TOP TEN TREATMENT UPDATES

FROM THE PAST YEAR

CHRIS AIKEN MD, September 2025

Editor-in-chief, Carlat Report | Director, Psych Partners | Instructor, WFU School of Med

No conflicts related to content

Placebo controlled?

Double blind?

Size (100-300)**?**

Drop out rate (<20%)**?**

Primary outcome positive?

Effect size (d, SMD) **or NNT?** (ideally < 10)

(d: buspirone 0.2, SSRIs 0.3-0.4, benzos 0.5, amphetamine 0.9, average psych 0.5)

Replicated?

Backed by basic science?

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

JCP

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.

High impact journal
Respected authors
Unmet need

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

JCP

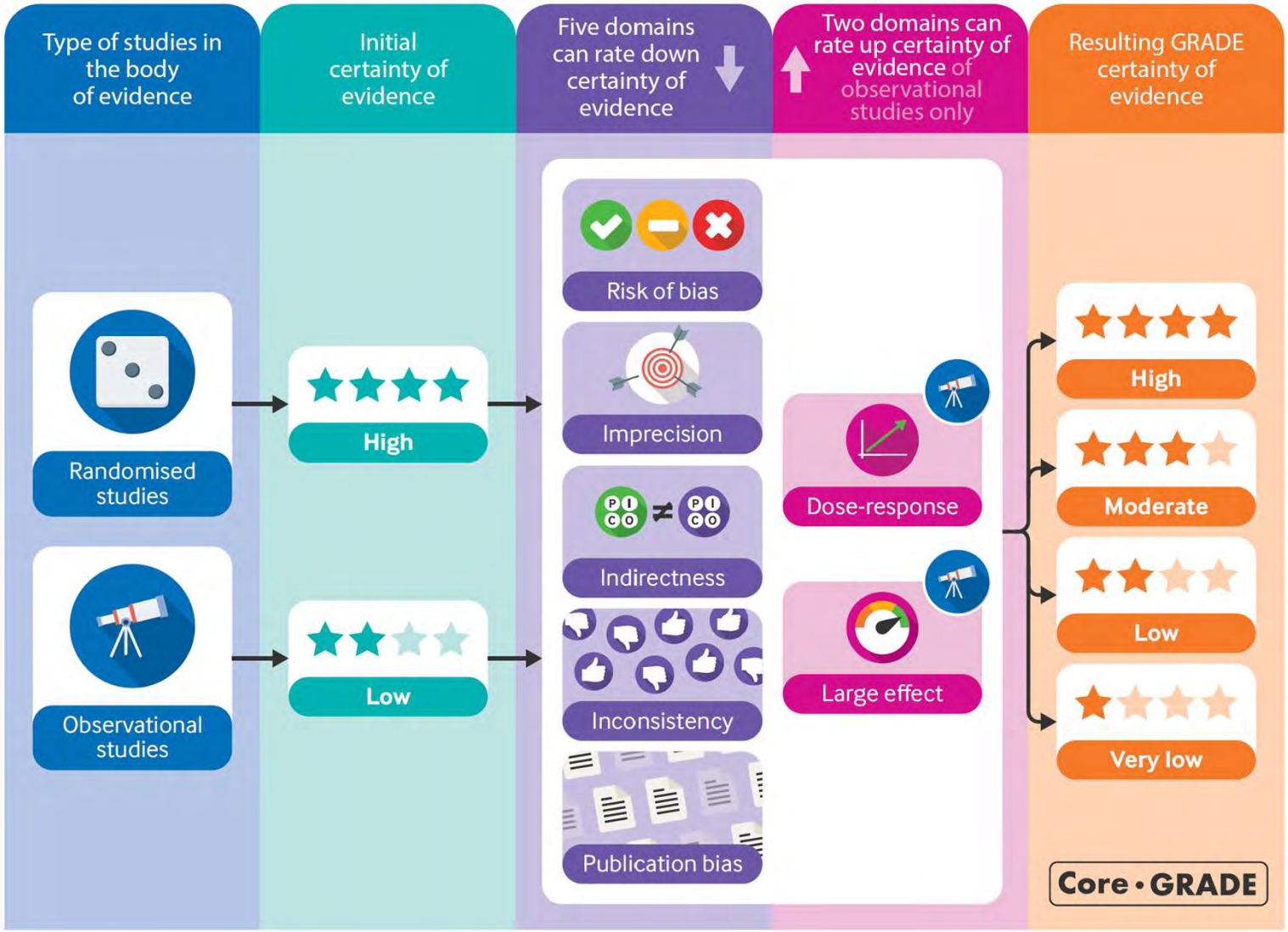
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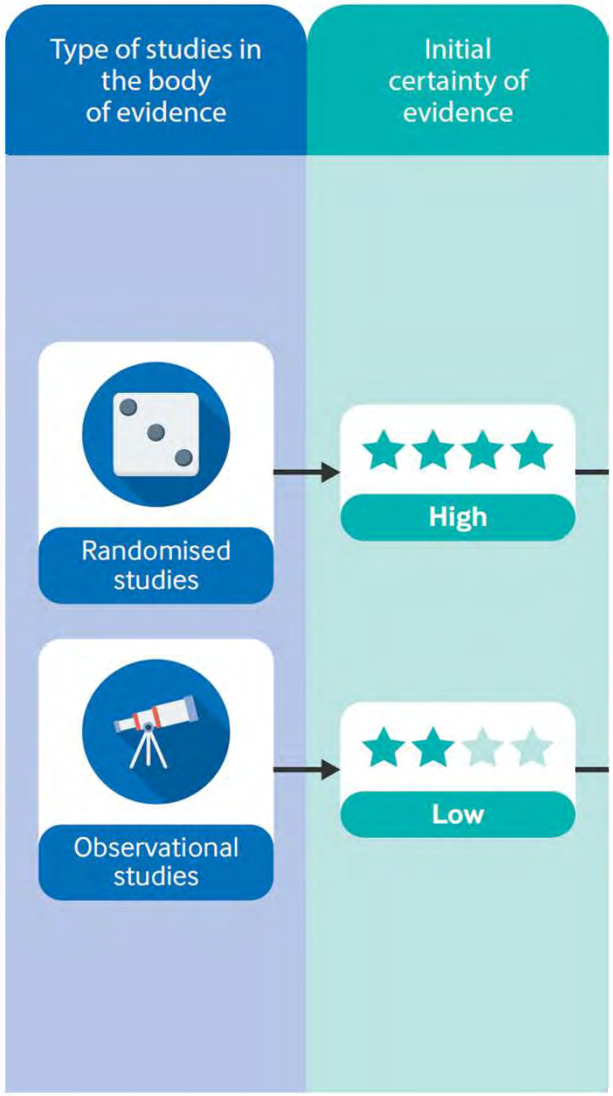
- ✔ Placebo control
- ✔ Double blind
- ✗ Size (60)
- ✗ Drop outs unaccounted (12%)
- ✗ Primary outcome not positive

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

- ✔ Effect size = medium
- ✔ Replicated (in healthy subjects)
- ✔ Backed by basic science



Guyatt G et al, Core GRADE 1: overview of the Core GRADE approach. BMJ 2025;389:e081903



Guyatt G et al, Core GRADE 1: overview of the Core GRADE approach. BMJ 2025;389:e081903


PRACTICE
CHANGING

1 Five Depression Strategies Compared

After SSRI failure, raising the dose won't help.
The other four strategies are about equal.

DEPRE'5: Five Strategies After SSRI Failure	
Design	Randomized assessor-blinded multi-center trial
Size	257 (90% completion)
Intervention	1. Raise SSRI (33 to 55mg fluoxetine equivalents) *Switch to* 2. Venlafaxine (225-300 mg) *Augment with* 3. Lithium (mean level 0.54) 4. Nortriptyline (50-75 mg) 5. Problem-solving therapy
Duration	6 weeks
Primary outcome	Response/remission rates on HAMD-17
Result	• Twice as likely to respond to any strategy except dose-increase (14% vs 28%) though remissions similar (12% vs 17%). • Nortriptyline = Most side effects • Lithium = Lowest adherence (39% vs 70-98%) • Non-significant trends favored venlafaxine and psychotherapy
Limitations	Small, no placebo. Patients not blinded. Lithium barely taken. Nortriptyline levels not checked.
Funding	Spanish government



Small

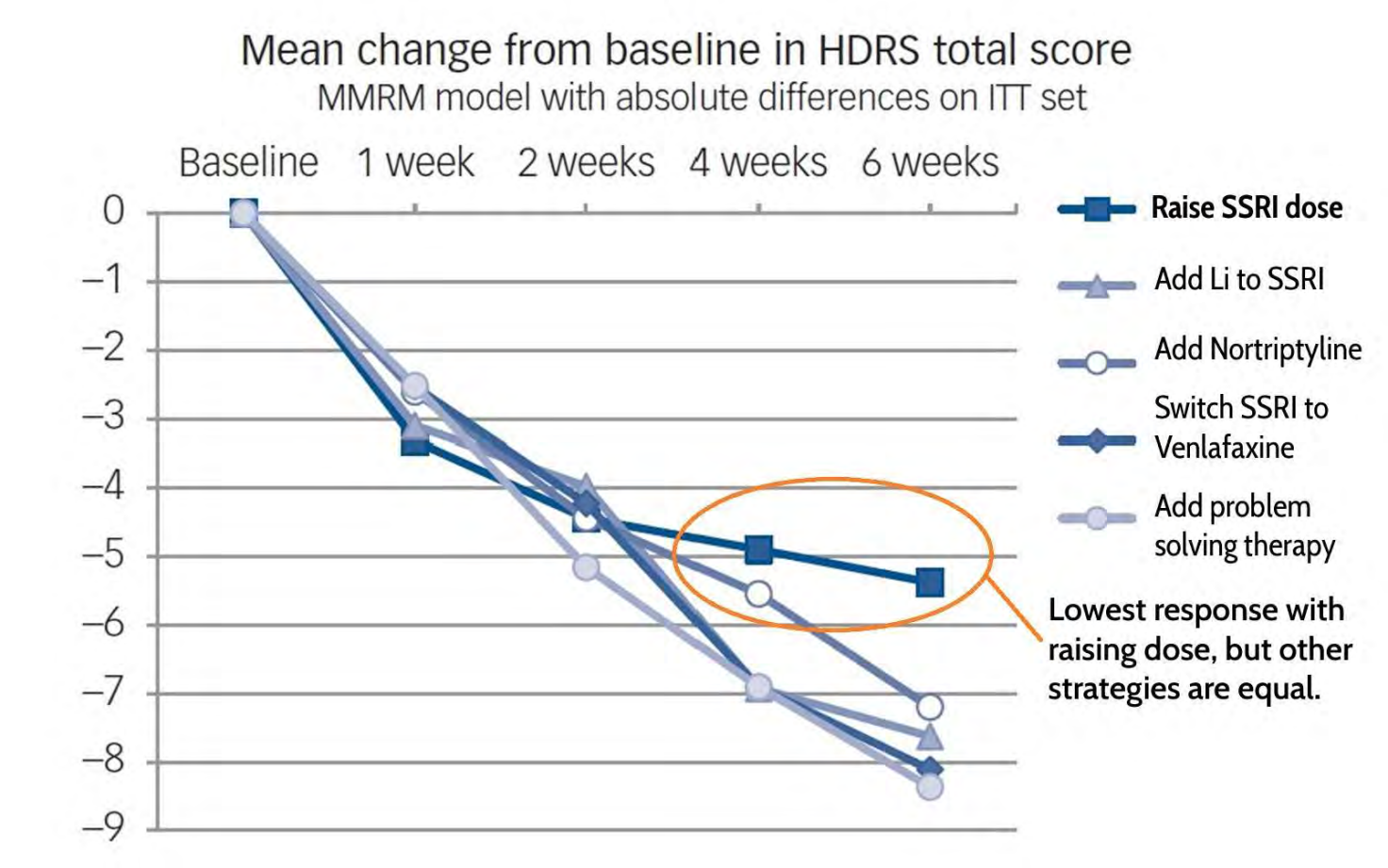
No Placebo

Unblinded

but Replicated

Pérez V et al, The DEPRE'5 study: pragmatic, multicentre, five-arm, parallel-group randomised controlled trial with blinded assessment to compare treatment strategies in major depression after a failed selective serotonin reuptake inhibitor treatment. Br J Psychiatry. 2025 Jun 18:1-8

Five Strategies After SSRI Failure in Depression



2

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)



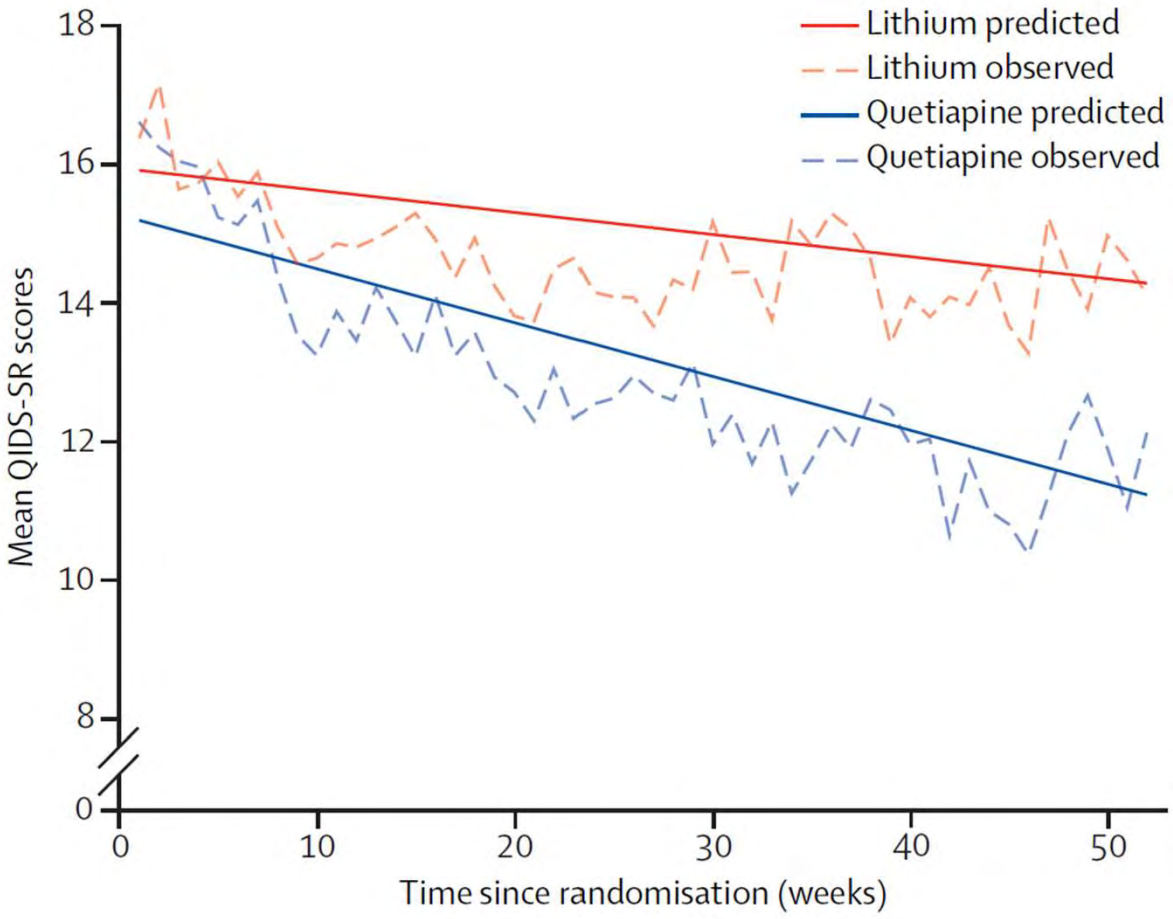
High Drop Out

No Placebo

Unblinded

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 Apr;12(4):276-288.

Quetipine vs Lithium Aug in TRD



3

Pramipexole in Treatment Resistant Depression

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

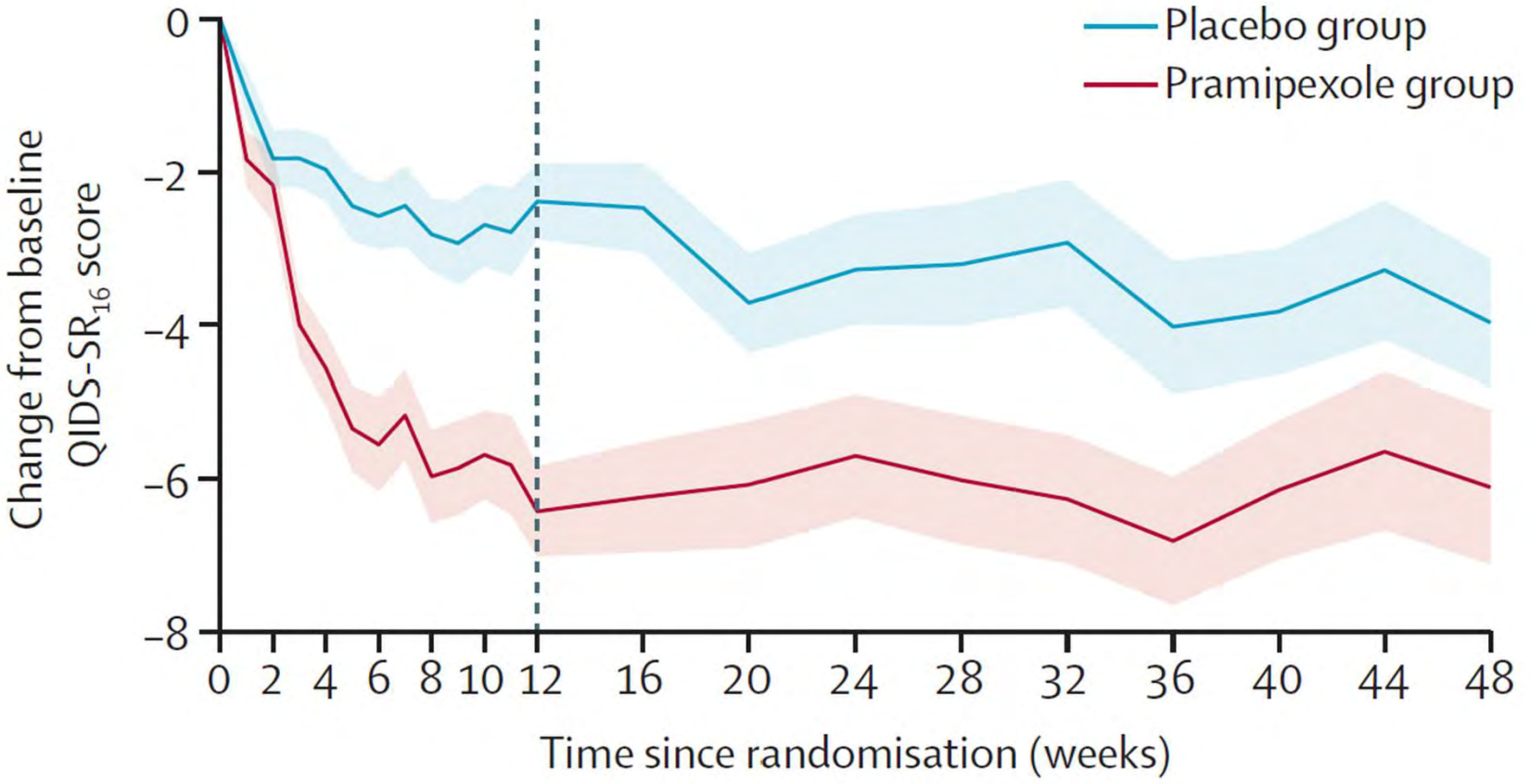
Pramipexole Augmentation in TRD	
Design	Randomized double-blind placebo-controlled trial
Size	150
Population	Adult MDD, failed ≥ 2 antidepressant trials (avg 3.5) 21% failed augmentation strategies
Intervention	Pramipexole 2.5 mg target (avg 2.3 mg) (start 0.25 mg qhs, raise by 0.25 q3 days)
Duration	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)



Minor 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, June 29, 2025.

Pramipexole Augmentation in TRD



3

Brexpiprazole in PTSD

Augmentation beat sertraline monotherapy, but was not tested in SSRI non-responders.

FDA likely to reject (2/3 trials positive).

Brexpiprazole Augmentation in PTSD	
Design	Randomized double-blind active-controlled trial
Size	416
Population	Adult PTSD NOT: early trauma (<16), other psych disorders, suicidality, on disability, responded to placebo
Intervention	Sertraline (150 mg) augmented with brexpiprazole 2-3 mg or placebo (flexibly dosed, mean 2.2 mg)
Duration	11 weeks
Primary outcome	Change in CAPS-5
Result	Greater improvement after 6 weeks
Limitations	High drop-out rate (40%, similar in both groups)
Risks	TD, metabolic, dystonia, akathisia, EPS, fatigue, hypotension However, most AEs worse with placebo (except weight)
Monthly cost	$1,600
Funding	Otsuka

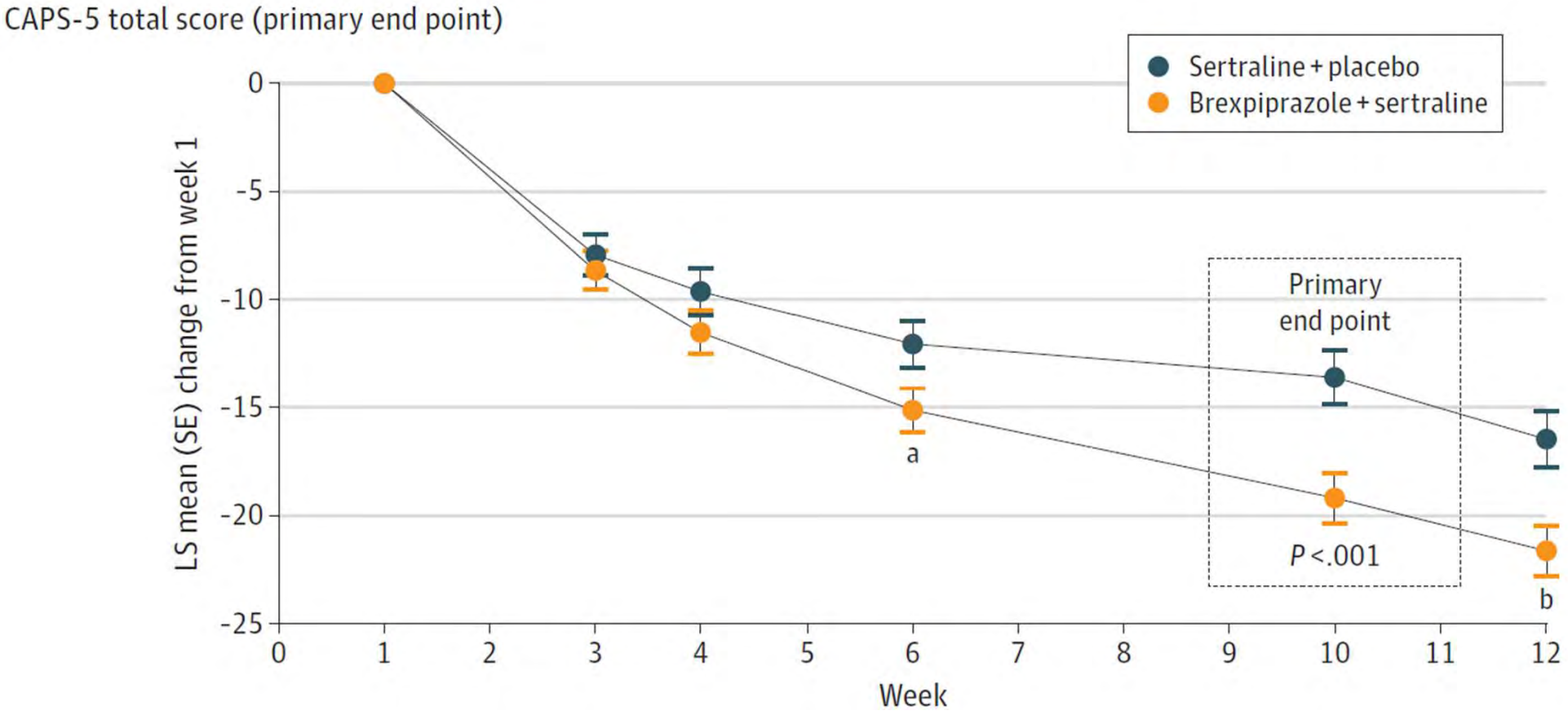


High Drop Out

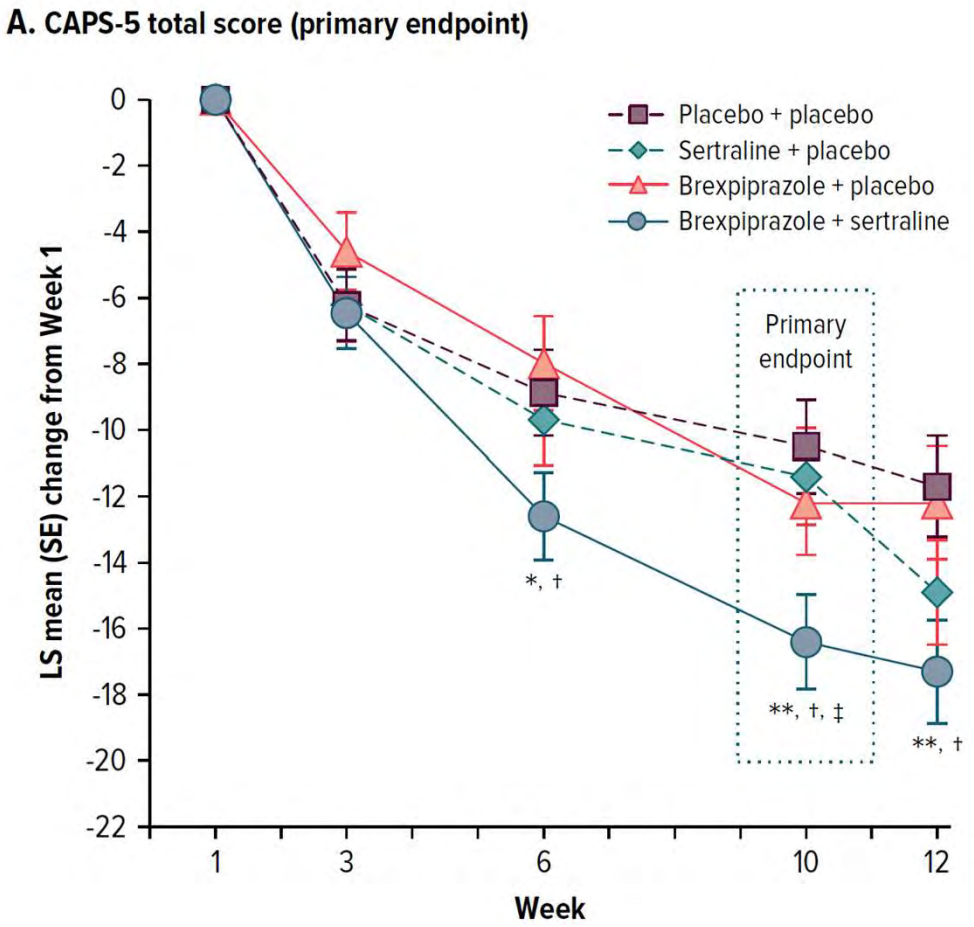
Inconsistent

Davis LL, Behl S, Lee D, et al. Brexpiprazole and Sertraline Combination Treatment in Posttraumatic Stress Disorder: A Phase 3 Randomized Clinical Trial. JAMA Psychiatry. Published online December 18, 2024.

Brexpiprazole augmentation in PTSD (phase III)



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



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.

Brexpiprazole in PTSD (phase III, unpublished)

Randomized, double-blind, 3-arm, fixed dose, n=533

- Brexpiprazole 2 mg + sertraline 150 mg
- Brexpiprazole 3 mg + sertraline 150 mg
- Placebo + sertraline 150 mg

Failed on primary endpoint of reduction in CAPS-5 scores.

Trial # NCT04174170



4

Lithium's Medical Risks

Associated with same rate of medical problems as anticonvulsants, with one exception

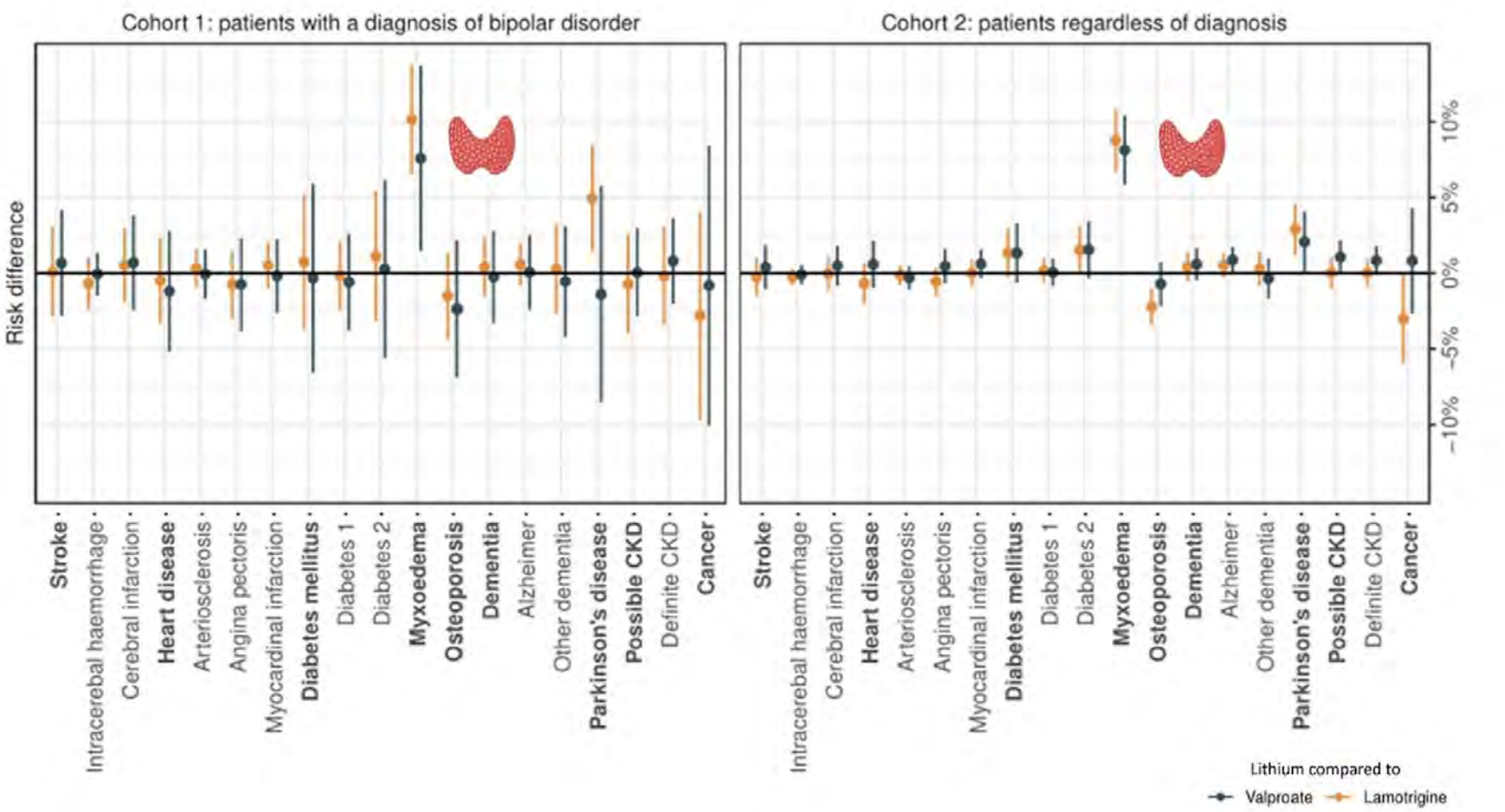
Lithium, Anticonvulsants, and Health	
Design	Prospective cohort
Size	Entire population of Denmark (5.9 million)
Population	Adults on lithium, valproate, or lamotrigine, either for bipolar (n=12,607) or for any diagnosis (n=156,678)
Duration	10 years
Primary outcome	New medical diagnoses
Adjusted for	Current and past psych meds, employment, age, sex (not for bipolar I vs II)
Result	All meds incurred same rate of new medical problems except hypothyroidism 7-10% higher on lithium
Limitations	Non-randomized
Funding	Independent Research Fund Denmark



Observational

Kessing LV et al, Lithium versus anticonvulsants and the risk of physical disorders - Results from a comprehensive long-term nation-wide population-based study emulating a target trial. Eur Neuropsychopharmacol. 2024 Jul;84:48-56.

New Medical Diagnosis on Lithium vs Anticonvulsants



Kessing LV et al, Eur Neuropsychopharmacol. 2024 Jul;84:48-56.

5

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 2nd psychosis: 51% Among hospitalizations, 23% were cannabis-induced 2nd 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

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.

6 Saffron in Subclinical Depression

Low-cost herb effective in its largest trial to date

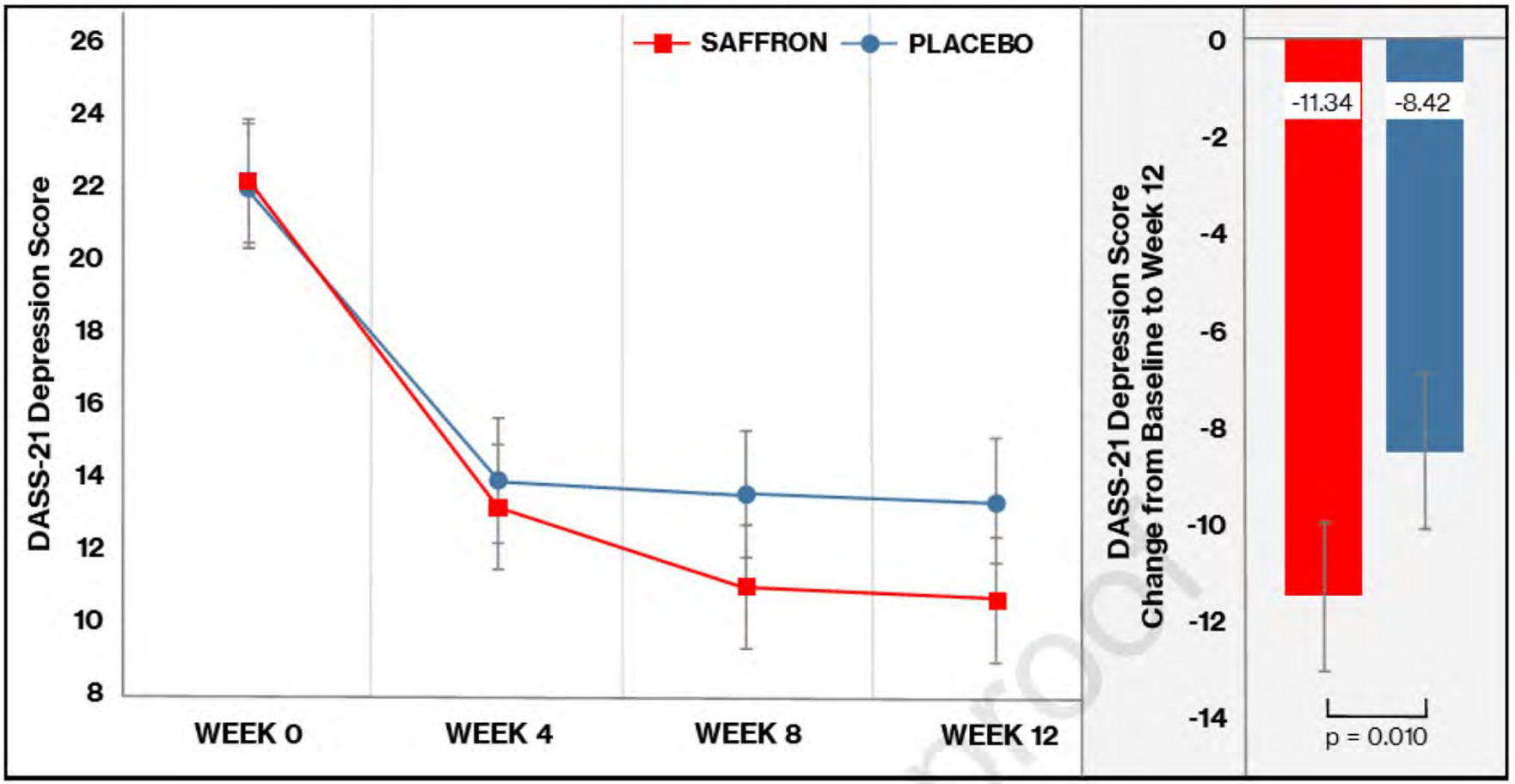
Saffron in Subclinical Depression	
Design	Randomized double-blind controlled trial
Size	202 healthy adults with depressive symptoms (not in full episode)
Intervention	Saffron extract 28 mg (Affron brand)
Duration	12 weeks
Primary outcome	Self-report DASS-21 (mix of depressive/stressed symptoms) Blind 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)



Replicated

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 May 23:S0022-3166(25)00306-2.

Saffron in Subclinical Depression







Affron
Proprietary extract

chrisaikenmd.com/supplements

8

Semaglutide in Alcohol Use

Controlled trial confirms impressions of this GLP-1 agonist in alcohol use disorder

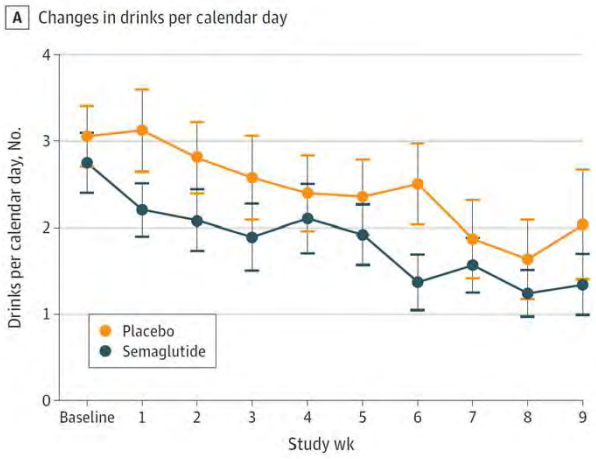
Semaglutide in Alcohol Use Disorder	
Design	Randomized double-blind, placebo controlled trial
Size	48 with moderate alcohol use disorder
Intervention	Semaglutide (0.25 mg/wk x4 wks, 0.5 mg/wk x4 wks, then 1mg/wk)
Duration	9 weeks
Primary outcome	Alcohol self-administration in lab (they could earn money to delay time to drinking)
Result	Reduction in alcohol consumed with medium to large effect size. Reduction in heavy drinking (drinks per drinking day) and cravings, but not in average drinks per day or number of drinking days. Reduction in cigarettes
Limitations	Small, laboratory setting, low dose
Funding	Government (National Institute on Alcohol Abuse and Alcoholism)

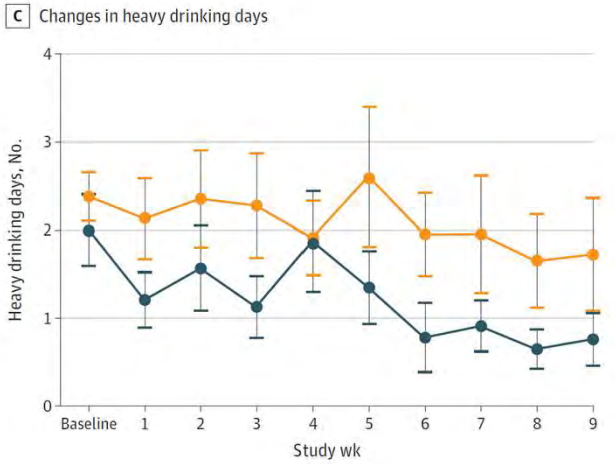


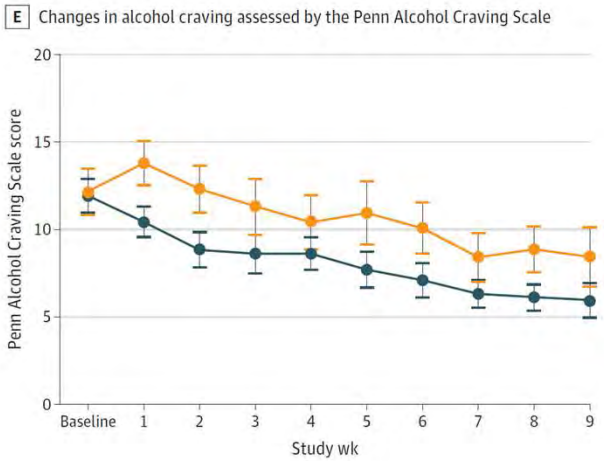
Small Sample

Hendershot CS et al, Once-Weekly Semaglutide in Adults With Alcohol Use Disorder: A Randomized Clinical Trial. JAMA Psychiatry. 2025 Apr 1;82(4):395-405.

Semaglutide in Alcohol Use Disorder? Maybe

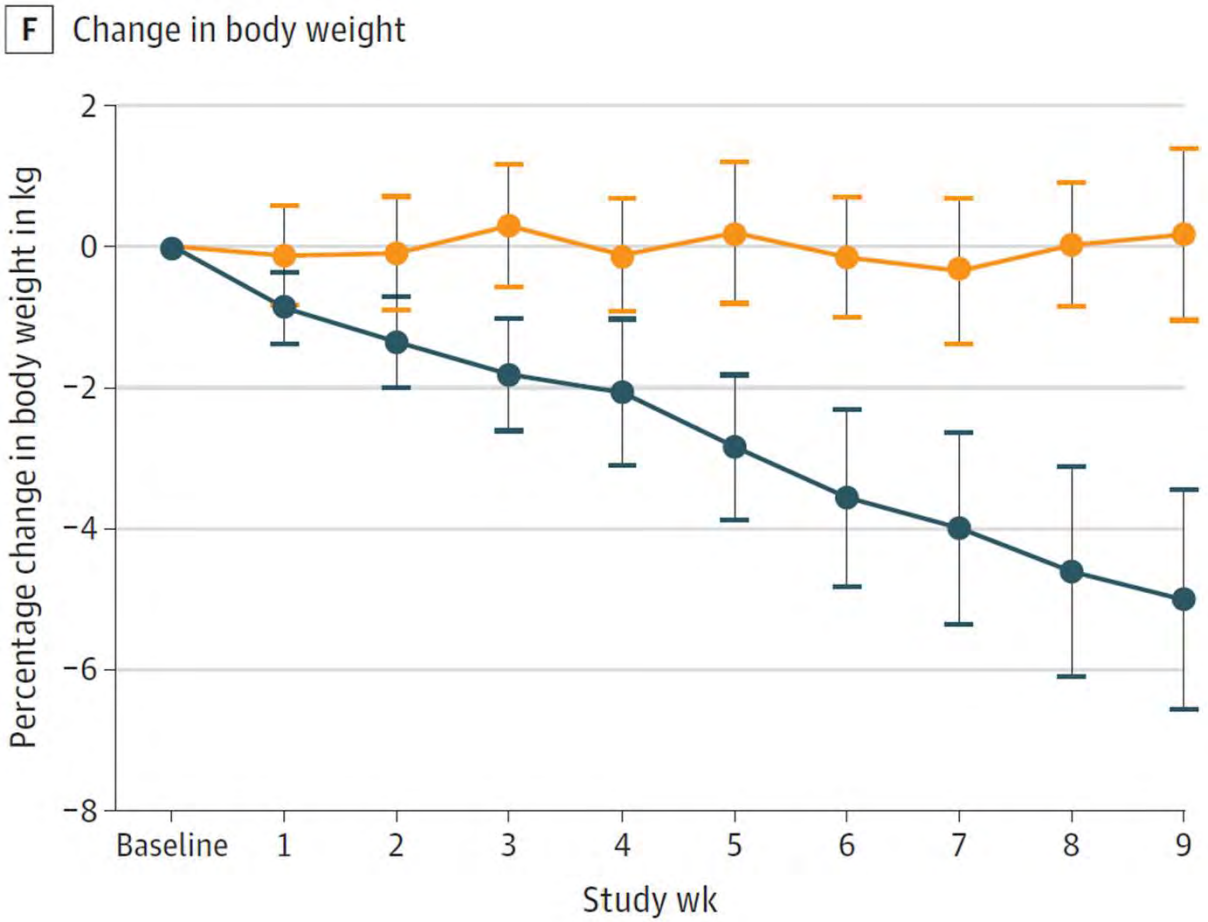






(these are the positive outcomes, 3 out of 6)

Semaglutide in Weight Loss? Definitely



9 Amphetamines, Psychosis, and Mania

Risk rises with amphetamine dose

No risk for methylphenidate

Mania and Psychosis on Amphetamine	
Design	Case control
Size	4,122
Population	First hospitalization for mania/psychosis vs. other psych diagnosis Age 16-35
Duration	1 month med exposure prior to admission
Primary outcome	Odds of mania/psychosis after amphetamine exposure, stratified by dose and compared to non-amphetamine controls
Secondary outcomes	Odds with methylphenidate exposure
Adjusted for	Age, sex, race, month, insurance type, immigration Other psych diagnoses or meds Family history of psychosis or bipolar
Result	Odds ratio rises with dose (low 1.8, medium 3.5, high 5.3) No risk for methylphenidate (0.91)
Limitations	Non-randomized, so possible that amphetamines prescribed to more severe cases. Did not account for duration of exposure.
Funding	NIMH

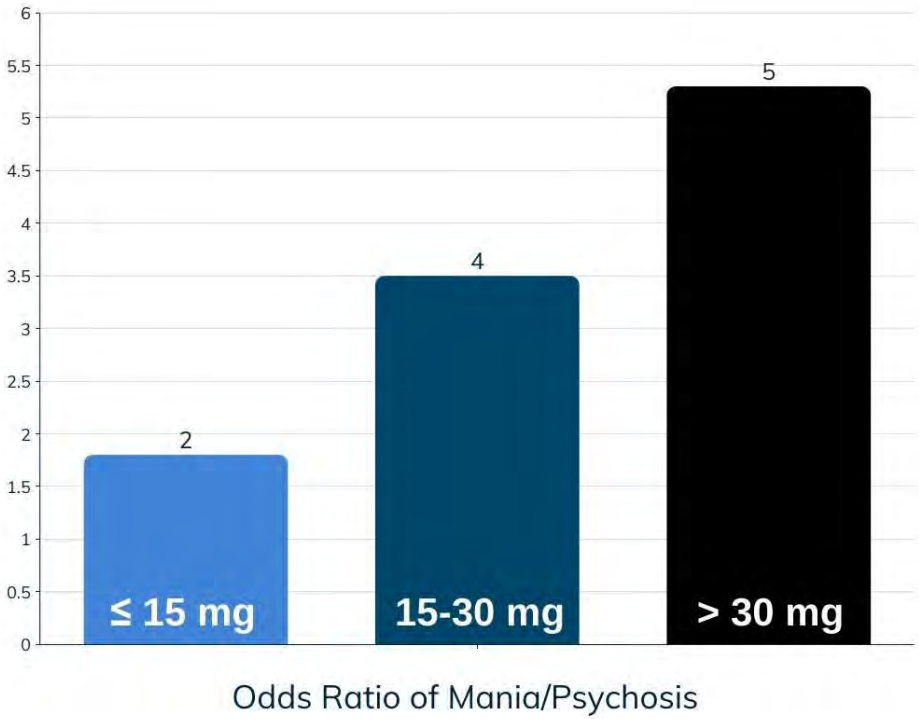


Observational

Dose-response

Moran LV et al. Risk of Incident Psychosis and Mania With Prescription Amphetamines. Am J Psychiatry. 2024 Oct 1;181(10):901-909.

Risk by dextroamphetamine dose



Formulation	Medium	High
Dextroamphetamine	15	30
Vyvanse	38	75
Adderall	18	36

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Psychosis with Methylphenidate or Amphetamine in Patients with ADHD

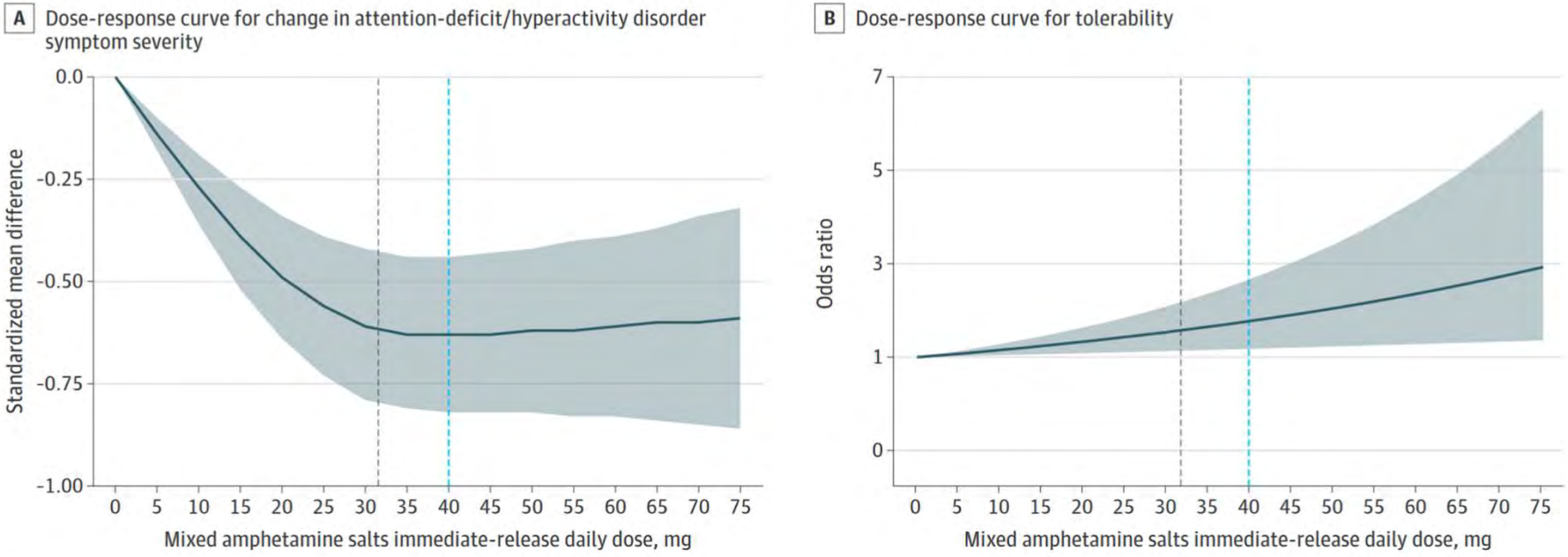
Lauren V. Moran, M.D., Dost Ongur, M.D., Ph.D.,
John Hsu, M.D., M.S.C.E., Victor M. Castro, M.S., Roy H. Perlis, M.D.,
and Sebastian Schneeweiss, M.D., Sc.D.

Psychosis risk double with amphetamines vs methylphenidate

after 2 mth use in 221,000 age 13-25 with ADHD

Adderall Dose-Response

Figure 4. Dose-Response Curves for Amphetamine



Dose-response curve for change in attention-deficit/hyperactivity disorder symptom severity (A) and tolerability (B). The curves are presented until the maximum dose for which data were available for equivalent doses of amphetamines. The shaded areas indicate 95% CIs. The black dotted line indicates the US Food and Drug Administration (FDA) maximum recommended dose for lisdexamfetamine; the blue dashed line indicates the FDA recommended maximum dose for immediate release mixed amphetamine salts.

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 mth 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.



tdscreen.ai

Small Scale Hope

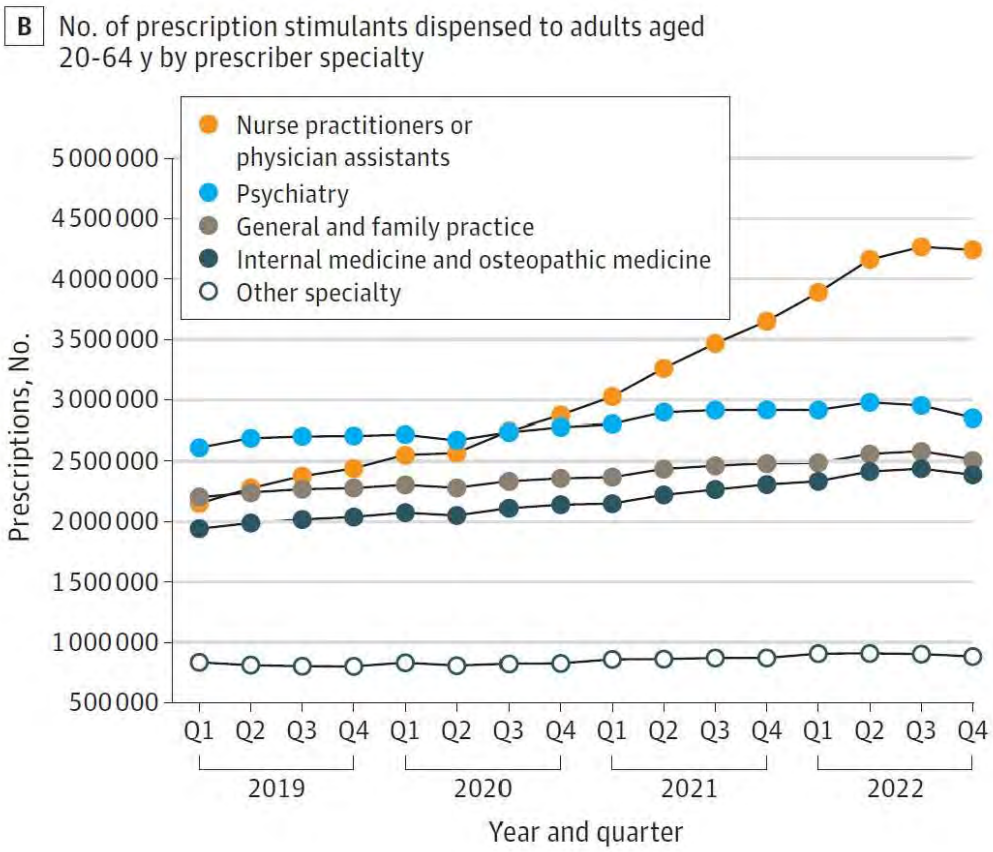
Treatment	Condition	Study
Viloxazine	ADHD (stimulant augmentation) 100-400 mg	RCT n=56, 6-17 yr, open-label PMID: 40014428
Varenicline	Alcohol use disorder	RCT n=384, 4-arm study PMID: 40487775
Levetiracetam	Mania (augmentation) 250 mg qhs	RCT n=65, PMID: 40447146
Prazosin	Depression with trauma history, 0.1 mg hs augmentation	RCT n=59, PMID: 39340191
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
Brexpiprazole	Maintenance in MDD (augmentation)	Large 6 mth phase-3 RCT PMID: 39415650
Cariprazine	Maintenance in bipolar (monotherapy)	Large 46 wk RCT
Cobenfy	Augmenting antipsychotics in schizophrenia	Phase-3 ARISE RCT n=386
Pimavanserin	Negative symptoms of schizophrenia Antidepressant augmentation	Phase-3 trial n = 484 PMID: 40181715
Vortioxetine	Bipolar II depression (augmentation)	RCT n=60 PMID: 39815608
Vagal Nerve Stimulation	Depression	Large, 12-mth sham controlled RCT, PMID: 39706521


TRENDS

Stimulant Prescriptions

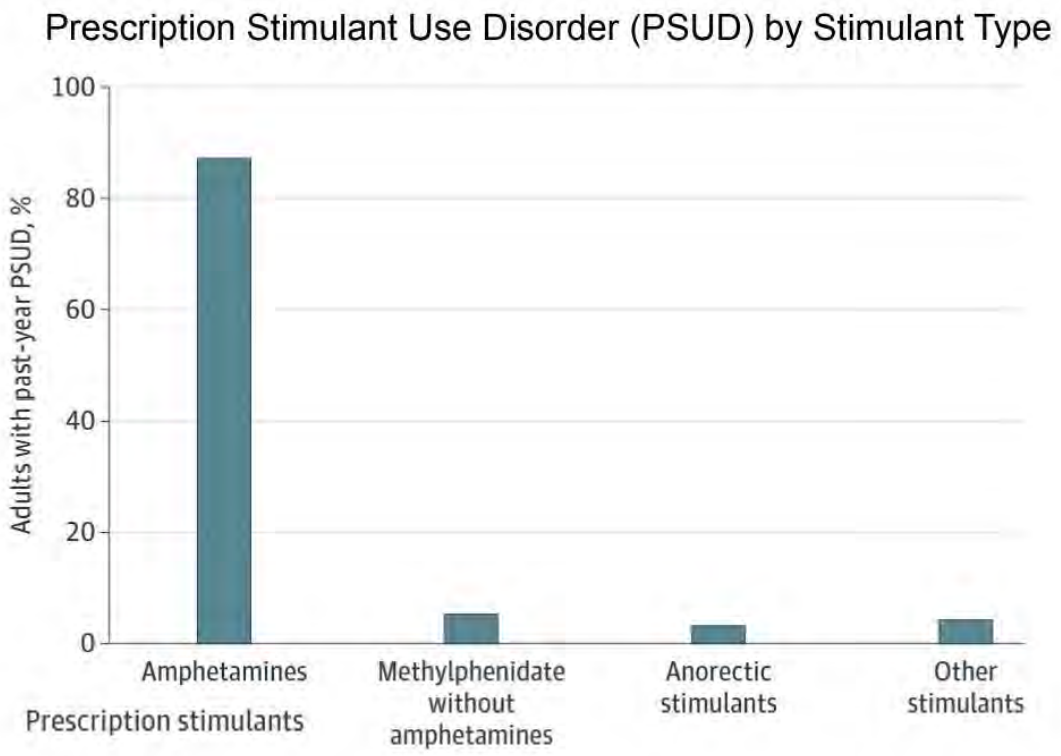


From 2019 to 2023:

- 24% increase in ADHD scripts
- Rise mainly in adults
- 1 in 4 scripts by NP/PA

Huskamp HA et al, *Psychiatr Serv*. May 28, 2025.

Stimulant Prescription Misuse



- 25% report misuse of Rx
- 9% have stimulant use disorder on Rx

From survey of 83,762 adults

Han B et al, *JAMA Psychiatry*. 2025;82(6):572-581

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

Palamar JJ, *Int J Drug Policy*. 2025;140:104825.
Rockhill KM et a, *Ann Intern Med*. April 22, 2025.

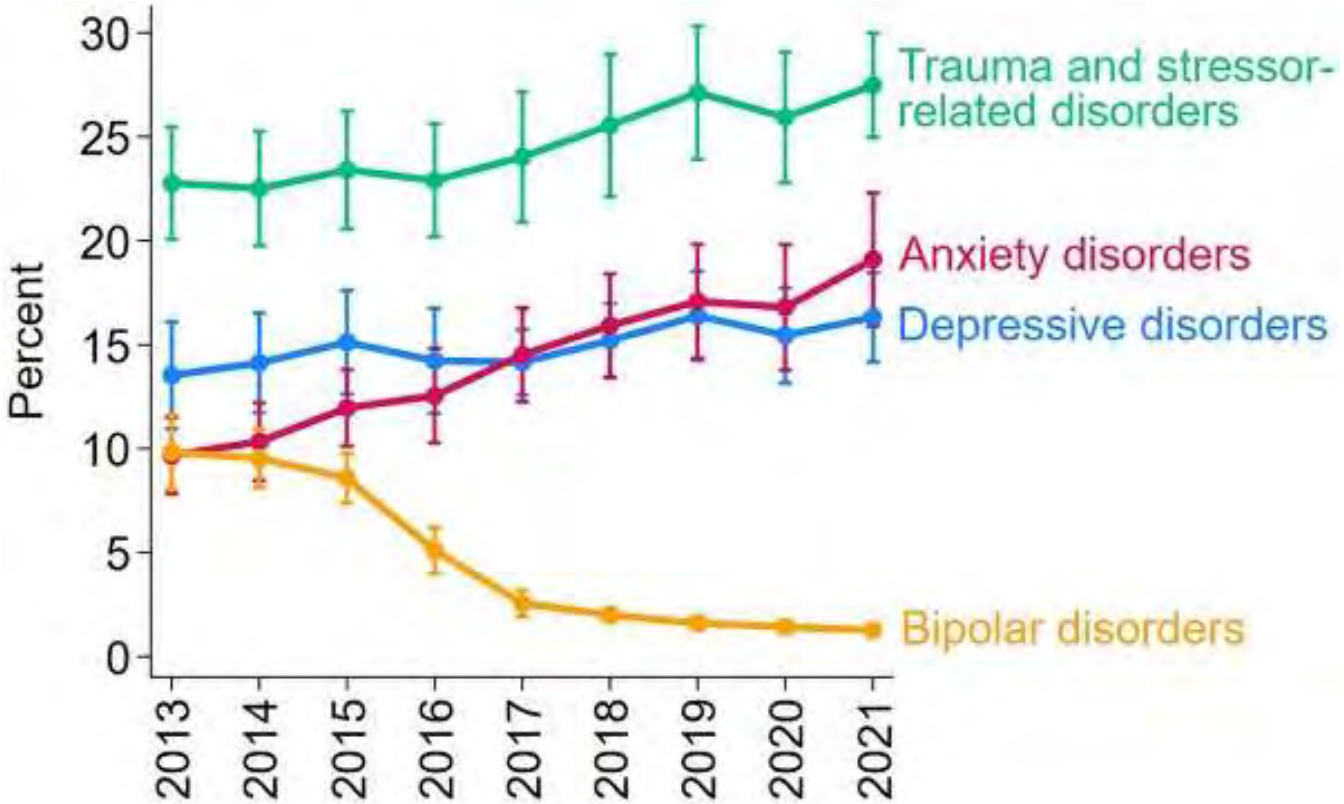
Accidental Exposures in Children

- 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

Rockhill KM et a, *Ann Intern Med*. April 22, 2025.

Bipolar Diagnosis in Children



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

Antipsychotic Overuse in Non-Whites

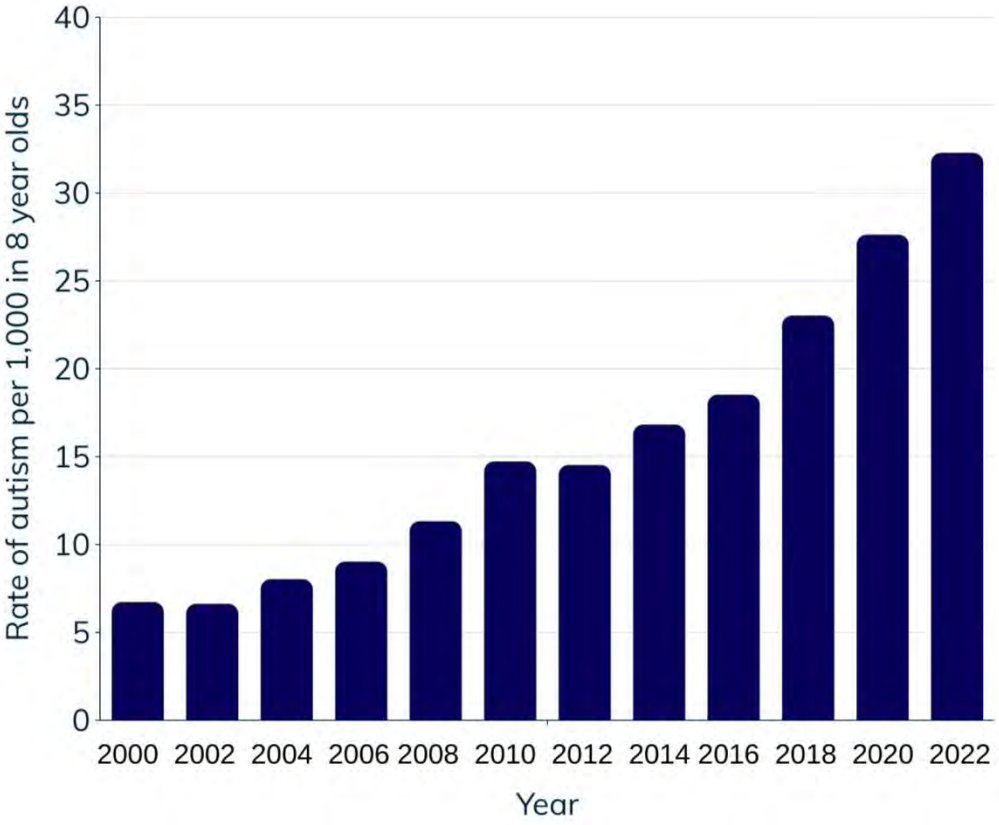
- *Schizophrenia:* Blacks and hispanics prescribed...
  More older antipsychotics (30-50%)
  Less clozapine (55-60%) and newer-but-generic second generations (50%)

- *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

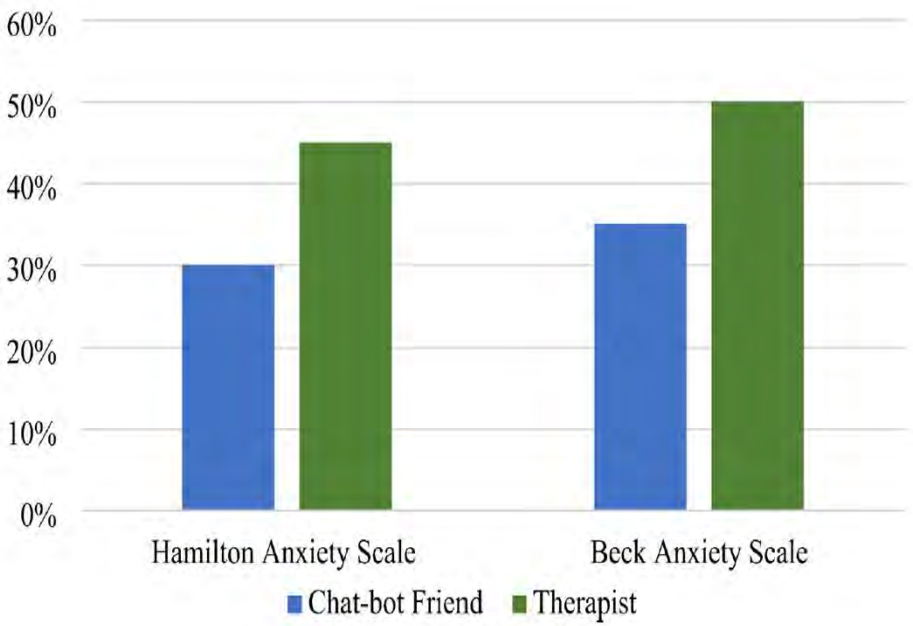
Medina C et al, *Schizophrenia (Heidelb)*. 2024;10(1):48.

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

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

FDA Updates Sept 2024 – Aug 2025

DayLightRx
App for GAD

Tirzepatide (Zepbound)
approved for sleep apnea with obesity

Clozapine
Mandatory REMS reporting ended

Antidepressants in Pregnancy
Advisory panel recommends stricter warnings (9/10 members have anti-med bias)

FDA Adopts AI
To speed scientific reviews

Tonmya
Cyclobenzaprine SL for fibromyalgia

9 10 11 12 1 2 3 4 5 6 7 8

Xanomeline-trospium (Cobenfy)
First cholinergic in schizophrenia

Alcohol-Cancer
Warning *recommended* by Surgeon General

Esketamine (Spravato)
approved as monotherapy in TRD

Suzetrigine (Journavx)
non-addictive alternative to opioids

Zulresso
Brexanolone discontinued

Alzheimer's Blood Test
Lumipulse for ß-amyloid

Brexpiprazole Rejected in PTSD
by FDA advisory panel

KetaRx
Ketamine IM approved for surgical pain

Arynta
Liquid lisdexamfetamine

XR Stimulants
Restricted under age 6 due to weight loss

NRX-101
Ketamine IV fast-tracked for depression, approval decision expected by 1/2026

Daily updates (@ChrisAikenMD)

LinkedIn, X, Facebook, or BlueSky

