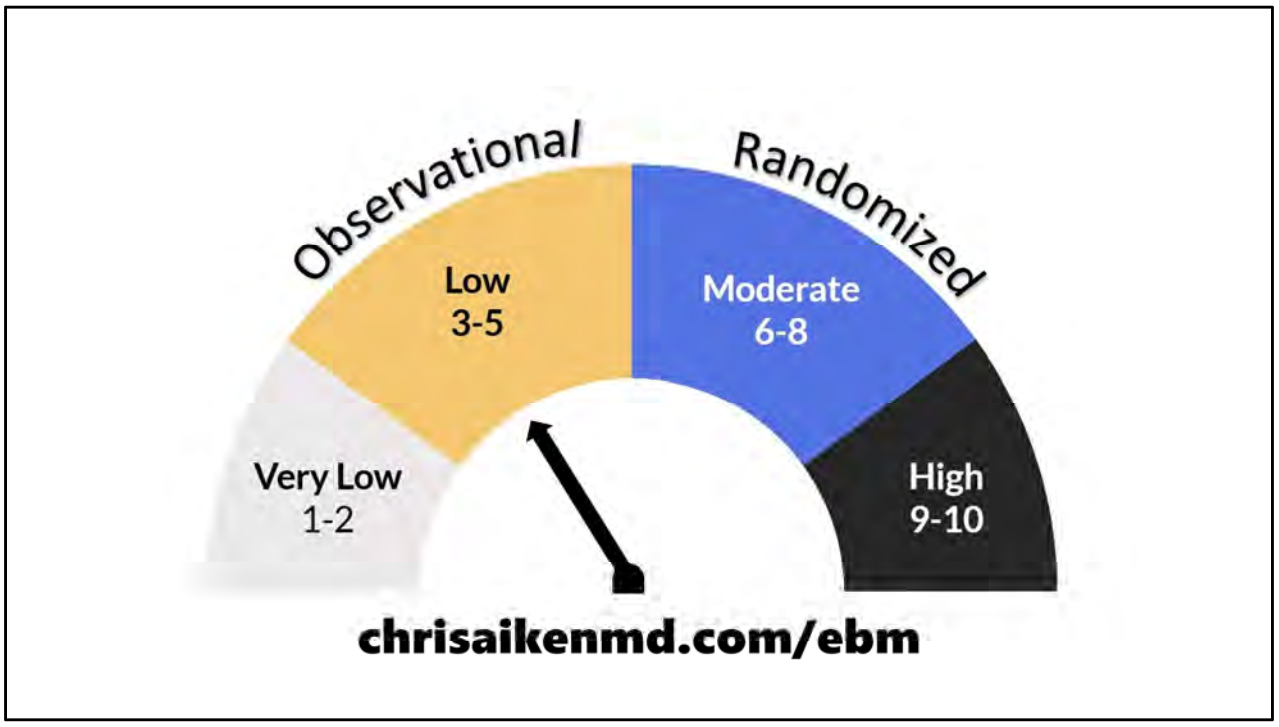

Placebo
Drug

	Ideal	Less Ideal
Control	Placebo or sham Blinding intact	Active treatment Treatment as usual or wait list
Size	At least 120, depending on potency	Smaller
Drop outs	Less than 20% Intention to treat analysis	20-30% is problem > 30% serious problem
Outcome	Primary outcome Pre-registered	Secondary outcomes

Effect Size	Ideal	
< 0.2	Negligible	Vortioxetine in GAD
0.3–0.5	Small	Antidepressants in MDD and GAD
0.5–0.8	Moderate	Benzodiazepines in GAD
> 0.8	Large	Stimulants in ADHD

Is it replicated? Backed by basic science?

Sample reprentative and outcome relevant?


Observational
Randomized
Low
3-5
Moderate
6-8
Very Low
1-2
High
9-10
chrisaikenmd.com/ebm

Top from 2025

1. Five strategies for treatment resistant depression (TRD) compared
2. Quetiapine vs lithium in TRD
3. Pramipexole in TRD
4. Brexpiprazole in PTSD
5. Lithium's medical risks reconsidered
6. Cannabis-induced psychosis: Treatment
7. Saffron in subclinical depression
8. Semaglutide in alcohol use disorder
9. Amphetamines and risk of psychosis/mania
10. An app for tardive dsykinesia

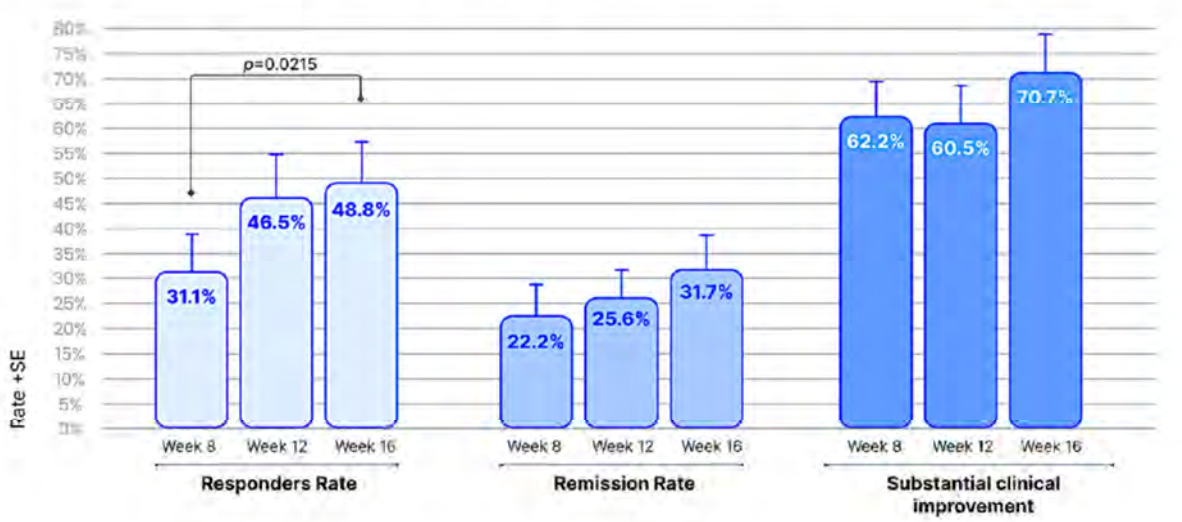
chrisaikenmd.com/2025top10findings

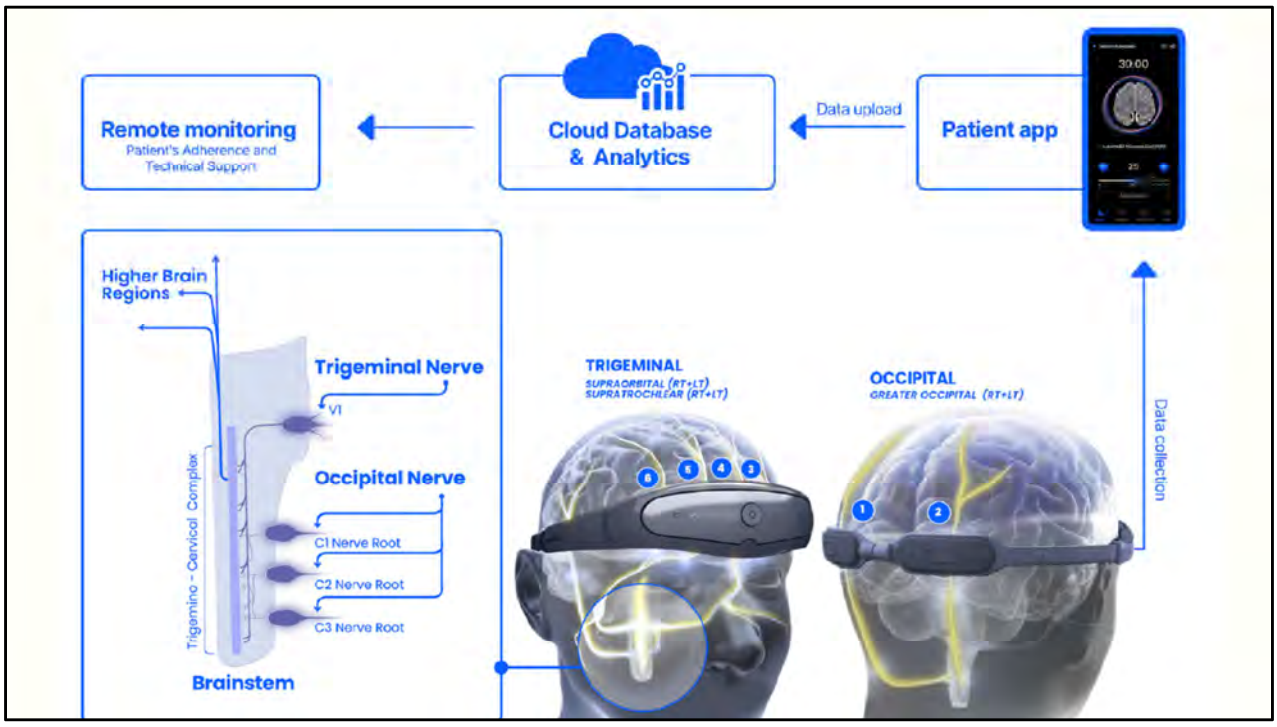
Stimulating trigeminal and occipital cranial nerves at home treated depression after ≥ 1 antidepressant failure

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 (Neurolief)

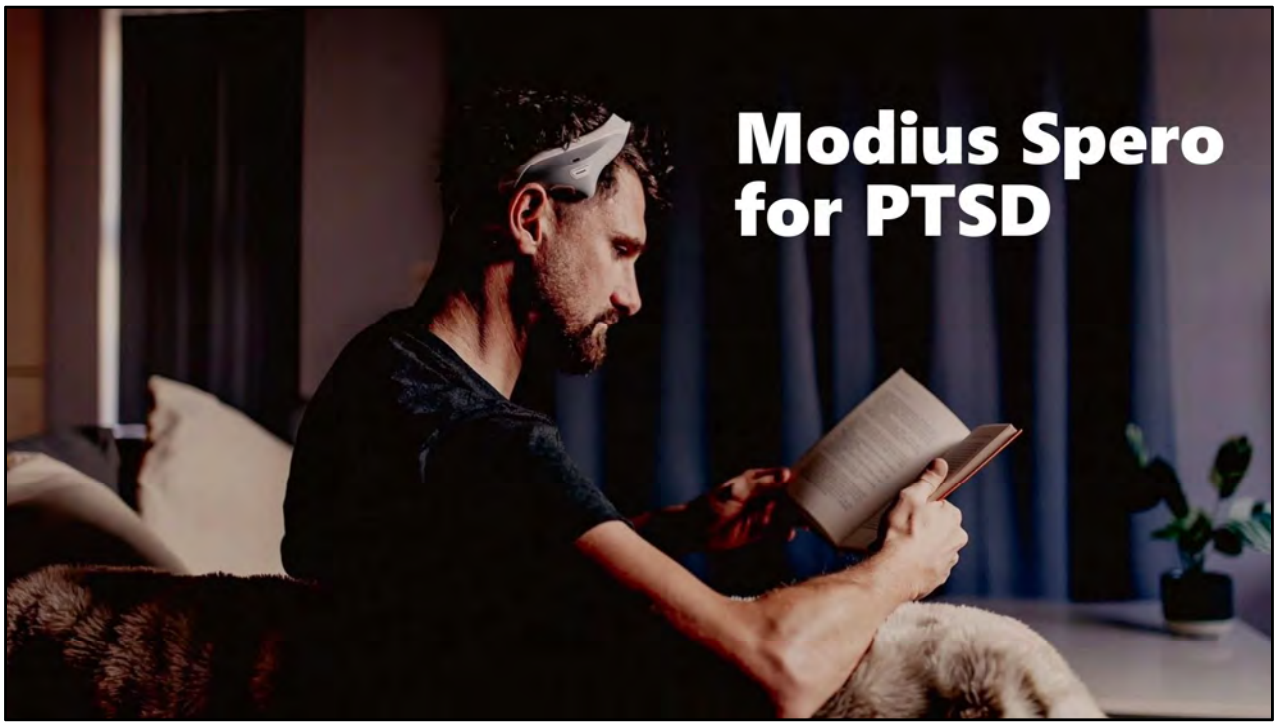
Carpenter LL et al, Brain Stimul 2025;18(5):1695-1704.

Remission builds over 8-16 weeks




Remote monitoring
Patient's Adherence and Technical Support
Cloud Database & Analytics
Data upload
Patient app
Higher Brain Regions
Trigeminal Nerve
V1
Occipital Nerve
C1 Nerve Root
C2 Nerve Root
C3 Nerve Root
Trigemino - Cervical Complex
Brainstem
TRIGEMINAL
SUPRAORBITAL (RT+LT)
SUPRATROCHLEAR (RT+LT)
OCCIPITAL
GREATER OCCIPITAL (RT+LT)
Data collection

Approved Dec 2025, about as effective as SSRI, works in vascular depression, but does not work in treatment resistant depression
Read more: https://psych-partners.com/flow-tdcs-depression/



Approved June 2026 based on one RCT, may only be available at VA, activates vestibular cranial nerve
Read more: https://psych-partners.com/at-home-device-approved-for-ptsd/

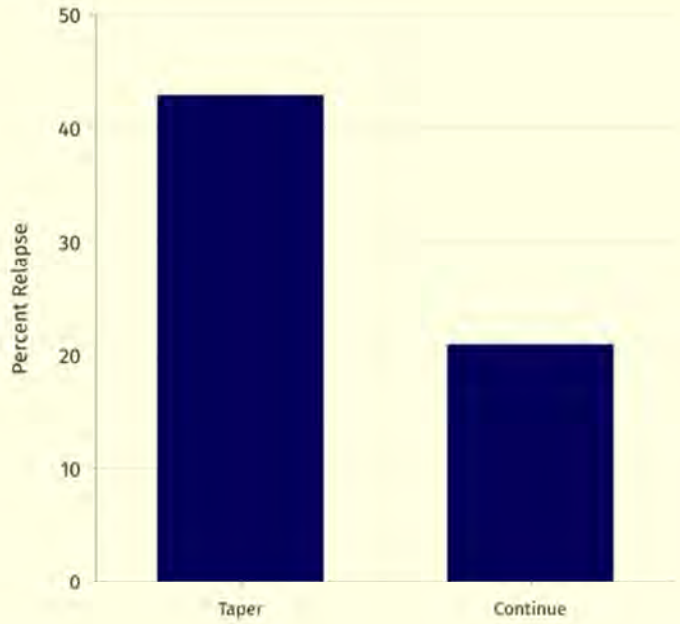
Magnetic EEG Resonance Therapy cleared June 2026.
Read more: https://psych-partners.com/fda-clears-a-new-type-of-tms/

The Ampa TMS aims to lower the barrier to entry, with a rental subscription ($3000 per month) and a smaller size that does not require a separate office. It is also simpler, with camera-guided placement, requiring less staff training time. Otherwise it is similar to traditional iTBS, a briefer version of TMS approved in 2019 that delivers treatment in 3 minutes instead of 20-60 min.


Antipsychotic Tapering in First Episode Psychosis

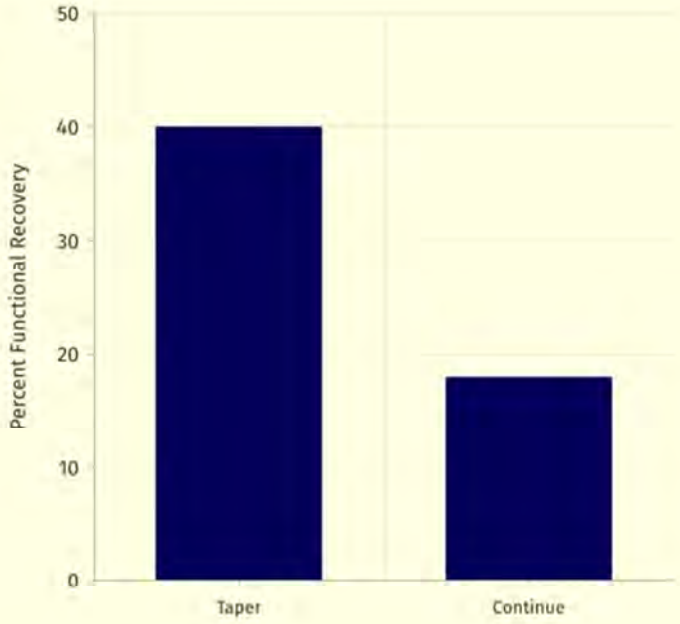

Lex Wunderink

At 18 months, higher relapse with taper



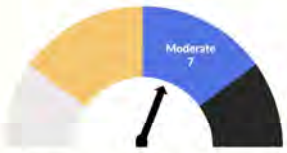
Wunderink L et al. Guided discontinuation versus maintenance treatment in remitted first-episode psychosis: relapse rates and functional outcome. J Clin Psychiatry. 2007;68(5):654-661.

At 7 years, higher functioning in taper group



Wunderink L et al, Recovery in remitted first-episode psychosis at 7 years of follow-up of an early dose reduction/ discontinuation or maintenance treatment strategy: long-term follow-up of a 2-year randomized clinical trial. JAMA Psychiatry. 2013;70(9):913-20.

Antipsychotic Reduction/Discontinuation in First Episode Psychosis	
Design	Randomized, rater-blind controlled trial
Size	347 first-episode psychosis after 3-6 mth remission Mean age 28, 70% male, 72% schizophrenia/schizophreniform 26 Dutch psychosis centers
Intervention	Gradual taper toward discontinuation
Duration	6 mth taper, 4 year follow up
Primary outcome	Patient-rated functioning (WHODAS-2) Secondary: Clinician-rated functioning (GAF), symptoms (PANSS), quality of life, and relapse rates
Result	First year: Higher relase (odds ratio 2.84) with taper 3+ years: Higher clinician-rated functioning with taper But medication use similar after one year
Funding	ZonMw (Netherlands Org for Health Research and Development)



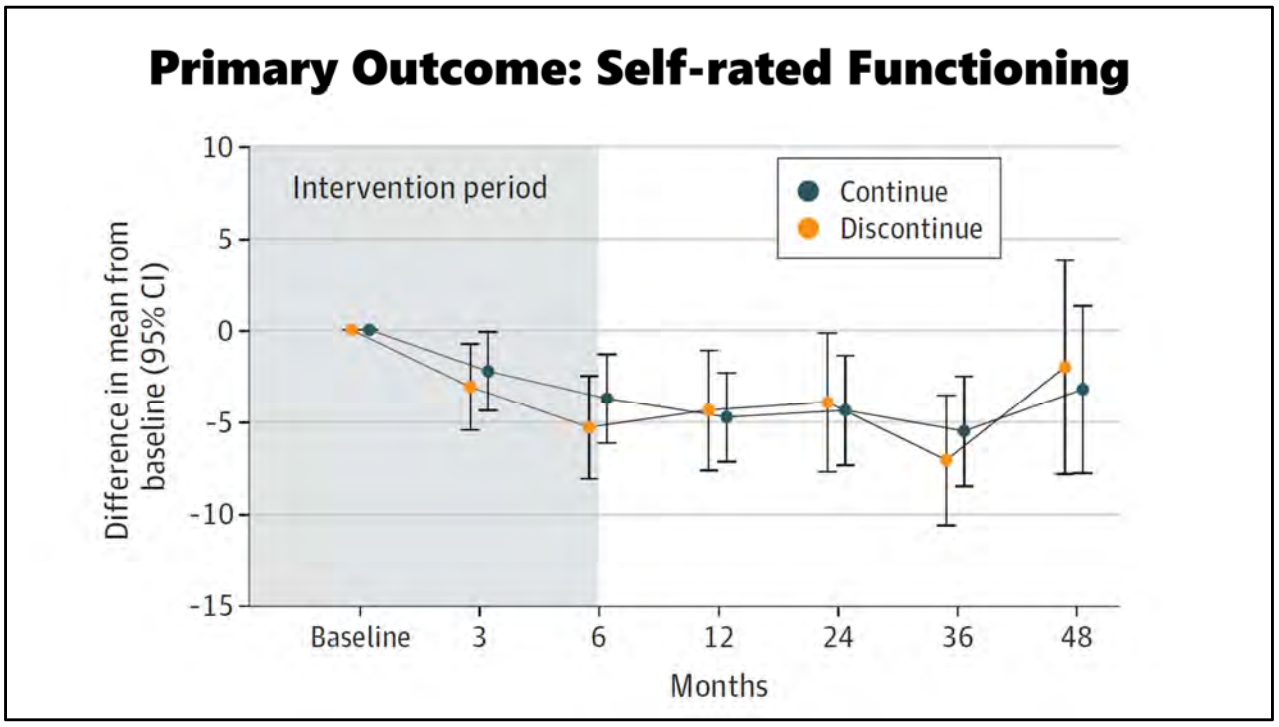
30% drop out
Only raters blinded

Sommer IE et al. Early Dose Reduction or Discontinuation vs Maintenance Antipsychotics After First Psychotic Episode Remission: A Randomized Clinical Trial. JAMA Psychiatry 2026;83(1):68-73.

Tapering didn't work well, and patients learned from the experience, with most going back on the medication or halting the taper. At 6-12 months, the tapering group was taking slightly less medication (2.4 to 2.8 mg less of olanzapine dose-equivalents), but after one year the two groups had similar rates of medication use.

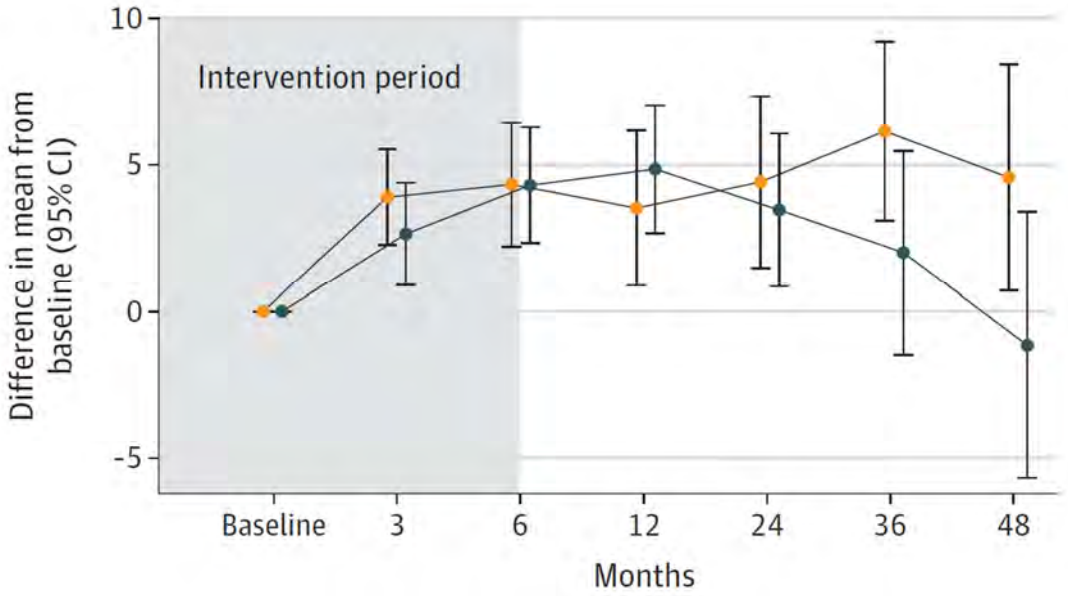
The continuation group was allowed to decrease dose by up to 25%, and 40% of the patients in this group actually tapered on their own (against protocol). In other trials, 70% of patients tend to self-taper after first-episode psychosis.

Read more: https://psych-partners.com/antipsychotic-deprescribing-trial-raises-questions/

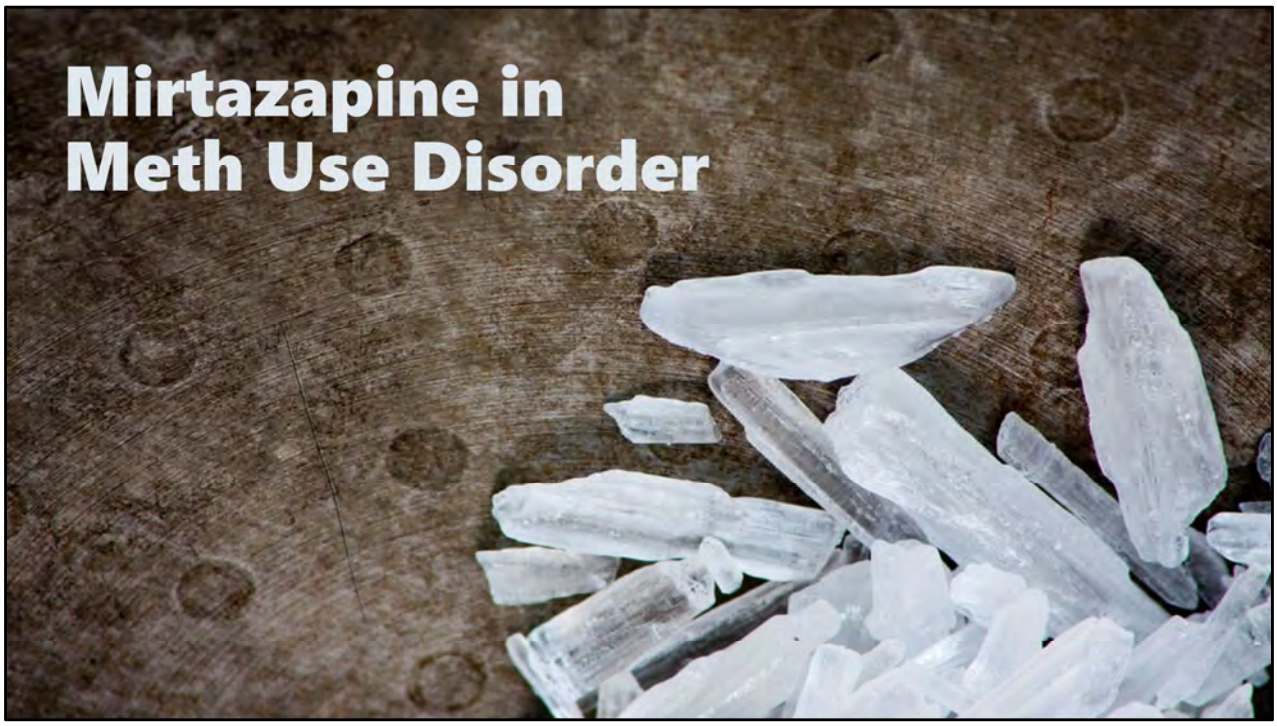


No difference on primary measure of self-rated functioning

Secondary Outcome: Clinician-rated Functioning



Only the secondary outcome was different, and not robustly so



Mirtazapine is an antidepressant that may reduce methamphetamine cravings and withdrawal problems by modulating dopamine, as well as serotonin and norepinephrine transmission. It has shown promise in two small trials of methamphetamine use disorder, but only in men who have sex with men, and the trials took place at a single site. This study furthers the evidence with a large, phase III trial.

Mirtazapine for Meth Use Disorder	
Design	Randomized, double-blind controlled trial
Size	339 adults with moderate-to-severe methamphetamine 37% women, 49% had depression 6 outpatient clinics in Australia
Intervention	Mirtazapine 30 mg vs placebo
Duration	12 weeks
Primary outcome	Days of methamphetamine use
Result	Reduced use by 7.0 days vs by 4.8 days per month (8%) Secondary outcomes = no difference
Risks	Drowsiness (47% vs 33%), weight gain (10% vs 3%); discontinuation due to adverse effects (23% vs 15%)
Funding	Australian Government Medical Research Future Fund

27% drop out

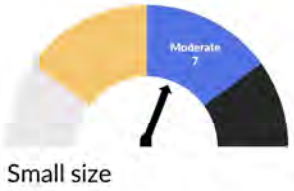
McKetin R et al. Mirtazapine for Methamphetamine Use Disorder: A Randomized Clinical Trial. JAMA Psychiatry. 2026;83(6):581-589.

The effect was consistent regardless of sex or depression status. No secondary outcomes (depression, insomnia, HIV risk, quality of life) reached significance overall, though insomnia improved significantly in participants with comorbid depression.

Read more: https://psych-partners.com/mirtazapine-reduces-meth-use/


Dextromethorphan
Augmentation

Dextromethorphan in OCD	
Design	Randomized, double-blind, placebo-controlled trial
Size	40 adults with OCD, non-response to SSRI Mean age 37, 30% male
Intervention	Dextromethorphan 15 mg bid augmentation vs placebo
Duration	12 weeks
Primary outcome	Y-BOCS
Result	Reduced Y-BOCS (effect size 0.7) by week 4
Risks	None, but can cause psychosis, delirium, dizziness, fatigue
Funding	Zanjan University



Zolghadriha A et al. Efficacy of Dextromethorphan Augmentation in SSRI-Resistant Obsessive-Compulsive Disorder: A Randomized Controlled Trial. Health Sci Rep. 2026;9(5):e72055.

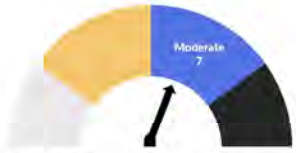
Glutamate dysregulation plays a role in OCD, and small trials have found promise with glutamatergic meds like amantadine, memantine, lamotrigine, and n-acetylcysteine. This trial tested dextromethorphan (DXM), originally developed as a cough syrup but more recently found to speed up antidepressants in the bupropion-combo Auvelity (also FDA-approved this month for agitation in dementia).

Mechanism: DXM blocks NMDA glutamate receptors and also modulates serotonin, norepinephrine, and sigma-1 receptors. Fluoxetine and paroxetine inhibit DXM metabolism and likely raised DXM levels in some participants, a pharmacokinetic variable that wasn't tracked.

https://psych-partners.com/dextromethorphan-for-ssri-resistant-ocd/

Dextromethorphan in Clozapine-Resistant Schizophrenia

Design	Randomized, double-blind, placebo-controlled trial
Size	40 adults with clozapine-resistant schizophrenia in India Mean age 34, 58% male
Intervention	Dextromethorphan 30 mg qd augmentation vs placebo
Duration	12 weeks
Primary outcome	Total positive and negative symptoms (PANNS)
Result	Improved PANNS (NNT 2 for response), including positive and negative scales CGI improved. MMSE unchanged
Risks	None, but can cause: Psychosis, delirium, dizziness, fatigue, abuse liability
Funding	None



Small size
But recruitment stopped early due to large effect

Hegde NC et al. Augmentation of clozapine with dextromethorphan in treatment-resistant schizophrenia: A randomized, group sequential adaptive design, controlled clinical trial. Asian J Psychiatr. 2026; 119:104919.

An adequate clozapine trial may up to 15 weeks. If it fails to reduce positive symptoms, maximize the serum level (350-550 ng/mL) (Wagner E et al, Schizophr Bull 2020;46(6):1459-1470). Reconsider the adequacy of previous trials, and consider other low-risk, long-term programs addressing diet, activity, and psychosocial needs. Other options for treatment-resistant schizophrenia include high-dose olanzapine (25-50 mg qd), TMS, and ECT, but the evidence for clozapine-resistant schizophrenia is limited. Small trials point to augmentation with aripiprazole (10-15 mg qd), topiramate (100-200 mg bid), lamotrigine (50-200 mg qd), or dextromethorphan (15 mg bid) (Grover S et al, Acta Neuropsychiatr 2023;35(2):65-75).

ECT used to be on that list, but has failed in newer trials. Psychotherapy may help. You should also check a clozapine level for pseudoresistance, when the medication is not working because it isn't getting in their system.

Glutamate dysfunction plays a role in schizophrenia

.

The benefits disappeared when tested in a subgroup of patients with pseudoresistance (those who appeared to have a poor response to clozapine but really just had low serum levels). That suggests dextromethorphan is only effective in true clozapine resistance. Clozapine levels similar between groups (427-475) but more in control needed clozapine

dose increase.

Clozapine carries a new risk of pneumonia, but does adding a cough suppressant like dextromethorphan increase that risk? Pulmonology research suggests it does not.

Runner up…

Buspirone 5-10 mg TID
for clozapine-resistant schizophrenia

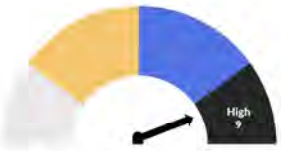
Study of 46 inpatients in China, improved cognition and positive/negative symptoms (Xia Y et al Br J Clin Pharmacol. 2026;92(8):2777-2787.).

Read more:
https://psych-partners.com/buspirone-augments-clozapine-in-schizophrenia

Semaglutide in Alcohol Use Disorder *with Obesity*


Negative trial in AUD
Secondarily positive in obesity
Retested in obesity with AUD
Mette Klausen

Semaglutide in Alcohol Use Disorder with Obesity	
Design	Randomized, double-blind, placebo-controlled trial
Size	108 moderate-severe AUD and obesity, treatment-seeking
Intervention	Semaglutide 2.4 mg SQ Qweek vs placebo Added to CBT therapy
Duration	6 months
Primary outcome	Heavy drinking days
Result	Reduction of heavy drinking days 41% vs 26%, effect size 0.57 Total alcohol lower by 1,550 g/mth vs 1,026 g/mth Weight loss (11 kg vs 2 kg) correlated with drinking reductions
Risks	Nausea (57% vs 7%), pancreatitis (elevated amylase in 7%)
Funding	Industry (Novo Nordisk) and government

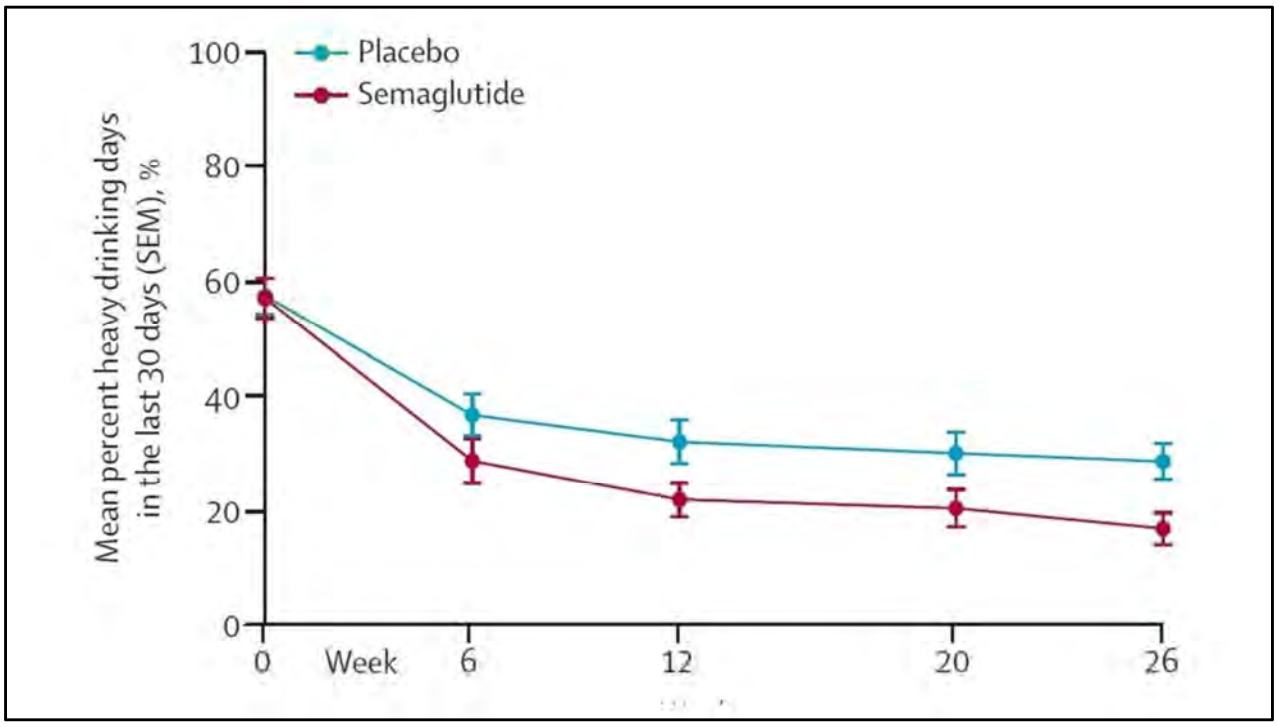


More drop outs in placebo, suggesting functional unblinding

Klausen MK et al. Once-weekly semaglutide versus placebo in patients with alcohol use disorder and comorbid obesity: a randomised, double-blind, placebo-controlled trial. Lancet. 2026;407(10540):1687-1698.

GLP-1 drugs like semaglutide (Ozempic) have a mix of positive and negative data in alcohol use disorder, but most of the research has involved non-treatment seeking populations, which often differ in their responses. This small trial delivers mixed results for an oral version of semaglutide in treatment-seeking patients.

Read more: https://psych-partners.com/a-glp-1-trial-changes-the-score-in-alcohol/



A moderate effect size for reduction in heavy drinking days

GLP-1 Score Card in Alcohol Use Disorder

Outcome	Med	Population	Grade	Study (PMID)
Positive	Semaglutide	Obesity, treatment seeaking	9	Klausen MK, 2026 (42070571)
Neg	Oral Semaglutide	Treatment seeking	8	Schacht JP, 2026 (42522065)
Neg*	Exenatide	Treatment seeking **positive in obese subgroup*	8	Klausen MK, 2022 (36066977)
Positive	Semaglutide	NOT treatment seeking	7	Hendershot CS, 2025 (39937469)
Positive	Dulaglutide	Nicotine (secondary analysis)	5	Probst L, 2022 (37991022)

GLP1s are effective in obesity, but otherwise their efficacy is limited to non-treatment-seeking populations. In addictions research, many therapies work in non-treatment-seeking populations but fail in clinical populations.

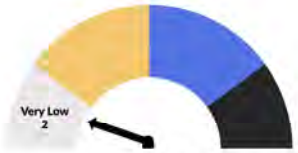
Levels can double with GLP-1s, particularly semaglutide, though unclear how often and who is at risk

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

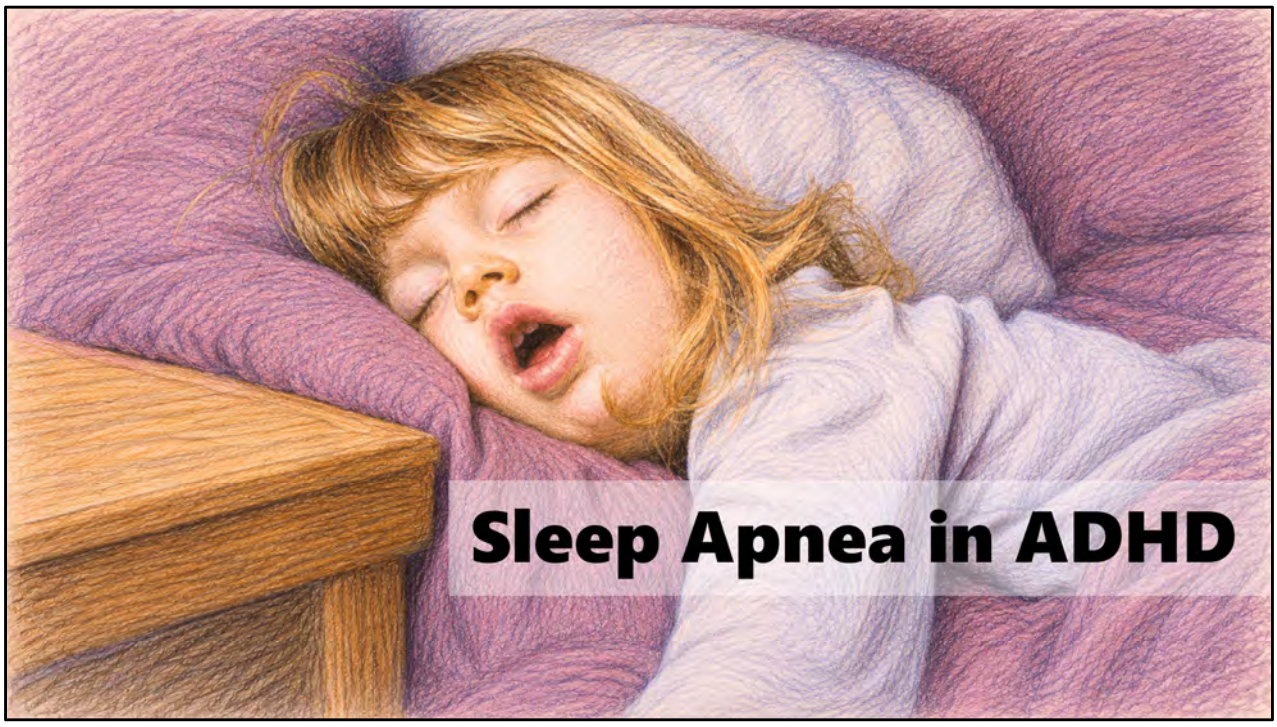
The cause of the interaction is not known:
> Dehydration
> Renal change (2 cases had elevated Cr)
> Delayed stomach emptying is unlikely, as pharmacokinetic data show it changes the timing of absorption, not the total amount absorbed.

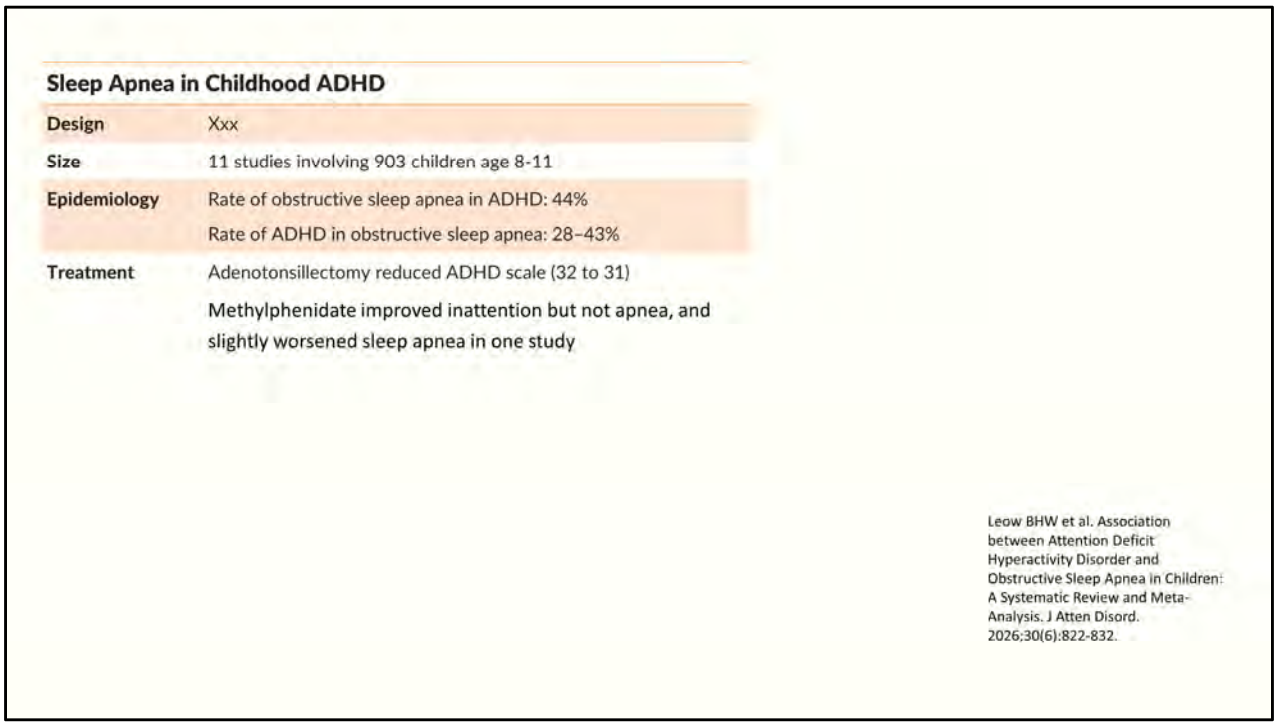
Read more: https://psych-partners.com/more-on-the-glp1-lithium-interaction/

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.


Sleep Apnea in ADHD

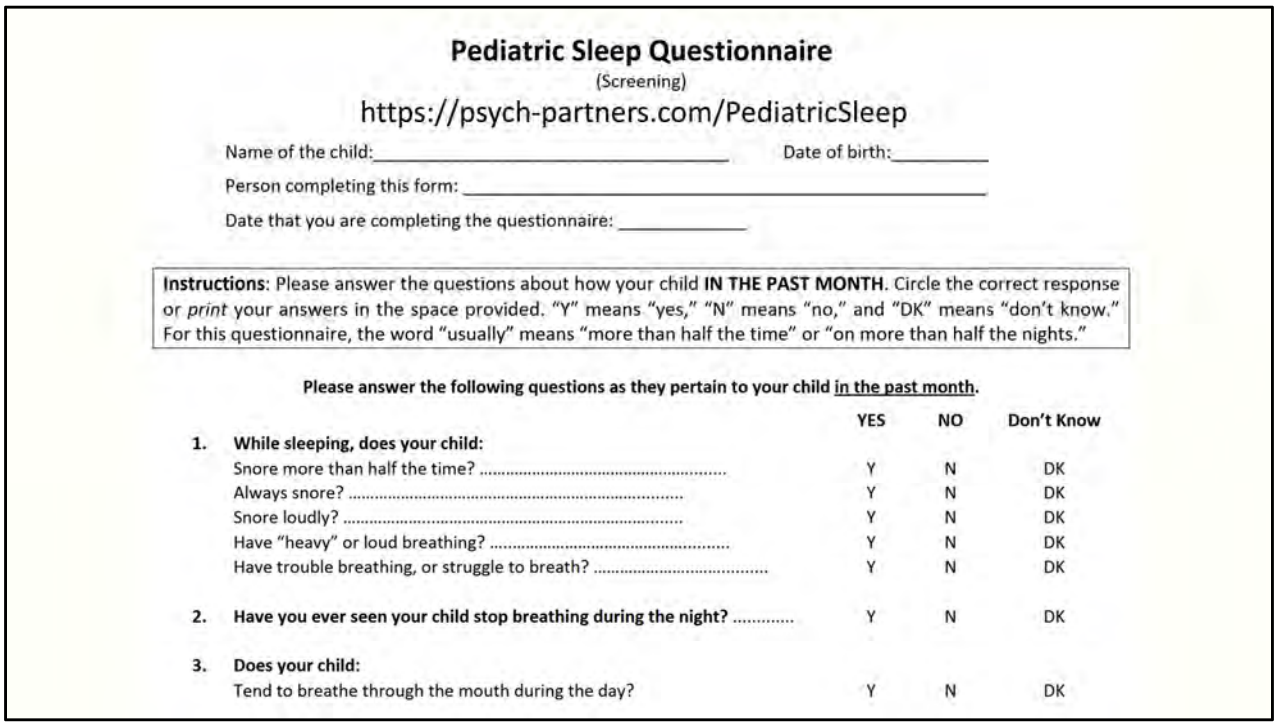


Obstructive sleep apnea causes fragmented sleep and intermittent oxygen drops that impair attention, impulse control, and behavior, symptoms that overlap closely with ADHD. Children with enlarged tonsils and adenoids are especially prone to both.

In adults, ADHD and sleep apnea overlap at about twice the rate in the general population. 20 to 30% of adults with ADHD have sleep apnea, and the rate is closer to 50% when broadened to include all types of sleep disordered breathing. Three months of CPAP treatment in adults leads to increases in gray matter volume within hippocampal and frontal structures

This doesn't mean that ADHD will resolve with treatment of sleep apnea, as the relationship is bidirectional. ADHD increases the risk of sleep apnea (about 10%), and sleep apnea increases the risk of ADHD (about 25%). The two disorders share common genetic and pathophysiologic pathways, including neuroinflammation and immune-related mechanisms in deep gray matter brain regions

Read more: https://psych-partners.com/sleep-apnea-common-in-childhood-adhd/



Pediatric Sleep Questionnaire

(Screening)

https://psych-partners.com/PediatricSleep

Name of the child:_____ Date of birth:_____

Person completing this form: _____

Date that you are completing the questionnaire: _____

Instructions: Please answer the questions about how your child **IN THE PAST MONTH**. Circle the correct response or *print* your answers in the space provided. "Y" means "yes," "N" means "no," and "DK" means "don't know." For this questionnaire, the word "usually" means "more than half the time" or "on more than half the nights."

Please answer the following questions as they pertain to your child in the past month.

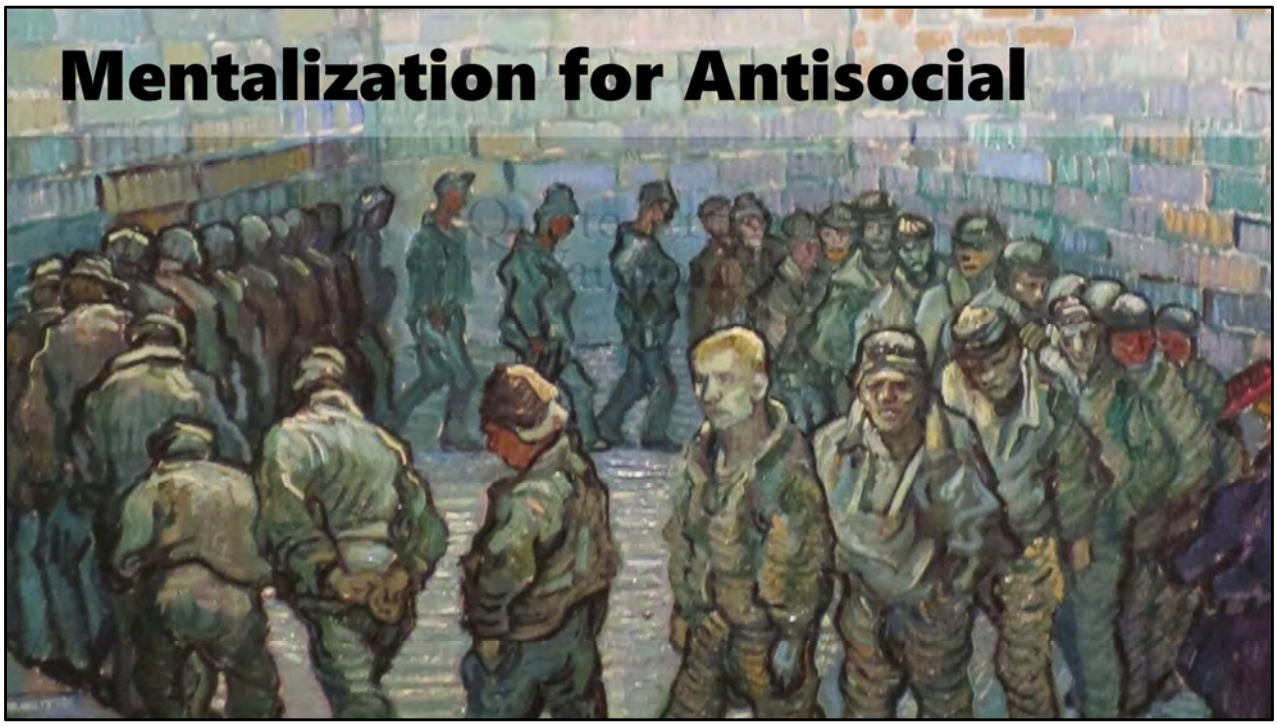
		YES	NO	Don't Know
1.	**While sleeping, does your child:**			
	Snore more than half the time?	Y	N	DK
	Always snore?	Y	N	DK
	Snore loudly?	Y	N	DK
	Have "heavy" or loud breathing?	Y	N	DK
	Have trouble breathing, or struggle to breath?	Y	N	DK
2.	**Have you ever seen your child stop breathing during the night?**	Y	N	DK
3.	**Does your child:**			
	Tend to breathe through the mouth during the day?	Y	N	DK

For children:
https://psych-partners.com/wp-content/uploads/2026/05/PediatricSleep

For adults:
Google STOP BANG Questionnaire

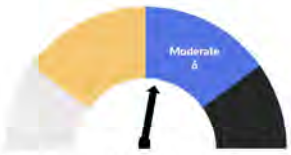
Together, atomoxetine and aroxybutynin stimulate the hypoglossal motor nucleus, increasing upper airway muscle tone during sleep

Read more: https://psych-partners.com/atomoxetine-combo-for-sleep-apnea/



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)

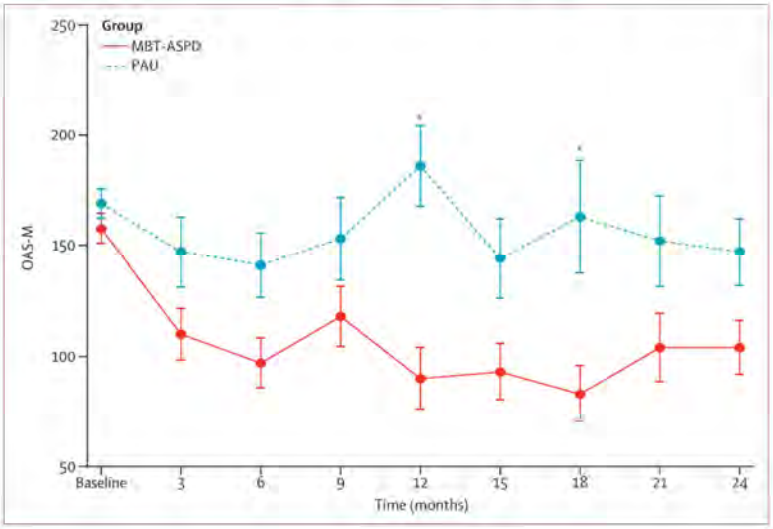


Inactive comparison
Single blind
High drop out
(41-45% @ 1 yr))

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.

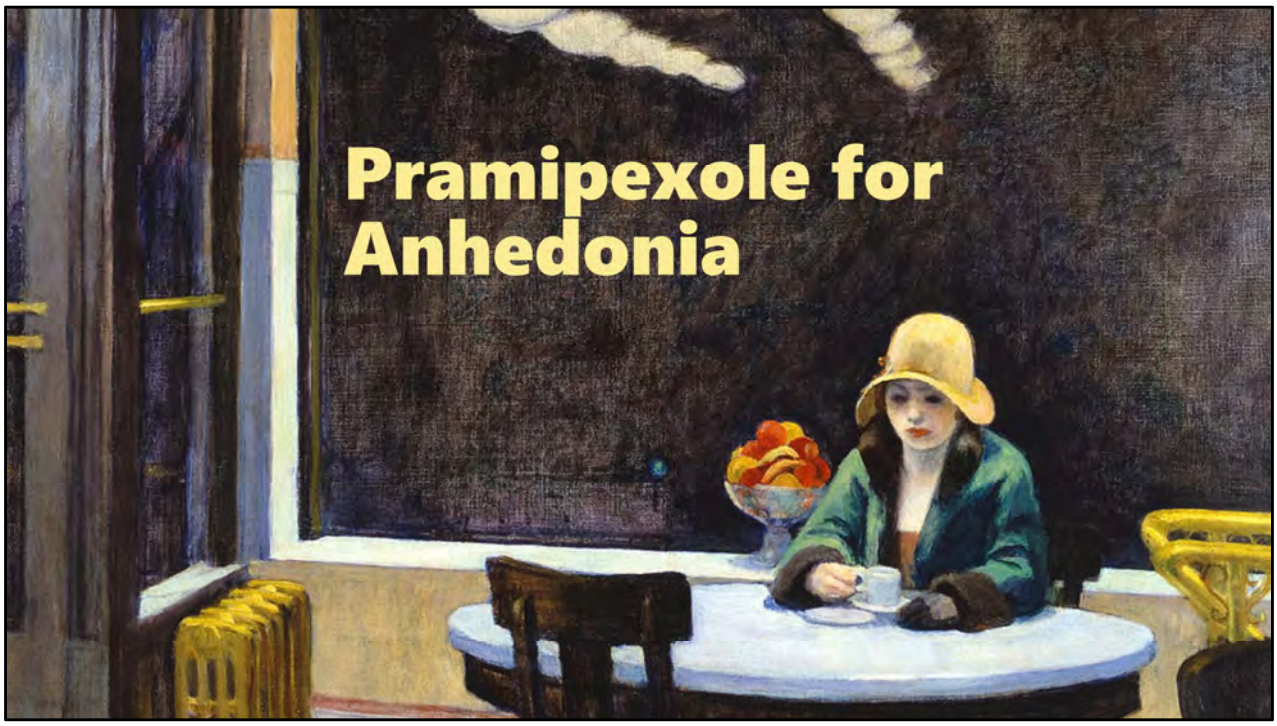
Read more: https://psych-partners.com/a-new-therapy-for-antisocial-personality-disorder/

Mentalization vs Parole as Usual

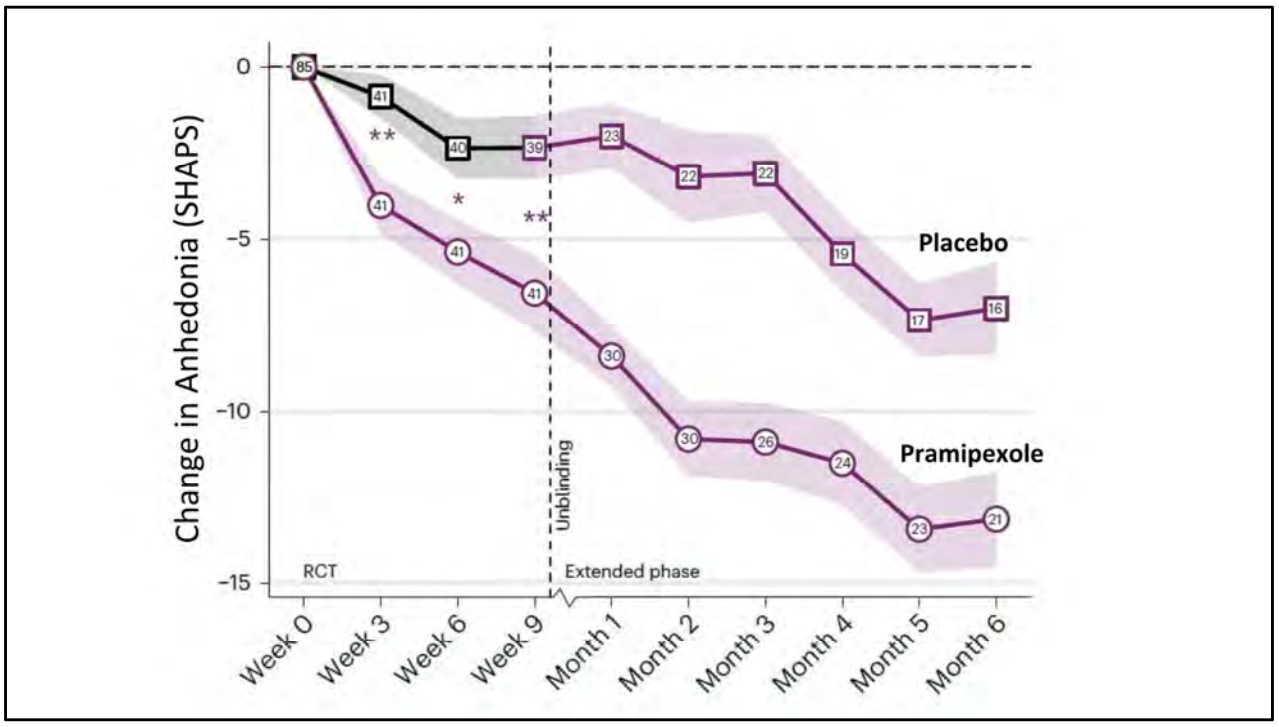


Manual

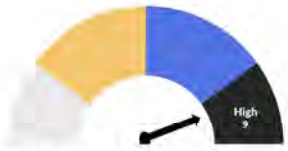
Google "mentalization therapy for antisocial personality manual pdf"



True to its mechanism, this D3 agonist improves a common (70%) type of depression.


Change in Anhedonia (SHAPS)
0
−5
−10
−15
85
41
40
39
23
22
22
19
17
16
41
41
41
30
30
26
24
23
21
**
*
**
Placebo
Pramipexole
Unblinding
RCT
Extended phase
Week 0
Week 3
Week 6
Week 9
Month 1
Month 2
Month 3
Month 4
Month 5
Month 6

Pramipexole for Anhedonic Depression	
Design	Randomized, double-blind, placebo-controlled trial
Size	82 adults with major depression (60%), dysthymia (38%), or bipolar depression (2%) with significant anhedonia 98% completed 9 weeks, 43% completed open-label 6 mth
Intervention	Flexible-dose adjunctive pramipexole (mean 3.5 mg)
Duration	9 weeks, followed by a 6-month open-label extension
Primary outcome	Change in Snaith–Hamilton Pleasure Scale (SHAPS)
Result	Improved anhedonia SHAPS (effect size 0.6), apathy, and physical activity On fMRI, preserved reward-related ventral striatal activation Blind intact for pramipexole, not for placebo
Risks	Sleep disturbances (72% vs 33%), nausea (60% vs 14%), dizziness, fatigue, and anxiety. Possible hypomania, hedonic dysregulation.
Funding	Swedish Research Council



Small size (82)

Ventorp F et al, Efficacy and target engagement of dopamine agonist pramipexole for anhedonic depression: a randomized placebo-controlled trial. Nat Med. 2026;32(7):2570-2578.

The dose is larger than typically used (3.5 mg, vs 1.5 mg for treatment-resistant depression and 2.5 mg for highly treatment-resistant depression).

Pramipexole

Target 1-3 mg hs (average 1.5)

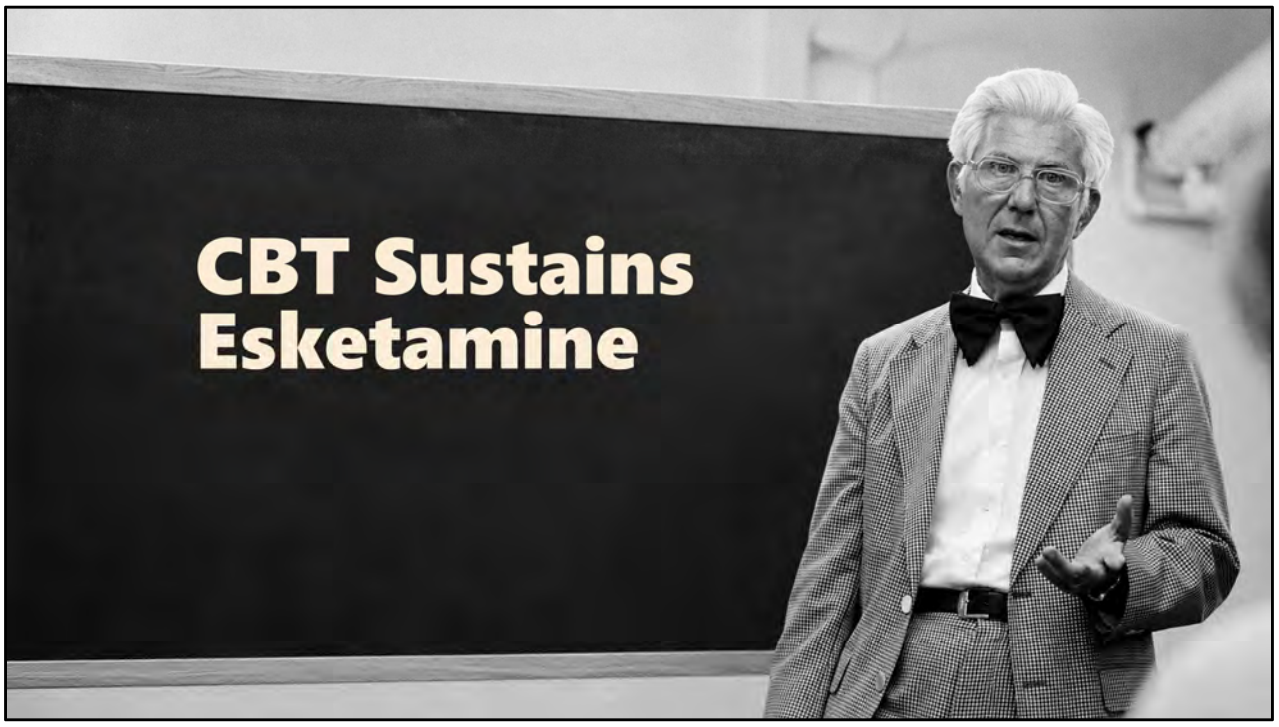
Start 0.125-0.25 mg,
raise by 0.125-0.25mg q3-7 days,
raise faster after 0.75 mg

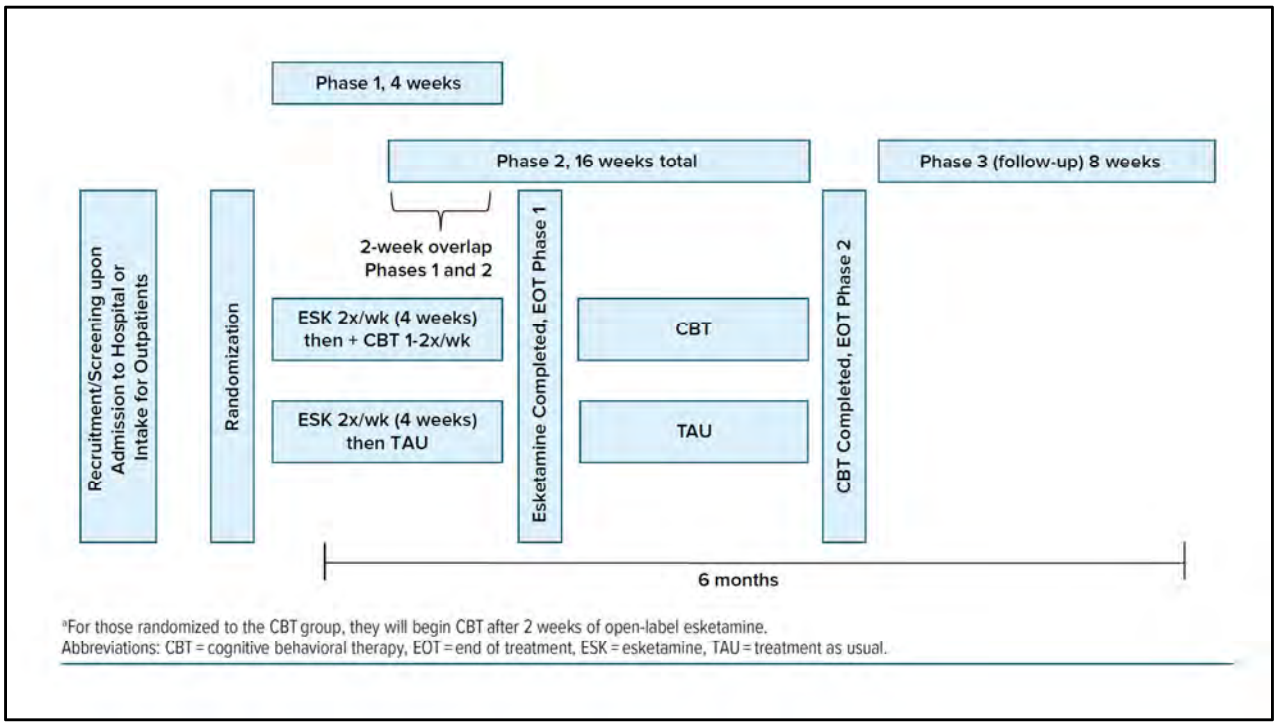
Large effect in RCTs of unipolar (5) and bipolar (2) depression

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

Tolerability
Nausea, sedation
No weight/sexual/cognitive

Risks
Hedonistic dysregulation (approx. 1-3%)
Hallucinations (rare at dose < 2 mg)
Hypotension


CBT Sustains
Esketamine

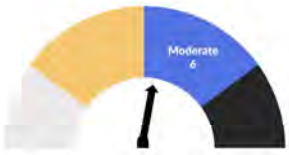


Therapy started 2 weeks into the 4-week esketamine course, and continued for 16 weeks total.

What they did in therapy

- Psychoeducation
- Cognitive restructuring
- Behavioral activation
- Changing schemas
- Homework: Activity logs, thought records
- Attention to suicide and risk assessment
- Computerized sessions used the *Good Days Ahead* model: https://www.c4tbh.org/program-review/good-days-ahead

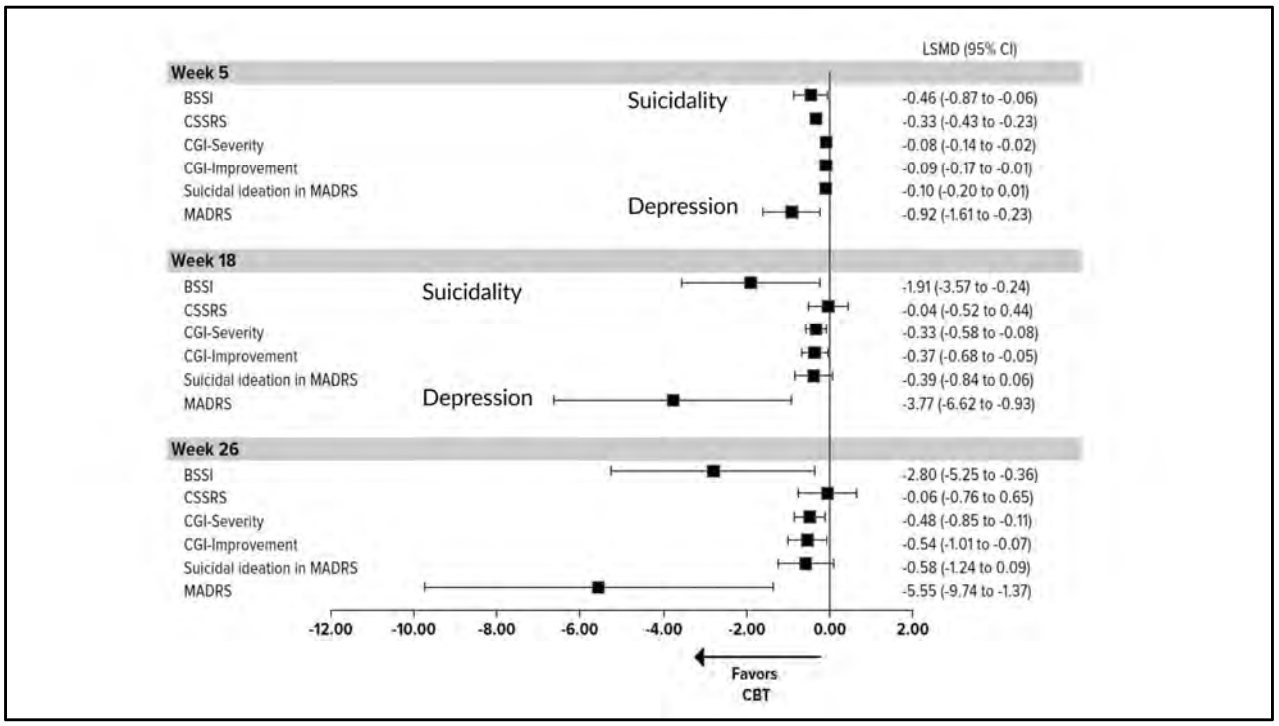
CBT with Esketamine	
Design	Randomized, rater-blind, controlled trial
Size	93 Mean age 38, 31% male, 62% inpatient
Intervention	During 4 week esketamine (twice weekly): CBT weekly, started mid-esketamine course vs treatment as usual CBT group then continued 1-2 sessions per week, 16 weeks total, individual and computer-assisted sessions
Duration	26 week: 4 wk esketamine, 16 wk CBT (2 wk overlap), 8 wk f/up
Primary outcome	Feasibility Secondary: Suicide (BSSI, CSSR), depression (MADRS), CGI
Result	CBT improved depression (MADRS difference 3.8) and CGI Mixed results suicidality (positive BSSI, negative CSSR)
Risks	None
Funding	NIMH



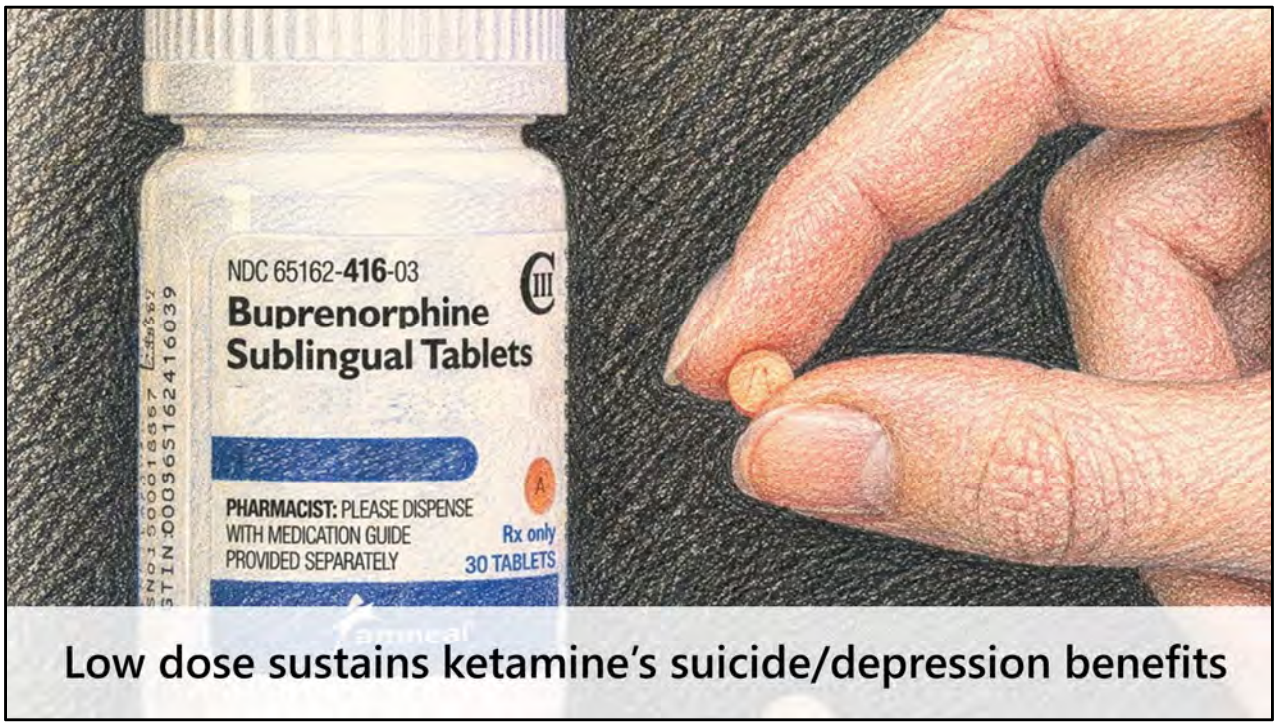
No primary outcome
Unblinded, treatment as usual comparison
Small size

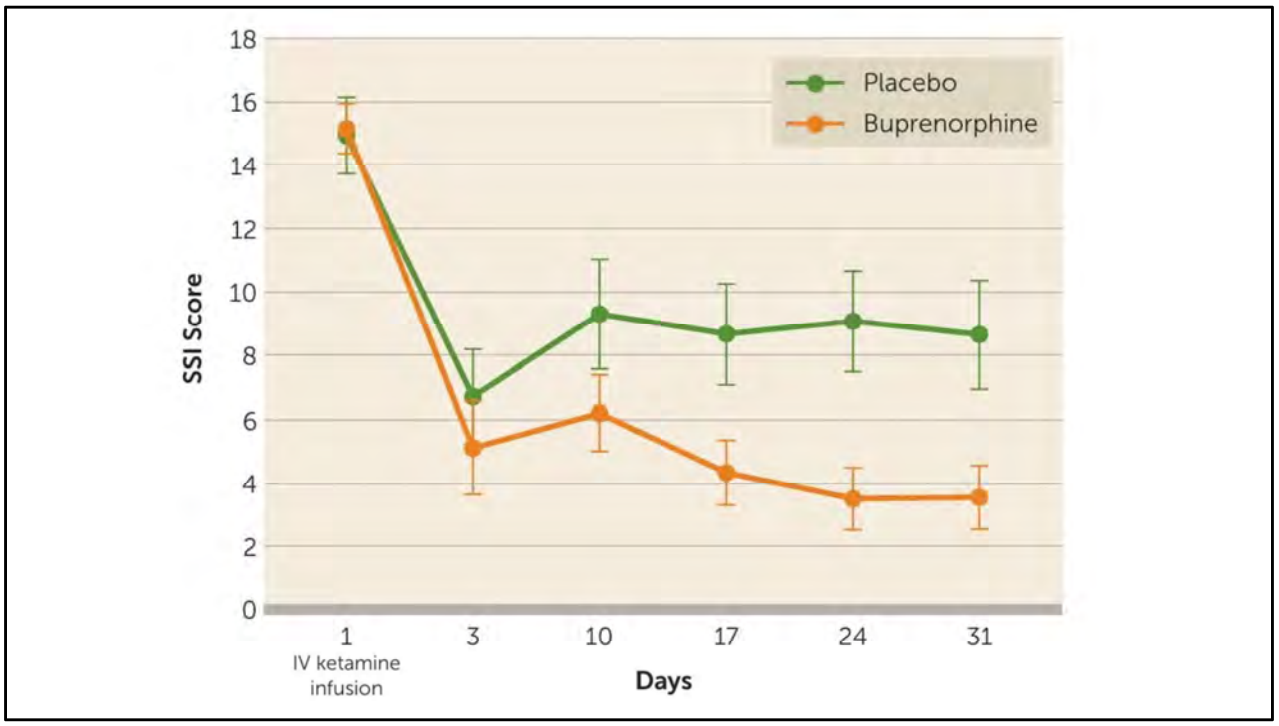
Wilkinson ST et al, Cognitive Behavioral Therapy Following Esketamine for Major Depression and Suicidal Ideation for Relapse Prevention: The CBT-ENDURE Randomized Trial. J Clin Psychiatry. 2026;87(2):25m16285.

They will publish scores of cognitive control, rumination, and health care utilization in future
Read more: https://psych-partners.com/cbt-helps-sustain-esketamine/



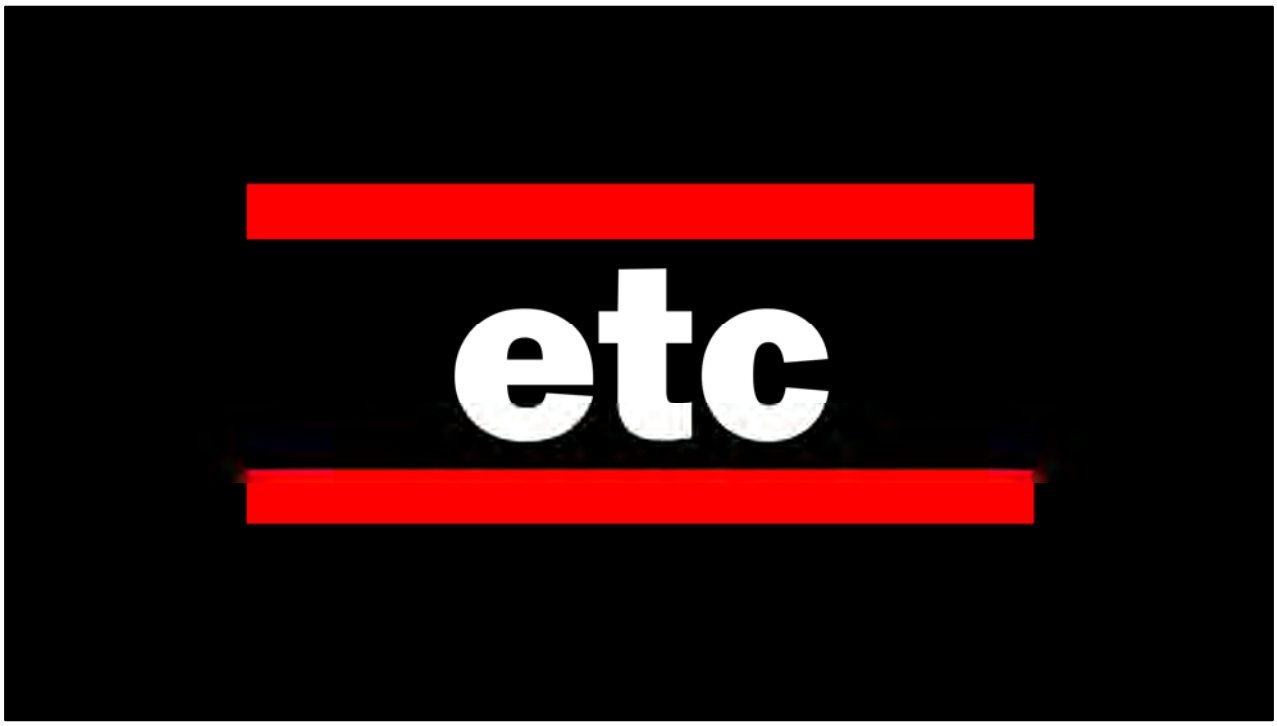
Depression and suicidality improved, with gains increasing over time


NDC 65162-416-03
Buprenorphine
Sublingual Tablets
CIII
PHARMACIST: PLEASE DISPENSE
WITH MEDICATION GUIDE
PROVIDED SEPARATELY
Rx only
30 TABLETS
A
Low dose sustains ketamine's suicide/depression benefits



50 adults randomized to buprenorphine (0.2–0.8 mg/day, titrated weekly) or placebo for 4 weeks after a single infusion of ketamine. However, withdrawal effects of stopping opioid not known, and trial suffered functional unblinding.

Read more: https://psych-partners.com/a-drug-that-sustains-ketamines-benefits/


etc

Runner Ups

1. Clozapine effective after one failed antipsychotic in schizophrenia
2. Psychodynamic therapy (DIP) had better long-term effects than CBT in a large, one-year trial of depression
3. Ketamine ➜ Elevated LFTs
4. Zolpidem ➜ Arrthymias
5. Finasteride (for hair-loss) ➜ Depression/suicidality
6. APA Guidelines recommend against antipsychotics in delirium

References by PMID (to find at pubmed.gov, search for #####[PMID]): 1. 41811299; 2. 41135204; 3. 42013657; 4. 41772758; 5. 41004169; 6. APA guidelines

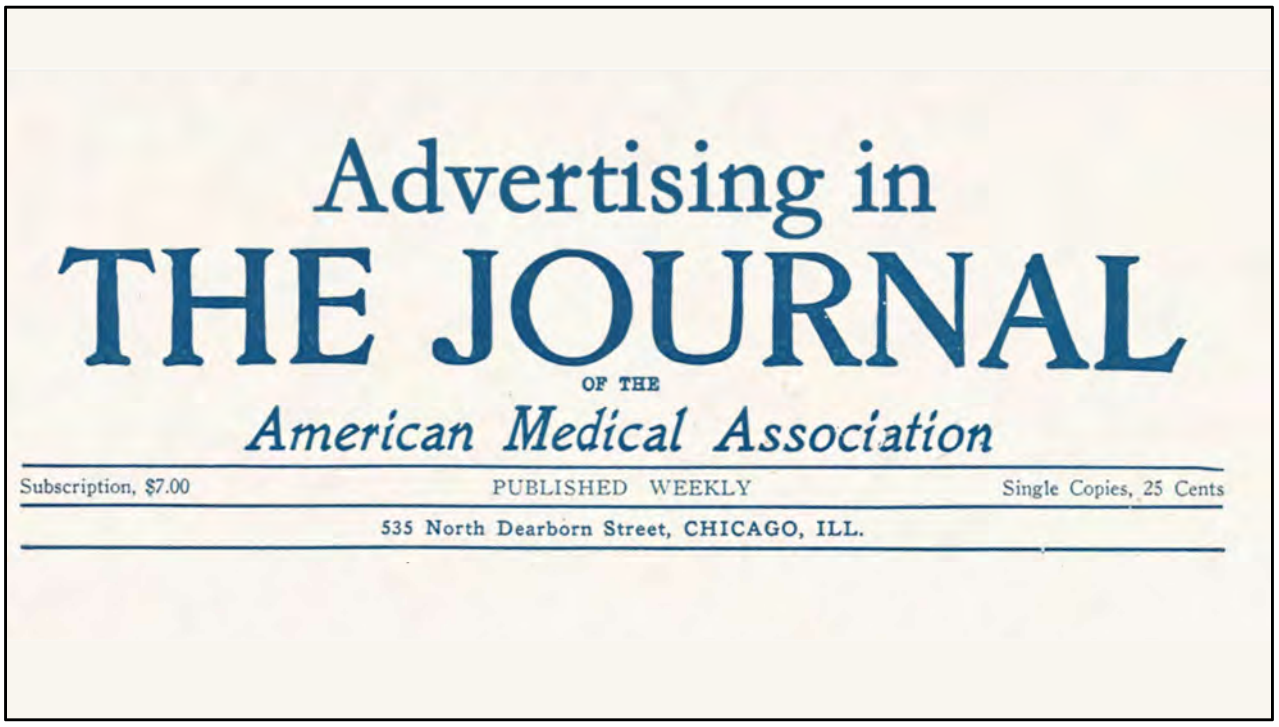
Small Scale Hope

Treatment	Condition	Trial (PMID)
Memantine	Child autism (normal IQ)	*Joshi G 2026 (41032298)*
Memantine	Cognition in remitted bipolar	*Mirzazadeh H 2026 (42498119)*
Prucalopride	Cognition in remitted MDD	*de Cates AN (42290157)*
Melatonin	Cognitive protection during ECT	*Shahrokhi M 2026 (42222553)*
L-Serine	Autism	*Kim JI 2026 (42305848)*
Naltrexone 50 mg + baclofen 40–60 mg qd	Alcohol use disorder	*Naqvi A 2026 (42036747)*
Cabergoline	Cocaine use disorder	*Amin-Esmaeili M 2026 (42234418)*

Robust but Negative

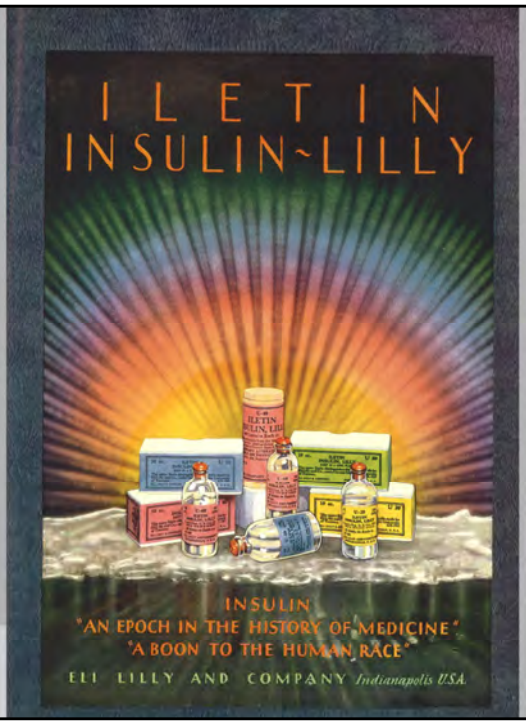
Treatment	Condition	Trial (PMID)
Gepirone	Depression	*Turner 2026 meta-analysis (42340691)*
Semaglutide	Depression	*Badulescu 2026 (41218611)*
Naltrexone low dose	Depression	*Maloney 2026 (41868116)*
Zuranolone	Depression (not peripartum)	*Kato M 2025 (41251319)*
Probiotics	Bipolar depression	*Shekarriz 2026 (41785480)*
Psilocybin	TRD	*Mertens 2026 (41848690)*
Lumateperone	Borderline	*Grant 2026 (42384092)*
Pimavenserin	Autism	*Bugarski-Kirola 2026 (42162607)*
Sertraline	Violence in past offenders	*Bulter T 2025 (41399477)*
Varenicline	Cannabis use disorder	*McRae-Clark AL 2026 (41536001)*
Lithium (195 mg)	Cognitive decline prevention	*Gildengers AG 2026 (41770546)*
Semaglutide	Dementia	*Cummings 2026 (41865758)*
Liraglutide	Dementia	*Edison 2026 (41326666)*
Genetic Testing	Depression	*Nierenberg AA 2026 (42572938); Blake KV 2026 (42090156); Minelli A 2025 (41277612)*


FDA

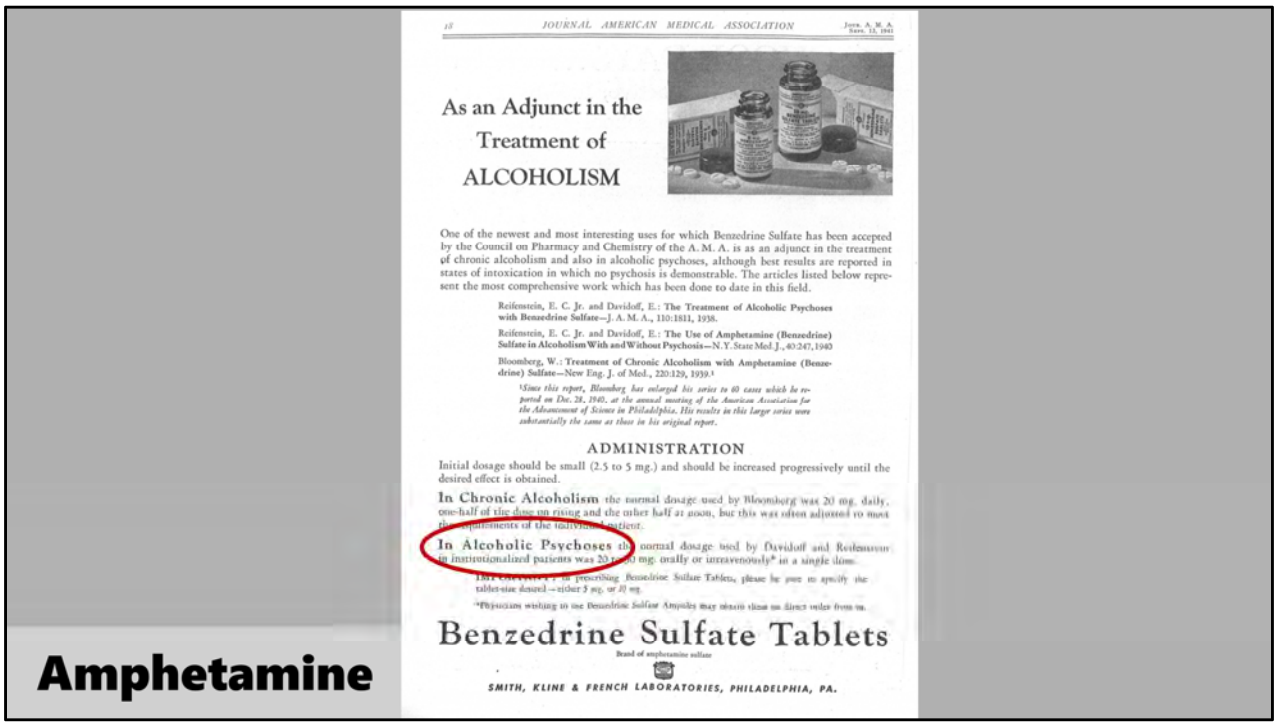


Before 1963, the AMA regulated drug indications. If approved, they allowed advertising in their journal (JAMA), but this created a conflict of interest favoring lenient approvals

Insulin



An insulin ad from 1930s



Dexamphetamine (Benzedrine) is advertised for Alcoholic Psychosis under approval from the “Council on Pharmacy and Chemistry of the AMA”

Cigarette ads were prominent, and even in 1950 a gun

The poor oversight by AMA lead the FDA to take over. Here, John F. Kennedy enacts that into law with the Kefauver-Harris Drug Amendments, which were also concerned with safety in wake of the thalidomide birth defect crisis. The legislation required drug makers to prove a medication's effectiveness and safety before marketing it, instituted clinical trial consent rules, and mandated adverse effect reporting. Two well-designed trials was the default, until 1997 when Congress allowed one trial at the FDA's discretion.

On October 11, 1988, about 1,500 members of ACT UP (AIDS Coalition to Unleash Power) shut down the Food and Drug Administration (FDA) headquarters in Rockville, Maryland. The historic "Seize Control of the FDA" protest demanded faster drug approvals, broader clinical trial access, and lower drug prices during the peak of the HIV/AIDS crisis

Fast Track, Breakthrough, Accelerated

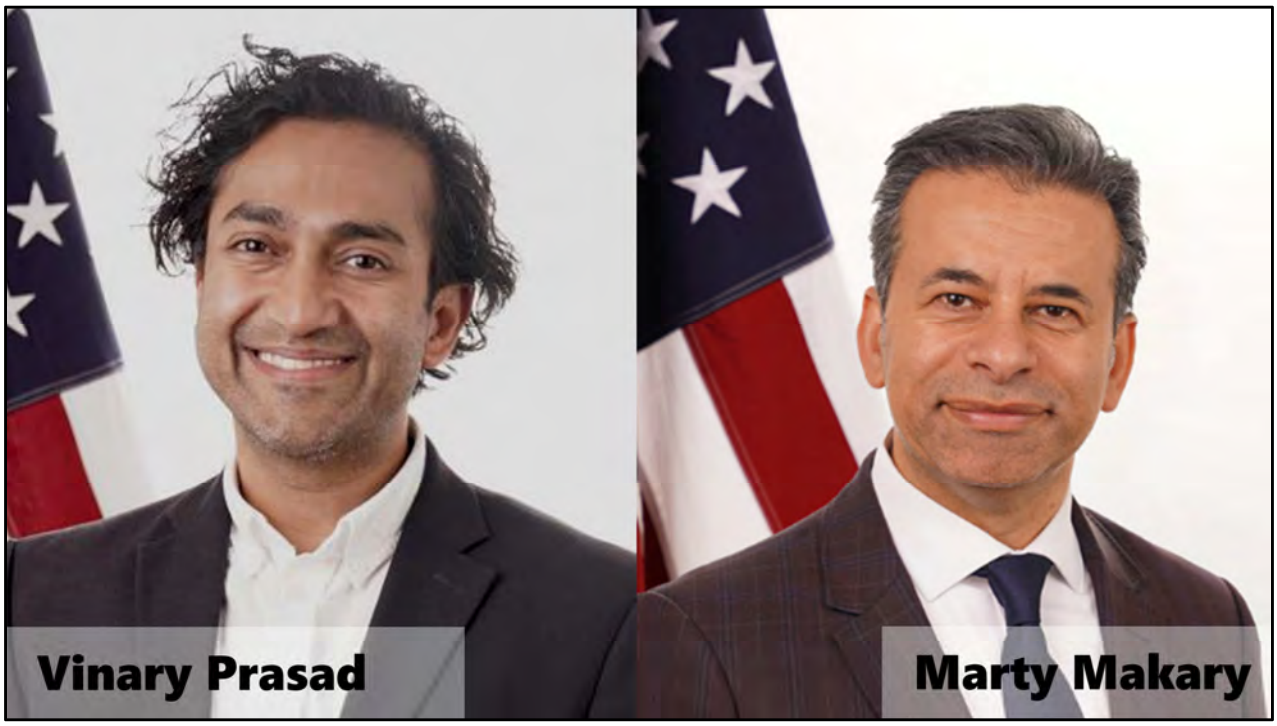
Depression
1. Esketamine
2. Dextromethorphan-bupropion
3. Gepirone *(not accelerated, but questionable evidence)*
4. Brexanolone
5. Zuranolone

Psychosis & Tardive Dyskinesia
1. Xanomeline-trospium (Cobenfy)
2. Pimavanserin
3. Deutetrabenazine
4. Valbenazine

Dementia
1. Aducanumab
2. Donanemab
3. Lecanemab

Device Approvals
1. Flow
2. Modius Spero
3. ProlivRx

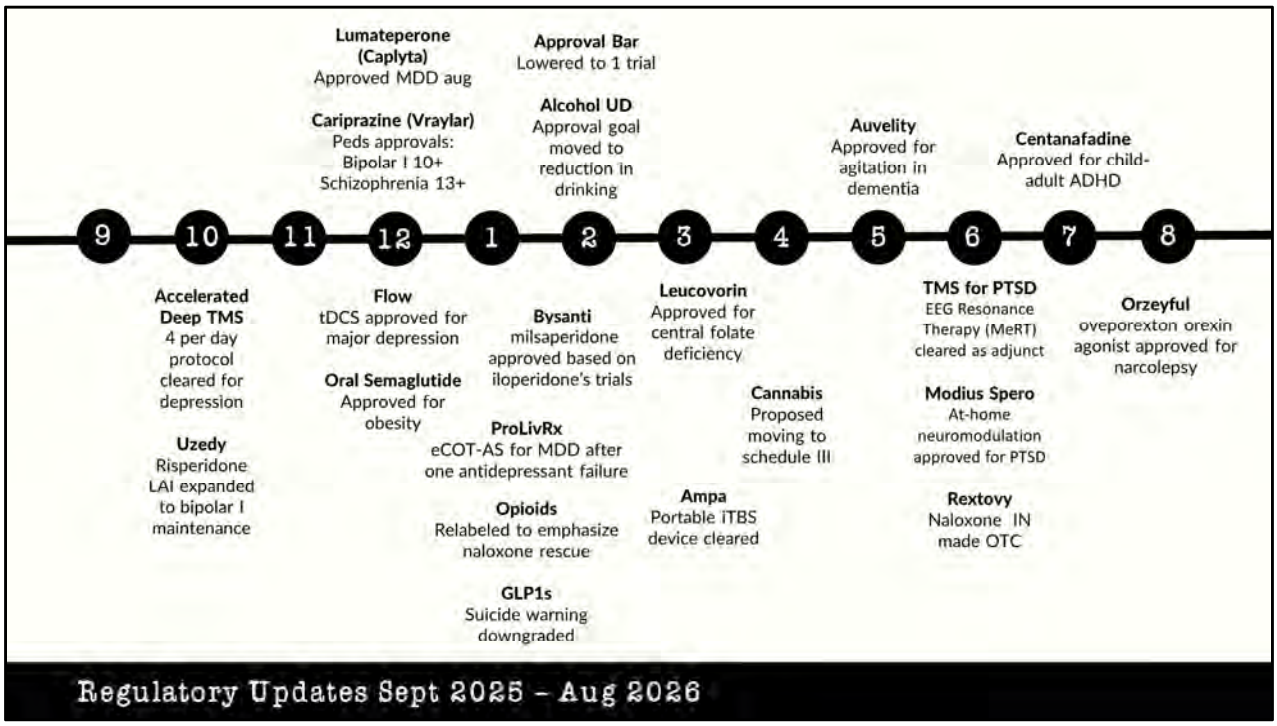
The accelerated pathways were intended for novel drugs and rare disease, but corporations have learned to exploit them, and accelerated approvals rose 3-fold from 2025-2020, involving around 65% of meds and nearly all psychiatric approvals in past 10 years. As single-trial approvals rose, so did the need to withdrawa unsafe or ineffective meds: rising to 18 withdrawals in 2021-22 compared to one withdrawal every tow years over prior three decades.



In Feb 2026, FDA lowered bar for approval from 2 to 1 well-designed RCT. They plan to require another level of proof, like biological mechanism, but have not consistently held up that ideal in the past.

Read more: https://psych-partners.com/doctors-pushback-on-fda/

FDA approval is not the gold-standard it used to be.


Lumateperone (Caplyta) Approved MDD aug
Approval Bar Lowered to 1 trial
Cariprazine (Vraylar) Peds approvals: Bipolar I 10+ Schizophrenia 13+
Alcohol UD Approval goal moved to reduction in drinking
Auvelity Approved for agitation in dementia
Centanafadine Approved for child-adult ADHD
9
10
11
12
1
2
3
4
5
6
7
8
Accelerated Deep TMS 4 per day protocol cleared for depression
Uzedy Risperidone LAI expanded to bipolar I maintenance
Flow tDCS approved for major depression
Oral Semaglutide Approved for obesity
Bysanti milsaperidone approved based on iloperidone's trials
ProLivRx eCOT-AS for MDD after one antidepressant failure
Opioids Relabeled to emphasize naloxone rescue
GLP1s Suicide warning downgraded
Leucovorin Approved for central folate deficiency
Cannabis Proposed moving to schedule III
Ampa Portable iTBS device cleared
TMS for PTSD EEG Resonance Therapy (MeRT) cleared as adjunct
Modius Spero At-home neuromodulation approved for PTSD
Rextovy Naloxone IN made OTC
Orzeyful oveporexton orexin agonist approved for narcolepsy
Regulatory Updates Sept 2025 – Aug 2026

Full database of research summaries: https://psych-partners.com/category/research/