

OREGON  
HEALTH  
& SCIENCE  
UNIVERSITY



## Depression Updates for the Internist

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Date: May 14, 2026

# Disclosure Statement:

Relevant financial relationships in the past 12 months



# Outline

1. 1. Newest antidepressants and approaches
2. 2. Metabolism and the role of therapeutic lifestyle change in depression
3. 3. Adverse effects to watch for when prescribing antidepressants
4. 4. Review of “alternative” approaches in TRD
5. 5. Lithium (and analogs in development)
6. 6. Suicide Recap

# STAR\*D Trial

N Engl J Med 2006;354:1231-42.

4041 Patients  
Citalopram

30% remission  
41.8mg avg.

727 Non-Remitters Randomized for 14 weeks to:

Bupropion SR  
Out of class

Max: 400mg  
25.5% Remission

Sertraline  
In-class

Max: 200mg  
26.6% Remission

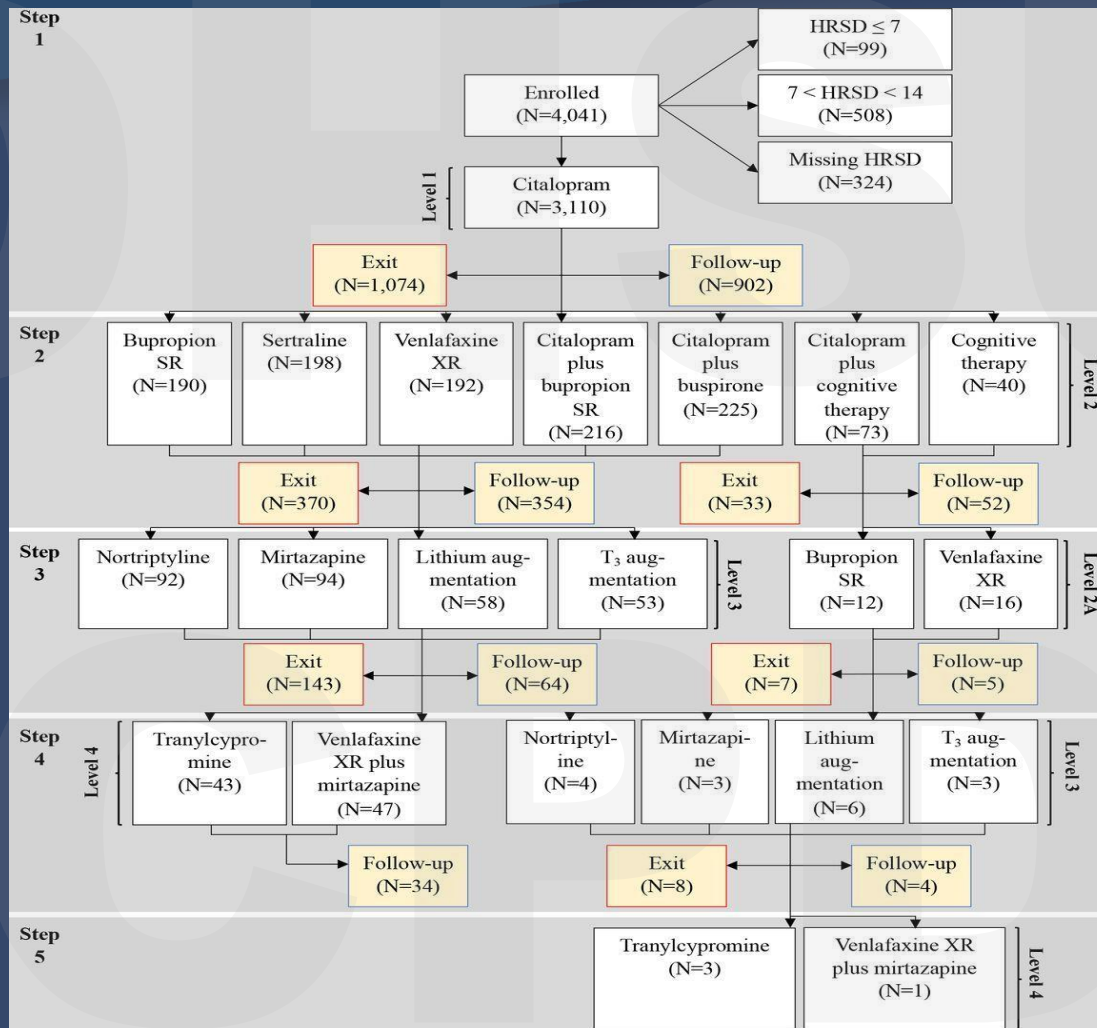
Venlafaxine XR  
Dual-action

Max: 375mg  
25.0% Remission

## Citalopram Warning Aug 24, 2011:

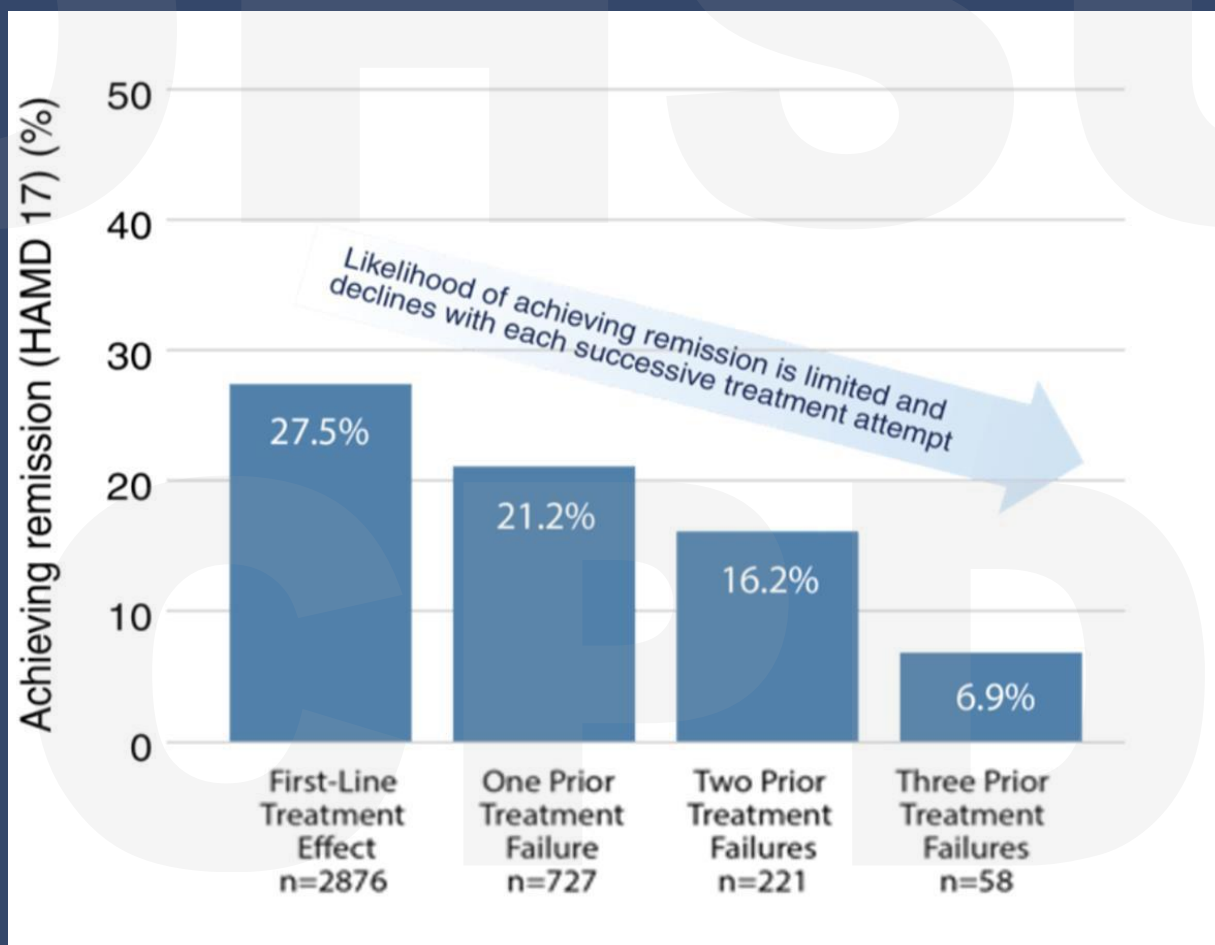
- Citalopram causes dose-dependent heart conduction issues (QT interval prolongation) on EKG.
- Citalopram should not be prescribed at doses greater than **40 mg** per day.
- 20 mg per day is the *maximum* recommended dose for patients with liver impairment or who are > than 60 years

# STAR\*D Recap



Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR\*D report. Am J Psychiatry. 2006 Nov;163(11):1905-17.

# STAR\*D Trial Bottom Line



# Antidepressant Timeline Recap

1950's  
Iproniazid &  
Imipramine

1960's  
Various  
MAOIs  
, TCAs

1970's  
ECT  
Re-  
Emergence

1987  
SSRI  
Fluoxetine

1993  
SNRI  
Venlafaxine

2008  
TMS

2019+  
Glutamatergic  
(Brexanolone),  
NMDA  
Antagonists  
(Esketamine)

## Clinical Case



- Dee Prest is a 61 yo WF with a h/o stage I HTN, who presents complaining of increased “stress,” poor sleep, and worsening mood that started with the pandemic but has worsened even more over the past year. Her vital signs are normal but she has been gaining weight (7 lbs in the past 6 months taking her BMI up to 35 kg/m<sup>2</sup>) and not motivated to engage in physical activity.
- Her PHQ9 score is 21 and rated “extremely difficult” in severity.

## Clinical Case cont.



- Dee's current medications: sertraline 200mg, bupropion XL 300mg, metoprolol XL 150mg, HCTZ 25mg, atorvastatin 10mg, and potassium supplement daily
- Past psychotropic medications: fluoxetine (stopped working), venlafaxine (worsened blood pressure), escitalopram (didn't work), selegiline patch (too expensive).
- What is your next move?

**What is Treatment Resistant Depression (TRD)?  
And is TRD the best name?**



# Treatment Resistant Depression (TRD)

- A failure of treatment to produce response or remission after **two** or more treatment attempts of adequate dose and duration.

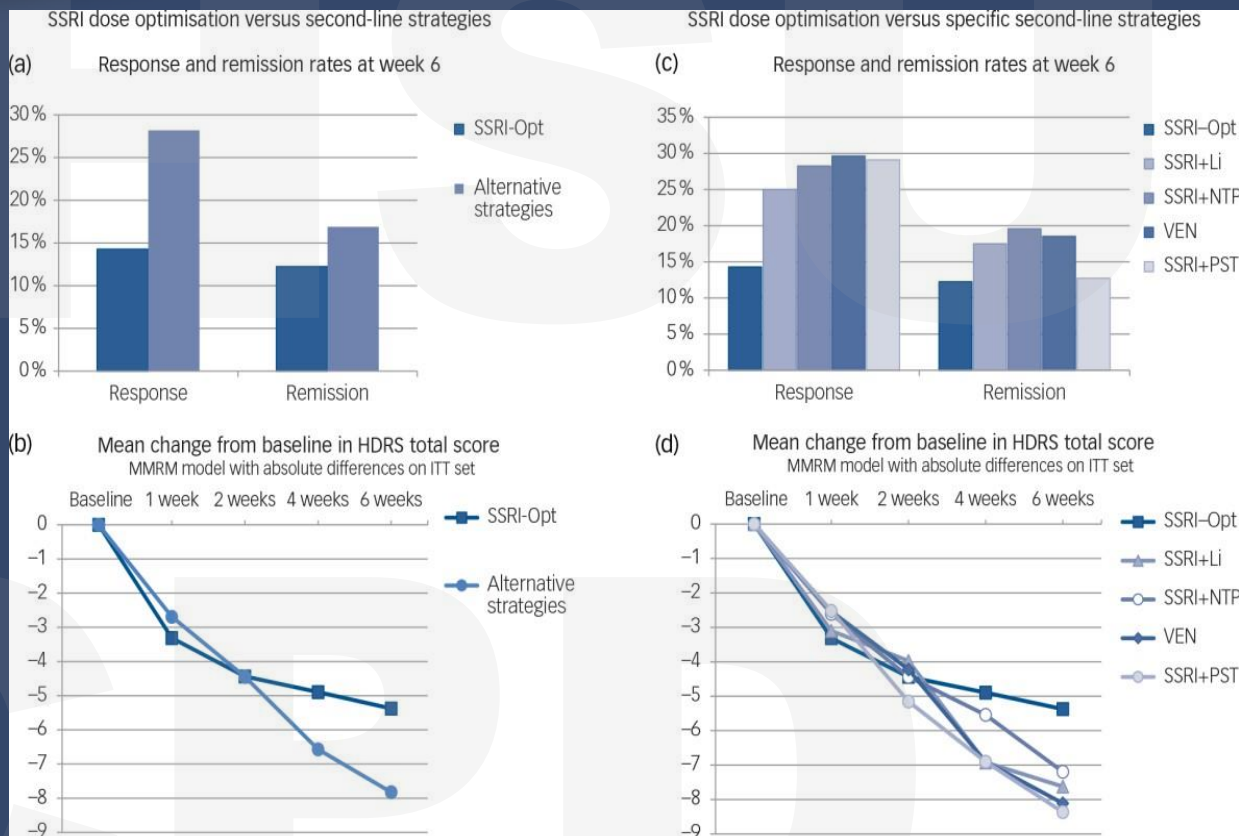


## Options for Dee with TRD (in no particular order)

1. - Bump the dose of bupropion XL to 450mg (work with what you've got)?
2. - A newer medication trial – I hear that gepirone is available?
3. - A “prescription” for lifestyle modification (TLC) including weight loss meds
4. - A referral for cognitive behavioral therapy (CBT)
5. - Partial hospitalization/intensive outpt (PHP/IOP) program enrollment
6. - Transcranial magnetic stimulation (TMS)
7. - Electroconvulsive therapy (ECT)
8. - Seek genetic testing or use biomarkers for guidance
9. - Prescribe and have her download the Rejoyn app
10. - Lower the doses of some of her medications?
11. - Start lithium carbonate?

# What do we think of Maximizing Doses?

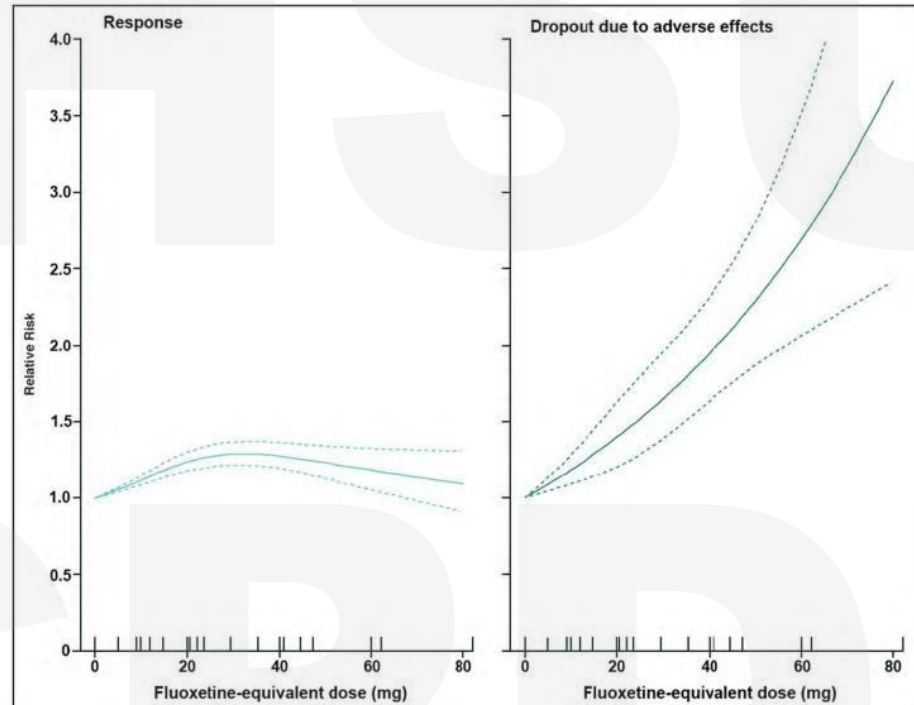
- DEPRE'5; 5-arm, multicenter RCT in Spain for pts with MDD and insufficient response to SSRIs (n = 257) is a mini-STAR\*D trial.
- SSRI titration targets: 60 mg for fluoxetine, 50 mg for paroxetine, 200 mg for sertraline, 60 mg for citalopram, 20 mg for escitalopram and 300 mg for fluvoxamine.



# SSRI Dose-Response

Peak benefits at 20-40 mg fluoxetine equivalents

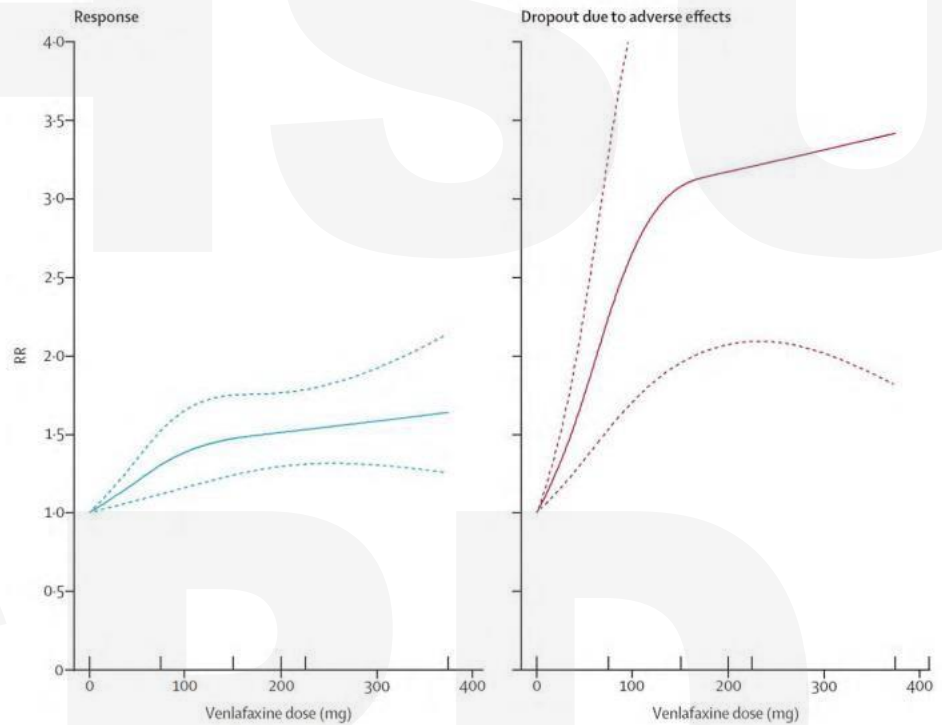
99 fixed-dose groups. Furukawa TA et al. Lancet Psychiatry. 2019;6(7):601-609.



# Venlafaxine Dose-Response

Peak effects at 75-150 mg  
followed by modest  
increase

17 fixed-dose groups. Furukawa TA et al.  
Lancet Psychiatry. 2019;6(7):601-609.



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# Gepirone ER (Exxua): A Study in Persistence

- Thrice rejected by the FDA: 2002, 2004, and 2007
- Approved: September 2023 (2 positive following 5-7 negative trials)
- MOA: the **first 5-HT<sub>1a</sub> agonist** with superior efficacy vs placebo as MDD monotherapy (through at least 48 weeks). 5-HT<sub>1a</sub> receptors are the most widespread of all the 5-HT receptors and are involved in neuromodulation. They decrease blood pressure and heart rate by inducing peripheral vasodilation, and by stimulating the vagus nerve.
- Rates of sexual dysfunction did not differ from placebo in the clinical trials.

Fabre-Kramer Pharmaceuticals announces FDA approval of Exxua, the first and only oral selective 5HT<sub>1a</sub> receptor agonist for the treatment of major depressive disorder in adults. News release. PR Newswire. September 28, 2023.

# Gepirone ER Prescribing

- Starting dose 18.2mg qd with food – dose may be increased to 36.3mg on day 4 and further to 54.5 after day 7 and to 72.6 after an additional week. **EKG needed!**
- Chemically related to buspirone and follow-up analysis of the original clinical trial data found that adults with anxious depression had a greater response than those with non-anxious depression.
- Role in anxiety: small pilot study showed that a low dose gepirone (10 to 45 mg/day – mean 41.5mg) can alleviate symptoms of generalized anxiety within 6 weeks with HAM-A scores going from 24.8 to 7.1. It is unknown whether larger doses (e.g., 40 to 80 mg/day) would result in a quicker onset of action.

• Csanalosi I, Schweizer E, Case WG, Rickels K. Gepirone in anxiety: a pilot study. *J Clin Psychopharmacol*. 1987 Feb;7(1):31-3.

# Have We Seen This



# Before?

- **Vilazodone**: FDA approved in 2011 as the first and only SSRI and 5-HT<sub>1a</sub> receptor partial agonist at the time
  - Must be taken with food for absorption
    - AUC and C<sub>max</sub> doubles with even a light meal
  - Dosing: start at 10mg but therapeutic doses are between 20 and 40 mg
  - What makes it special? **Weight loss and preservation of sexual function**
- Small RCT of 60 patients: 30 vilazodone and 30 sertraline.  
Examined efficacy, weight gain, and sexual dysfunction using HDRS and ASEX at baseline, 4-week, and 12-week intervals.  
Results: both had equal efficacy but vilazodone did not cause weight gain (over 5kg difference) or sexual dysfunction per the ASEX scale (nearly 8 points improved!).

» *Indian J Pharmacol.* 2020 Jan-Feb; 52(1): 10–15.

# STAR\*D said pick a med, any med...

- 2018 metanalysis: 522 trials with 116,477 patients
- **Efficacy:** agomelatine\*, amitriptyline, escitalopram, mirtazapine, paroxetine, venlafaxine, and vortioxetine were more effective than other antidepressants (range of ORs 1·19–1·96),
  - Least efficacious: fluoxetine, fluvoxamine, reboxetine, and trazodone (OR 0·51–0·84).
- **Acceptability:** agomelatine\*, citalopram, escitalopram, fluoxetine, sertraline, and vortioxetine were more tolerable than other antidepressants (range of ORs 0·43–0·77)
  - Highest dropout rates: amitriptyline, clomipramine, duloxetine, fluvoxamine, reboxetine, trazodone, and venlafaxine.

» Cipriani et al. *Lancet* 2018; 391: 1357–66.

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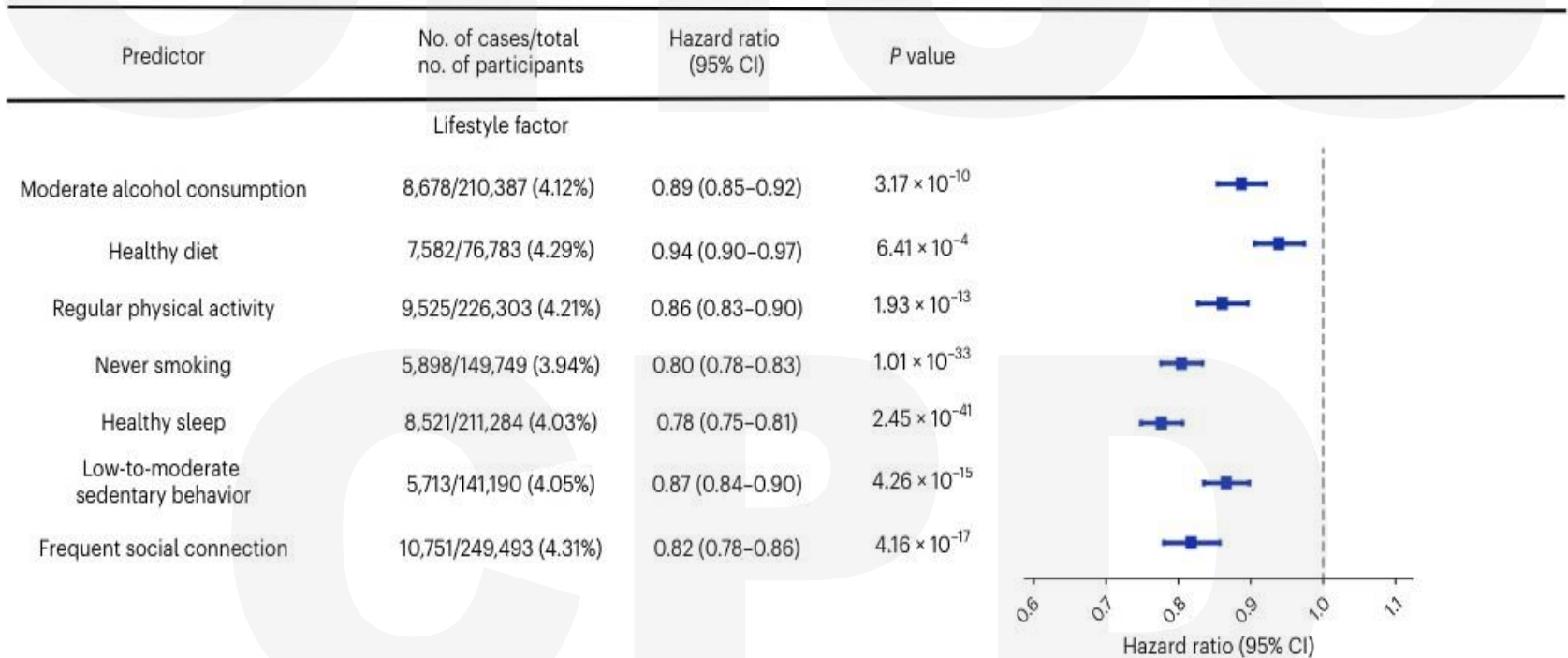
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# Which Lifestyle Predictors Have Greatest Impact on Depression?



Zhao, Y., Yang, L., Sahakian, B.J. et al. The brain structure, immunometabolic and genetic mechanisms underlying the association between lifestyle and depression. *Nat. Mental Health* 1, 736–750 (2023).

## Pearl: Prescription for Better Sleep is the Best Next Step?



## Insomnia Question

Since Dee is also struggling with insomnia, you consider CBT-I but are having a hard time finding a therapist. According to the most recent recommendations of the American Academy of Sleep Medicine, which medication would be the best long-term option for sleep maintenance insomnia?

- A. Suvorexant
- B. Diphenhydramine
- C. Trazodone
- D. Melatonin
- E. Valerian

# Insomnia Question

Since Dee is also struggling with insomnia, you consider CBT-I but are having a hard time finding a therapist. According to the most recent recommendations of the American Academy of Sleep Medicine, which medication would be the best long-term option for sleep maintenance insomnia?

- A. Suvorexant (a dual orexin receptor antagonist)
- B. Diphenhydramine
- C. Trazodone
- D. Melatonin
- E. Valerian

# The Down Side (per Good Rx in January, 2025)

## Quiviviq

as low as **\$480**

DARIDOREXANT treats [insomnia](#). It helps you go to sleep faster and stay asleep through the night.

[See prices](#)

[More info](#)

## Dayvigo

as low as **\$329**

Dayvigo (lemborexant) CIV is used to treat [insomnia](#) in adults.

[See prices](#)

[More info](#)

## Belsomra

as low as **\$453**

Belsomra (suvorexant) is used to treat [insomnia](#). Belsomra is an orexin receptor antagonist which works by inhibiting the neurotransmitter orexin, which is involved in wakefulness. The most common form of belsomra is a 10mg tablet. It is also

[See prices](#)

[More info](#)

# The Better Side (per Good Rx as of April 28, 2026)

## Orexin Receptor Antagonists

[About this drug class](#)

97222



Quviviq

Exclusive discount

[50mg 30 tablets](#)

**\$135.00**

[View prices](#)



Dayvigo

Exclusive discount

[10mg 30 tablets](#)

**\$135.00**

[View prices](#)



Belsomra

[10mg 30 tablets](#)

**\$459.82**

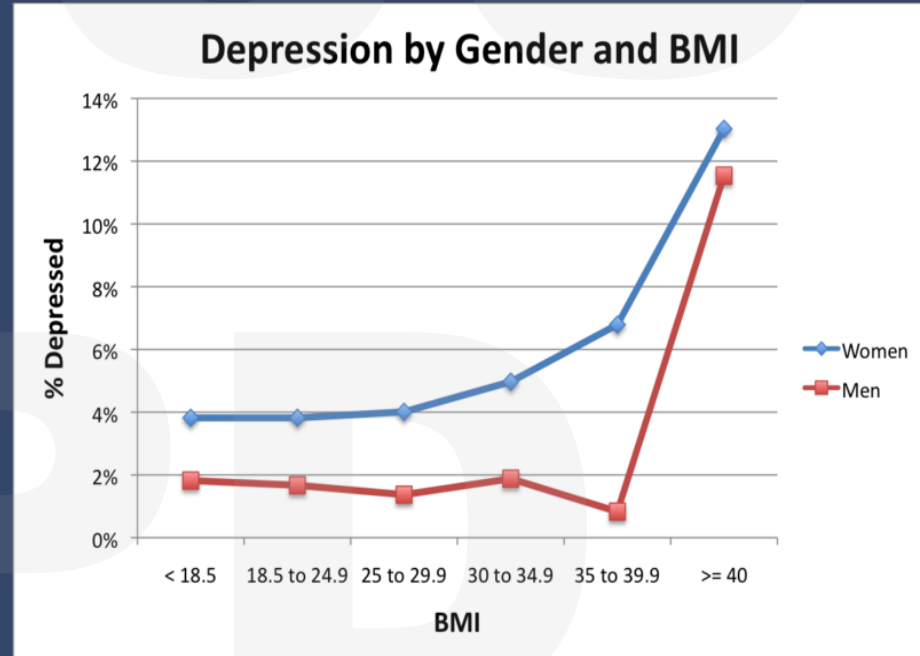
[View prices](#)

# Other Risk Factors for Depression

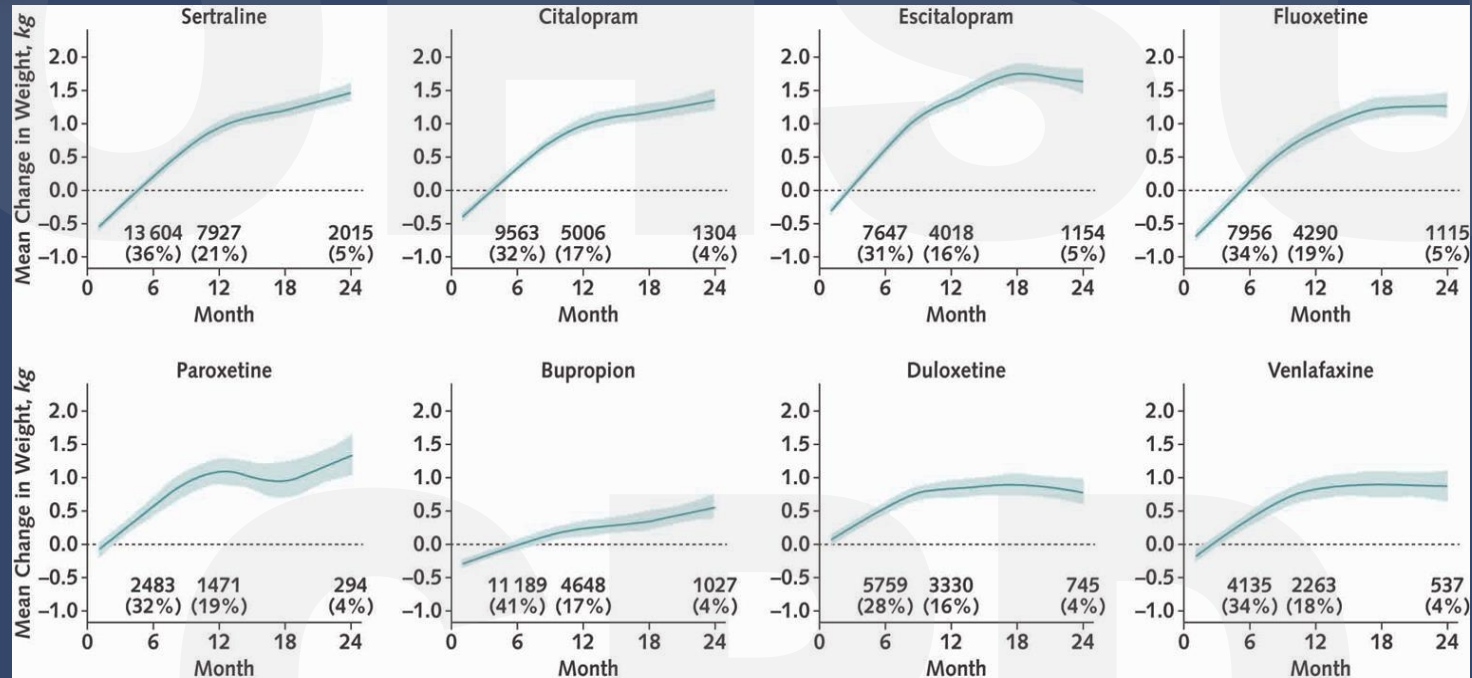


# Only Some Obesity Associated with Higher Rates of Depression?

- NHANES data ('88-'94) showed being overweight or even mildly obese is not associated with substantially increased rate of depression, it is the severely obese (BMI  $\geq 40$ ) who suffer markedly higher rates.
- One might argue that the data suggest that there is little need to worry about mild obesity and depression. I think this misses the dynamics of obesity. No one is born at BMI  $\geq 40$ . You get there through a developmental process that includes a point when you have BMI = 35.



# Associations of Antidepressant Treatment Initiation with Weight Change over 24 Months



- Observational cohort study including >180,000 patients aged 20-80 years, which examined the association between first-line antidepressant treatments and weight changes over time
- Funded by National Institutes of Health and published in the Annals of Internal Medicine on July 2, 2024.

# TLC in the Depressed Patient

## Think 4Fs: Food, Feet, Fingers, Fall Asleep

**Food:** Diet (500-1000 kcal/d energy deficit,  $\approx$ 1–2 lbs/wk weight loss)  
- think one bag of gummy bears!

**Feet:** Think physical activity (not exercise)

**Fingers:** Smoking/Behavior modification has a complicated relationship with weight but we know it increases depression

**Fall Asleep:** Sleep hygiene and treatment discussion

# Feet Pearls

Copyright 2003 by Randy Glasbergen.  
www.glasbergen.com



**“What fits your busy schedule better, exercising one hour a day or being dead 24 hours a day?”**

- Adults should accumulate at least 30 minutes of moderate-intensity physical activity (not necessarily exercise) each day
- This is equivalent to walking about 1.5 miles at a pace of 3-4 mph
- Doing more exercise and perhaps more strenuous exercise may provide additional health benefits

Statement endorsed by American College of Sports Medicine/Centers for Disease Control and Prevention, American Heart Association, NIH, the Surgeon General, and US Dietary Guidelines since 2005.



## TLC: Exercise Equivalent to Pharmacotherapy

- SMILE study: 16 weeks of aerobic exercise training was comparable to that of standard pharmacotherapy (sertraline) and combined exercise/meds

- Blumenthal JA et al. *Arch Intern Med* 1999;159:2459-56.

- 10 Month Continuation study: Remitted subjects in the exercise group had significantly lower relapse rates than subjects in the medication group.

- Babyak M, Blumenthal JA et al. *Psychosom Med* 2000;62:633-38.

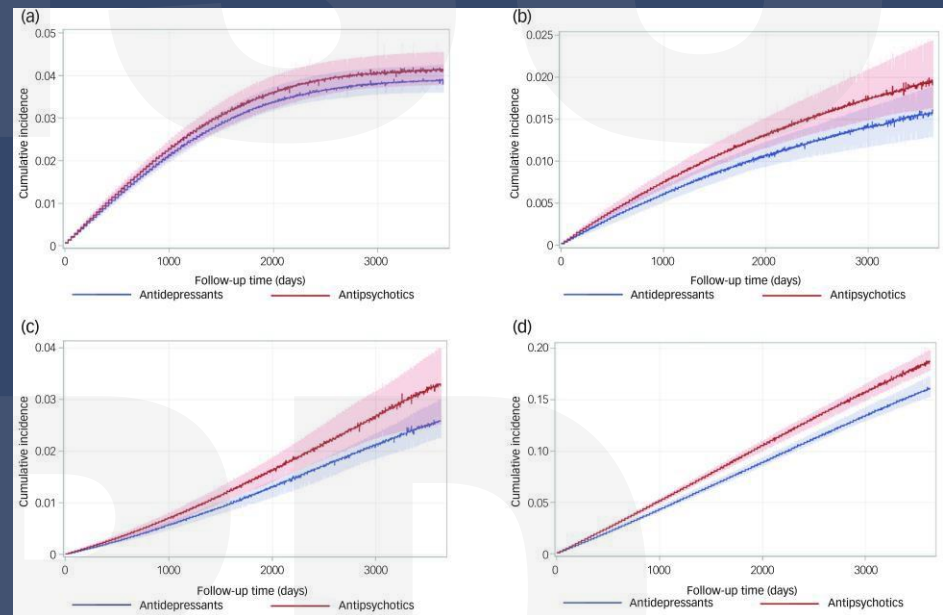


# SGAs FDA-approved for Augmentation in MDD

- Aripiprazole – 2007
- Olanzapine-Fluoxetine – 2009 (TRD)
- Quetiapine ER - 2009
- Brexpiprazole – 2022
- Cariprazine – 2022
- Lumateperone - 2025

Suicide attempt

Suicide death



Cardiovascular death

All-cause mortality

Tsai DH-T, Yang AS-H, Wong Z-X, et al. Antipsychotic therapy and suicide risk in patients with treatment-resistant depression: target trial emulation framework study. The British Journal of Psychiatry. Published online 2025:1-9

**So, you're telling  
me several  
negative things  
about  
antidepressants.  
Anything else?**



# A Final Word on Tolerability



Created 2/15/26 using ChatGPT

## A Final Word on Tolerability

- Mr. T is a 38-year-old male who has been doing very well on sertraline 150mg daily you started for anxious depression. However, he tells you that his libido is lower and causing marital distress.
- He had the same situation a few years ago when taking fluoxetine 40mg daily. At that time, bupropion XL 150mg daily was added to the fluoxetine to mitigate the symptoms but he got too jittery and restless on it.
- What would you recommend he do now?

# Drug Holidays for non-fluoxetine SSRI-ASD?

- 8 Week open label RCT in Iran among married men (n=50) found potential for weekend drug holidays.
  - Previous psychiatric diagnosis: Depressive disorders 13 (52%) in intervention vs 6 (24%) in control, Anxiety disorders 10 (40%) vs 12 (48%), and Obsessive-compulsive and related disorders 2 (8%) vs 7 (28%)
- Alipour-Kivi et al. BMC Psychiatry (2024) 24:67.



Fig. 3 MSHQ erection score changes of the participants during the course of trial. \*significant difference between the two groups

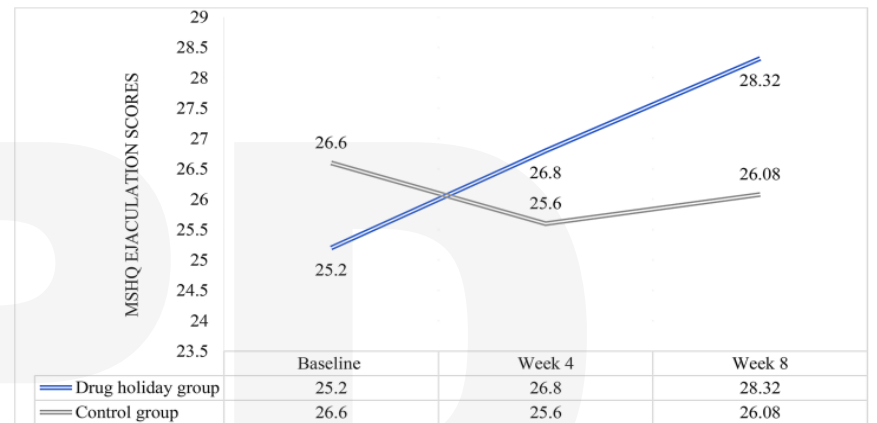


Fig. 4 MSHQ ejaculation score changes of the participants during the course of trial

# Other Ways to Combat SSRI-ASD

- 1. The “wait-and-see” approach - a spontaneous resolution of sexual dysfunction may occur in 6–12% of cases, with a marked or moderate improvement within 4–6 months. However, it may lead to non-adherence due to the significant required time.
- 2. Dose reduction - may be considered if the underlying psychiatric disorder is well-controlled, as it carries the risk of symptom relapse.
- 3. Delaying the dose until after sexual activity - may be effective for patients on antidepressants with short half-lives. However, planned sexual intercourse can cause stress and interfere with sexual performance and satisfaction.\*
- 4. Switching to a different medication - often preferred over adjunctive therapies as it improves adherence, reduces side effects and drug interactions, and decreases costs for the patient, e.g., mirtazapine and vortioxetine appear to have a lower risk of sexual dysfunction compared to SSRIs and SNRIs.
- 5. Adjuvant therapy - bupropion, buspirone, VML-670, granisetron, nefazodone, bethanechol, maca root, ginkgo biloba, and yohimbine have studies. However, this approach requires careful follow-up and monitoring of drug interactions and side effects. **Overall, the most promising adjuvant therapy has been adding bupropion at higher doses (150 mg twice daily).**

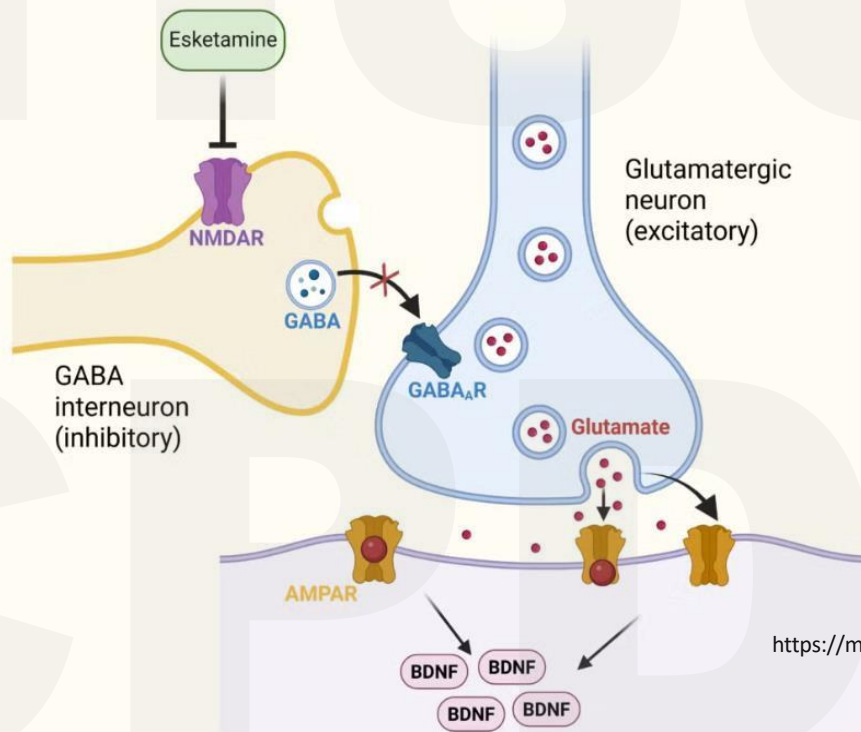
# Final Word: Augment vs Switch?

- 10 week randomly assigned study in patients older than 60:
  - 211 aripiprazole augmentation (remission 28.9%, wellbeing 4.83 point improvement)
  - 206 bupropion augmentation (remission 28.2%, 4.33 point improvement)
  - 202 switch to bupropion (remission 19.3%, 2.04 point improvement)
- The wellbeing difference between the aripiprazole-augmentation group and the switch-to-bupropion group was 2.79 points (P=0.014)
- Secondary study: augmentation with Li+ or switch to nortriptyline (similar remission rates)

• Lenze EJ et al. *N Engl J Med* 2023; 388:1067-1079

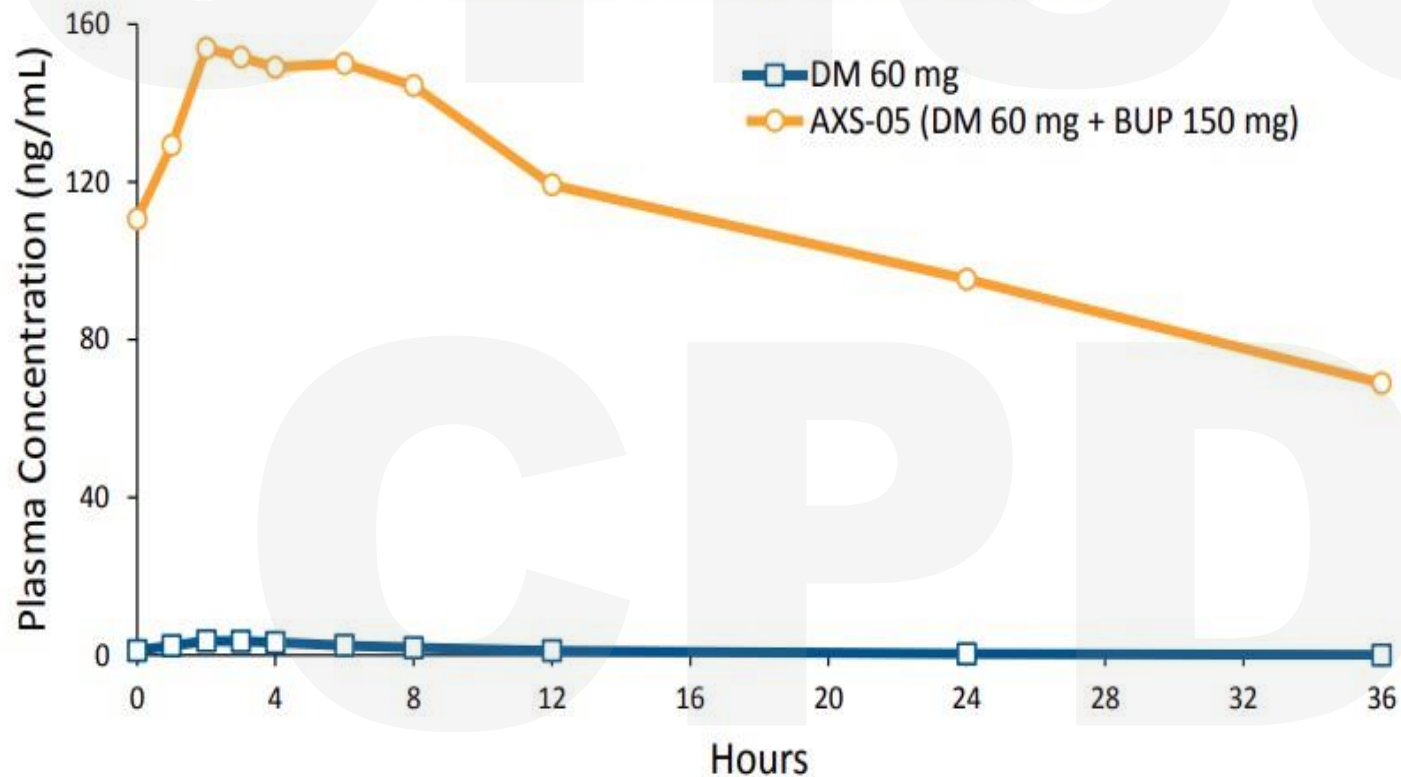
# Newer Glutamatergic Pathway: Esketamine (and Dextromethorphan)

1. Esketamine binds to NMDA receptors on GABA interneuron
2. GABA inhibition is reduced
3. Nearby glutamatergic neurons are disinhibited, causing a temporary increase in glutamate release
4. Increase in postsynaptic AMPA receptor activation
5. Downstream postsynaptic signaling cascade causes an increase in BDNF and synaptogenesis



# Oral NMDA Antagonist: Dextromethorphan- Bupropion (AXS-05)

DM Plasma Concentrations over Time  
with AXS-05 and DM on Day 8



# Esketamine for TRD and MDSI



- Phase 3 double-blind, active-controlled study in non-responders to 2 prior antidepressants
- 227 adults randomized (1:1) to flexibly dosed intranasal esketamine (56 or 84 mg twice weekly) and a new oral antidepressant or intranasal placebo and a new oral antidepressant
- Result: More than half of the esketamine-treated TRD patients achieved remission by the 4-week endpoint. Common AEs – dysgeusia, nausea, vertigo dizziness (>2-fold higher than placebo)

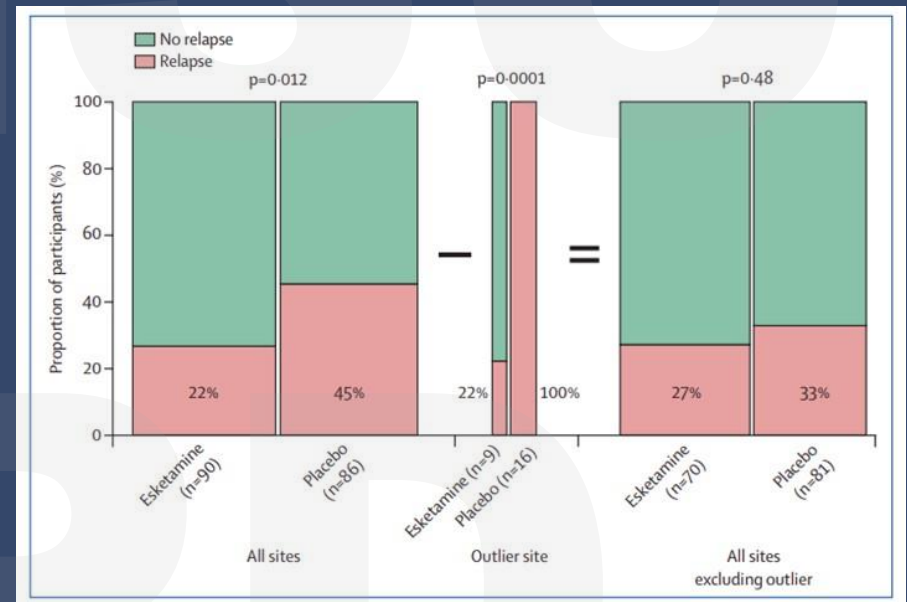
• Popova V, Daly E, Trivedi M, et al. Efficacy and safety of flexibly dosed esketamine nasal spray combined with a newly initiated oral antidepressant in treatment-resistant depression: a randomized double-blind active- controlled study. *Am J Psychiatry*. 2019;176(6):428-438.

# Criticism of Esketamine

- 49 of 227 in the only successful efficacy trial had failed just one class of oral antidepressants. “They weeded out the true treatment-resistant patients”

Erick Turner. Esketamine for treatment-resistant depression: seven concerns about efficacy and FDA approval. *Lancet Psychiatry* 2019 Dec;6(12):977-979

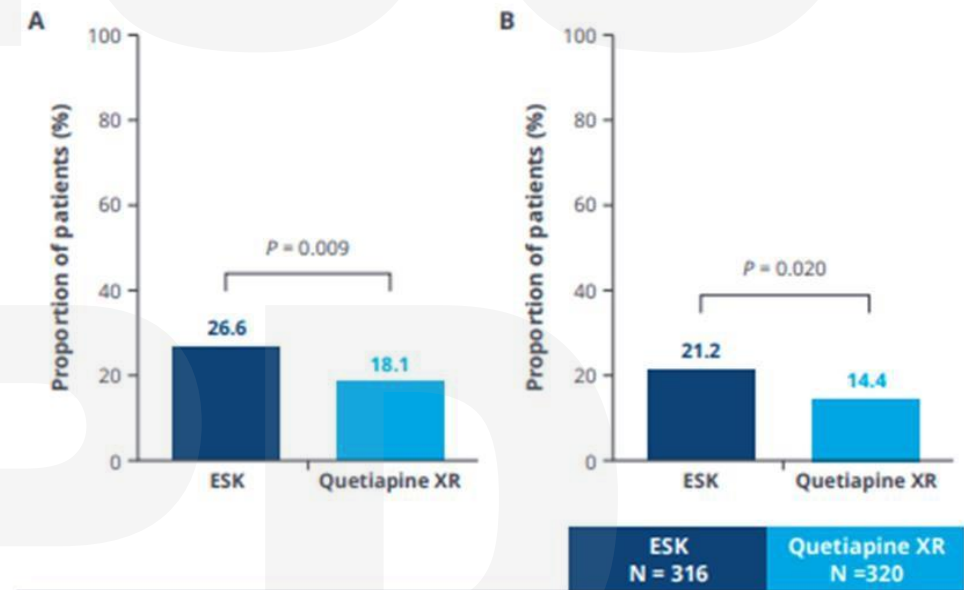
- Three patients died by suicide during clinical trials, compared with none in the control group; but since 2020 is also approved for MDSI



# ESCAPE-TRD Study

- Esketamine Nasal Spray Versus Quetiapine Extended Release in Patients With Treatment-Resistant Depression showed merit of esketamine vs an active comparator (also FDA-approved for augmentation in MDD)

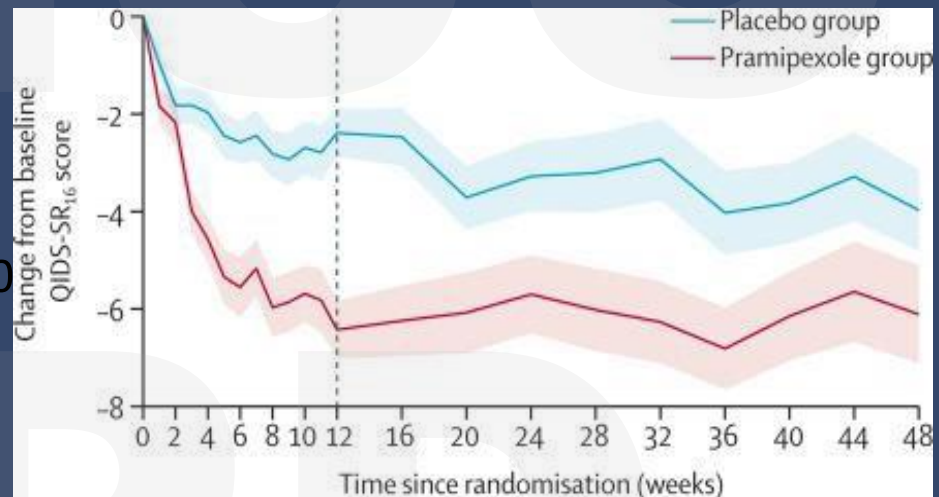
Figure 2. Proportion of patients (A) who achieved remission at week 8 and (B) remained relapse-free through week 32 after remission at week 8 without treatment discontinuation





## Dopamine Agonism: Pramipexole?

- 48 week RCT of pramipexole titrated to 2.5 mg in TRD (n = 151)
- Adjusted mean decrease from baseline to week 12 of the QIDS-SR<sub>16</sub> total score was 6.4 (SD 4.9) for the pramipexole group and 2.4 (4.0) for the placebo group; the mean difference between groups was -3.91 (95% CI -5.37 to -2.45; p<0.0001).



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 *The Lancet Psychiatry*, Volume 0, Issue 0. Published June 29, 2025.



# New Spin on an Older Med: Mirtazapine

## JAMA Psychiatry

### RCT: Mirtazapine for Methamphetamine Use Disorder

#### POPULATION

213 Male, 126 Female



Adults with moderate to severe methamphetamine use disorder  
**Mean (SD) age, 42.0 (8.6) y**

#### SETTINGS / LOCATIONS



**6 Outpatient clinics in Australia**

#### INTERVENTION

344 Participants randomized



**172 Mirtazapine**  
Mirtazapine, 30 mg/d for 12 wk



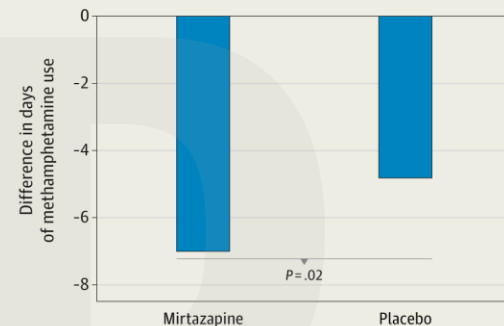
**172 Placebo**  
Matched placebo

#### PRIMARY OUTCOME

Change in self-reported days of methamphetamine use in the past 28 d from baseline to week 12 (possible range, 0-28 d of the past 28 d). Self-reported days of methamphetamine use was assessed at baseline and wk 4, 8, and 12.

#### FINDINGS

The mirtazapine group had a greater reduction in days of methamphetamine use in the past 28 d from baseline to wk 12 than the placebo group



#### Difference in days of methamphetamine use:

**Mirtazapine group:** -7.0 d; 95% CI, -8.5 to -5.6

**Placebo group:** -4.8 d; 95% CI, -6.3 to -3.4

**Mean group difference:** -2.2 d; 95% CI, -4.2 to -0.2;  $P = .02$

# Antidepressants and Abnormal Bleeding



- A recent meta-analysis (20 studies) provided evidence that the studied antidepressants are associated with 31% (paroxetine) to 50% (venlafaxine) increase in the risk of GIB.

» *Br J Clin Pharmacol*. 2025 Dec 29;92(3):793–808.

- “While we observe no differences across these antidepressants (SSRI: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline; and SNRIs: desvenlafaxine, venlafaxine, and duloxetine), clinicians may wish to consider initially prescribing medications with the lower risk of GIB, all other factors being equal.”

# What About the Psychedelics?



# Psilocybin

## (A new take on an old way to use 5HT2A Agonism)

- Small phase 2 trial over 6 weeks (n = 59).
- Psilocybin **25 mg** twice 3 weeks apart vs 1 mg + escitalopram 10mg in depression.
- Outcome: QIDS score non-inferior to the SSRIs
  - NEJM 2021;384:1402-1411.
- Larger phase 2 trial (n=233) in TRD.
- Psilocybin high dose **25mg** vs intermediate dose 10mg vs placebo 1mg.
- 37% response rate for 25mg group at wk 3.
- Still awaiting larger trials head-to-head with SSRI therapy but hard to do given hallucinogenic effect.

– NEJM 2022;387:1637-48.

# Phase 3 Trials: Psilocybin-assisted psychotherapy

## Usona Institute (Madison, WI)

- uAspire trial (March 2024) evaluating the efficacy and safety of psilocybin 25 mg for MDD administered with psychosocial support. Following an initial 6-week randomized, double-blind treatment period, pts will be monitored for one year to assess durability and long-term safety. [ClinicalTrials.gov Identifier: NCT06308653](https://clinicaltrials.gov/ct2/show/study/NCT06308653)

## Compass (UK)

- Phase 3 COMP 005 and COMP 006 form the largest RCT psilocybin treatment clinical program ever conducted and follows promising results from the phase 2b study of COMP360 psilocybin treatment. COMP 006 will take place in the UK and globally and will study three dose arms of COMP360 (25mg, 10mg and 1mg). COMP 005 is a US-based trial examining the effect of a single 25mg dose of COMP360 psilocybin, compared with placebo.
- COMP360 given as a single dose along with psychological support from a licensed professional is also being studied in PTSD.

# Press Release April 24, 2026: COMP360

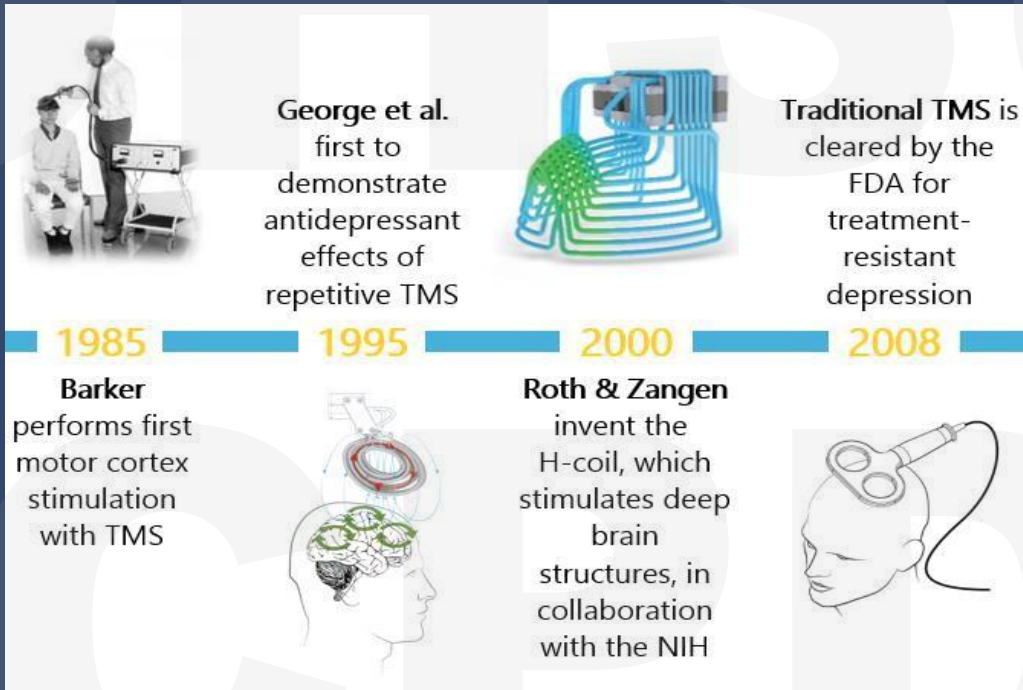
- **Compass Pathways Announces FDA Granted NDA Rolling Review Request and Awarded Commissioner's National Priority Voucher**
- A single administration of COMP360 demonstrated a highly statistically significant and clinically meaningful reduction in symptom severity as measured by MADRS1 with a **mean difference of -3.6** comparing 25 mg to placebo ( $p < 0.001$ )
- Ongoing pivotal Phase 3 COMP005 trial is the first study of an investigational, synthetic psilocybin, and the first classic psychedelic, to report Phase 3 efficacy data
- Second ongoing pivotal Phase 3 COMP006 trial continues to enroll well, with 26-week data expected in the second half of 2026

# MDMA-assisted Therapy for PTSD

- MDMA for PTSD on June 12, 2024: the nine-hour hearing concluded with committee members voting 9-2 that the available data **do not show** "that the drug (midomafetamine) is effective" for PTSD, and voting 10-1 that the benefits of MDMA do not outweigh the risks. August 11, 2024 final vote.



# A Brief TMS History

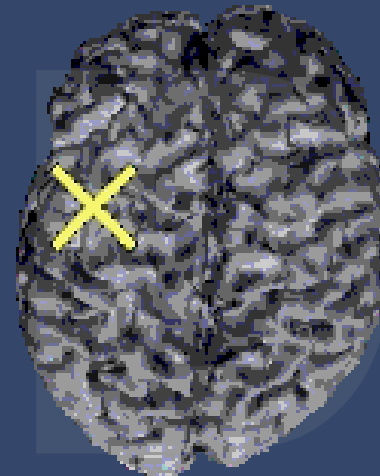


*Lancet*. 1985 May 11;1(8437):1106-7

Slide adapted from BrainsWay

# A Final Word on TMS

- FDA cleared (2008) for TRD (and now OCD, anxious depression, smoking cessation – some devices neuropathic pain)
- Durability studies (Dunner et al) showing response rate of 67.7% and remission rate of 45.1% at one year
- SAINT gets all the press high-dose, iTBS protocol with fcMRI-guided targeting (86.4% remission) but more to come...
- Traditional TMS Covered by most insurance!
- Minimal adverse effects
- Approval age lowered to 15



# Reminders Before Treating “Depression”

- Nearly **74%** of people seeking help for depression are treated by their primary care physician
- **60%** of people with bipolar disorder are in the depressed phase when they go to their primary care physician for help
- Up to **30%** of primary care patients treated for depression and/or anxiety actually have bipolar disorder

# Teasing Bipolar from Unipolar Depression

## 5 Differentiating Features of Bipolar Depression



Ask about APA 5 differentiating features of bipolar depression:

- Response to antidepressant therapy may have included:
  - Erratic or uneven response
  - Treatment-emergent mania
  - Multiple antidepressant failures or “misadventures”
- Abrupt onset and termination of depressive episodes
- Family history of mood disorders
- Age of onset is typically <25, with episodic presentation
- Past manic episode

The American Psychiatric Association (APA) recommends that every patient with symptoms of depression be screened for bipolar disorder.

APA. *Am J Psychiatry*. 2002;159(4 suppl):1-50.

# Bipolar Screening: MDQ (RMS is Alternative)

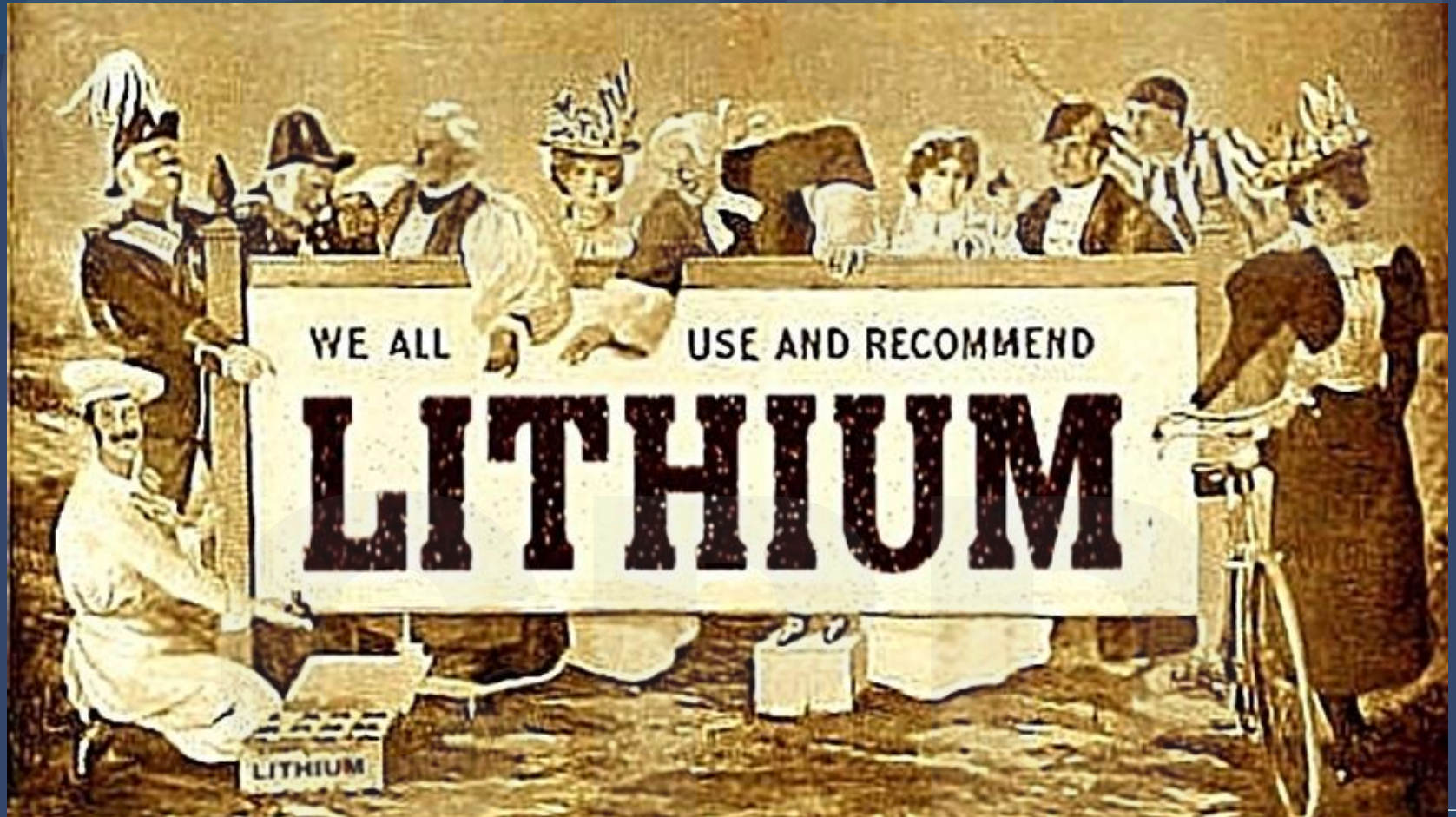
- Mood Disorders Questionnaire (MDQ)

Self-reported validated instrument where affirmative answers to 7 of 13 main “criteria” questions and 2 other timing and spectrum of severity questions constitutes a positive screen for “bipolar illness” (bipolar I, II, and NOS)

– Hirschfeld RM et al. *Am J Psychiatry*. 2000;157(11):1873-5.

MOOD DISORDER QUESTIONNAIRE (MDQ)			
INSTRUCTIONS: Please answer each question as best you can.		Yes	No
<b>1</b>	Has there ever been a period of time when you were not your usual self and ...		
	–you felt so good or so hyper that other people thought you were not your normal self or you were so hyper that you got into trouble?		
	–you were so irritable that you shouted at people or started fights or arguments?		
	–you felt much more self-confident than usual?		
	–you got much less sleep than usual and found that you didn't really miss it?		
	–you were more talkative or spoke much faster than usual?		
	–thoughts raced through your head or you couldn't slow your mind down?		
	–you were so easily distracted by things around you that you had trouble concentrating or staying on track?		
	–you had much more energy than usual?		
	–you were much more active or did many more things than usual?		
	–you were much more social or outgoing than usual, for example, you telephoned friends in the middle of the night?		
	–you were much more interested in sex than usual?		
	–you did things that were unusual for you or that other people might have thought were excessive, foolish, or risky?		
	–spending money got you or your family in trouble?		
<b>2</b>	If you checked YES to more than one of the above, have several of these ever happened during the same period of time?		
<b>3</b>	How much of a problem did any of these cause you-like being unable to work, having family, money or legal trouble, getting into arguments or fights? <input type="checkbox"/> No problem <input type="checkbox"/> Minor problem <input type="checkbox"/> Moderate problem <input type="checkbox"/> Serious problem		

# Lithium in Depression?



# Lithium Carbonate Concerns



myoclonic jerks, seizures

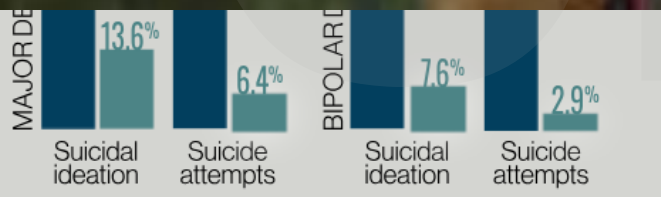
- Kidney: deteriorating kidney function



# Lithium: Suicide/Harm Reducer

## Key Outcomes Before & After Lithium Treatment

Clinical recurrence



- Pompili M, et al. Acta Psychiatr Scand. 2025 Oct;152(4):290-298.

# New Form of Lithium: AL001

- Low-dose (2.25 mmol lithium/kg/day) novel ionic cocrystal of lithium salicylate proline (LISPRO aka AL001), lithium carbonate (LC), and lithium salicylate (LS) treatment prevent spatial cognitive decline and depression-like behavior, while LISPRO prevented hippocampal-dependent associative memory decline and irritability in APP<sup>swe</sup>/PS1<sup>dE9</sup> mice treated over 9 months.

» *J of Neuroscience Research* 2019; Vol 97(9):1066-1080.

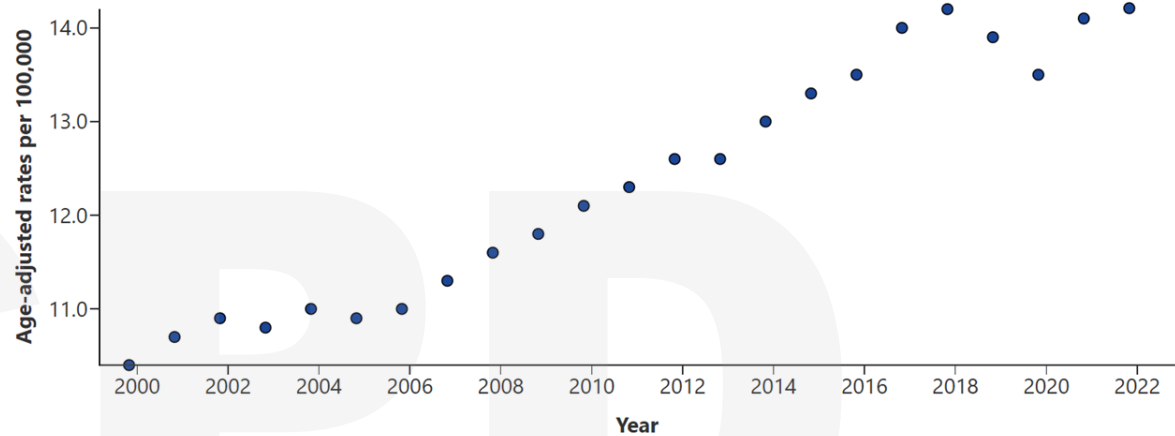
- Press Release from May 19, 2025 (first patients enrolled in Phase II studies): “In collaboration with Massachusetts General Hospital as its clinical trial site, Alzamend aims to explore the unique properties of AL001 and its potential to deliver lithium more effectively in the brain compared to marketed lithium salts...potentially eliminating the need for lithium therapeutic drug monitoring (“TDM”)”

# When a Patient Mentions Suicide (Question 9 is Positive on the PHQ-9)



## Suicide rates

Suicide rates increased 37% between 2000-2018 and decreased 5% between 2018-2020. However, rates returned to their peak in 2022.



# Systematic Suicide Assessment

- Ask gently if suicidal thoughts are still active (review protective factors too) – if **no** then:
  - **Assess for delirium**

# Screening for Delirium

## Several Tests Extrapolated from Dementia Screens

- Mini-Cog: 3 item recall + clockface (less than 3/4 = impaired)
- Six-item Screener (4 = impaired)
  - What year is this?
  - What month is this?
  - What day of the week is this?
  - Three item recall (1 minute) Apple Table Penny
    - Higher sensitivity (94%) than Mini-Cog (75%)

» Wilber ST et al. *Acad Emerg Med* Volume 12, Issue7 612-616

# MOTYB (or MBT)

## Attention! A good bedside test for delirium?

Niamh A O'Regan,<sup>1</sup> Daniel J Ryan,<sup>1</sup> Eve Boland,<sup>2</sup> Warren Connolly,<sup>2</sup> Ciara McGlade,<sup>1</sup> Maeve Leonard,<sup>3</sup> Josie Clare,<sup>4</sup> Joseph A Eustace,<sup>5</sup> David Meagher,<sup>6,7</sup> Suzanne Timmons<sup>1</sup>

### ABSTRACT

**Background** Routine delirium screening could improve delirium detection, but it remains unclear as to which screening tool is most suitable. We tested the diagnostic accuracy of the following screening methods (either individually or in combination) in the detection of delirium: MOTYB (months of the year backwards); SSF (Spatial Span Forwards); evidence of subjective or objective 'confusion'.

**Methods** We performed a cross-sectional study of general hospital adult inpatients in a large tertiary referral hospital. Screening tests were performed by junior medical trainees. Subsequently, two independent formal delirium assessments were performed: first, the Confusion Assessment Method (CAM) followed by the Delirium Rating Scale-Revised 98 (DRS-R98). DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, fourth edition) criteria were used to assign delirium diagnosis. Sensitivity and specificity ratios with 95% CIs were calculated for each screening method.

**Results** 265 patients were included. The most precise screening method overall was achieved by simultaneously performing MOTYB and assessing for subjective/objective confusion (sensitivity 93.8%, 95% CI 82.8 to 98.6; specificity 84.7%, 95% CI 79.2 to 89.2). In older patients, MOTYB alone was most accurate, whereas in younger patients, a simultaneous combination of SSF (cut-off 4) with either MOTYB or assessment of subjective/objective confusion was best. In every case, addition of the CAM as a second-line screening step to improve specificity resulted in considerable loss in sensitivity.

**Conclusions** Our results suggest that simple attention tests may be useful in delirium screening. MOTYB used alone was the most accurate screening test in older people.

diagnoses were missed by the referring team.<sup>3</sup> Detection rates are lower in older patients,<sup>4</sup> those with pre-morbid dementia<sup>5</sup> and in hypoactive cases.<sup>6,7</sup> Collins *et al* found recognition rates to be as low as 28% in older medical inpatients<sup>8</sup> and studies in the emergency department (ED) show similar rates of underdetection.<sup>9,10</sup> The reasons for poor recognition are multifactorial. 'Confusion' is commonly considered normal in older patients, who are most at risk. The symptom profile varies greatly from patient to patient, and the prevailing

The increasing use of routine and systematic cognitive testing in clinical environments creates a need for brief and efficient methods for formalised testing. The MBT has many characteristics that make it an attractive option in this regard, both for cognitive screening and for assessing the character of impairment where it is present.

O'Regan NA, Ryan DJ, Boland E, et al. *J Neurol Neurosurg Psychiatry* Published Online First: Feb 25, 2014.

# Systematic Suicide Assessment

- Ask gently if suicidal thoughts are still active (review protective factors too) – if **no** then:
  - Assess for delirium
  - **Assess for psychosis** – for the internist, the standard of care is to simply ask about hallucinations

# Systematic Suicide Assessment

- Ask gently if suicidal thoughts are still active (review protective factors too) – if **no** then:
  - Assess for delirium
  - Assess for psychosis – ask about hallucinations
  - **Assess for mood disorders (i.e. PHQ-2 then PHQ-9)**

# Systematic Suicide Assessment

- Ask gently if suicidal thoughts are still active (review protective factors too) – if **no** then:
  - Assess for delirium
  - Assess for psychosis – ask about hallucinations
  - Assess for mood disorders (i.e. PHQ-2 then PHQ-9)
  - **Quote what the patient plans to do/aftercare plan – offer a suggestion if needed (adding a safety plan is ideal)**

# Systematic Suicide Assessment

- Ask gently if suicidal thoughts are still active (review protective factors too) – if **no** then:
  - Assess for delirium
  - Assess for psychosis – ask about hallucinations
  - Assess for mood disorders (i.e. PHQ-2 then PHQ-9)
  - Quote what the patient plans to do/aftercare plan – offer a suggestion if needed (adding a safety plan is ideal)
  - **Collateral from a third party**

# Summary Statement

- Patient says that she is no longer feeling suicidal. There is no evidence of delirium or psychotic features. She acknowledges her family problems and says that counseling makes sense. She has agreed to a follow-up appointment at the mental health center tomorrow and plans to call her employer today to say she will be back at work next week. She has discussed these plans with her husband who agrees to be seen with her at the initial psychiatric assessment following discharge. Pt no longer needs constant observation.

» Goldberg RJ. The Assessment of Suicide Risk in the General Hospital. *General Hospital Psychiatry* 9;446-52, 1987.

“Fortune Favors the Prepared Mind” – Louis Pasteur

**THANK YOU!**

**TIME FOR QUESTIONS**