TOP TEN TREATMENT UPDATES

FROM THE PAST YEAR

CHRIS AIKEN MD, NCPA 2024

Assist Prof, *NYU School of Med* Editor-in-chief, *Carlat Report* Instructor, *WFU School of Med*

No conflicts related to content

Placebo controlled?

Double blind?

Size (>100)?

Drop out rate (<20%)?

Primary outcome positive?

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

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

Replicated?

Backed by basic science?


PRACTICE
CHANGING

1

TMS in Treatment Resistant Depression

Outperforms switching and augmentation

TRD: rTMS vs Aripiprazole Aug vs Switch	
Design	Randomized open label controlled trial
Size	278 with treatment resistant depression (≥ 2 failed trials)
Intervention	rTMS Aripiprazole (mean 9 mg) Switch to SNRI (venlafaxine 191 mg or duloxetine 98 mg)
Duration	8 weeks
Primary outcome	Change in MADRS
Secondary outcomes	Symptoms of Depression Questionnaire Response & remission on MADRS
Result	Only rTMS superior to switching (4.17 point MADRS)
Limitations	Open label, underpowered
Risks	Seizures, headache with rTMS
Funding	Patient-Centered Outcomes Research Institute
Cost	$6,000-12,000 for rTMS 6 week course

Papakostas GI, Trivedi MH, Shelton RC, et al. Comparative effectiveness research trial for antidepressant incomplete and non-responders with treatment resistant depression (ASCERTAIN-TRD) a randomized clinical trial. Mol Psychiatry. March 7, 2024.

Aripiprazole augmentation numerically but not statistically significant. Underpowered study?

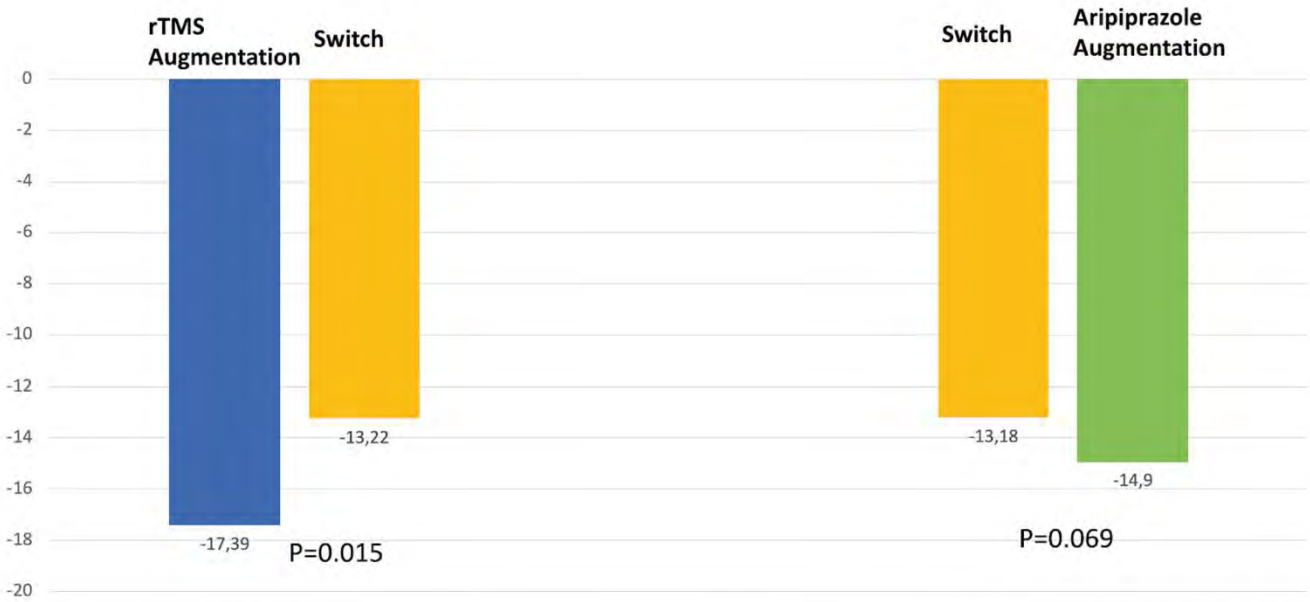


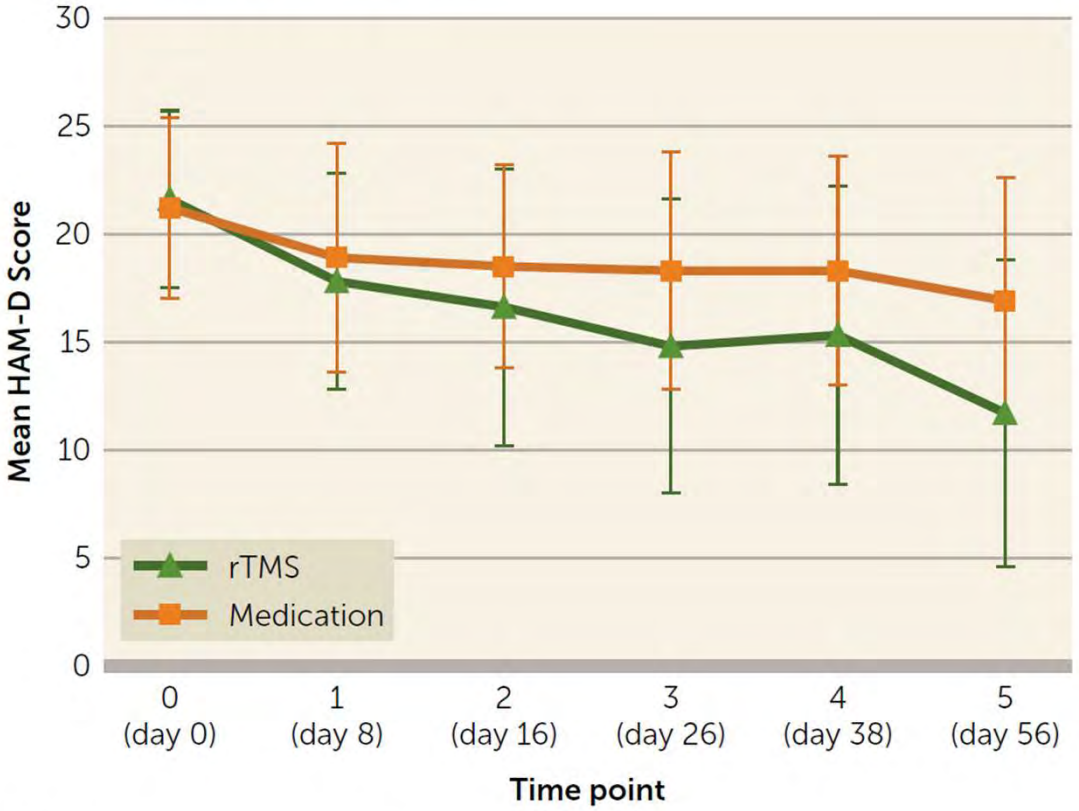
Fig. 2 Model adjusted change in MADRS scores. MADRS Montgomery Asberg Depression Rating Scale, rTMS Repetitive Transcranial Magnetic Stimulation. Alpha = 0.025.

TRD: rTMS vs Med Switch	
Design	Randomized open label controlled trial
Size	89 with treatment resistant depression (≥ 2 failed trials)
Intervention	rTMS vs. med (switch to tricyclic (88%) or aug with lithium or atypical antipsychotic (13%) All had CBT
Duration	8 weeks
Primary outcome	Change in HAM-D
Result	rTMS > switch in HAM-D, response, remission, anxiety, anhedonia Effect size 0.77
Limitations	Open label
Risks	Seizures, headache with rTMS
Funding	Netherlands Organization for Health Research and Development
Monthly cost	$6,000-12,000 for rTMS 6 week course

Dalhuisen I, van Oostrom I, Spijker J, et al. rTMS as a Next Step in Antidepressant Nonresponders: A Randomized Comparison With Current Antidepressant Treatment Approaches. Am J Psychiatry. 2024;181(9):806-814.

rTMS vs med switch in Treatment Resistant Depression

FIGURE 2. Depression severity over time with repetitive transcranial magnetic stimulation (rTMS) or a switch in antidepressant medication[a]



[a] Error bars represent standard deviation.

2

Benzodiazepines

Discontinuing them is risky, even in the elderly and those on opioids

Dose escalation is rare

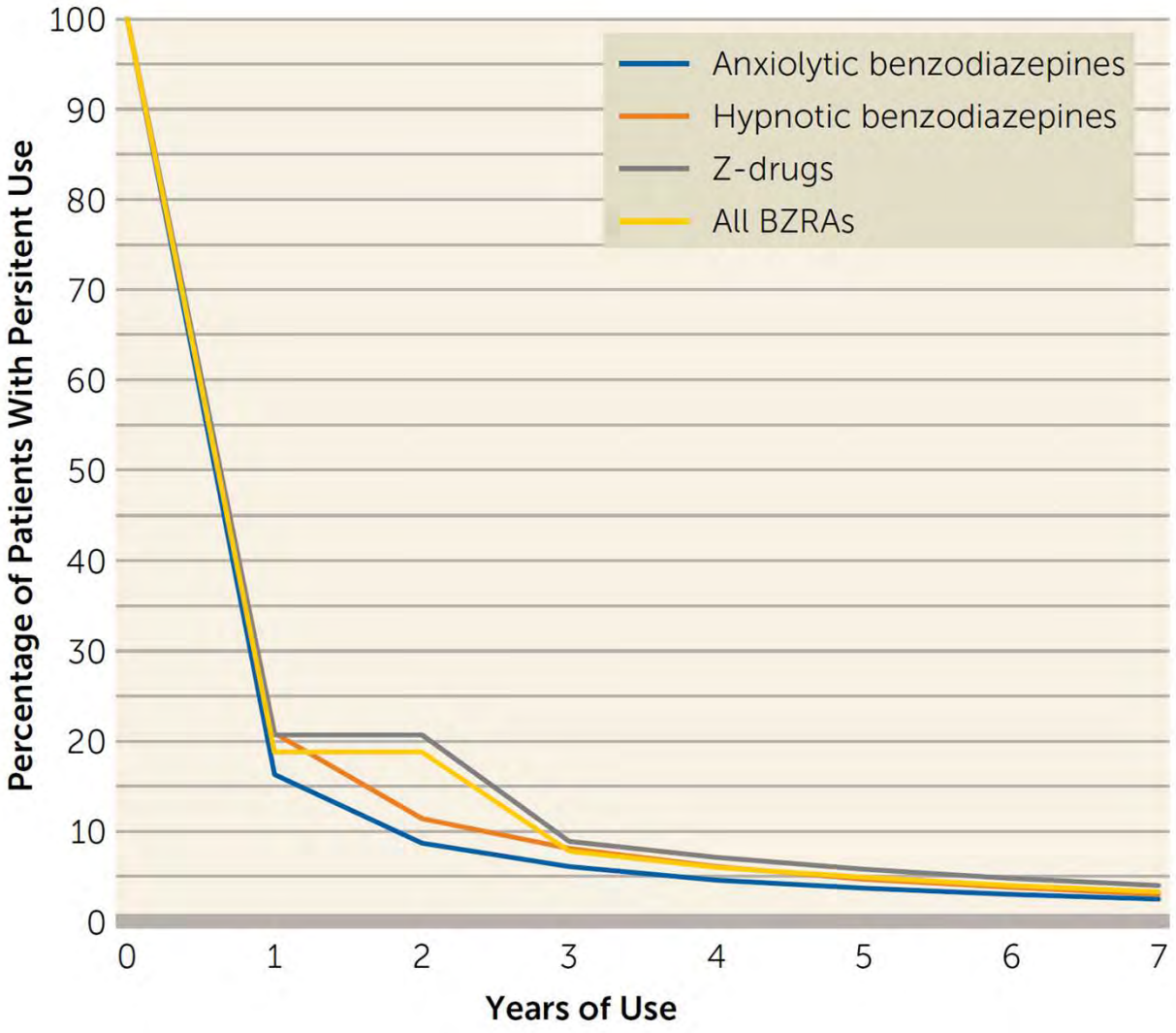
New guidelines on deprescribing

Benzodiazepine Discontinuation	
Design	Retrospective cohort
Size	213,011
Subjects	Adults with stable long-term benzodiazepine from US commercial insurance database (excluding cancer, hospice, seizures, h/o OD)
Duration	1 year
Primary outcome	Mortality in benzo discontinuers vs. continuers
Secondary outcomes	Nonfatal overdose, suicide attempt/ideation, ED visits
Adjusted for	Adjusted for age, sex, race, location, benzo-dose, neuropsych meds, comorbidities (pain, insomnia, bipolar, psychosis, addiction)
Result	Mortality 1.6x higher for discontinuers for both opioid and non-opioid groups (cl 1.5-1.7) All secondary outcomes worse for discontinuers (1.2-1.4x) No difference for older vs. younger patients
Limitations	Non-randomized Cause of death unknown May not generalize to Medicaid populations
Funding	National Institute on Drug Abuse

Maust DT, Petzold K, Strominger J, Kim HM, Bohnert ASB. Benzodiazepine discontinuation and mortality among patients receiving long-term benzodiazepine therapy. JAMA Netw Open. 2023;6(12):e2348557.

Benzodiazepine and z-Hypnotic Dose Escalation	
Design	Retrospective cohort
Size	4,297,045 (22% had benzo)
Subjects	Adults age 20-80 (entire population of Denmark on 1/1/2000)
Duration	20 year
Primary outcome	Use longer than 1 or 7 years Dose escalation beyond max recommended
Result	Long term use rare (15% >1 yr, 5% > 3 yr, 3% >7 yr) ➢ More common with z-hypnotics, sub use d/o Dose escalation rare (7% of those on > 3 yr, i.e. 0.4% of sample) ➢ More common with hypnotic benzos, sub use d/o
Limitations	May not generalize beyond Denmark where restrictions are in place since 1980s, but similar to 2003 NJ Medicaid study Did not account for long term episodic use
Funding	University Hospital of Copenhagen

Rosenqvist TW, et al. Long-term use of benzodiazepines and benzodiazepine-related drugs: a register-based Danish cohort study on determinants and risk of dose escalation. Am J Psychiatry. 2024;181(3):246-254.



Chronic use beyond one year was rare

ASAM Guidelines for Benzo Discontinuation

- See patients who are on benzodiazepines at least every 3 months
- Consider taper in:
  - Patients at risk for falls, car accidents, cognitive impairment, overdose
  - Elderly, pregnancy, substance use disorders, or taking opioids
- Taper by 5-25% every 2-4 weeks
- Guidelines are preliminary, subject to revision

https://downloads.asam.org/sitefinity-production-blobs/docs/default-source/guidelines/bzd-cpg-narrative-draft-for-public-comment.pdf?sfvrsn=6d96408_2

3

Lumateperone in Depression

The antipsychotic moves closer to FDA approval for antidepressant augmentation

Lumateperone Augmentation in Major Depression	
Design	Randomized double-blind placebo-controlled trial
Size	485 patients with 1-2 antidepressant failures
Intervention	Lumateperone 42 mg
Duration	6 weeks
Primary outcome	?
Result	Effective (effect size 0.6)
Limitations	Study published in abstract form only
Risks	Fatigue, dry mouth, tremor were the main side effects in addition to known antipsychotic risks
Funding	Intracellular Therapies

https://ir.intracellulartherapies.com/news-releases/news-release-details/intra-cellular-therapies-announces-positive-phase-3-topline

Other Antipsychotic Updates

Successes

- Iloperidone approved in bipolar mania
  (study presented at 2023 NCPA, small effect size = 0.2)
- Brexpiprazole submits for PTSD
  (as augmentation of sertraline, 1-3 mg/day, 2 out of 3 trials positive)

Failures

- Cariprazine in maintenance phase of bipolar
- Pimavanserin in negative symptoms of schizophrenia and augmentation in major depression

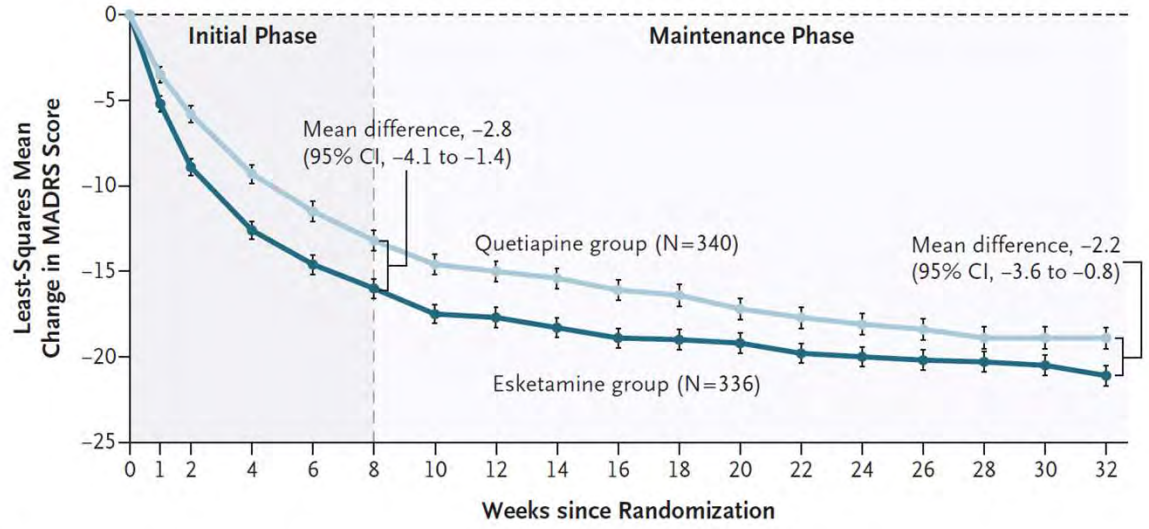
4 Esketamine vs Quetiapine

Which will prevail in ESKAPE-TRD?

Esketamine vs Quetiapine in Treatment Resistant Depression (TRD)	
Design	Randomized, placebo controlled
Interventions	Esketamine IN vs. Quetiapine XR Flexibly dosed and added to SSRI or SNRI
Size	676 adults, failed 2-6 antidepressants from different classes
Duration	32 weeks (8 months)
Primary outcome	Remission rates (MADRS < 10)
Secondary outcomes	Relapse at 32 weeks. Remission at 8 weeks.
Result	Esketamine had significantly greater... Remission (27% vs 18%) Response (76% vs 56%) Sustained remission (27% vs. 14%)
Limitations	Patients not blinded to treatment. No placebo.
Risks	Similar rates of severe adverse effects (5%) but more discontinuations on quetiapine (40 vs 23%)
FDA Approval	Yes
Cost	Esketamine (Spravato) $4,720-6,785/month + visit costs
Funding	Janssen (Spravato manufacturer)

Reif A, Bitter I, Buyze J, et al. Esketamine Nasal Spray versus Quetiapine for Treatment-Resistant Depression. N Engl J Med. 2023;389(14):1298-1309.

Esketamine vs Quetiapine in TRD



No. at Risk

Quetiapine group	326	315	295	285	265	242	235	232	223	219	214	214	209	206	205	200	203
Esketamine group	325	324	317	312	300	288	285	280	277	267	269	263	259	257	252	250	255

Figure 3. Change in MADRS Score from Baseline over Time.

The least-squares mean change from baseline in the MADRS score in the esketamine group and the quetiapine group is shown according to treatment phase and weeks since randomization. I bars indicate standard errors. Data are from the full analysis set, which includes all patients who underwent randomization. The analyses were performed with the use of a mixed model for repeated measures with an unstructured covariance matrix, with treatment, age group, number of past failed treatments, time, time-by-treatment interaction, and MADRS score at baseline as co-variates.

5

Lavender (Silexan)

A European med for generalized anxiety disorder breaks through in depression

Lavender (Silexan) in Depression	
Design	Randomized, placebo controlled
Interventions	1) Silexan 80 mg 2) Sertraline 50 mg or 3) Placebo
Size	498 adults with mild-moderate depression
Duration	2 months
Primary outcome	Change on MADRS
Secondary outcomes	Response, remission, depression self-rated (BDI-II, PHQ-9), CGI, disability scale (SDS)
Result	Silexan and sertraline beat placebo with similar improvements: Silexan NNT 9 for response/remission Sertraline NNT 8 for response/remission Secondary outcomes showed similar trends, although only Silexan positive for improvement on disability scale
Limitations	Somewhat high placebo response rate
Risks	Lavender flavored burping
Dose	Silexan “Calm Aid” 80 mg/night (dose in GAD is 160 mg/night)
FDA Approval	No (approved for GAD in Europe)
Cost	$15 per month
Funding	Medical University of Vienna

Kasper S, Volz HP, Möller HJ, et al. Lavender oil preparation Silexan is effective in mild-to-moderate major depression: a randomized, placebo- and reference-controlled trial. Eur Arch Psychiatry Clin Neurosci. Published online April 1, 2024.

Lavender, Sertraline, Placebo in MDD

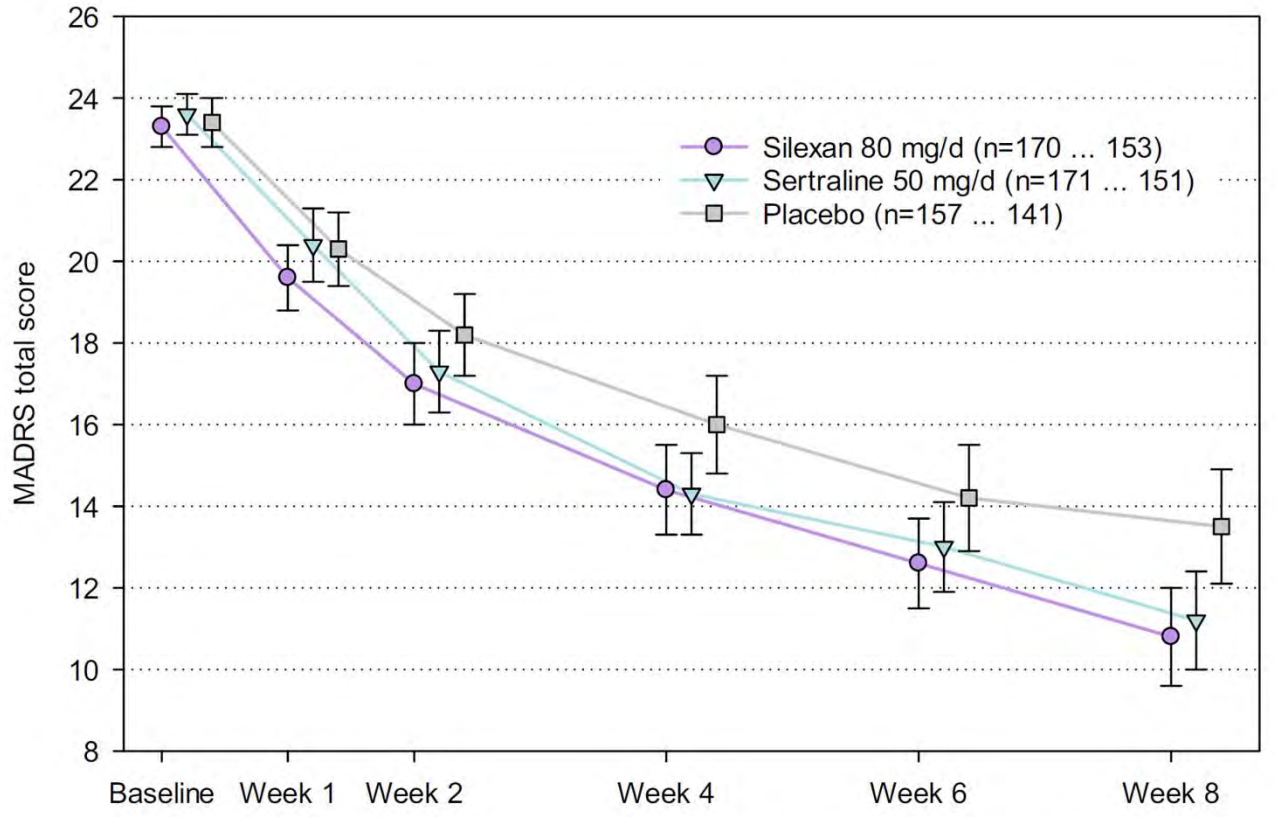


Fig. 2 Montgomery-Åsberg Depression Rating Scale (MADRS) total score (means and 95% confidence intervals; primary estimand without imputation of missing values, full analysis set; legend shows numbers of subjects with valid data at baseline and week 8; $p < 0.01$ for change from baseline to week 8 for silexan vs. placebo and for sertraline vs. placebo)

Calm Aid uses Schwabe Pharmaceuticals

Supplement Facts

Serving Size 1 Softgel

Amount per Serving	% DV**
Silexan™ English Lavender *(Lavandula angustifolia)* Flower Essential Oil	80 mg**

**Daily Value (DV) not established.

6

Lithium

Reassurance on weight gain and renal impairment
New crystal formulation underway

Lithium and Weight Gain	
Design	Meta-analysis (PRISMA guidelines)
Studies	Meta-analysis: 9 trials (n=2,212) Systemic review: 20 trials (n=10,812) 90% were RCTs with placebo or active comparator
Subjects	Bipolar disorder, children (15%) and adult (85%) trials
Duration	2-12 months
Primary outcome	Change in weight pre/post lithium Comparison of weight gain lithium vs. placebo or other med
Meta-analysis Results	Lithium vs placebo: non-significant weight loss on lithium Lithium pre/post: non-significant weight gain on lithium Lithium vs other med: significant weight loss on lithium (3.2 lb)
Review Results	These were consistent with meta-analysis: ➢ Weight gain on Li in 1 of 6 placebo trials ➢ Only lamotrigine and venlafaxine has less weight gain as active comparators
Limitations	Outcomes varied among studies
Funding	None

Gomes-da-Costa S, Marx W, Corponi F, et al. Lithium therapy and weight change in people with bipolar disorder: A systematic review and meta-analysis. Neurosci Biobehav Rev. 2022;134:104266.

Greil W, de Bardeci M, Müller-Oerlinghausen B, et al. Controversies regarding lithium-associated weight gain: case-control study of real-world drug safety data. Int J Bipolar Disord. 2023;11(1):34.

Lithium and Weight Gain

More variability in long term trials

Short (< 12 wks)

Long (> 12 wks)

Group by Length 12 weeks	Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
< 12 weeks	Geller. 2012	1.420	0.206	0.042	1.017	1.823	6.902	0.000
< 12 weeks	Findling. 2015	0.900	1.600	2.560	-2.236	4.036	0.563	0.574
< 12 weeks	Amsterdam. 2016	-0.240	0.311	0.097	-0.850	0.370	-0.771	0.441
< 12 weeks	Keck. 2009	0.620	0.076	0.006	0.472	0.768	8.207	0.000
< 12 weeks	Bowden. 2010	0.200	0.289	0.084	-0.367	0.767	0.691	0.490
< 12 weeks		0.552	0.277	0.077	0.010	1.095	1.995	0.046
>12 weeks	Gao. 2018	-1.590	1.132	1.282	-3.809	0.629	-1.404	0.160
>12 weeks	Yaramala. 2020	2.400	0.544	0.296	1.333	3.467	4.408	0.000
>12 weeks	Findling. 2019	1.800	0.649	0.721	0.136	3.464	2.120	0.034
>12 weeks	Tohen. 2005	-1.400	0.342	0.117	-2.070	-0.730	-4.096	0.000
>12 weeks		0.336	1.174	1.379	-1.966	2.638	0.286	0.775
Overall		0.541	0.269	0.073	0.013	1.069	2.008	0.045

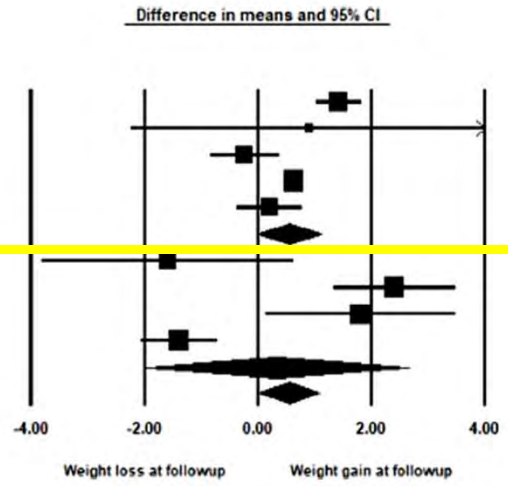
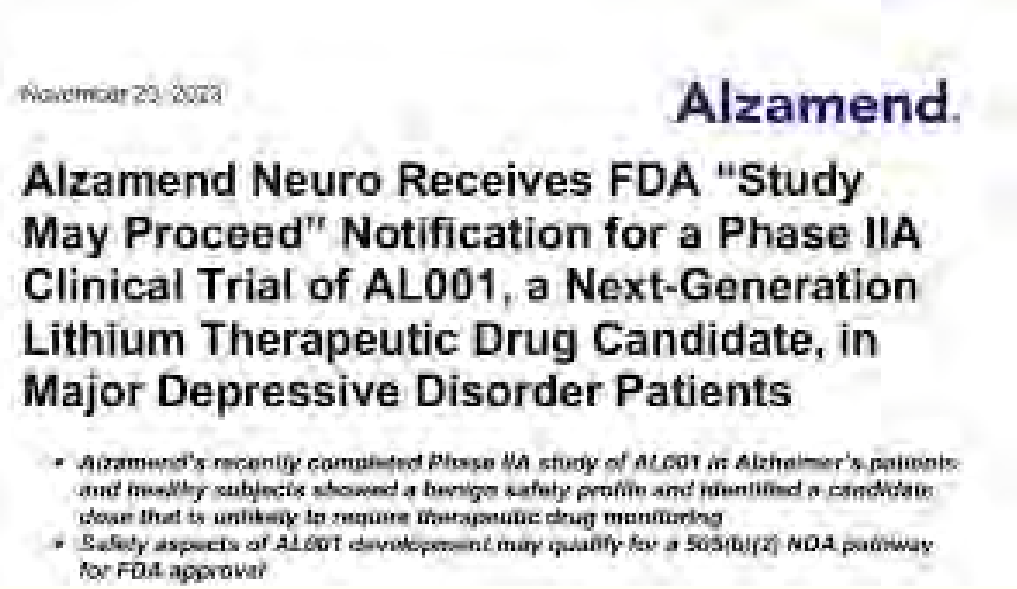


Fig. 3. Weight change during lithium treatment according trial length – Forest plots with the summary effect size (Difference in means) of weight gain, between patients treated with lithium in 2 subgroups: shorter than 12 weeks and longer than 12 weeks.

LiProSal



November 20, 2023

Alzamend.

Alzamend Neuro Receives FDA "Study May Proceed" Notification for a Phase IIA Clinical Trial of AL001, a Next-Generation Lithium Therapeutic Drug Candidate, in Major Depressive Disorder Patients

- *Alzamend's recently completed Phase IIA study of AL001 in Alzheimer's patients and healthy subjects showed a benign safety profile and identified a candidate dose that is unlikely to require therapeutic drug monitoring*
- *Safety aspects of AL001 development may qualify for a 505(b)(2) NDA pathway for FDA approval*

Branded formulation pairs lithium with the amino acid proline and salicylate (Aspirin) to allow higher CNS levels and lower serum levels, potentially reducing side effects.

Studies underway in bipolar, depression, PTSD, and dementia

7

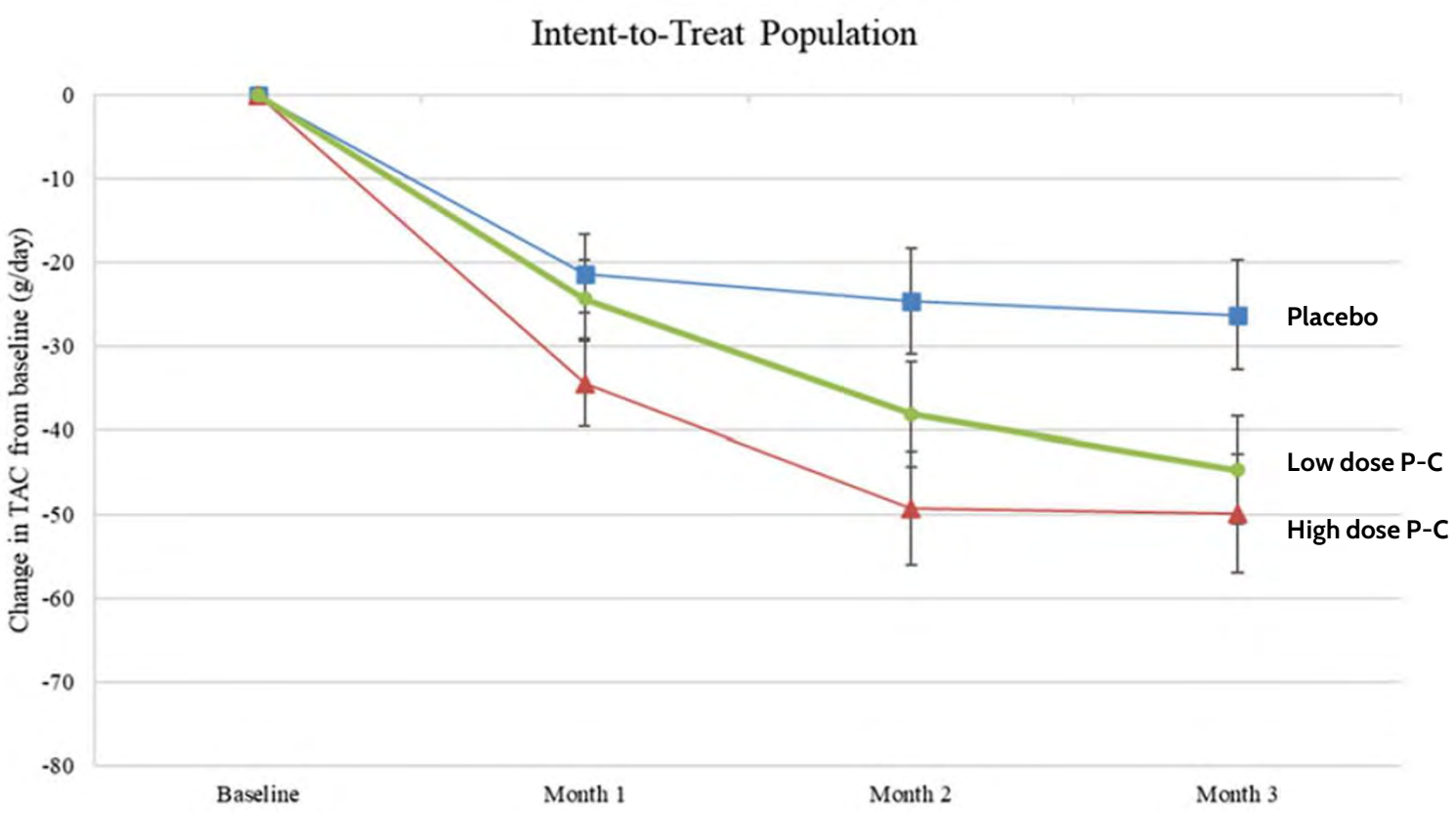
Prazosin-Cyproheptadine

Combination effective in severe alcohol use disorder

Prazosin-Cyproheptadine in Alcohol Use Disorder (AUD)	
Design	Randomized double-blind placebo-controlled trial
Size	154 adults with severe AUD
Intervention	Low dose: prazosin ER 5mg + cyproheptadine 8mg High dose: prazosin ER 10mg + cyproheptadine 12mg Placebo
Duration	12 weeks
Primary outcome	Total alcohol consumption (TAC)
Result	Positive for both, but p-value borderline for low dose (0.048): ➢ High dose vs PB: −23.6 g/day, effect size 0.44 ➢ Low dose vs PB: −18.4 g/day, effect size 0.36 Those who drank more had more benefit
Limitations	Small size
Risks	CYPRO: Weight gain, sedation. PRAZ: Hypotension
Funding	Kinnov Therapeutics
Monthly cost	Low cost, but ER prazosin not available

Aubin HJ, Berlin I, Guiraud J, et al. Prazosin and cyproheptadine in combination in the treatment of alcohol use disorder: A randomized, double-blind, placebo-controlled trial. Addiction. 2024;119(7):1211-1223.

Prazosin-Cyproheptadine in AUD



8 ADHD with Cannabis Use

Though small and problematic, this trial illustrates a point. Stimulants don’t work well when cannabis is on board.

Amphetamine Salts for Adult ADHD with Cannabis Use Disorder	
Design	Randomized, double blind, placebo controlled
Interventions	Amphetamine Salts (Adderall ER) 80 mg/day All received weekly supportive behavioral abstinence coaching
Size	28 adults with ADHD and Cannabis Use Disorder
Duration	12 weeks
Primary outcome	1. ADHD: Response (≥30% symptom reduction, measured by the Adult ADHD Investigator Symptom Rating Scale (AISRS)) 2. Cannabis: Abstinence during last 2 weeks of trial
Secondary outcomes	1. ADHD: AISRS change, CGI 2. Cannabis: Weekly use, weekly urine THC levels, total number of positive urine tests
Result	No significant difference ➢ ADHD response 83% stimulant vs 71% placebo ➢ Cannabis abstinence 15% stimulant vs 0% placebo Among secondary outcomes, only days of use showed significant decline (with stimulant)
Limitations	Small size, high drop outs (46% on stimulant 27% on placebo; also non-adherence 45% by UDS) Though likely underpowered to detect real difference, results are in line with larger trials of methylphenidate (n=303) and atomoxetine
Risks	Both amphetamines and cannabis can cause psychosis
Funding	NIH/NIDA (National Institute on Drug Abuse)

Levin FR, Mariani JJ, Pavlicova M, et al. Extended-Release Mixed Amphetamine Salts for Comorbid Adult Attention-Deficit/Hyperactivity Disorder and Cannabis Use Disorder: A Pilot, Randomized Double-Blind, Placebo-Controlled Trial. *J Atten Disord*. Published online July 25, 2024.

Riggs PD, Winhusen T, Davies RD, et al. Randomized controlled trial of osmotic-release methylphenidate with cognitive-behavioral therapy in adolescents with attention-deficit/hyperactivity disorder and substance use disorders. *J Am Acad Child Adolesc Psychiatry*. 2011;50(9):903-914.

9

Max Stimulant Dosing

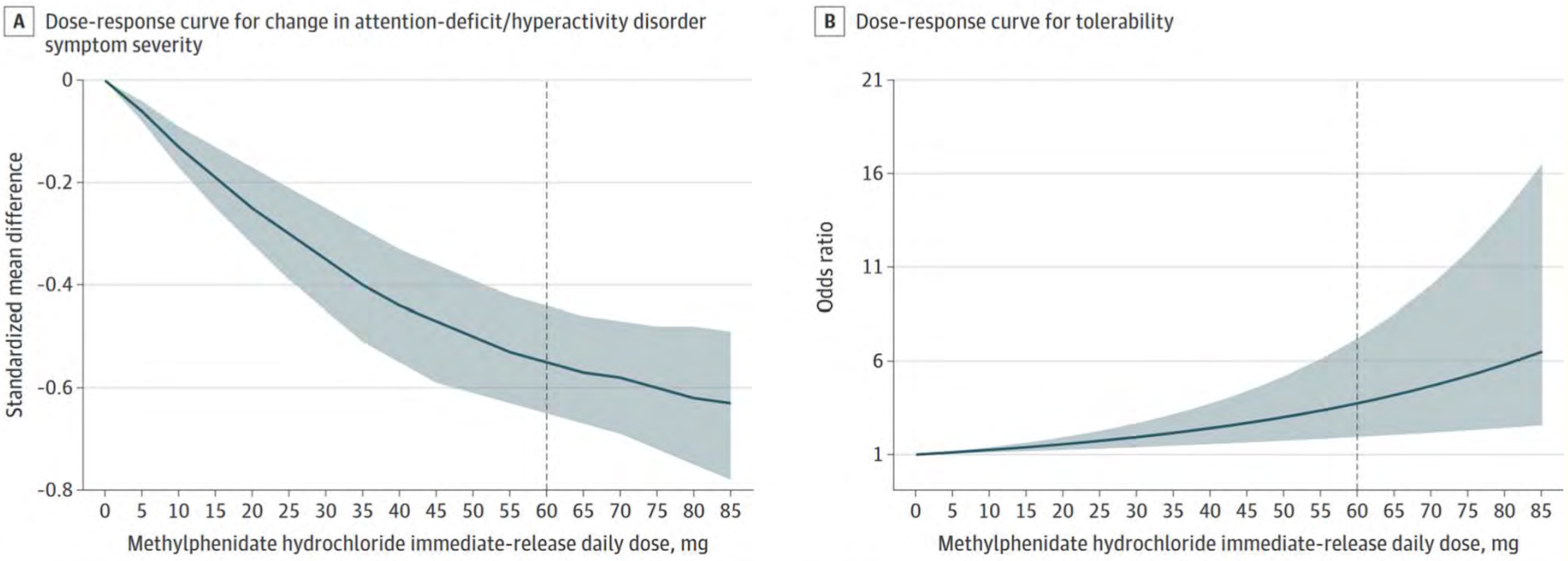
Unlicensed dosing is rarely worthwhile, particularly with the amphetamines

Dose-Response in ADHD	
Design	Systematic Review and Meta-Analysis
Studies	47 RCTs, most flexibly dosed 29 methylphenidate 15-82.5mg, 18 amphetamines 12.5-75mg n = 7714; mean age, 35 +/- 11 years; 56% male
Primary outcome	Change in ADHD symptoms Discontinuations due to adverse events
Result	**Methylphenidate:** Improvement began to plateau at 35-40 mg. Above FDA max 60 mg lead to small, diminishing gains (effect size 0.2) but higher rate of AEs (2-fold). **Amphetamines:** Dosing beyond 30-35 mg lead to no further improvement. However, AEs increased steadily with higher doses throughout entire dosing range.
Limitations	Doses converted for different formulations. Does not account for specific AEs or outlier responses. Heterogeneous results for amphetamine efficacy.
Funding	Various international health institutes

Farhat LC, Flores JM, Avila-Quintero VJ, et al. Treatment Outcomes With Licensed and Unlicensed Stimulant Doses for Adults With Attention-Deficit/Hyperactivity Disorder: A Systematic Review and Meta-Analysis. JAMA Psychiatry. 2024;81(2):157-166.

Methylphenidate Dose-Response

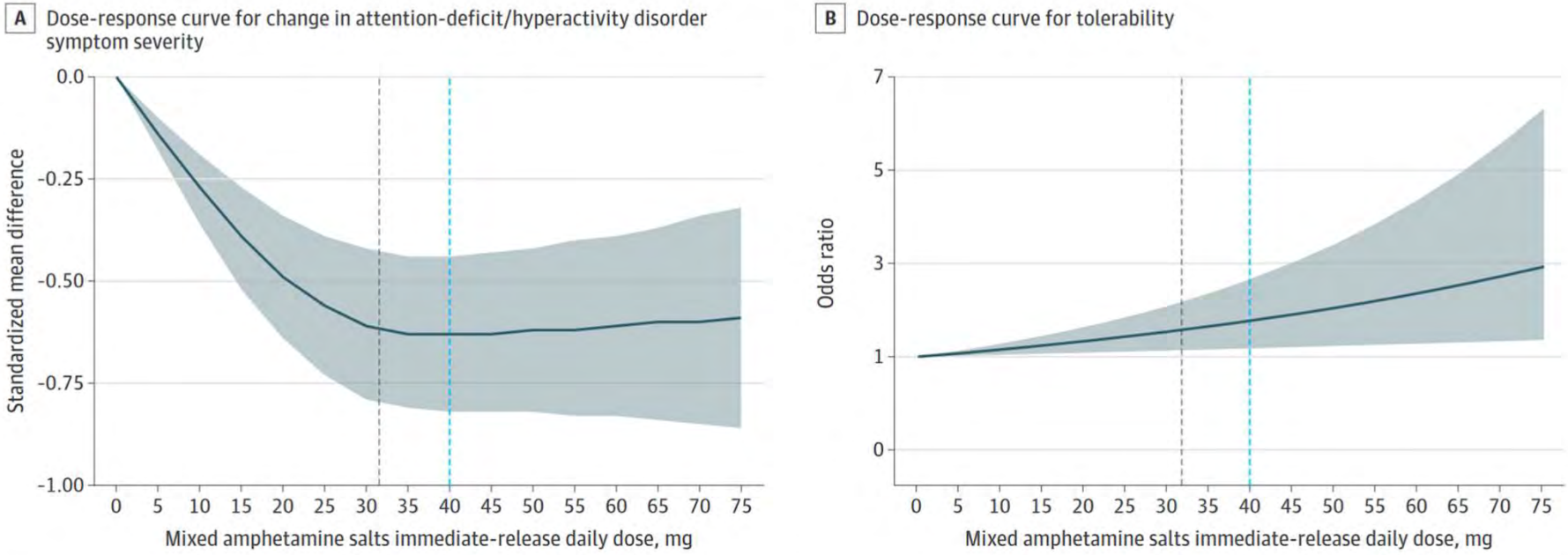
Figure 2. Dose-Response Curves for Methylphenidate



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 methylphenidate. The shaded areas indicate 95% CIs. The dotted line indicates the US Food and Drug Administration maximum recommended dose for immediate-release methylphenidate hydrochloride.

Amphetamine-Salts 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

Lowering Antipsychotics

Low-doses in schizophrenia were once thought to improve social functioning.
The RADAR trial calls that to question.

Antipsychotic Dose Reduction in Schizophrenia	
Design	Randomized trial at 19 centers in England
Intervention	Flexible, gradual dose reduction vs maintenance Mean reduction 67% at 1 year, 33% at 2 years
Subjects	253 adults with non-affective psychosis on antipsychotic Mean age 46. No recent hospitalizations. Drop out 28%.
Duration	2 years
Primary outcome	Social functioning (Social Functioning Scale)
Secondary outcomes	Relapse requiring hospitalization
Result	No difference in social functioning More hospitalization with reduction (39 vs 16%)
Limitations	COVID lockdown limited assessment of social functioning Only assessors blinded. Duration (earlier study found functional improvements with dose reduction after *7 years*)
Funding	UK National Institute for Health Research

Moncrieff J, Crellin N, Stansfeld J, et al. Antipsychotic dose reduction and discontinuation versus maintenance treatment in people with schizophrenia and other recurrent psychotic disorders in England (the RADAR trial): an open, parallel-group, randomised controlled trial. Lancet Psychiatry. 2023;10(11):848-859.

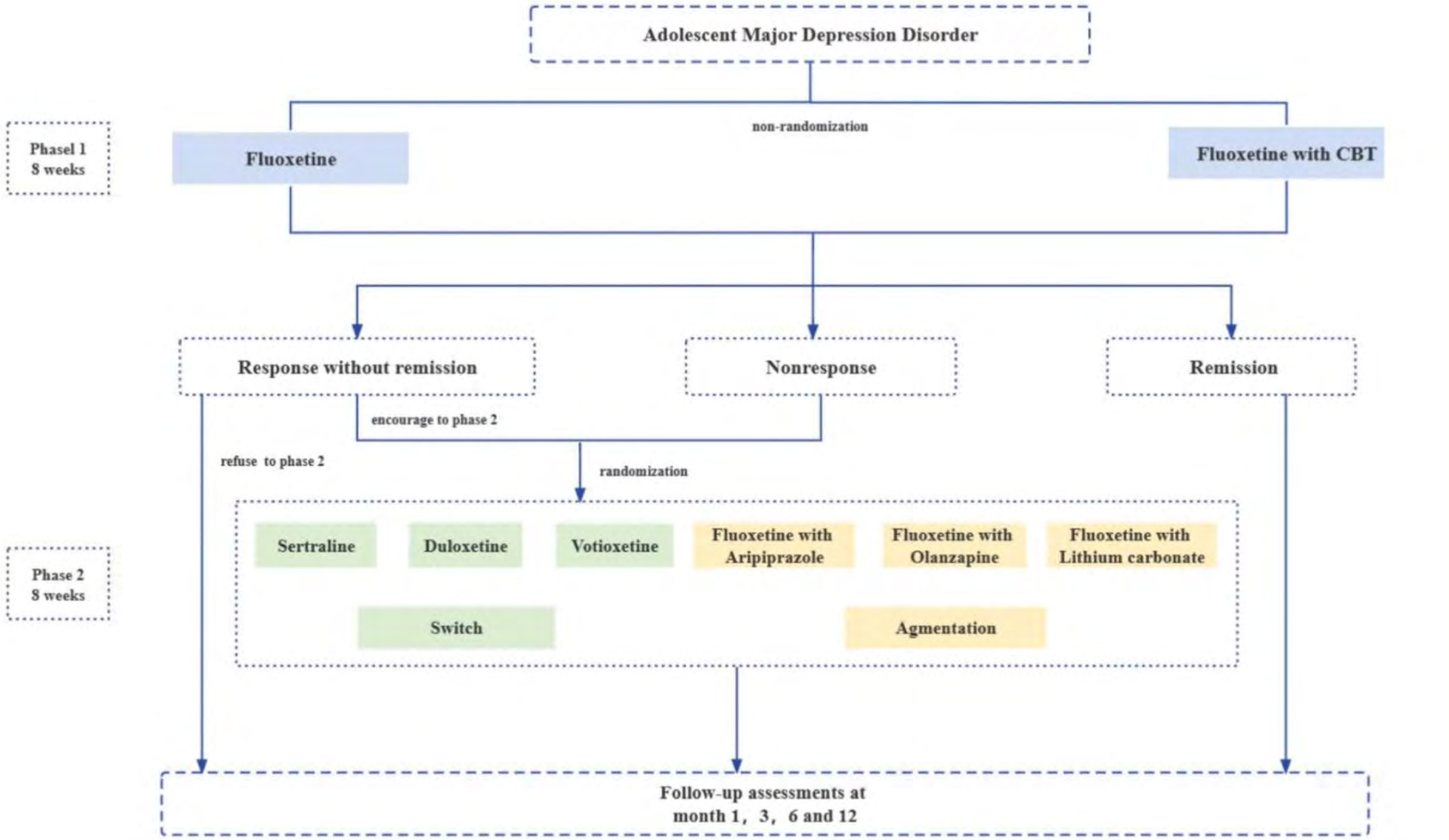
SUMMARY

Treatment	When to use	Daily Dose
Prazosin-Cyproheptadine	Alcohol Use Disorder	P/C: 5/8 - 10/12 mg/day
rTMS Esketamine	Treatment resistant depression in place of switching/augmenting	
Lumateperone	Antidepressant augmentation Bipolar depression	42 mg/night
Brexpiprazole	Await approval in PTSD (aug)	1-3 mg/day
Lavender (Silexan)	Mild-moderate Major Depression Generalized Anxiety Disorder	80-160 mg/day
Stimulants	Caution in adult ADHD beyond methylphenidate 60mg, Adderall 35 mg ADHD meds unlikely to help if comorbid cannabis use disorder	
Benzos	Extreme distress during taper warrants reconsideration of plan	
Antipsychotics	Dose reduction may the raise risk of relapse without improving functioning, but follow-up study is pending.	

STAR*D for Adolescents

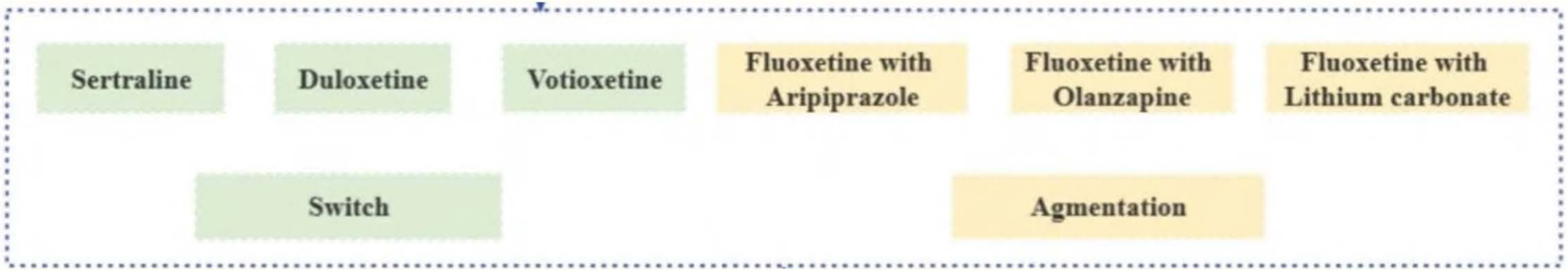
Algorithm is out. Results pending.

Star*D For Adolescent Depression



He Y, Gan X, Li X, et al. Sequenced treatment alternatives to relieve adolescent depression (STAR-AD): a multicentre open-label randomized controlled trial protocol. BMC Psychiatry. 2023;23(1):789.

Star*D For Adolescent Depression



FUN BONUS

Psychosis in Magicians?

Nope. It’s the rest of us who have a thin grasp on reality.

Psychotic and Autistic Traits in Professional Magicians	
Design	Correlational survey
Subjects	195 magicians, 233 matched adults (mean 56 years, 82% women)
Outcomes	**Schizotypal traits** (Oxford–Liverpool Inventory of Feelings and Experiences) **Autistic traits** (Abridged Version of the Autism-Spectrum Quotient) **Creativity** (Short Scale of Creative Self)
Result	Magicians scored lower on psychotic traits Higher on creative traits No difference in autistic traits
Limitations	Self-report. Although age/sex matched, sample tended toward older males. Higher rate of doctorate education among magicians.
Funding	None

Greengross G, Silvia PJ, Crasson SJ. Psychotic and autistic traits among magicians and their relationship with creative beliefs. BJPsych Open. 2023;9(6):e214.

Comparison with other studies

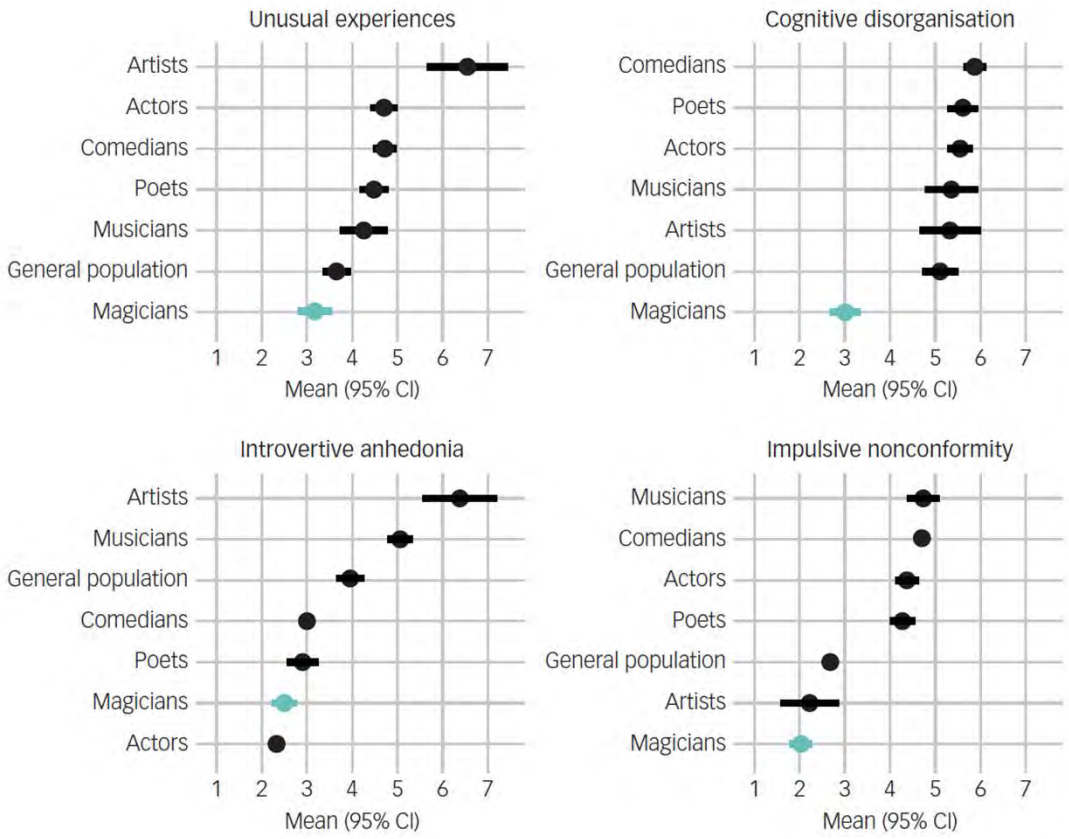
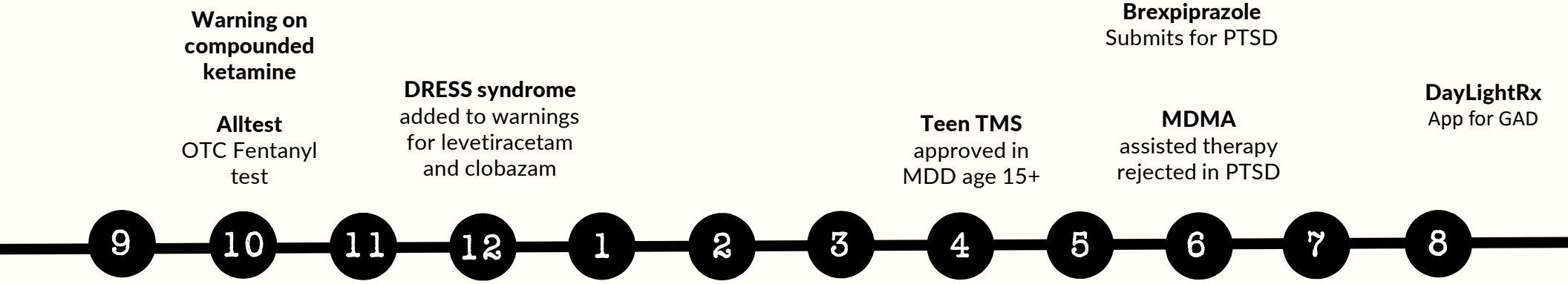


Fig. 2 Comparison of the four Oxford–Liverpool Inventory of Feelings and Experiences scales (unusual experiences, cognitive disorganisation, introvertive anhedonia and impulsive nonconformity) for various creative groups and the general sample.

Thanks for listening, and now...

A timeline of recent psychiatric updates from the FDA



Exxua
Gepirone for MDD

Warning on compounded ketamine

Alltest
OTC Fentanyl test

DRESS syndrome
added to warnings for levetiracetam and clobazam

Nuplazid
patent extended to 2038

AvertD
Genetic test for risk of opioid UD

Vortioxetine
Orally disintegrating tablets

Teen TMS
approved in MDD age 15+

Rezenopy
High-dose 10mg naloxone

Ingrezza Sprinkles
valbenazine for TD

Onyda
Liquid clonidine XR

Brexpiprazole
Submits for PTSD

MDMA
assisted therapy rejected in PTSD

NJOY Menthol
First flavored vape authed

Erzofri
paliperidone palmitate monthly LAI

Zurnai
nalmefene opioid OD reversal

DayLightRx
App for GAD

FDA Updates Sept 2023 – Aug 2024