Neuroscience Education Institute

# TREATMENT RESISTANT DEPRESSION

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# Disclosure

## Faculty Editor / Presenter

**Stephen M. Stahl, MD, PhD, DSc (Hon.),** is a clinical professor in the Department of Psychiatry and Neuroscience at the University of California, Riverside School of Medicine in Riverside, CA; an adjunct professor of psychiatry at the University of California, San Diego School of Medicine in La Jolla, CA; an honorary visiting senior fellow at the University of Cambridge in Cambridge in the UK; Editor-in-Chief of CNS Spectrums; and the Director of Psychopharmacology Services for the California Department of State Hospitals in Sacramento, CA.

Grant/Research: Acadia, Alkermes, Allergan/AbbVie, Arbor, AssureX, AstraZeneca, Avanir, Axovant, Biogen, Braeburn, BristolMyer Squibb, Celgene, CeNeRex, Cephalon, Dey, Eisai, Forest, GenOmind, Glaxo Smith Kline, Harmony Biosciences, Indivior, Intra-Cellular, Ironshore, Janssen, JayMac, Jazz, Lilly, Lundbeck, Merck, Neurocrine, Neuronetics, Novartis, Otsuka, Pear, Pfizer, Reviva, Roche, Sage, Servier, Shire, Sprout, Sunovion, Supernus, Takeda, Teva, Tonix, Torrent, Vanda

Consultant/Advisor: Acadia, Adamas, Alkermes, Allergan/AbbVie, Arbor, AstraZeneca, Avanir, Axovant, Axsome, Biogen, Biomarin, Biopharma, Celgene, ClearView, Concert, DepotMed, EMD Serono, Eisai, Eurolink, Ferring, Forest, Genomind, Innovative Science Solutions, Impel, Intra-Cellular, Ironshore, Janssen, Jazz, Karuna, Lilly, Lundbeck, Merck, Neos, Neurocrine, NeuroPharma, Novartis, Noveida, Otsuka, Perrigo, Pfizer, Pierre Fabre, Proxymm, Relmada, Reviva, Sage, Servier, Shire, Sprout, Sunovion, Takeda, Taliaz, Teva, Tonix, Tris, Trius, Vanda, Vertex, Viforpharma

Speakers Bureau: Acadia, Genentech, Janssen, Lundbeck, Merck, Otsuka, Servier, Sunovion, Takeda, Teva

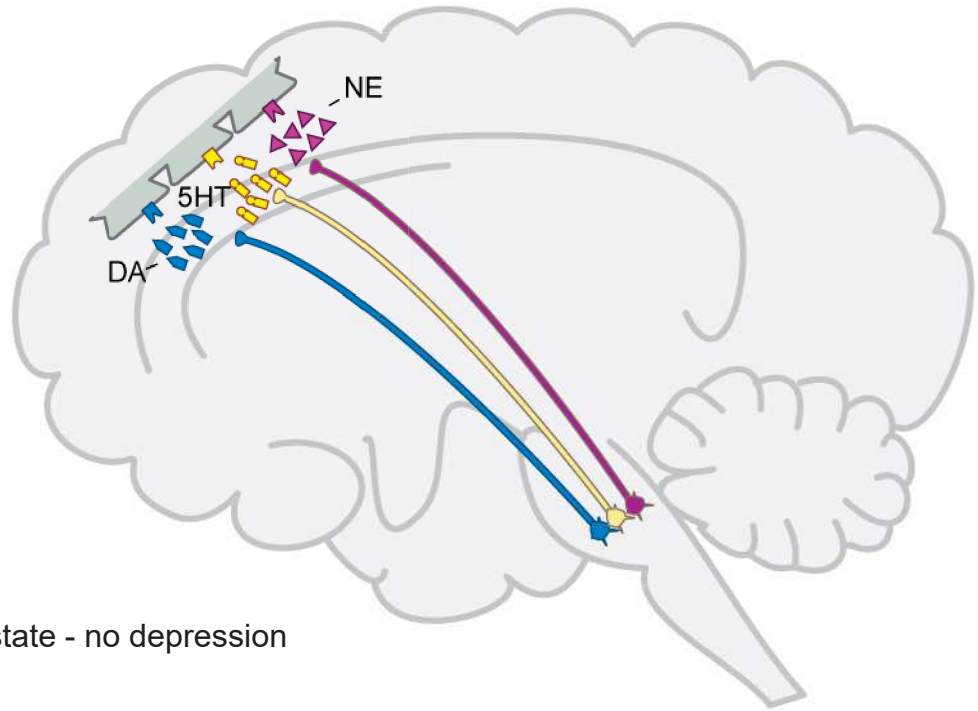
Board Member: Genomind, RCT Logic

Options Holdings: Delix, Genomind, Lipidio

# Learning Objectives

- To present the options for treating unipolar major depressive disorder when first line treatments have failed
- To explain, compare and contrast the various initial targets of pharmacologic action for multiple new treatment options d
- To discuss the role of neuronal plasticity in the mechanism of action of rapid acting agents with antidepressant action

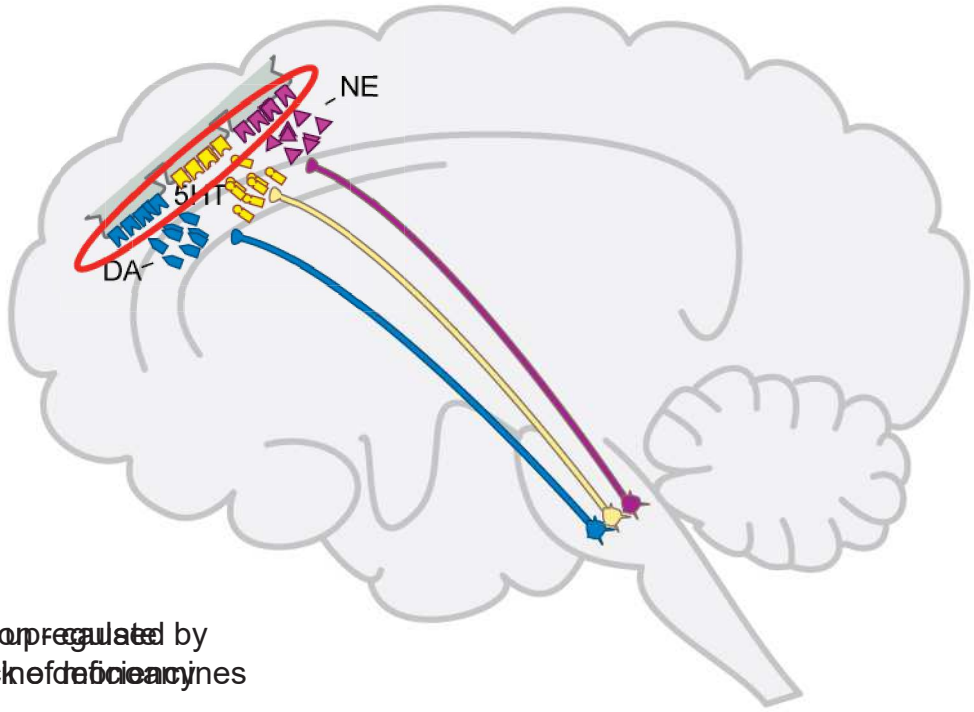
## Monoamine Hypothesis of Depression




normal state - no depression

5HT, 5-hydroxytryptamine (serotonin); DA, dopamine; NE, norepinephrine

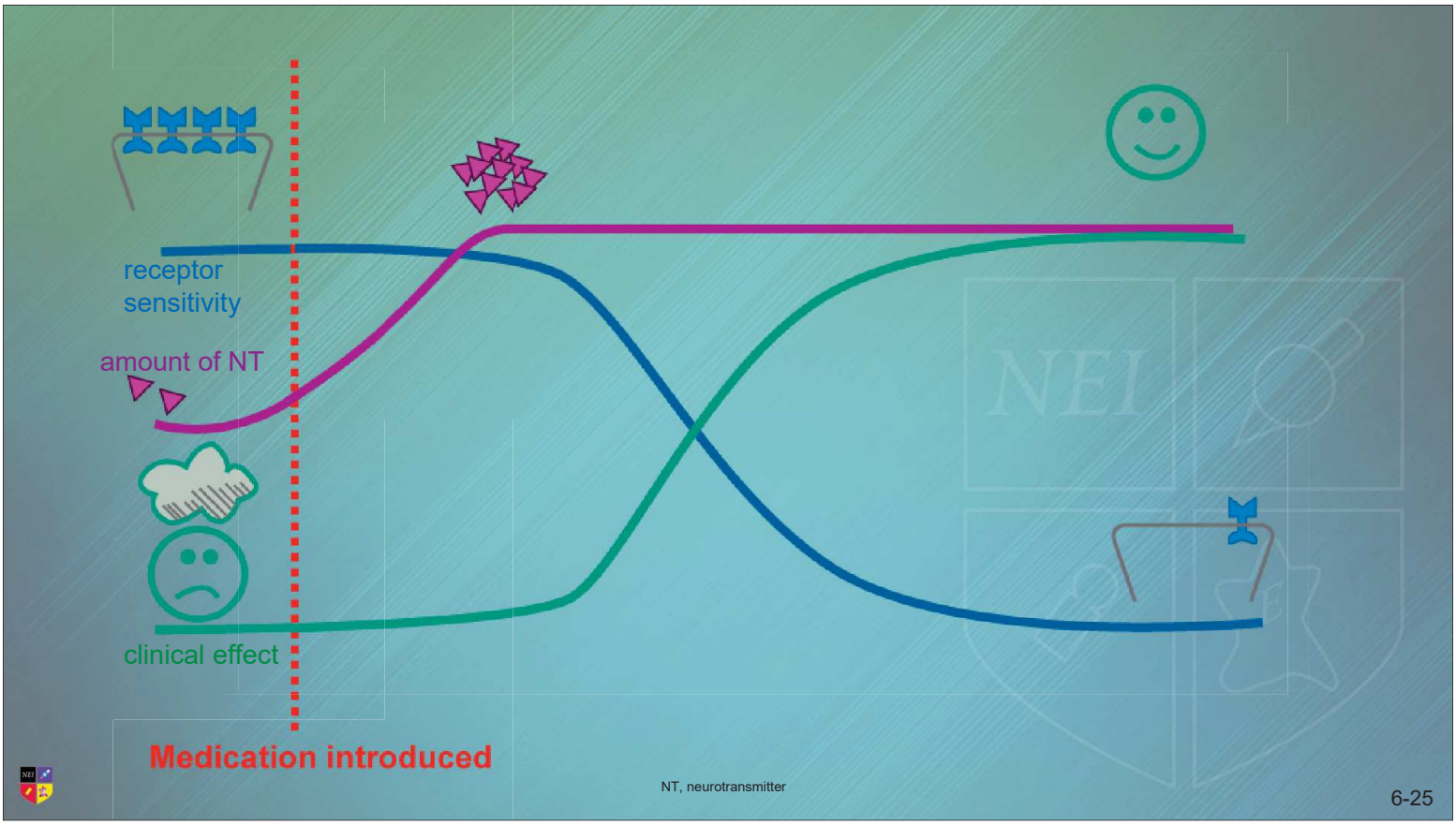
# Monoamine Hypothesis of Depression




depression caused by deficiency of monoamines

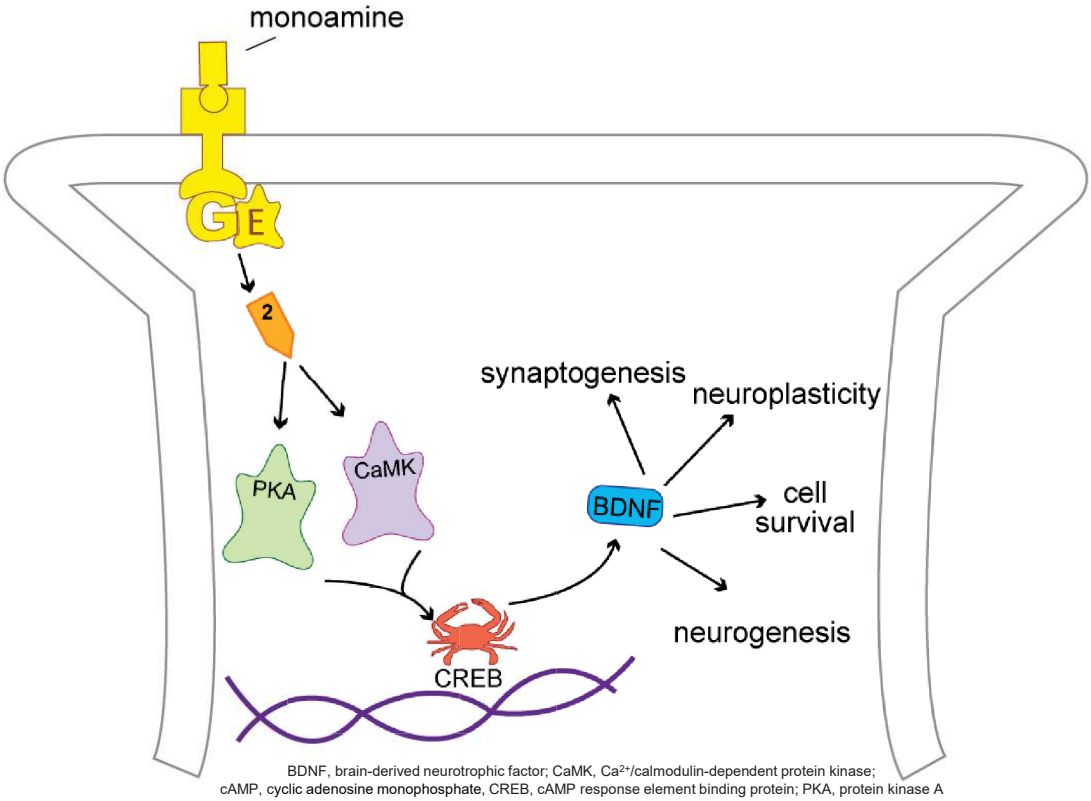
5HT, 5-hydroxytryptamine (serotonin); DA, dopamine; NE, norepinephrine





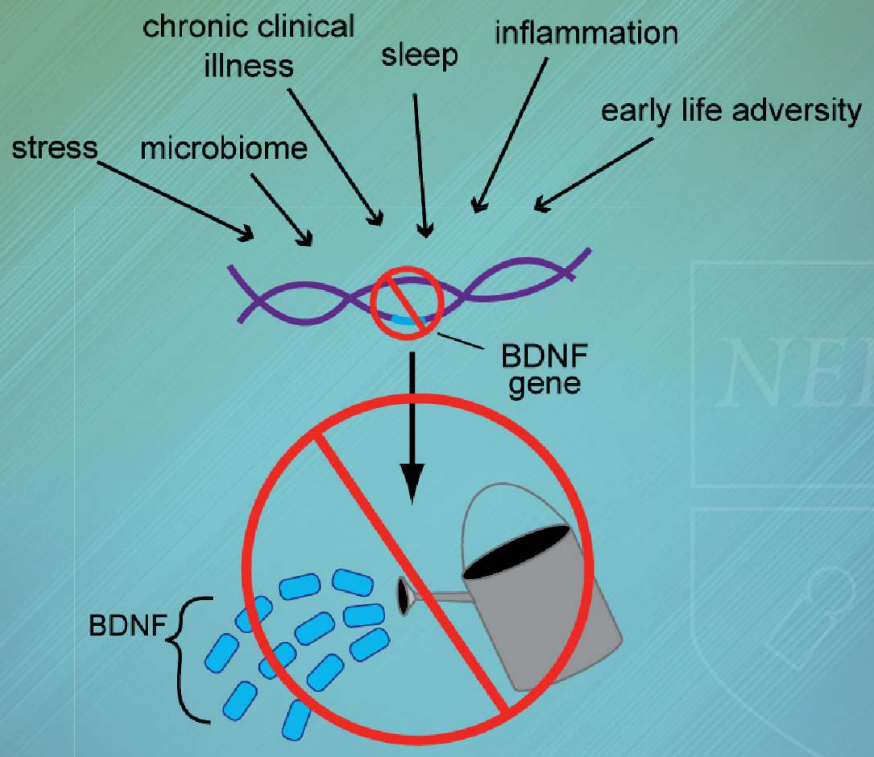

NT, neurotransmitter

## Monoamine Signaling Increases BDNF Release Which Modifies Monoamine Innervation

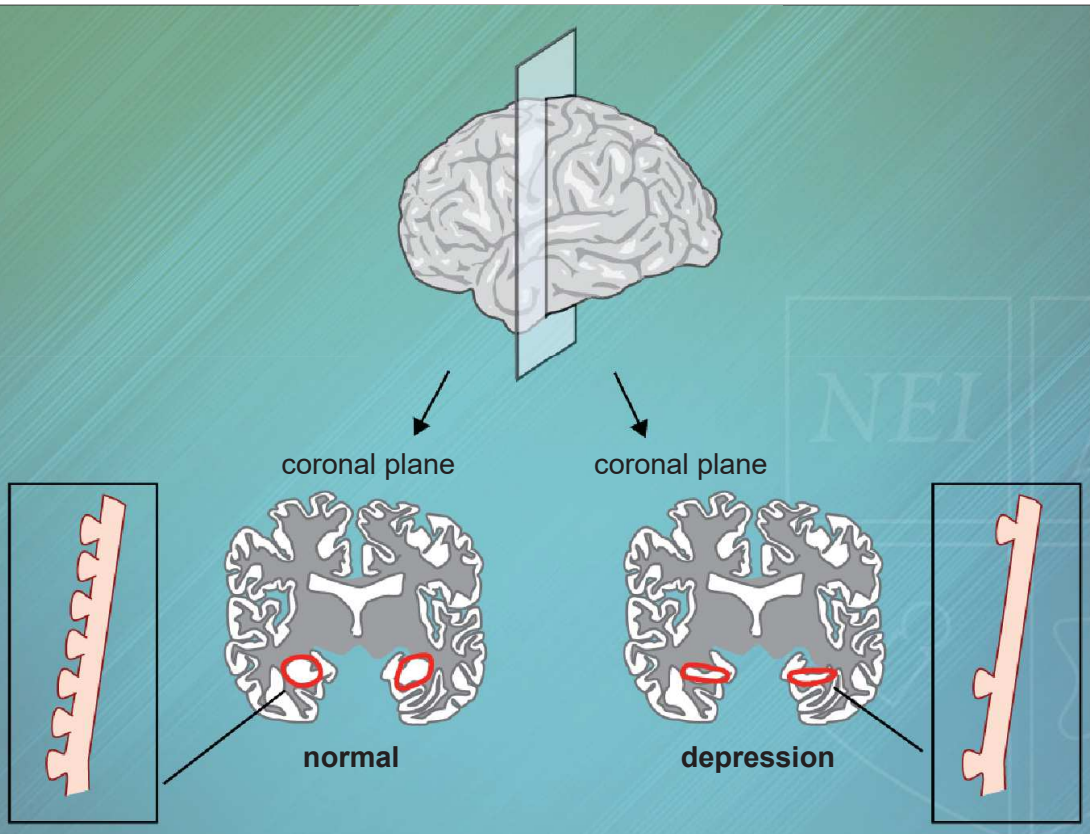



BDNF, brain-derived neurotrophic factor; CaMK, $Ca^{2+}$/calmodulin-dependent protein kinase; cAMP, cyclic adenosine monophosphate, CREB, cAMP response element binding protein; PKA, protein kinase A



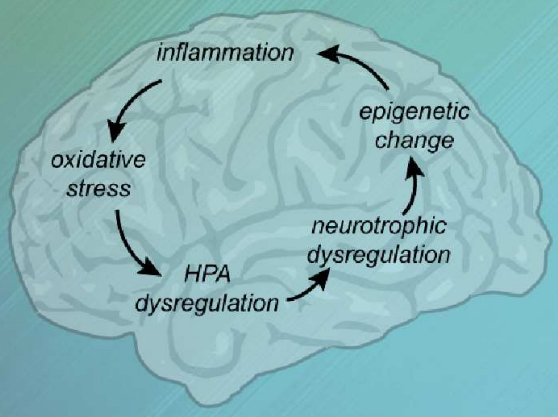



BDNF, brain-derived neurotrophic factor





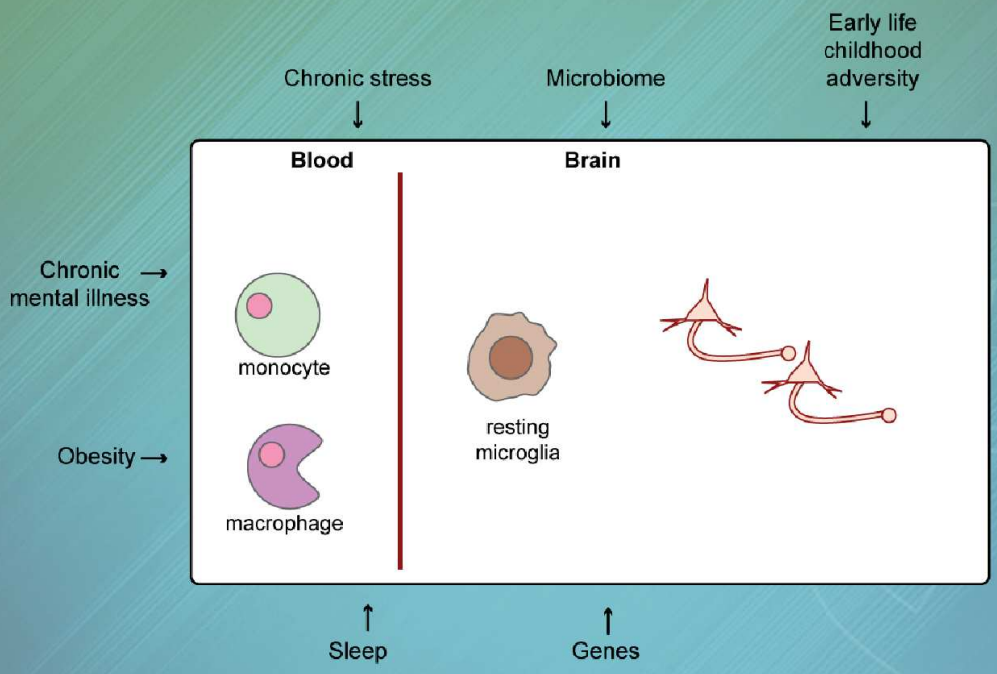

**Symptomatic Brain Network**



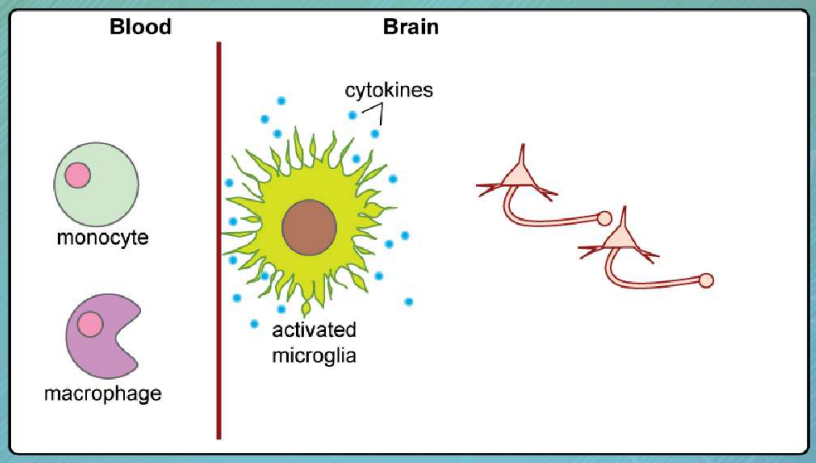

**Neuroprogression**

Vulnerability to relapse
Treatment resistance
↑
Functional brain abnormalities
↑
**Damage to synapses and neurons**
↓
Structural brain abnormalities
↓
Cognitive decline

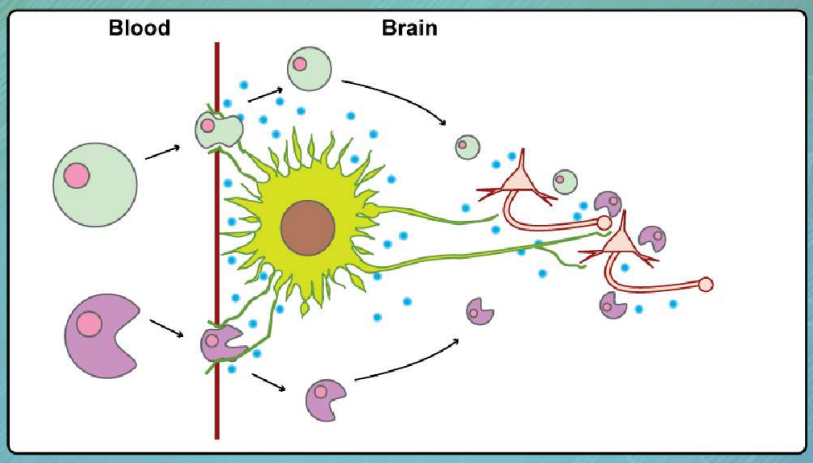
HPA, hypothalamic–pituitary–adrenal axis


Chronic stress
Microbiome
Early life childhood adversity
Blood
Brain
Chronic mental illness
monocyte
resting microglia
Obesity
macrophage
Sleep
Genes

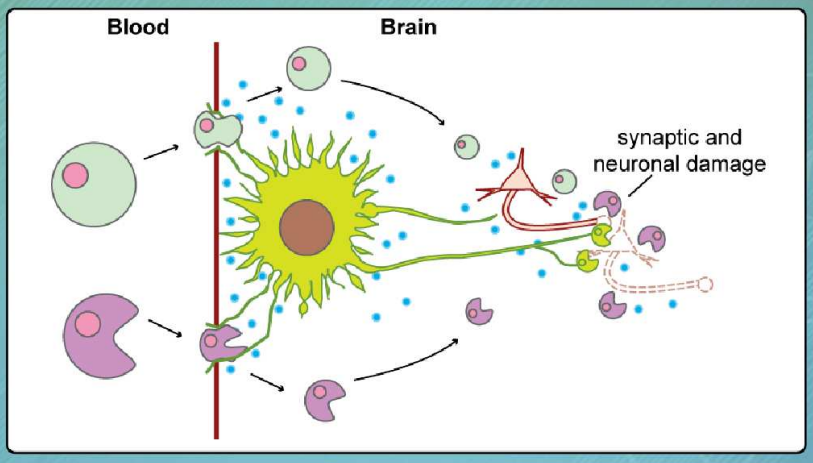
6-33A


Blood
Brain
cytokines
monocyte
activated microglia
macrophage

6-33B

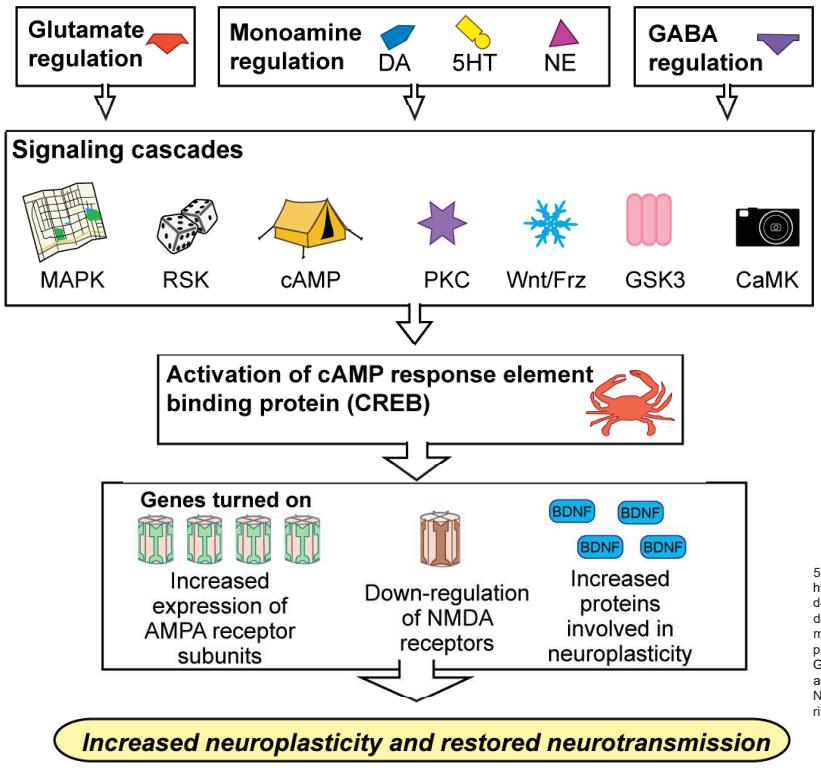



6-33C




6-33D

# Downstream Improvement in Neuroplasticity with Novel Drugs for Depression

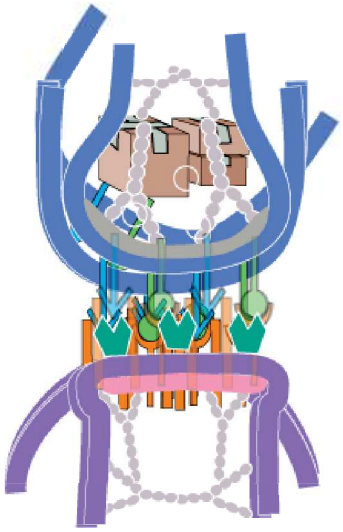



5HT, 5-hydroxytryptamine (serotonin); AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; BDNF, brain-derived neurotrophic factor; CaMK, $Ca^{2+}$/calmodulin-dependent protein kinase; cAMP, cyclic adenosine monophosphate; CREB, cAMP response element binding protein; DA, dopamine; GABA, gamma-aminobutyric acid; GSK3, glycogen synthase kinase 3; MAPK, mitogen-activated protein kinase; NMDA, *N*-methyl-D-aspartate; NE, norepinephrine; PKC, protein kinase C; RSK, ribosomal S6 kinase; Wnt/Frz, Wnt/Frizzled



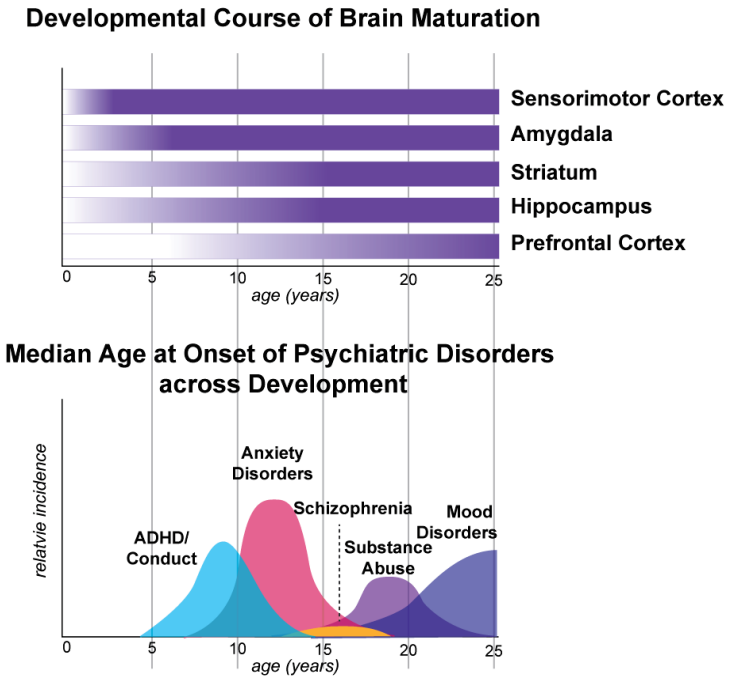
# What is Neuroplasticity?

synaptogenesis



Stahl's Essential Psychopharmacology, 3rd edition, 2008, copyright NEI. All rights reserved.

# What Triggers Neuroplasticity?




ADHD, attention-deficit/hyperactivity disorder
Meyer HC, Lee FS. Am J Psychiatry 2019;176:179–85.

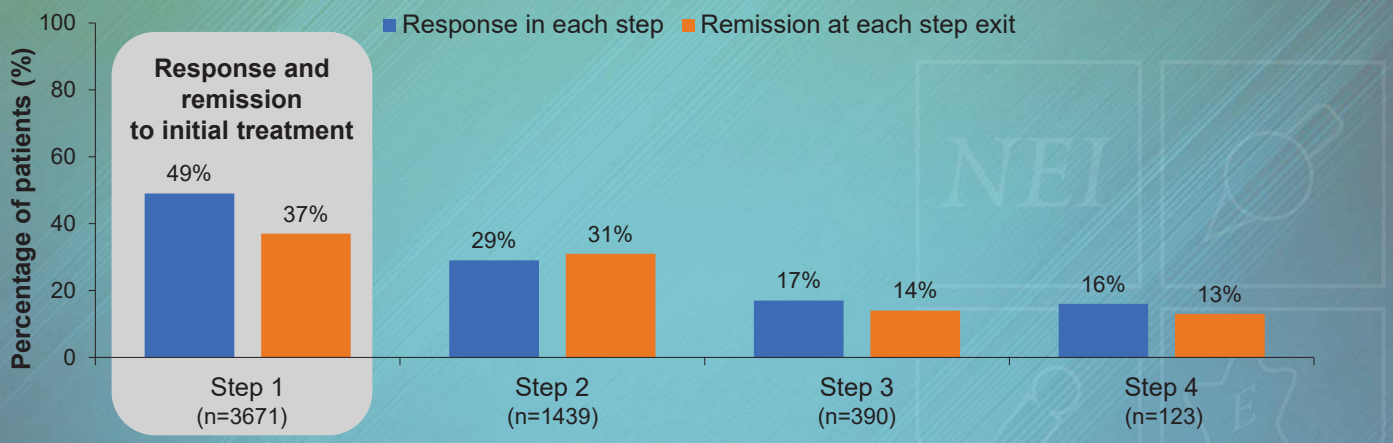
# What Else Triggers Neuroplasticity?

- Epigenomics[1,2]
  - Healthy neurodevelopment
  - Exercise
  - Learning
- Responding to antidepressants[3,4]
- Responding to psychotherapy[5–7]
  - Therapeutic persuasion or therapeutic brainwashing?
  - Psychedelic assisted psychotherapy (there are no skills in pills)
    - emotional sympathy
    - mystical and spiritual experiences
    - vs dysphoria and anxiety

1. Albert PR. J Psychiatry Neurosci 2019;44:147–50; 2. Voss P, et al. Front Psychol 2017;8:1657;
3. Murrough JW, et al. Nat Rev Drug Discov 2017;16:472–86; 4. Duman RS. F1000Res 2018;7:pii:F1000;
5. Lepow L, et al. Front Neurosci 2021;15:710004; 6. Förster K, Kanske P. Curr Opin Behav Sci 2021;39:64–71; 7. Dupuis D. Front Psychol 2021;12:730031.

# 50% of Patients With MDD Do Not Respond Adequately to Initial Antidepressant Treatment[1,2]

**Patients achieving response at each treatment step in the STAR*D study[1]**

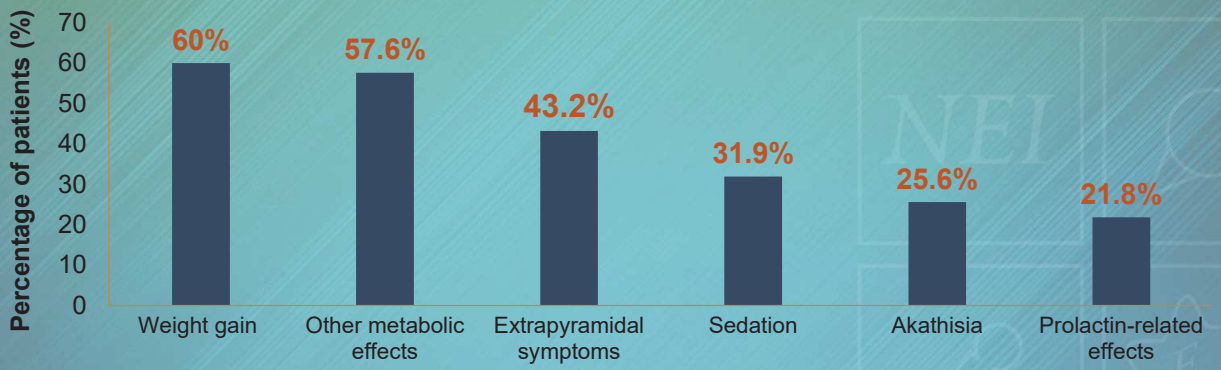



**Even in remission, patients with MDD receiving antidepressants can still experience residual symptoms, such as anhedonia, emotional blunting, and lack of motivation, which can negatively impact patient outcomes[3–5]**


Adapted from [1] Rush AJ et al. Am J Psychiatry 2006;163(11):1905-17; [2] Keitner GI, Mansfield AK. Psychiatr Clin North Am 2012;35(1):249-65; [3] Judd LL et al. Am J Psychiatry 2000;157(9):1501-4; [4] Conradi HJ et al. Psychol Med 2011;41(6):1165-74; [5] Culpepper L et al. Am J Med 2015;128(9 Suppl):S1-15.


# Concern Over Specific Side Effects May Limit the Use of Adjunctive Antipsychotics for Some Patients With MDD

Main tolerability or safety concerns reported by physicians for patients in whom antipsychotic prescription was delayed or prevented (n=458):




A recent survey of 447 patients with MDD reported weight gain being the adverse effect that most commonly led to discontinuation, followed by lethargy, emotional blunting, and anxiety


McIntyre RS, Weiller E. Adv Ther 2015;32(5):429-44; Rosenblat JD et al. J Affect Disord 2019;243:116-20.

# What to Investigate if a Patient Does Not Respond to Treatment

**Check the diagnosis**
**(bipolar disorder?)**

## Physical comorbidities?

Hypothyroidism
Cushing's syndrome
Parkinsonism
Malignancy
Anemia
Viral infections
Vitamin deficiencies
Dietary deficiencies

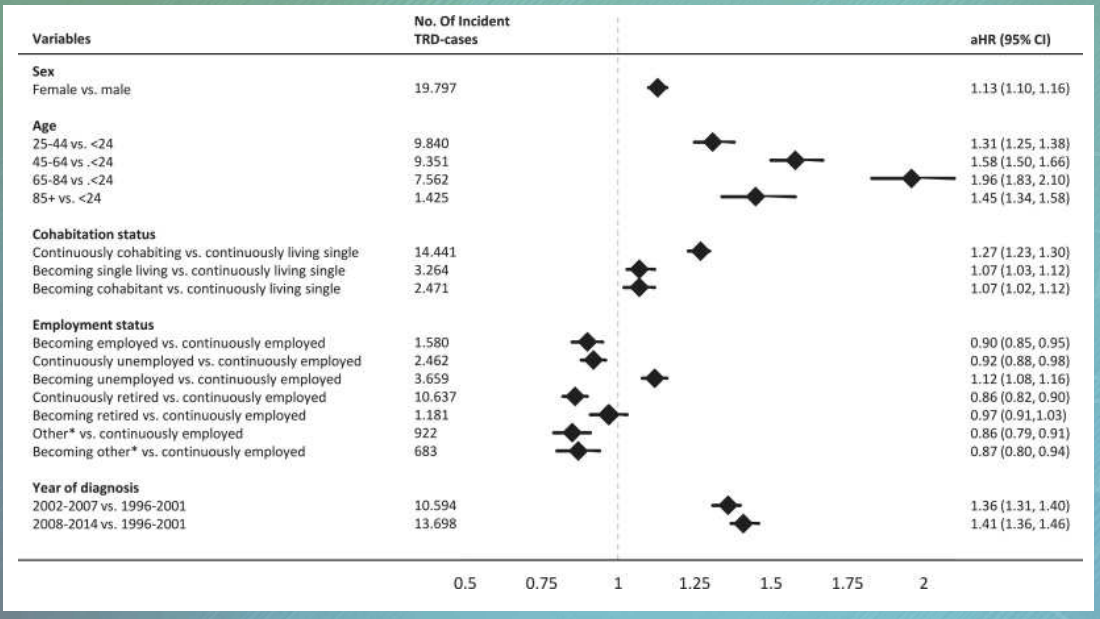
## Psychiatric comorbidities?

Substance misuse, dependency
Anxiety disorders
Eating disorders
Personality disorders
Post-traumatic disorders

Influence of metabolic factors: depression and obesity are risk factors for type 2 diabetes

Pandarakalam JP. Psychiatr Danub 2018;30(3):273-84; Tsenkova VK, Karlamangla A. PLoS One 2016;11(10):e0164802.

# Risk Factors for TRD (1)




**Sex—female**

**Age—older**

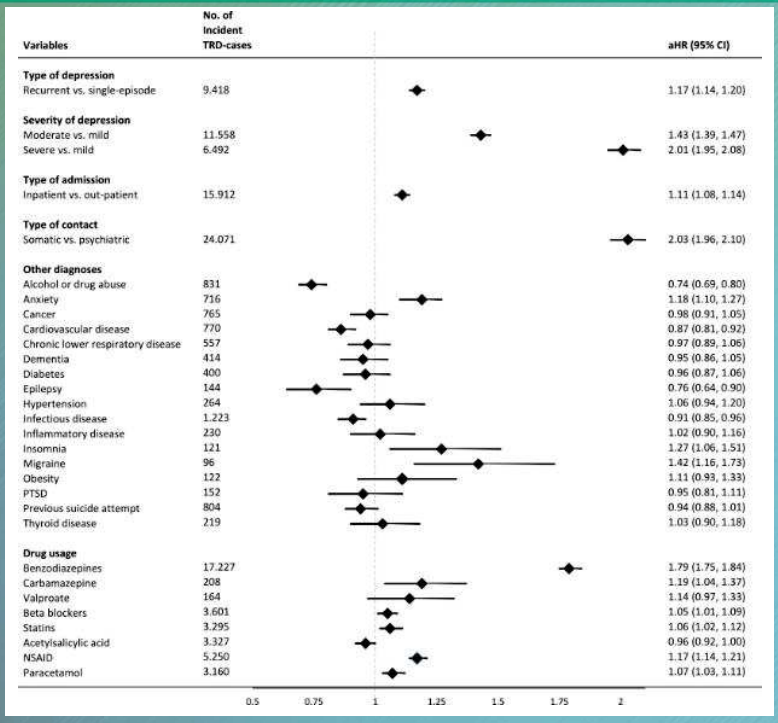
**Becoming single or Cohabiting**

**Becoming unemployed**

**More common over time (could be artefactual)**

Gronemann et al. J Affect Disord 2020;261:221-9.

# Risk Factors for TRD (2)




**Recurrent depression**

**Severe depression**

**Inpatients**

**Psychiatric hospital**

**Anxiety**

**Insomnia**

**Migraine**

**(other conditions protective?**

**or less likely to receive treatment)**

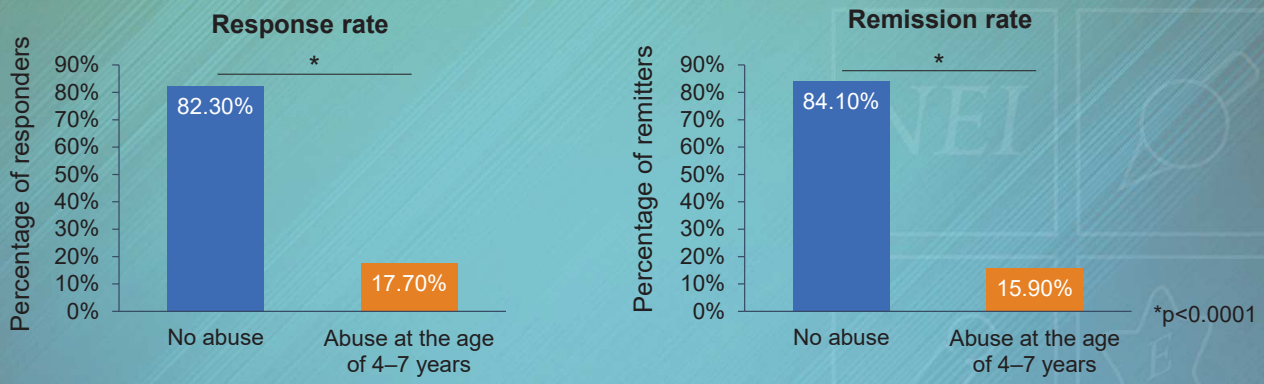
**Benzodiazepine use**

**(confounded by anxiety)**

Gronemann et al. J Affect Disord 2020;261:221-9.

# Childhood Trauma Can Lead to Poor Treatment Outcomes in Patients With MDD

**Response and remission rates in MDD patients receiving SSRI/SNRIs with or without childhood trauma as measured by HAM-D (N=722)**

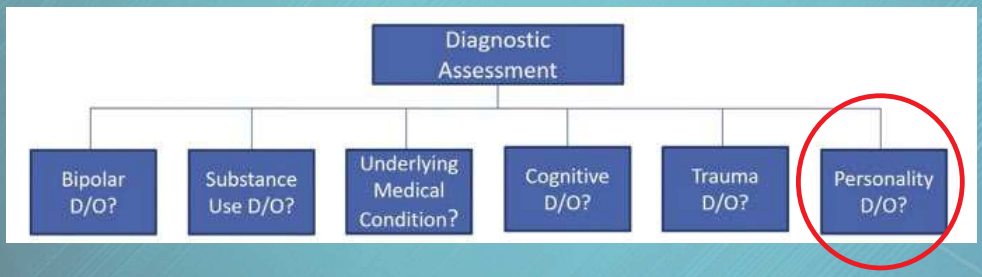


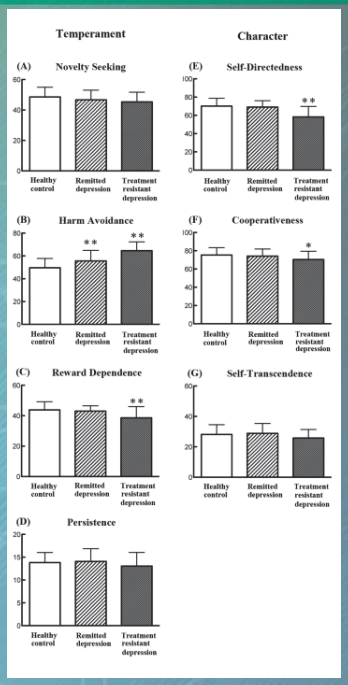

In a separate analysis, patients with MDD were **1.6 times less likely** to achieve response or remission if exposed to abuse at the age of 4−7 years: OR=1.574 for response (p=0.034); OR=1.606 for remission (p=0.032)

Adapted from Williams LM et al. Transl Psychiatry 2016;6(5):e799.

# Personality Disorder and Treatment Resistance

- Regardless of DSM-5, patients with low reward dependence > low cooperativeness had more TRD
- Personality disorder creates greater TRD than
  - Comorbid anxiety, addiction, etc.
  - Comorbid medical conditions
- However, personality disorder diagnoses often reduced 50% after successful MDD treatment
  - State vs Trait



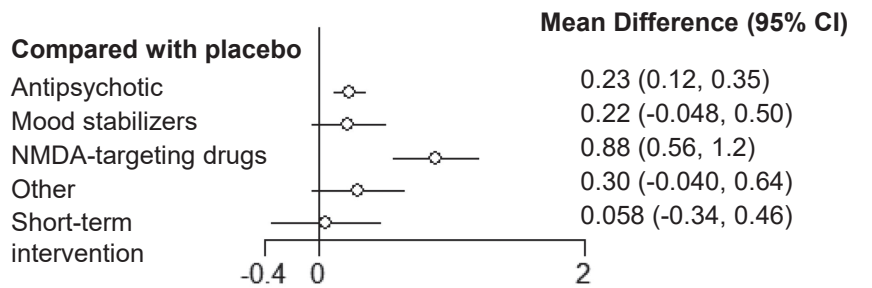

Thase ME. Psych Clinics NA 1996;19(2):287-309; Fava M. Biol Psychiatry 2003;53(8):649-659; Young M. Psychiatr Clin North Am 2018;41(2):249-61; Takahashi M et al. PLoS One 2013;8(5);e63756.

# What Are the Treatment Options if the First-Line Antidepressant Is Suboptimal?

- Combine antidepressants
- Switch antidepressants
- Add second-generation atypical antipsychotic agent (e.g., brexpiprazole, aripiprazole, quetiapine)
- Consider other (e.g., L-methylfolate, stimulant)
- Add or switch to psychotherapy
- Consider neurostimulation

McIntyre RS et al. J Clin Psychiatry 2017;78(6):703-13.

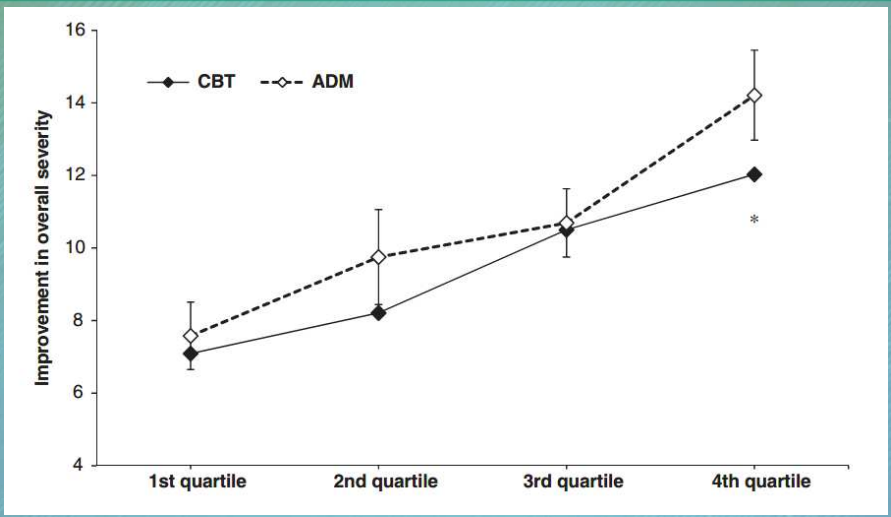
# Relative Effectiveness of Augmentation Treatments for Treatment-Resistant Depression




- Network meta-analysis (NMA) of 27 randomized trials comparing effectiveness of pharmacological interventions with placebo for adults meeting clinical criteria for treatment-resistant depression
- NMA showed that NMDA treatments were markedly superior to placebo and head-to-head NMA suggested that NMA therapies had the highest chance of being an effective treatment option compared to other pharmacological classes

Carter B et al. Int Rev Psychiatry 2020;32(5-6):477-90.

# Antidepressants Are More Effective Than Psychotherapy in Targeting Fatigue, Cognitive Impairment, and Motivational Deficits



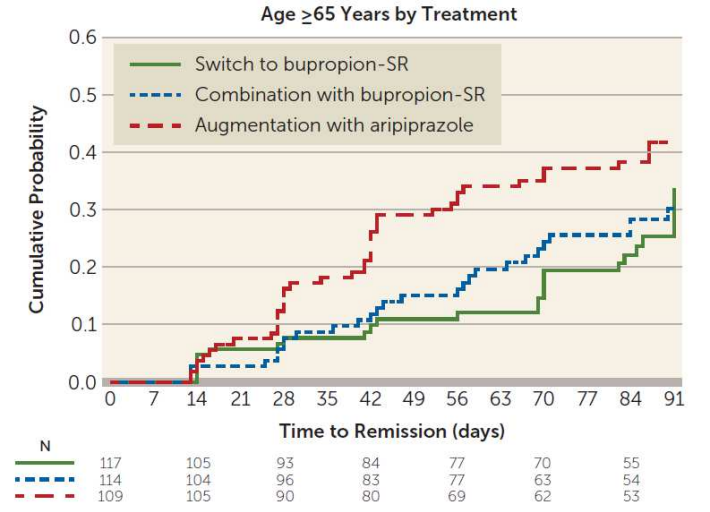

ADM: antidepressant medication
CBT: cognitive behavioral therapy

Five symptoms (i.e., “depressed mood,” “feelings of guilt,” “suicidal thoughts,” “psychic anxiety,” and “general somatic symptoms”) showed larger improvements in the medication compared to the CBT condition (effect sizes ranging from .13 to .16), whereas no differences were found for the twelve other symptoms.

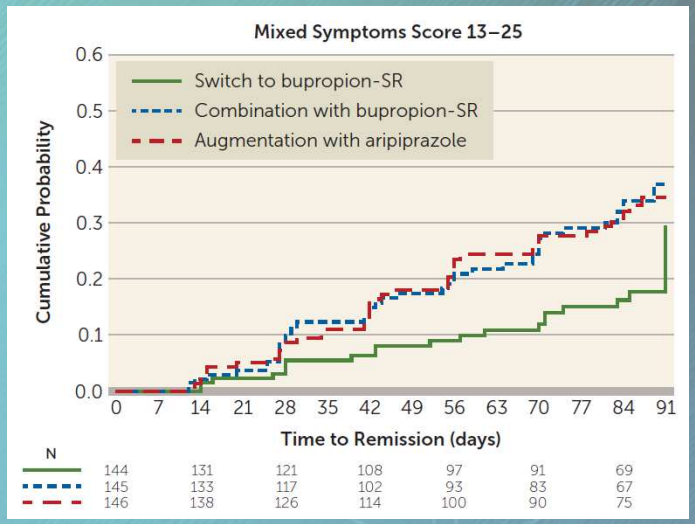
Boschloo L et al. World Psychiatry 2019;18(2):183-91 .

# Moderators of Depression Remission in Patients Without Adequate Response to at Least One Antidepressant

### Higher Remission Rates With Aripiprazole Augmentation Among Those Age 65 Years or Older

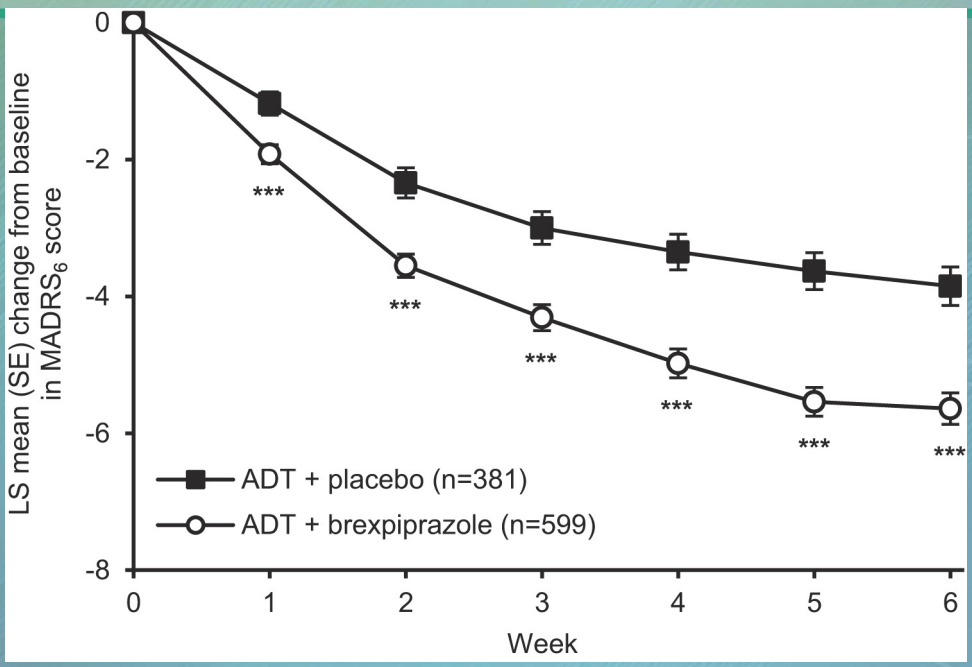



### Lower Remission Rates With Switch to Bupropion-SR Among Those Endorsing the Greatest Levels of Mixed Symptoms



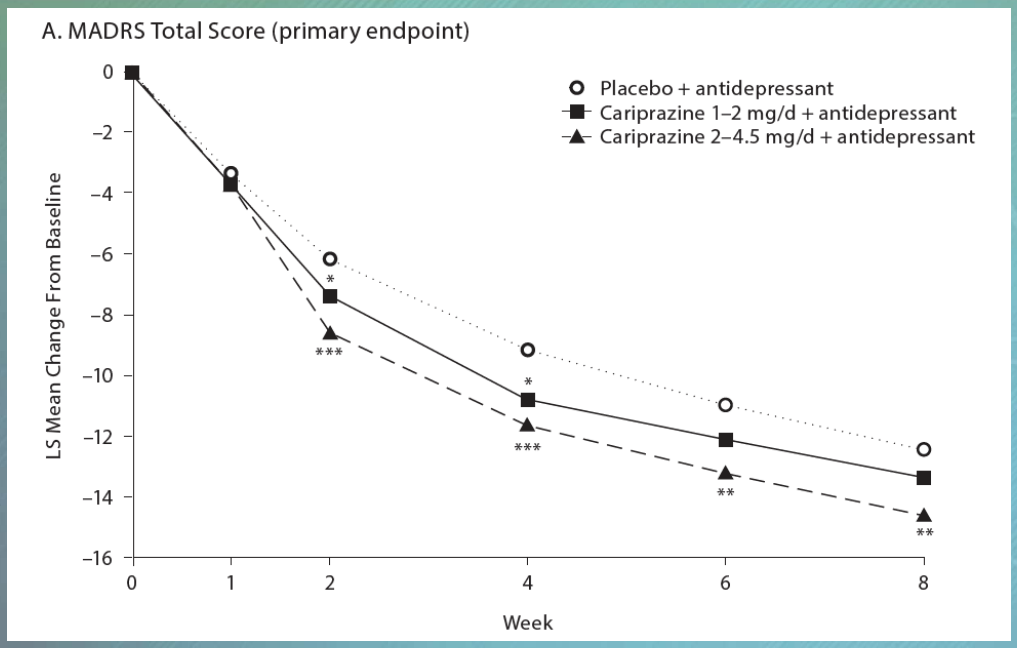

Zisook S et al. Am J Psychiatry 2019;176(5):348-57.

# Adjunctive Brexpiprazole (1-3 mg/day) for the Treatment of MDD




Nelson JC et al. J Affect Disord 2018;227:103-8.

# Adjunctive Cariprazine (2–4.5 mg/day) Is Effective for MDD With Inadequate Antidepressant Response




Treatment-emergent adverse events (TEAEs) that occurred in ≥ 10% of patients in either cariprazine group and at incidence greater than placebo were akathisia, insomnia, and nausea

*P<.05. **P<.01. ***P<.001 versus placebo for pairwise comparisons; not adjusted for multiple comparisons

LS=least squares
MADRS = Montgomery-Åsberg Depression Rating Scale

Durgam S et al. J Clin Psychiatry 2016;77(3):371-8.

# Three Innovative Pharmacologic Targets Linked to Rapid Onset Neuroplasticity and Rapid Onset Antidepressant Actions

## NMDA (N-methyl-d-aspartate) glutamate receptor antagonists

- Ketamine
- Esketamine
- Arketamine
- Dextromethorphan
- Esmethadone

## GABA (gamma amino butyric acid) A Receptor Positive Allosteric Modulators (PAMs)

- Zuranolone
- Brexanolone

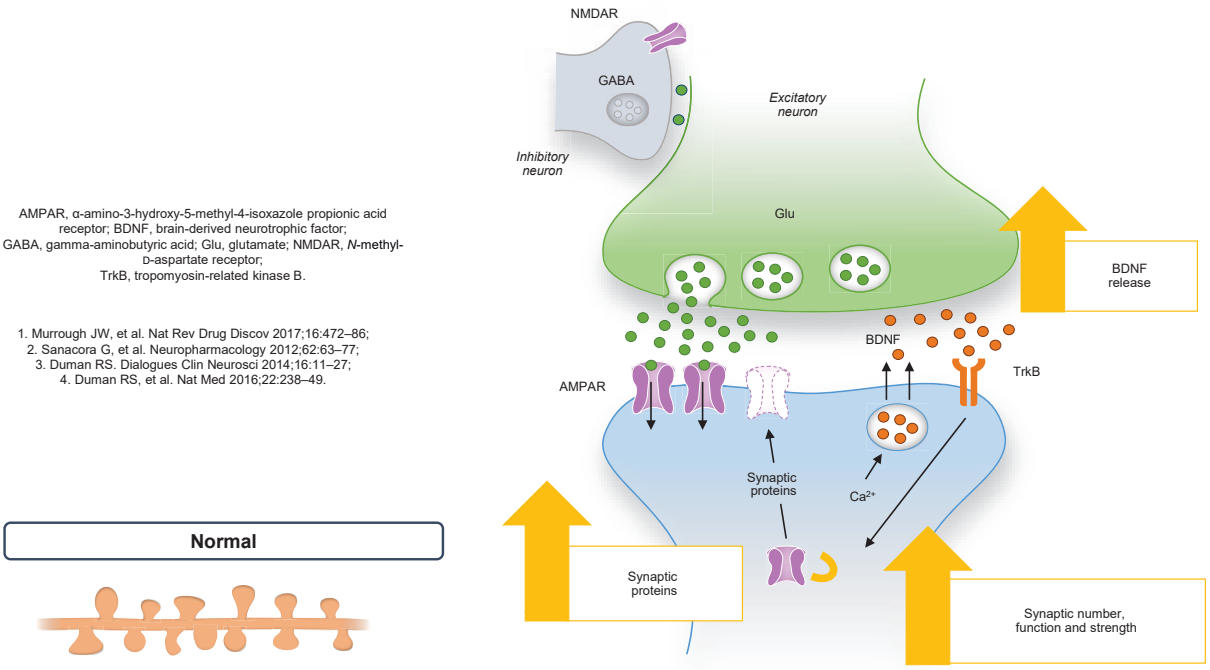
## Psychedelics

- Psylocybin
- Dimethyl tryptamine
- LSD lysergic acid diethylamine
- Mescaline
- Ayhawasca
- Ibogaine
- New chemical entity analogues of psychedelics

Cooper, Seigler and Stahl, J Psychopharmacol in press

# The Role of the Glutamatergic System in Normal Synaptogenesis

Glutamate is a major excitatory neurotransmitter that plays an important role in maintaining synaptic connections[1–4]




AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor; BDNF, brain-derived neurotrophic factor; GABA, gamma-aminobutyric acid; Glu, glutamate; NMDAR, *N*-methyl-D-aspartate receptor; TrkB, tropomyosin-related kinase B.


1. Murrough JW, et al. Nat Rev Drug Discov 2017;16:472–86;
2. Sanacora G, et al. Neuropharmacology 2012;62:63–77;
3. Duman RS. Dialogues Clin Neurosci 2014;16:11–27;
4. Duman RS, et al. Nat Med 2016;22:238–49.


- Hyperactive NMDARs play an important role in the pathophysiology of MDD

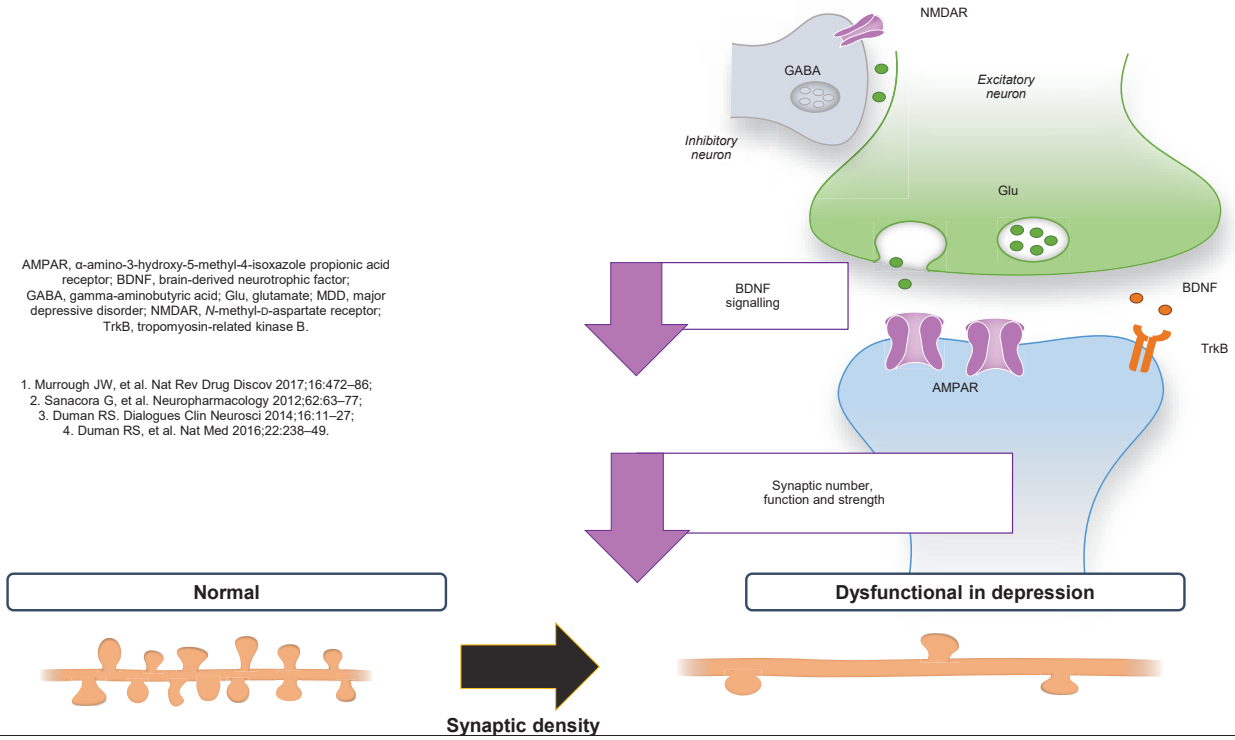
| Nondepressed brain | Depressed brain |
|---|---|
| Regulated NMDAR signaling | Dysregulated NMDAR signaling |
| Constant synaptic remodeling | Synaptic impairment |
| Constant neural plasticity | Neural plasticity impairment |
| Normal synaptic protein and BDNF transcription and production | Decreased synaptic protein and BDNF transcription and production |

- Targeting hyperactive NMDAR dysfunction in MDD offers a novel therapeutic approach that differs from existing treatments

BDNF, brain-derived neurotrophic factor; MDD, major depressive disorder; NMDAR, *N*-methyl-D-aspartate receptor

Murrough JW, et al. Nat Rev Drug Discov 2017;16:472–86.

# The Role of the Glutamatergic System in Depression




AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor; BDNF, brain-derived neurotrophic factor; GABA, gamma-aminobutyric acid; Glu, glutamate; MDD, major depressive disorder; NMDAR, *N*-methyl-D-aspartate receptor; TrkB, tropomyosin-related kinase B.

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3. Duman RS. Dialogues Clin Neurosci 2014;16:11–27;
4. Duman RS, et al. Nat Med 2016;22:238–49.

# Ketamine/Esketamine

- It is proposed that esketamine modulates glutamate neurotransmission, restoring synaptic function[2]

Evidence suggests that through NMDA receptor blockade, esketamine produces a surge in glutamate release[3–6]

↓

This surge in glutamate transmission leads to increased AMPA receptor stimulation[3,5,6]

↓

AMPA receptor stimulation leads to a release of BDNF, activating downstream neurotrophic signalling to increase synaptic protein synthesis synaptogenesis[3–6]

↓

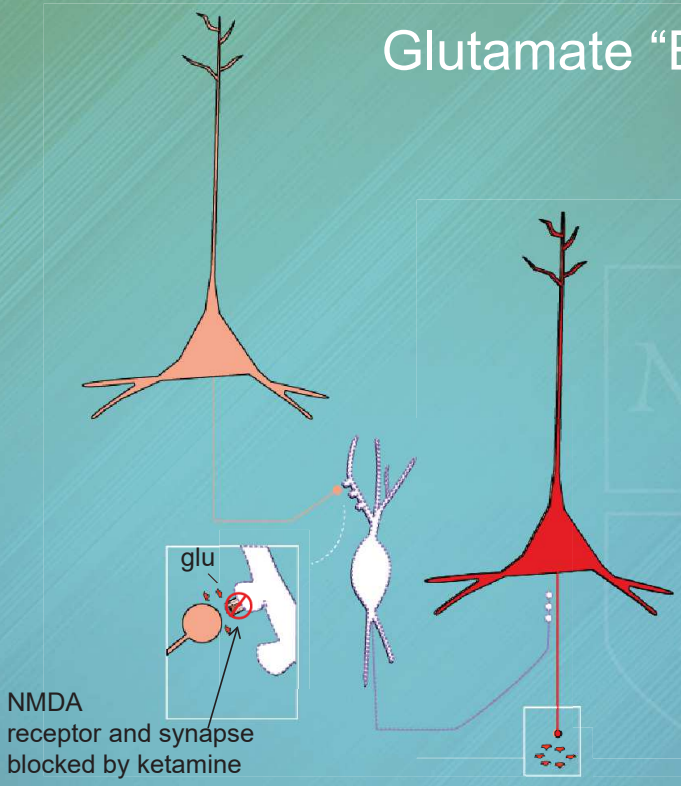
Restoring synaptic function[3–6]

*First approved by US FDA, March 2019

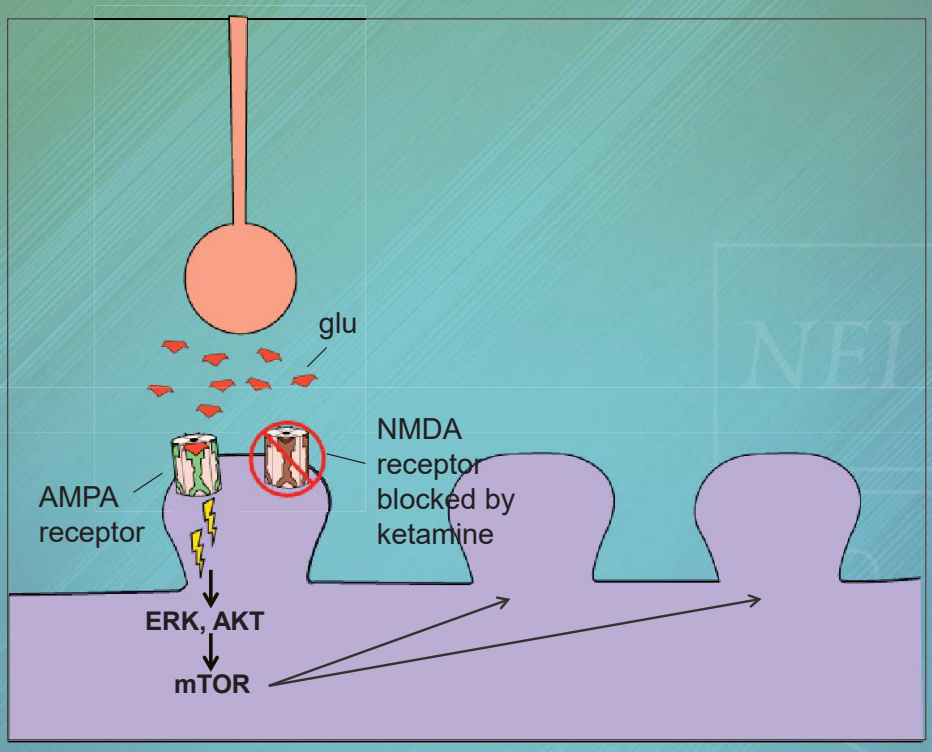
AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; BDNF, brain-derived neurotrophic factor; GABA, gamma-aminobutyric acid; Glu, glutamate; NMDA, *N*-methyl-D-aspartate; NMDAR, *N*-methyl-D-aspartate receptor; TrkB, tropomyosin receptor kinase B.

1. Janssen Press Release, March 2019: https://www.jnj.com/janssen-announces-u-s-fda-approval-of-spravatotm-esketamine-ciii-nasal-spray-for-adults-with-treatment-resistant-depression-trd-who-have-cycled-through-multiple-treatments-without-relief. Accessed May 2022. 2. Duman RS et al. Mol Psychiatry 2019;24:1816–32; 3. Murrough JW, et al. Nat Rev Drug Discov 2017;16:472–86; 4. Sanacora G, et al. Neuropharmacology 2012;62:63–77; 5. Duman RS, et al. Nat Med 2016;22:238–49; 6. Dale E, et al. Biochem Pharmacol 2015;95:81–97.

# Glutamate “Burst” Hypothesis




glu, glutamate; NMDA, *N*-methyl-D-aspartate




AKT, protein kinase B; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; ERK, extracellular signal-regulated kinase; glu, glutamate; mTOR, mechanistic target of rampamycin; NMDA, *N*-methyl-D-aspartate

# Ketamine/Esketamine

- It is proposed that esketamine modulates glutamate neurotransmission, restoring synaptic function[2]

Evidence suggests that through NMDA receptor blockade, esketamine produces a surge in glutamate release[3–6]

↓

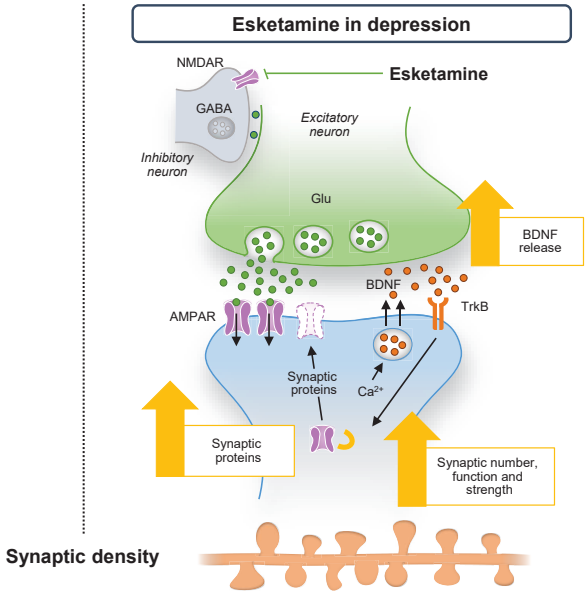
This surge in glutamate transmission leads to increased AMPA receptor stimulation[3,5,6]

↓

AMPA receptor stimulation leads to a release of BDNF, activating downstream neurotrophic signalling to increase synaptic protein synthesis synaptogenesis[3–6]

↓

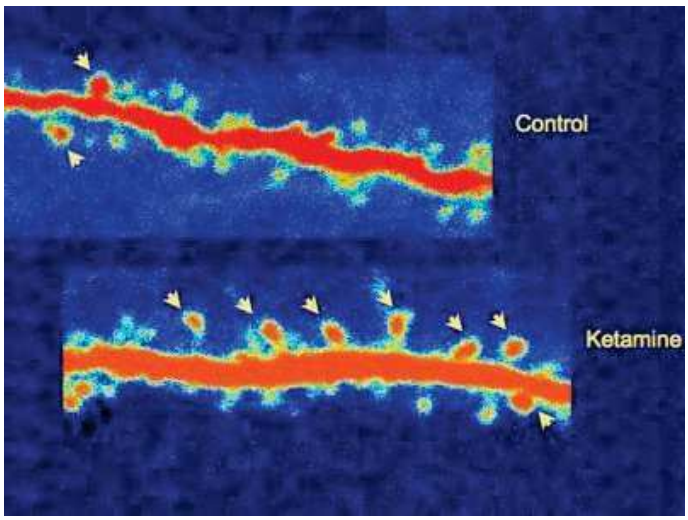
Restoring synaptic function[3–6]




*First approved by US FDA, March 2019
AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; BDNF, brain-derived neurotrophic factor; GABA, gamma-aminobutyric acid; Glu, glutamate; NMDA, N-methyl-D-aspartate; NMDAR, *N*-methyl-D-aspartate receptor; TrkB, tropomyosin receptor kinase B.

1. Janssen Press Release, March 2019: https://www.jnj.com/janssen-announces-u-s-fda-approval-of-spravatotm-esketamine-ciii-nasal-spray-for-adults-with-treatment-resistant-depression-trd-who-have-cycled-through-multiple-treatments-without-relief. Accessed May 2022. 2. Duman RS et al. Mol Psychiatry 2019;24:1816–32; 3. Murrough JW, et al. Nat Rev Drug Discov 2017;16:472–86; 4. Sanacora G, et al. Neuropharmacology 2012;62:63–77; 5. Duman RS, et al. Nat Med 2016;22:238–49; 6. Dale E, et al. Biochem Pharmacol 2015;95:81–97.

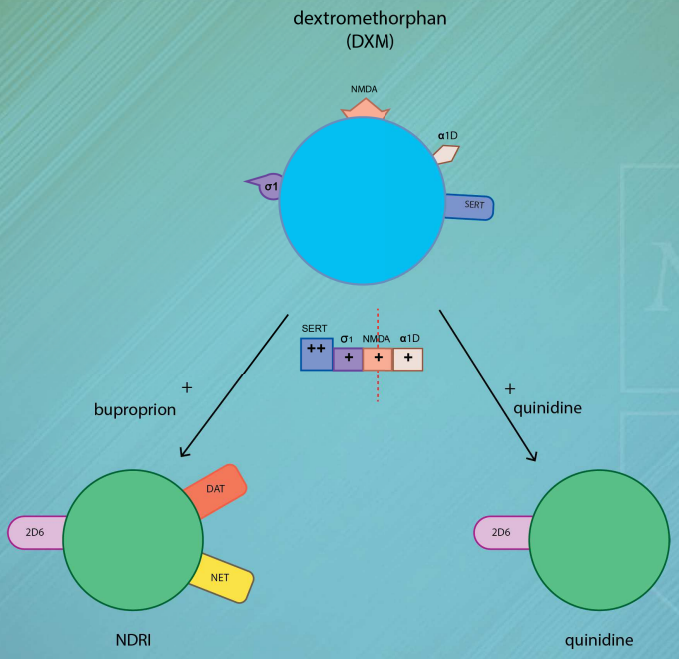
# Ketamine Rapidly Increases the Density and Function of the Dendritic Spines of Layer V Pyramidal Neurons in the Prefrontal Cortex




Bottom of the slide shows regeneration of synaptic connections in group receiving ketamine compared to control group

(Courtesy of Yale University)

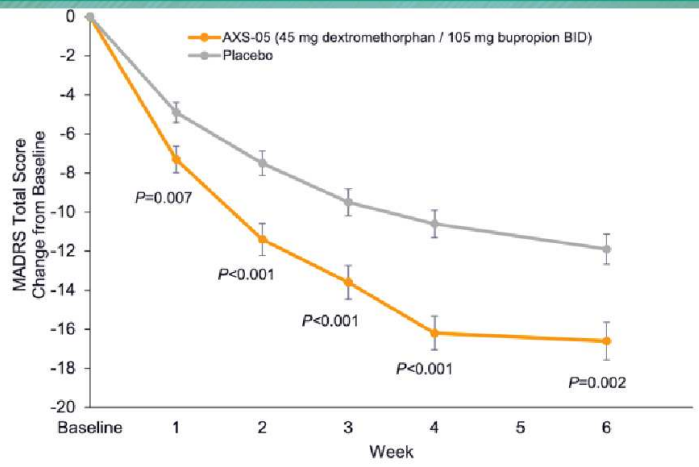
# Dextromethorphan (DXM)




Stahl SM. Stahl's Essential Psychopharmacology, 5th ed; 2021.

# Combination DXM-Bupropion (AXS-05) Effective in the Treatment of Adults With MDD

GEMINI Study (Phase 3, randomized, double-blind, placebo-controlled)




| | AXS-05 (n=156) | Placebo (n=162) | Difference | *P*-Value |
|---|---|---|---|---|
| **Primary Endpoint** | | | | |
| Change in MADRS Total Score at Week 6 | -16.6 | -11.9 | -4.7 | 0.002 |
| **Key Secondary Endpoint** | | | | |
| Change in MADRS Total Score at Week 1 | -7.3 | -4.9 | -2.4 | 0.007 |

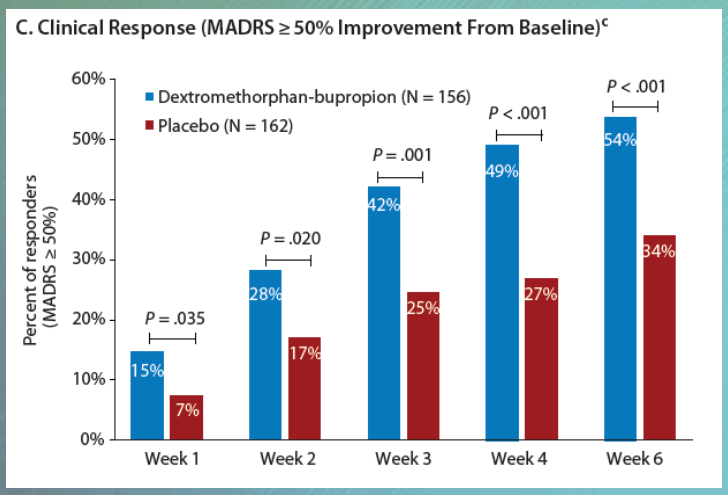
Notes: P-values calculated from LSMean. Abbreviations: BID = twice daily; MADRS = Montgomery-Åsberg Depression Rating Scale

Treatment with AXS-05 resulted in rapid and statistically significant improvements in depressive symptoms and function and QoL across multiple efficacy endpoints compared to placebo

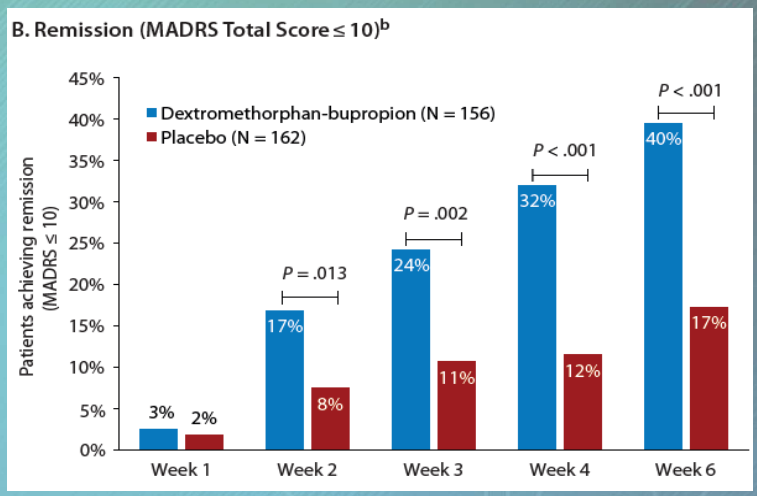
O'Gorman C et al. J Clin Psychiatry 2022;83(4):21m14345. doi: 10.4088/JCP.21m14345.

# AXS-05 GEMINI Trial

## Response



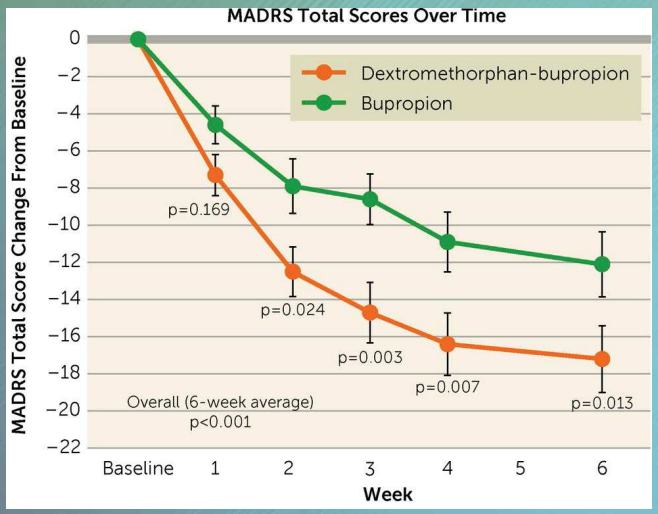

## Remission

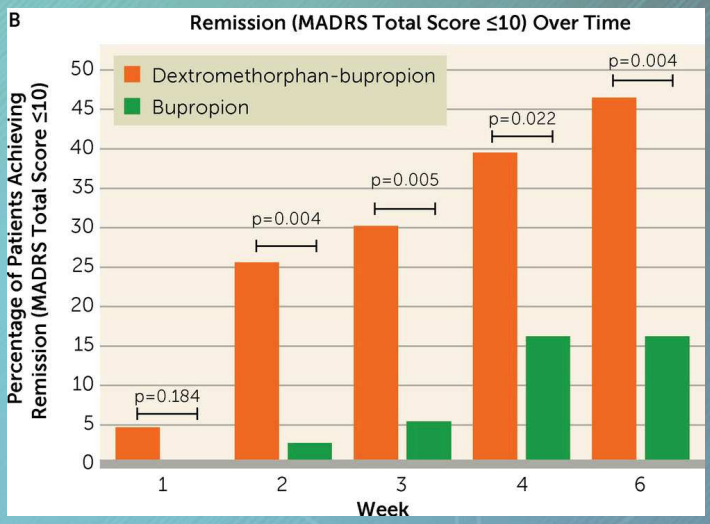



Iosifescu DV et al. J Clin Psychiatry 2022;83(4):21m14345.

# AXS-05: RCT of 80 patients

Rationale: Bupropion (2D6 inhibitor) boosts Dextromethorphan levels



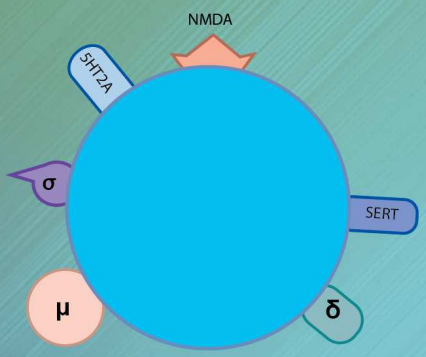



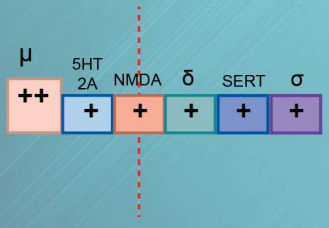

Tabuteau H et al., Am J Psychiatry 2021; 179:490–499

# Adverse Events Associated with Dextromethorphan/Bupropion

- Dizziness (16%)
- Headache (8%)
- Diarrhea (7%)
- Somnolence (7%)
- Dry mouth (6%)
- Sexual dysfunction (6%)
- Hyperhidrosis (5%)

# Dextromethadone/ S-methadone/Esmethadone

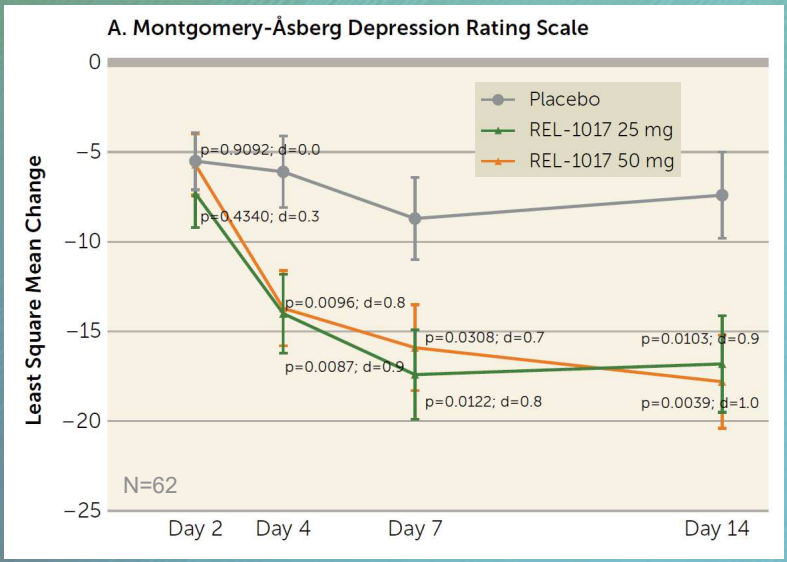



- esmethadone (REL-1017) is the (S)-enantiomer of methadone
- Also an NMDA receptor antagonist
- The (S)-enantiomer has much less potent μ-opioid agonism than racemic methadone or (R)-methadone
- In clinical development as a rapid-onset treatment for major depressive disorder (MDD)

Stahl SM. Stahl's Essential Psychopharmacology, 5th ed; 2021.

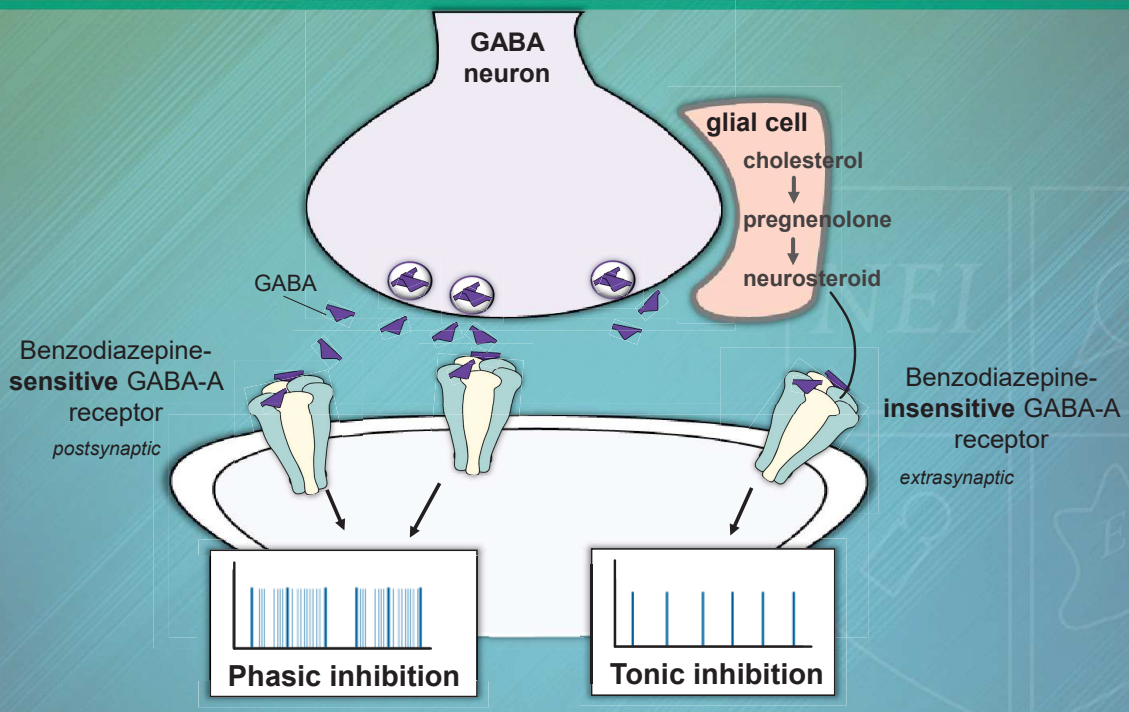
# REL-1017 (Esmethadone) as Adjunctive Treatment in MDD: A Phase 2a Randomized Double-Blind Trial




- The most common treatment-emergent adverse events that occurred in at least 5% of all patients were headache, constipation, nausea, and somnolence
- No evidence of dissociative or psychotomimetic effects, opioid effects, or withdrawal signs and symptoms

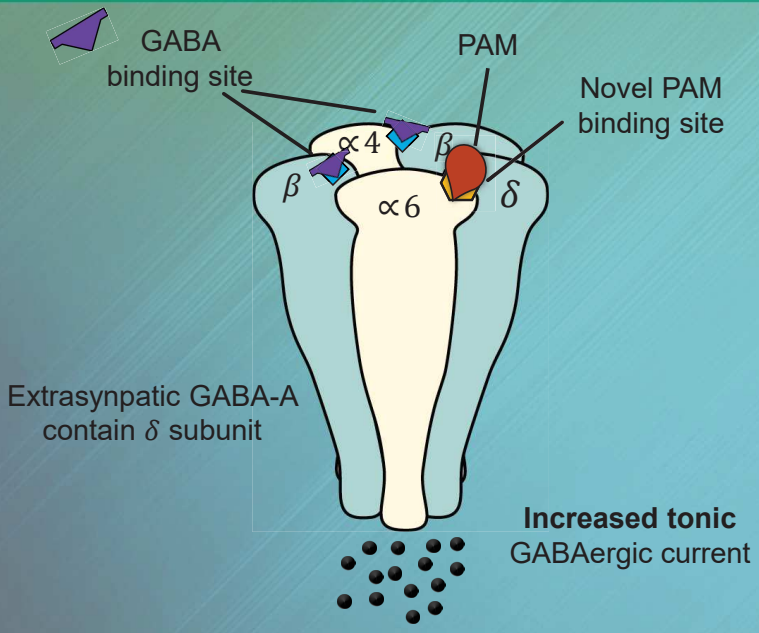
Fava M et al. Am J Psychiatry 2022;179(2):122-31.

# Two Types of GABA-A Mediated Inhibition




Stahl SM. Stahl's Essential Psychopharmacology. 4th ed. 2013.

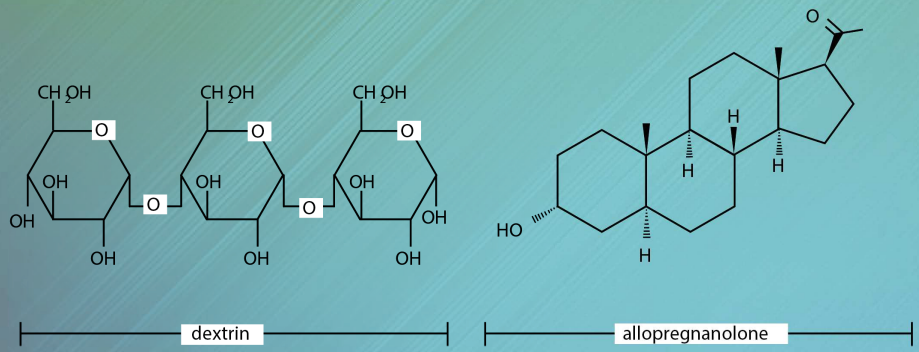
# Allosteric Modulation of Extrasynaptic GABA-A Receptors




Positive Allosteric Modulation (PAM) can increase receptor efficiency and/or potency

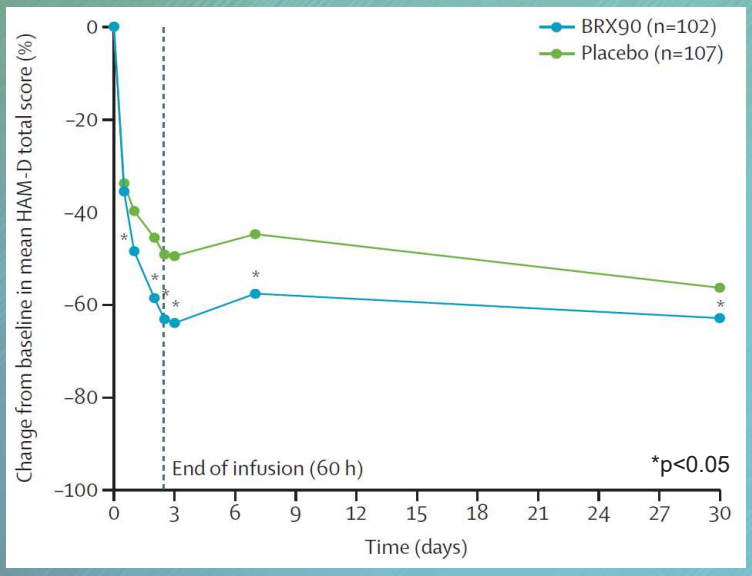
Stahl SM. Stahl's Essential Psychopharmacology. 4th ed. 2013;
Tuem KB, Atey TM. Front Neurol. 2017;8:442.

# Brexanolone and Zuranolone




Stahl SM. Stahl's Essential Psychopharmacology, 5th ed; 2021.

# Single Brexanolone (90 µg/kg per hour) Intravenous Injection Improves Post-Partum Depression




HAM-D: Hamilton Rating Scale for Depression (17-item)

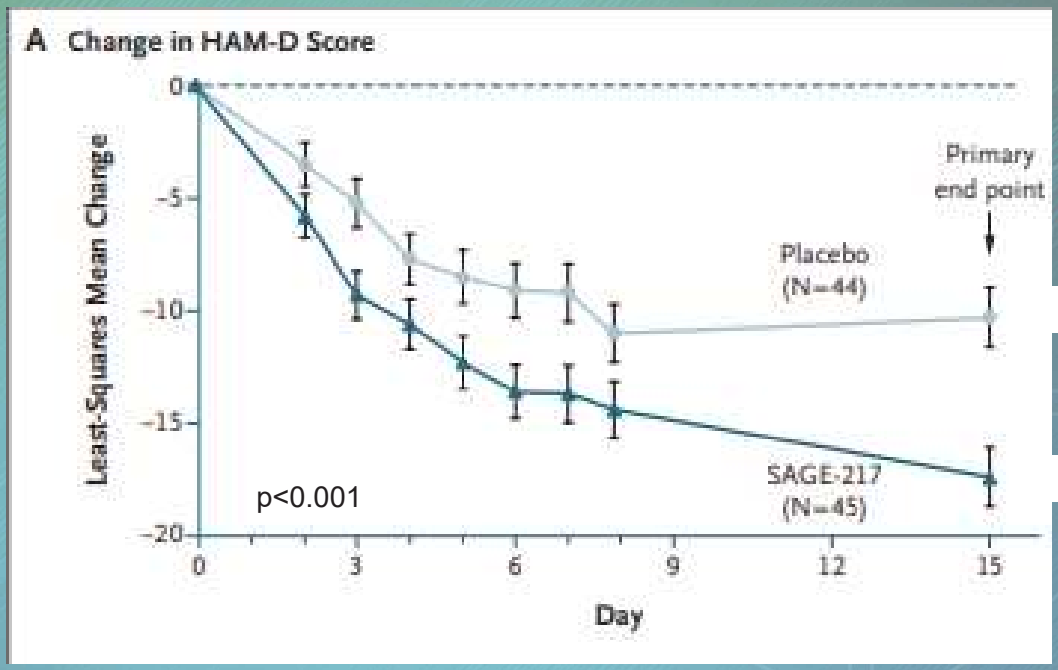
The most common treatment-emergent adverse events were headache, dizziness, and somnolence

Meltzer-Brody S et al. Lancet 2018;392(10152):1058-70.

# Zuranolone (SAGE-217)

28-day response:
Zuranolone: 62%
Placebo: 46%

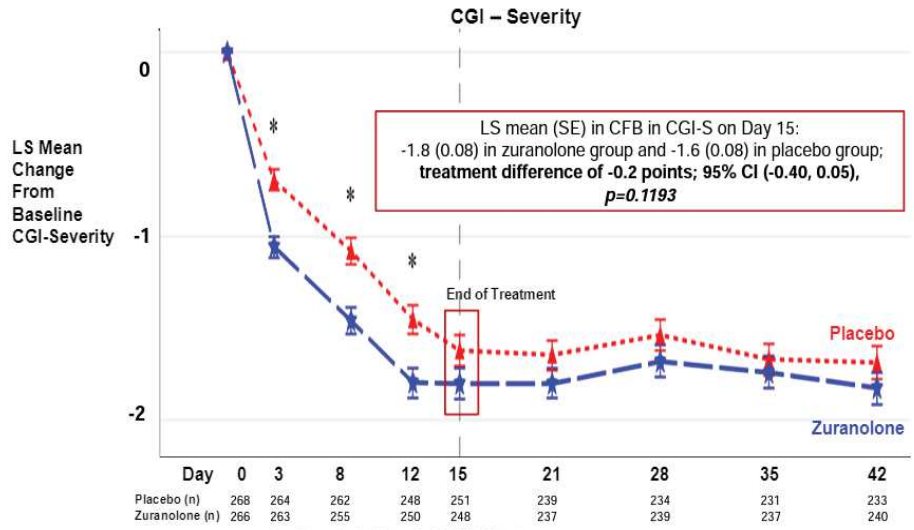
29-day remission:
Zuranolone: 52%
Placebo: 28%




Gunduz-Bruce H et al. N Engl J Med 2019;381(10):903-11.

# Zuranolone: WATERFALL Study

*Clinical Global Impression-Severity of Illness (CGI-S) - First Key Secondary endpoint*



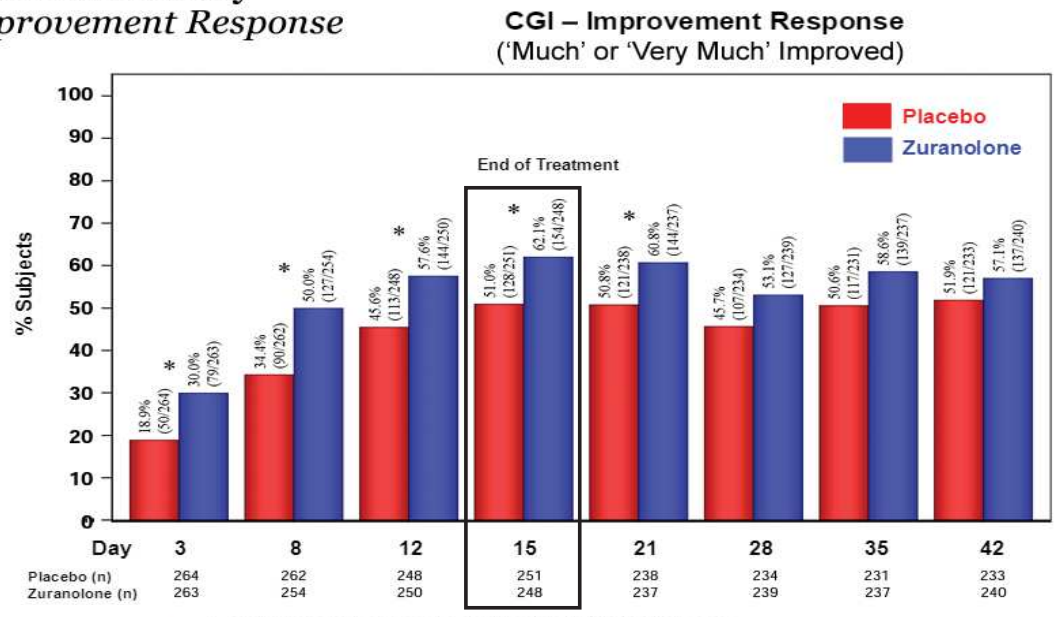

| CGI-S Scale | |
|---|---|
| Normal, not at all ill | 1 |
| Borderline ill | 2 |
| Mildly ill | 3 |
| Moderately ill | 4 |
| Markedly ill | 5 |
| Severely ill | 6 |
| Among the most extremely ill | 7 |

12

Sage Therapeutics © 2021

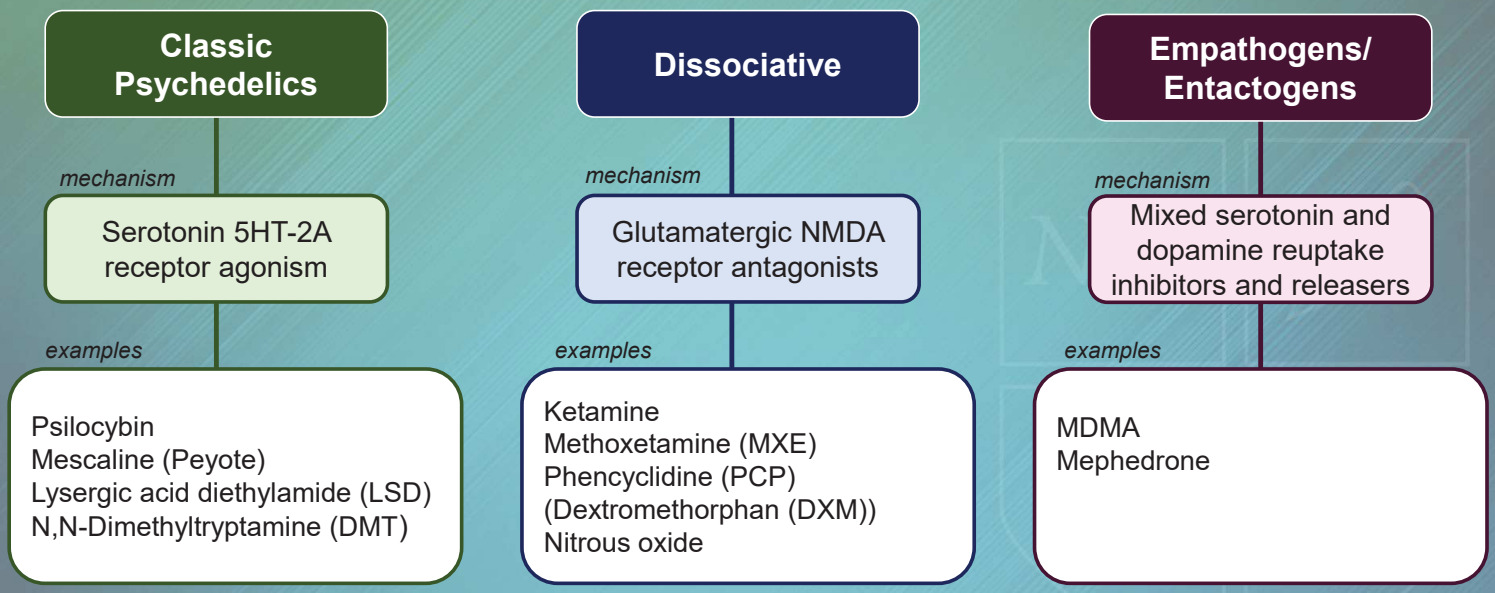
# Zuranolone: WATERFALL Study

WATERFALL Study
*CGI-Improvement Response*




* =p <0.05 for odds ratio. Sage Therapeutics, Inc. Data on file. 217-MDD-301 B topline memo.

# Antidepressant Efficacy with Mental Status Changes




Reiff CM et al. Am J Psychiatry 2020;177(5):391-410.

# Definitions

## Plastogens

- **agents that induce neuronal plasticity**

## Psychoplastogens

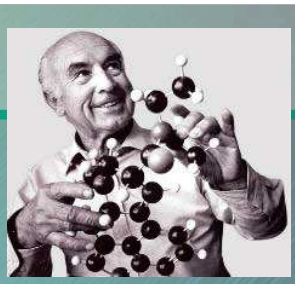
- **agents that induce neuroplasticity and subjective mental states such as dissociation or hallucinations/psychotomimetic symptoms (e.g., ketamine, psilocybin, MDMA)**

## Neuroplastogens

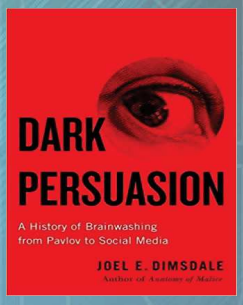
- **agents that induce neuroplasticity without inducing subjective mental states (e.g., esmethadone, dextromethorphan/bupropion, zuranolone)**

Cooper, Seigler and Stahl J Psychopharmacol, in press

# Hallucinogen History



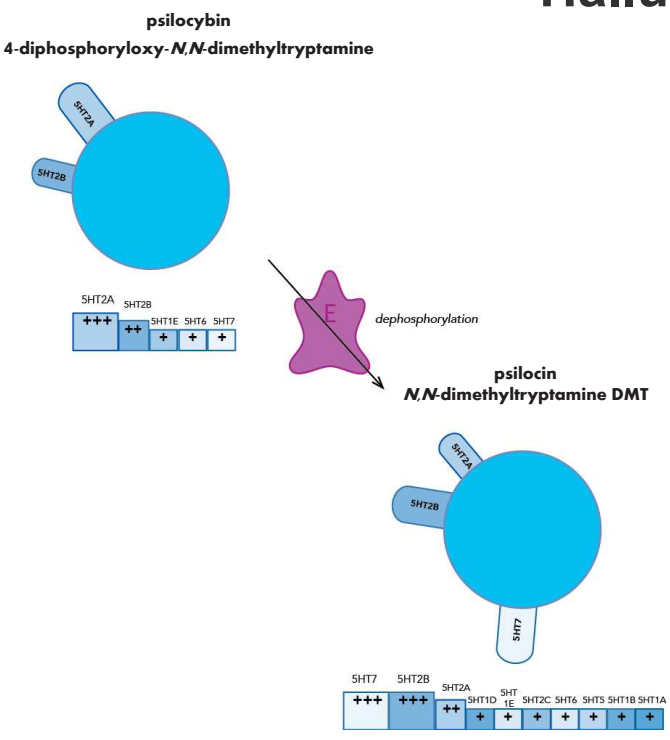
- Hallucinogens (i.e., psychedelic substances) have been used by humans for at least 5 millennia
- 1943: Albert Hofmann discovers LSD by accident
- 1957: Albert Hofmann isolates psilocybin from hallucinogenic mushrooms
- 1950s–1970: Over 1000 studies published looking at classic hallucinogens as models of psychosis and as therapeutics for a variety of psychiatric disorders
  - Results indicated potential therapeutic value however…
  - Most were small studies with no control conditions
  - Also used by the CIA to attempt to coerce confessions/truth serum
  - and also to "brainwash" and change ideology from communism to capitalism

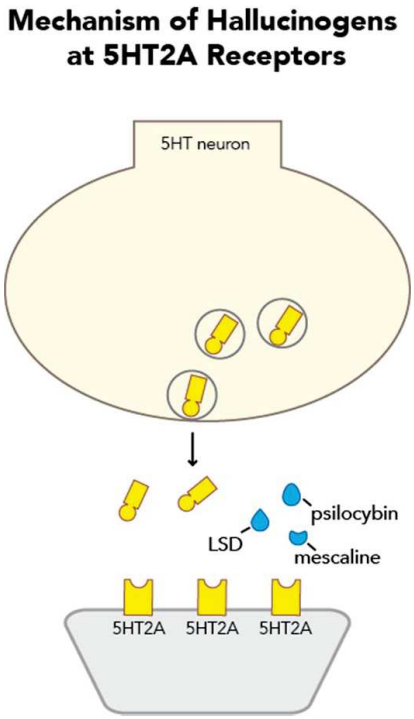



- 1970: Most hallucinogens placed into Schedule I of the 1970 Controlled Substances Act
- Today: renewed interest in the therapeutic value of hallucinogens

Johnson M et al. J Psychopharmacol 2008;22(6):603-20;
Bogenschutz MP, Ross S. Curr Top Behav Neurosci 2018;36:361-91.

# Hallucinogen




5HT, 5-hydroxytryptamine (serotonin); DMT, dimethyltryptamine; LSD, lysergic acid diethylamide

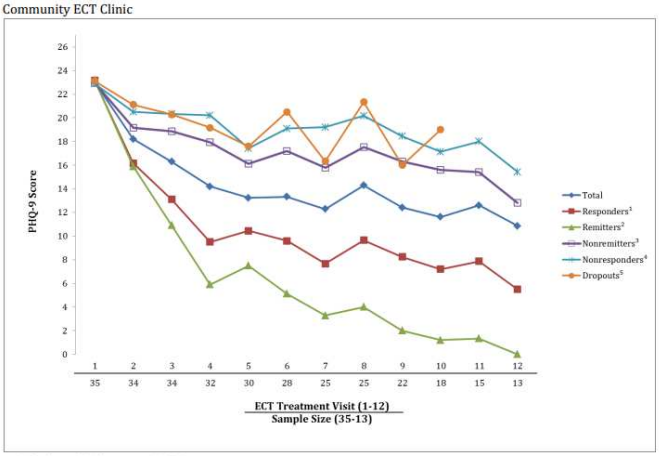
Stahl's Essential Psychopharmacology, 5th edition, 2021, copyright NEI. All rights reserved.

# TMS

- TMS can be considered, especially early in the treatment failure algorithm
- May be especially useful in those who cannot tolerate medication side effects
- New ideas include MRI guided TMS
- Also, VNS may be making a comeback
- Few studies to compare head to head with medications or with ECT

# ECT: Effects

**Figure 1.** Trajectory of Mean Patient Health Questionnaire (PHQ-9) Scores, by Outcome Group, in Community ECT Clinic




[1]Defined as ≥50% decrease in PHQ-9 score.
[2]Defined as final PHQ-9 score <5.
[3]Defined as completing 12 treatments without ≥50% decrease in PHQ-9 score.
[4]Defined as completing 12 treatments with final PHQ-9 score ≥5.
[5]Defined as completing <12 treatments without ≥50% decrease in PHQ-9 score.

- Efficacy: Meta-analysis in 2012 indicated that overall remission rate for patients given a round of ECT treatment was 51.5% for unipolar depression, and 50.9% for bipolar depression

Meta analysis in 2022 indicates that ECT may be superior to ketamine for improving depression in the acute phase

- MDD – mixed results:

50% of patients relapse after ECT treatment followed by antidepressants, and twice as many relapse if only given ECT treatment

- ECT is viewed as the gold standard for catatonia

VanBronkhorst SB et al., medRxiv 2021. Dierckx et al., PMID 2012; 14(2):146-150. Jelovac et al. Neuropsychopharmacology 2013; 38(12):2467-74. Micallef-Trigona, Depress Res Treat 2014; Rh et al., JAMA Psychiatry 10.1001/jamapsychiatry2022.3352.

# Summary

- First-line antidepressant treatment response is often insufficient
- There are multiple novel treatment options emerging, none compared to each other, so selection of a treatment requires a personalized approach giving consideration to various patient factors, including psychiatric and physical comorbidities, prior treatments, side effects and symptom profiles
- Neuroplasticity is the hypothetical final common pathway to successful antidepressant treatment, especially for the rapid acting agents
- Treatment options for second-line/third line courses of treatment include combining or switching antidepressants, augmenting with other psychotropic medications or psychotherapy, and neurostimulation
- Mechanisms of TRD treatments include

  - Monoaminergic (psychedelics and augmentation with atypical antipsychotics)
  - Glutamatergic (ketamine, esketamine, dextromethorphan/bupropion and several others in late stage development)
  - GABAergic (GABA A PAMS brexanolone/zuranolone