My Antidepressant/Anxiolytic Prescriptions Aren't Working: Now What?

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Disclosure Statement:

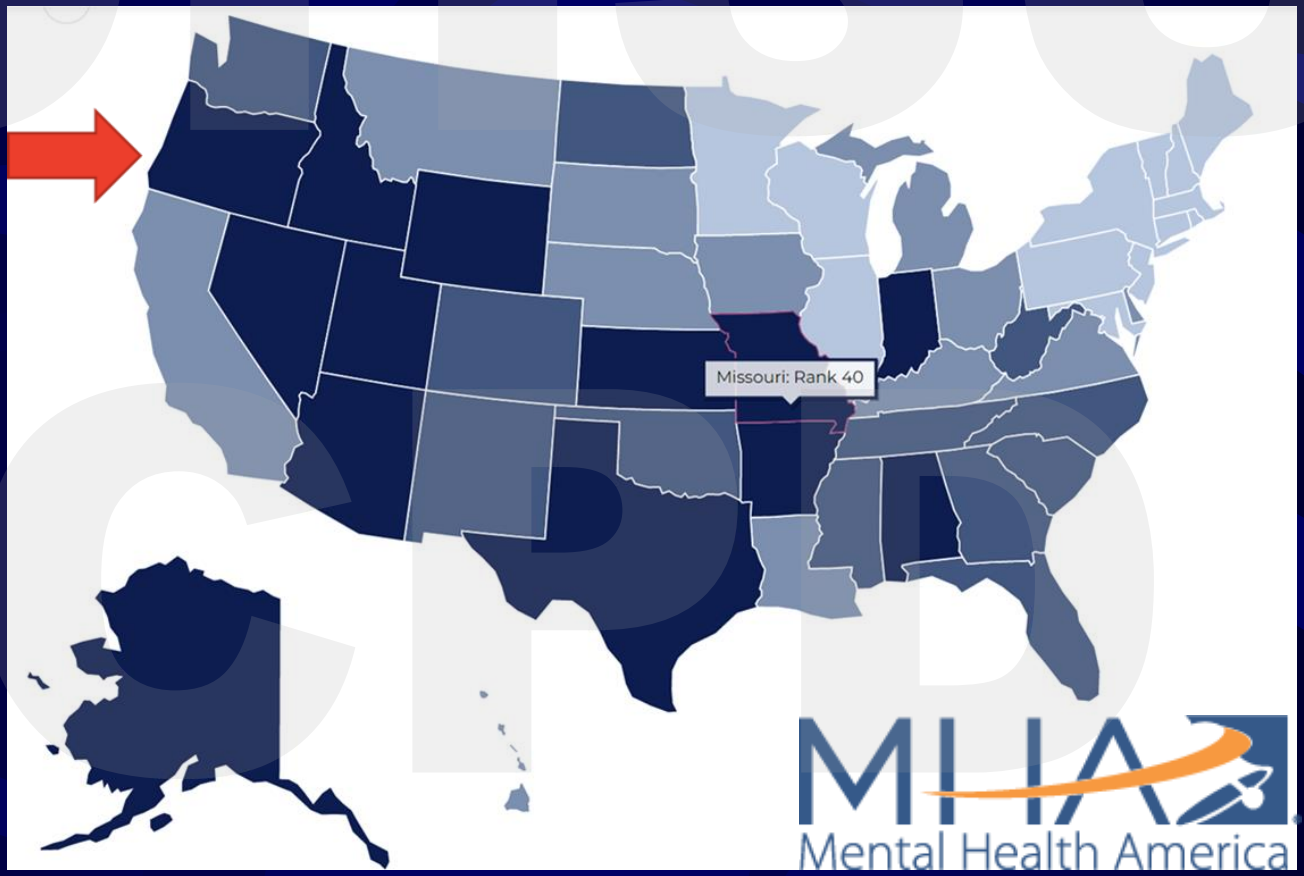
Relevant financial relationships in the past 12 months

- Consultant/S and Horizon CME
- Financial: I a Mental Health – specializing i d esketamine.

Why is a talk on depression and anxiety at the Primary Care Review important?

State of Mental Health Care 2024-25

Oregon: 47th



2 Quick Burnout Prevention Tips

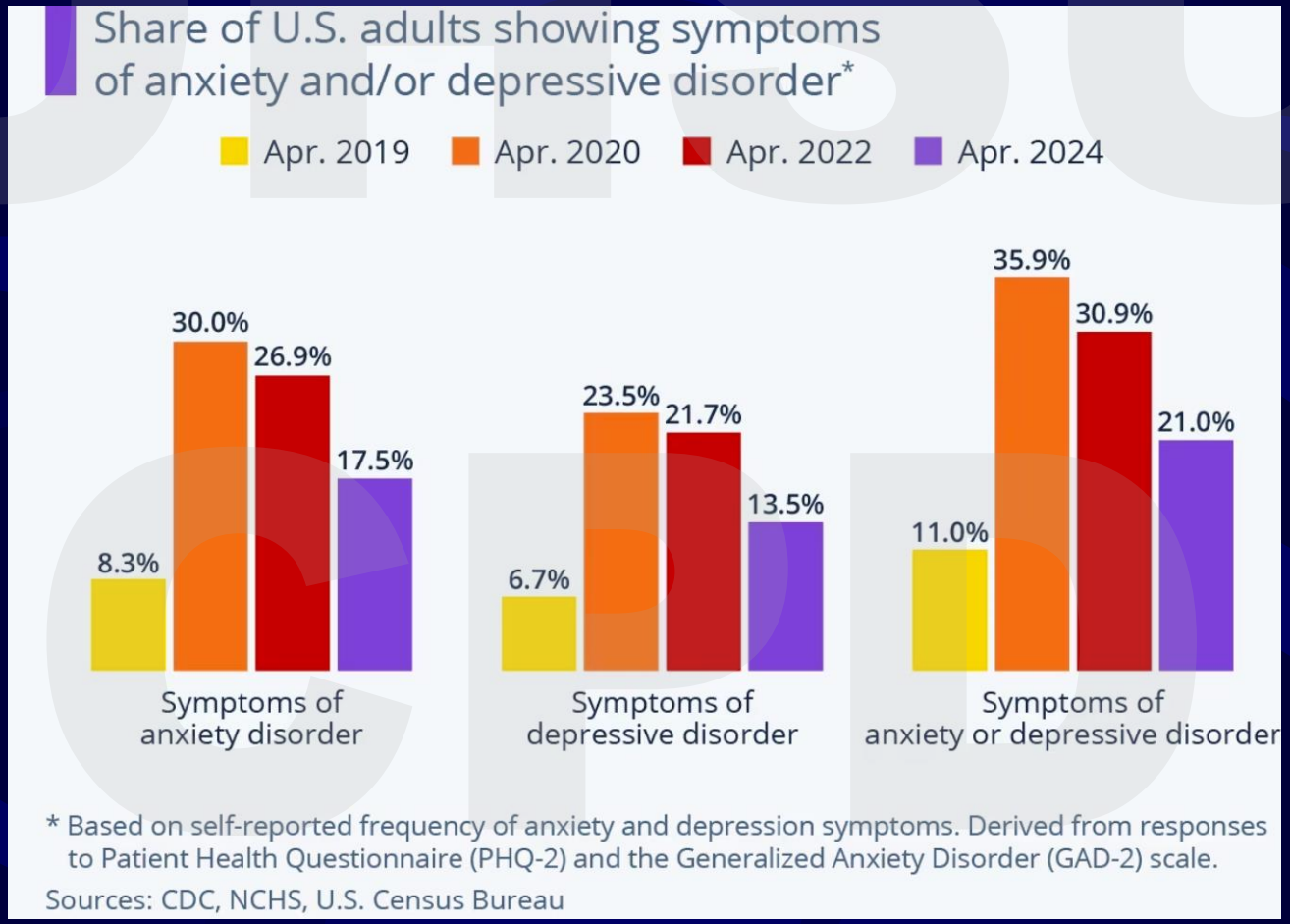
- "Three Good Things" exercise
  - In a trial of 148 IM residents at Duke, a 15% decrease in burnout was seen in 2 weeks and a year after the intervention, 48% remained resilient. 10 days appears to be the sweet spot.
    - » www.dukepatientsafetycenter.com Sexton, B et al.

- Never forget the power of "career fit" – save 10% of your work life for you to do what you are most passionate about.
  - » Shanafelt T. *Arch Intern Med.* 2009;169(10):990-995.

Clinical Case

- Dee Prest is a 61 yo white female with a h/o hypertension, who has been complaining of increased “stress”, poor sleep, worsening mood, and increased anxiety during the pandemic. Her vital signs are normal but she has been gaining weight (7 lbs in the past 6 months) and also reports some suicidal ideation.

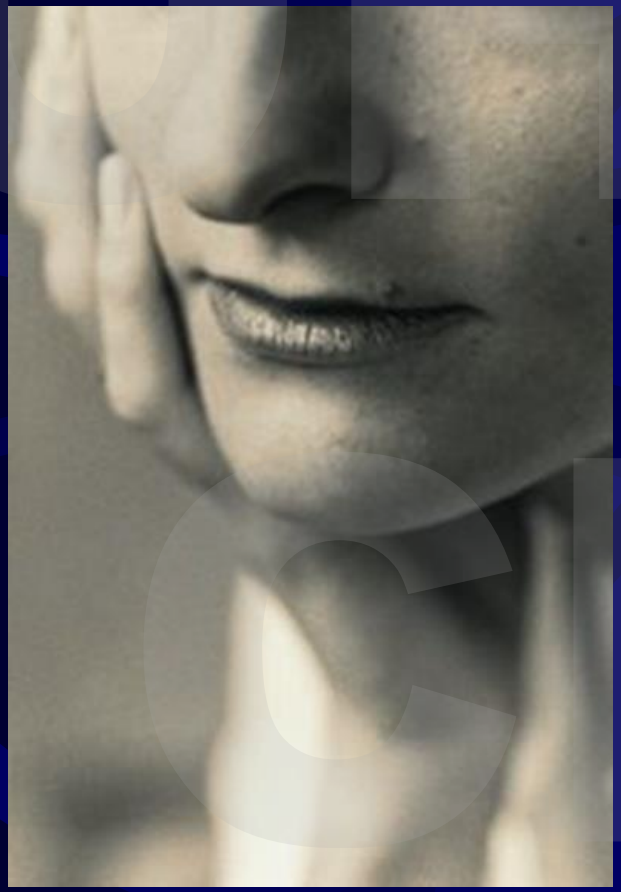
Are Rates of Depression and Anxiety Still Increasing Post-Pandemic?



Clinical Case continued

- 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?

Reminder: Screening For Depression



- 2-Item PRIME-MD Screening
- Have you had little interest or pleasure in doing things? (anhedonia)
- Have you been feeling down, depressed or hopeless over the past month?

Some Options for Consideration

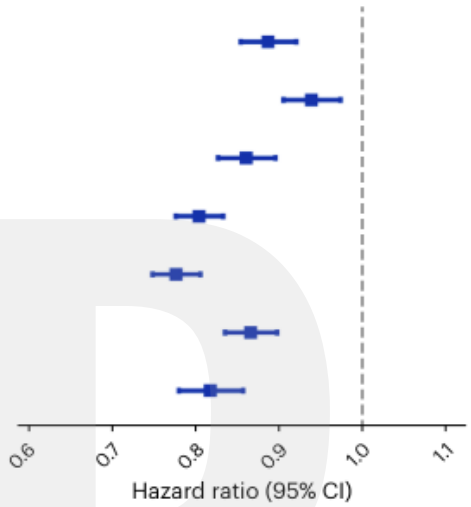
1. Another medication trial
2. A “prescription” for physical activity
3. A referral for cognitive behavioral therapy
4. Mindfulness training
5. Transcranial magnetic stimulation (TMS)
6. Electroconvulsive therapy (ECT)
7. A referral to an Intensive Outpatient Program
8. A prescription for the Rejoyn App

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.

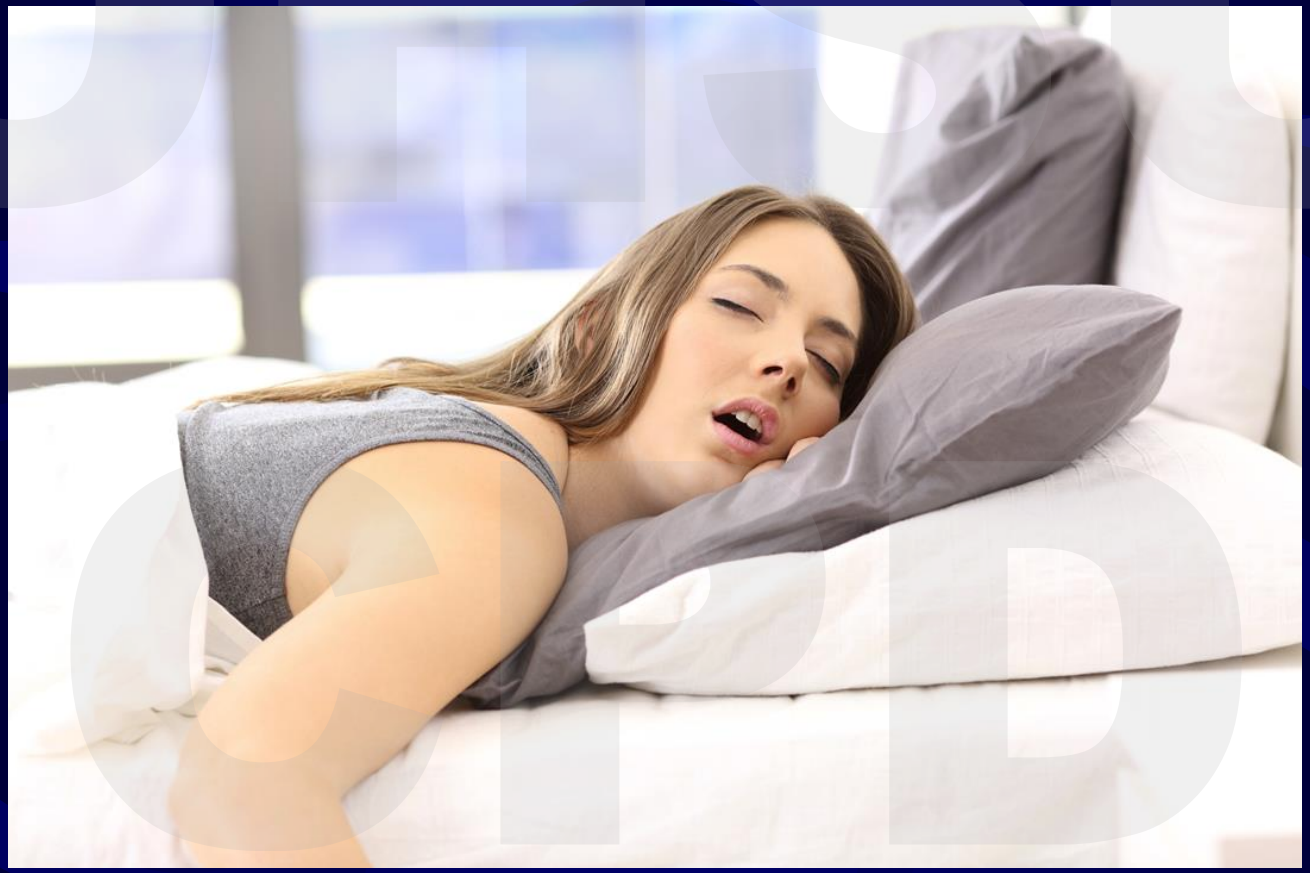
Which Lifestyle Predictors Have Greatest Impact on Depression?

Predictor	No. of cases/total no. of participants	Hazard ratio (95% CI)	*P* value
	Lifestyle factor		
Moderate alcohol consumption	8,678/210,387 (4.12%)	0.89 (0.85–0.92)	3.17×10^{-10}
Healthy diet	7,582/76,783 (4.29%)	0.94 (0.90–0.97)	6.41×10^{-4}
Regular physical activity	9,525/226,303 (4.21%)	0.86 (0.83–0.90)	1.93×10^{-13}
Never smoking	5,898/149,749 (3.94%)	0.80 (0.78–0.83)	1.01×10^{-33}
Healthy sleep	8,521/211,284 (4.03%)	0.78 (0.75–0.81)	2.45×10^{-41}
Low-to-moderate sedentary behavior	5,713/141,190 (4.05%)	0.87 (0.84–0.90)	4.26×10^{-15}
Frequent social connection	10,751/249,493 (4.31%)	0.82 (0.78–0.86)	4.16×10^{-17}



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 Could be 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

What is Treatment Resistant Depression (TRD)?

Treatment Resistant Depression (TRD)

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

An Antidepressant Timeline

Are all antidepressants created equal?

STAR*D

4041 Patients

Citalopram

30% Remission
Higher dose – 41.8mg
Longer duration – 47 days

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

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 8/24/11:

- 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

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4041 Patients

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30% Remission
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Longer duration – 47 days

N Engl J Med 2006;354:1243-52.

565 Non-Remitters Augmented for 12 weeks with:

Bupropion SR

DA + NE reuptake inh.

Max: 400mg
39% Remission

Buspirone

5HT-1A partial agonist

Max: 60mg
32.9% Remission

Cognitive Therapy

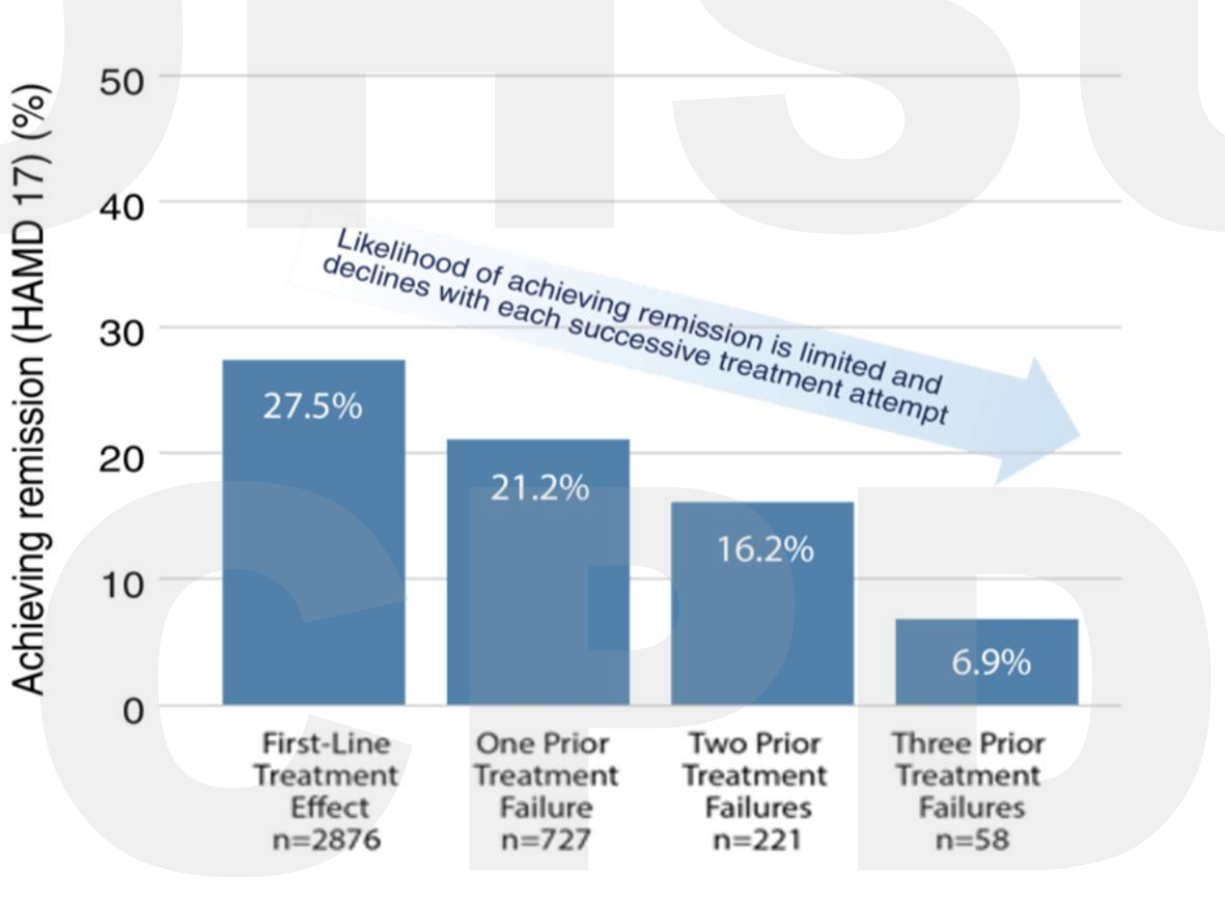
STAR*D says pick a med, any med…

- 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.

STAR*D Trial and TRD



Does Age Impact Antidepressant Response?

A. No
B. Yes, patients younger than 21 do best
C. Yes, patient older than 55 do best
D. Yes, patients between 21-35 do best
E. As Cochrane would say, we don't have enough data to definitively know

Does Age Impact Antidepressant Response?

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D. Yes, patients between 21-35 do best

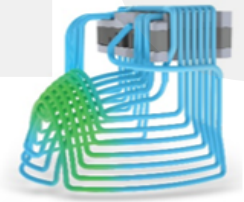
In a recent mega-analysis of 907 pts from large NIH-sponsored trials in individuals with MDD aged 12-74, it was found that those <21 and >55 had slower and less response compared to those between 21-35.

Strawn JR, Mills JA, Suresh V. et al. *J Pscychiatr Res.* 2023 Mar;159:266-273.

Repetitive Transcranial Magnetic Stimulation (rTMS)

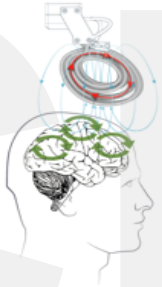
A Brief TMS History

George et al. first to demonstrate antidepressant effects of repetitive TMS



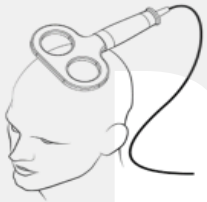
Traditional TMS is cleared by the FDA for treatment-resistant depression

1985 **Barker** performs first motor cortex stimulation with TMS



1995

2000 **Roth & Zangen** invent the H-coil, which stimulates deep brain structures, in collaboration with the NIH



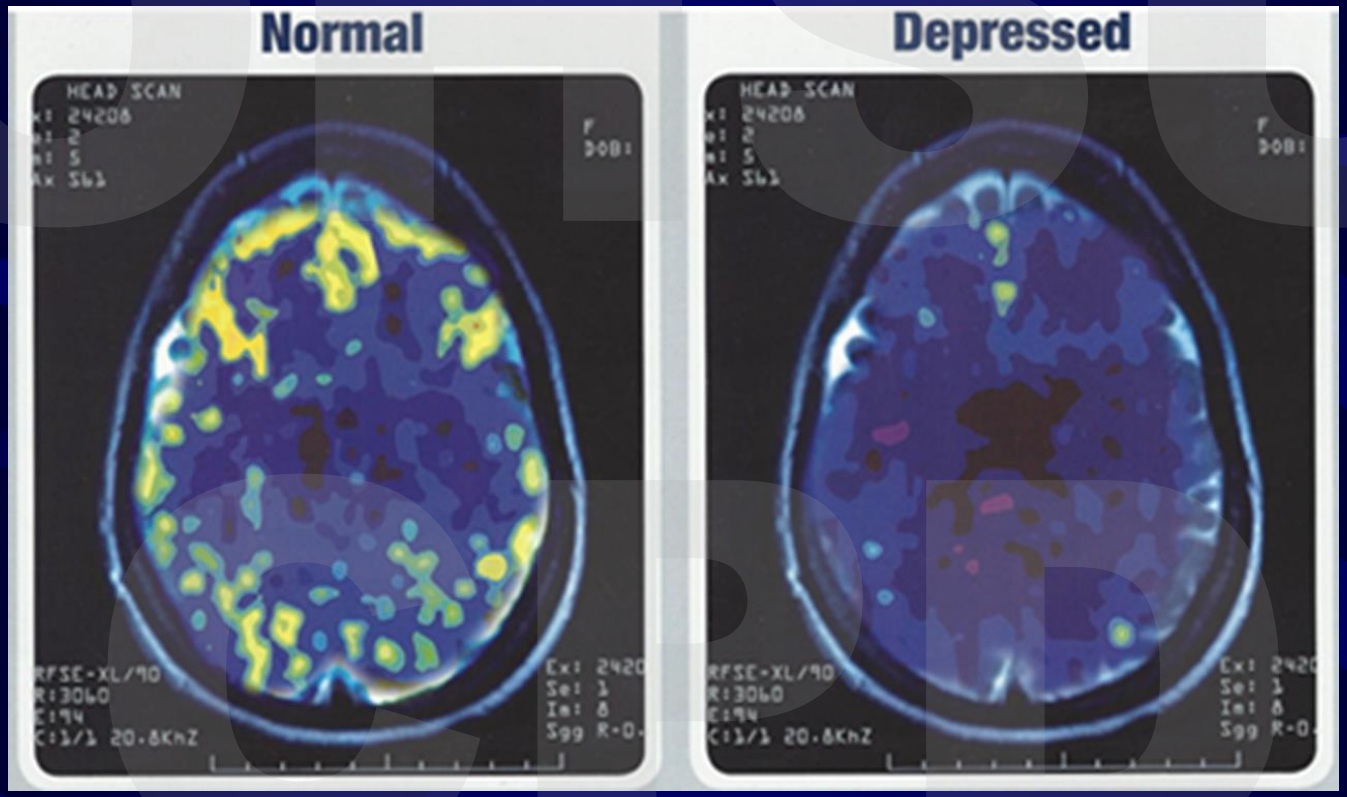
2008

2022 **Raj & Lindberg** DONT H8 study Presented 10th Annual CTMSS Meeting

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

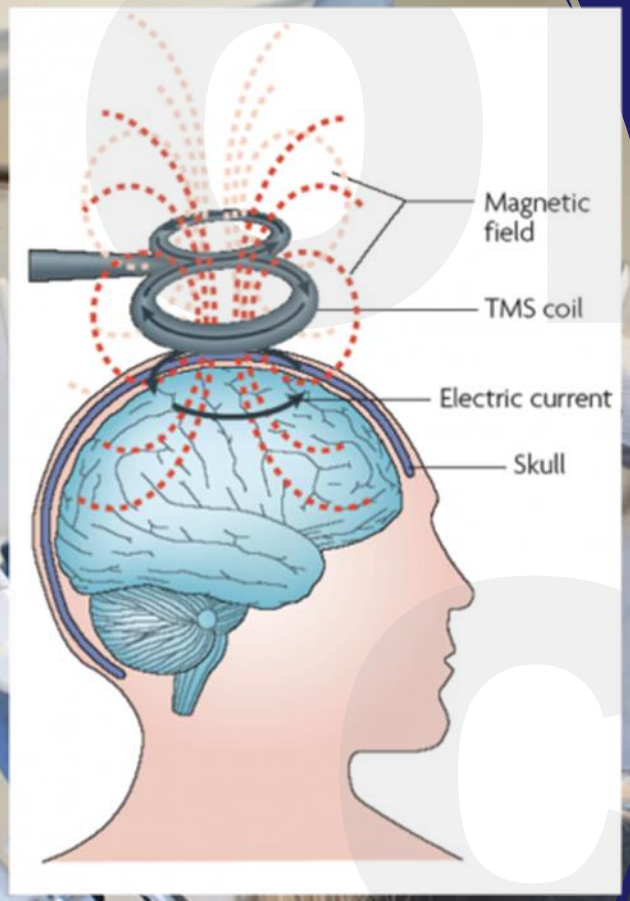
Slide adapted from BrainsWay

Depressed Brains Look Different



Mark S. George, MD. Fluorodeoxyglucose positron emission tomography (PET) images acquired at the National Institute of Mental Health (NIMH, Bethesda, MD), 1994.

How Does TMS Work?



A pulsing magnetic coil induces electrical activity in conductive tissue

The magnet itself is similar to an MRI and the coil induces a magnetic field.

Changing magnetic field induces electrical field in the brain.

Electric field stimulates localized neurons in the brain.

Neuronal stimulation modulates neuronal “firing”, resulting in behavioral effects.

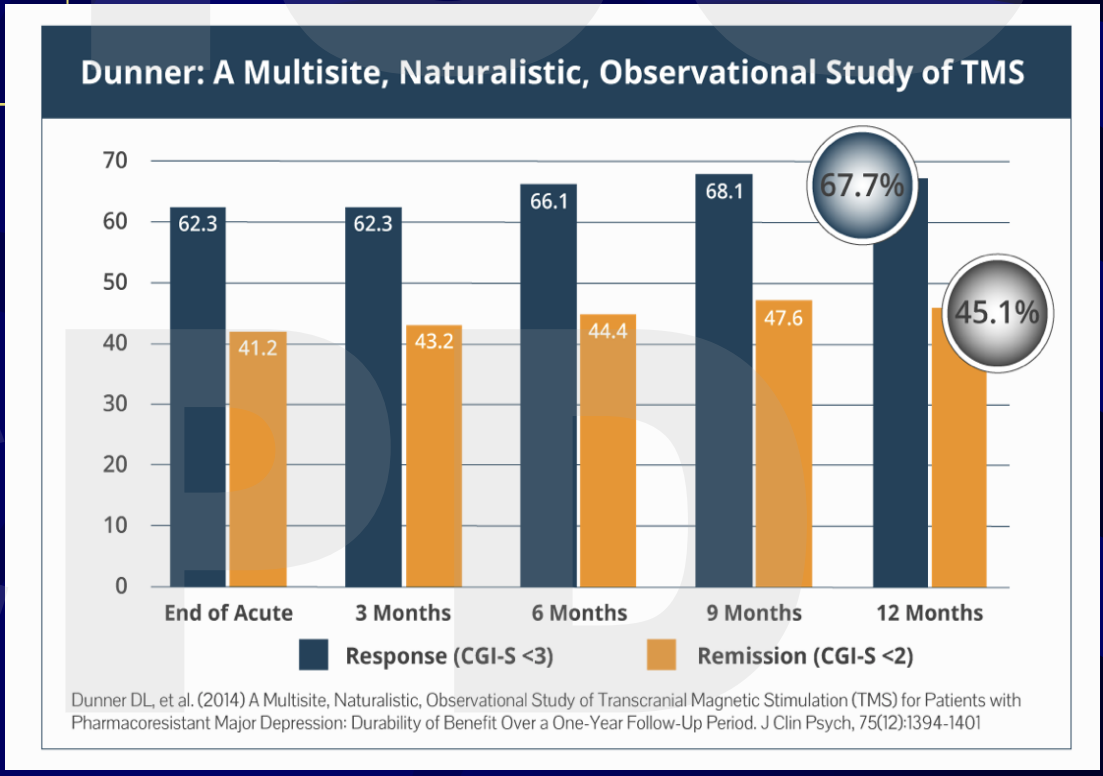
What is the Evidence for TMS in Depression?

Dunner, et al 2014:

67.7% of acute remitters sustained response at one year.

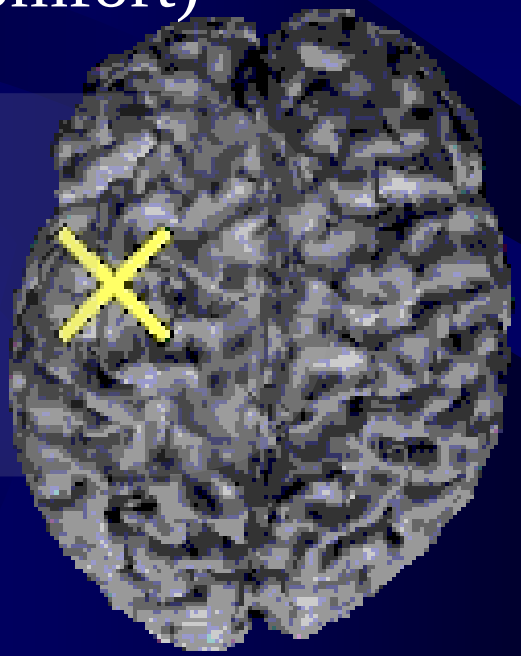
- Responders tended to maintain their gains over the year.

2014



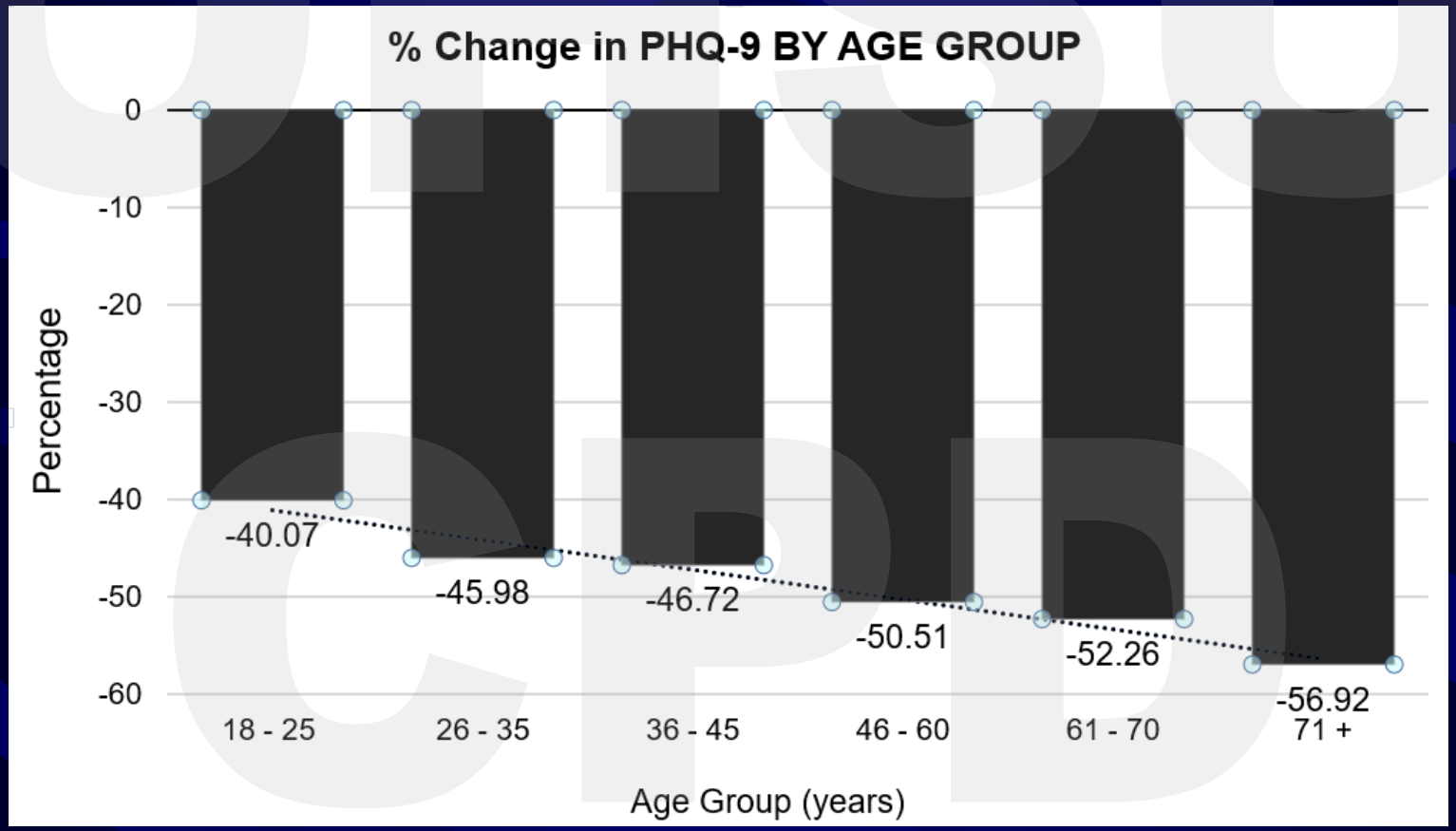
Summary on TMS

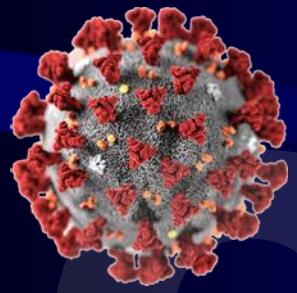
- FDA cleared (2008) for TRD, OCD, anxious depression, smoking cessation
- 20 minute protocol
- Durability studies (Dunner et al) showing response rate of 67.7% and remission rate of 45.1% at one year
- Covered by most insurance!
- Minimal AE: (scalp discomfort)



Does age make a difference for TMS? Didn't you just say patients 21-35 do better with depression treatment?

Trend Towards Improvement by *Ascending* Age





Breakdown by Age

- The mean age of patients treated pre-COVID-19 was 52.42 years compared to a post-COVID-19 mean age of 47.03 years. The 5.39 mean age difference was statistically significant ($p<0.0005$).
- However, patients older than age 60 (n = 186) had statistically significant improvement in PHQ-9 scores (54%) compared to the younger patients (mean range of improvement 40-49%) ($p = 0.01928$).

– Raj YP, Lindberg N. rTMS Outcomes pre- and post-COVID-19: A deeper dive into the Dual Observation Naturalistic TMS study comparing H1 and Figure-8 coil outcomes (DONT H8). 10th Annual Clinical TMS Society Meeting. May, 2022.

Other Neuromodulation Options

- Vagal nerve stimulator (VNS): approved by the FDA in 2005 for TRD. Stimulates the brain via electrical signals from the implanted device.
  - Downside: invasive
- ECT: use of electric current to trigger a brief seizure (30-60 seconds) – boasts a 90% efficacy rate in older studies.
  - Downside: short-term memory impact and requires general anesthesia

“Newer” Pharmacotherapy Options

Vortioxetine (Trintellix)

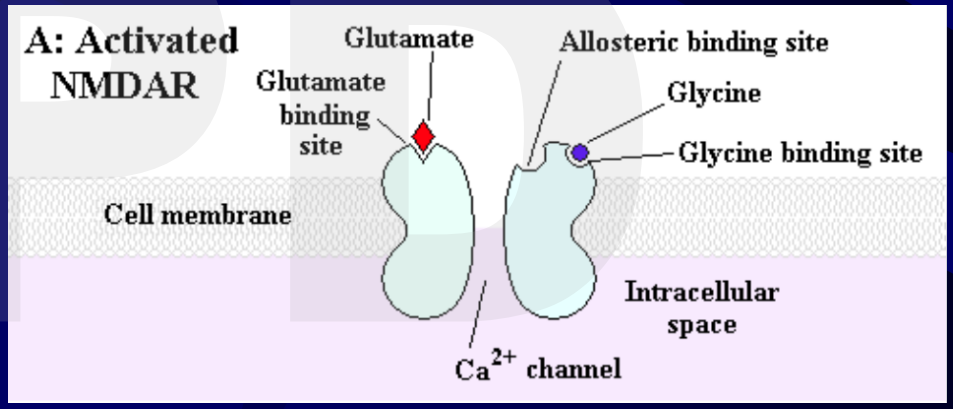
- 2013 - formerly called Brintellix, but renamed to avoid confusion with the blood-thinning medication Brilinta)
- Cognitive enhancement across multiple domains: At Week 1, vortioxetine 10mg/day separated from placebo for attention/speed of processing and Digit Symbol Substitution Test (DSST) number of correct symbols, and for executive function. At Week 8, vortioxetine 10mg/day and 20mg/day separated from placebo for executive function and attention/speed of processing.

  - Harrison JE, Lophaven S, Olsen CK. Which Cognitive Domains are Improved by Treatment with Vortioxetine? Int J Neuropsychopharmacol. 2016 May 26;19(10).

NMDA Antagonist
Esketamine (Spravato) INH

INDUCTION (twice weekly)	MAINTENANCE (once weekly)	(weekly or every 2 weeks)
WEEKS 1-4	WEEKS 5-8	WEEKS 9 AND AFTER*
Day 1 starting dose: **56 mg** Subsequent doses: **56 mg** or **84 mg**	**56 mg** or **84 mg** once weekly	**56 mg** or **84 mg** every 2 weeks or once weekly†

- In Study 2 (long-term), 39% of patients received the 56-mg dose, and 61% received the 84-mg dose of

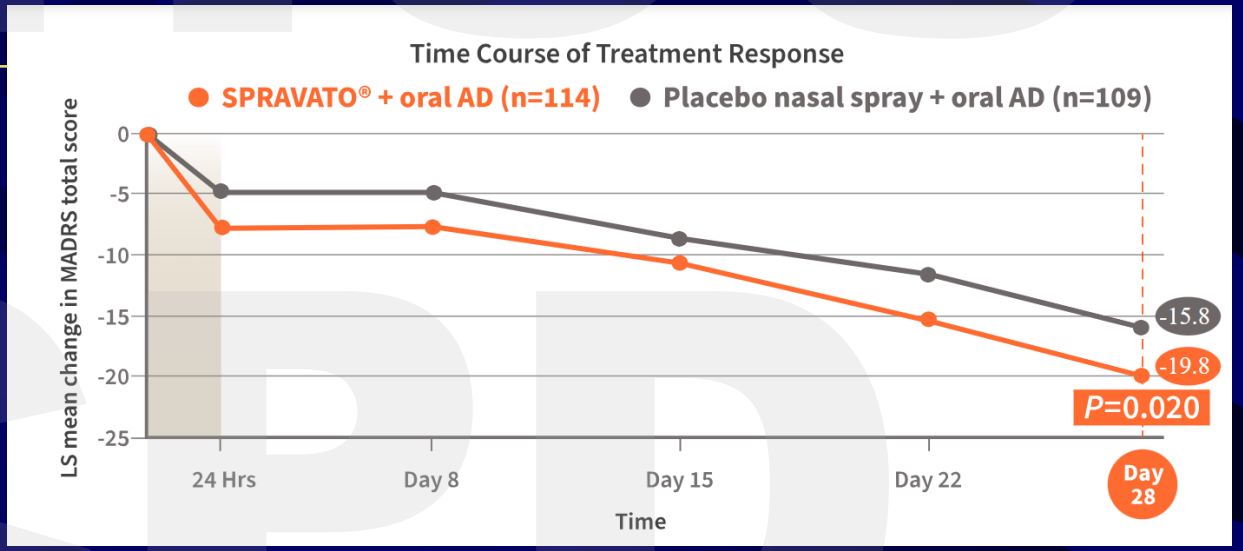


What is the Evidence for esketamine (Spravato) in Depression?

Popova, et al 2019:

Most of the treatment efficacy with Spravato was within the first 24 hours.

2019



Approved for TRD and MDSI

- 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)

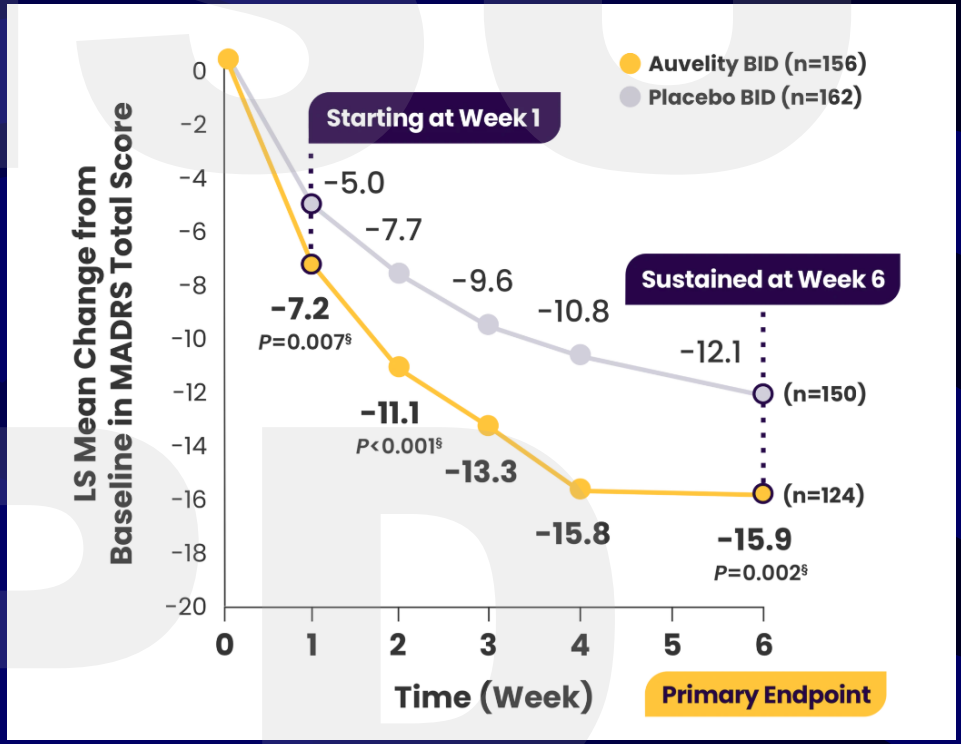
» Popova V, et al. Poster presented at the 2018 Annual Meeting of the American Psychiatric Association (APA), May 8, 2018, New York, NY.

Another New Antidepressant (also using NMDA Antagonism)

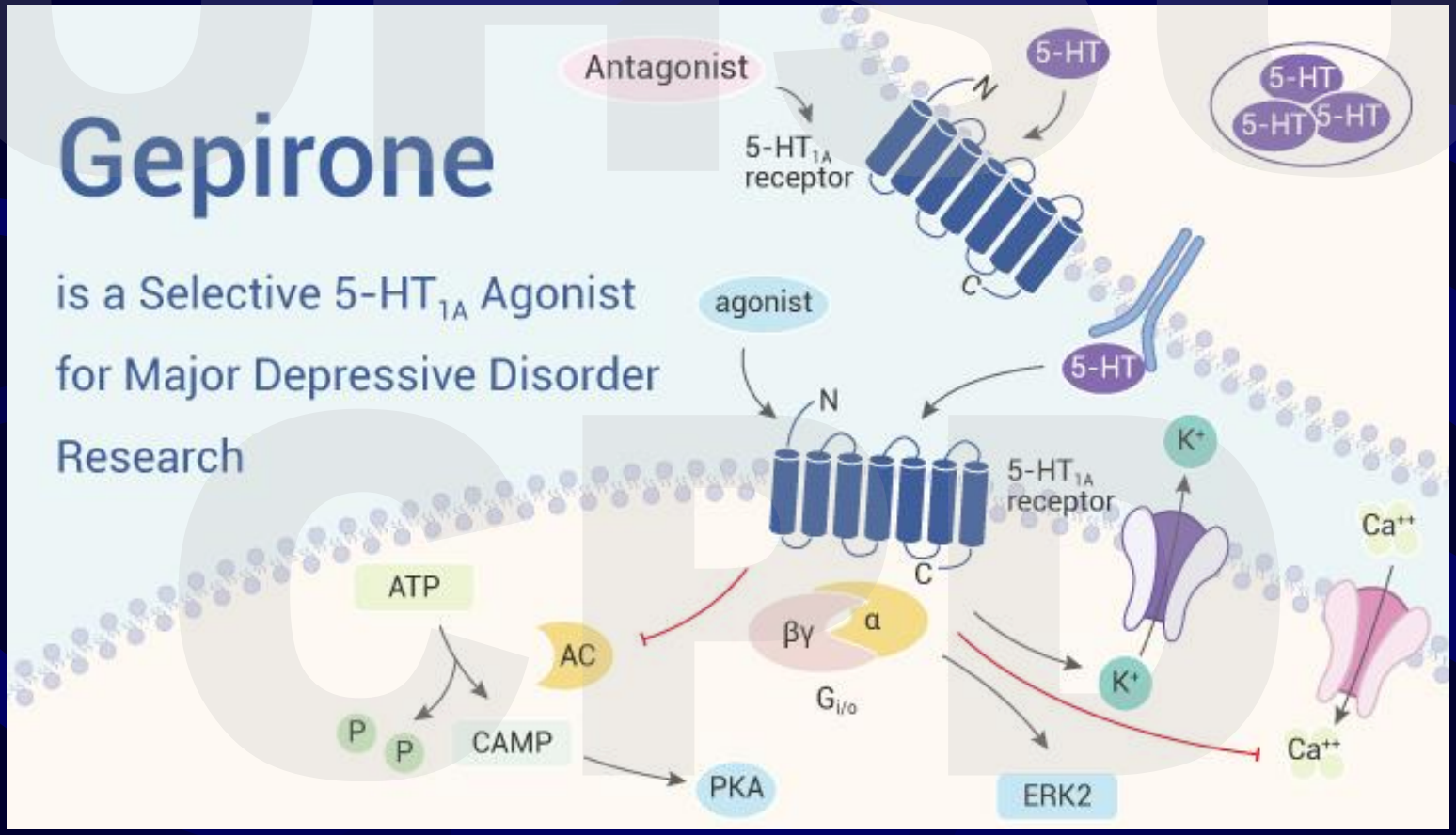
- New medication that has clinical response rate of 80% and a remission rate of almost 70%; functional improvements were "substantial“
- AEs: dizziness =12.7%, nausea = 11.9%, h/a = 8.8%, dry mouth = 7.1%, decreased appetite = 6.1%

Auvelity: Dextromethorphan HBr 45mg + Bupropion HCl 105mg

- Oral med taken 1 time a day for 3 days, then increase to 2 times a day (max dose taken at least 8 hours apart).
- Bupropion is a potent cyp2D6 inhibitor that prolongs the action of dextromethorphan



Gepirone ER (Exxua): A Study in Persistence



Gepirone ER:
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-HT1a agonist with superior efficacy vs placebo as MDD monotherapy (through at least 48 weeks). 5-HT1a 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 5HT1a 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.
- Safety profile: no AEs on weight, blood pressure, heart rate, or liver function. The most frequent AEs included dizziness and nausea, which were reported to be mild, short in duration, related to dose escalation, and did not lead to discontinuation of treatment.

Have We Seen This  Before?

- Vilazodone: FDA approved in 2011 as the first and only SSRI and 5-HT1a receptor partial agonist at the time
  - Must be taken with food for absorption
    - ➢ AUC and Cmax 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.

What About?

Psilocybin

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

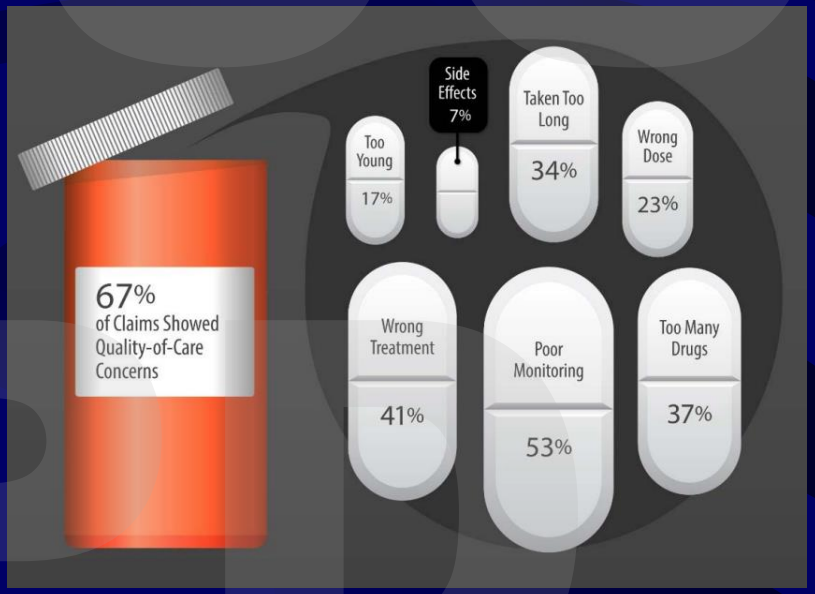
- Small trial over 6 weeks (n = 59).
- Psilocybin 25 mg twice 3 weeks apart vs 1 mg + escitalopam 10mg in depression.
- Outcome: depression scores non-inferior to the SSRIs
  - NEJM 2021;384:1402-1411.

- Larger 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.

Several “Antipsychotics” are now FDA-approved for Depression

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



My Anxiolytic Is Not Working!

Background

- Evidence suggests that patients with anxiety disorders, in particular generalized anxiety disorder (GAD) and social anxiety (SAD), have high rates of recurrence and/or experience persistent anxiety symptoms, especially if they have comorbid MDD

- SSRI/SNRIs are considered first line

Adding Long-term Benzos (“Z”-drugs) for Anxiety:

A Few Words About The Benzos

- Best if used for a SHORT period of time
- Multiple risk factors for dependence
  - Alcoholic use disorder
  - Use of benzos with short half lives/rapid onset of action (alprazolam, diazepam, triazolam, clorazepate)
  - Use of higher potency benzos (clonazepam, alprazolam, lorazepam, diazepam)
- Associated with Falls in the elderly
- Suppress REM sleep and stage 3 and 4 sleep

So, You're Telling Me No Benzos?

- Other agents that are not BZDs that may have a role in anxiety management
  - Propranolol – helps physiologic triggers (Off-label), does not treat emotional component of anxiety
  - Hydroxyzine – FDA indication for GAD
  - Gabapentin – Off-label evidence for SAD & PD
  - Pregabalin – Off-label evidence for SAD & GAD
  - Buspirone – FDA indication for GAD
  - Clomipramine – FDA indications for OCD & Panic
  - Olanzapine – Off-label evidence for N/V especially in cancer (anxiety equivalent in some)
  - Other SGAs have promise as well

Lavender?

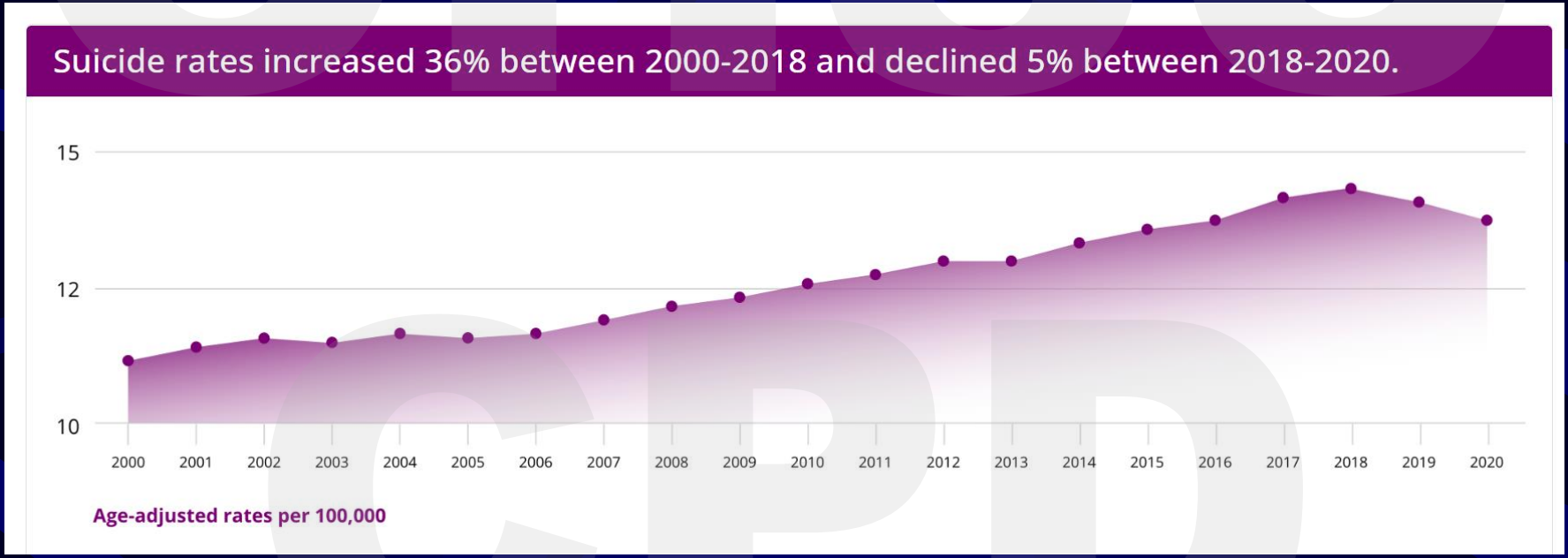
Silexan

- In pts with subsyndromal anxiety or generalized anxiety, an anxiolytic effect of Silexan (daily dose 80 – 160 mg) was evident after 2 weeks via scale score reductions
- Results were comparable with those achieved with lorazepam or paroxetine in patients with GAD.
- Additional benefit was seen for concomitant symptoms such as impaired sleep, somatic complaints, co-morbid depression or decreased quality of life.
- Only AE: mild gastrointestinal symptoms

– Kasper S, Müller WE, Volz HP, Möller HJ, Koch E, Dienel A. Silexan in anxiety disorders: Clinical data and pharmacological background. World J Biol Psychiatry. 2018 Sep;19(6):412-420.

Suicide

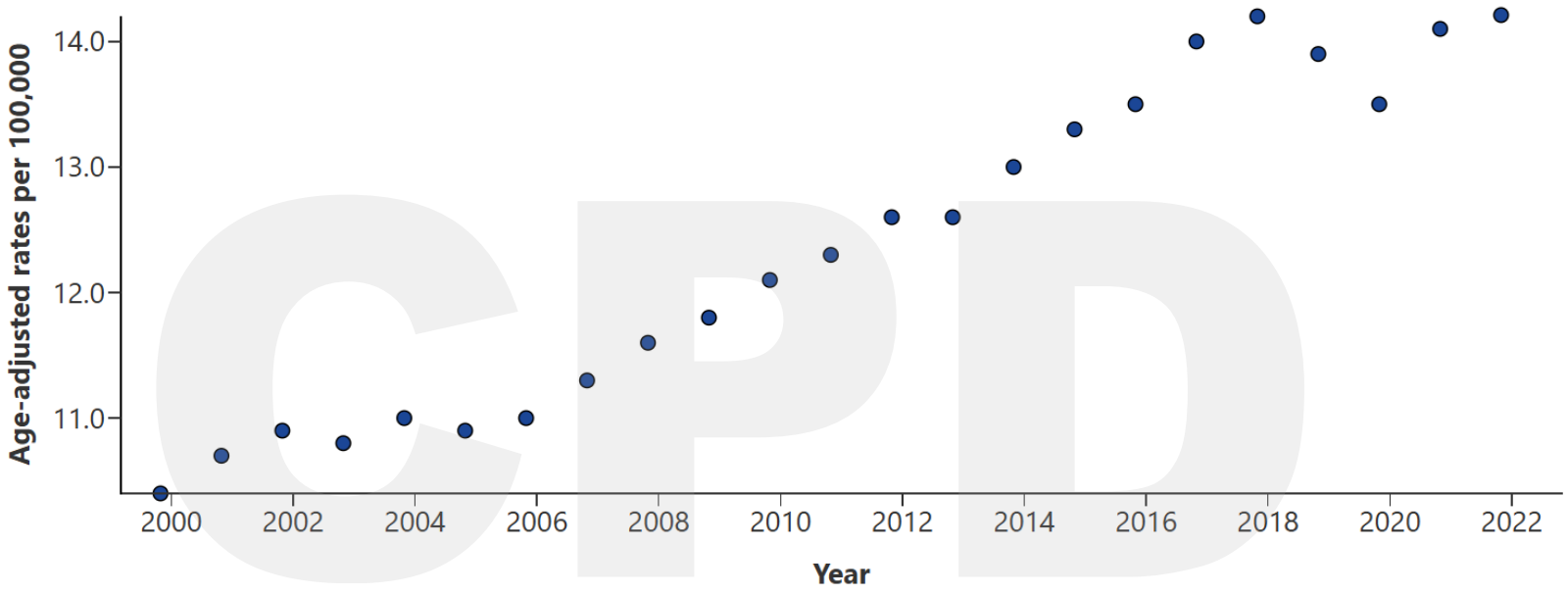
Suicide Trend



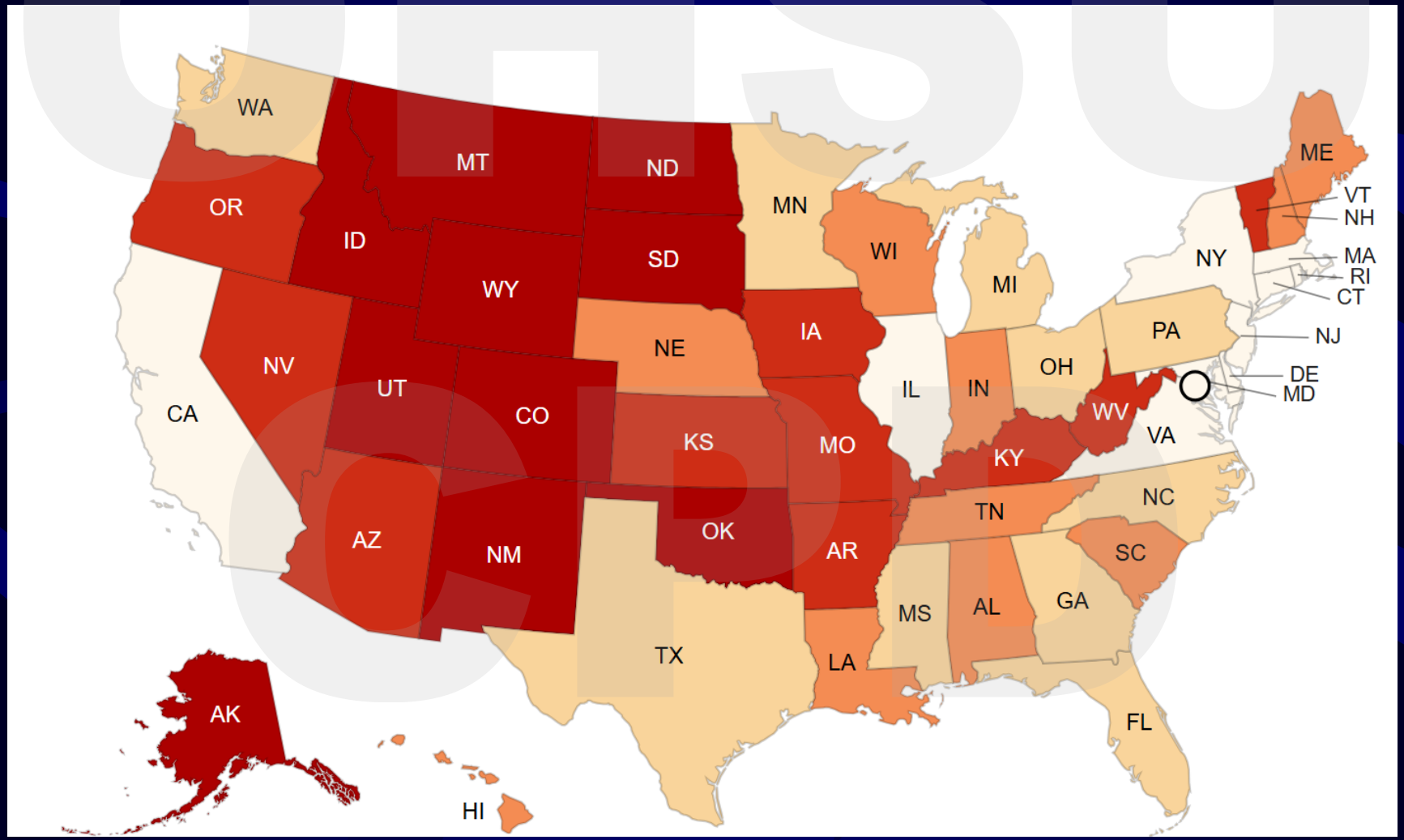
Suicide Trend

Suicide rates

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



Suicide Rate 2022:
Oregon 19.3 per 100K



Suicide Pearls

- Most deaths by suicide are male (77%)
- Highest suicide rate is for those older than 85
- Firearms are used in 52.8-55% of suicide completions (25% by hanging)
- Highest risk in American Indian/Alaska Native and Non-Hispanic Whites
- Counties with the highest risk of suicide:
  - Western states (e.g., Colorado, New Mexico, Utah, and Wyoming)
  - Appalachia (e.g., Kentucky, Virginia, and West Virginia)
  - Ozarks (e.g., Arkansas and Missouri)

Systematic Suicide Assessment

- Ask gently if suicidal thoughts are still active (review protective factors too) – if no then:
  - Assess for delirium
  - Assess for psychosis – hallucinations
  - Assess for mood disorders
  - 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.

Thank You

Fortune Favors the Prepared Mind

- Louis Pasteur