
# What's New In Mental Health

## Hallucinogens for the Depressed, Anti-Hallucinogens for the Psychotic

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05/12/2023

# Disclosures

- None

- Pharmaceutical manufacturer reference only for treatments in development
- Generic names for all medications used throughout, but provided experimental names of investigational treatments for ease of reference

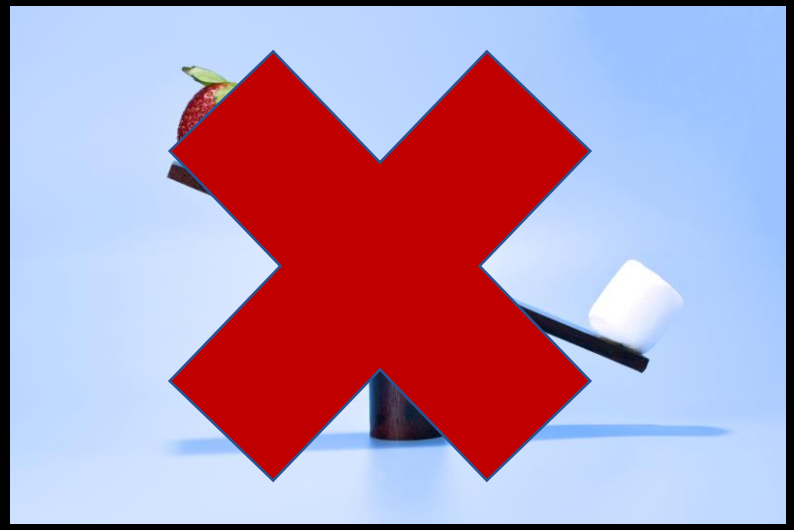
# Preface

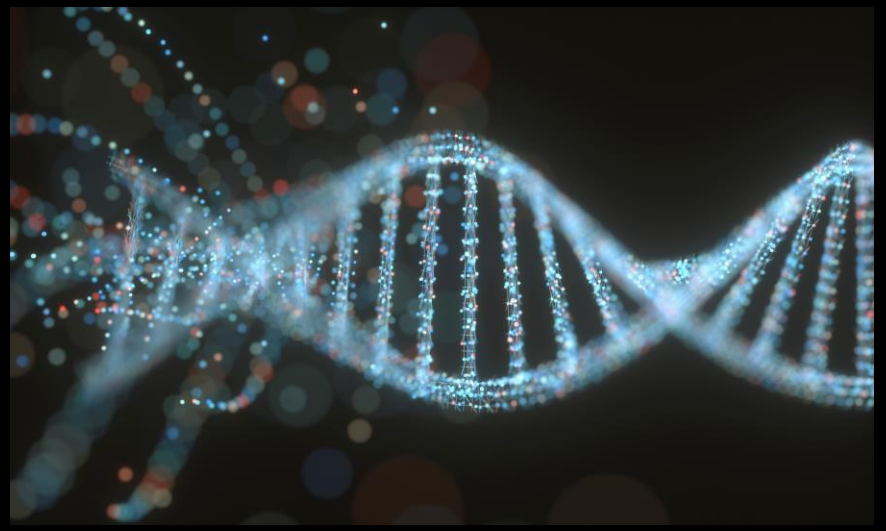
- Dozens of ongoing clinical trials for new treatments and several hundred ongoing studies for medications and non-medications to treat psychiatric illness
  - Medications further along in clinical trials, appear the most promising, or have atypical mechanisms of action
- Focus will be on treatments, including new research
  - Major depressive disorder (to represent mood disorders)
  - Schizophrenia (to represent thought disorders)

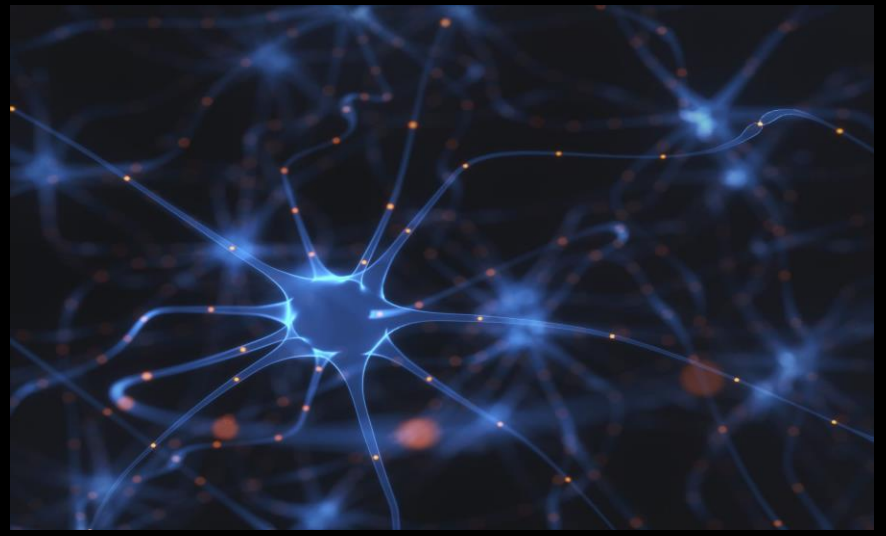
# Goals & Objectives

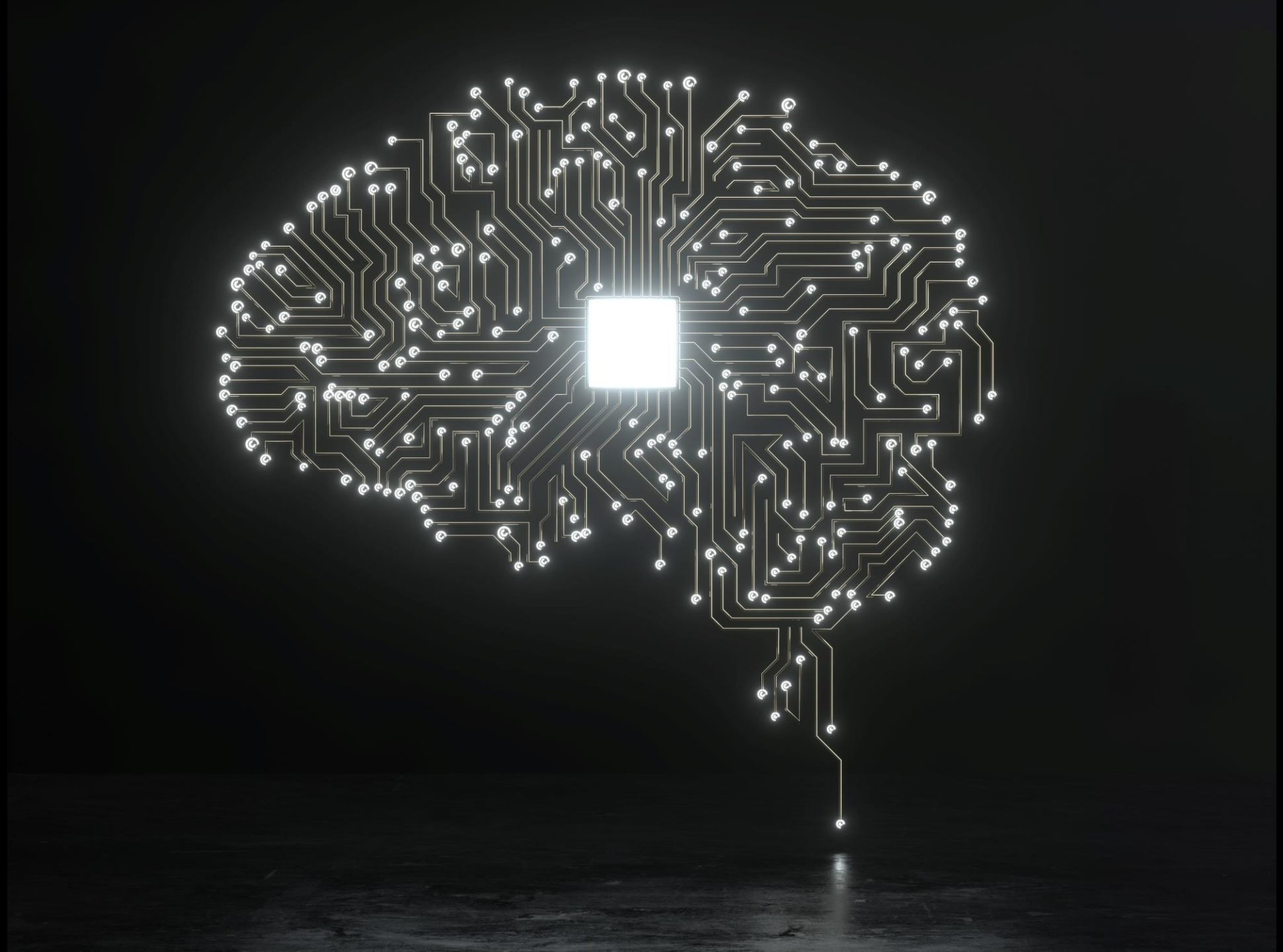
- Discuss and review recently FDA approved medications and treatments for major depressive disorder, including for treatment resistant depression
- Discuss potential treatments that have “novel” mechanisms of action for major depressive disorder, including for treatment resistant depression
- Discuss potential treatments that have “novel” mechanisms of action for schizophrenia with emphasis on negative symptoms and cognitive symptoms

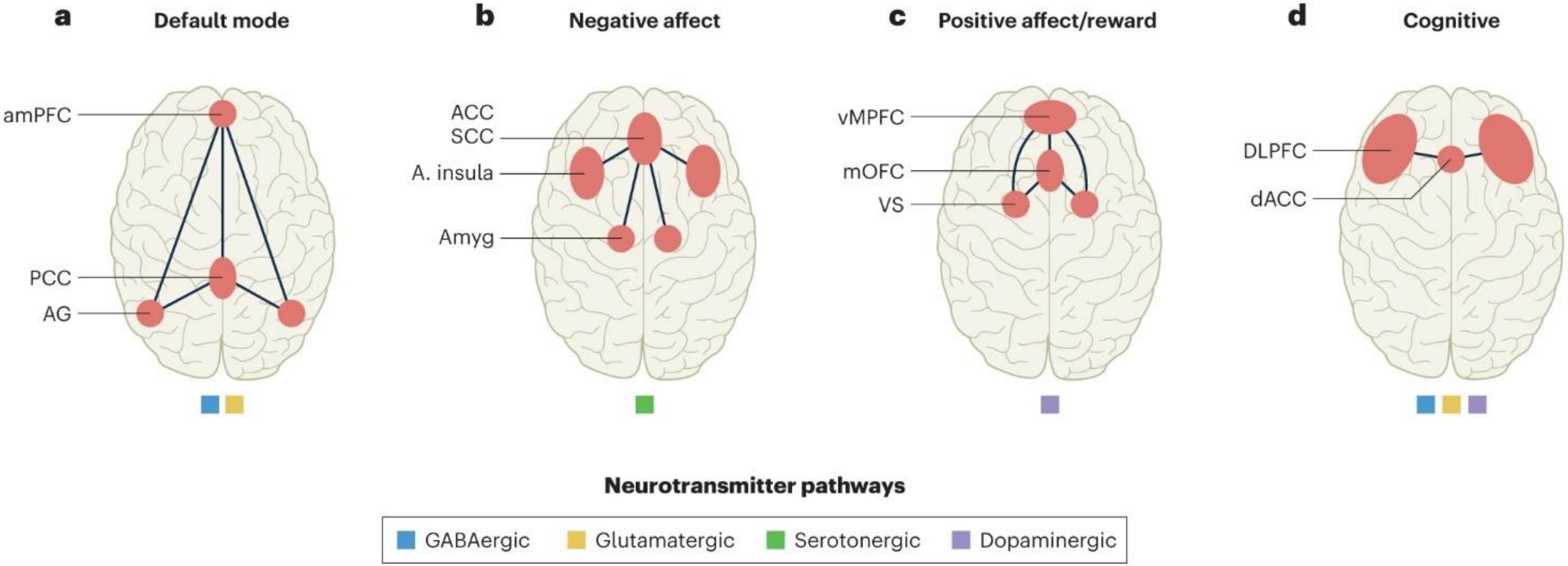
# The Concept of Psychiatric Illness



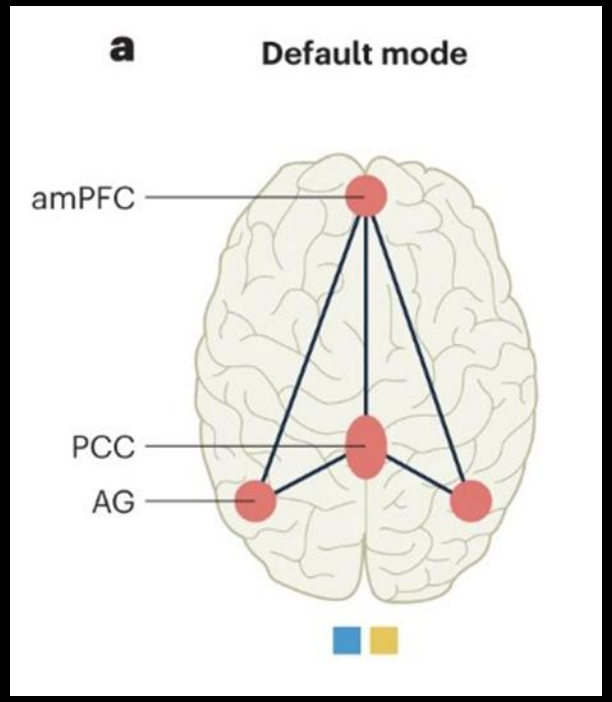


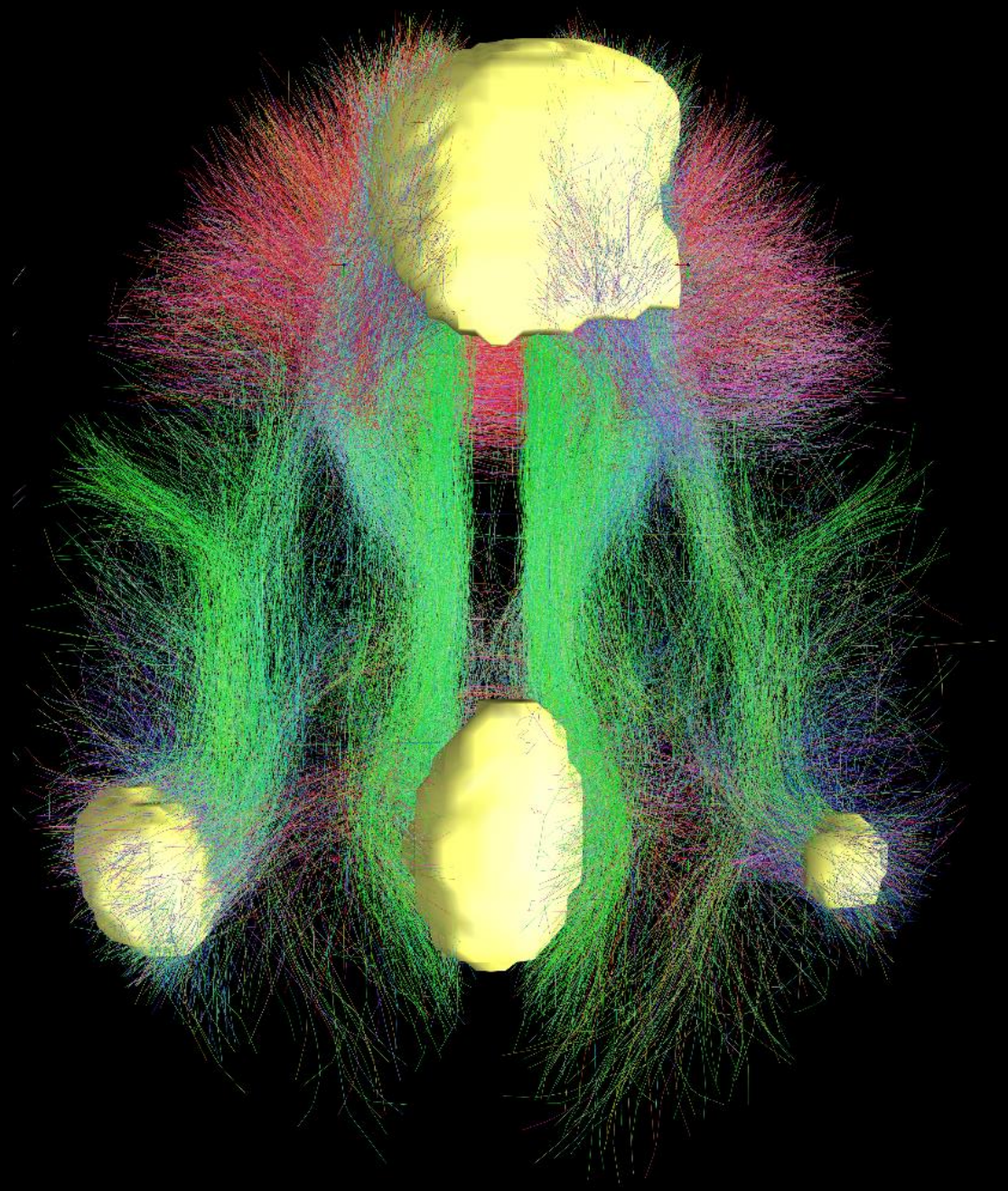







Scangos et al. 2023



Andreas Horn, MD, PhD
Wikipedia

# Example of Targeting Medications

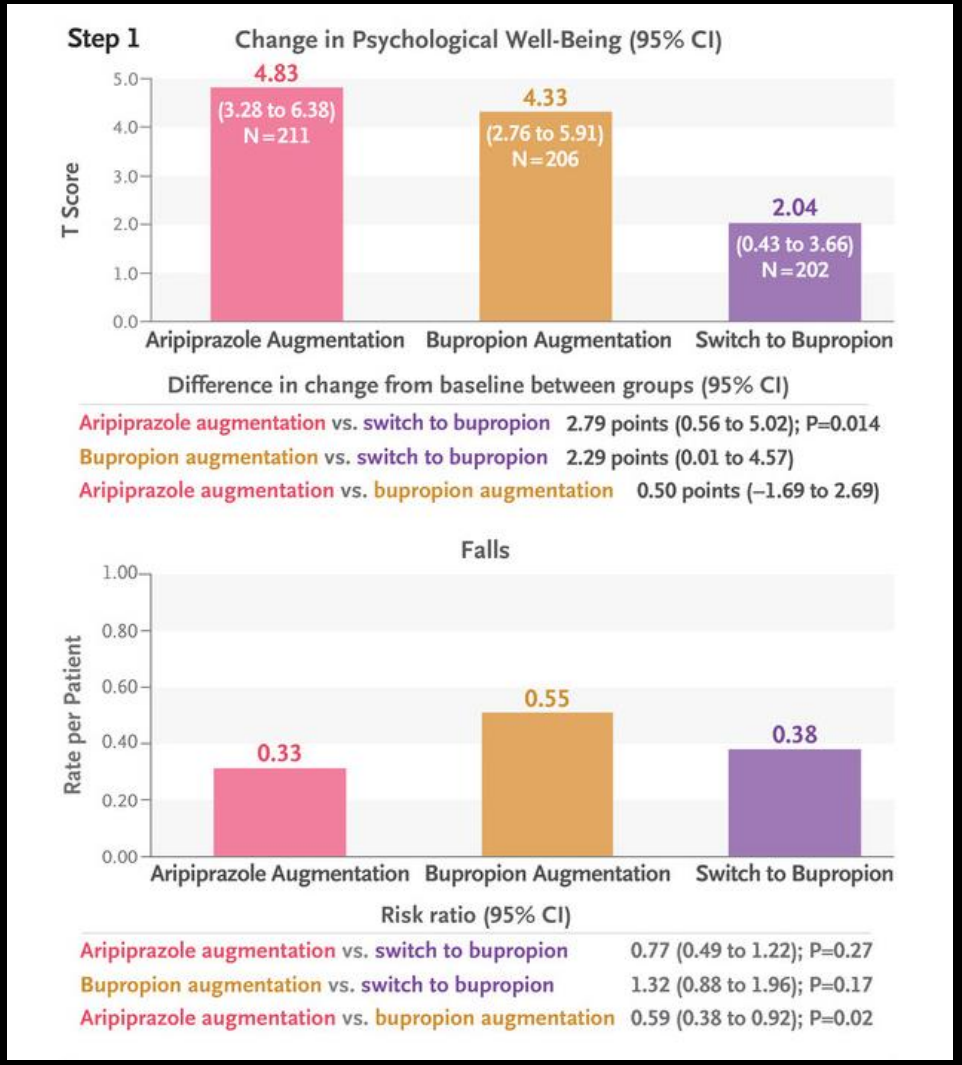
- DMN hypoactivity correlated with persistent depressive disorder
- In late-life depression, improvement with escitalopram results in improved posterior node functioning
- In late-life depression with anxiety, antidepressants normalize function of frontal nodes

# Medications for Major Depressive Disorder

What's New?

# Augmentation in Geriatric Treatment Resistant Depression: The OPTIMUM Trial

- Lenze et al. (2023) used patient recommended psychological well-being as an outcome measure to study treatment resistant depression in patients older than 60
- Step 1: add aripiprazole OR add bupropion OR switch to bupropion
- Step 2: add lithium OR switch to nortriptyline
  - Equivalent regarding effectiveness and safety



# Cariprazine

- FDA approved for adjunctive treatment of MDD in December 2022
- Partial agonism $D_3 > D_2$
- Randomized, double-blind, placebo-controlled phase 3 study of 757 patients with MDD with inadequate response to 1-3 antidepressants in the current episode (Sachs et al. 2023)
  - Adjunctive cariprazine 1.5 mg/day showed significant benefit
  - Adjunctive cariprazine 3 mg/day did not
  - No significant remission in either group
  - Akathisia was most common adverse effect
    - 7.9% in 3 mg group, about that for aripiprazole and brexpiprazole


DO NOT EXCEED THE
May cause drowsiness.
not drive or operate
DOSE

poison.org

# Dextromethorphan-Bupropion

- FDA approved for MDD in August 2022
  - Results for TRD encouraging but did not separate from bupropion
- Non-competitive NMDA receptor antagonism
  - Sigma-1 receptor agonism
  - Inhibition of SERT, NET, and DAT
- Use of bupropion for its CYP2D6 inhibition
- Most common adverse effect dizziness (20%) and nausea (16.7%)
  - No psychotomimetic effects

# Dextromethorphan-Bupropion

- In the larger of two double-blind phase 3 trials (GEMINI, Iosifescu et al. 2022)
  - Greater MADRS total score reductions vs placebo beginning at week 1
  - Earlier remission significant at week 2 (39.5% vs 17.3%)
  - Improvement in functional disability beginning at week 2

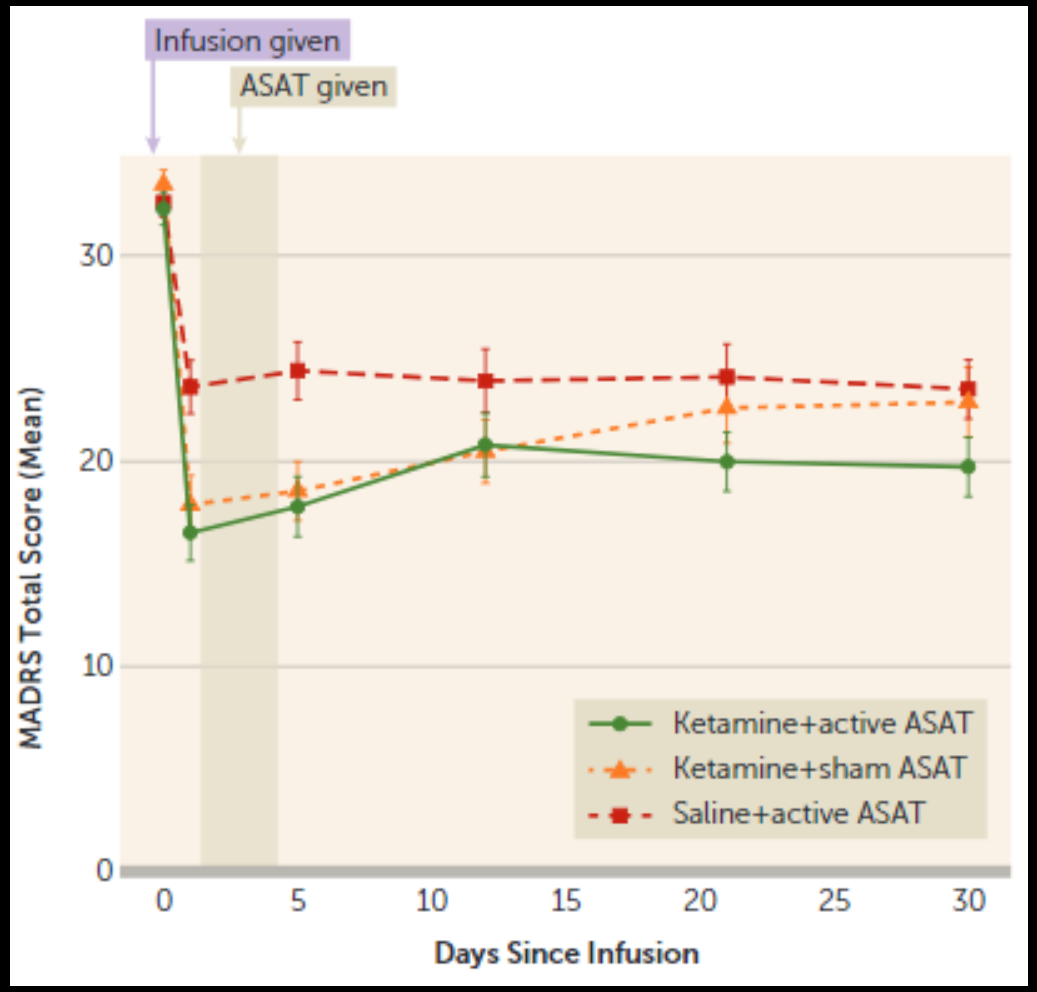
"Th78blue"
Wikipedia

# Ketamine

- Esketamine nasal spray was the first non-monoaminergic antidepressant approved by the FDA
  - For adjunctive treatment in TRD in 2019
  - For MDD with acute suicidal ideation or behavior in 2020
- Durability problem
  - Continued esketamine (or ketamine) administration appears to help the durability effect seen initially with ketamine studies

# Ketamine's Durability Problem (Price et al. 2022)

- Automated Self-Association Training (ASAT) with ketamine
  - A self-training computerized program that promotes, via classical conditioning principles, positive self-associations
- Antidepressant effects remained stable 30 days post-infusion
  - Statistically significant but clinically significant?



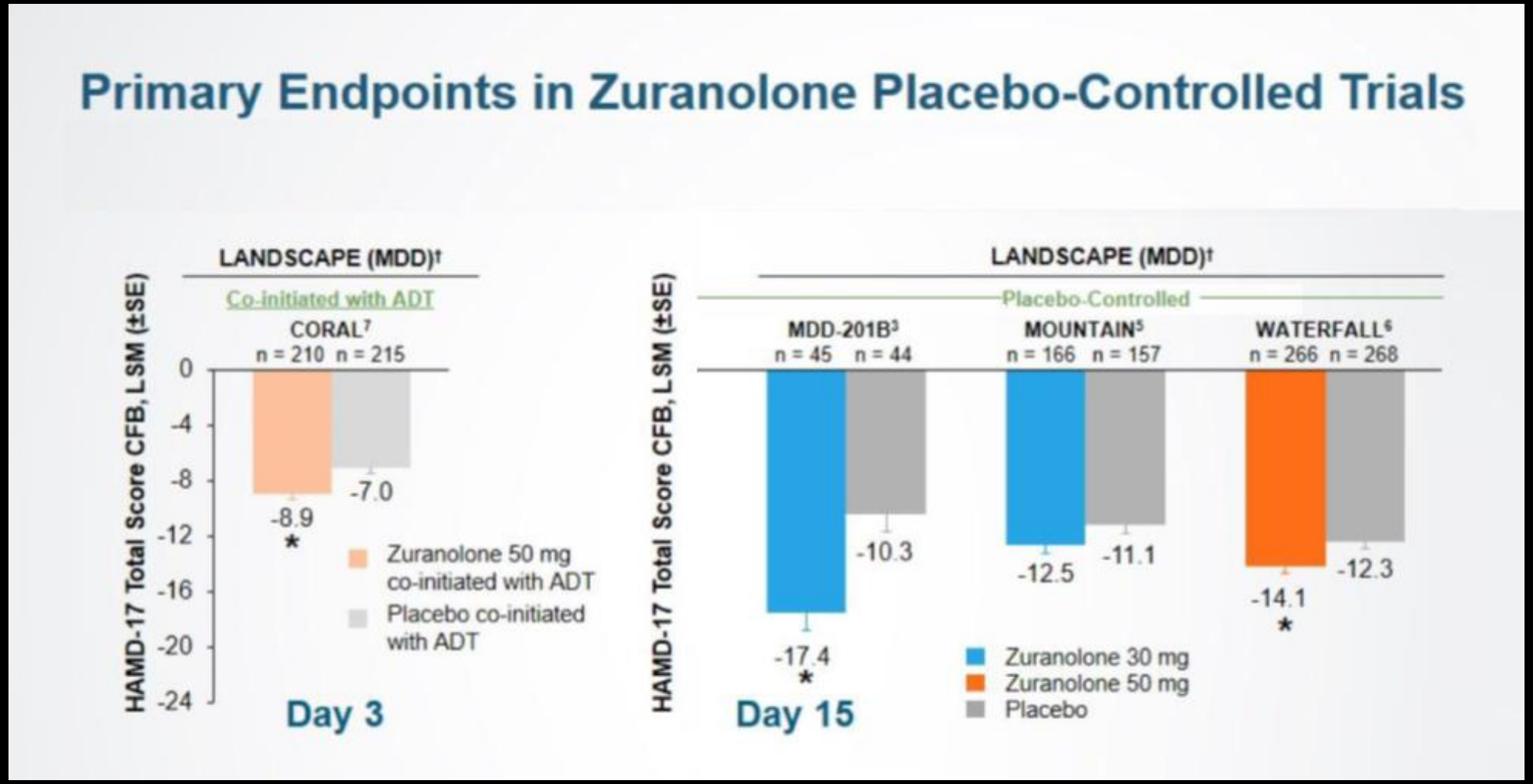
# Ketamine vs ECT

- 6 clinical trial studies, 340 patients, all ECT candidates (Rhee et al. 2022)
  - Ketamine inferior to ECT re: improvement of depressive symptoms
- Equivalent antisuicidal effects (Kheirabadi et al. 2020)
- Equivalent serious adverse events (Ekstrand et al. 2022)
- Neurocognitive performance with ketamine > ECT (Basso et al. 2020)
  - However, final measurement of the study done one day after final ECT
- One study showed after 3 months depression severity was equivalent (Kheirabadi et al. 2019)
- Remission rates equivalent at 12 months (Ekstrand et al. 2022)

# Zuranolone (SAGE-217)

- Neuroactive steroid that modulates resting DMN connectivity via $GABA_A$ excitatory-inhibitory balance
- Administered in pill form once daily for 2 weeks

# Zuranolone (SAGE-217)



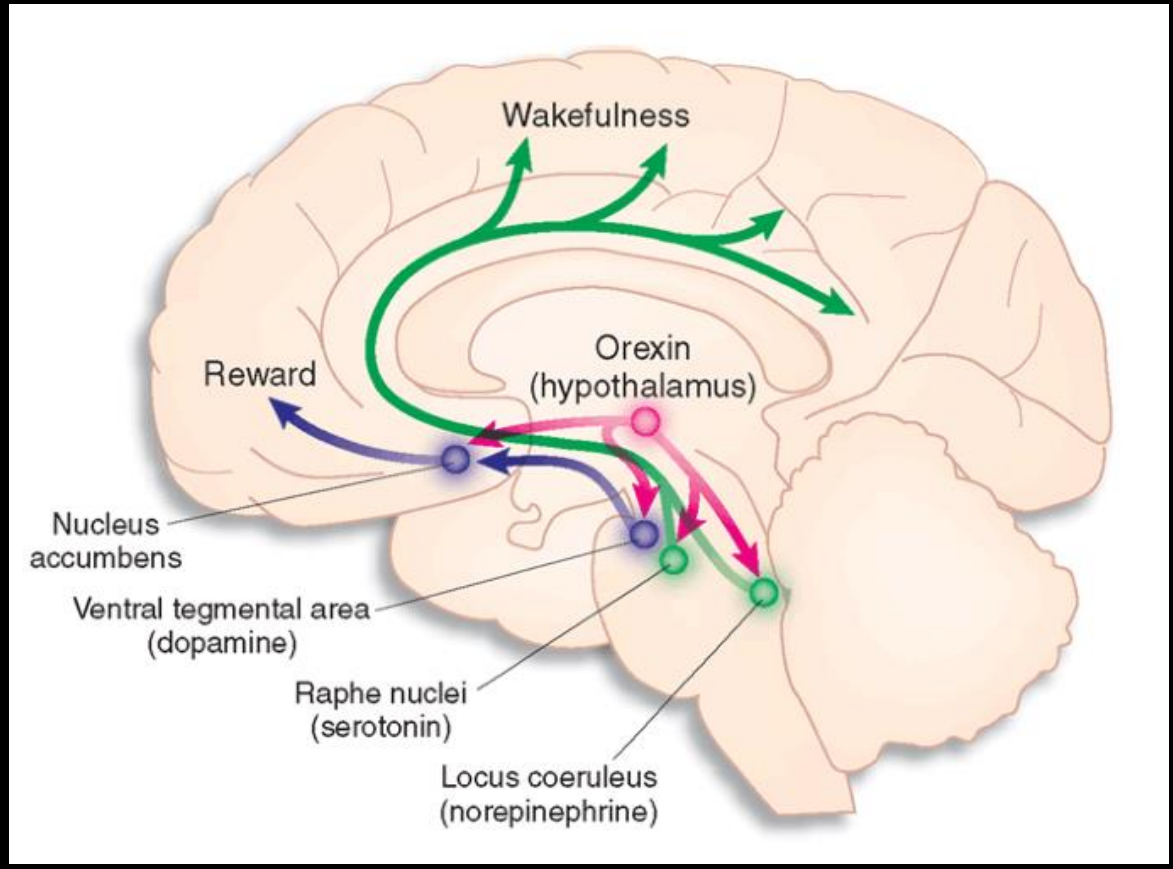

Modified from Sage Therapeutics; Biogen (2022)

# Zuranolone (SAGE-217)

- Shown to improve measures of functioning and well-being at Day 15 and Days 42-45
- SHORELINE Study demonstrated that median days for repeat treatment course was 135 days for 30 mg and 249 days for 50 mg
- Most common adverse effects: headache, somnolence, dizziness, nausea, sedation
  - No emerging suicidality, withdrawal, weight gain, or sexual dysfunction
- New Drug Application submitted, has been granted priority review

# Orexin/Hypocretin

- Dual Orexin Receptor Antagonists:
  - Suvorexant FDA approved for insomnia in 2014
  - Lemborexant in 2019
  - Daridorexant in 2022
- Those clinical trials excluded depression




Scammell & Saper 2007

# Seltorexant (JNJ-42847922)

- Multicenter, international, double-blind, placebo controlled, parallel group phase 2 study in patients with moderate MDD and failure to achieve remission with between 1 and 3 preselected SSRIs or SNRIs (Savitz et al. 2021)
- No dose-response relationship was significant though there was a trend for 20 mg dose >> 10 mg and > than 40 mg
- When separated by presence or absence of moderate to severe insomnia:
  - At week 3, with moderate to severe insomnia, 20 mg > both 10 mg and 40 mg
  - At week 6, with moderate to severe insomnia, 20 mg ≈ 40 mg > 10 mg
  - At week 6, without moderate to severe insomnia, all doses ≈ placebo
- Phase 3 studies will look at 20 mg dose in MDD + mod/sev insomnia + failure to respond to 1-3 medications

# Psychedelics

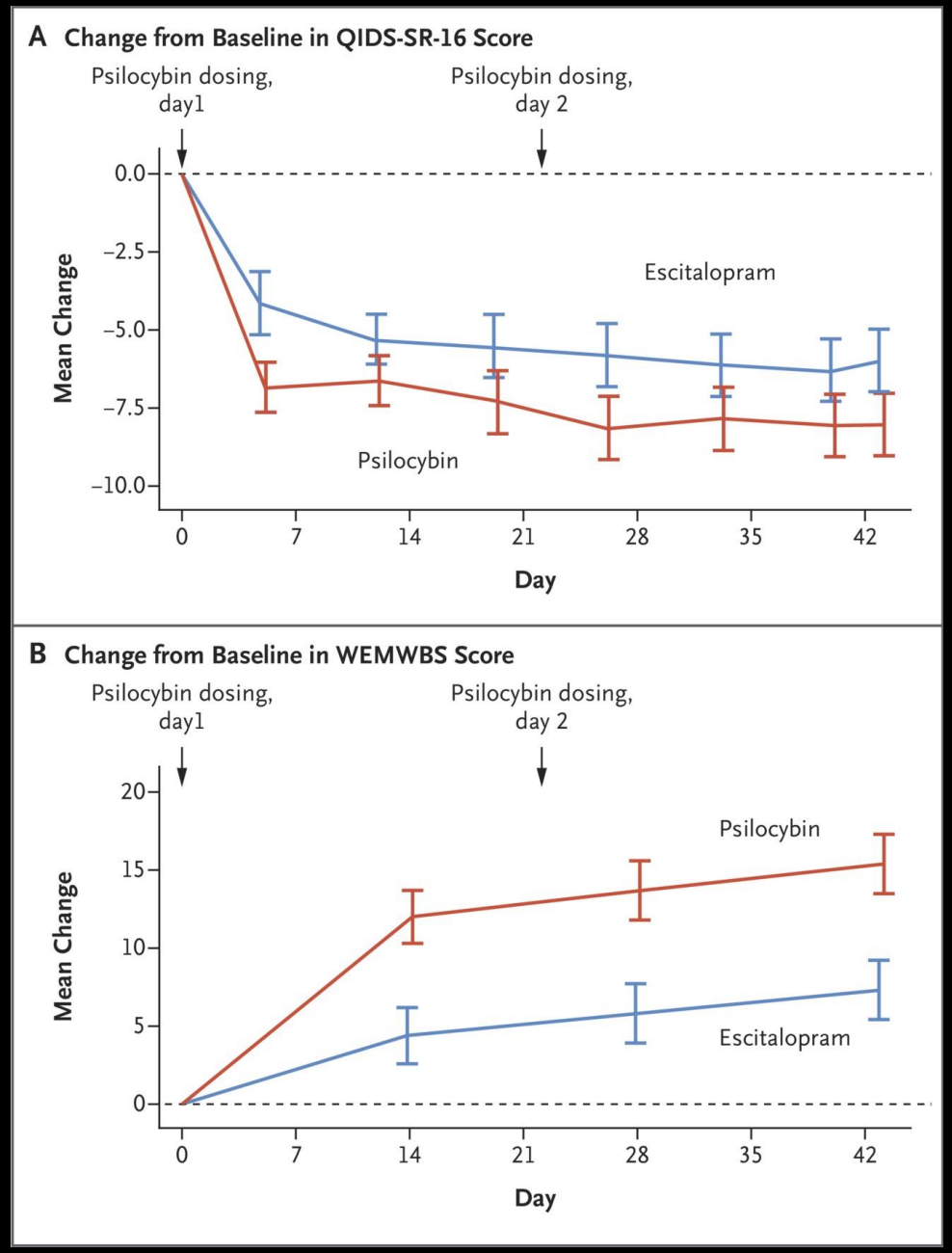
mushroomobserver.org

# Psilocybin

- Open-label study (Carhart-Harris et al. 2018) showed 6-month sustained antidepressant response to two doses of psilocybin in TRD (N=26)

# Psilocybin

- Double-blind RCT in MDD (N=59)
  (Carhart-Harris et al. 2021)
  - Psilocybin 25 mg q3weeks x2 + placebo daily
  - Psilocybin 1 mg q3weeks x2 + escitalopram 10 mg daily x3 weeks and then 20 mg daily x3 weeks
  - No difference in self-reported depressive symptoms
  - Essentially equivalent results*



# Psilocybin

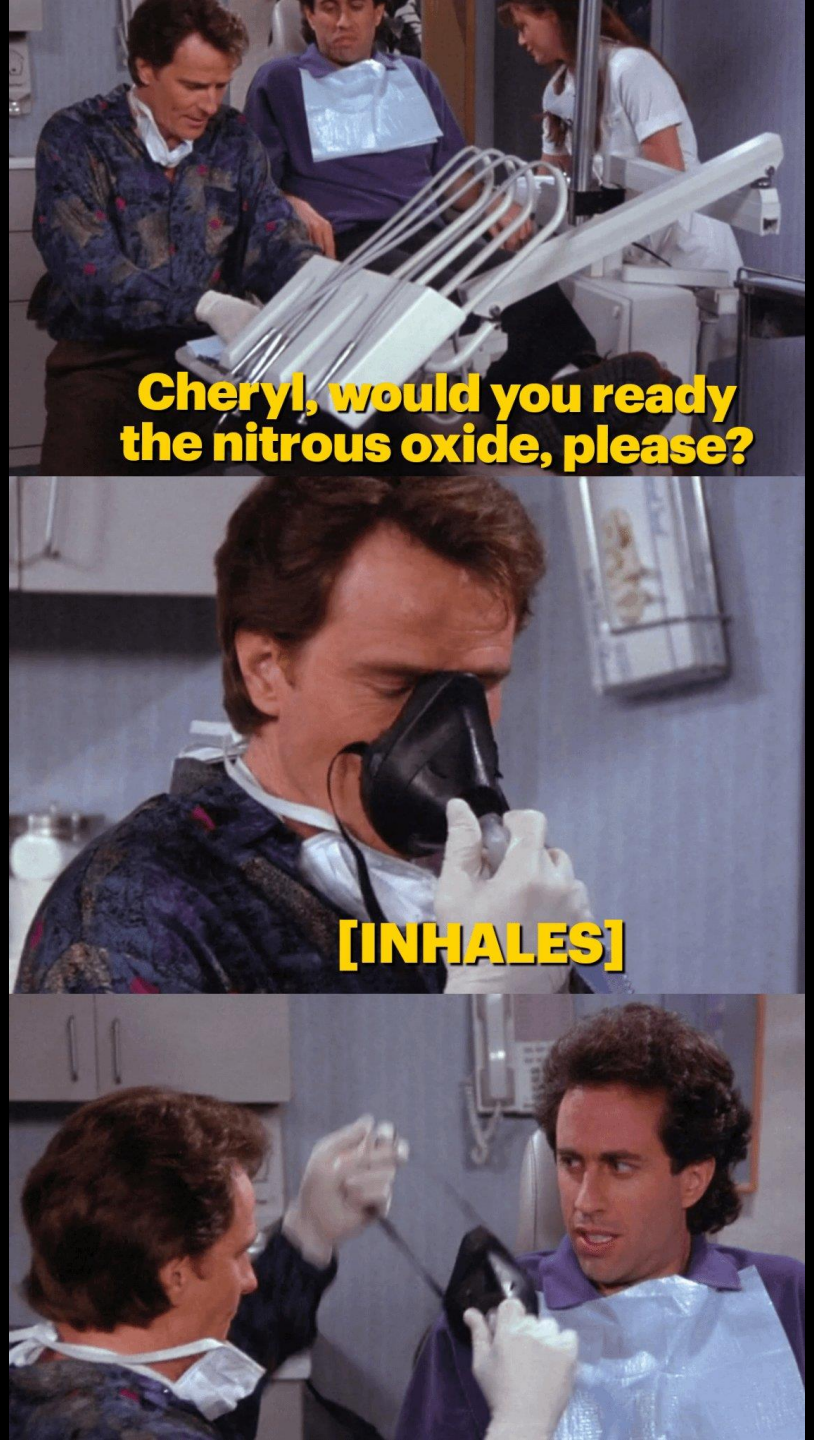
- Phase 2 double-blind RCT in moderate to severe TRD (N=79) (Goodwin et al. in 2022)
  - Single dose of psilocybin 25 mg, 10 mg, or placebo
  - Depressive symptom improvement and remission significant for 25 mg only
    - At 3 weeks, response rate 37%, remission 29%

# Psilocybin -- it's not all fun(gi) and games…

- A survey among recreational psilocybin users (Carbonaro et al. 2016)
  - 39% of respondents rated psychedelic use "among the top five most challenging experiences of his/her lifetime"
  - 11% had put themselves or others at risk of physical harm while on psilocybin
- In a study by Davis et al. (2021) in which psilocybin was shown to reduce symptoms of MDD
  - A majority of patients experienced challenging psychological states, from "sadness" and "grief" to "emotional suffering" and "despair" during the dosing session
  - 31% of patients were "afraid that the state I was in would last forever"

# Psilocybin -- it's not all fun(gi) and games…

- Headache, nausea, dizziness, fatigue
- Numerically higher incidence of suicidal ideation or self-injurious behavior



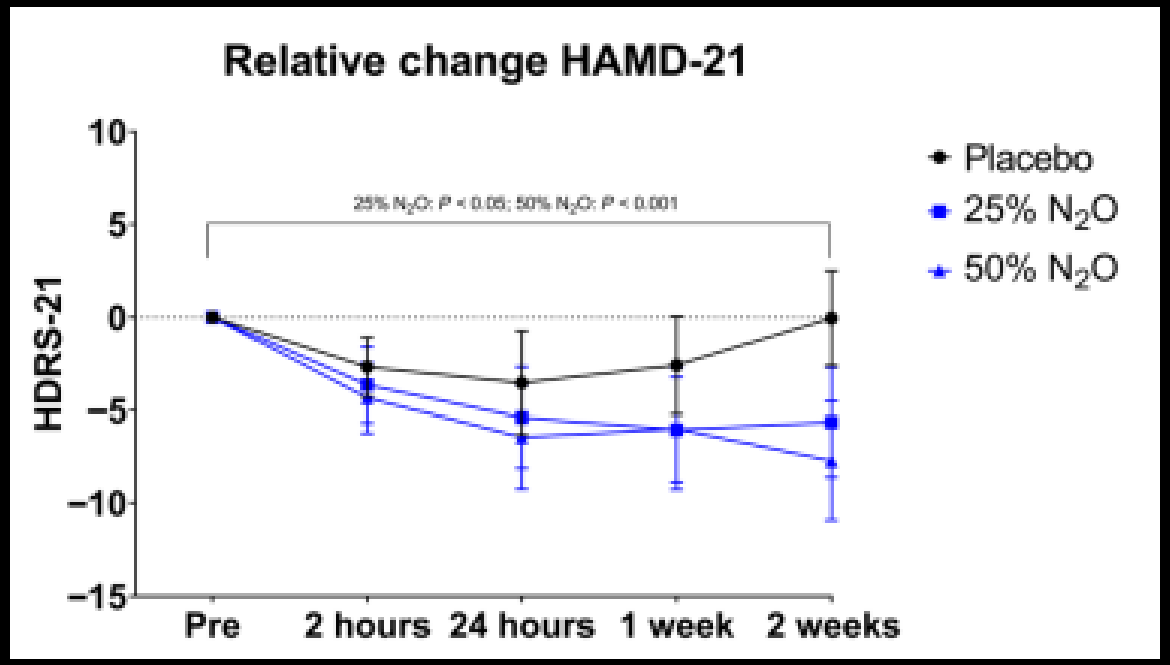

“u/HurricaneBetsy”
www.reddit.com/r/seinfeld/

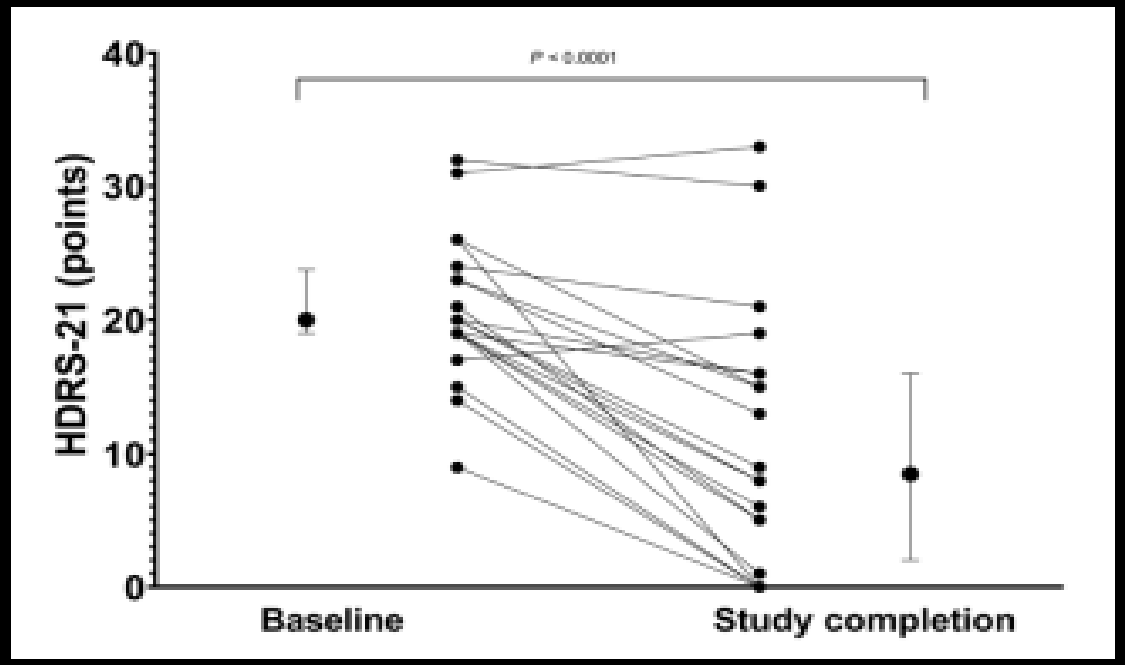
# Nitrous Oxide

- 1-hour inhalation of 50% $N_2O$ caused rapid antidepressant effects in TRD (N=20) (Nagele et al. 2015)
  - Limited to 24 hrs follow-up, high dose

# Nitrous Oxide

- Phase 2 trial, Nagele et al. (2021) studied severe resistant depression (avg 17.5 lifetime years of MDD and median 4.5 drug trials) (N=24)
  - Single, 1-hour inhalation of $N_2O$ at either 25% or 50% versus placebo



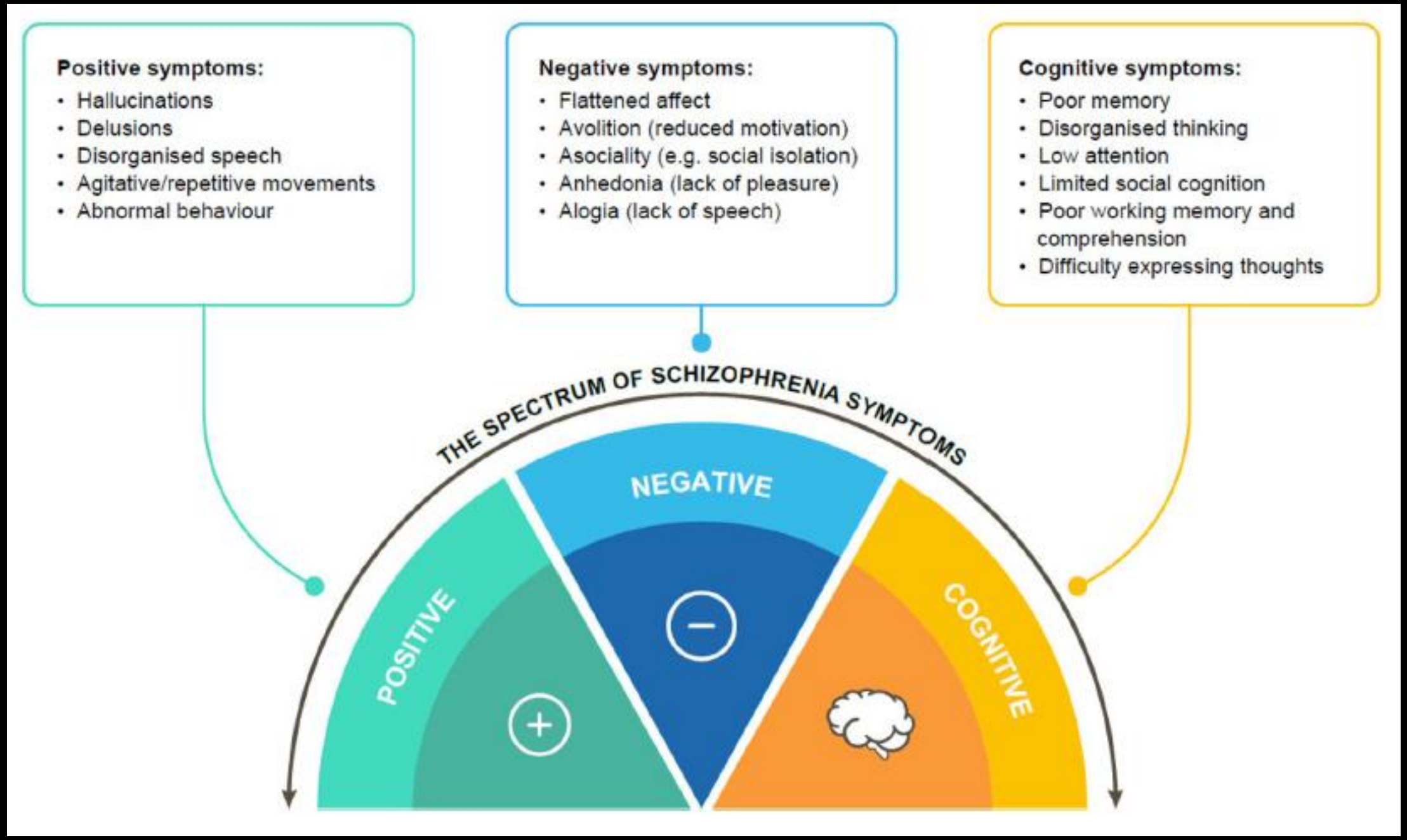



# Medications with Less Compelling Evidence

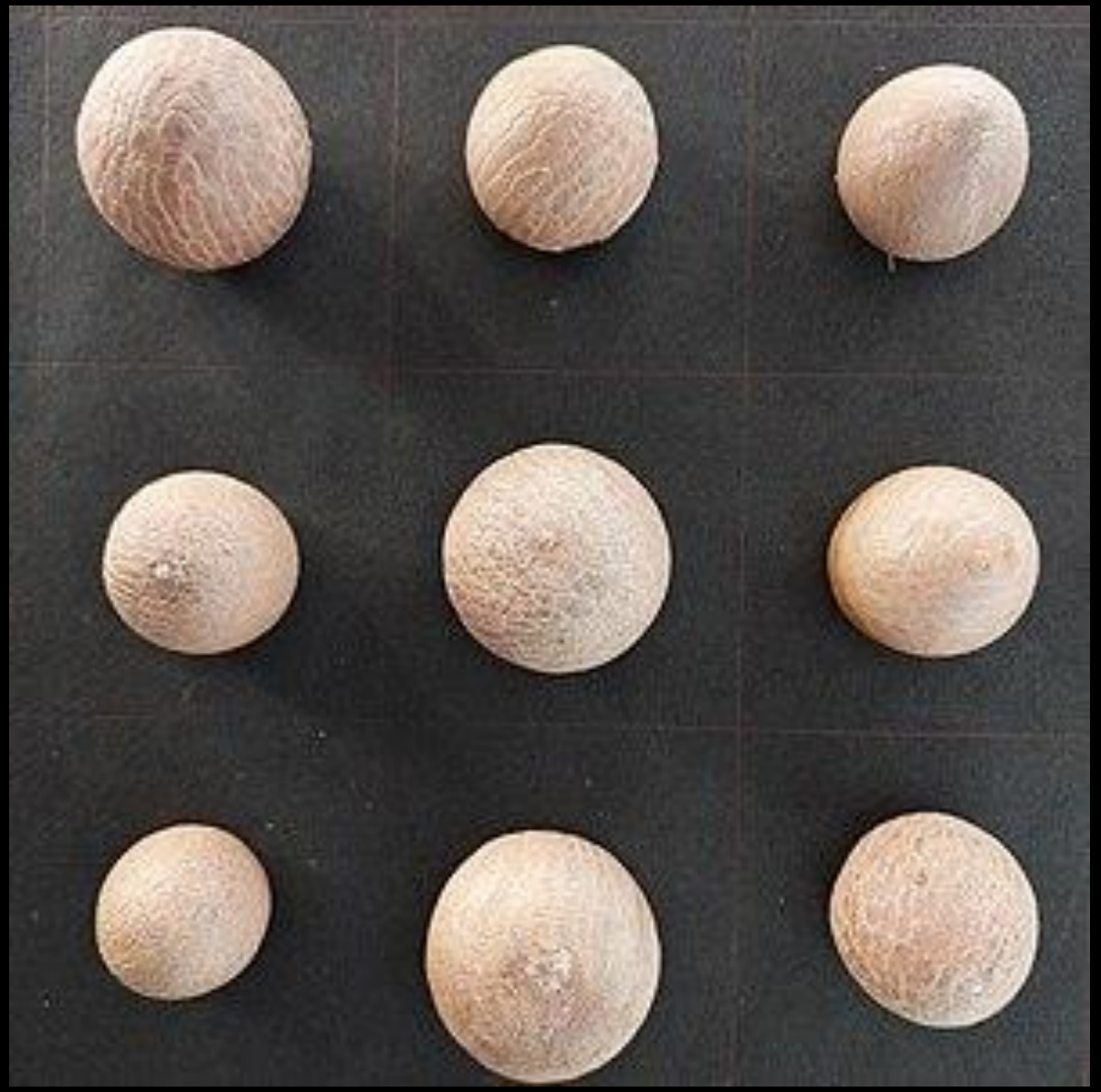
- Anti-inflammatory medications
  - Celecoxib, minocycline, sirukumab
- Esmethadone
  - Two failed phase 3 trials

# Medications for Schizophrenia

What's New?




Rosenbrock et al. 2023



# Xanomeline

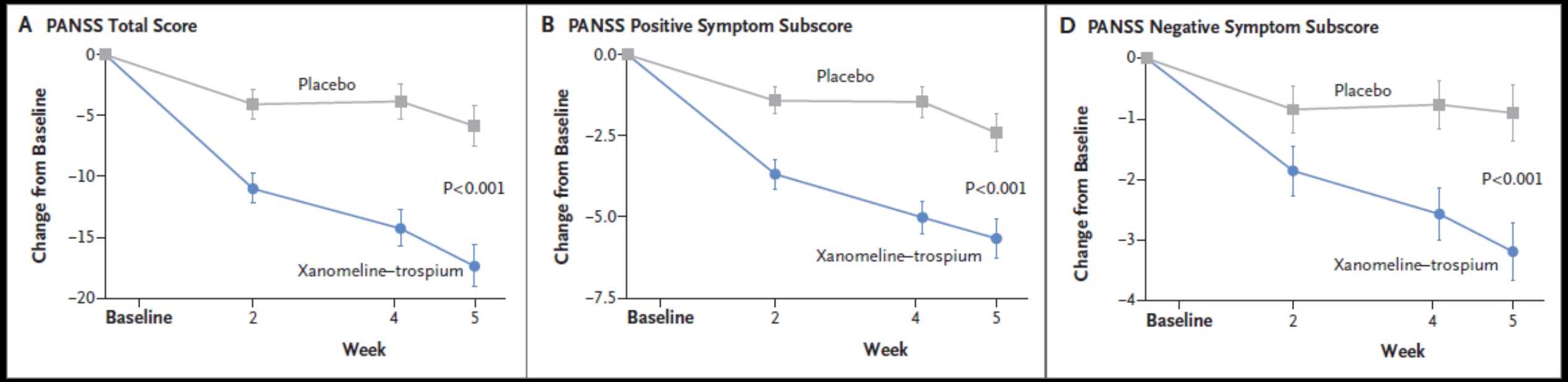
- Derivative of arecoline, mAChR ($M_1$/$M_4$) agonist
  - $M_4$ receptors reduce downstream DA release
- Xanomeline improved cognition in patients with Alzheimer's disease (Bodick et al. 1997)
  - Serendipitously, they also found rapid and dose-dependent reduction in psychosis
  - Substantial, limiting cholinergic side effects
- In a phase 2 trial xanomeline improved psychosis and cognition in patients with schizophrenia (Shekhar et al. 2008)
  - Still problem of cholinergic side effects

# Xanomeline-Trospium (KarXT)

- Central $M_1/M_4$ agonism via xanomeline
  - Xanomeline appears to selectively target VTA DA neurons but not SN DA neurons
- Peripheral anticholinergic activity via trospium

# Xanomeline-Trospium (KarXT)

- Phase 2 clinical trial (Brannan et al. 2021)



# Xanomeline-Trospium (KarXT)

- Sauder et al. (2022) performed a post-hoc analysis of phase 2 study data (double-blind, placebo controlled RCT; EMERGENT-1)

- With pretreatment cognitive impairment
  - Cognitive performance improved with a medium-large effect size both relative to baseline and compared to placebo
- Without pretreatment cognitive impairment
  - No cognitive performance improvement was noted

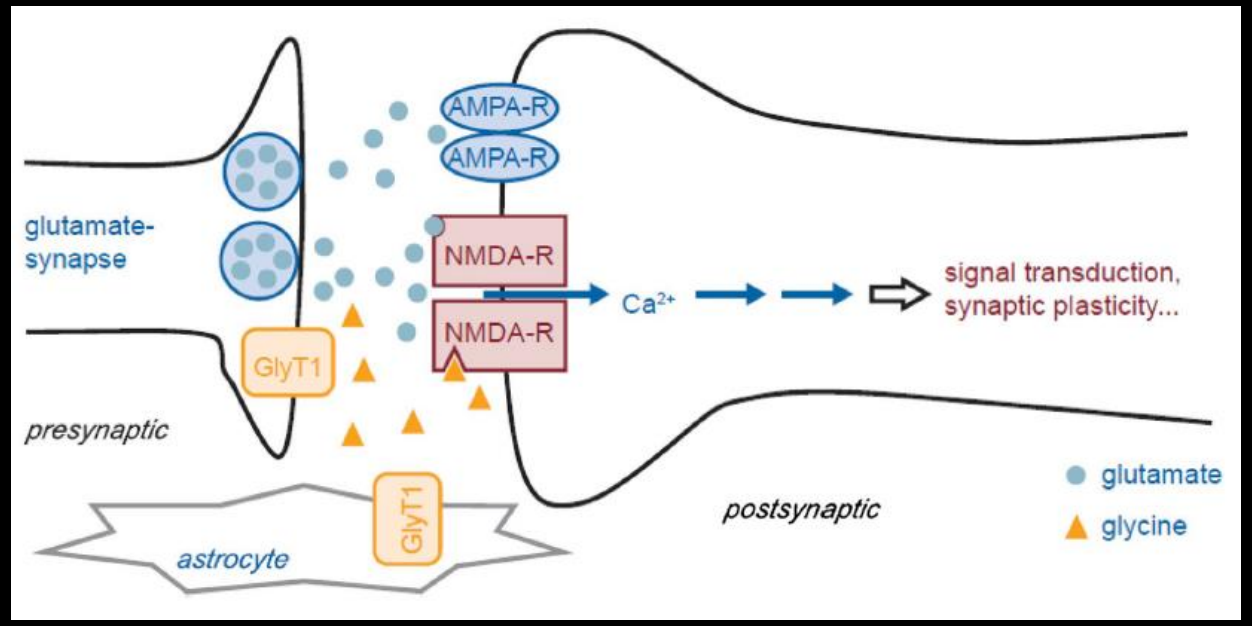
# Xanomeline-Trospium (KarXT)

- Phase 3 EMERGENT-2 measures at week 5
  - PANSS total score significant (beginning at week 2) (effect size 0.61)
  - PANSS positive score significant (beginning at week 3)
  - PANSS negative score significant (beginning at week 4)
- Phase 3 EMERGENT-3 measures at week 5
  - PANSS total score significant (beginning at week 2) (effect size 0.60)
  - PANSS positive score significant at week 5
  - PANSS negative score significant at week 4 but not week 5

# Xanomeline-Trospium (KarXT)

- Most common adverse effects were all mild to moderate
  - Nausea, dyspepsia, vomiting, constipation, headache, hypertension, diarrhea, and insomnia
  - No EPS, no risk of tardive dyskinesia?
- Long-term safety data pending from EMERGENT-4 and -5 trials
- New Drug Application submission planned imminently

# NMDA Receptors in Schizophrenia




Rosenbrock et al. 2023

- NMDA-R dysfunction contributes to cognitive disturbance and psychosis
- Glycine is a co-agonist for NMDRs in excitatory glutamatergic neurotransmission
- GlyT1 is the primary transporter for the release and reuptake of glycine

# Iclepertin (BI 425809)

- GlyT1 inhibitor
- Multicenter, double-blind, placebo-controlled RCT phase 2 study across 11 countries (Fleischhacker et al. 2021)
  - 509 patients with schizophrenia assigned to 2 mg, 5 mg, 10 mg, 25 mg, placebo given daily for 12 weeks in addition to their stable antipsychotic
  - Treatment with iclepertin 10 mg or 25 mg demonstrated the greatest improvements in cognition but 25 mg not better than 10 mg
- Three international phase 3 trials underway
- FDA designation of breakthrough therapy

# Transcranial Magnetic Stimulation for Major Depressive Disorder

What's New?

# Transcranial Magnetic Stimulation (TMS)

- Non-invasive use of an alternating magnetic field to stimulate the brain
  - Magnetic field → electric field
- Synaptic plasticity with TMS is NMDA-R dependent

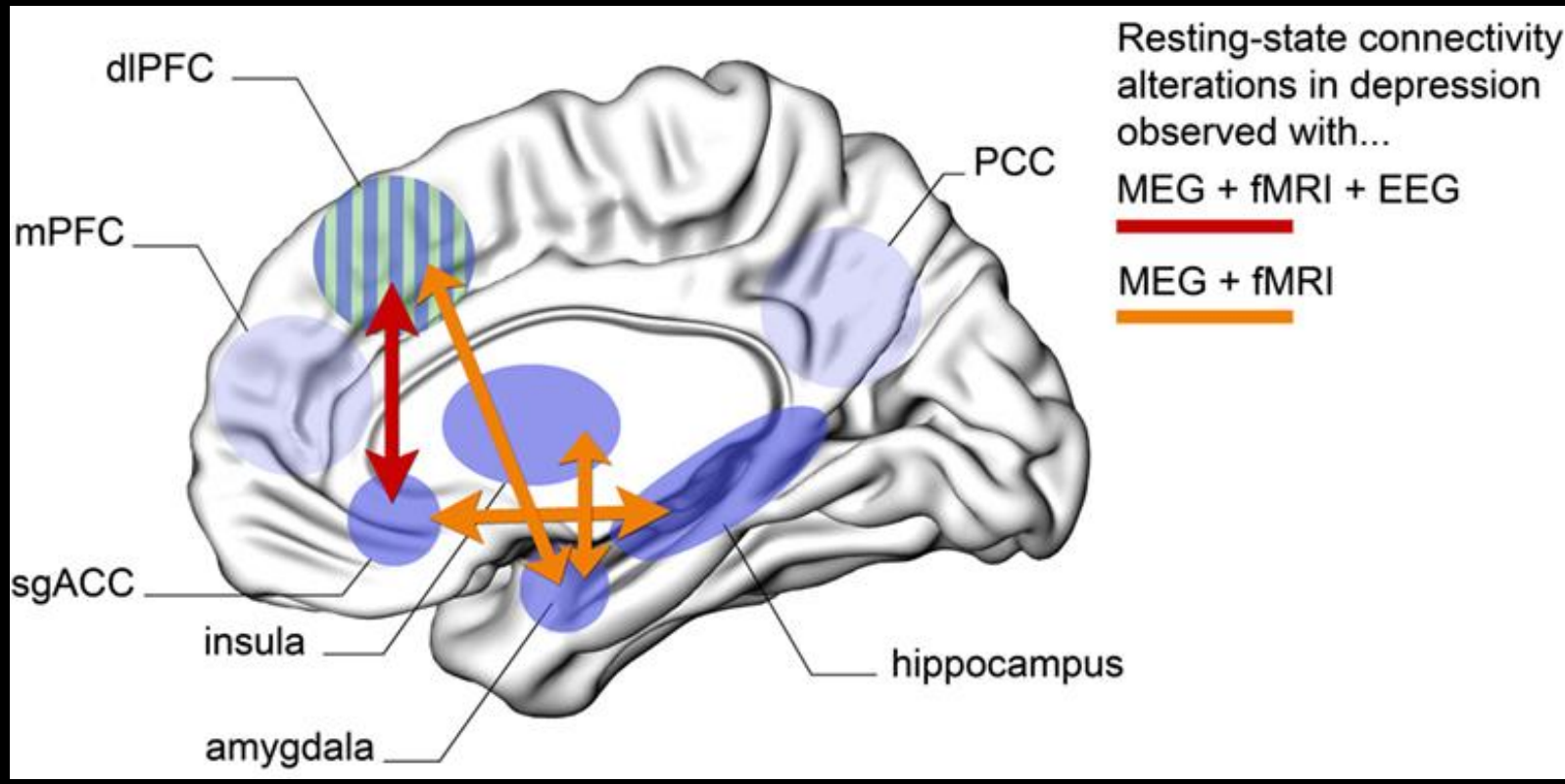
# Transcranial Magnetic Stimulation (TMS)

- 30-45 min 10 Hz treatment sessions daily for 4-6 weeks
  - Evidence suggests that 2-15 treatments/day at 10 Hz is not inferior to once per day protocols
- Most common adverse effects are headache and scalp discomfort
- Durability of response is “good” after 1 year (approaching 50%)

# Transcranial Magnetic Stimulation (TMS)

- sgACC is overactive in depression
- sgACC anticorrelated with DLPFC

- Left DLPFC is targeted in TMS




Alamian et al. 2017

# Theta-Burst Stimulation (TBS)

- TBS uses 50 Hz with a much shorter treatment time (just over 3m) and is non-inferior to 10 Hz TMS (THREE-D trial, Blumberger et al. 2018)
  - TBS mimics endogenous theta rhythms → LTP
  - Response rate of 49% and remission rate of 32% for TRD

# TMS for Geriatric Depression (Cappon et al. 2021)

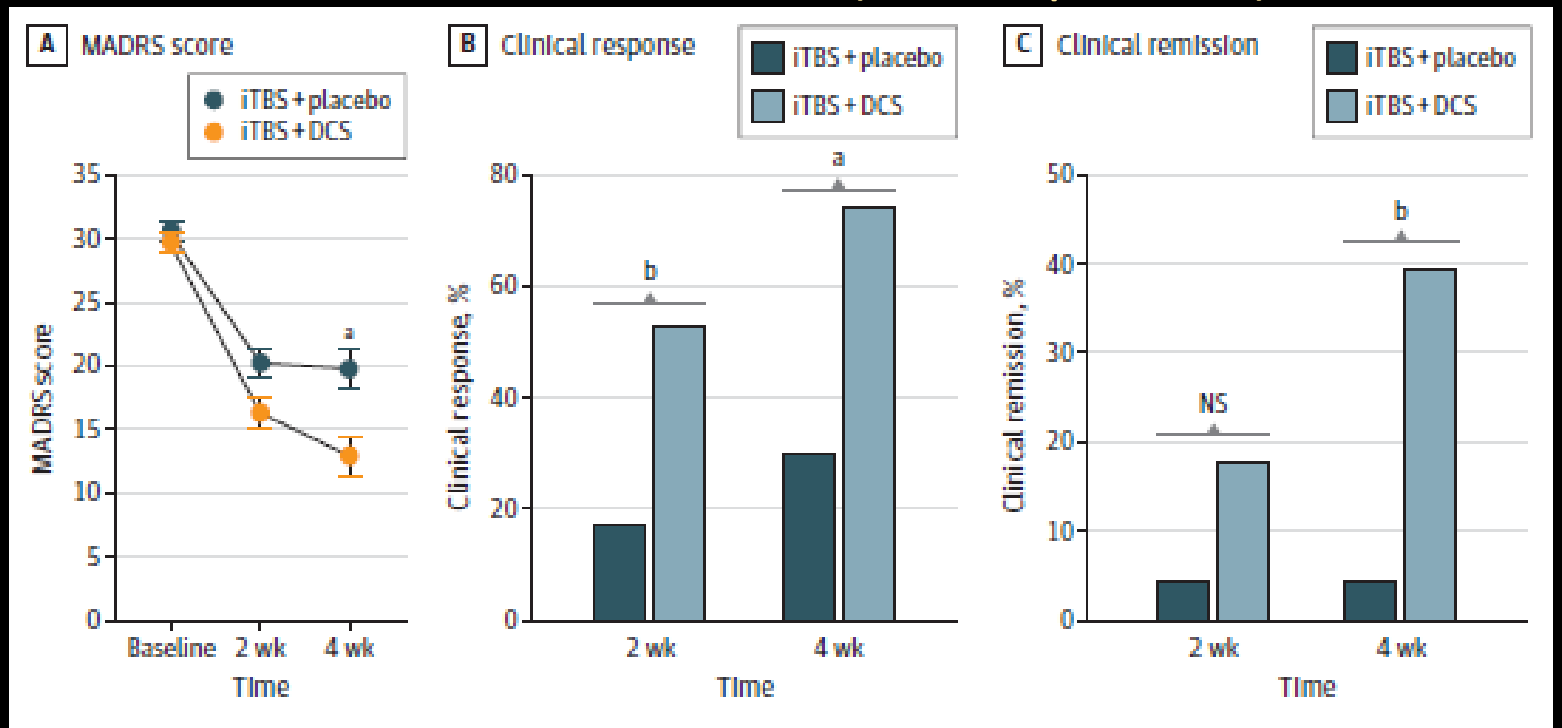
- Three of the six RCTs that reported on response rates found significant difference with TMS versus sham
- Three of the five RCTs that reported on remission rates found significant difference with TMS versus sham
- Considerable variability in response and remission rates
  - Normal brain related atrophy?
  - Different methodologies between studies
  - Pulse count lower than FDA protocol
  - *Older studies tended to have less impressive results

# iTBS for Geriatric Depression (Cristancho et al. 2020)

- Open label trial, 13 patients with geriatric depression treated with daily iTBS sessions over 4 weeks
  - 1/3 response rate
  - 1/3 remission rate

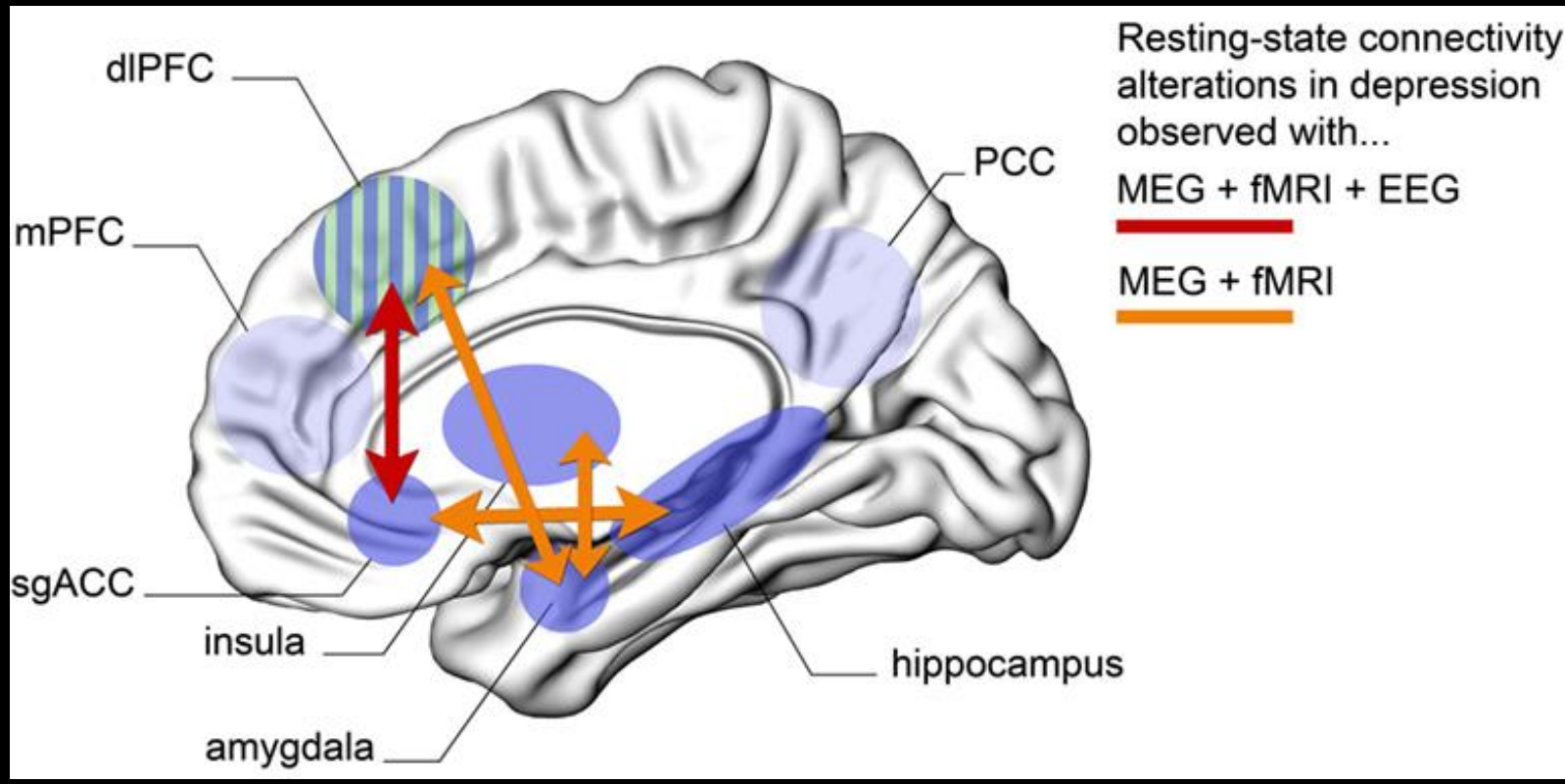
# Improving TMS with Medications?

- Cole et al. 2022 studied D-cycloserine with iTBS for patients 18-65 yo with moderately severe MDD and failure of at least 1 antidepressant trial (but not more than 4) (N=50)
  - D-cycloserine for the first 2 of 4 weeks (versus placebo)



# Improving TMS with Radiology?

- Greater anticorrelation between the left DLPFC and the sgACC predicts response to TMS

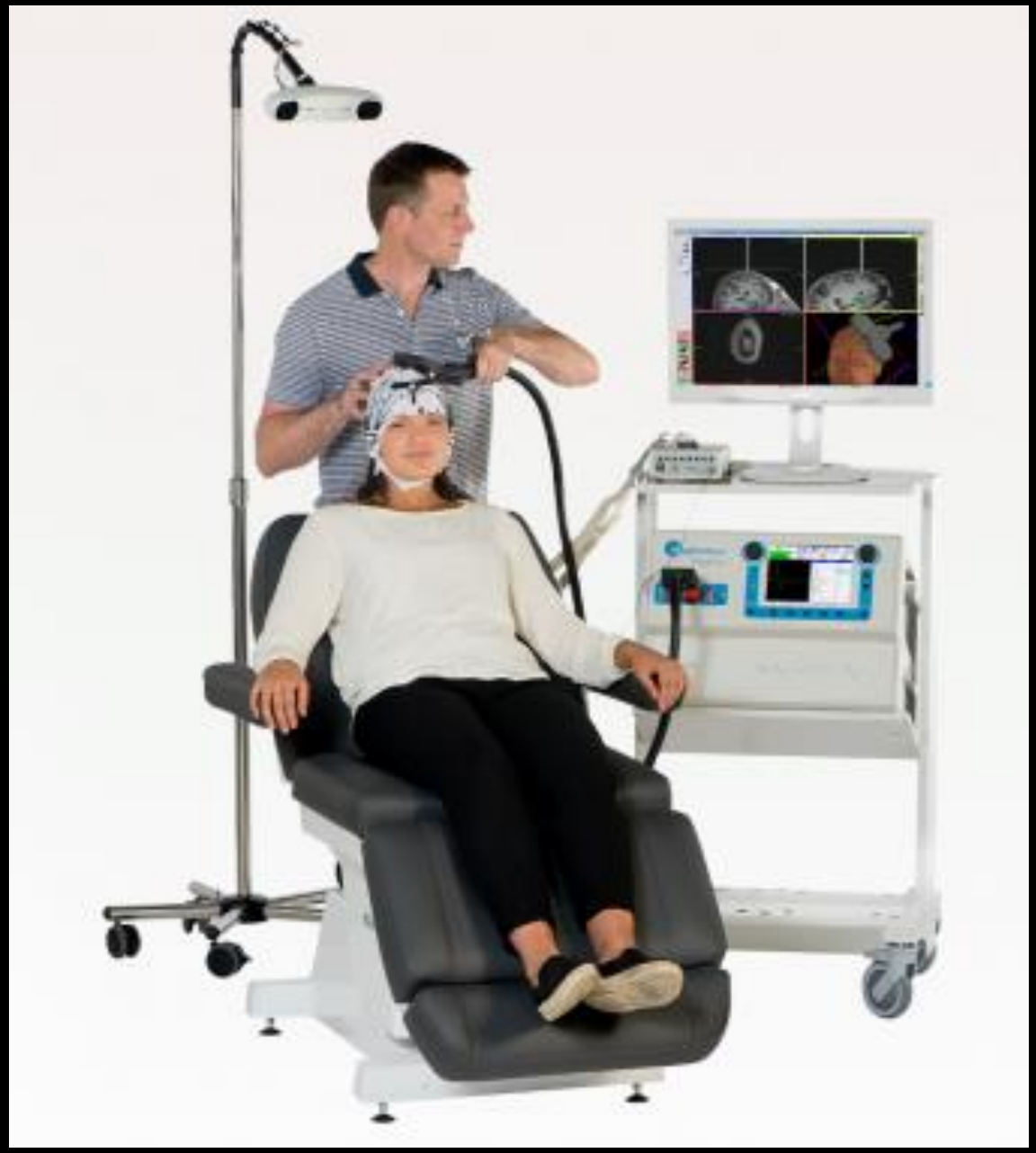



Alamian et al. 2017

# Stanford Accelerated Intelligent Neuromodulation Therapy (SAINT → SNT)

1. iTBS (90,000 pulses)
2. Multiple iTBS sessions per day, optimally spaced
   - 1 hr spacing for 10 hrs/day for 5 days (1,800 pulses/session x 10 sessions)
3. Higher overall pulse dose of stimulation
   - 90% rMT
4. Personalized targeting via imaging (fcMRI)

- Open-label trials of the SNT protocol have shown a remission rate of approximately 90% even in TRD



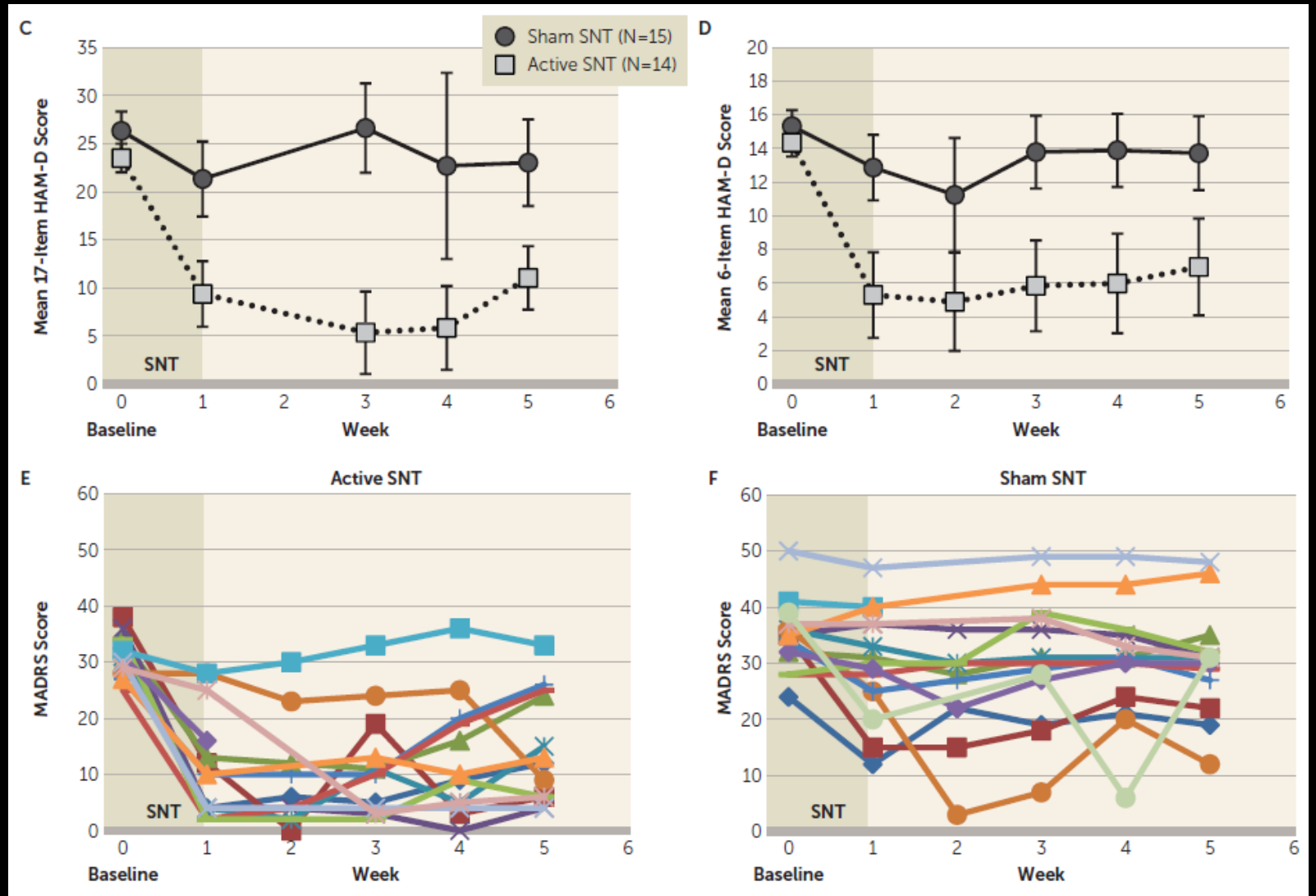
www.localite.de

www.neurolite.ch

# SNT Double-Blind RCT (Cole et al. 2022)

- Moderate to severe depressive episodes based on scales
- Moderate to severe levels of treatment resistance
- The trial was halted at the midpoint because the planned interim analysis demonstrated a large effect size of active compared with sham treatment (Cohen's $d>0.8$)

# SNT Double-Blind RCT (Cole et al. 2022)



# SNT Double-Blind RCT (Cole et al. 2022)

| Active SNT Group | Response Rate | Remission Rate |
|---|---|---|
| 0 weeks after treatment | 71.4% | 57.1% |
| 1 week after treatment | 77.8% | 66.7% |
| 2 weeks after treatment | 84.6% | 53.8% |
| 3 weeks after treatment | 69.2% | 61.5% |
| 4 weeks after treatment | 69.2% | 46.2% |

- FDA approved this protocol in October 2022

# Transcranial Magnetic Stimulation for Schizophrenia

What's New?

# Negative Symptoms in Schizophrenia

- fMRI studies have demonstrated that negative symptoms are a result of dysfunctional connectivity between the DLPFC and VTA (the mesocortical pathway)
- Excitatory TMS protocols (e.g., 10 Hz rTMS, iTBS) over the left DLPFC had the highest probability of reducing negative symptom severity (Tseng et al. 2022)
  - Also considered other NIBS protocols not covered in this talk

# TMS for Negative Symptoms of Schizophrenia

(Lorentzen et al. 2022)

- Systematic review and meta-analysis
  - 1714 studies screened → 57 studies included
- Significant effect of active TMS on negative symptoms compared to sham treatment (SMD = 0.41, NNT = 5)
- Considerable heterogeneity, but it appeared that >1 Hz stimulations and targeting the L-DLPFC may be more effective protocols

# iTBS for Neurocognitive Dysfunction in Older Adults with Schizophrenia (Zhang et al. 2023)

Zhao et al. 2021

- iTBS superior to sham treatment in improving neurocognitive function measured by MDRS-2 and subscales
  - Attention
  - Initiation/perseveration
  - Conceptualization
  - Construction
  - Memory

Zhen et al. 2018

- Mixed results from Digit span test; Spatial span test; WCST

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# References


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