

# Difficult to Treat Depression

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# **No conflicts**

In compliance with the ACCME Standards for Commercial Support of CME, as the speaker I do not have any relevant financial relationships to disclose in relation to this presentation.

# Old Ways

Switching antidepressants

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High dose antidepressants

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Stimulant augmentation

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Aug with buspirone or antidepressants

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Antipsychotic augmentation\*

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Rapid acting treatments\*

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Impressionistic care

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\*Effective short-term, not long-term

# New Ways

Psychotherapy

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Personalize by subtypes

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Address deficits

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Aug with lithium or pramipexole

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Neuromodulation (TMS, ECT, ProLivRx)

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Long lasting treatments

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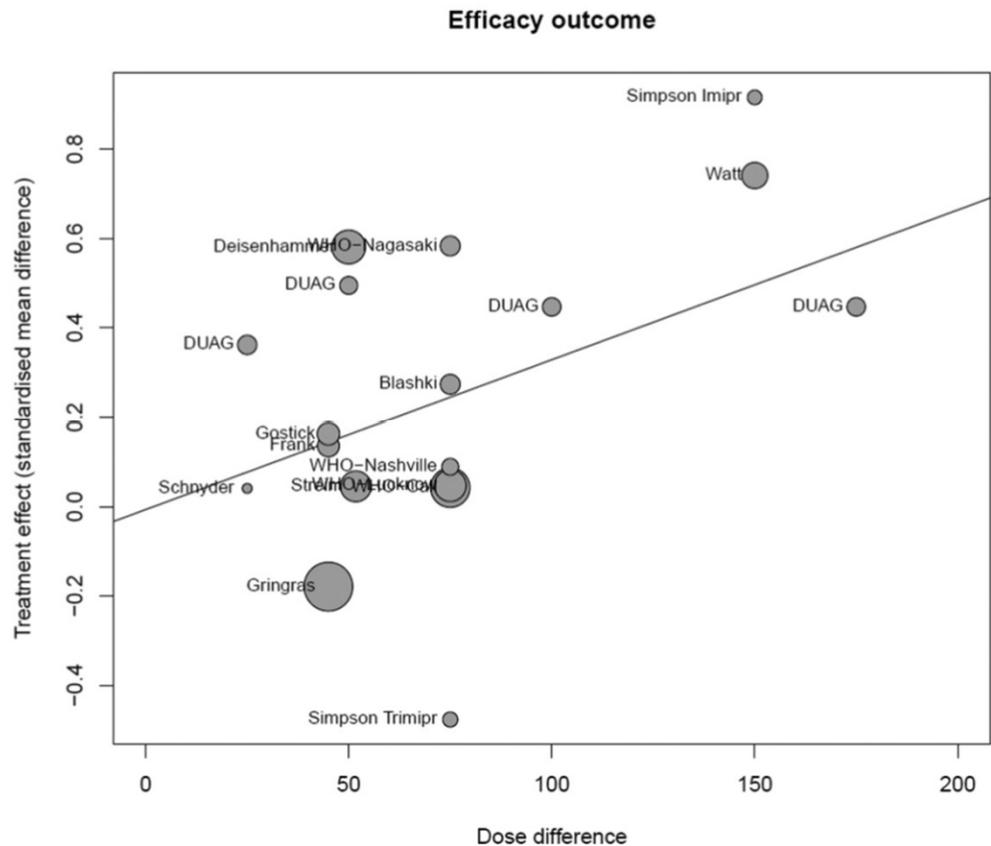
Measurement-based care

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# Tricyclic Dose Response

Every increase of 100 mg imipramine equivalents = 0.34 effect size difference

Imipramine 100 mg =  
Amitriptyline, desipramine, doxepine 100 mg =  
Amoxapine 167 mg =  
Clomipramine, maprotiline 83 mg =  
Nortriptyline 74 mg =  
Protriptyline 19 mg =  
Trimipramine 85 mg

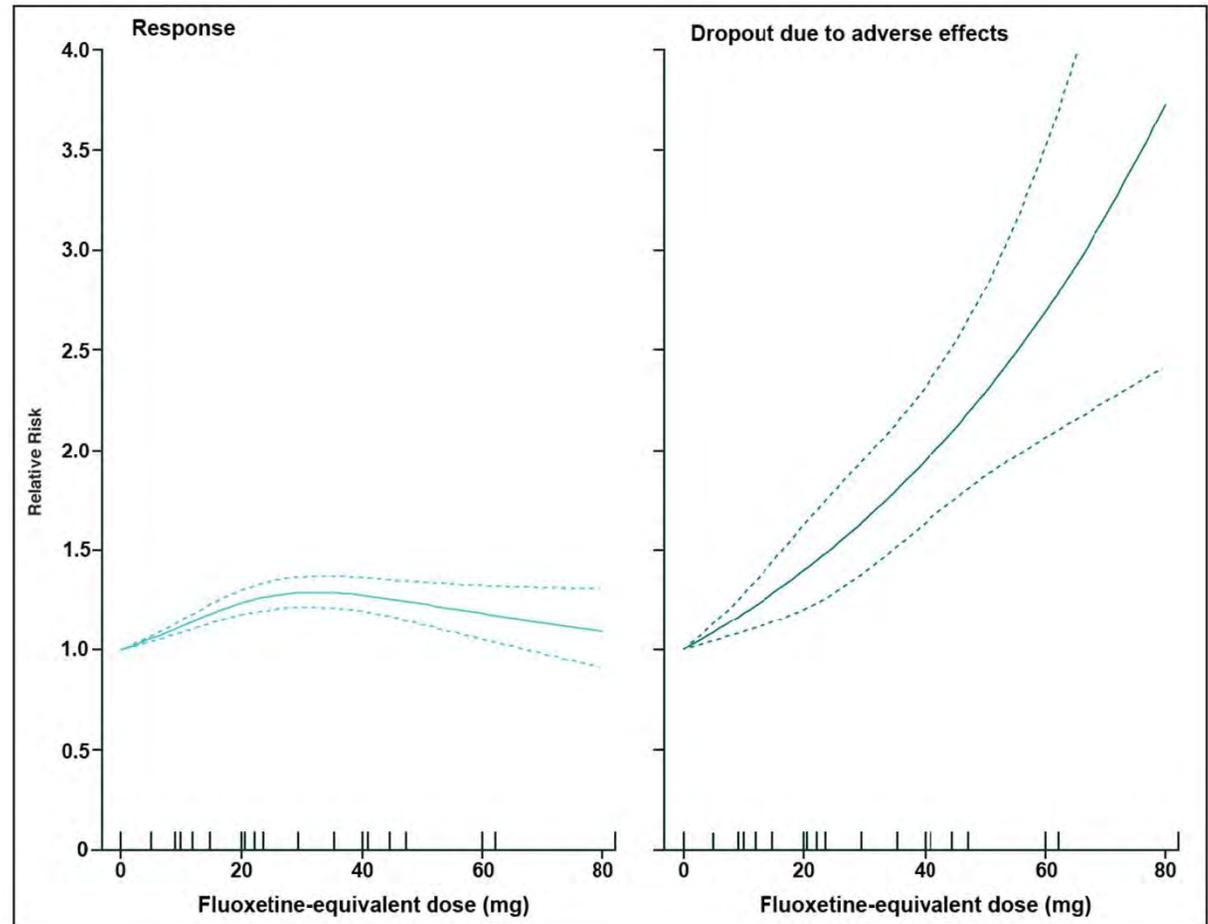


15 RCTs of fixed dose comparisons.  
Baethge C et al. J Affect Disord. 2022;307:191-198.

# 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.



# Antidepressant Dose-Response

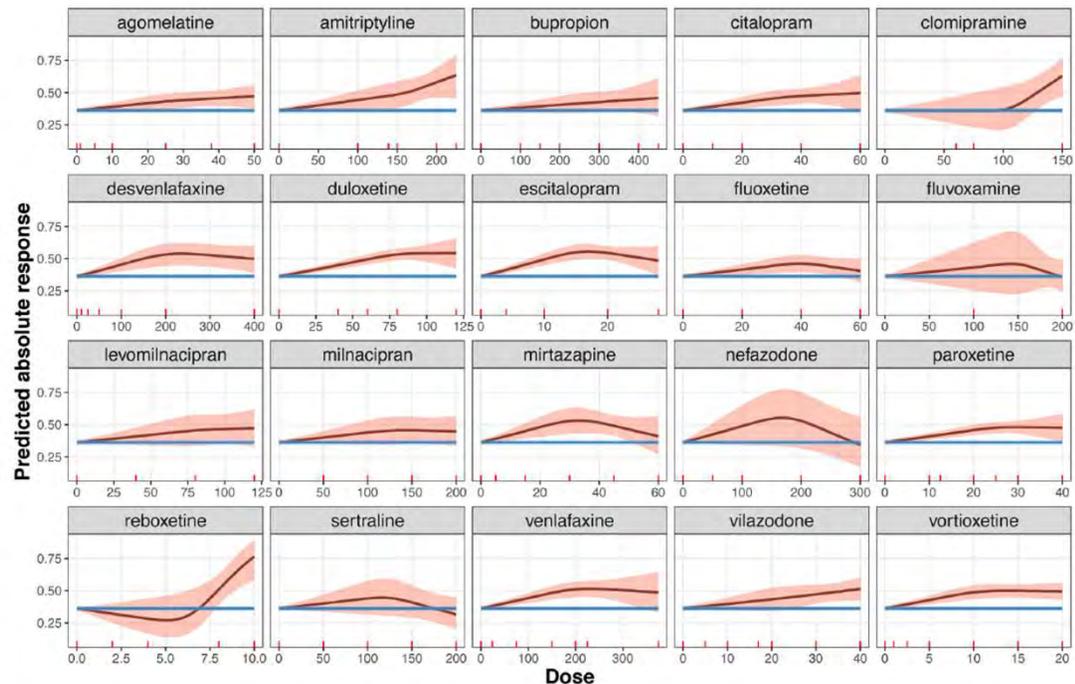
*Dose-response:*

Tricyclics

Reboxetine

Venlafaxine (to 225 mg)

Desvenlafaxine (to 200 mg)



Network metaanalysis of 120 trials. Hamza T et al, Stat Methods Med Res, 2/2022.

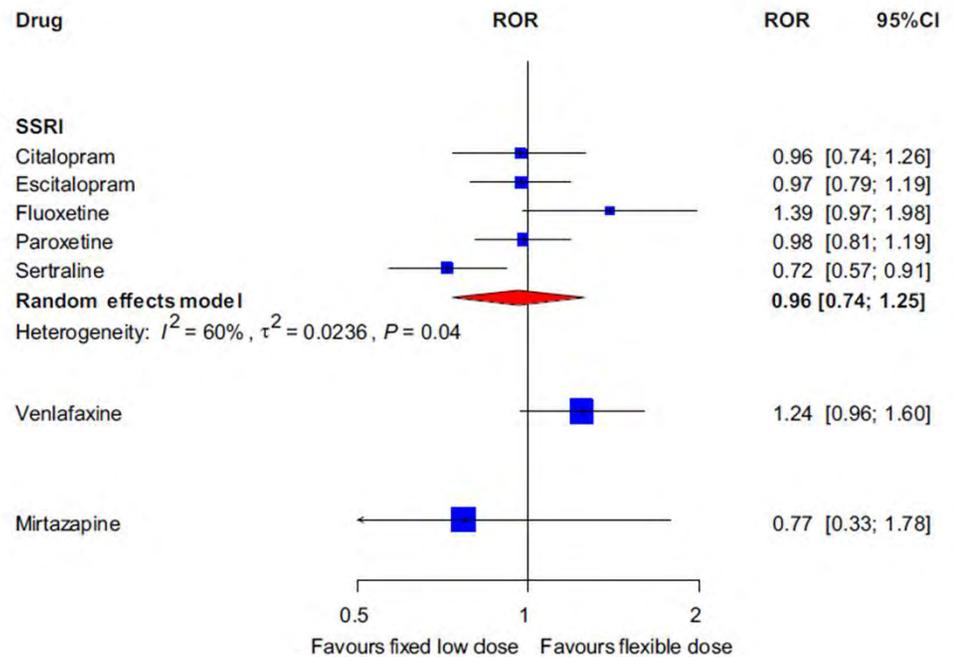
**Figure 2.** Dose–effect network meta-analysis summary curve for each antidepressant. The blue line depicts the effect estimated from all placebo arms in the network (36.2%) with its 95% credible region. The red line represents the absolute response to each antidepressant (estimated from model M1) and the shaded area is its 95% credible region.

# Raise the dose vs. give it more time?

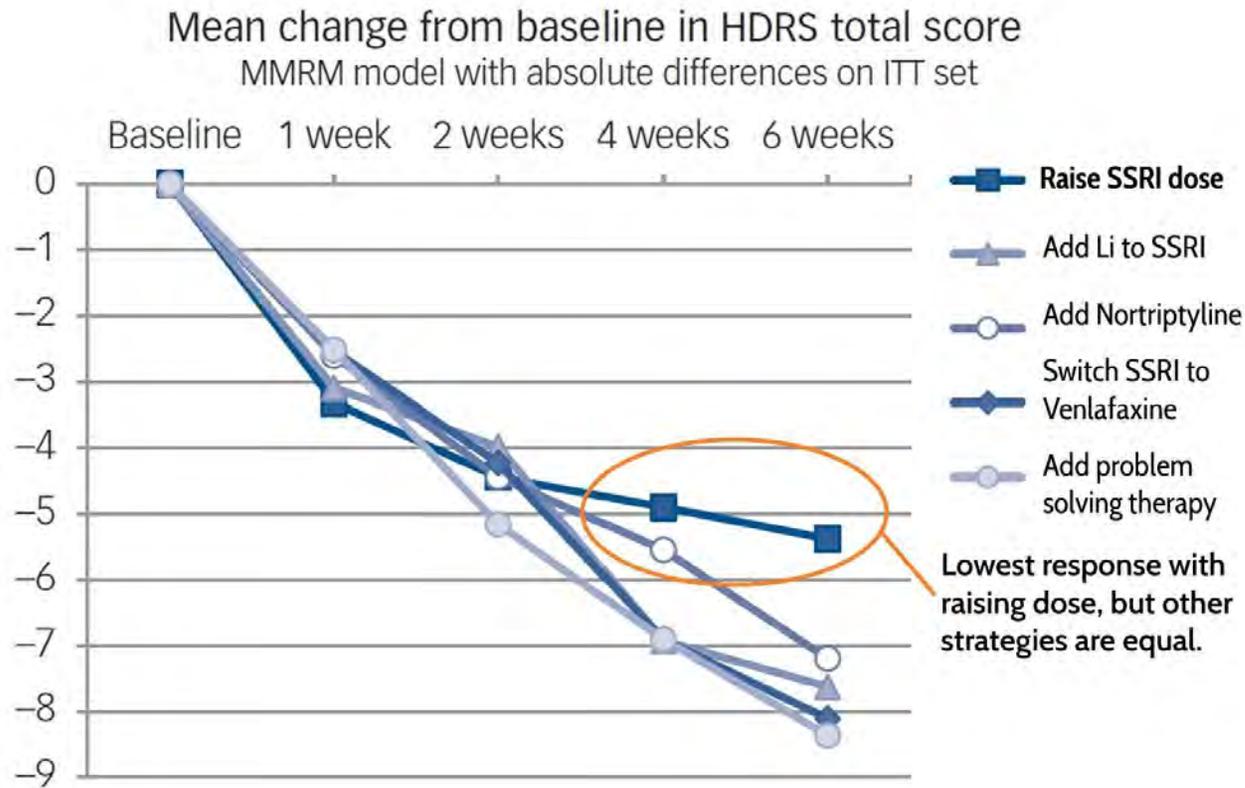
*No benefit:* Raising SSRIs or mirtazapine.

*Yes benefit:* Raising venlafaxine 75 → 150 mg.

Metaanalysis of 123 trials. Furukawa TA et al, Acta Psychiatr Scand. 2020;141(5):401-409.



# Raising Dose = Least Effective Strategy



# Stimulant Augmentation

*No benefit:*

Lisdexamfetamine (3 RCTs n=1,218)

Methylphenidate ER (2 RCTs n=205)

*Other failures in large augment trials:*

Bupropion, mirtazapine, buspirone

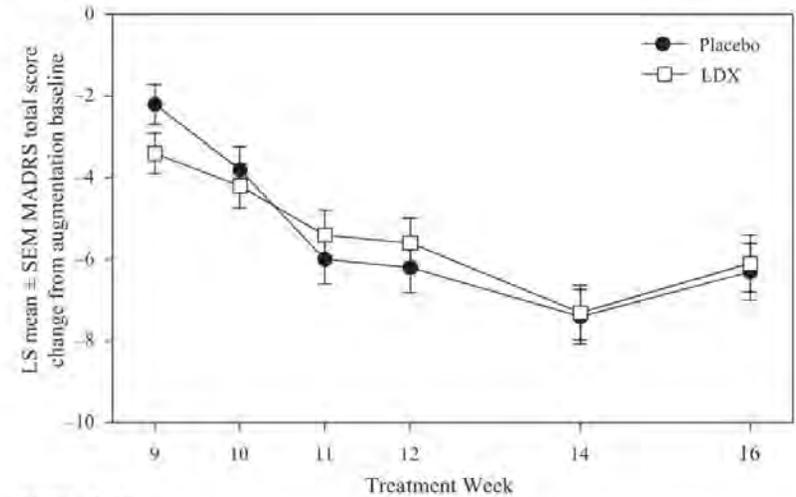
Richards C, et al. J Affect Disord 2016;206:151-160.

Ravindran AV et al, J Clin Psychiatry. 2008;69(1):87-94.

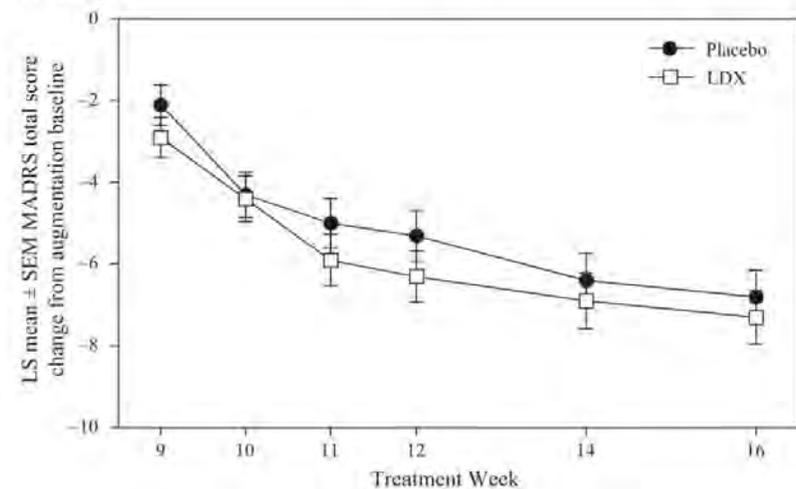
Patkar AA et al, J Clin Psychopharmacol. 2006;26(6):653-656.

Trivedi MH et al, J Clin Psychiatry. 2013;74(8):802-809.

A. Study 1



B. Study 2



# Personalize by Subtype



## What Type of Depression?

**Bipolar depression (30-40%)**

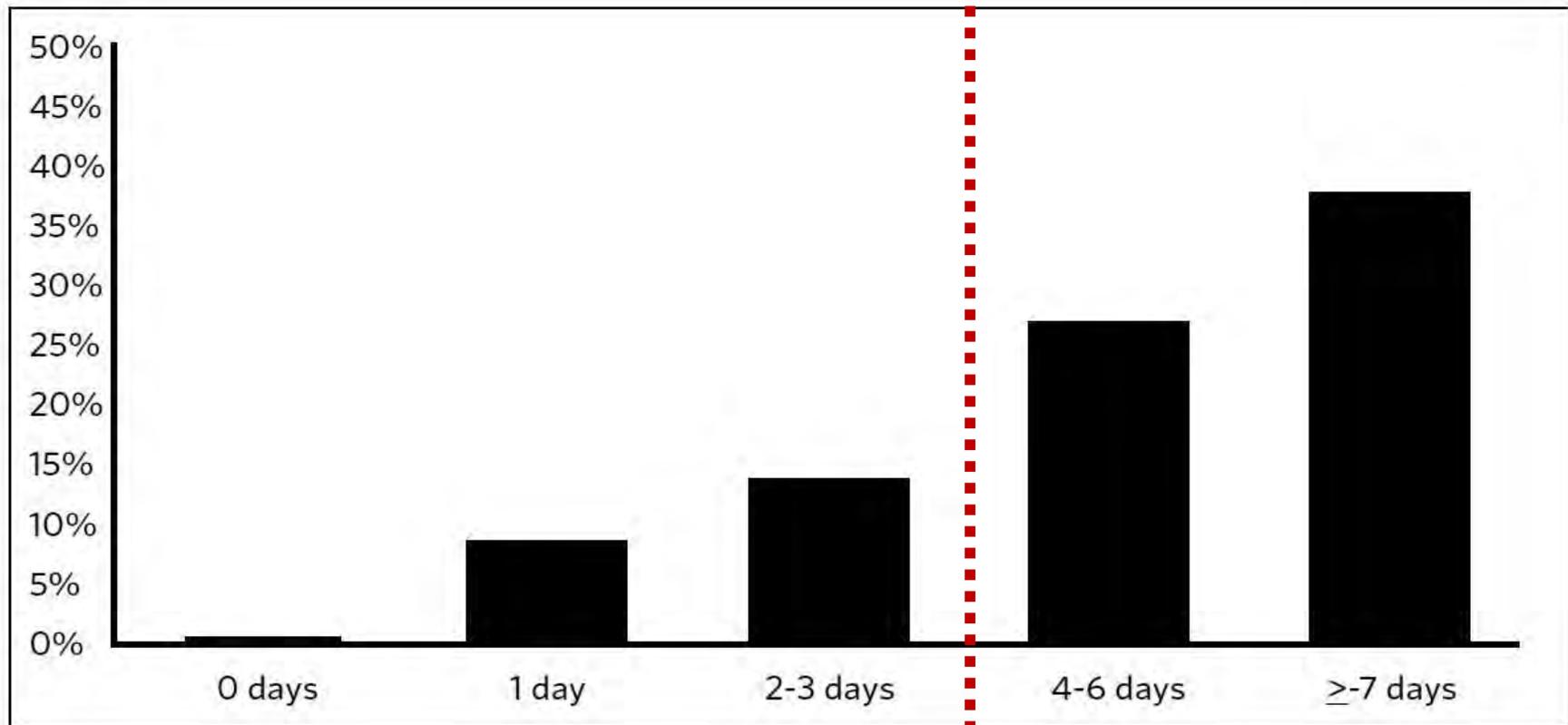
**Unipolar with mixed features (25%)**

**Psychotic depression (20%)**

**Vascular depression (50% after age 65)**

**Inflammatory depression (30%)**

*These rates are ~30% higher in TRD*



**Risk of (h)mania on antidepressant rises with duration of past (h)manic symptoms**

Angst J et al, *Eur Arch Psychiatry Clin Neurosci*, 2012, 262(1), 3-11.



# Psychotic Depression

**30% of cases are missed**

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**ECT is gold-standard (>90% remission)**

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**Antipsychotic augmentation is intuitive but weak ( $d=0.25$ ) and requires schizophrenia-level dosage**

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**Lithium augmentation (uncontrolled trials)**

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Rothschild AJ et al, J Clin Psychiatry 2008;69(8):1293-1296; Petrides G et al, J ECT. 2001;17(4):244-253; Farahani A and Correll CU, J Clin Psychiatry 2012;73(4):486-496; Birkenhäger TK et al, J Clin Psychopharmacol 2009, 29(5):513-515; Ebert D, J Clin Psychopharmacol 1997;17(2):129-130



# Inflammation

**Childhood trauma**

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**Mixed features, Anhedonia**

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**Chronic medical illness**

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**Obesity (BMI  $\geq$  30), Western diet**

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**Smoking, sedentary lifestyle**

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**Recent chemotherapy or radiation**

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**Recent bodily injury or surgery**

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**Recent infection**

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**Postpartum, Menopause, Older age**

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**Elevated C-Reactive Protein (hs-CRP)  $\geq$  3**

# Medication for Inflammatory Depression

	Rationale
<b>Bupropion</b>	↑CRP and obesity predicts response to augmentation
<b>Celecoxib</b>	↑CRP predicts response. Anti-inflammatory with 17 randomized trials in depression (200 mg BID).
<b>Pramipexole</b>	Targets the dopamine tracks that are disrupted by inflammation. Reduced inflammatory markers and anhedonia in trials of depression (0.5-2.5 mg QHS)
<b>? Lithium</b>	Anti-inflammatory mechanisms
<b>Nortriptyline</b>	↑CRP predicts response (versus SSRI)
<b>Minocycline</b>	Anti-inflammatory properties. Results mixed in depression, but trend positive with ↑CRP (100 mg BID).

# Naturals for Inflammatory Depression

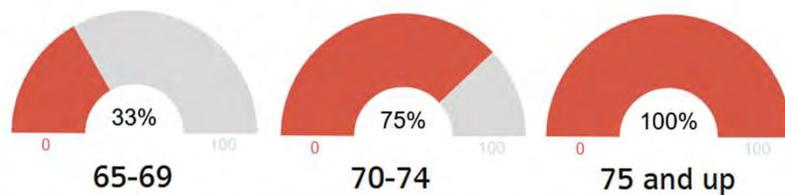
	Rationale
<b>Omega-3</b>	↑CRP predicts response, esp to higher dose (4,000 mg/day, EPA:DHA ≥ 2:1)
<b>N-Acetylcysteine (NAC)</b>	↑CRP predicts response
<b>L-Methylfolate</b>	↑CRP predicts response in unipolar; positive trials in bipolar
<b>Lifestyle</b>	Exercise, Mediterranean diet, CBT-insomnia, stress reduction

Mischoulon D et al, J Clin Psychiatry 2022;83(5):21m14074

Shelton RC et al, J Clin Psychiatry 2015;76(12):1635-1641

Porcu M et al, Psychiatry Res 2018;263:268-274

# Vascular Depression



**Cardiovascular risk factors**

**MRI white matter hyperintensities**

**Cognitive deficits**

**Psychomotor retardation, lack of insight**

**Lower response to antidepressants (35%)**

**Responsive to TMS, tDCS, or nimodipine  
(start 15-30 mg TID, target 90 mg TID)**

Taylor WD et al, *Am J Psychiatry* 2018;175(12):1169-1175  
Park JH et al, *J Affect Disord* 2015;180:200-206  
Taragano FE et al, *Int J Geriatr Psychiatry* 2001;16(3):254-260  
Taragano FE et al, *Int Psychogeriatr* 2005;17(3):487-498



# Address Deficits

# Treatments that address deficits in depression

Light therapy

Methylfolate

Vitamin D

Omega-3 fatty acids

Probiotics

Maybe: Acetyl-l-carnitine

Penders TM et al, Prim Care Comp CNS Disord 2016;18(5).  
Maruf AA et al, Pharmacopsychiatry 2022;55(3):139-147  
Zhang Q et al, BMC Psychiatry 2023;23(1):477.  
Liao Y et al, Transl Psychiatry 2019;9(1):190.  
Veronese N et al, Psychosom Med 2018;80(2):154-159.

# Methylfolate effect size = 0.4-0.9\*

## Risks

None

## Tolerability

None

## Cost

15 mg/day, \$7.50/month

## Recommended Products:

[chrisaikenmd.com/supplements](http://chrisaikenmd.com/supplements)

\*0.9 as monotherapy with vitamin-complex **Enlyte** in depression with MTHFR genotype abnormalities  
0.4 in metaanalysis of depression augmentation trials.

Mech AW and Farah A, J Clin Psychiatry 2016;77(5):668-71  
Maruf AA et al, Pharmacopsychiatry 2022;55(3):139-147

# Light Therapy effect size = 0.5-0.8\*

## Risks

Photosensitivity  
Caution in eye disease

## Tolerability

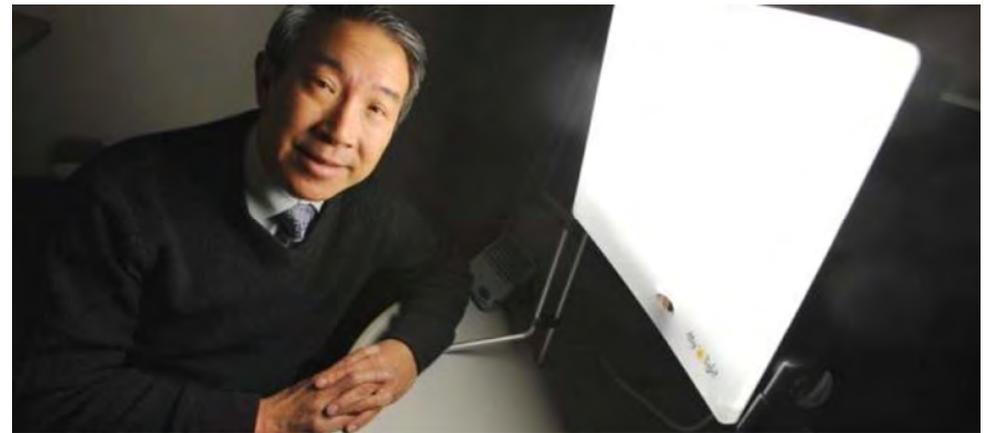
Headache, eye strain.

## Cost

\$120-200

## Recommended Products:

[chrisaikenmd.com/lighttherapy](http://chrisaikenmd.com/lighttherapy)



\*0.5 in non-seasonal depression  
0.5-0.8 in winter seasonal depression  
0.4 in bipolar depression

Mårtensson B et al, J Affect Disord 2015;182:1-7  
Tao L et al, Psychiatry Res 2020, 291:113247  
Lam RW et al, Can J Psychiatry 2020;65(5):290-300

# Antipsychotic effect size = 0.3-0.4

## **Risks**

Tardive dyskinesia  
Metabolic syndrome  
Hyperprolactinemia  
Orthostatic hypotension  
Arrhythmias  
Hyperthermia  
Neuroleptic Malignant  
Syndrome  
Priapism  
Neutropenia

Elevated LFTs

Mortality in dementia

## **Tolerability**

Akathisia

Dystonia

Muscle stiffness (EPS)

Weight gain

Sedation

Sexual dysfunction

Anticholinergic effects

# Think Longterm



## Rapid Action

### OLD

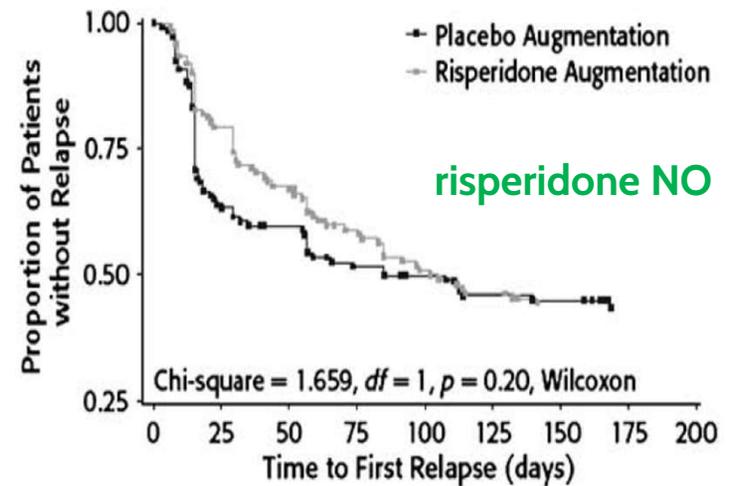
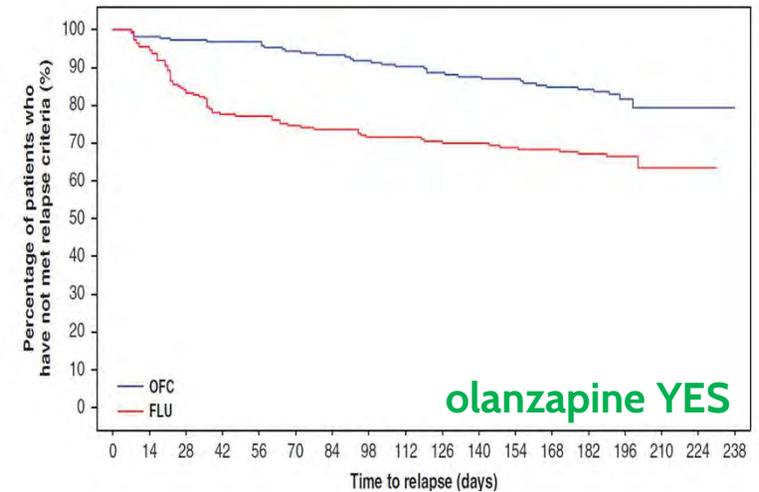
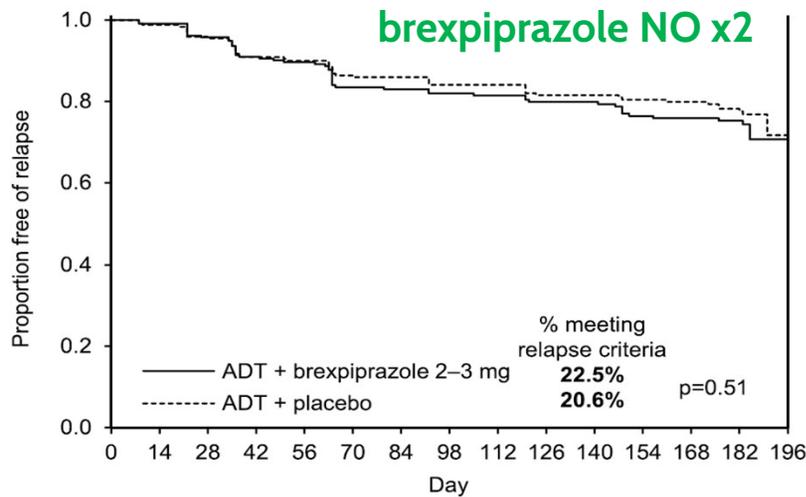
- Benzodiazepines (alprazolam)
- Eszopiclone
- Pindolol
- Thyroid (T3)

### NEW

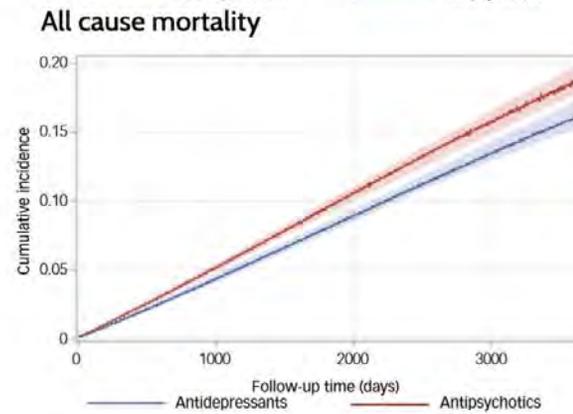
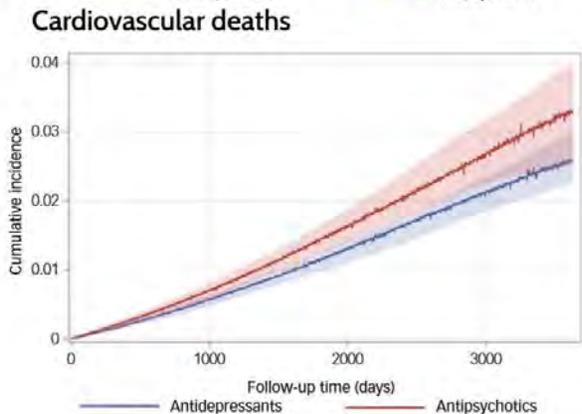
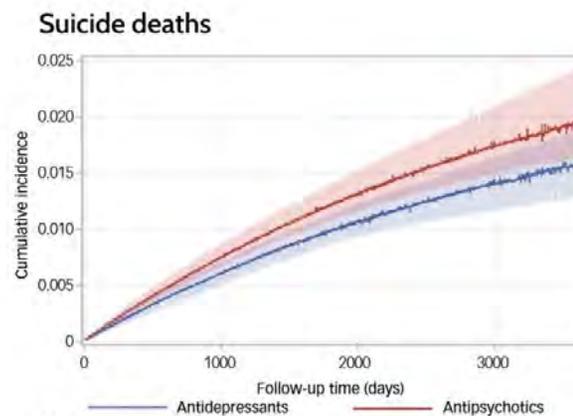
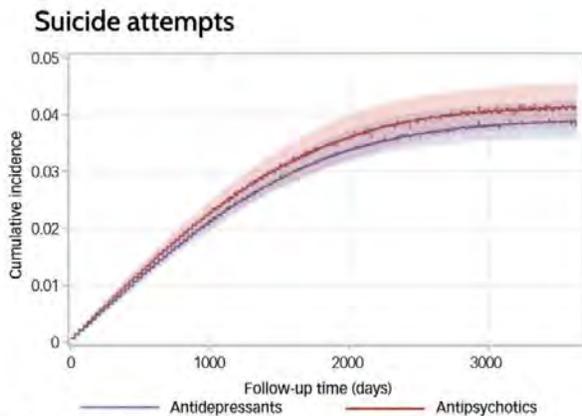
- Bupropion-Dextromethorphan (Auvelity)
- Ketamine and Esketamine
- Zuranolone (for postpartum)
- Psychedelics

# Does antipsychotics prevent depression?

Not in 3/4 trials (6 months, n=2,308)



# Antipsychotics don't prevent suicide, may raise mortality

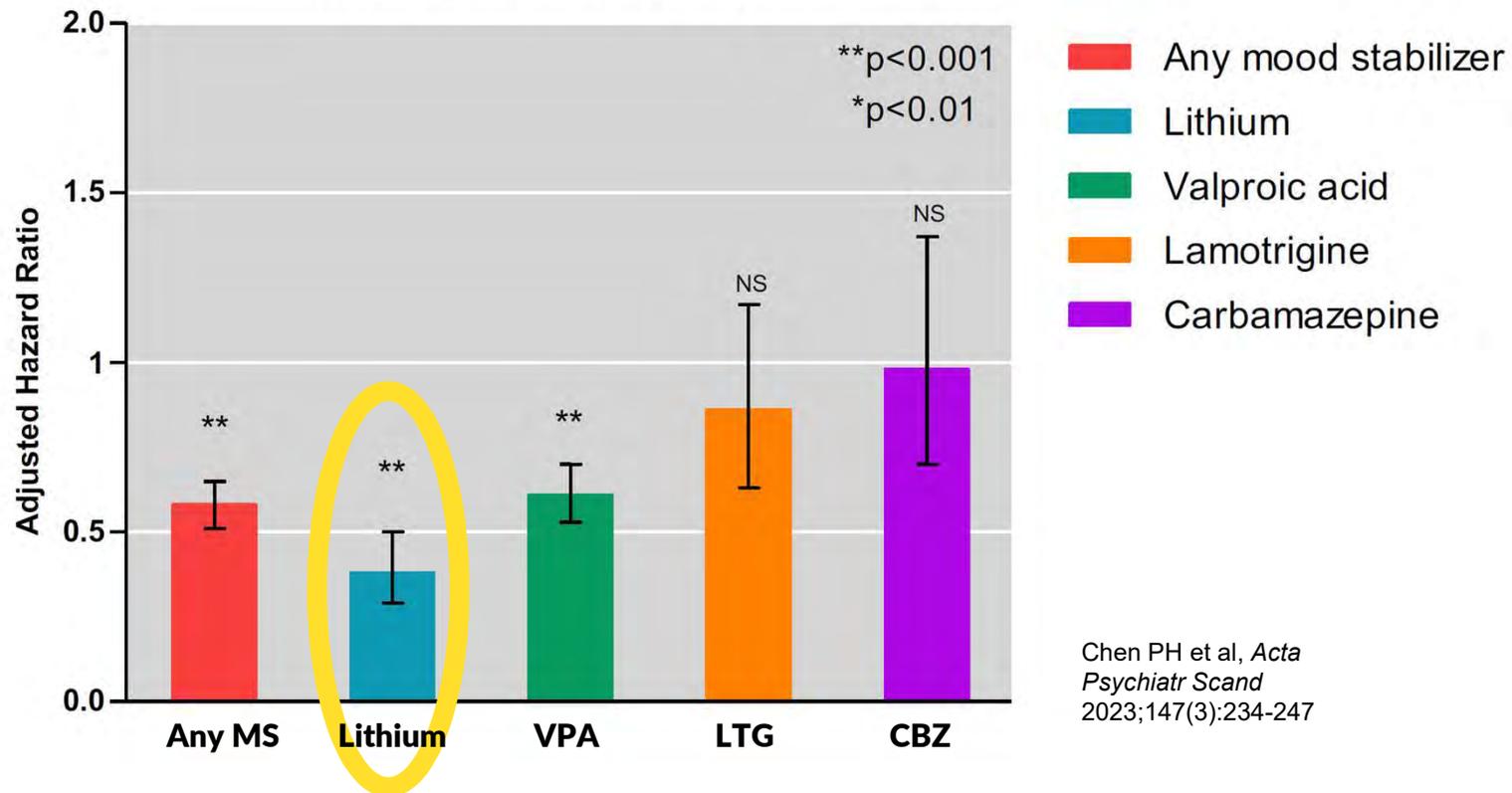


Comparative cohort study of 79,898 patients with TRD.

Antipsychotic augmentation vs. matched controls who received third-line antidepressants

# Lithium lowers medical and suicide mortality

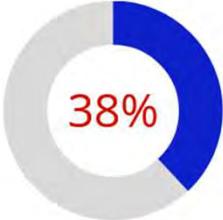
## All-Cause Mortality



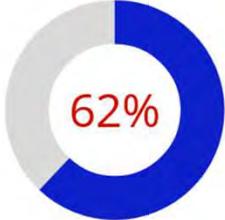
# Lithium prevents unipolar depression

**21** Randomized  
Controlled Trials

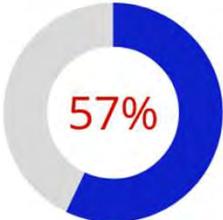
**2** Years avg  
duration



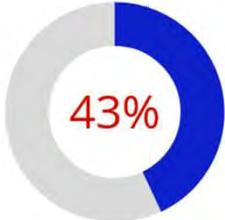
Placebo-  
Controlled



Antidepressant-  
Controlled



Monotherapy



Augmentation

# Lithium in Unipolar

# 50%

Lower risk of relapse after ECT  
Lower risk of rehospitalization

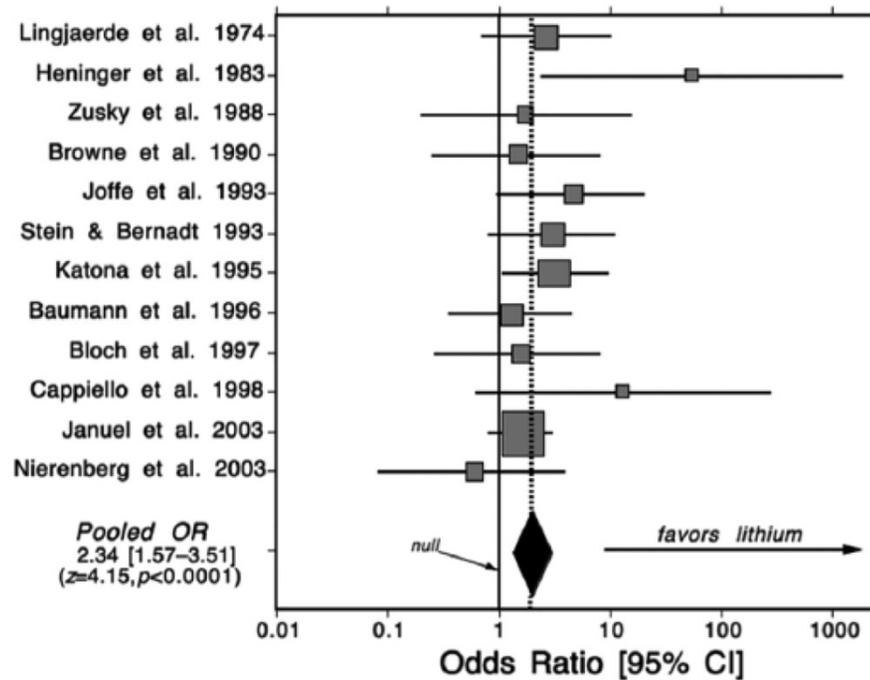
Tiihonen J et al, Lancet Psychiatry. 2017;4(7):547-553  
Pompili M et al, J Affect Disord 2023, 340:245-249

Undurraga J et al, J Psychopharmacol 2019;33(2):167-176  
Lambrichts S et al, Acta Psychiatr Scand 2021;143(4):294-306

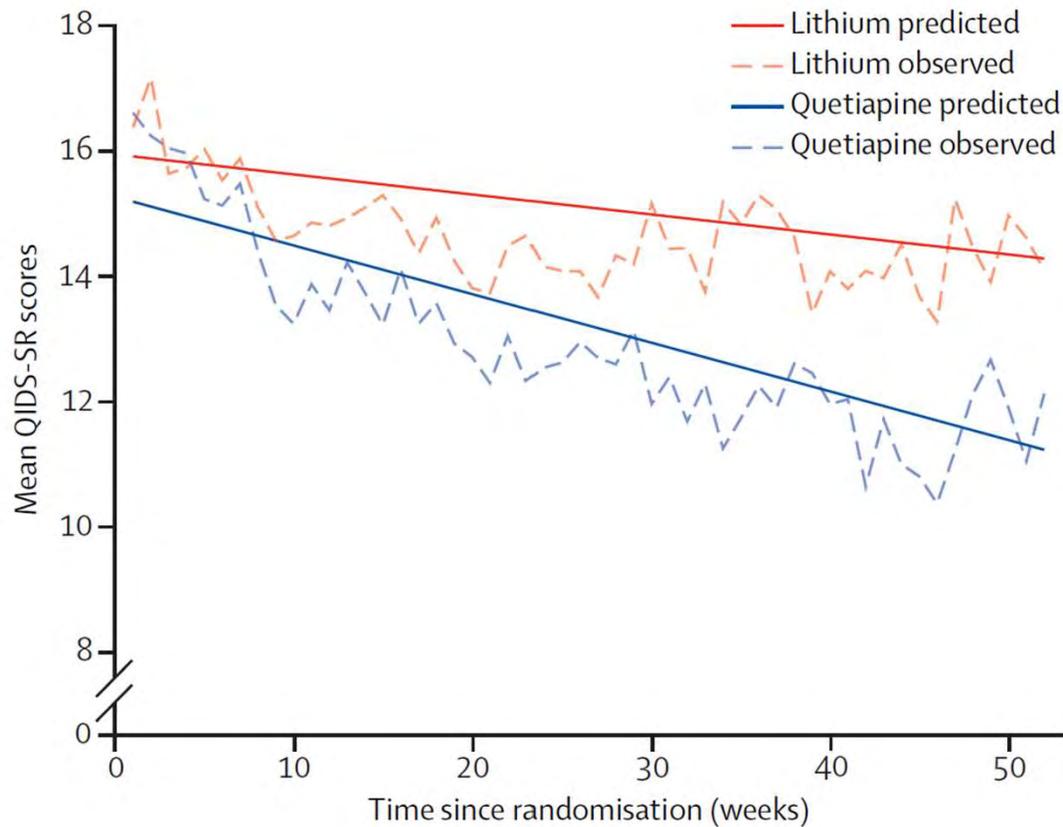
# Lithium in Acute Unipolar Depression

12 Placebo  
Controlled Trials

5 NNT



# Quetiapine vs Lithium Augmentation in TRD



## *Randomized controlled trial*

- One year
- n = 212, 60% failed  $\geq 3$  antidepressants
- Lithium mean 0.85, quetiapine 195 mg

# Lithium

Start 150-300 mg hs  
Raise every 3-5 days to 600-900 mg  
Target level 0.6-0.8  
(aim ~30% lower if age 65+)

Labs every 3-12 months  
Li, electrolytes (Ca, Cr, eGFR), TSH  
Check parathyroid if ↑Ca

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**Preferential response in recurrent depression,  
suicidality, elderly, post-ECT**

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## Tolerability

Nausea, tremor

Low weight gain and sedation (1:28)

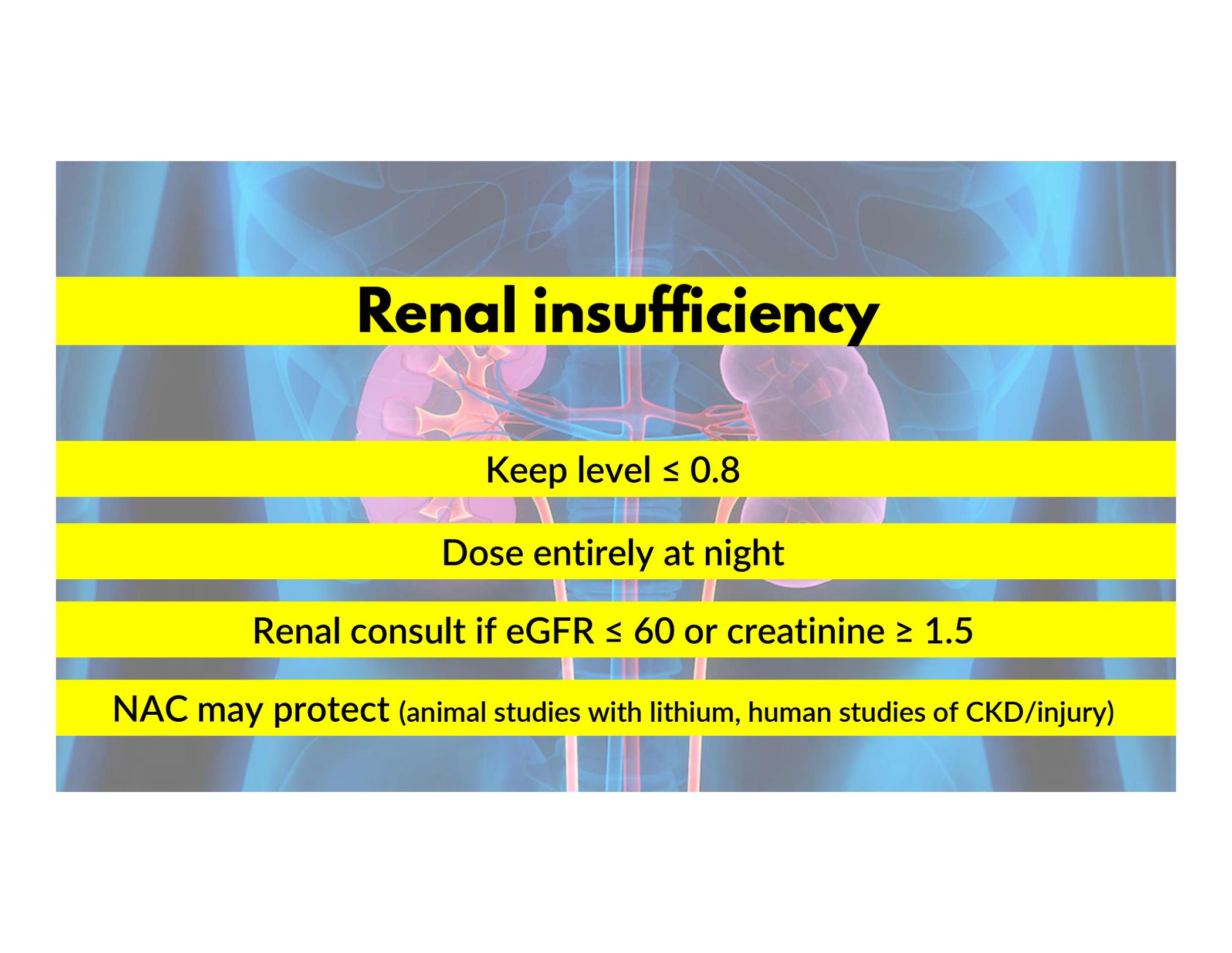
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## Risks

Renal insufficiency, hypothyroidism (15%),  
hyperparathyroidism (4%), SIADH, psoriasis, cardiac  
(bundle branch block), drug interactions, toxicity

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Lambrichts S et al, Acta Psychiatr Scand 2021;143(4):294-306; Buspavanich P et al, J Affect Disord. 2019;251:136-140; Christl J et al, 2023;56(5):e1



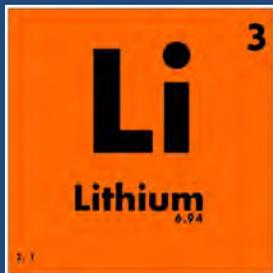
# Renal insufficiency

Keep level  $\leq 0.8$

Dose entirely at night

Renal consult if eGFR  $\leq 60$  or creatinine  $\geq 1.5$

NAC may protect (animal studies with lithium, human studies of CKD/injury)



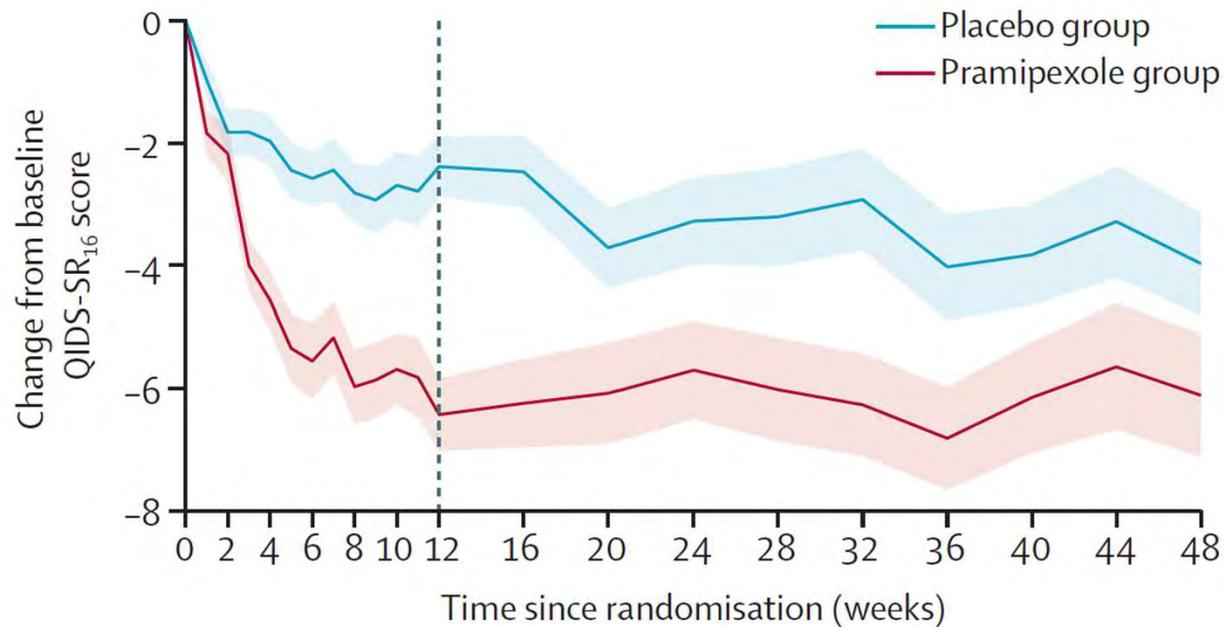
# Side Effect Guide

Antidote	Use	Potential Psych Benefits	Dose (mg/day)
<b>Propranolol</b>	Tremor	Anxiety. AP-akathisia.	80-240
<b>Vitamin B6*</b>	Tremor	Depression. AP-akathisia, EPS, prolactinemia, TD.	500-1,000 divide BID-TID
<b>Nimodipine</b>	Tremor	Ultra-rapid cycling	240-480 divide TID
<b>Gabapentin</b>	Tremor	Social anxiety, alcohol, cannabis	600-1200 divide BID-TID
<b>Ondansetron</b>	Nausea	OCD, binge drinking, bulimia	4 mg q12 hr
<b>Ginger</b>	Nausea	Cognitive decline	1,000-2,000 mg q12hr
<b>Amiloride</b>	Nephro. Diabetes Insipid.	n/a	5
<b>Aspirin</b>	Sex dysfunct in men	n/a	240
<b>Minocycline</b>	Acne	Depression	100-200
<b>Probiotics</b>	Acne	Depression, anxiety	Take with fiber
<b>Omega-3</b>	Acne, psoriasis	Depression	2000-3600 of EPA + DHA
<b>Inositol</b>	Psoriasis	Depression, bulimia	12,000-18,000
<b>NAC*</b>	Renal protect	Depression, cannabis	1,200-2,000

\*Risk of neuropathy may be avoided by using active form, pyridoxal 5'-phosphate, at 50-70% lower dose

\*NAC (N-acetylcysteine) has animal studies for lithium-renal toxicity, human trials in renal failure and bipolar depression

# Pramipexole Augmentation in TRD



*Randomized, placebo controlled trial:*

- 48 weeks
- n = 150, avg 3.5 trials; 21% tried augmentation
- 2.3 mg qhs (mean)
- Effect size 0.9

Browning M et al, Lancet Psychiatry, June 29, 2025.

# Pramipexole

Target 1-3 mg hs (average 1.5)

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

Large effect in RCTs of unipolar (4) and bipolar (2) depression

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

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## Tolerability

Nausea, sedation

No weight/sexual/cognitive

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## Risks

Hedonistic dysregulation (approx. 1-3%)

Hallucinations (rare at dose < 2 mg)

Hypotension

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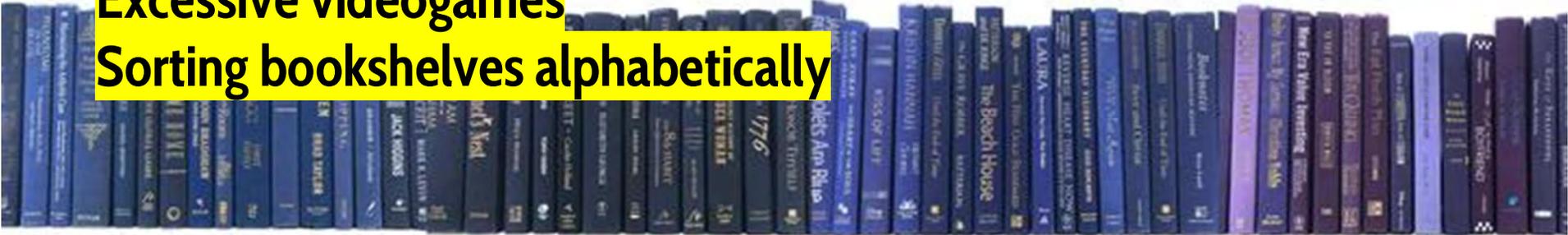
Dopamine D3  
receptors in  
the nucleus  
accumbens  
regulate  
hedonic drive



**Hedonic Homeostatic Dysregulation (1-3%)**



**Compulsive masturbation at work**  
**Cleaning garage**  
**Excessive videogames**  
**Sorting bookshelves alphabetically**



# Neuromodulation

"by this method we eliminate the pain for the moment being and cure evil pain in the future"

–*Scribonius Largos (1st century AD)*



# TMS More Effective than Aripiprazole Aug in TRD

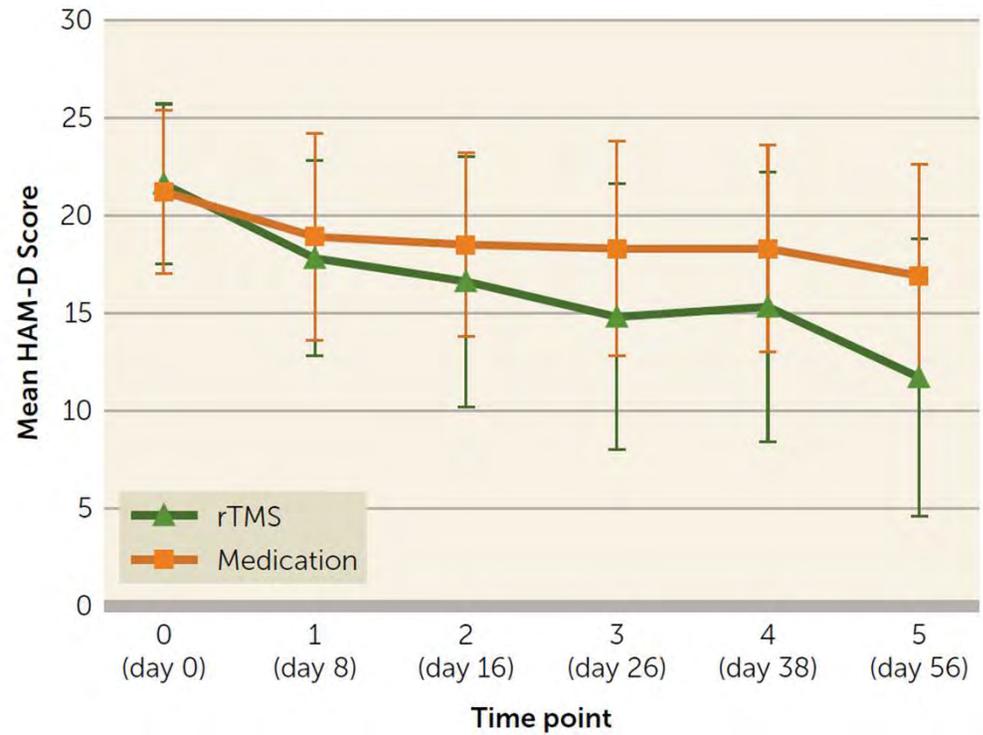


8 wk RCT, n = 278, mean 9 mg aripiprazole

Papakostas GI et al, Mol Psychiatry. March 7, 2024.

# rTMS vs Tricyclic Switch in TRD

FIGURE 2. Depression severity over time with repetitive transcranial magnetic stimulation (rTMS) or a switch in antidepressant medication<sup>a</sup>



Dalhuisen I et al, Am J Psychiatry. 2024;181(9):806-814.

# Flow

Transcranial direct current stimulation (tDCS)

30 min QD

**FDA Approved:**  
Major depression



# ProLivRx

External combined occipital and  
trigeminal afferent stimulation  
(eCOT-AS)

40 min BID

**FDA Approved:**  
Depression after antidepressant  
failure (1 trial, large effect size 0.8)



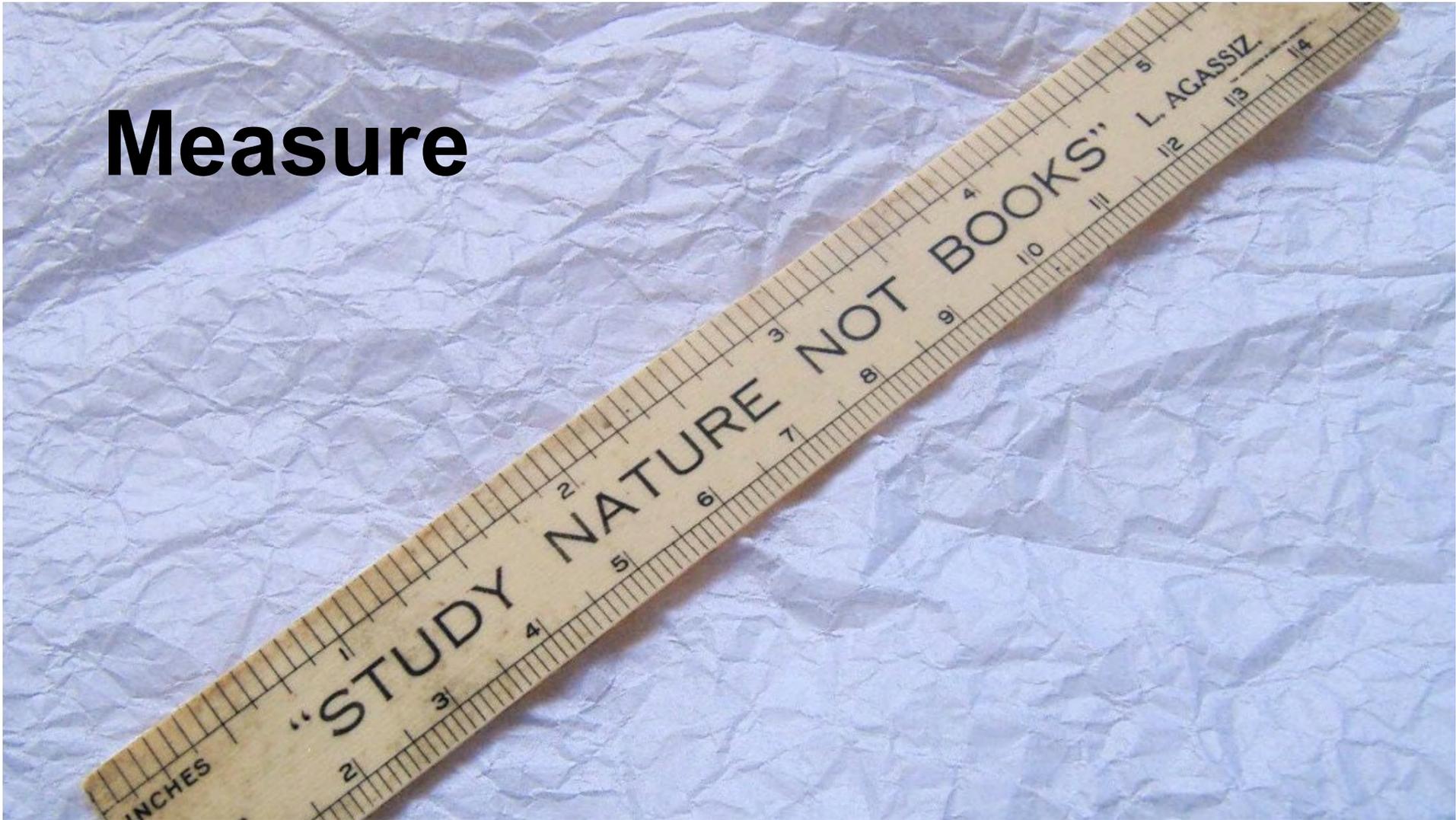
# SAINT TMS

- Five day course
- Ten hours a day
- One 3-minute iTBS per hour
- fMRI guided magnet placement
- Remission 79% (vs 13% sham)
- Maintained at one year with PRN treatment (based on biometrics, approx. 1 day/month)



Cole EJ et al, Am J Psychiatry 2022;179:132–41  
Stimpson K et al, Brain Stimul 2025, 18:208e617

# Measure



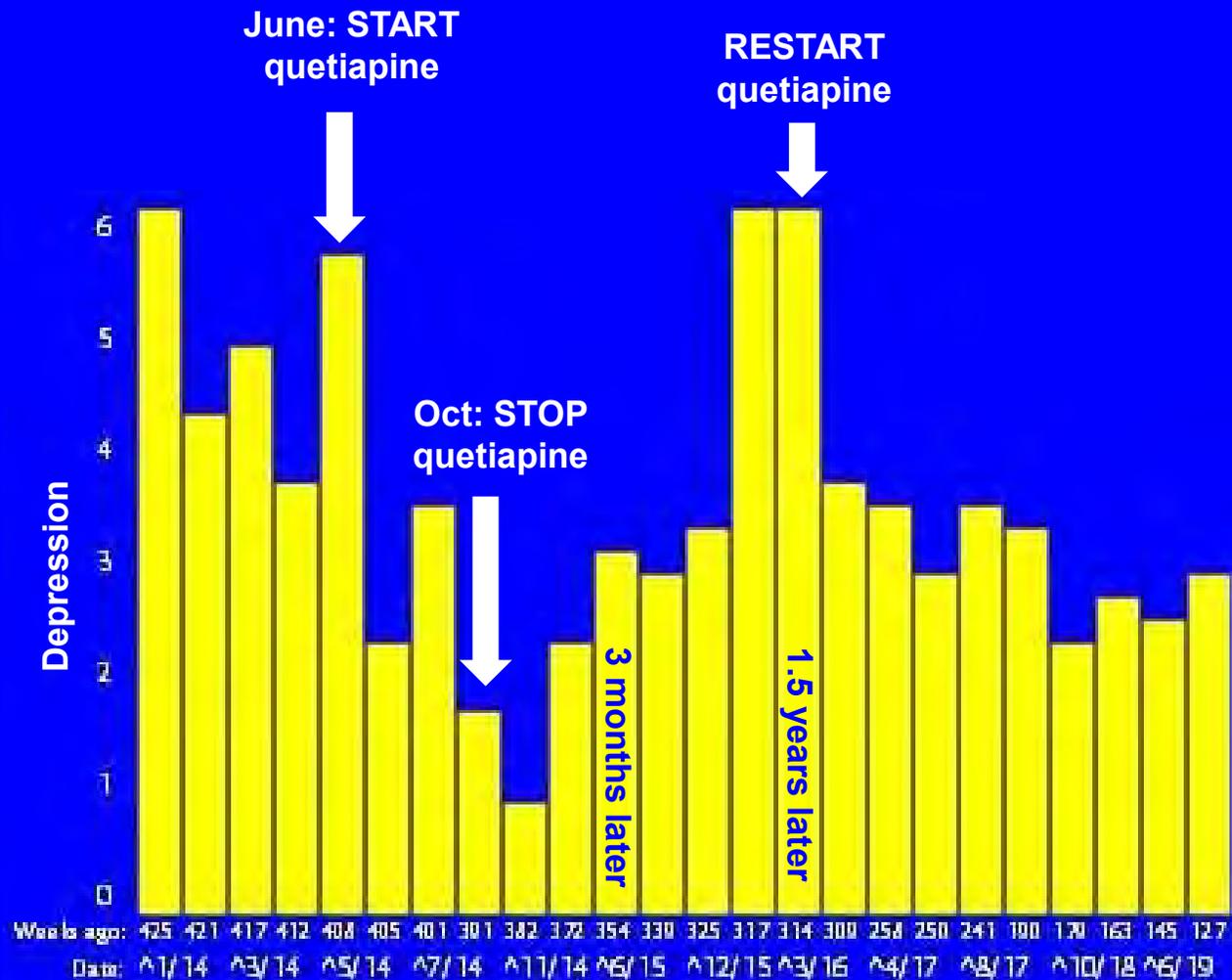
# Regular Measurement Raises Remission in Depression



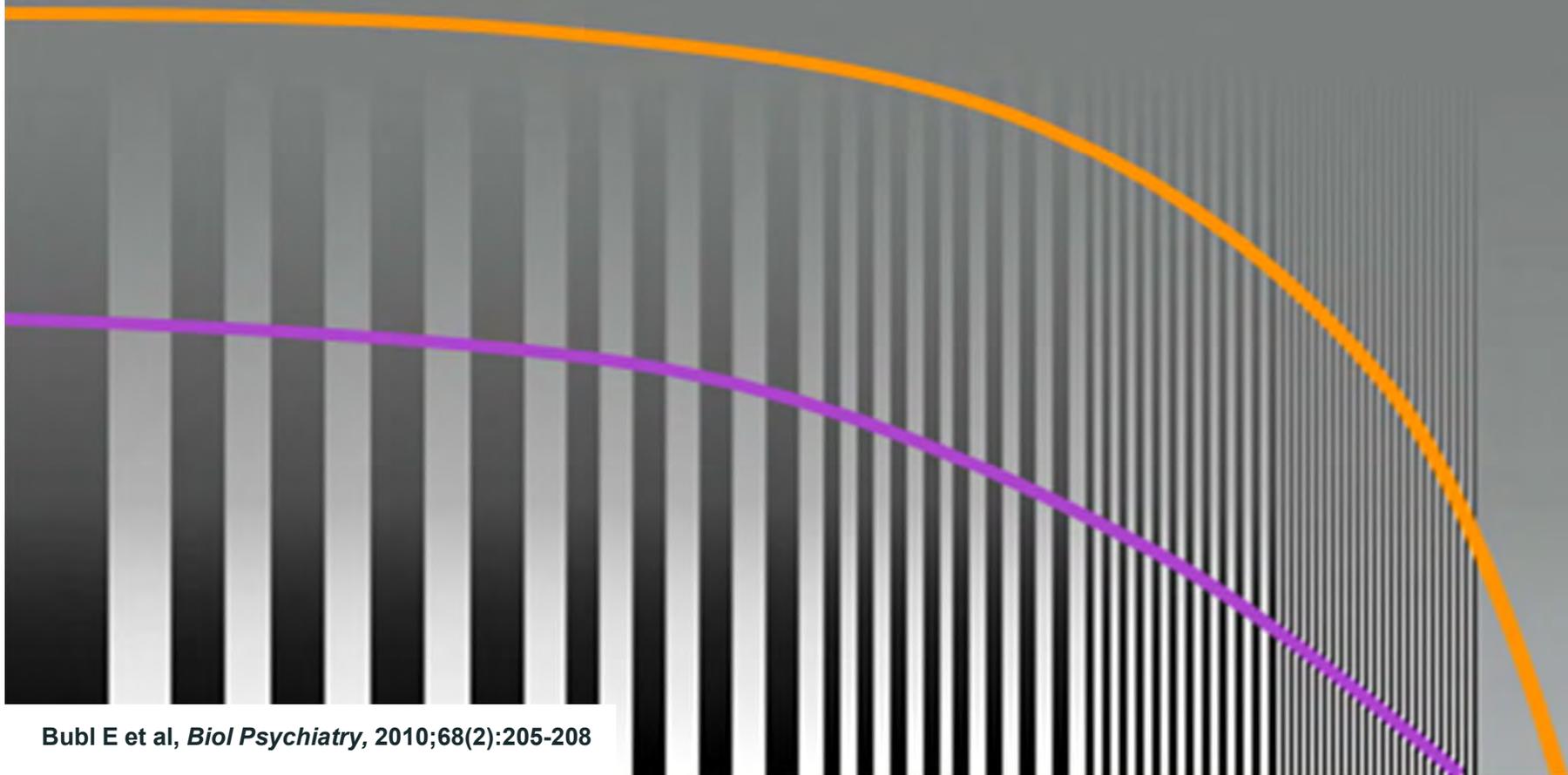
Guo T et al, *Am J Psych*,  
2015;172:1004-13

\*Self-rated QIDS with algorithm-guided care based on QIDS level.  
Both groups only allowed paroxetine and venlafaxine (n=120).

# Patient Report Doesn't Match Rating Scale



# Depression impairs ability to distinguish shades of gray



Bubl E et al, *Biol Psychiatry*, 2010;68(2):205-208

# Questions?

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