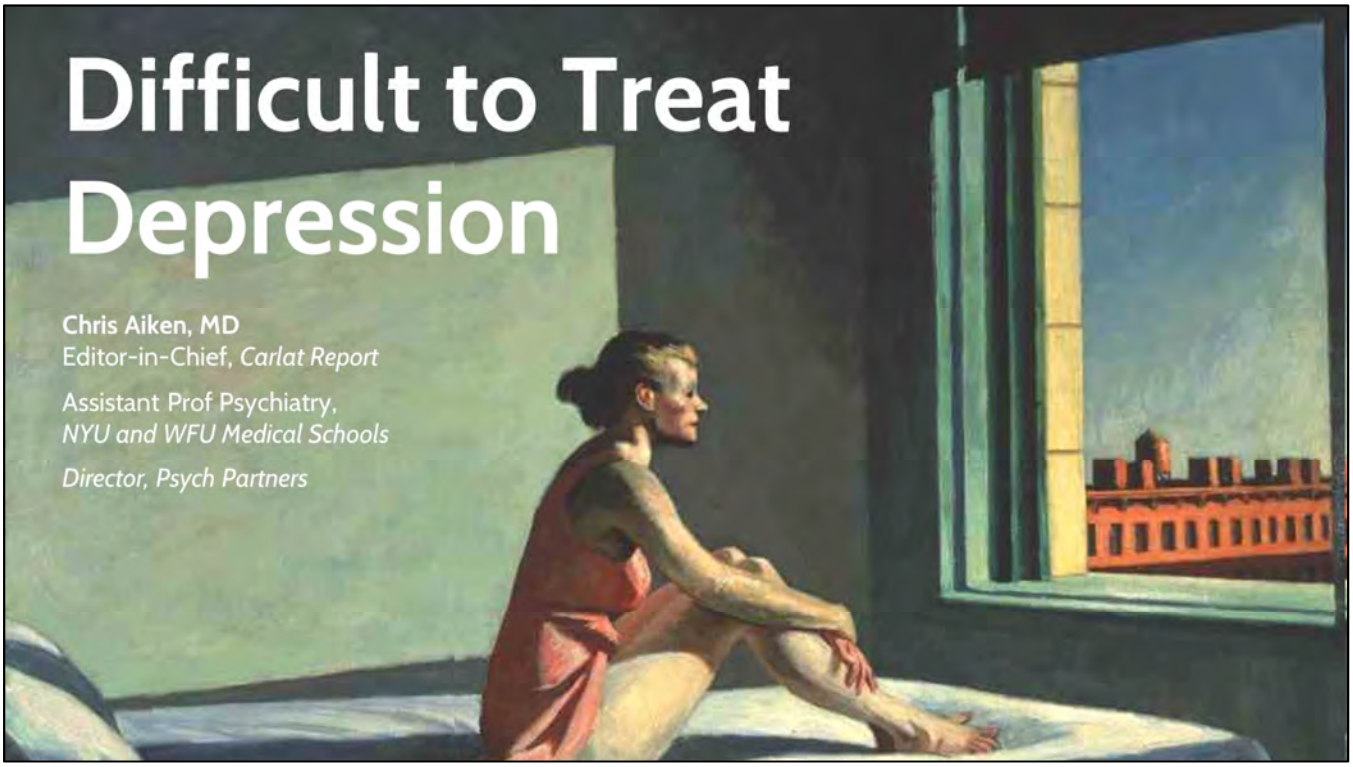

Difficult to Treat Depression
Chris Aiken, MD
Editor-in-Chief, Carlat Report
Assistant Prof Psychiatry,
NYU and WFU Medical Schools
Director, Psych Partners

No conflicts

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

All treatments discussed are off-label in depression except:

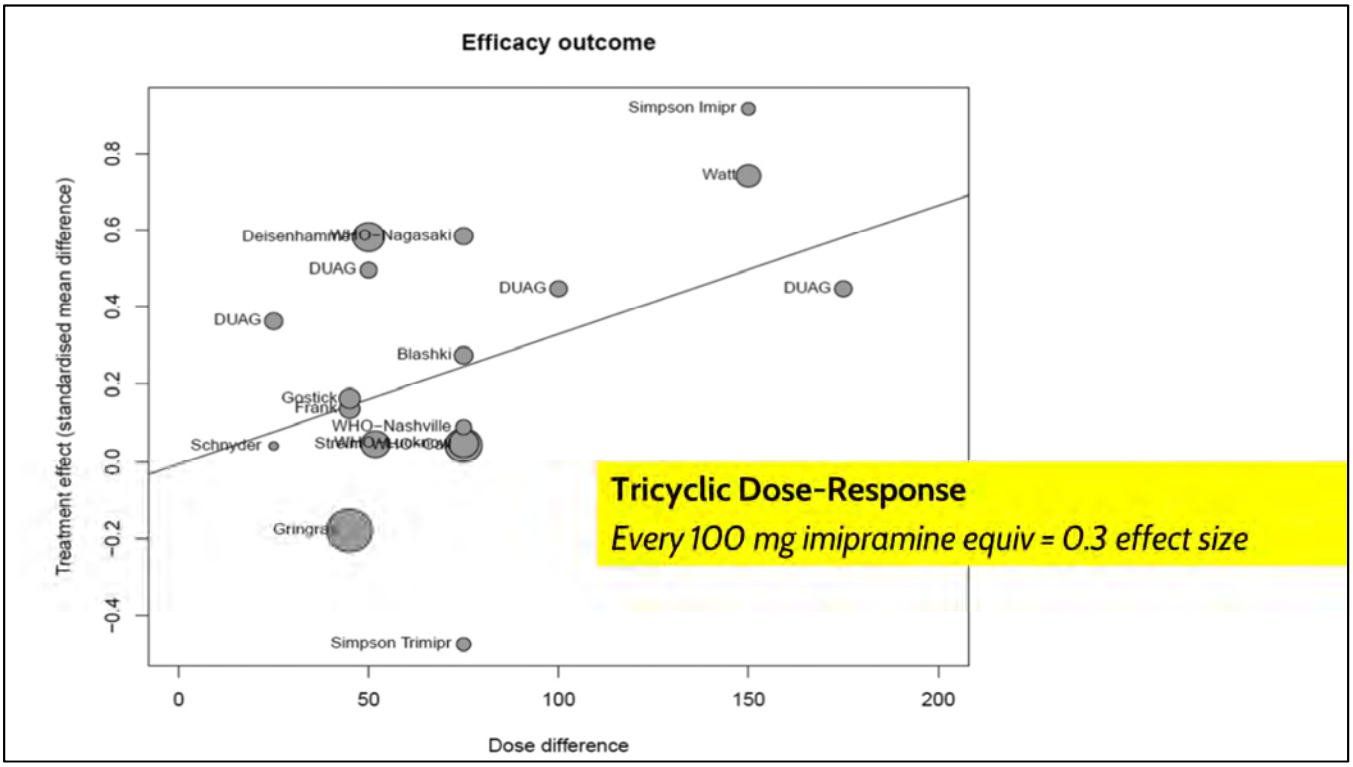
- Antidepressants (approved)
- Antipsychotic augmentation (approved)
- l-Methylfolate (cleared)
- tDCS and eCOT-AS (approved)
- TMS and SNT (cleared)

Old Ways

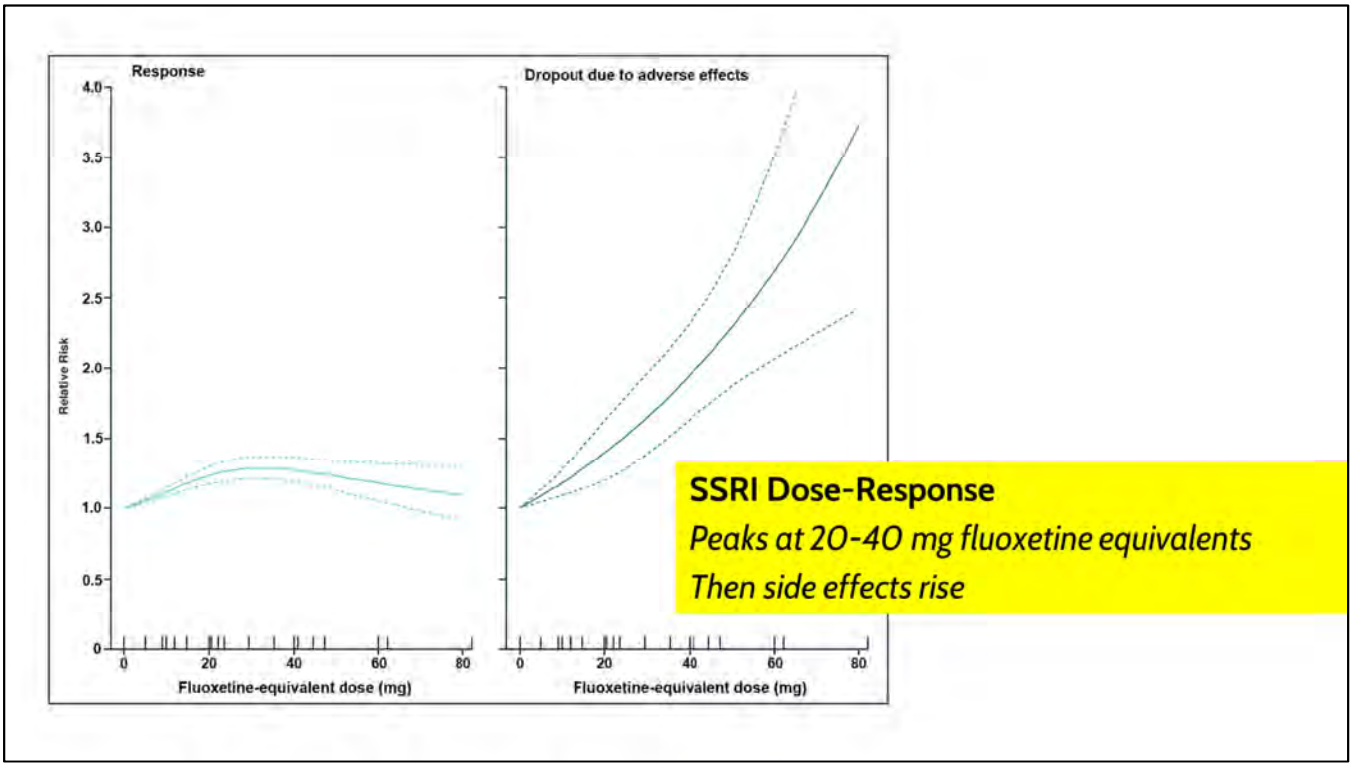
- Switching antidepressants
- High dose antidepressants
- Stimulant augmentation
- Aug with buspirone or antidepressants
- Antipsychotic augmentation
- Rapid acting treatments
- Impressionistic care

New Ways

- Psychotherapy
- Personalize by subtypes
- Address deficits
- Aug with lithium or pramipexole
- Neuromodulation (TMS, ECT, ProLivRx)
- Long lasting treatments
- Measurement-based care



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, from Baethge C et al. J Affect Disord. 2022;307:191-198.



Based on 99 fixed-dose groups. Furukawa TA et al. Lancet Psychiatry. 2019;6(7):601-609. There are 39 similar analyses, and only 20% found a dose response, but those included flexible dose trials which are less reliable as they insert uncontrolled variables. Other trials show giving the med more time is equivalent to raising the dose, raising doubt about flexible-dose results (Metaanalysis of 123 trials. Furukawa TA et al, Acta Psychiatr Scand. 2020;141(5):401-409).

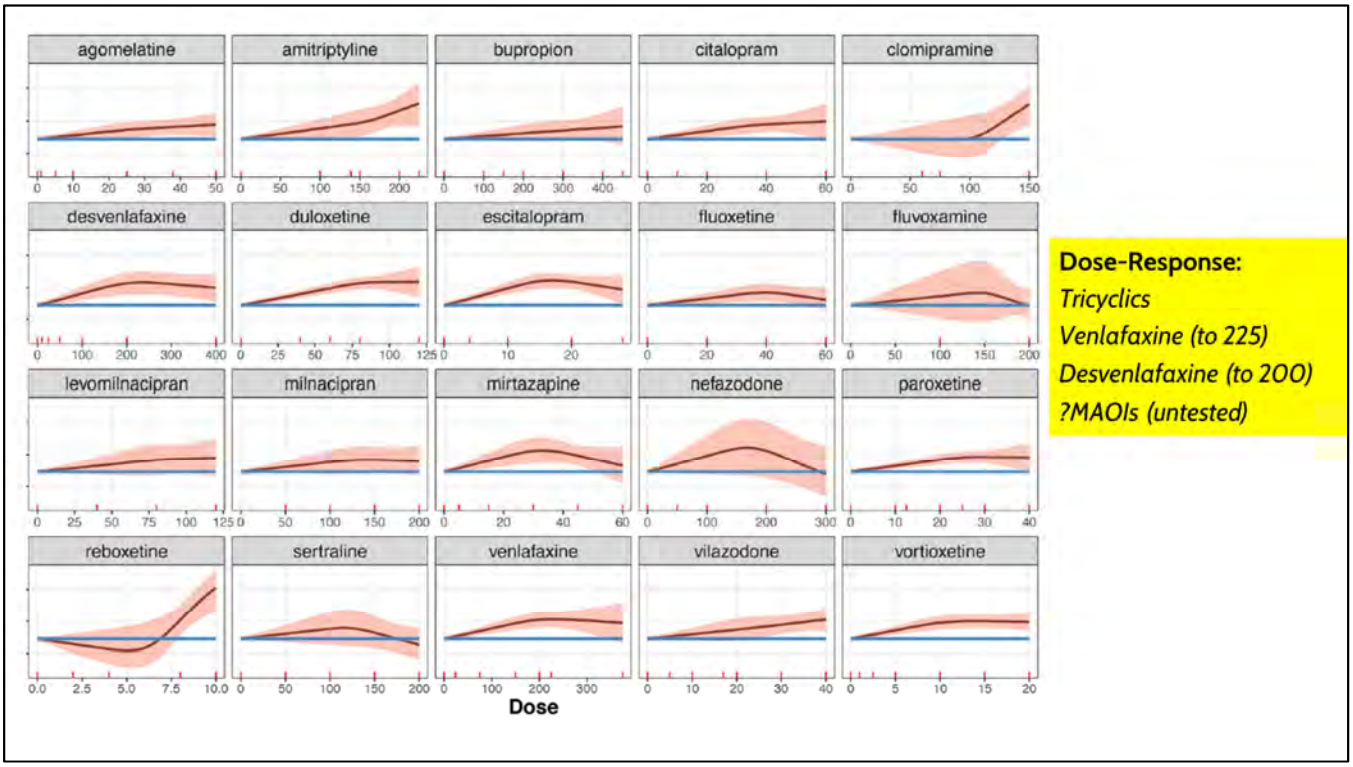


Figure: Network metaanalysis of 120 trials. Hamza T et al, Stat Methods Med Res, 2/2022.

1	3	2
Bupropion	**Mirtazapine**	**Buspirone**
5	8 small	
Stimulants	**Lamotrigine**	

These strategies gained popularity through small or uncontrolled trials, only to fail in large trials.

Above each medication are the large randomized controlled trials where it failed as antidepressant augmentation. In most cases, these are large randomized trials and there are no positive large trials (lamotrigine is an exception where all are small trials, and failed in meta-analysis of them).

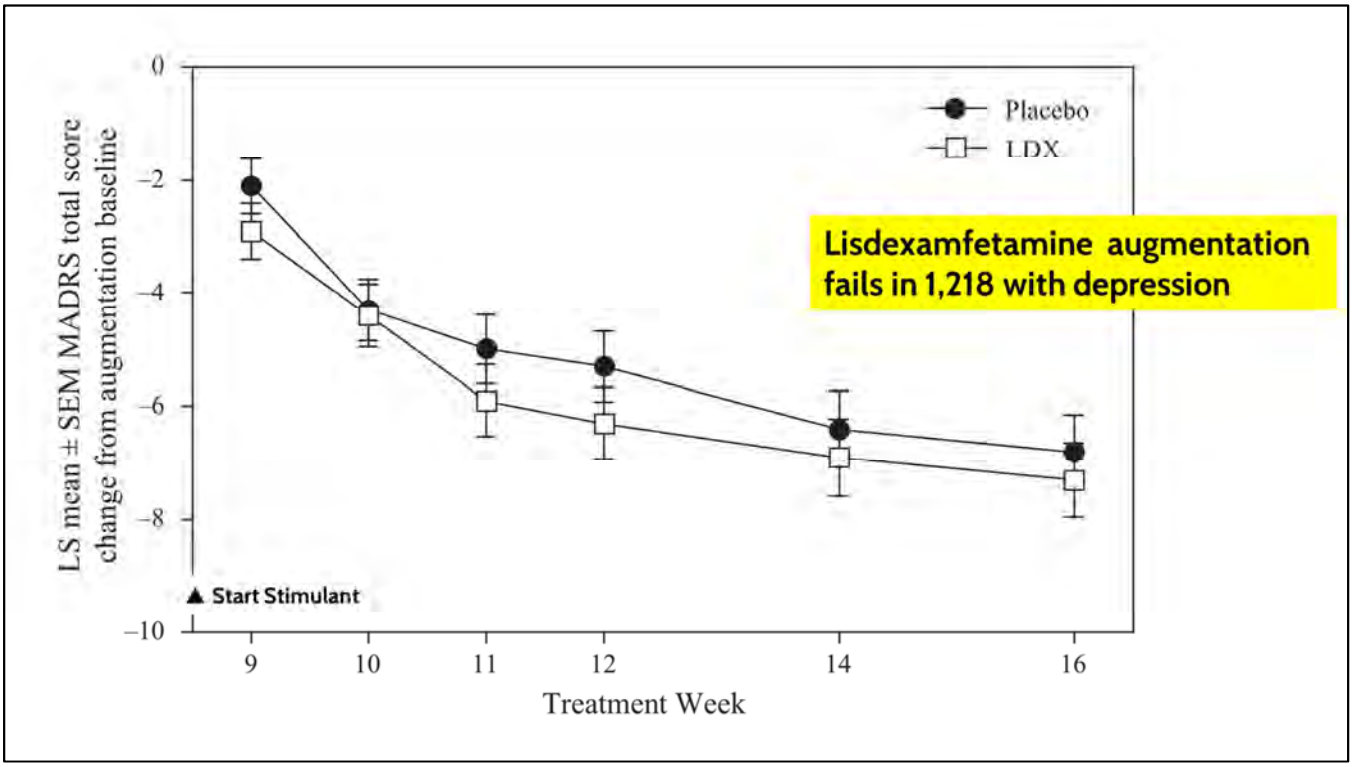
Mirtazapine looked positive in a 2022 meta-analysis from JAMA, but in that analysis all the well-designed, large trials were negative, and most of the positive ones were small in size.

However, there are exceptions where these strategies might work. The next page shows how they might be personalized, with the caveat that this is based on secondary analysis of the large trials - data fishing for a positive signal.

Obesity (BMI ≥ 30) Inflammation (CRP ≥ 3) Nicotine cessation	Anxious Depression	Anxious Depression (as first-line monotherapy)
Bupropion	**Mirtazapine**	**Buspirone**
Methylphenidate: elderly w/apathy, medical d/o Lisdexamfetamine Depression w/ executive dysf	Chronic Depression (over 8 years)	
Stimulants	**Lamotrigine**	

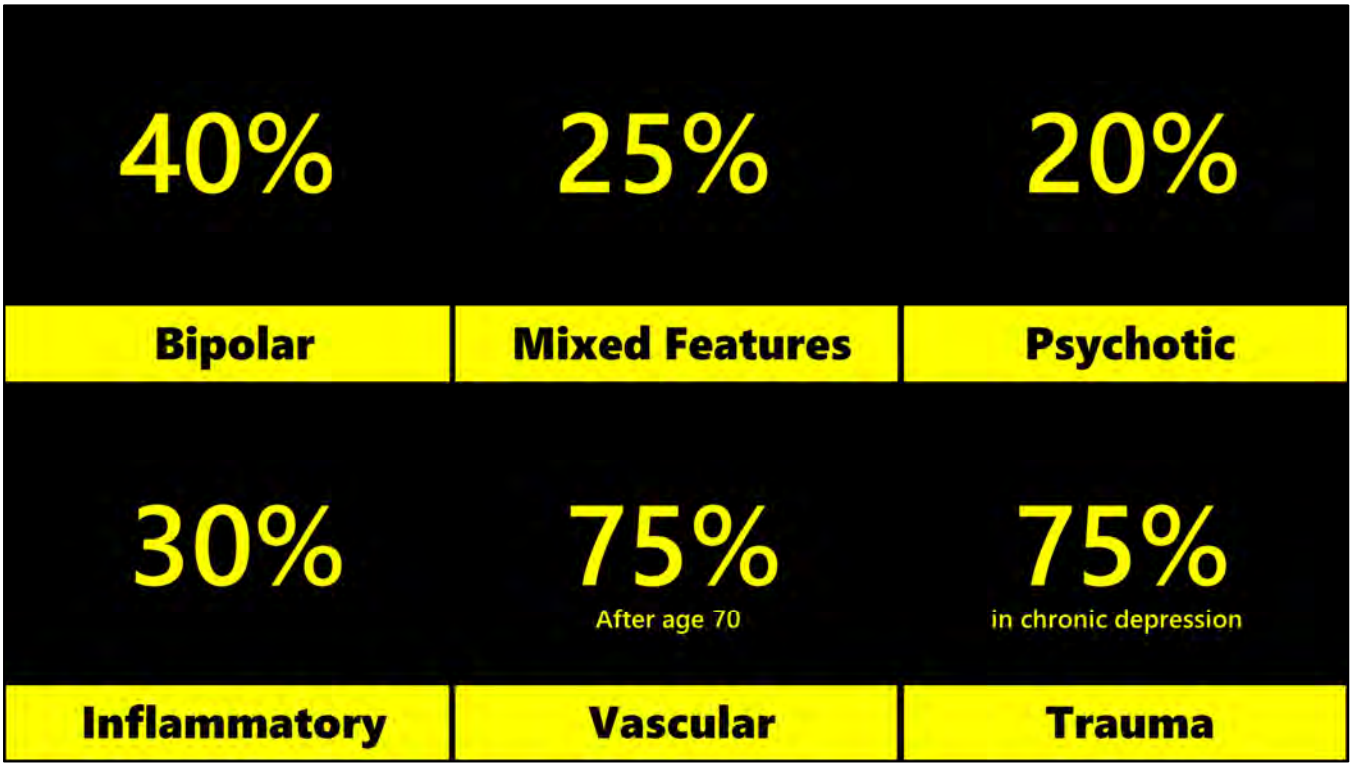
These are subtypes where the augmentation may have benefits (most are based on secondary findings)

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.

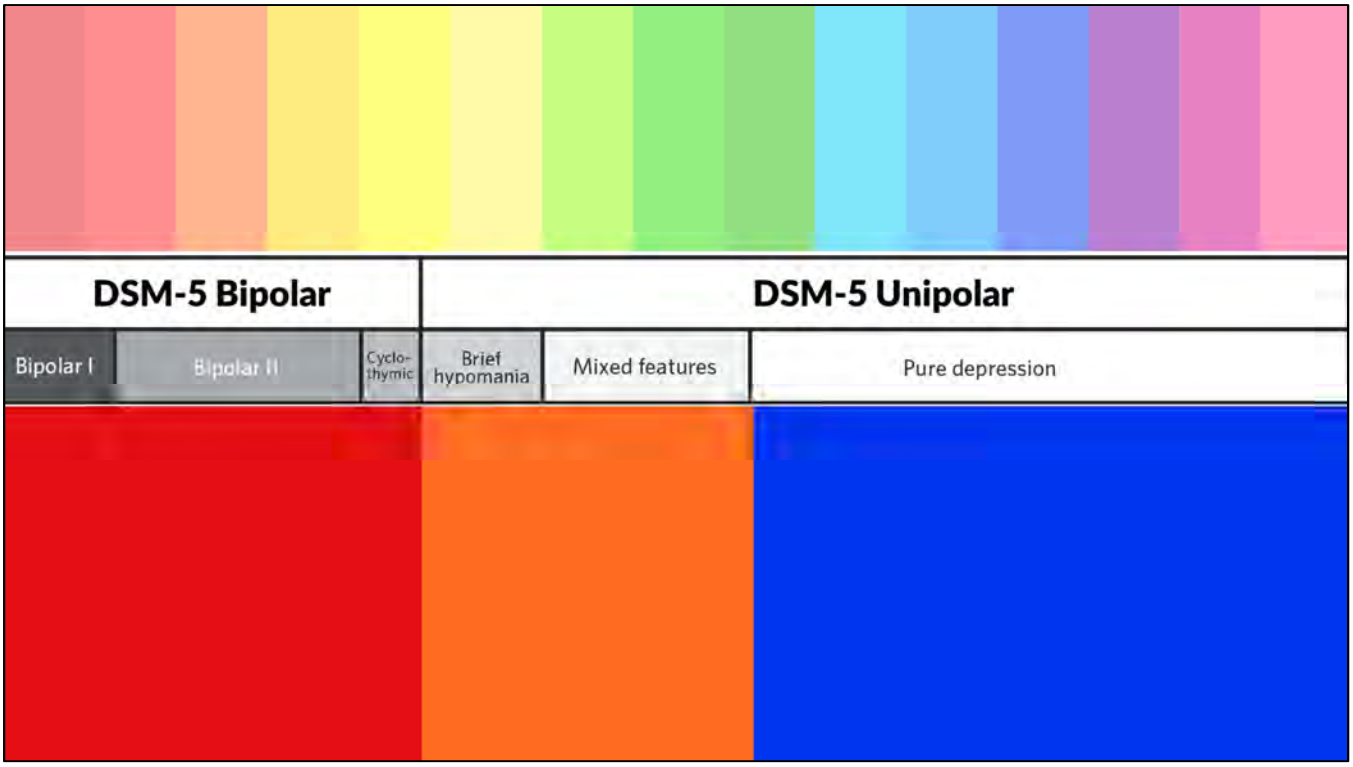


No benefit for Lisdexamfetamine (3 RCTs n=1,218), Methylphenidate ER (2 RCTs n=205);
Richards C, et al. J Affect Disord 2016;206:151-160

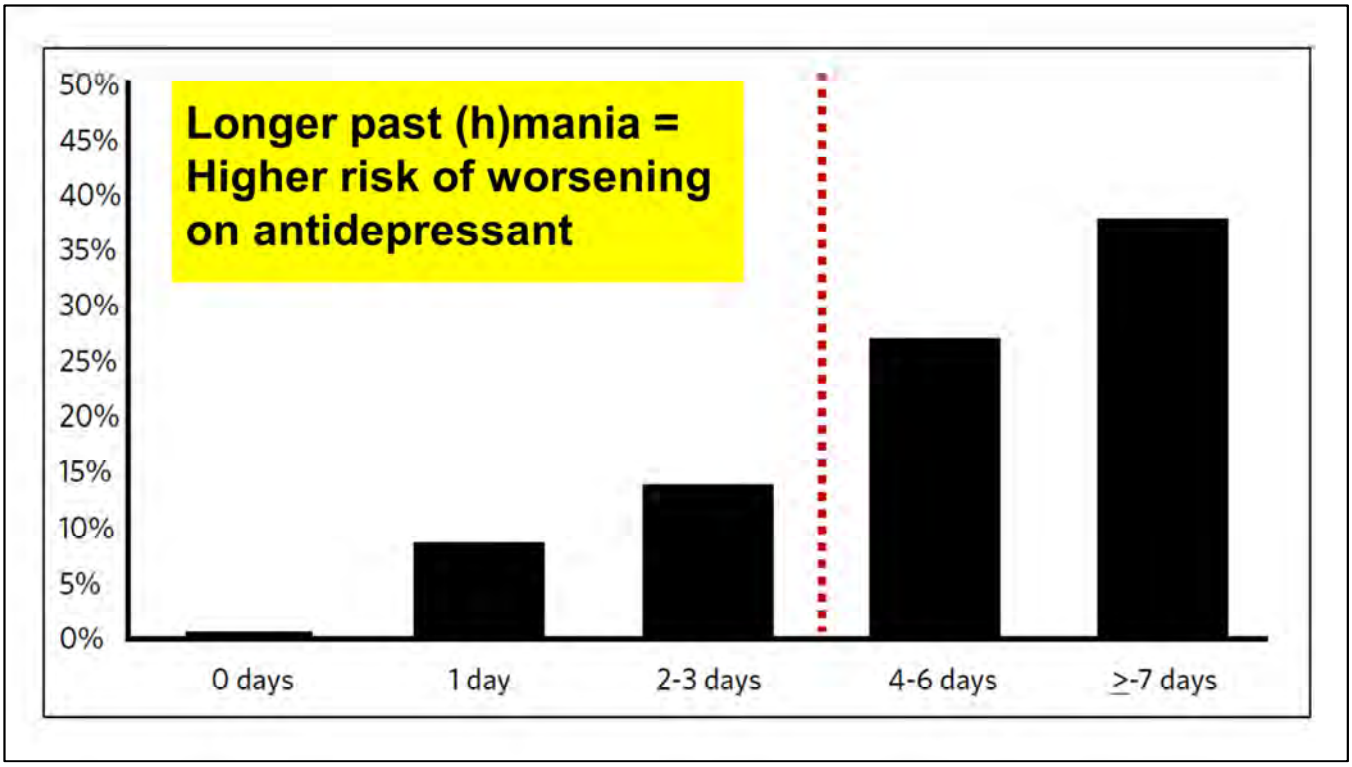
Personalize by Subtype



The rates above are approximately 30% higher in treatment-resistant populations. The figures add up to more than 100% because of significant overlap (eg mixed states, trauma, and vascular disease predict higher inflammation).



Before DSM-III, bipolar was a spectrum that included unipolar (manic-depressive illness). Today's DSM preserves those spectrum concepts but in separate boxes. When lined up together, nearly half of all depressives have bipolar features



Think of bipolar-unipolar as a spectrum, where antidepressants have relative risks that rise with degree of bipolar features. Angst showed that hypomania occurs on a spectrum – there is no sharp line dividing bipolar from everyone else. Some people have had a few symptoms of hypomania, some have had the whole syndrome, and there is no clear line that separates the bipolar person from the rest of humanity on this. He also found that the risk of mood worsening on an antidepressant rises with the longest duration of people's hypomania, and you see that here – it's a steady increase, [B] although only those with 4 days or more in a row would qualify for DSM bipolar (Angst J et al, *Eur Arch Psychiatry Clin Neurosci*, 2012, 262(1), 3-11)

Psychotic Depression

- 30% of cases are missed
- ECT is gold-standard (> 90% remission)
- Antipsychotic augmentation is intuitive but weak (effect size 0.25) and requires schizophrenia-level dosage
- Lithium augmentation (uncontrolled trials)

Recent infection (within 6 months) is a risk factor for depression and suicide. Suicide rates go up in the spring, in part due to allergies.

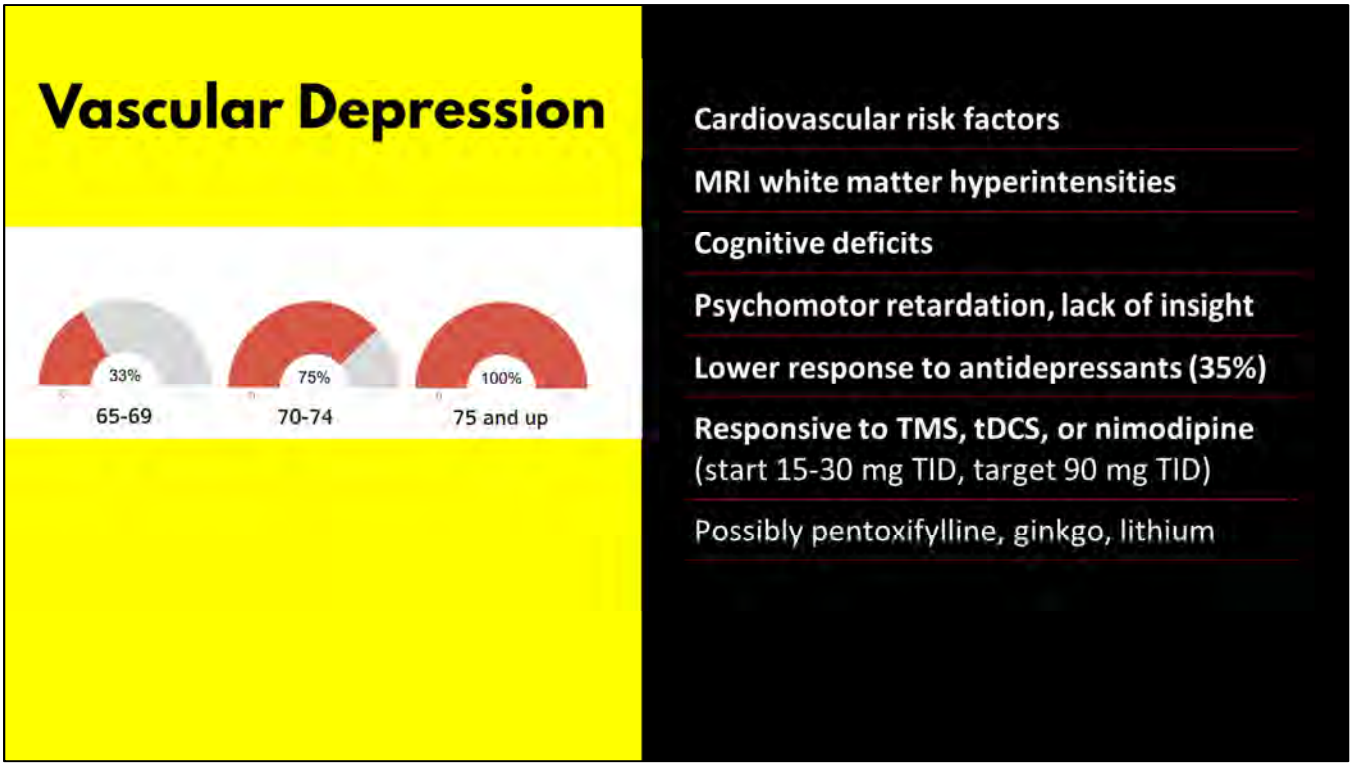
Medication for Inflammatory Depression

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

Naturals for Inflammatory Depression

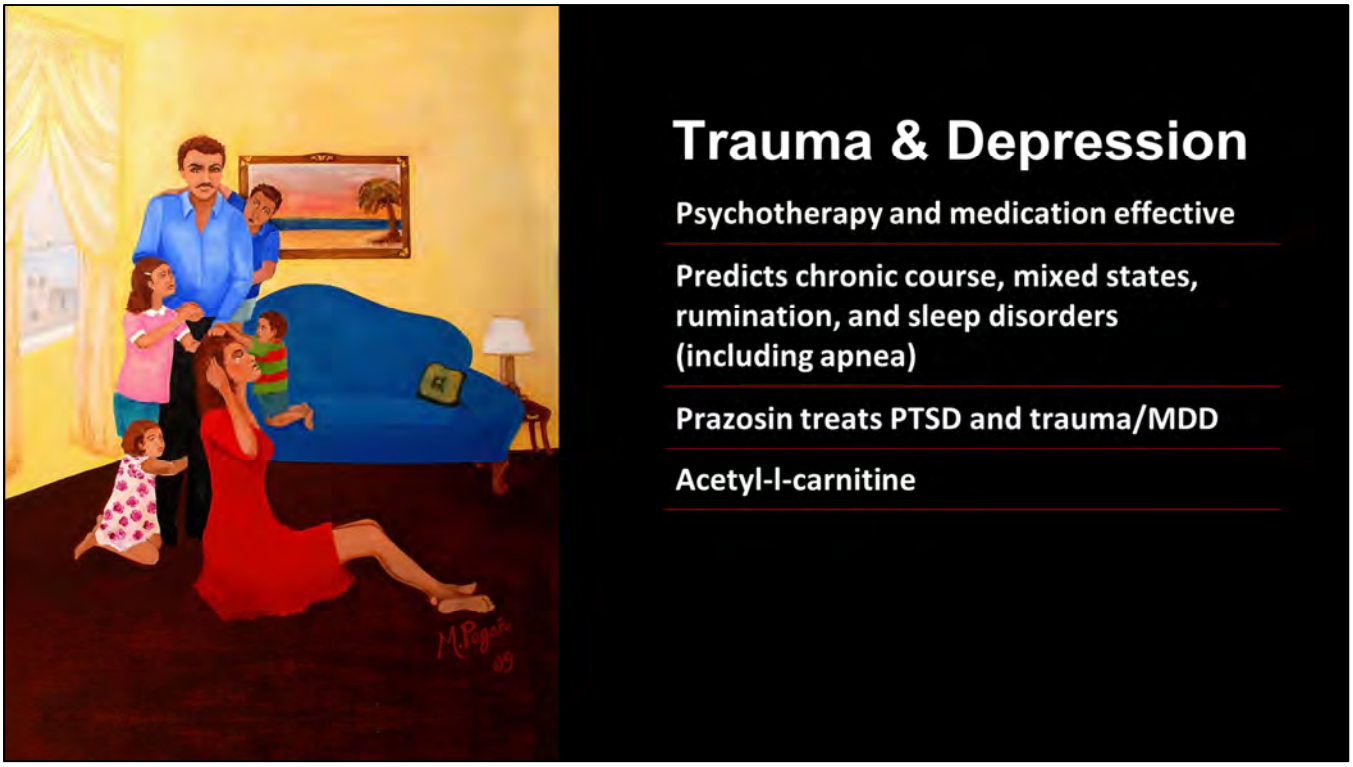
	Rationale
Omega-3	↑CRP predicts response, esp to higher dose (4,000 mg/day, EPA:DHA ≥ 2:1)
N-Acetylcysteine (NAC)	↑CRP predicts response
L-Methylfolate	↑CRP predicts response in unipolar; positive trials in bipolar
Lifestyle	Exercise, Mediterranean diet, CBT-insomnia, stress reduction

References: 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



Tandospirone, which is similar to buspirone, has positive trials (available in Asia). Post stroke depression is different (larger injury) and responds to antidepressants better. Read more: https://psych-partners.com/what-works-for-vascular-depression/

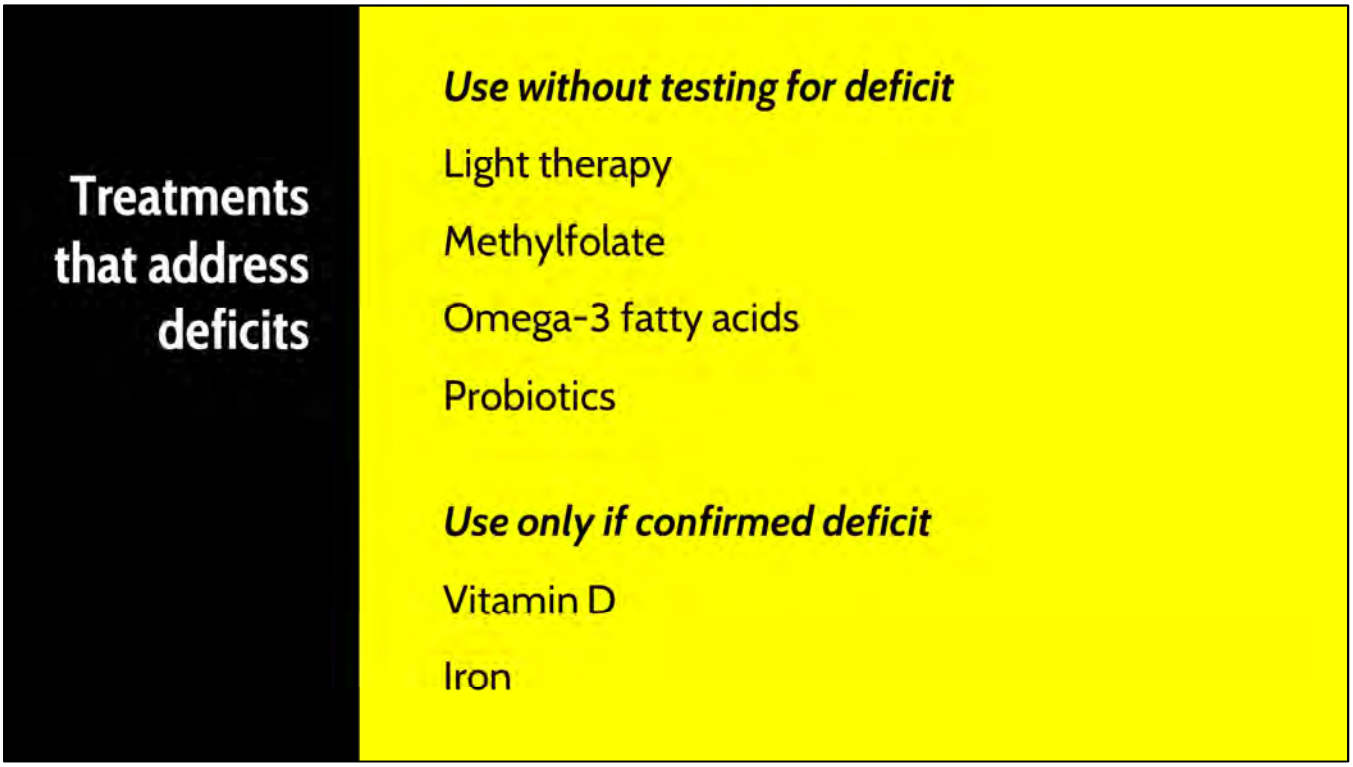
Ref: Taylor WD et al, Am J Psychiatry 2018;175(12):1169-1175; Park JH et al, J Affect Disord 2015;180:200-206; Taragano FE et al, Int J Geriatr Psychiatry 2001;16(3):254–260; Taragano FE et al, Int Psychogeriatr 2005;17(3):487–498



Childhood trauma predicts more severe and chronic course, but not necessarily poor response to treatment. Prazosin dosing in PTSD: Start 1 mg QHS, raise by 1–2 mg every 4–7 days based on response. Average 12–16 mg/day; max 25 mg/day for men and 12 mg/day for women. Divide the dose at ≥ 3–5 mg/day (give 25% in morning). For depression, trial used 0.5-1 mg qhs (Guo P et al, Acta Psychiatr Scand 2025;151(2):142–151).

Acetyl-l-carnitine has 1 large and 4 small trials in depression; past trauma predict lower ALC levels, and chronicity, older age, and treatment-resistant predict resposne. Dose 500 mg QD, raise by 500 mg every 3–7 daysto 2,000–3,000 mg divided BID (Veronese N et al, Psychosom Med 2018;80(2):154-159). Well tolerated; occurs naturally in the body (it is amodified form of the amino acid L-carnitine). It shuttles fatty acids into mitochondria for energy production, donates acetyl groups for the synthesis of acetylcholine and other neurotransmitters, and supports neuroplasticity and reduces neuroinflammation. Animal studies suggest ALC works by upregulating glutamatergic mGlu2 receptors, producing antidepressant effects faster than traditional medications.

Address Deficits



REF: 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.

Methylfolate effect size = 0.4-0.9

Risks

None

Tolerability

None

Cost

$8 per month (15 mg)

Recommended Products

chrisaikenmd.com/supplements

Effect size 0.9 as monotherapy with vitamin-complex **Enlyte** in depression with MTHFR genotype abnormalities, but included heterozygous abn which is common and does not impede folate. Effect size 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

Effect size 0.5 in non-seasonal depression, 0.5-0.8 in winter seasonal depression, 0.4 in bipolar depression

Ref: 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

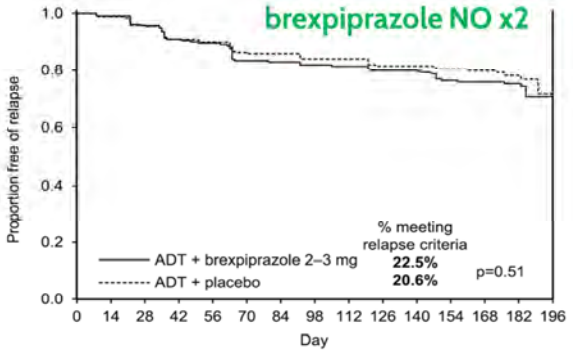
Tardive dyskinesia (3-5%/yr)
Metabolic syndrome
Hyperprolactinemia
Orthostatic hypotension
Arrhythmias
Hyperthermia
Neuroleptic Malignant Syndrome
Priapism
Neutropenia
Elevated LFTs
Mortality in dementia

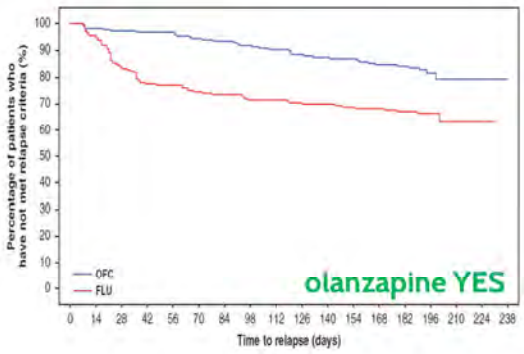
Tolerability

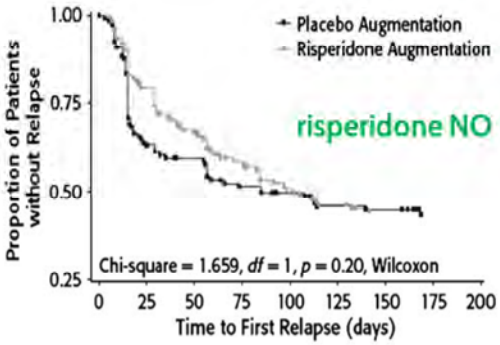
Akathisia
Dystonia
Muscle stiffness (EPS)
Weight gain
Sedation
Sexual dysfunction
Anticholinergic effects

Does antipsychotics prevent depression?

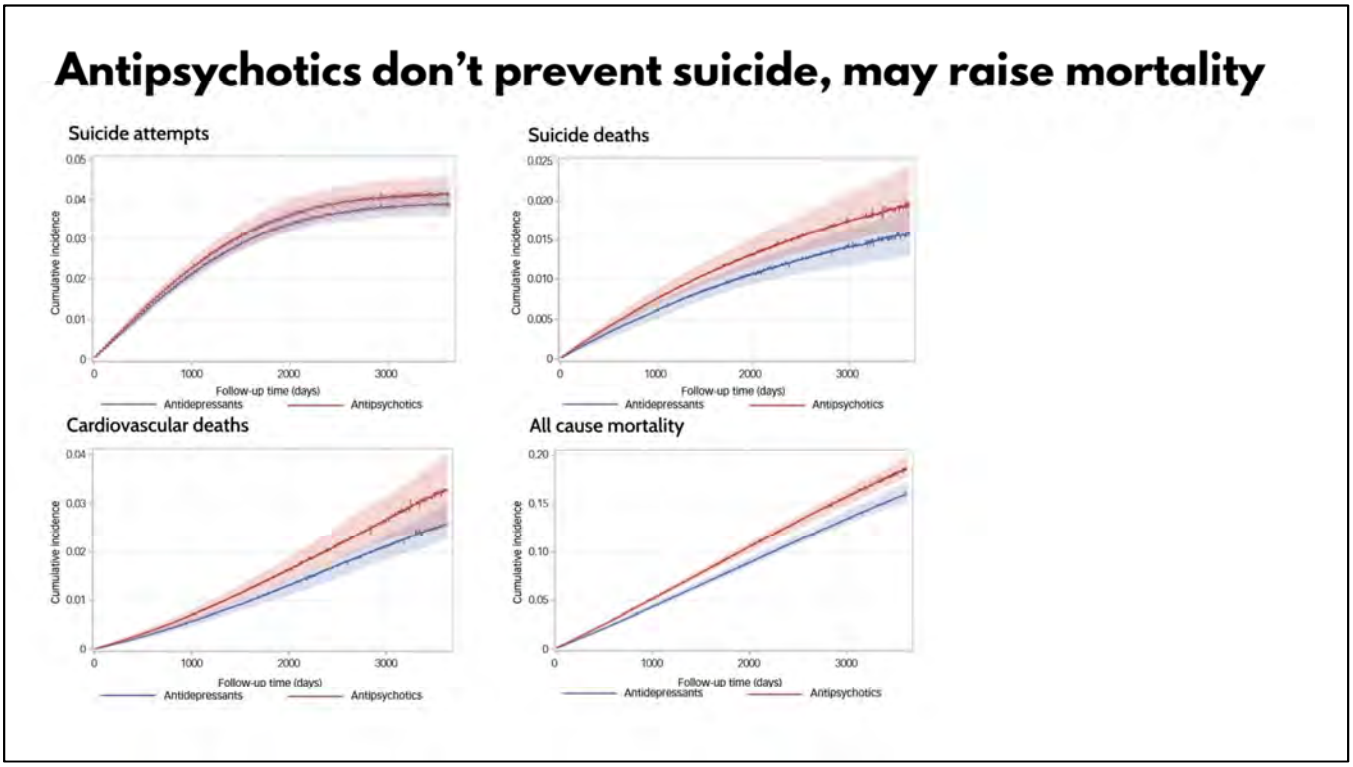
Not in 3/4 trials (6 months, n=2,308)



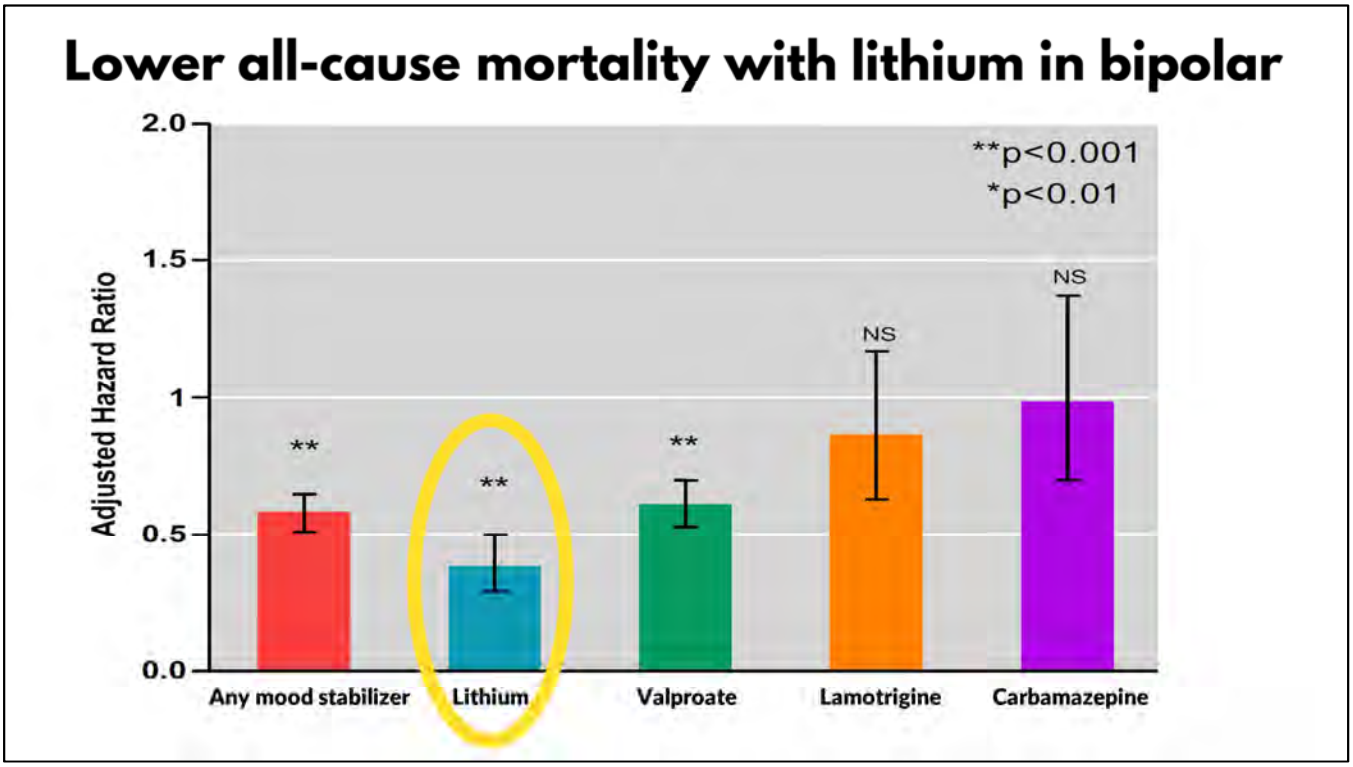




Quetiapine and aripiprazole may have long-term efficacy, but those trials are not gold-standard (lacking placebo control)



Comparative cohort study of 79,898 patients with TRD, tested antipsychotic augmentation vs. matched controls who received third-line antidepressants (Tsai DH et al, Brit J Psychiatry 2025;1-9)



Mortality data found in bipolar (Chen PH et al, *Acta Psychiatr Scand* 2023;147(3):234-247); anti-suicide data in unipolar and bipolar.

Think Longterm

Among these, only T3 and esketamine have positive long-term, placebo-controlled data

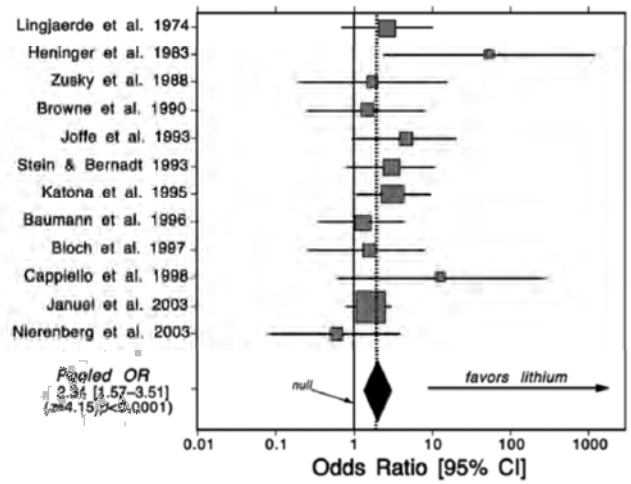
Alprazolam has short-term data (1 month) to treat core depressive symptoms (as monotherapy) or to accelerate antidepressants as augmentation (from a Cochrane meta-analysis of 21 randomized controlled trials involving 2,693 subjects) (van Marwijk H et al, *Cochrane Database Syst Rev* 2012;2012(7)). Eszopiclone has large RCTs to accelerate antidep in GAD and MDD. Pindolol effective only for acceleration of SSRIs (when started with an SSRI), not for longer-term or for non-SSRIs.

Auvelity failed in TRD (unpublished data). Psilocybin also failed in TRD: https://psych-partners.com/psilocybin-in-treatment-resistant-depression

Lithium in Acute Unipolar Depression

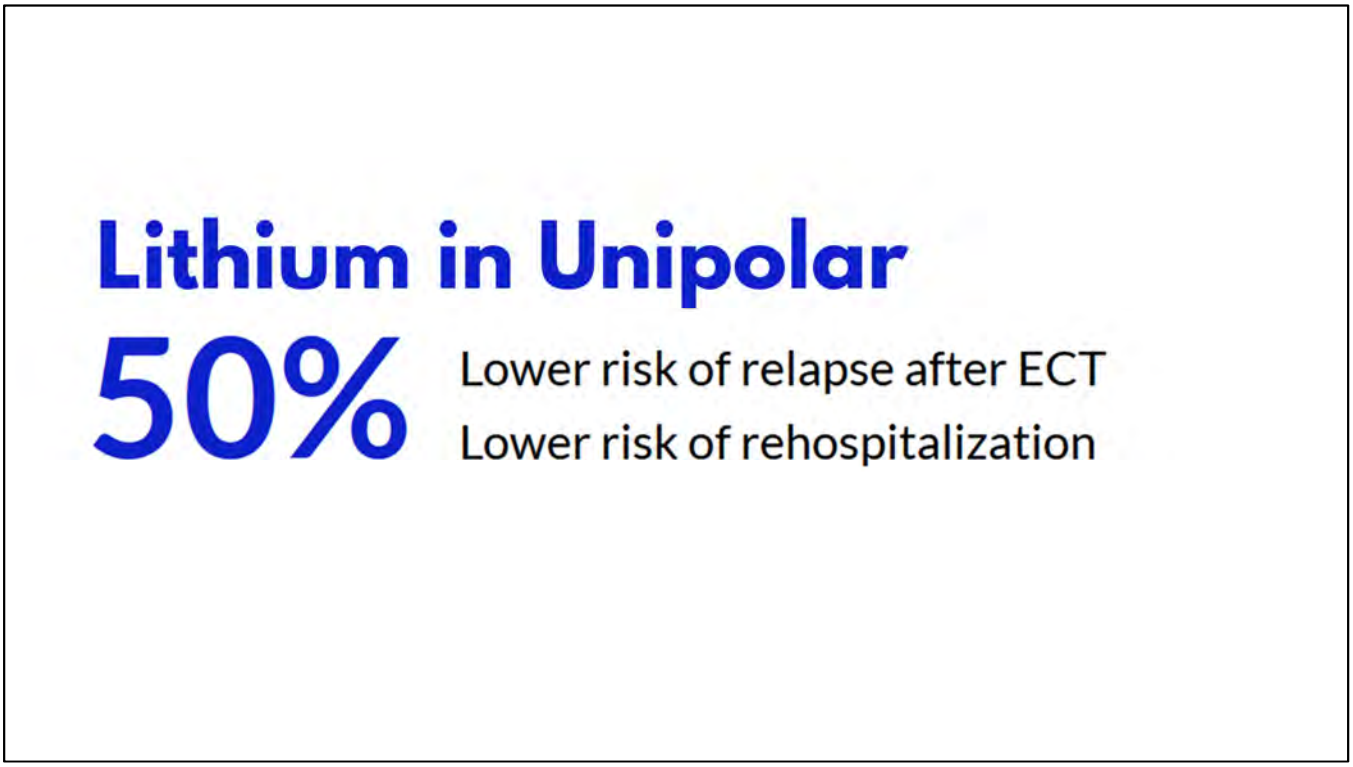
12 Placebo Controlled Trials

5 NNT



Lithium effective as both monotherapy and augmentation in unipolar depression, but may not work for non-recurrent depression. Acute benefits similar to antipsychotics (12 trials, NNT=5)

Reference: Undurraga J et al, J Psychopharmacol 2019;33(2):167-176



The reduction in rehospitalization not seen with antipsychotics or antidepressants.

REFERENCE: 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 prevents unipolar depression

21 Randomized Controlled Trials

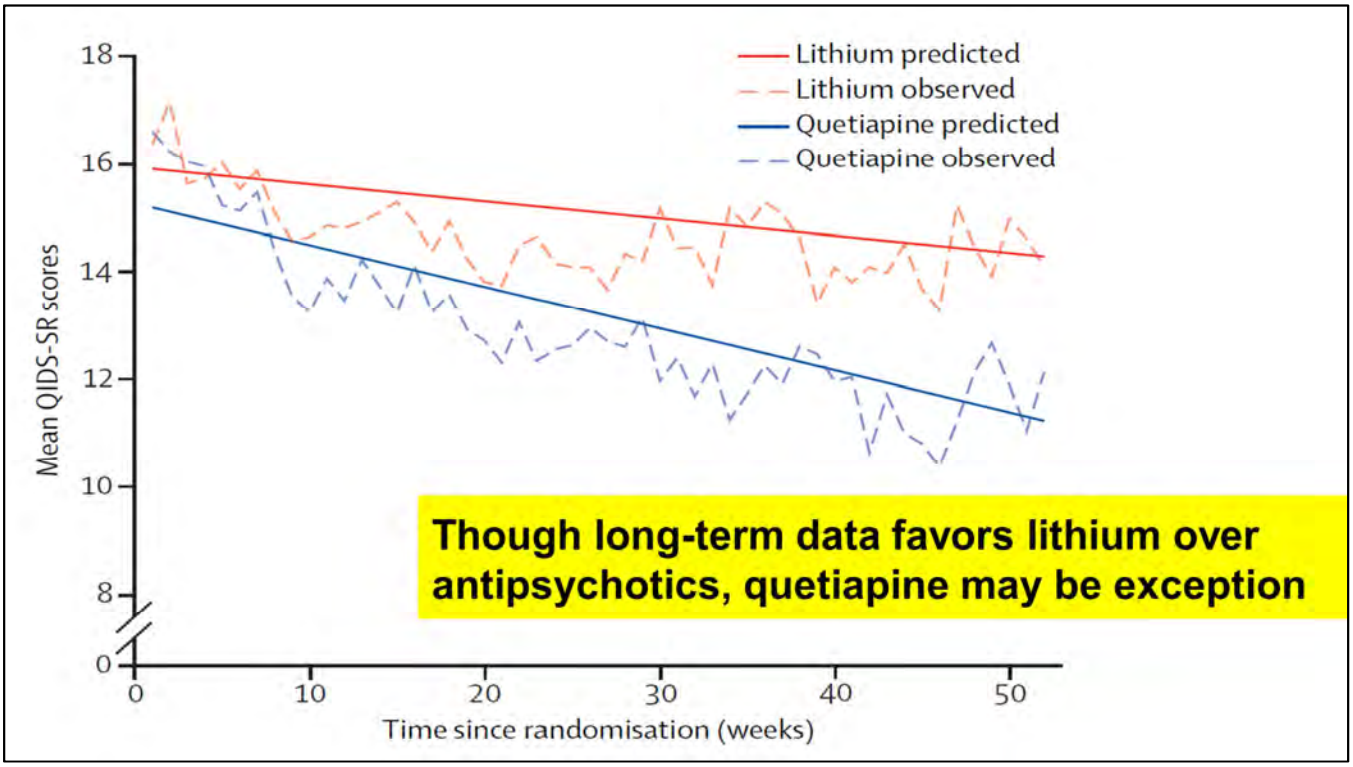
2 Years avg duration

Placebo-Controlled

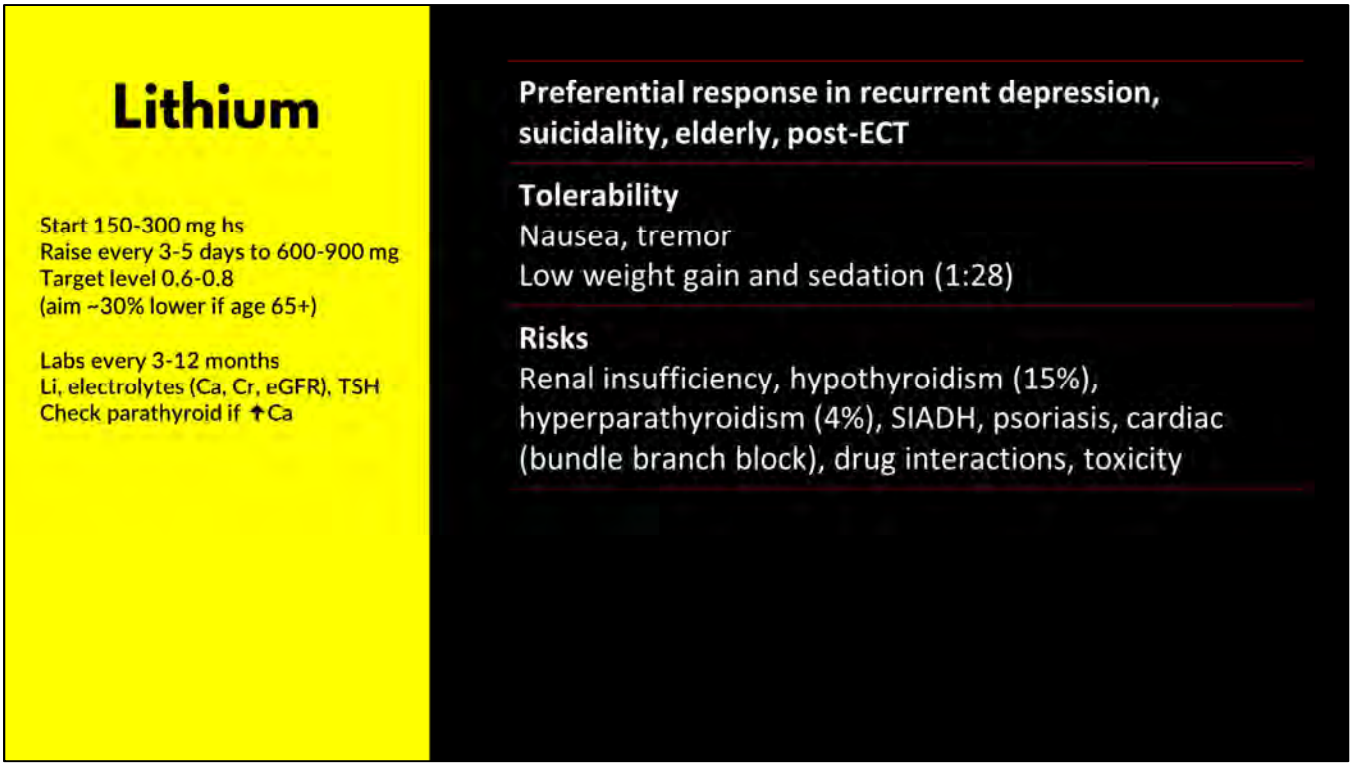
Antidepressant-Controlled

Monotherapy

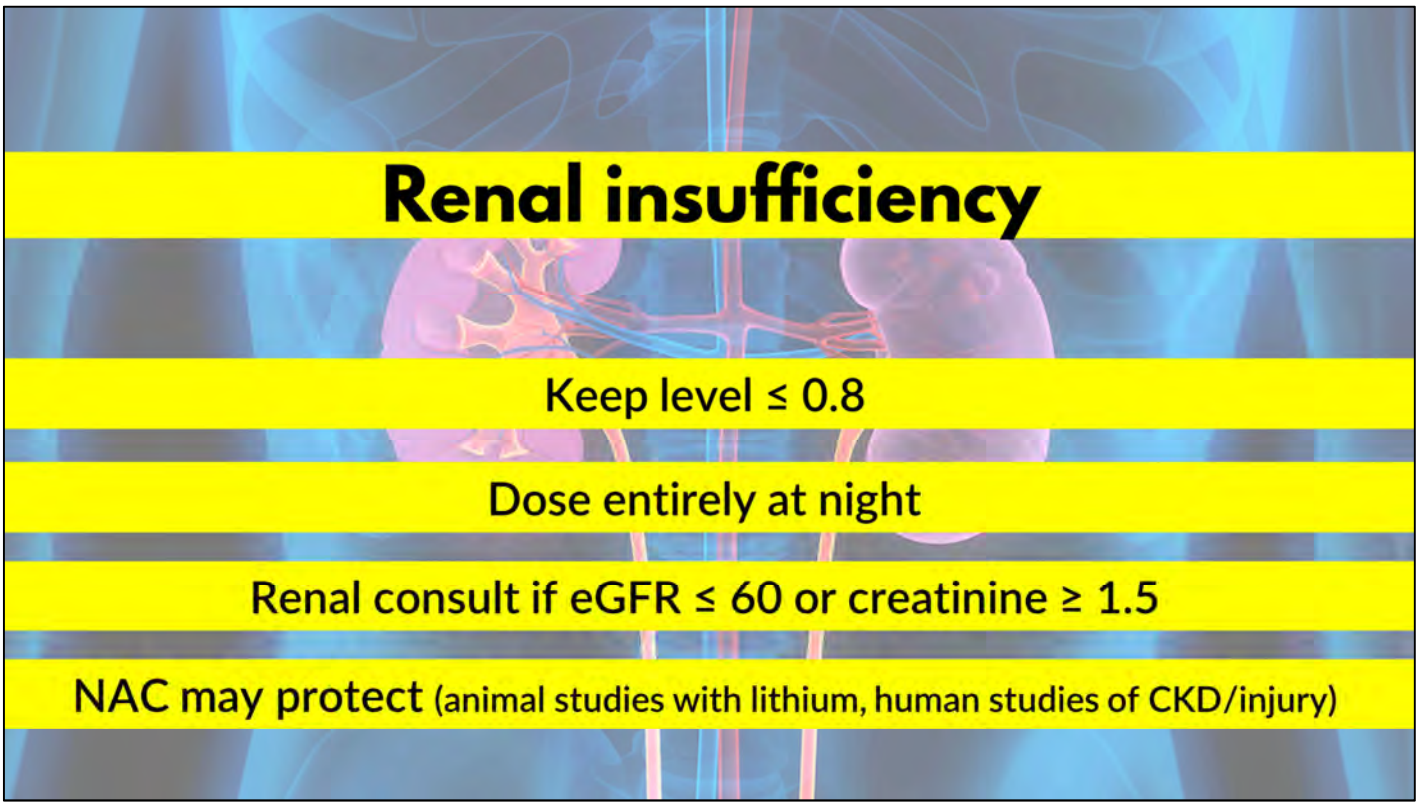
Augmentation



Randomized controlled one-year augmentation trial, n = 212, 60% failed ≥ 3 antidepressants, Lithium mean 0.85, quetiapine 195 mg. In secondary analysis, quetiapine was only more effective in severe anxiety with TRD, though strangely did not reduce anxiety, so maybe just in more severe cases (Pérez V et al, Br J Psychiatry. 2025 Jun 18:1-8).



Ref: 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



Read more:
https://psych-partners.com/lithium-and-the-kidneys-new-guidelines/

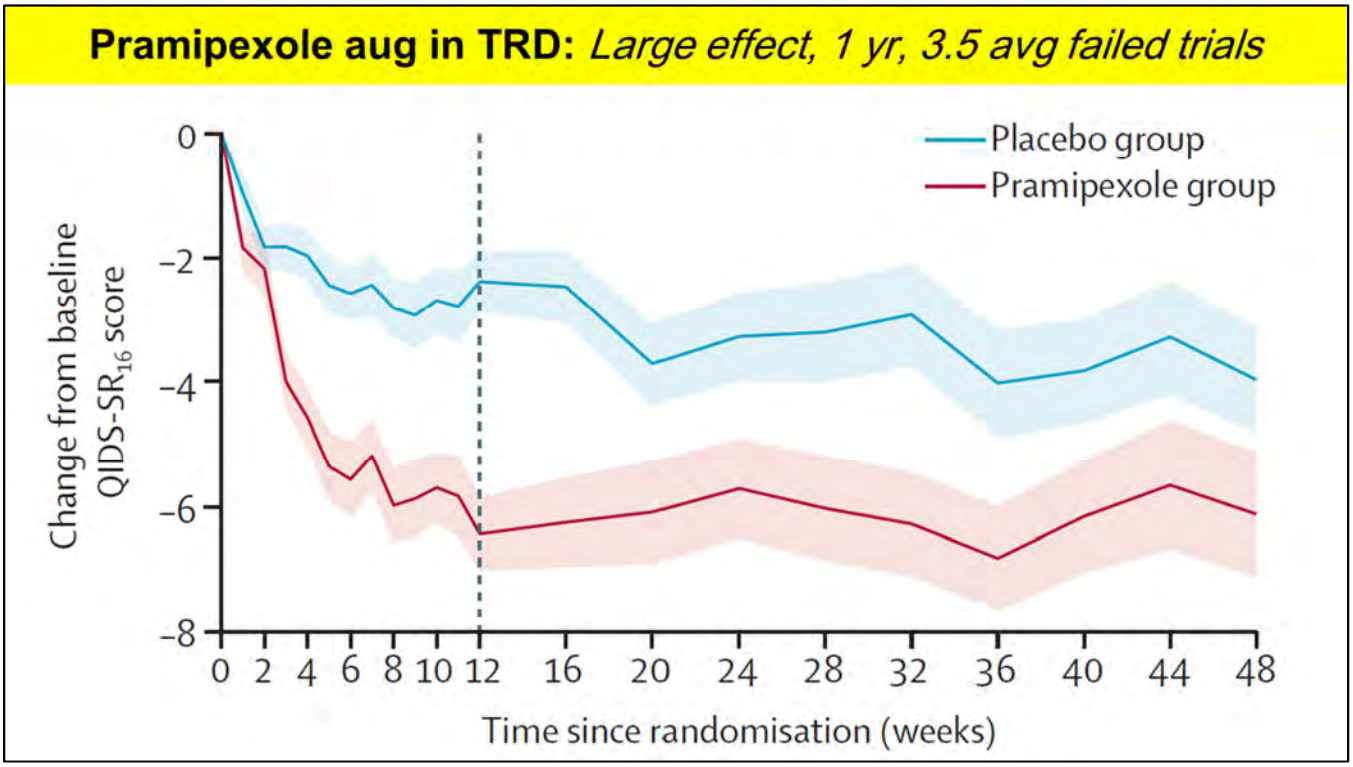
Side Effect Guide

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

Pramipexole aug in TRD: *Large effect, 1 yr, 3.5 avg failed trials*



Randomized, placebo controlled trial, 48 weeks, n = 150, avg 3.5 failed 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)

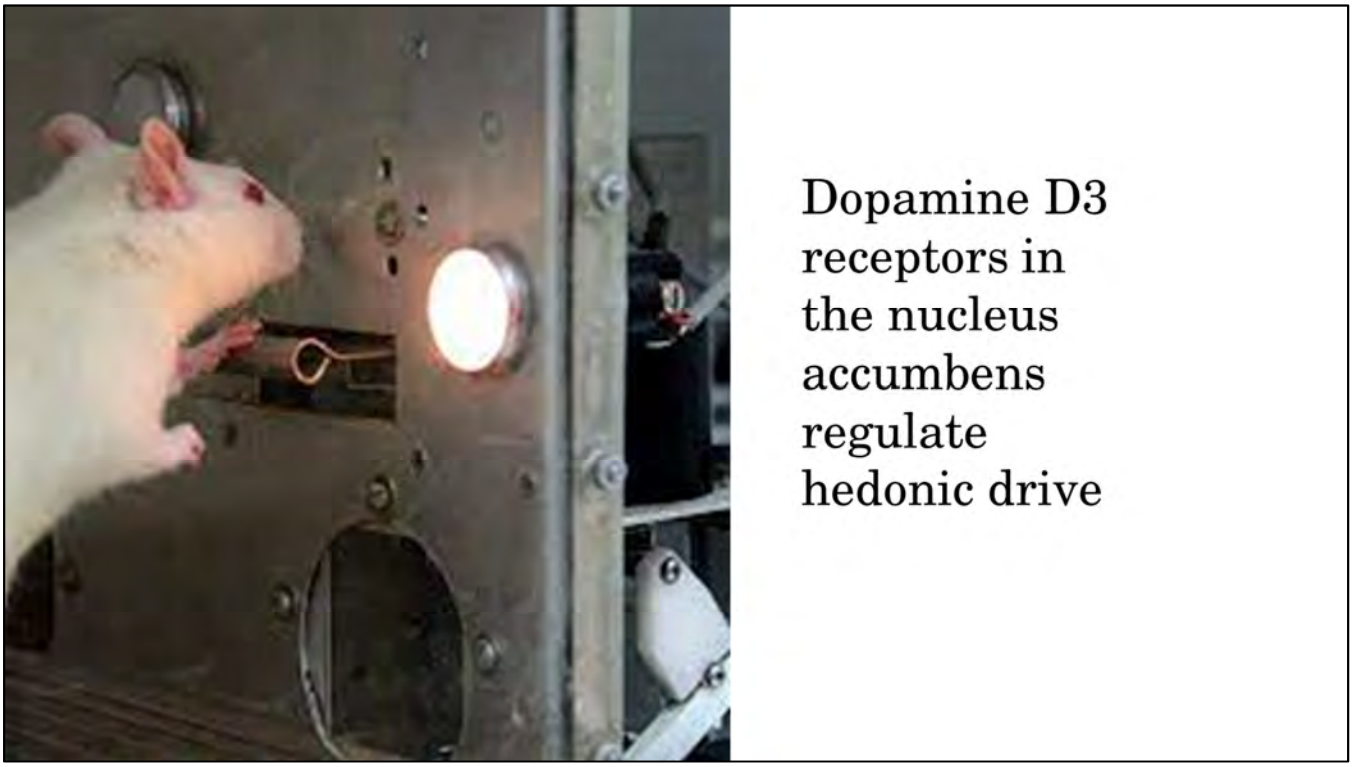
Start 0.125-0.25 mg,
raise by 0.125-0.25mg q3-7 days,
raise faster after 0.75 mg

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

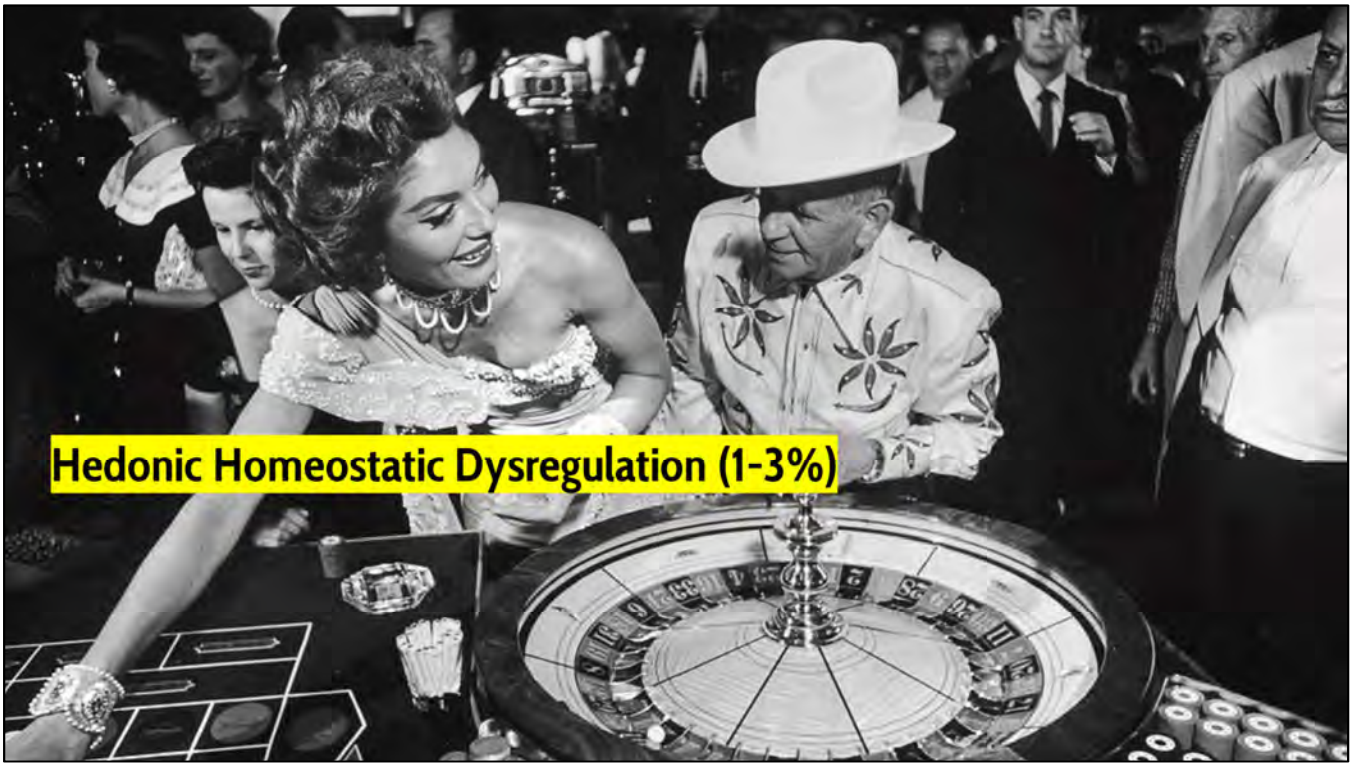
Prefer for anhedonia, inflammation, bipolar spectrum, comorbid restless leg syndrome

Tolerability
Nausea, sedation
No weight/sexual/cognitive

Risks
Hedonistic dysregulation (approx. 1-3%)
Hallucinations (rare at dose < 2 mg)
Hypotension



Pramipexole effective in anhedonic depression:
https://psych-partners.com/pramipexole-for-anhedonic-depression/


Hedonic Homeostatic Dysregulation (1-3%)

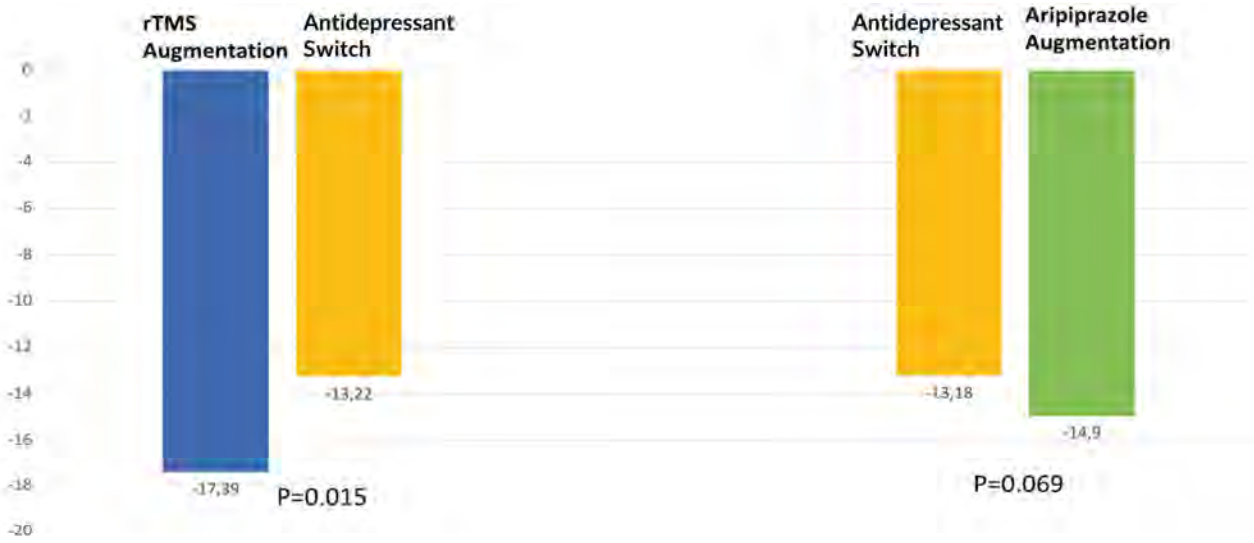
Compulsive masturbation at work
Cleaning garage
Excessive videogames
Sorting bookshelves alphabetically

Neuromodulation

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

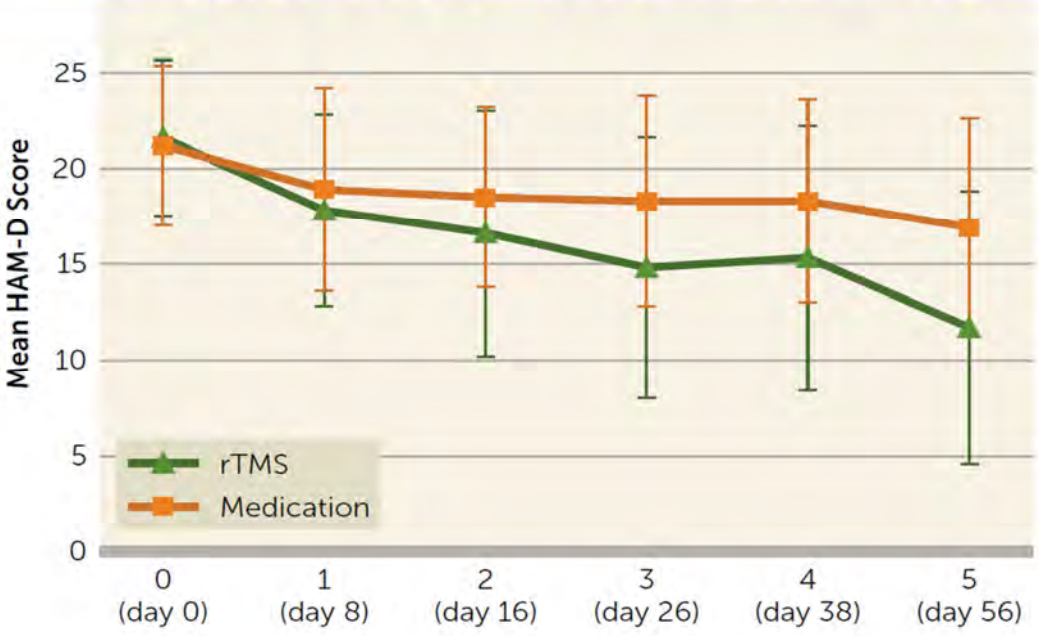
–Scribonius Largos (1st century AD)

TMS Beat Aripiprazole Augmentation in TRD



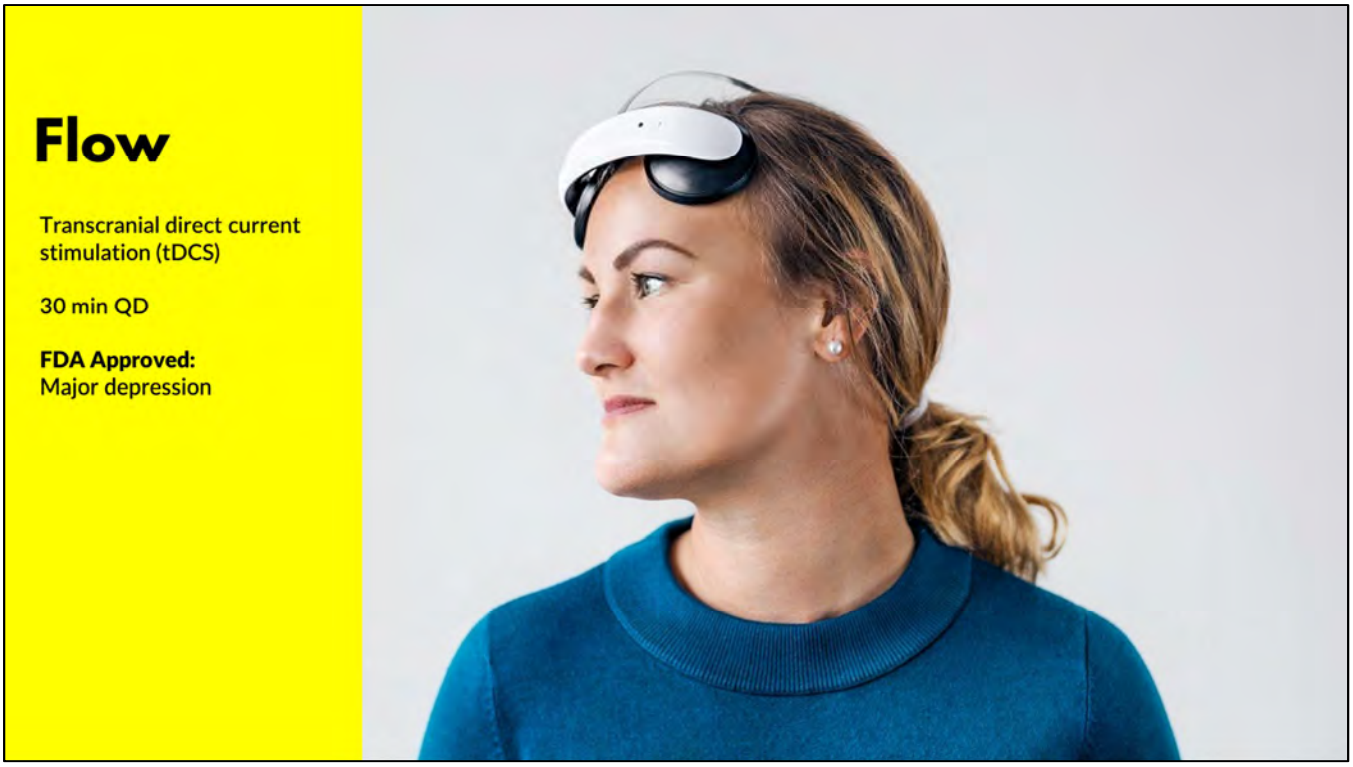
8 wk RCT in TRD, n = 278, mean 9 mg aripiprazole (Papakostas GI et al, Mol Psychiatry. March 7, 2024)

TMS Beat Nortriptyline Augmentation in TRD



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

The maintenance data is based on a small, uncontrolled trial that used biometric data to prompt PRN treatment, delivered approx. 1 day/month. REF: Cole EJ et al, Am J Psychiatry 2022;179:132–41; Stimpson K et al, Brain Stimul 2025, 18:208e617

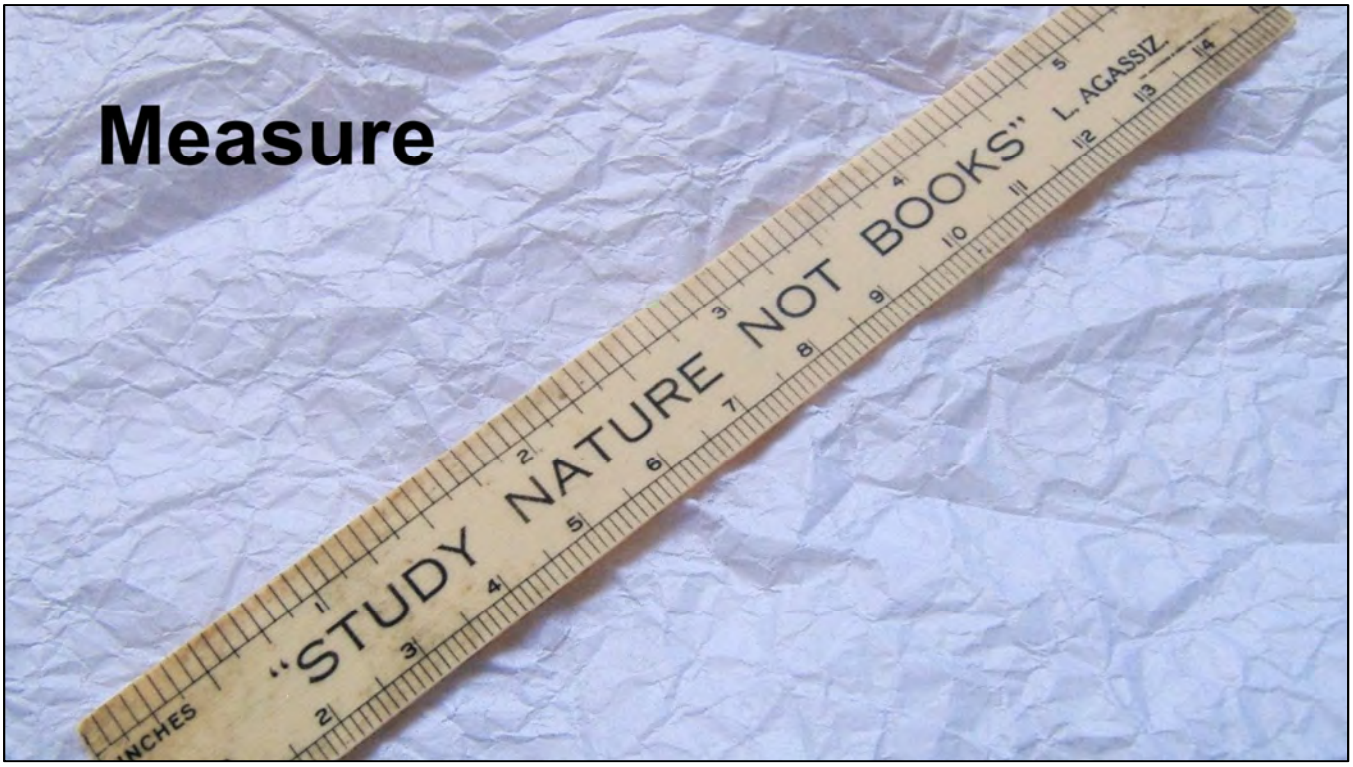


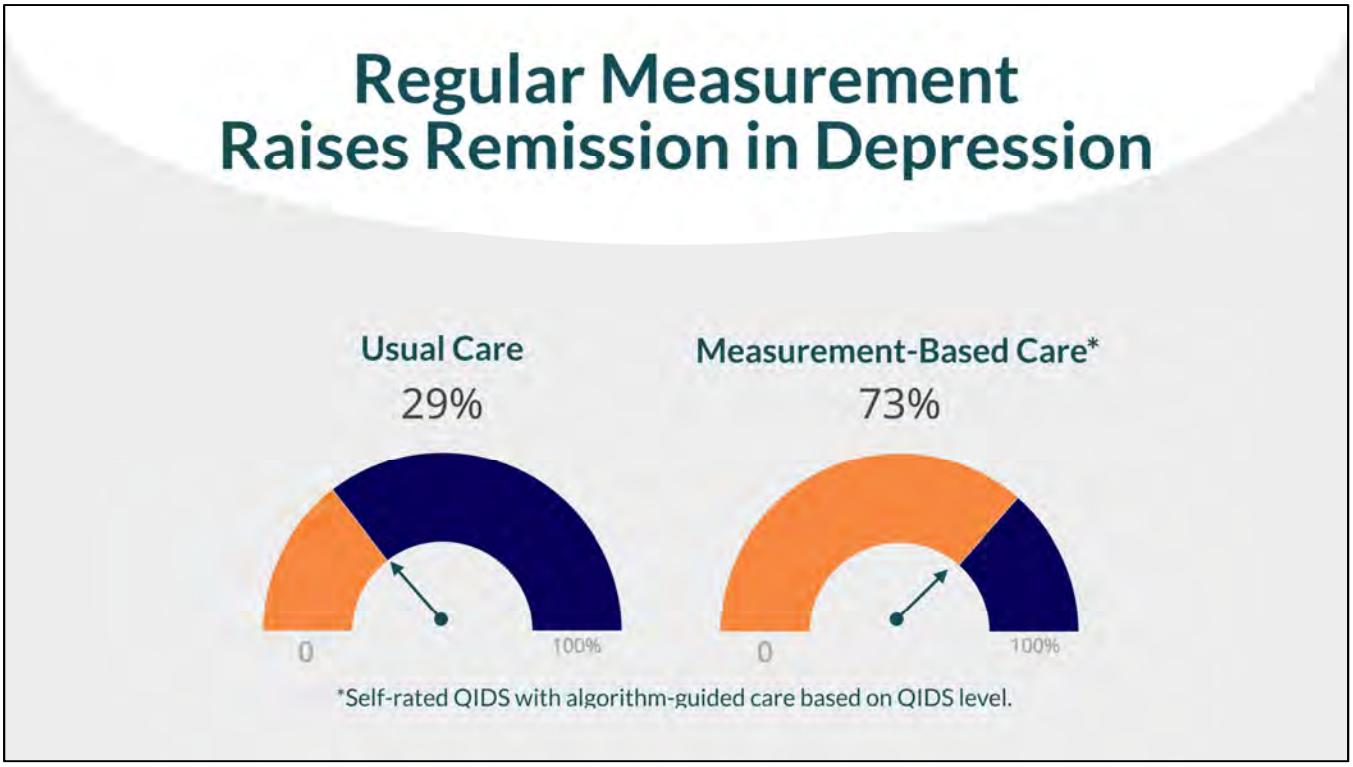
Also has a trial in vascular depression, but failed in TRD.

Read more: https://psych-partners.com/flow-tdcs-depression/

Well tolerated. Sold by treatment course (not by device, which is disposable after a few treatment courses). Stimulates sensory nerves (occipital and trigeminal cranial nerves), which affect brainstem pathways involved in mood regulation. Read more: https://psych-partners.com/wearable-headset-depression.

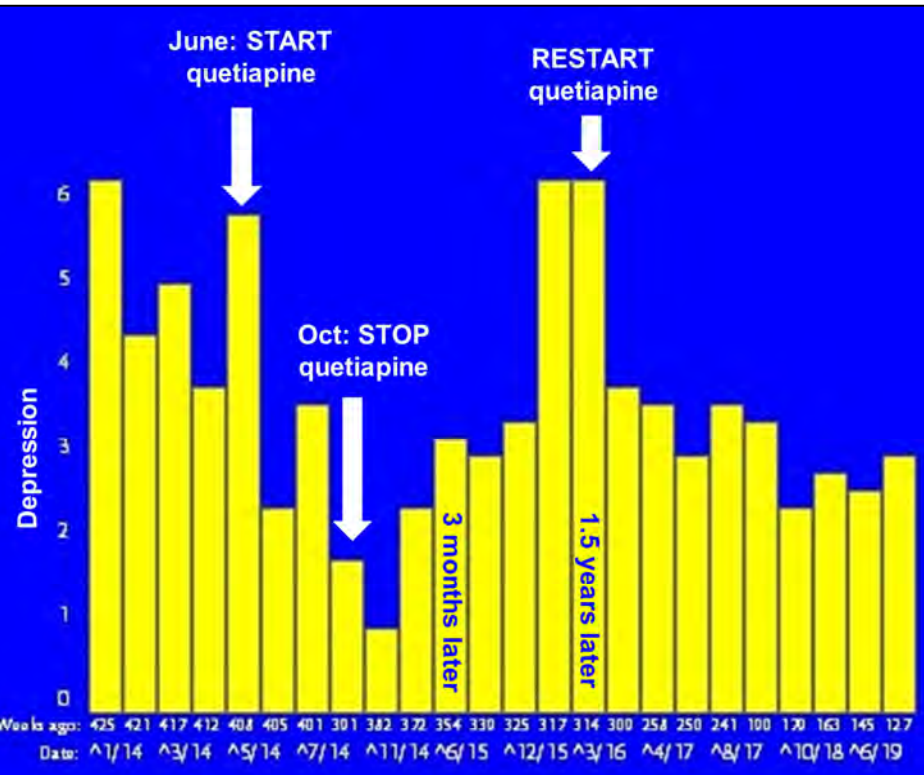
Measure

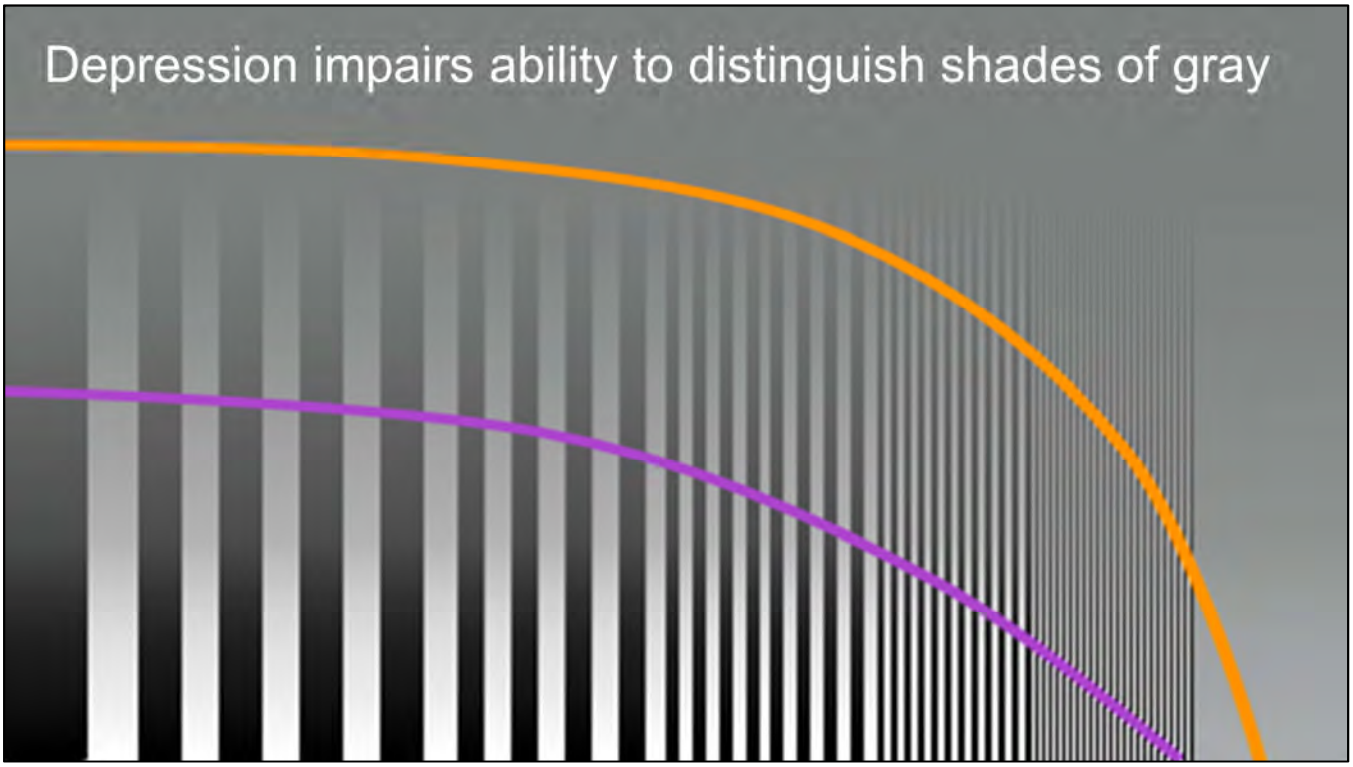




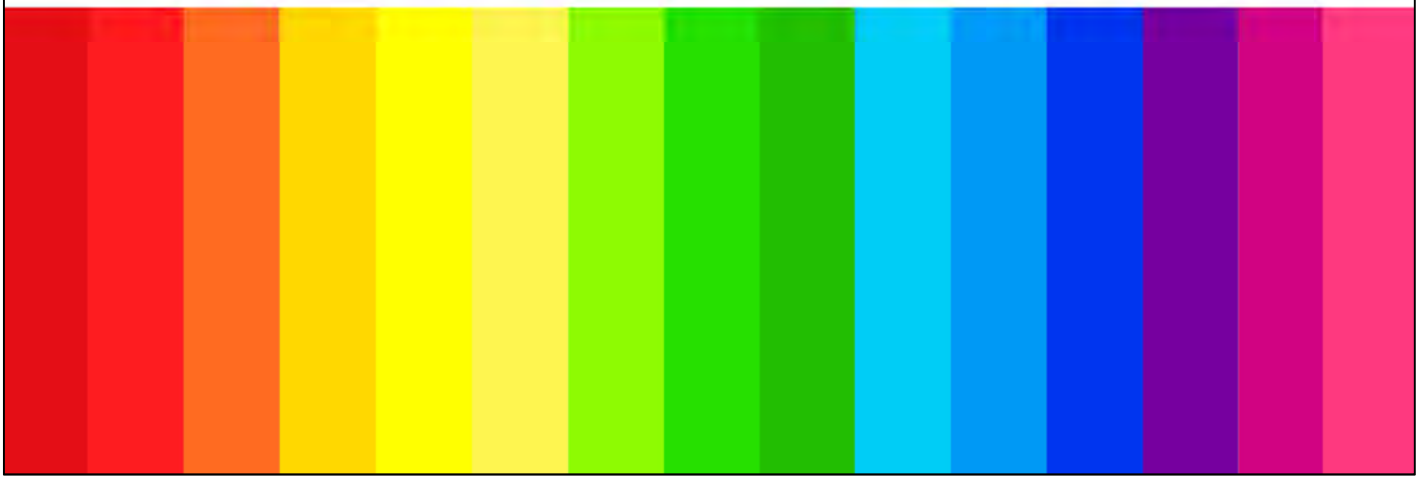
Both groups were only allowed paroxetine or mirtazapine (n=120) (Guo T et al, Am J Psych 2015;172:1004-1013)

Patient Report Doesn't Match Rating Scale





Study of 40 patients (Bubl E et al, *Biol Psychiatry*. 2010;68(2):205-208)

Questions?

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