THERAPEUTICS AND ADJUNCTIVE THERAPEUTICS FOR MENTAL HEALTH DISORDERS

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THERAPEUTICS AND ADJUNCTIVE THERAPEUTICS FOR MENTAL HEALTH DISORDERS

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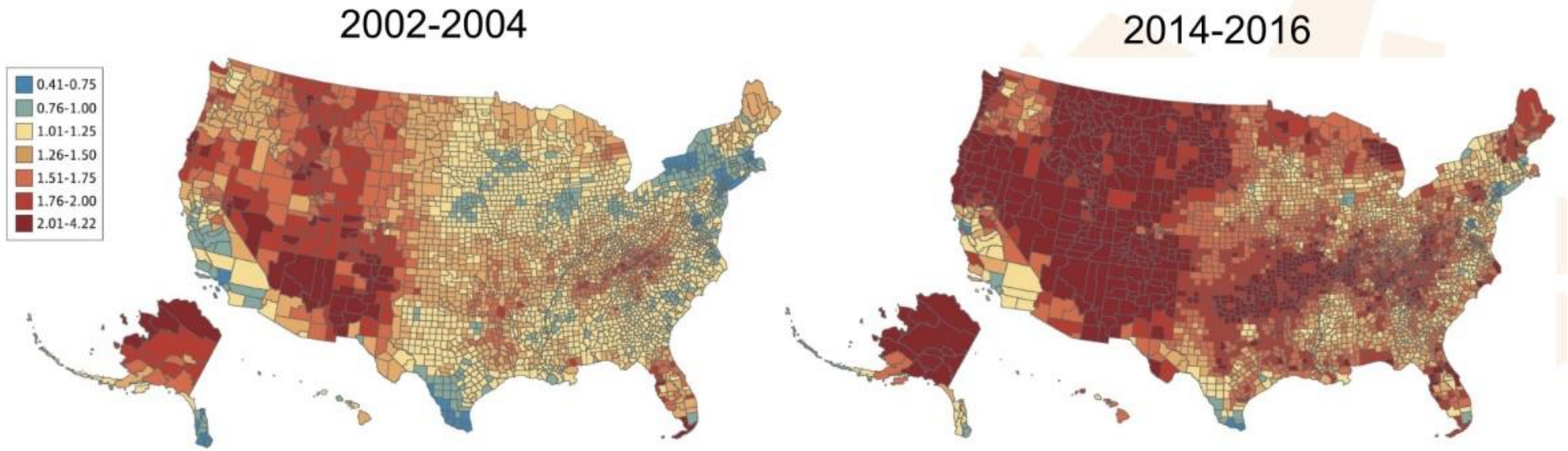
THERAPEUTICS AND ADJUNCTIVE THERAPEUTICS FOR MENTAL HEALTH DISORDERS

- DEPRESSION

HEAT MAP

A Heat Map of the United States

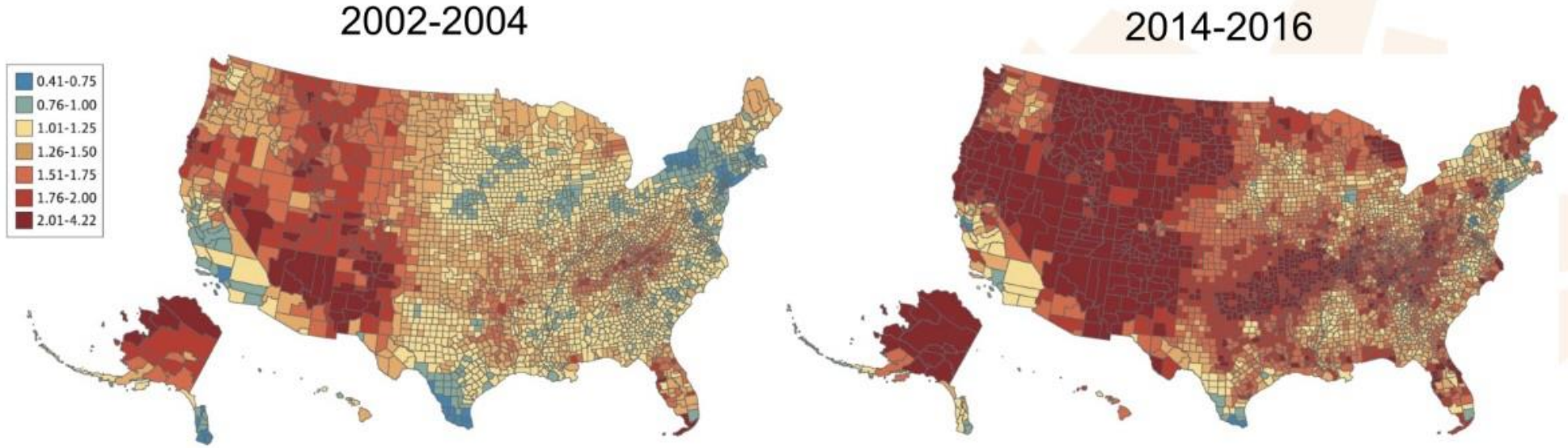


Steelesmith DL, et al. *JAMA Netw Open*. 2019;2(9):e1910936.

SUICIDE RATE BY COUNTY IN THE US

A Heat Map of the United States

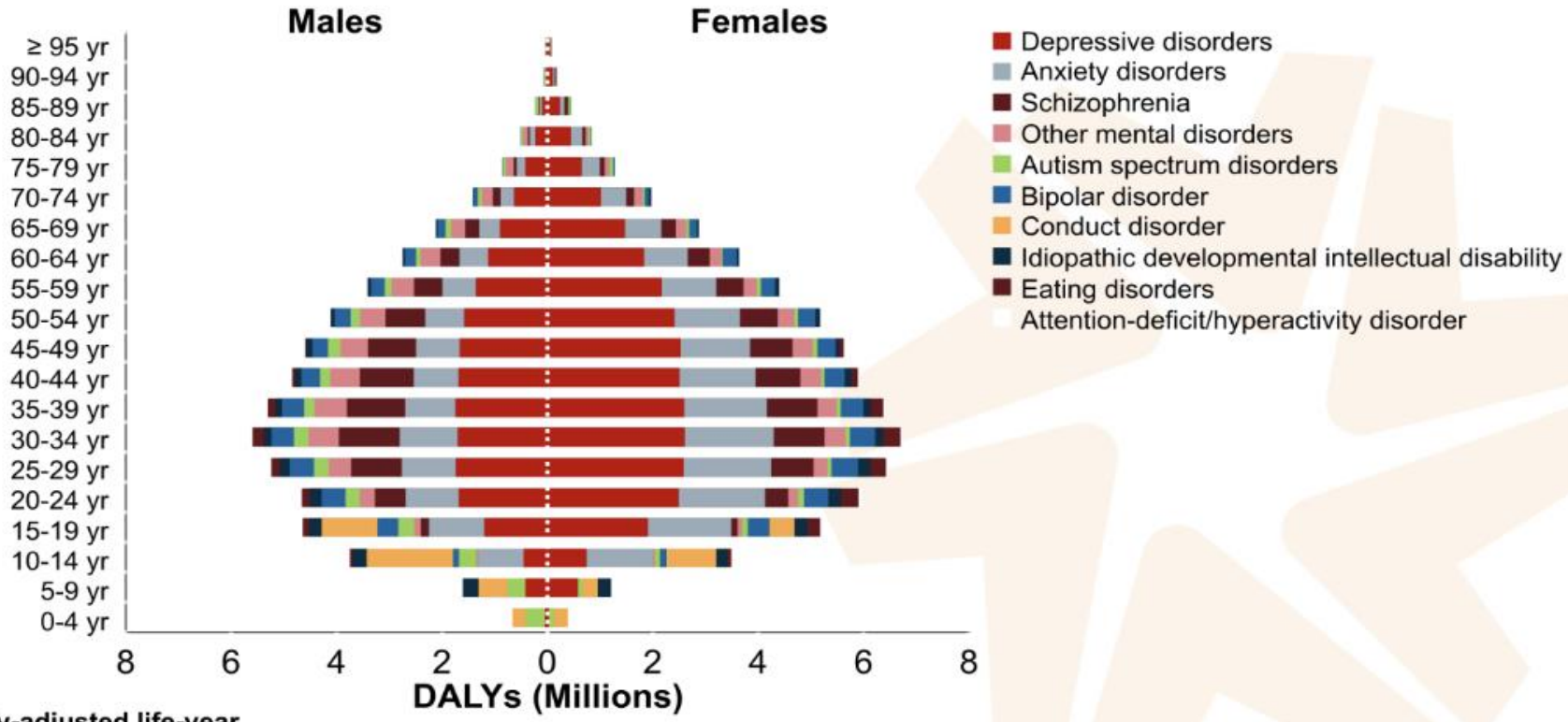
Suicide rate by county in the US



Steelesmith DL, et al. *JAMA Netw Open*. 2019;2(9):e1910936.

MENTAL ILLNESS EPIDEMIOLOGY

Global Causes of Mental Health Disability
Mood Disorders Still Lead the Way!



DALY = disability-adjusted life-year.

GBD 2019 Mental Disorders Collaborators. *Lancet Psychiatry*. 2022;9(2):137-150.

MENTAL ILLNESS EPIDEMIOLOGY

Major Depression on A Steady Rise

MDD Prevalence

Global

- 280 million people in the world have depression
- 3.8% of the population
- 50% more common in women than men

United States

- Highest among ages 18-25 (17.0%)
- Higher among adolescent females (25.2%) compared to males (9.2%)
- Highest among those who report having 2 or more races (15.9%)

MDD = major depressive disorder.

Institute of Health Metrics and Evaluation (IHME) [www.healthdata.org]. Last updated 2023. Accessed May 18, 2023. https://vizhub.healthdata.org/gbd-results. Woody CA, et al. *J Affect Disord*. 2017;219:86-92. National Institute of Mental Health (NIMH) [www.nimh.nih.gov]. Last updated July 2023. Accessed May 18, 2023. https://www.nimh.nih.gov/health/statistics/major-depression.

DEPRESSION EPIDEMIOLOGY

- Lifetime prevalence: 12% worldwide.
- Onset at any age, but the age of onset peaks in the 20's
- 1.5-2 times as prevalent in women than men during reproductive years.
- No ethnic or socioeconomic differences.
- Lifetime prevalence in the elderly: <10%
- Depression can increase mortality for patients with other comorbidities such as diabetes, stroke, and cardiovascular disease.

DEPRESSION EPIDEMIOLOGY

Depression by the Numbers

- **~21 million** US adults in the US had at least 1 major depressive episode making up 8.3% of U.S Adults in 2021.

- 14.5 million adults had at least 1 major depressive episode with **severe impairment** in the past year as of 2021.
  - MDD has severe impact on daily functioning and quality of life
  - Economic burden of adults with MDD in the US is $326 billion

National Institute of Mental Health (NIMH). *Major Depression*. (n.d.). Accessed August 23, 2023. https://www.nimh.nih.gov/health/statistics/major-depression. Greenberg PE, et al. *Pharmacoeconomics*. 2021;39(6):653–665.

DEPRESSION GENETICS

- 1st degree relatives are 2-4 times more likely to have MDD.
- Concordance rate for monozygotic twins in <40% and dizygotic twins is 10-20%

COURSE AND PROGNOSIS

- If left untreated, usually self-limiting but can last from 6-12 months
- Increased frequency as the djisorder progresses.
- Subsequent Major Depressive Episode in 50-60% within the first 2 years after the 1st episode
- 15% of patients with MDD eventually commit suicide
- 60-70% of patients improve with antidepressants and psychotherapy TOGETHER

HISTORY OF ANTIDEPRESSANTS

- A search for a Tuberculosis CURE
- IPRONIAZID AND ISONIAZID

HISTORY OF ANTIDEPRESSANTS

- Treatment ultimately failed to cure patients of TB
- Researchers noticed the beneficial effects the drugs had on Mental States
- Tricyclic's and Monoamine Oxidase inhibitors (MAOI) emerged
- First tested on people with Schizophrenia BUT showed better results with Depression
- Imipramine was 1st therapeutic approved as an antidepression drug in 1959

HISTORY OF ANTIDEPRESSANTS

- SIDE EFFECTS

TRICYCLIC ANTIDEPRESSANTS AND THE NEUROTRANSMITTERS

- Serotonin, Norepinephrine, Dopamine, antihistaminic, anticholenergic

HISTORY OF ANTIDEPRESSANTS

- The prevailing theory of Antidepressants was born!
- Most Psychiatrists are taught and/or teach this theory
- Depression is due to a decrease of Serotonin, Norepinephrine, and/or Dopamine in the brain

HISTORY OF ANTIDEPRESSANTS

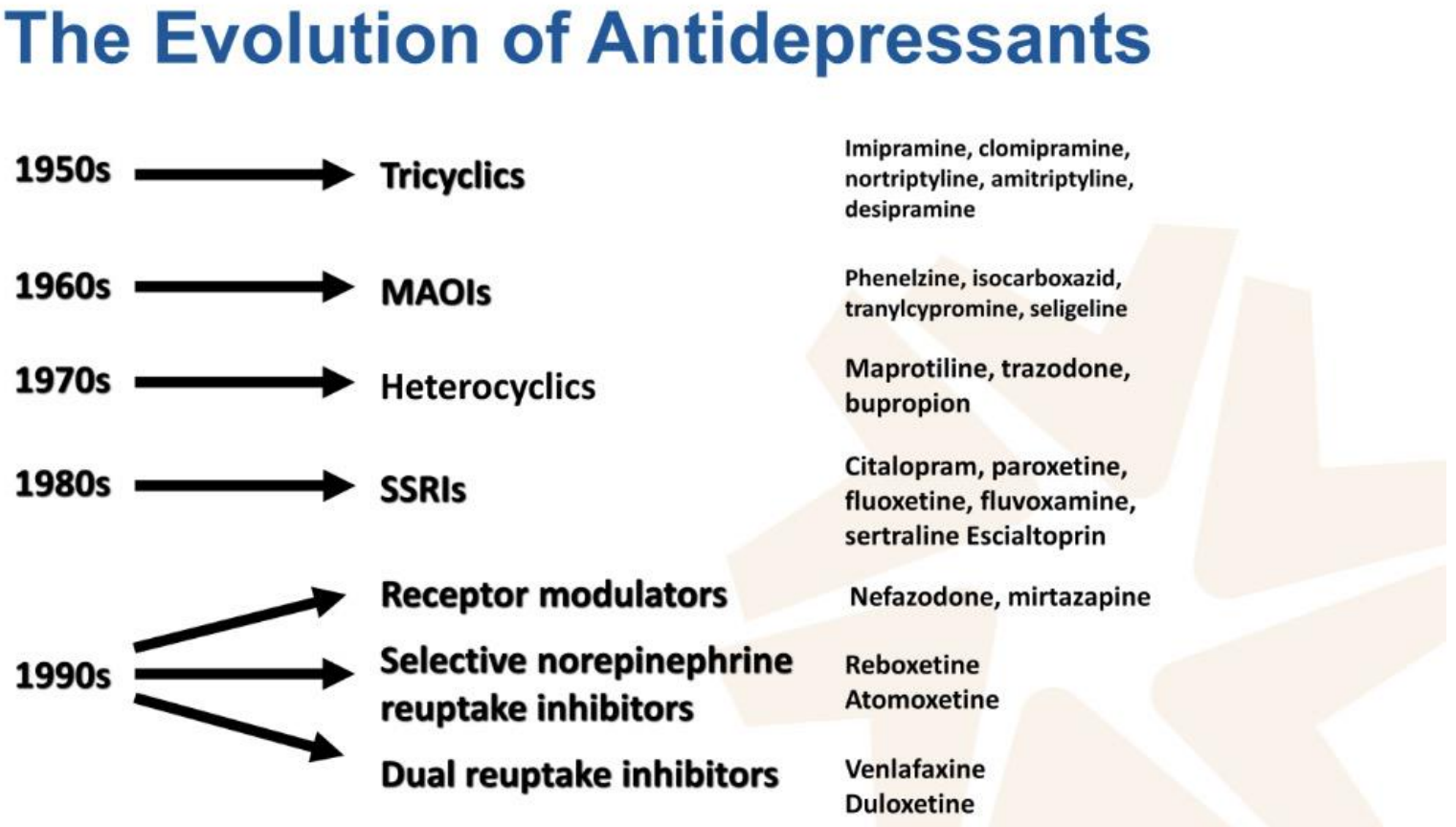
- Tryptophan → Serotonin
- Tyrosine → Norepinephrine and Dopamine
- Experiment done on normal subjects restricting Tryptophan or Tyrosine
  - The Tryptophan group got Depressed especially in vulnerable individuals

Fernstrom JD, Wurtman RJ, Hammarstrom-Wiklund B, et al, Diurnalvariations in plasma concentrations of tryptophan, tyrosine, and other neutral amino acids: effect of dietary protein intake. Am J Clin Nutr, 1979;32:1912-22

HISTORY OF ANTIDEPRESSANTS

- Second Generation Antidepressants
- Selective Serotonin Reuptake Inhibitors (SSRI's)
- 1st SSRI PROZAC, Late 1987's, Perceived to not be as effective for severe depression as the 1st generation
- Wellbutrin approved 1989
- Developed Serotonin Norepinephrine Reuptake inhibitors (SNRI's)
  - Venlafaxine 1993

HISTORY OF ANTIDEPRESSANTS



STAR D TRIAL

- Sequenced Treatment Alternatives to Relieve Depression (STAR D)
  - Collaborative study on the treatment of depression, Funded by the National Institute of Mental Health
  - Focused on treatment of depression where the first prescribed antidepressant proved inadequate

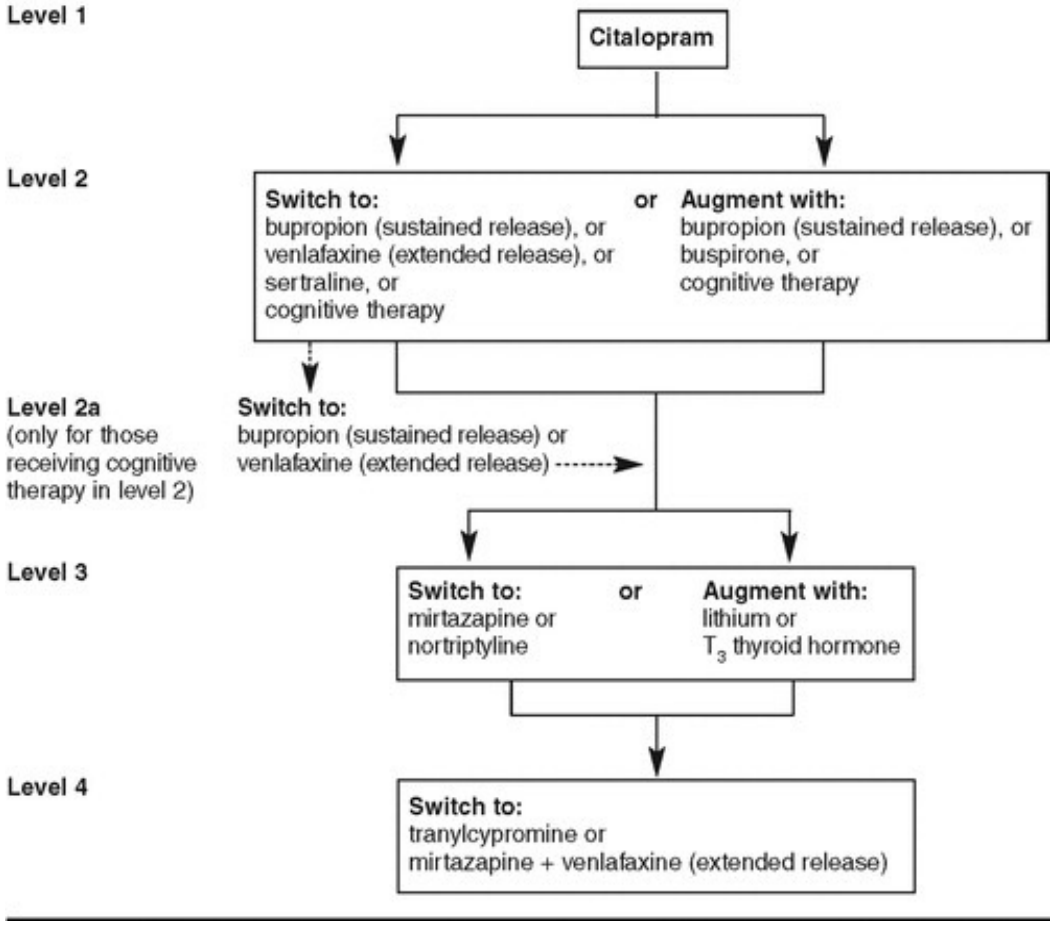
STAR D TRIAL

- Enrolled 4,041 outpatients with nonpsychotic depression at 23 psychiatric and 18 primary care sites
- Completed in 2006

STAR D TRIAL

Figure 1

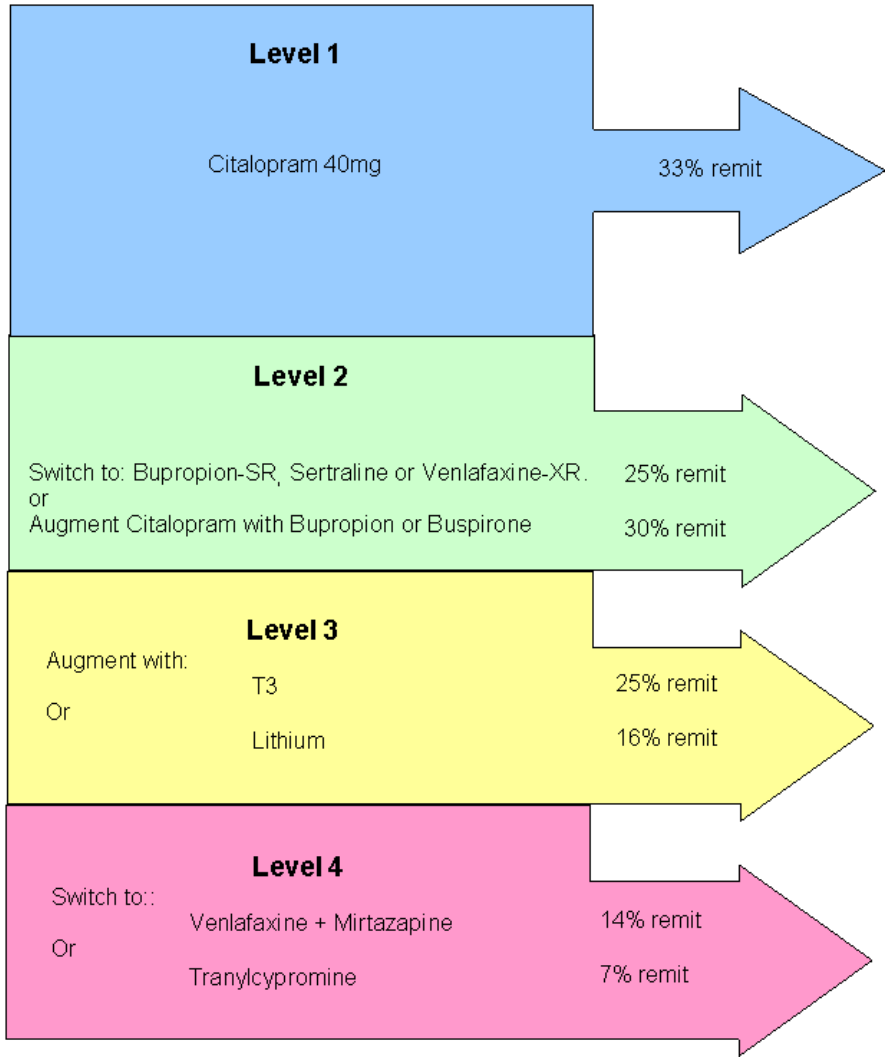
STAR*D treatment levels



STAR D TRIAL

- After receiving citalopram (level 1), participants without sufficient symptomatic benefit are eligible for randomization to level 2 treatments, which entail four switch options (sertraline, bupropion, venlafaxine, cognitive therapy) and three citalopram augment options (bupropion, buspirone, cognitive therapy).
- Those who receive cognitive therapy (switch or augment options) at level 2 without sufficient improvement are eligible for randomization to one of two level 2A switch options (venlafaxine or bupropion).
- Level 2 and 2A participants are eligible for random assignment to two switch options (mirtazapine or nortriptyline) and to two augment options (lithium or thyroid hormone) added to the primary antidepressant (citalopram, bupropion, sertraline, or venlafaxine) (level 3).
- Those without sufficient improvement at level 3 are eligible for level 4 random assignment to one of two switch options (tranylcypromine or the combination of mirtazapine and venlafaxine). The primary outcome is the clinician-rated, 17-item Hamilton Rating Scale for Depression, administered at entry and exit from each treatment level through telephone interviews by assessors masked to treatment assignments.
- Secondary outcomes include self-reported depressive symptoms, physical and mental function, side-effect burden, client satisfaction, and health care utilization and cost. Participants with an adequate symptomatic response may enter the 12-month naturalistic follow-up phase with brief monthly and more complete quarterly assessments.

STAR D TRIAL

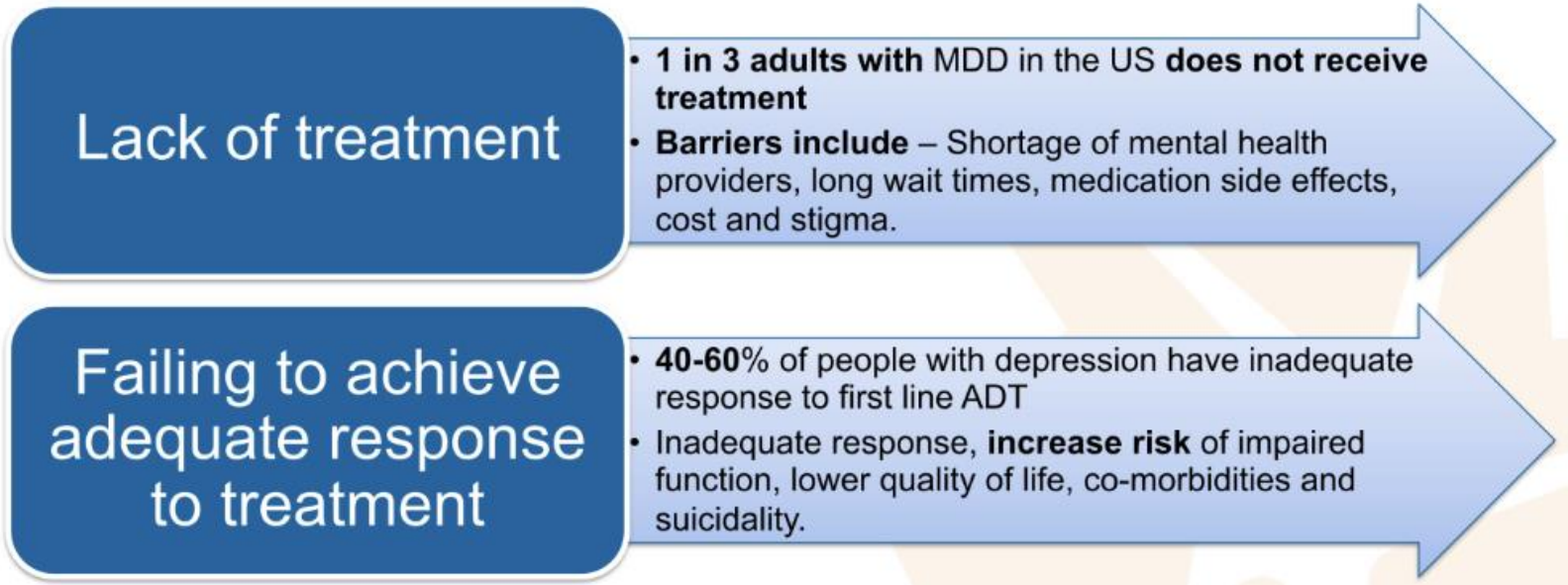

Level 1
Citalopram 40mg
33% remit
Level 2
Switch to: Bupropion-SR, Sertraline or Venlafaxine-XR.
or
Augment Citalopram with Bupropion or Buspirone
25% remit
30% remit
Level 3
Augment with:
T3
Lithium
25% remit
16% remit
Or
Level 4
Switch to::
Venlafaxine + Mirtazapine
Tranylcypromine
14% remit
7% remit
Or

STAR D TRIAL

- In conclusion, about 50 percent of participants in the STAR*D study became symptom-free after two treatment levels. Over the course of all four treatment levels, almost 70 percent of those who did not withdraw from the study became symptom-free.

BARRIERS TO TREATMENT

Unmet Needs in MDD Treatment

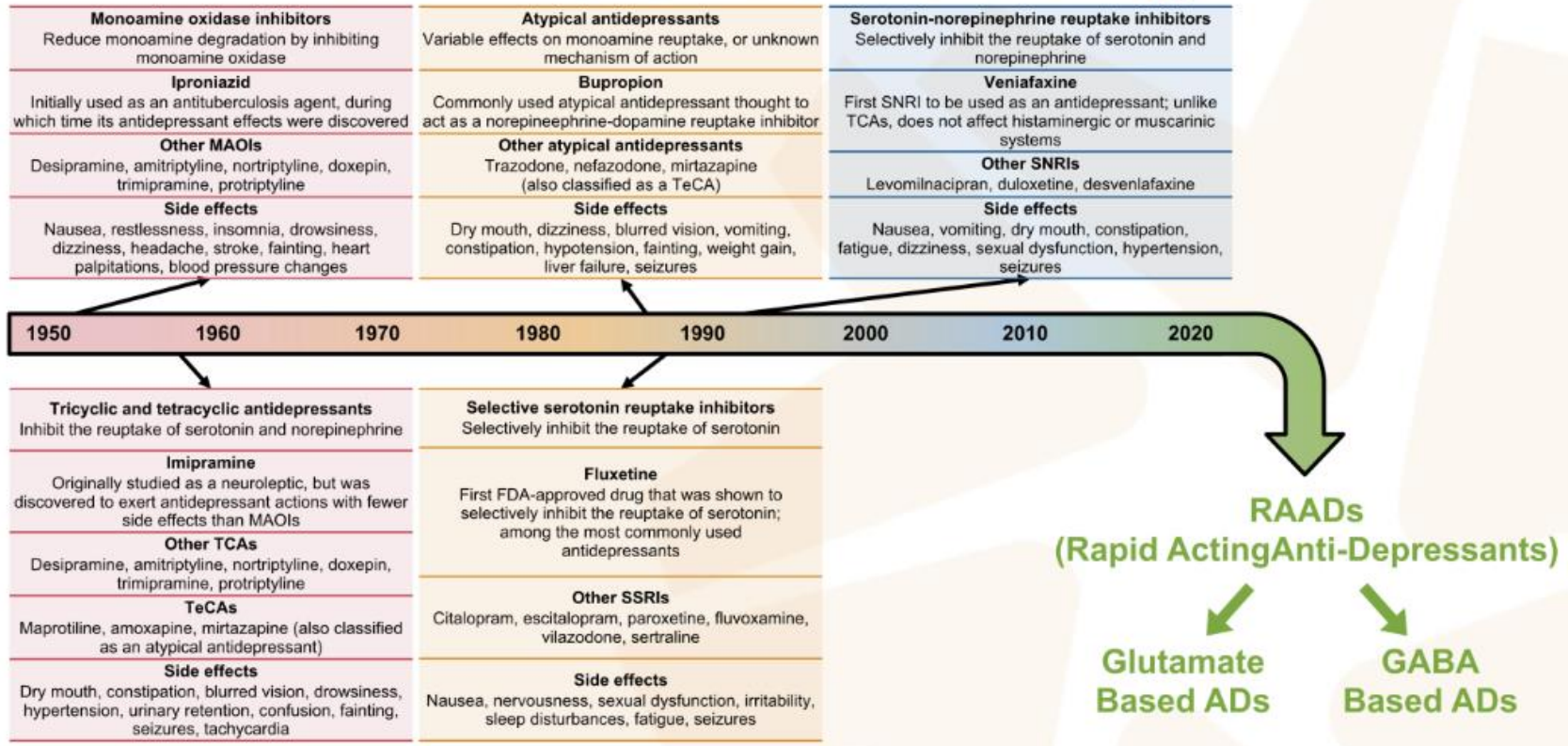


MDD=major depressive disorder; ADT=antidepressant treatment.

HasinDS, et al. *JAMA Psychiatry*. 2018 Apr 1;75(4):336–346. Mongelli F, et al. *Focus (Am PsychiatrPubl)*. 2020;18(1):16–24. Ofonedu ME, et al. *J Child Fam Stud*. 2017;26(3):863–876. Marasine NR, et al. *Turk J Pharm Sci*. 2021;18(2):242–249. MacQueen G, et al. *Can J Psychiatry*. 2017;62(1):11–23. Rush AJ, et al. *Am J Psychiatry*. 2006;163(11):1905–1917. Lye MS, et al. *PLoS One*. 2020;15(3):e0230363. Mauskopf JA, et al. *Depress Anxiety*. 2009;26(1):83–97.

WHAT'S NEXT

Antidepressant Evolution: Where Have We Been? And Where Are We Going?



Riggs LM, Gould TD. *Annu. Rev. Clin. Psychol.* 2021.17:207–31.

SUBOPTIMAL OUTCOMES

Delays in Resolution of MDD Symptoms Can Cause Suboptimal Outcomes

- A 286-patient chart review in the Netherlands found that longer episode duration may be associated with
  - Poorer symptomatic and functioning outcomes
  - Increased co-morbidities such as anxiety disorder and suicidal behavior

- Two Canadian psychiatric epidemiological studies showed that the probability of recovery from an MDD episode was found to **decline with increasing episode duration.**

- Per DSM-V, increased depressive duration has been associated with increased risk of reoccurrence

MDD=Major Depressive Disorder.

Ten Have M, et al. Duration of major and minor depressive episodes and associated risk indicators in a psychiatric epidemiological cohort study of the general population. *Acta Psychiatr Scand.* 2017;136(3):300-312. Patten SB. A major depression prognosis calculator based on episode duration. *Clin Pract Epidemiol Ment Health.* 2006;2:13. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. American Psychiatric Association Publishing; 2013.

THEORETICAL MODELS FOR DEPRESSION

- Monoamine Hypothesis
- Inflammatory Hypothesis
- Opioid System Hypothesis
- Glutamate Hypothesis
- Gaba Hypothesis
- Acetylcholine Hypothesis

MONOAMINE DEFICIENCY THEORY

Monoamine Deficiency Theory

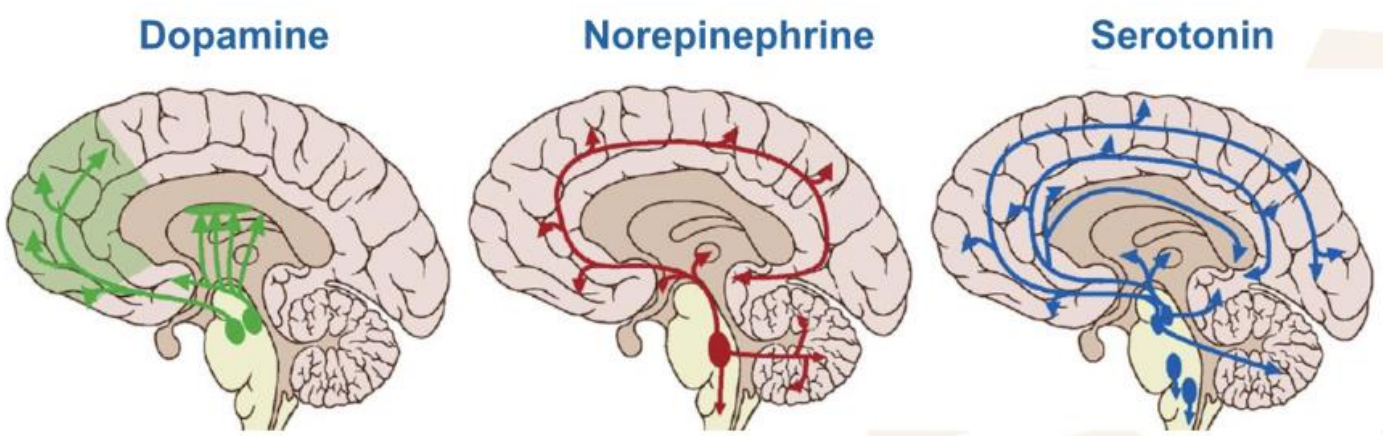
- Current, 'standard of care' ADT's are largely based on monoamine deficiency hypothesis
- Monoamine hypothesis theorizes that depression is cause by depletion of serotonin, norepinephrine and dopamine.

- The serotonin, dopamine and norepinephrine pathways project throughout the cerebral cortex and overlap in many regions involved in regulation of depressive symptoms
  - Serotonin – may present with "anxious depression"
  - Dopamine- may present with altered reward, motivation and arousal
  - Norepinephrine – may present with low energy

Reimolod M, et al. *Mol Psychiatry*. 2008 Jun;13(6):606-13, 557.doi: 10.1038/sj.mp.4002149.Epub 2008 Feb 12.
Moret C, et al. *Neuropsychiatr Dis Treat*. 2011; 7(Suppl 1): 9–13. Belujon P, et al. *Int J Neuropsychopharmacol*. 2017 Dec;20(12):1036–1046.
Mulinari S. Monoamine theories of depression: historical impact on biomedical research. *J Hist Neurosci*. 2012;21(4):366-92.
doi:10.1080/0964704X.2011.623917. PMID: 22947380.

MONOAMINE DEFICIENCY THEORY

Monoamines Have Been the "Law of The Land" for 50+ Years



- Monoamine neurotransmitters are involved in the regulation of movement, basal muscle tone, activity levels, mood, attention, sleep, vascular tone, circulation, thermoregulation, and pain modulation
- Monoamines are synthesized in pre-synaptic neurons and packaged into vesicles by a vesicular monoamine transporter 2 (VMAT2) for subsequent release into the synaptic cleft, where they bind to post-synaptic receptors

Froböse MI, et al. Curr Opin Behav Sci. 2018;22:121-127. Ng J, et al. *Nat Rev Neurol.* 2015;11(10):567-584.

A STRESSED BRAIN

The Good and the Bad: The Brain as a Dynamic Organ

- Neuroplasticity is the ability of the nervous system to reorganize its structure, functions, and connections in response to internal or external stimuli.
- Changes can be on
  - Structural level – eg, density of dendric spines
  - Functional level – eg, firing rate, how firing is occurring (synchronous vs. asynchronous).

Neuroplasticity changes can be **adaptive** or **maladaptive**.

Mateos-Aparicio P, et al. *Front Cell Neurosci.* 2019;13:66. Dean J, et al. *Asian J Psychiatr.* 2017;27:101–111. Tartt AN, et al. *Mol Psychiatry.* 2022;27(6):2689–2699. Bennett SH, et al. *Neurosci Biobehav Rev.* 2018;88:51–62.

A STRESSED BRAIN

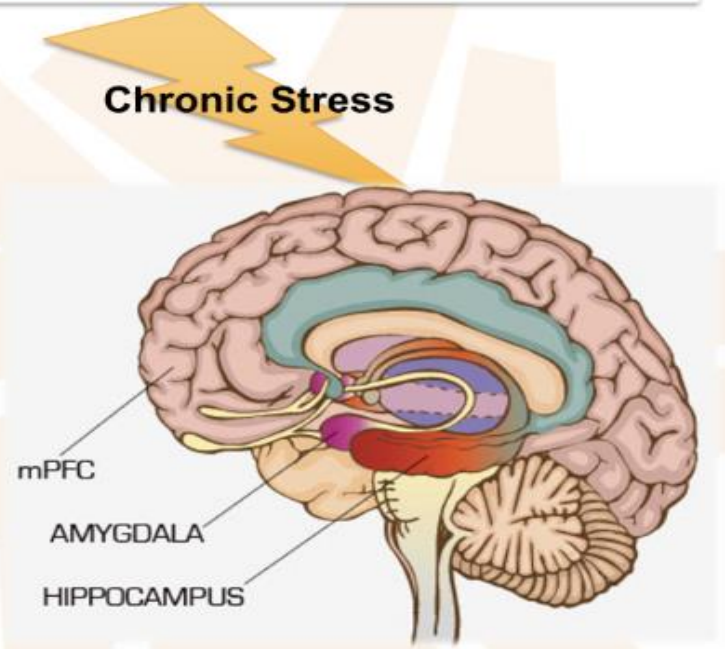
A Stressed Brain: Neuroplasticity Hypothesis of Depression

Maladaptive neuroplasticity may occur in patients with depression

Increase microglia activation → increase in neuronal atrophy

Decrease in mTORC1 signaling → decrease synapse formation in PFC
(has been show to induced depressive like behaviors in rodent models)

In the mPFC and hippocampus:
Decrease in BDNF
Increase in ProBDNF
Decrease in synaptic number and function
Increase in neuronal atrophy
Increase activity in amygdala



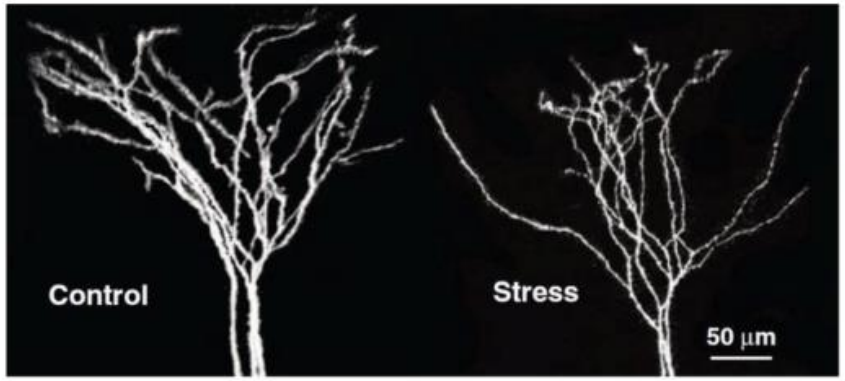
BDNF=brain-derived neurotrophic factor; mPFC=medial prefrontal cortex; mTORC1=mammalian target of rapamycin complex 1; PFC=prefrontal cortex.

Price RB, et al. *Mol Psychiatry*. 2020;25(3):530–543. Xue Y, et al. *Behav Brain Res*. 2021;404:113162.

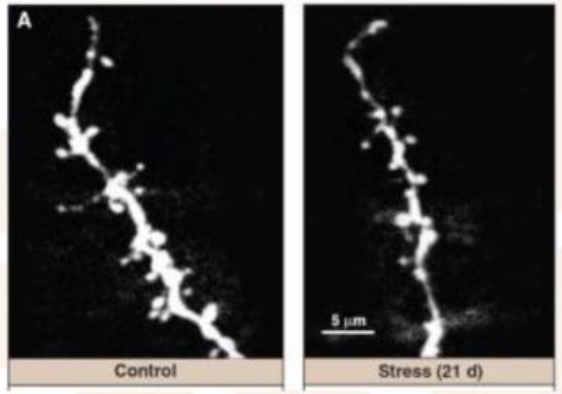
A STRESSED BRAIN

Reduced Neuroplasticity and Synaptogenesis Are Associated with Depressive States and MDD

Chronic stress, as a model for depression, reduced dendrite length and branching in the PFC of rodents1



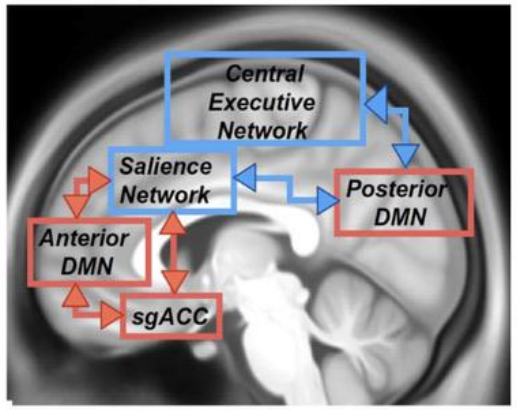
Chronic stress decreases synaptic connections and produces depressive-like behavior



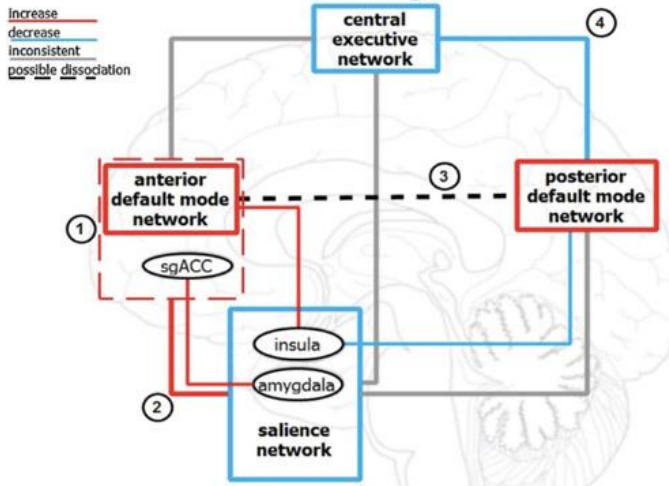
Duman RS, et al. *Science*. 2012;338(6103):68-72.

A STRESSED BRAIN

Symptoms of Depression Reflect Aberrant Functional Network Connectivity in MDD



Increased Connectivity Decreased Connectivity



MDD = major depressive disorder; DMN = default mode network; sgACC = subgenual anterior cingulate cortex.
Dunlop et al. *Curr Psychiatry Rep.* 2019;21:87. Mulders PC, et al. *Neurosci Biobehav Rev.* 2015;56:330-344.

A STRESSED BRAIN

Key Learning Points

- Monoamine hypothesis may explain only a portion of the pathophysiology of MDD
- The core pathology of the role of neuroplasticity in MDD is best described as maladaptive plasticity
- Harnessing neuroplasticity with learning/positive events may provide resilience to depression, even in genetically vulnerable individuals

A STRESSED BRAIN

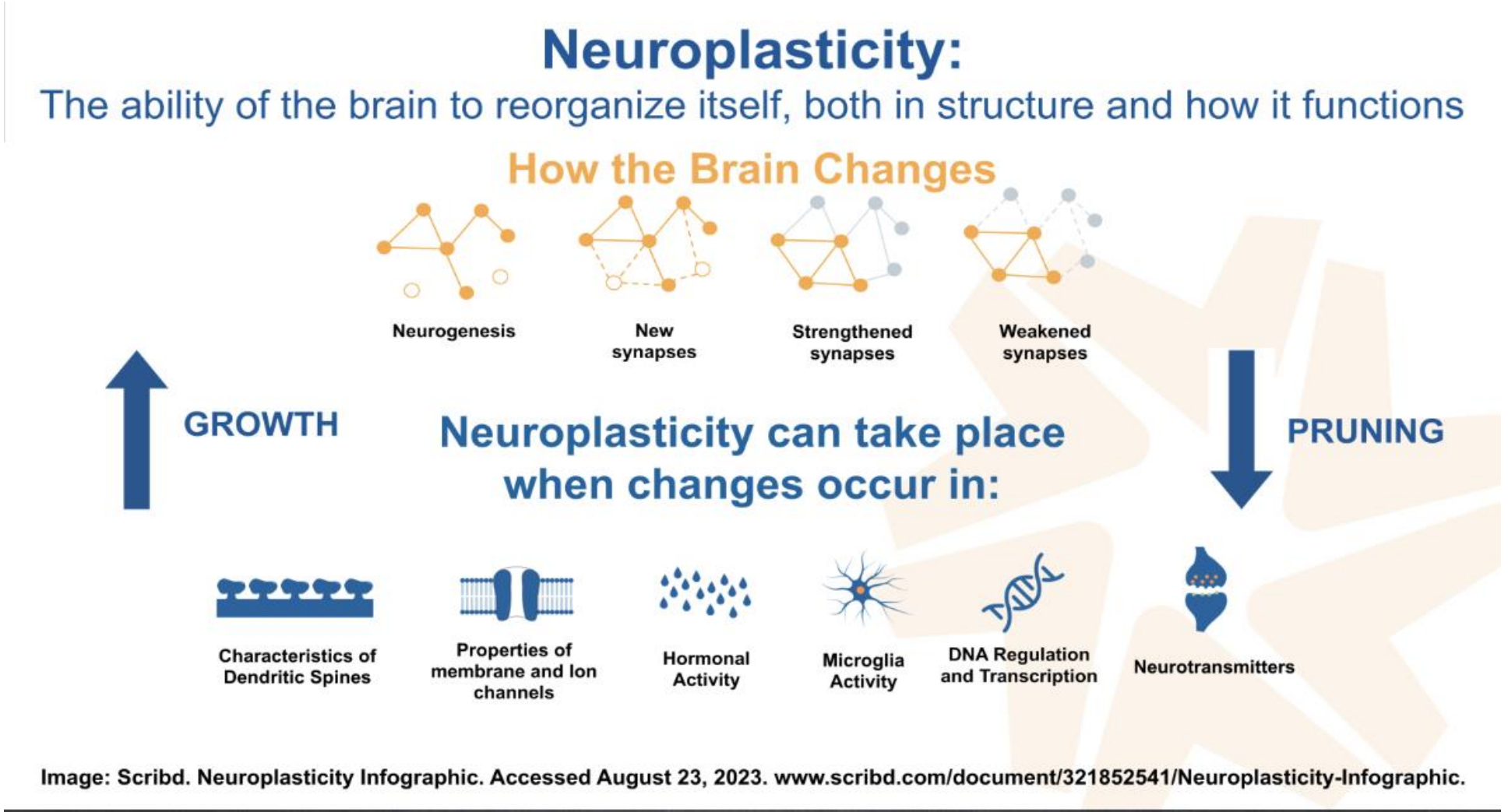
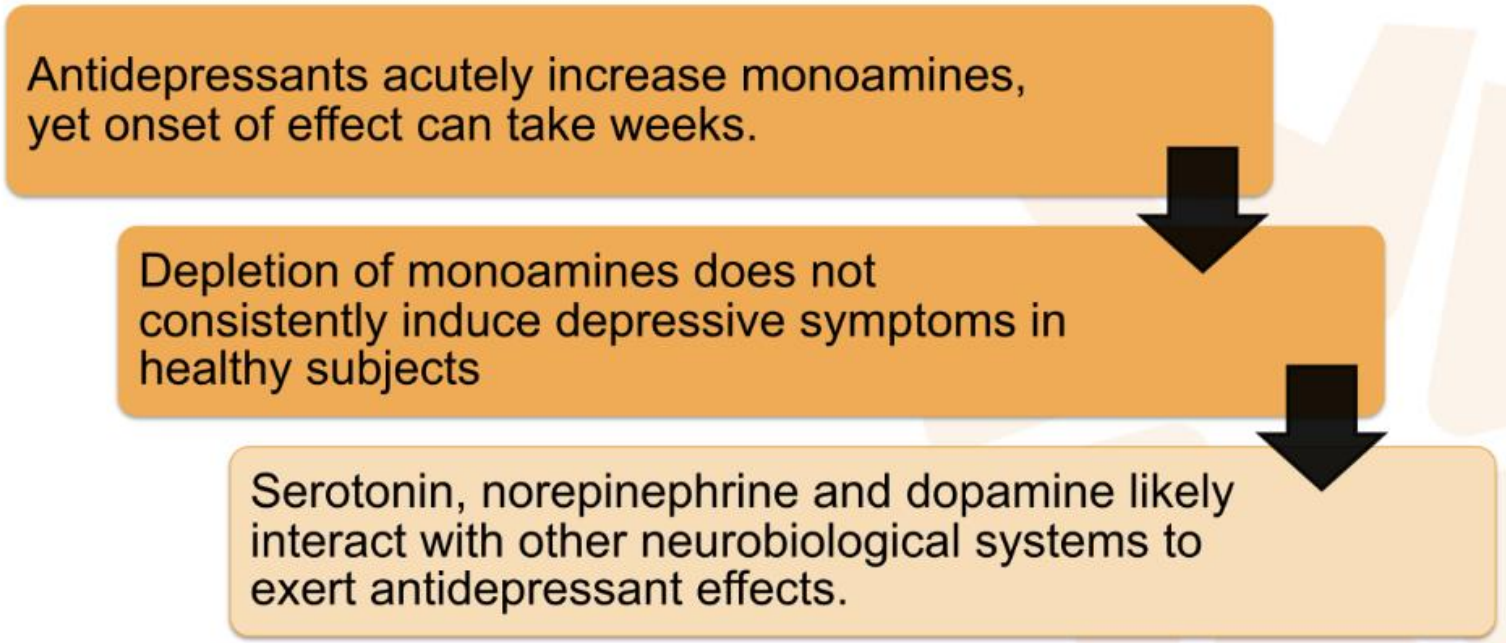


Image: Scribd. Neuroplasticity Infographic. Accessed August 23, 2023. www.scribd.com/document/321852541/Neuroplasticity-Infographic.

SHORTCOMINGS

Limitations of Monoamine Theory of Depression

Gaps in the monoamine depletion hypothesis



MDD=major depressive disorder.

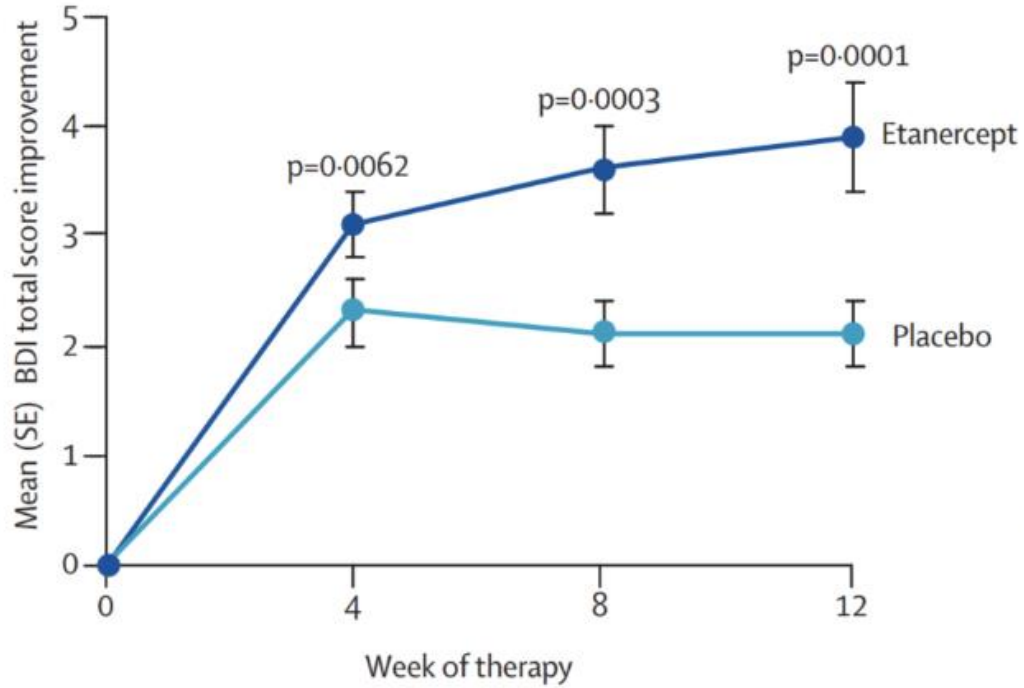
Boku S, et al. *Psychiatry Clin Neurosci.* 2018;72(1):3-12. Racagni G, et al. Dialo*gues Clin Neurosci.* 2008;10(4):385-400. Ruhé HG, et al. *Mol Psychiatry.* 2007;12(4):331-359. Heninger GR, et al. *Pharmacopsychiatry.* 1996;29(1):2-11. Pitsillou E, et al. *Mol Biol Rep.* 2020;47(1):753-770. Berman RM, et al. *Biol Psychiatry.* 2002;51(6):469-473.

HOW TO INTERPRET SCALES FOR DEPRESSION

- Montgomery-Asberg Depression Rating Scale (MADRS)
  - The MADRS scoring instructions indicate that a total score ranging from 0 to 6 indicates that the patient is in the normal range (no depression), a score ranging from 7 to 19 indicates “mild depression,” 20 to 34 indicates “moderate depression,” a score of 35 and greater indicates “severe depression,” and a total score of 60 or greater indicates “very severe depression.
- Hamilton Rating Scale for Depression
  - Scoring is based on the 17-item scale and scores of 0–7 are considered as being normal, 8–16 suggest mild depression, 17–23 moderate depression and scores over 24 are indicative of severe depression [3]; the maximum score being 52 on the 17-point scale.
- **Beck Depression Inventory (BDI)**
  - Measures of 0–9 indicates that a person is not depressed, 10–18 indicates mild-moderate depression, 19–29 indicates moderate-severe depression and 30–63 indicates severe depression.

INFLAMMATION THEORY

If Inflammation Causes Depression, Blocking Inflammation Should Treat Depression

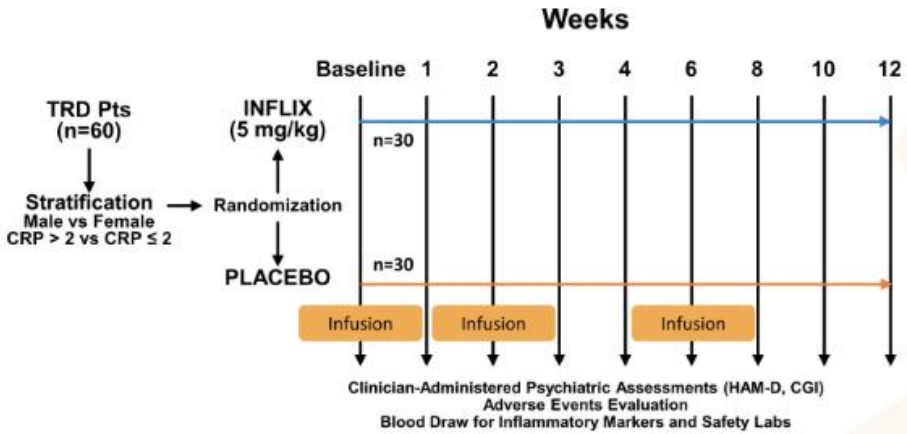


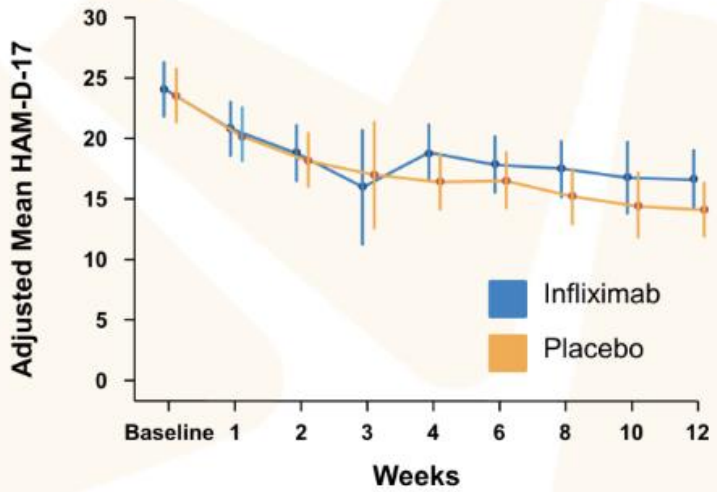
618 patients with moderate to severe psoriasis received double-blind treatment with placebo or 50 mg twice-weekly etanercept. Greater proportions of patients receiving etanercept had at least a 50% improvement in Ham-D or BDI at week 12 compared with placebo. Improvements in symptoms of depression were less correlated than fatigue with objective measures of skin clearance or joint pain.

Tyring S et al. *Lancet.* 2006 Jan 7;367(9504):29-35.

INFLAMMATION THEORY

A Specific, Powerful Anti-Inflammatory Agent Should Produce an Antidepressant Effect…





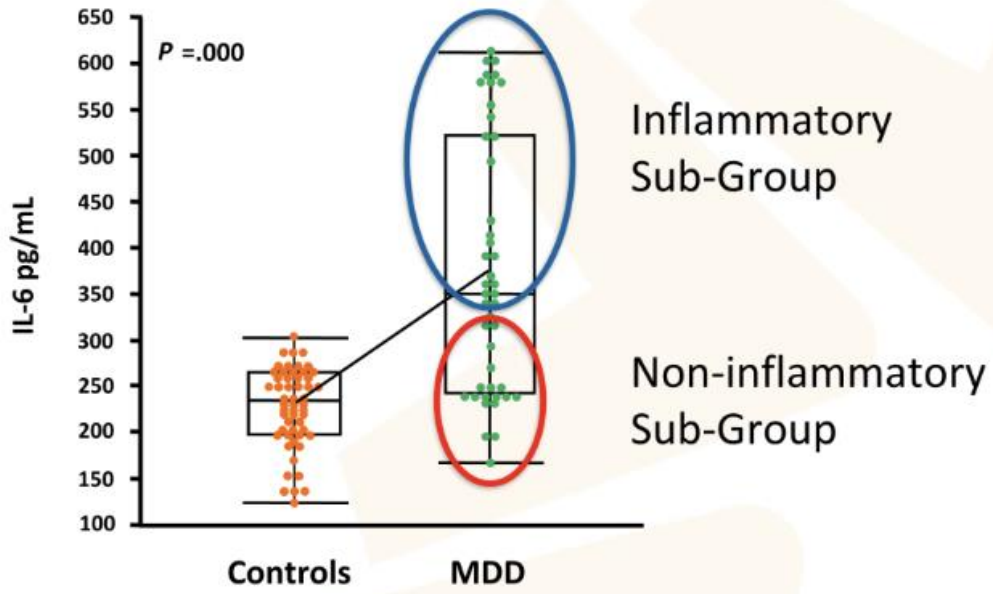
60 patients with TRD were randomized on a 1-to-1 basis to receive either 3 infusions of the TNF antagonist infliximab vs a saline placebo at baseline, Week 2, and Week 6. Depressive symptoms were assessed pre-treatment and at weeks 1, 2, 3, 4, 6, 8, 10, and 12.

TRD = treatment-resistant depression; HAM-D = Hamilton Rating Scale for Depression; CGI = Clinical Global Impression.

Raison CL, et al. *JAMA Psychiatry*. 2013;70(1):31-41.

INFLAMMATION THEORY

The Deeper Truth About the Relationship Between Inflammation and Major Depression

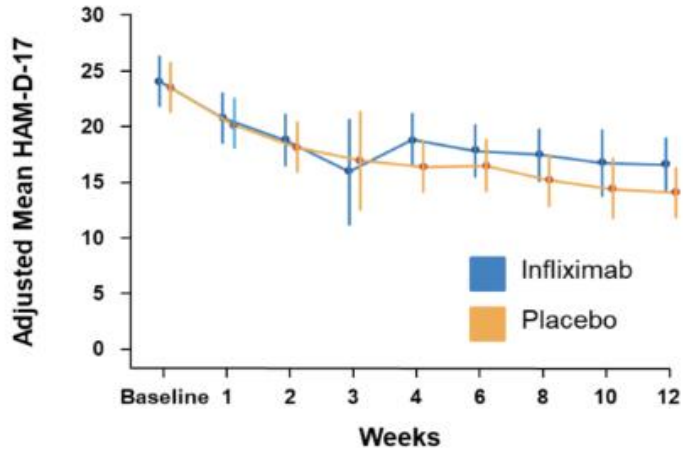


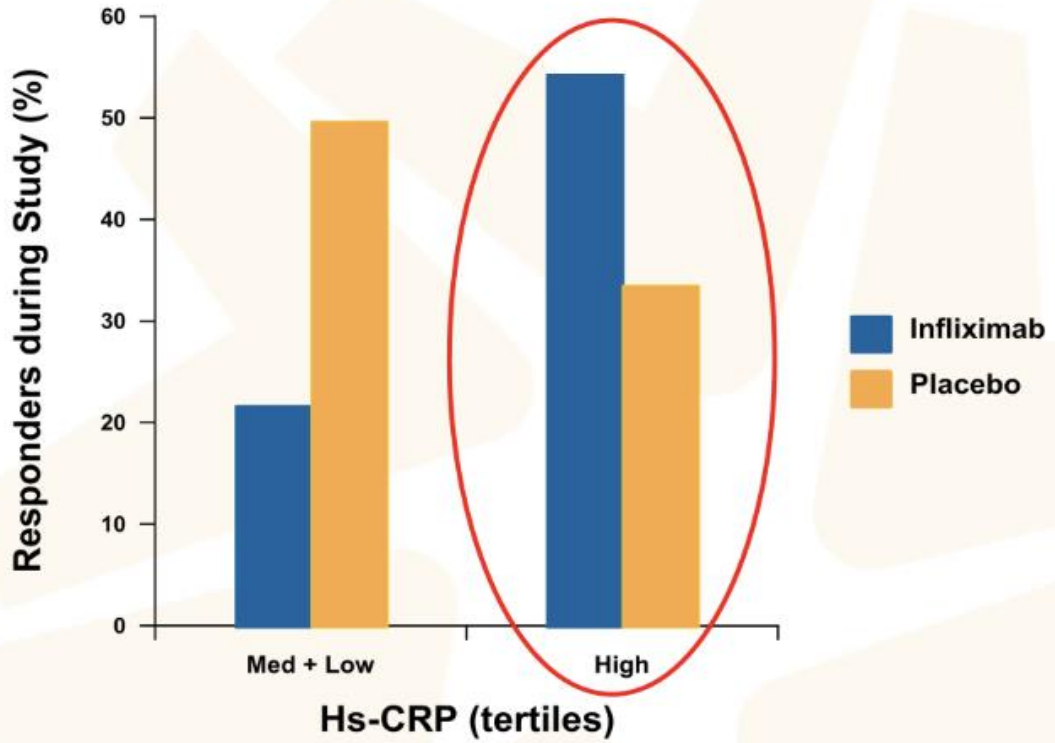
IL-6 = interleukin 6.

Kim YK, et al. *Prog Neuropsychopharmacol Biol Psychiatry*. 2007;31(5):1044-1053

INFLAMMATION THEORY

Blocking Inflammation Only Worked in Patients with Elevated Inflammation





Hs-CRP = high-sensitivity CRP.

Raison CL, et al. *JAMA Psychiatry*. 2013;70(1):31-41

More Evidence That Anti-Inflammatory Strategies Only Work in the Inflamed: Minocycline

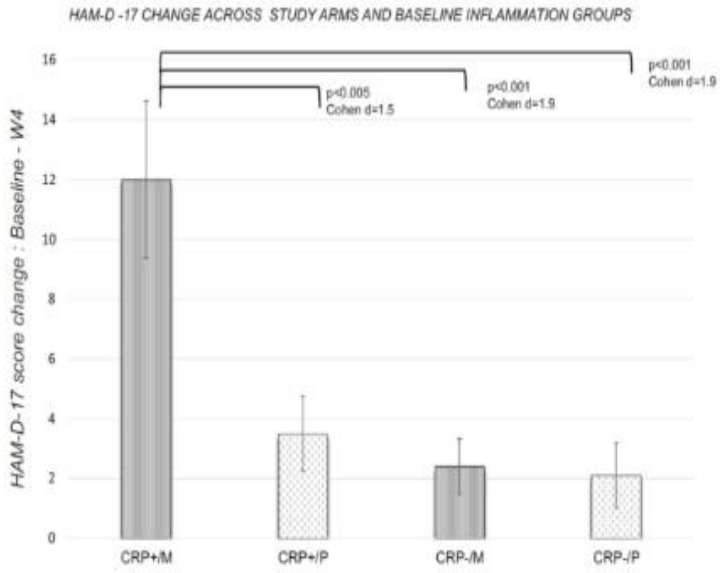


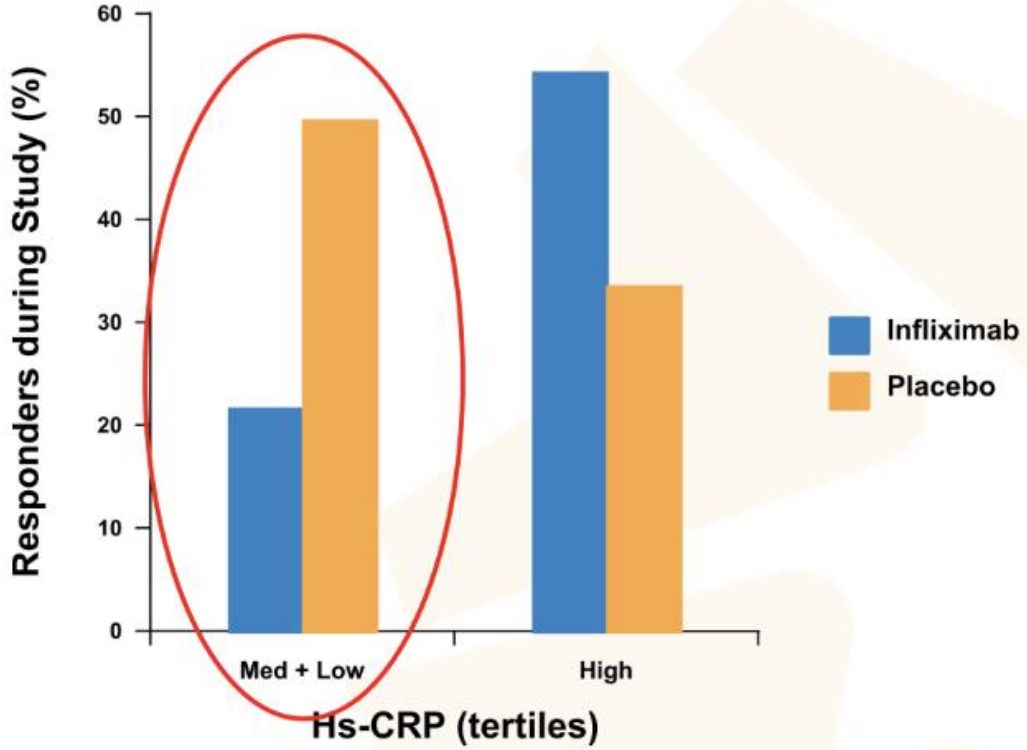
Fig. 1 Difference in HAM-D-17 mean change, calculated as baseline scores minus week 4 scores, between patients divided by Study Arm X baseline hsCRP. Patients with hsCRP levels ≥ 3 mg/L and taking minocycline (CRP^{+}/M) showed a significantly larger improvement compared with all other patients. HAM-D-17 = Hamilton Depression Rating Scale. CRP^{+} = baseline hsCRP levels ≥ 3 mg/L. CRP^{-} = baseline hsCRP levels <3 mg/L. M = Minocycline, P = Placebo.

A 4-week, placebo-controlled, randomized clinical trial of minocycline (200 mg/day) added to antidepressant treatment in 39 patients selected for elevated levels of serum C-reactive protein (CRP ≥1 mg/L), n=18 randomized to minocycline (M) and n=21 to placebo (P). The main outcome was the change in HAM-D-17 score from baseline to week 4, in the overall sample and after further stratification for baseline CRP ≥3 mg/L. After stratification for CRP levels <3 mg/L (CRP−) or ≥3 mg/L (CRP+), **CRP+/M patients showed the largest changes in HAM-D-17 scores (mean ± SD = 12.00 ± 6.45) compared with CRP-/M (2.42 ± 3.20, *P*<.001), CRP+/P (3.50 ± 4.34, *P*=.003) and CRP−/P (2.11 ± 3.26, *P*=.006) patients, and the largest proportion (83.3%, *P*=.04) of partial treatment response at week 4.** The threshold point for baseline CRP to distinguish responders from nonresponders to minocycline was 2.8 mg/L. Responders to minocycline had higher baseline IL-6.

Nettis MA, et al. *Neuropsychopharmacology*. 2021;46(5):939-948.

INFLAMMATION THEORY

Now the Wrinkle:
Beware an Anti-Inflammatory "One Size Fits All"



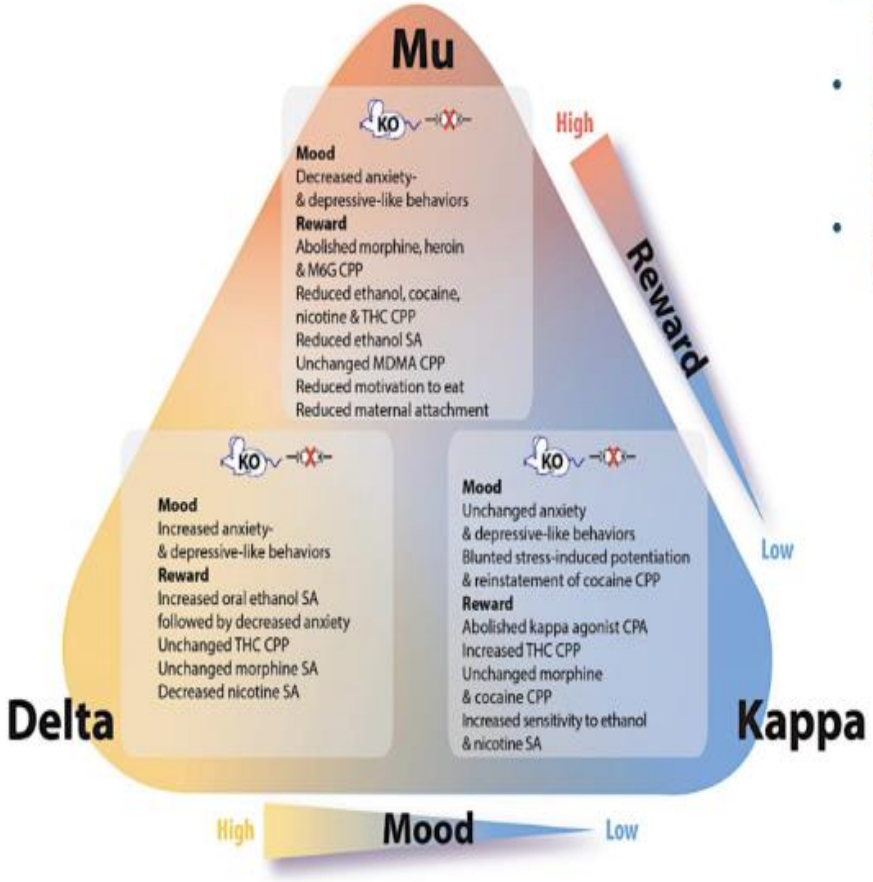
Hs-CRP = high sensitivity c-reactive protein.
Raison CL, et al. *JAMA Psychiatry*. 2013;70(1):31-41.

INFLAMMATION THEORY

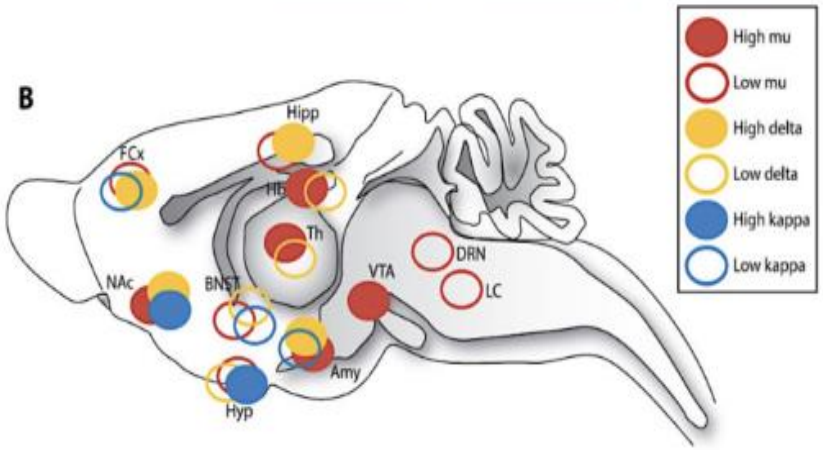
Novel Antidepressant Agents

- Psychedelics: Psilocybin, (DMT, Ibogaine)
- Gaba A receptor allosteric modulators: Zuranolone, Brexanolone
- Opiate-like agents: *Esmethadone, (Alkermes 5461, tianeptine, KOR agents)
- NMDA antagonists: *Ketamine/Esketamine
- Combo: Bupropion/Dextromethorphan

Primer on Opioid Receptors in Mood Disorders



- Mu opioid receptors (MORs) are key mediators of both natural and artificial rewards
- Kappa opioid receptors (KORs) mediate dysphoria, particularly under stressful conditions where the dynorphin/KOR activity is higher
- Delta opioid receptors (DORs) decrease levels of anxiety and reduce depressive-like behaviors

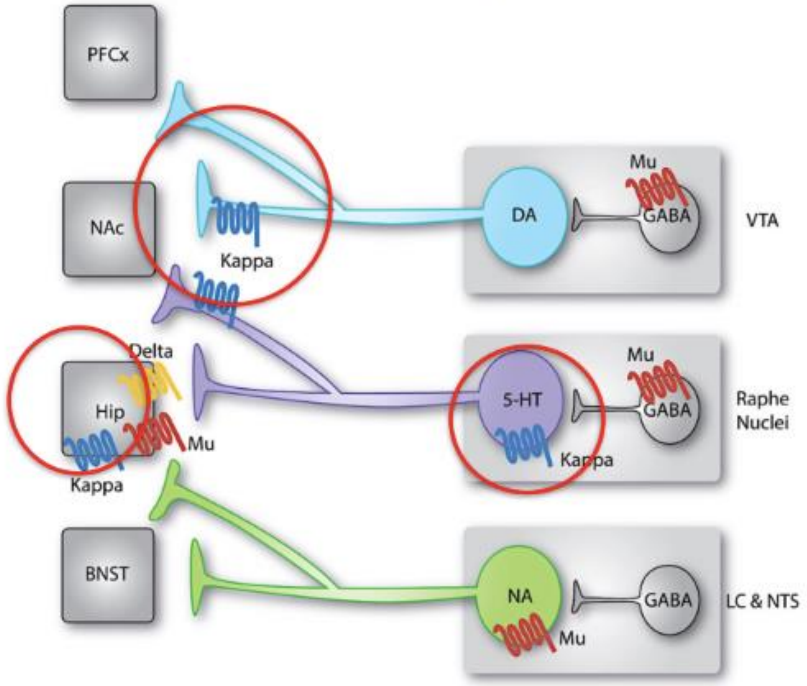


M6G = morphine-6-glucuronide; CPP = conditioned place preference; THC = tetrahydrocannabinol; SA = substance abuse; MDMA = 3,4-methylenedioxymethamphetamine; CPA = conditioned place aversion.

Lutz PE, et al. *Trends Neurosci.* 2013;36(3):195-206.

OPIOID HYPOTHESIS

Focus on Kappa Receptors: Functional Interactions with Monoaminergic Systems Relevant to Mood



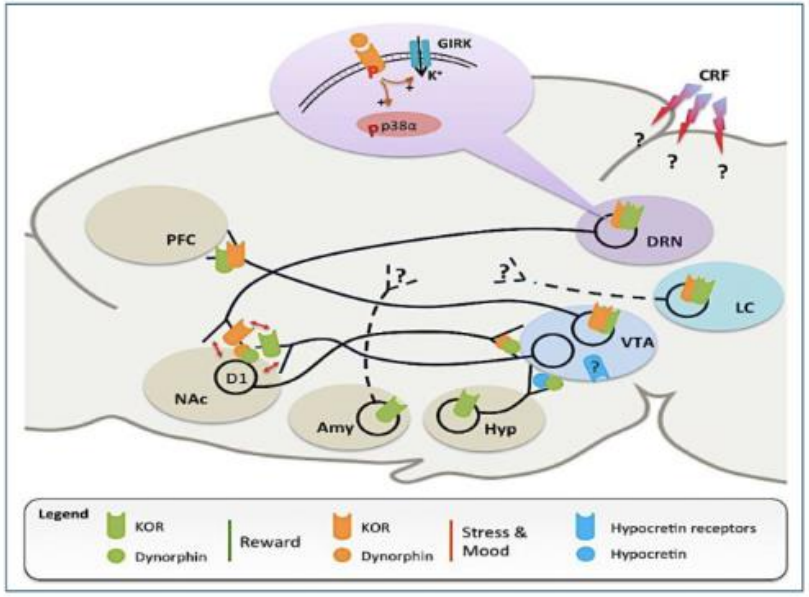
- Monoaminergic neurons synthesizing dopamine (DA), serotonin (5-HT), and nordrenaline (NA) neurons are regulated by opioid receptors at multiple sites
- Activation of mu opioid receptors (MORs) expressed in the dorsal raphe nucleus (DRN) and ventral tegmental area (VTA) by local GABAergic interneurons disinhibit 5-HT
- Kappa opioid receptors (KORs) expressed presynaptically in the nucleus accumbens (NAc) by 5-HT neurons
- In addition, stress potentiates the activity of the dynorphin/KOR system, which targets both (i) DA neurons (and possibly 5-HT neurons) in the NAc to produce depressive-like behaviors, and (ii) 5-HT neurons in the DRN to mediate acute social avoidance

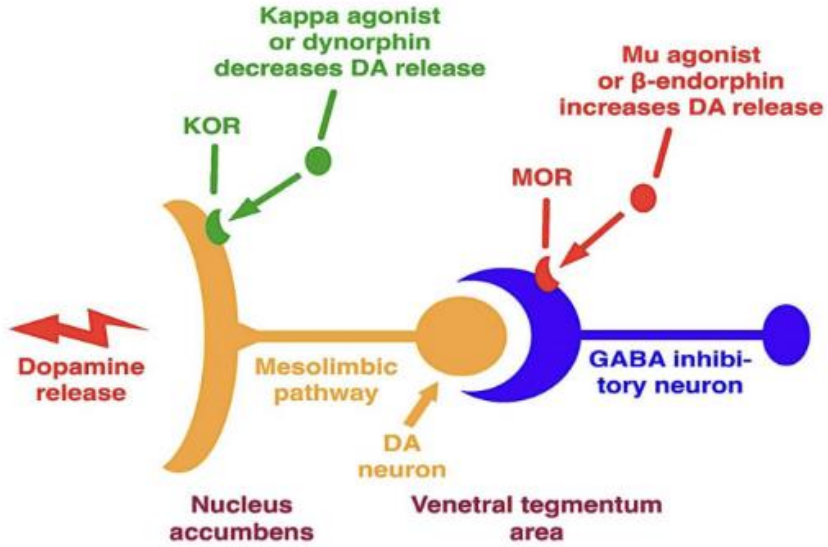
Lutz PE, et al. *Trends Neurosci.* 2013;36(3):195-206.

OPIOID HYPOTHESIS

Excess Kappa Receptor Activity Leads to Stress Impairment and Depression—Especially Anhedonia

Neuronal circuits implicated in the regulation of reward (green) and stress (orange), which are both modulated by dynorphins and the kappa opioid receptor (KOR)



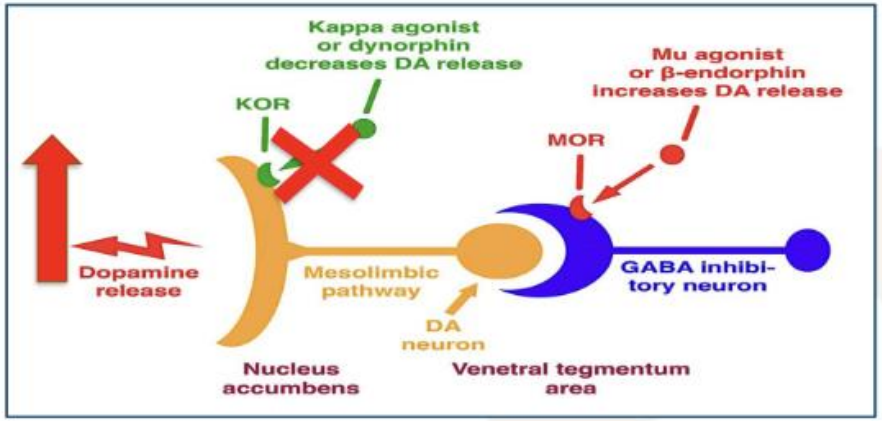


GIRK = G protein-gated inwardly rectifying potassium; amy = amygdala.
Lalanne L, et al. *Front Psychiatry*. 2014;5:170. Carroll FI, et al. *J Med Chem*. 2013;56(6):2178-2195.

OPIOID HYPOTHESIS

Excess Kappa Receptor Activity Leads to Stress Impairment and Depression—Especially Anhedonia

Blocking Kappa Receptors = Increase in Dopamine in the Nucleus Accumbens



Take-Home Message: Potential Benefits of Blocking Kappa Receptors

- Improve stress tolerance
- Decrease social isolation
- Improve depression
- Specific reward enhancement (reduce anhedonia)

Lalanne L, et al. *Front Psychiatry*. 2014;5:170. Carroll FI, et al. *J Med Chem*. 2013;56(6):2178-2195.

OPIOID HYPOTHESIS

Key Learning Points

- **Depression is associated with a depletion in dopamine, norepinephrine, and/or serotonin**
- Stimulation of the GABA and **glutamate** neurotransmitter systems leads to increased neuroplasticity and synaptogenesis, and has been proposed as a mechanism for the rapid therapeutic regulation of excessive default-mode network activity in MDD
- Precision psychiatry is an emerging paradigm
- Selective orexin receptor antagonism and kappa receptor antagonism are promising pathways to targeting sub-groups of MDD patients

OPIOID HYPOTHESIS

- Opiate like Agents
  - Alkermes 5461: (buprenorphine and naloxone) + samidorphan
  - Buprenorphine + Mu opioid receptor (MOR) antagonist
  - Decreases risk of addiction, Kappa antagonism decreases dynorphin level, increases DA
  - Phase two trials of add on to SNRI or SSRI showed 5-8 point MADRS drops (1)
  - 2/3 Phase III have failed
- Tianeptine (Mu opiod agonist, glutamate modulation) approved in MDD in France (2)
- Low dose buprenorphine for suicidal thoughts/behavior (3)

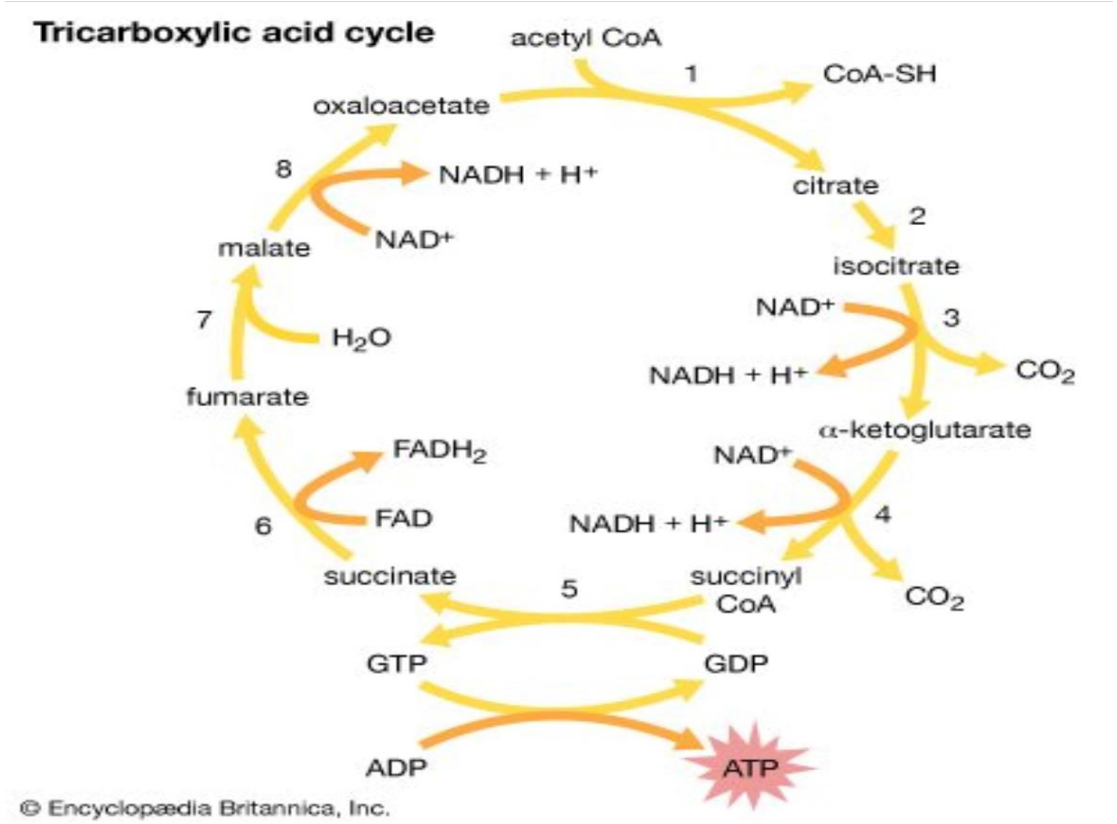
DA = Dopamine; SNRI = Serotonin-norepinephrine reuptake inhibitor; SSRI = Selective serotonin reuptake inhibitor; MADRS =, Montgomery-Asberg Depression Rating Scale. Fava M et al. Am J Psychiatry. 2016 May 1;173(5):499-508 1. 2. Alamo C, Rev Psiquiatr, Salud Ment (Engl Ed). 2019 Jul-Sep; 12(3):170-186. 3. Yovell Y, e tl. J. Am J Psychiatry. 2016 May 1;173(5):491-8.

GLUTAMATE HYPOTHESIS AND GABA HYPOTHESIS

- Glutamate is the new kid on the block
- One of the most prolific Neurotransmitters
- Where did it come from?
- -Naturally from protein containing foods such as cheese, milk, mushrooms, meat, fish and vegetables
- -Probably is recycled converting to Glutamine→Glutamate
- -Maybe coming from the Krebs cycle

GLUTAMATE HYPOTHESIS AND GABA HYPOTHESIS

- KREBS CYCLE

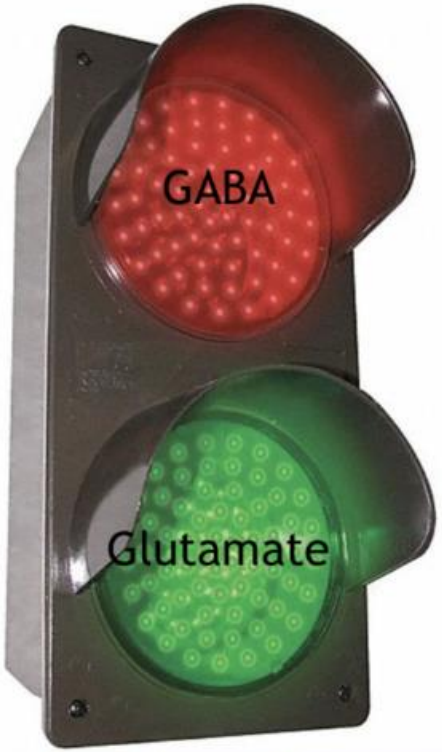


GLUTAMATE HYPOTHESIS AND GABA HYPOTHESIS

Our Reward System: Glutamate and GABA

- A way to think about our dopamine reward system would be to think about Glutamate and GABA as traffic lights. The green light is Glutamate (Go), and the red light is GABA (Stop)

- Normally both chemicals act together to keep dopamine production regulated and balanced

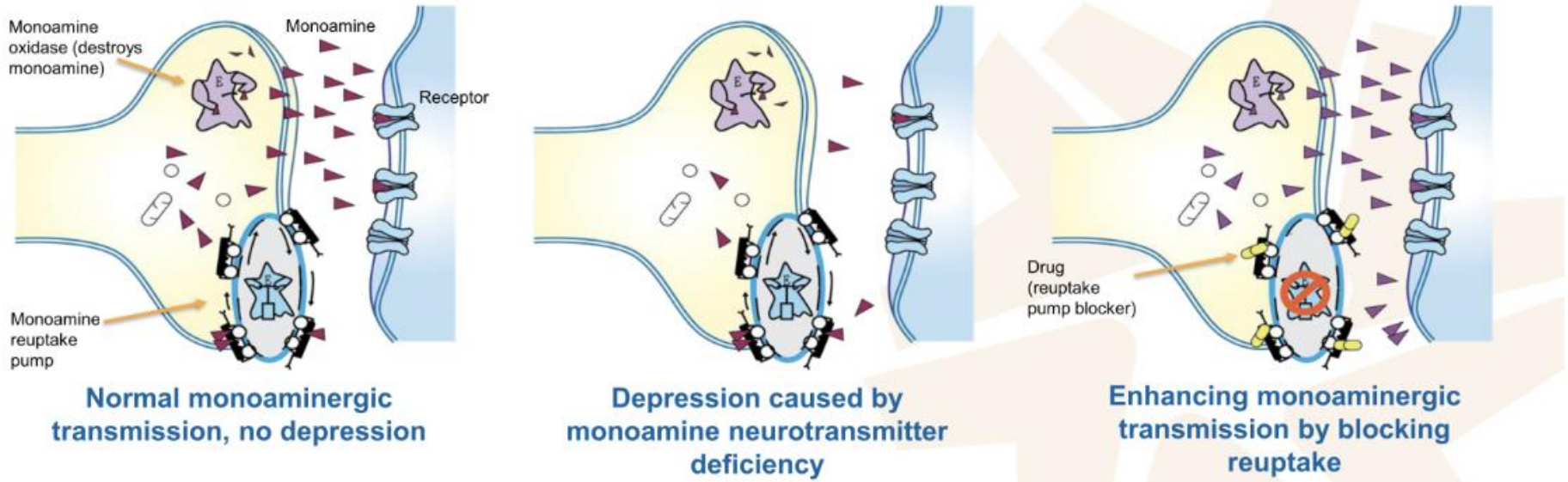


GABA = gamma-aminobutyric acid.

Perlman WR. Why Marijuana Displeases. NIH: National Institute on Drug Abuse. March 8, 2018. Accessed April 12, 2023. https://archives.nida.nih.gov/news-events/nida-notes/2018/03/why-marijuana-displeases.

GLUTAMATE HYPOTHESIS AND GABA HYPOTHESIS

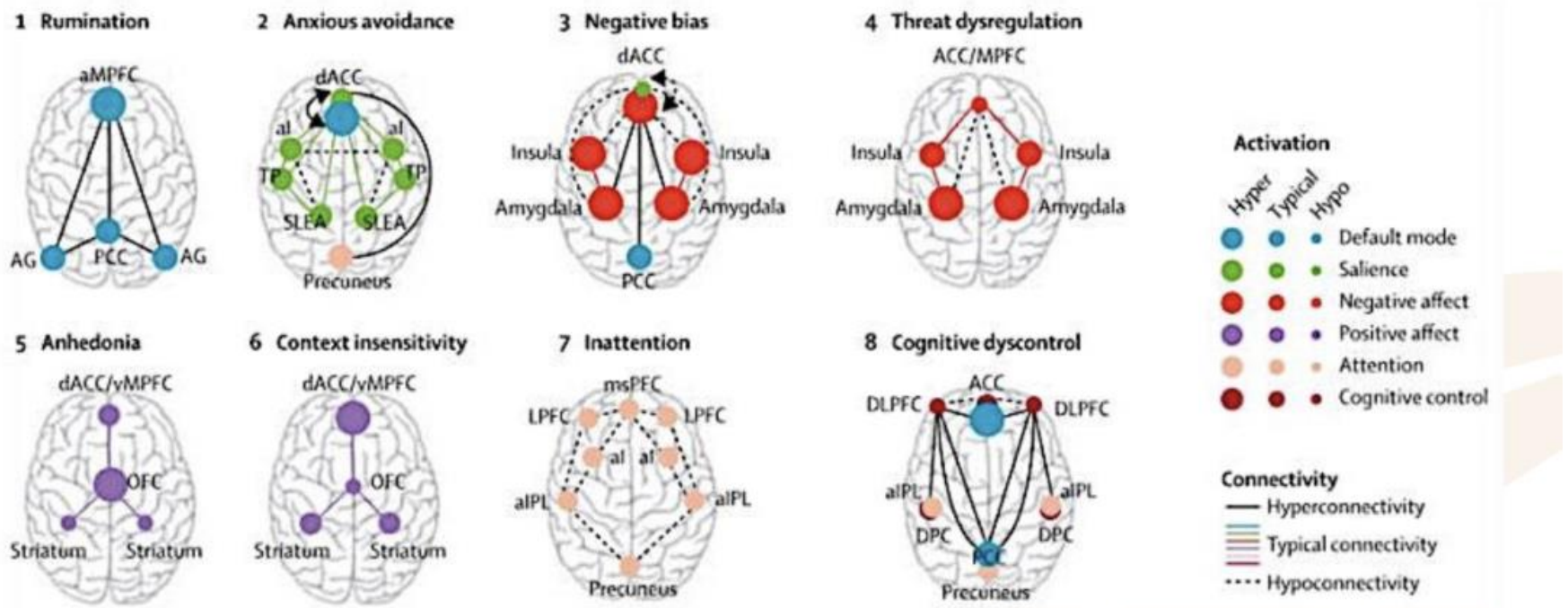
The "Simple" Monoamine Hypothesis of MDD Does Not Explain Everything



Malhi GS, et al. *Lancet*. 2018;392(10161):2299-2312. Stahl SM. *Essential Psychopharmacology*. 2nd ed. Cambridge University Press; 2000.

GLUTAMATE HYPOTHESIS AND GABA HYPOTHESIS

Network Dysfunction Hypothesis IS Rapidly Gaining Traction in MDD

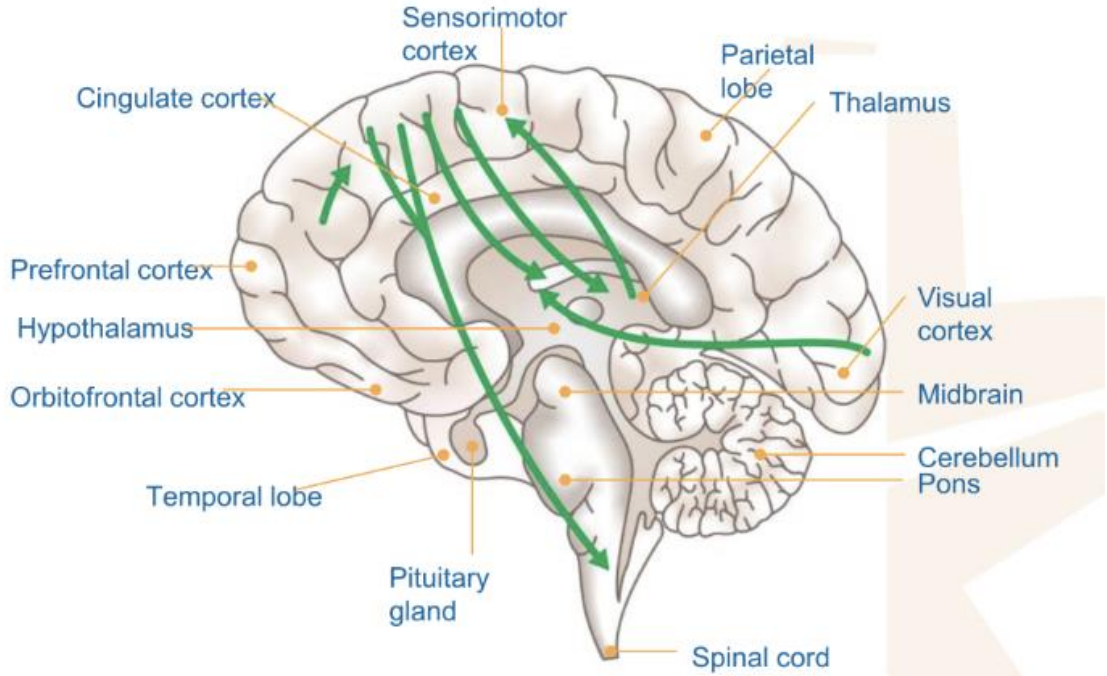


Williams LM. *Lancet Psychiatry.* 2016;3(5):472-480.

GLUTAMATE HYPOTHESIS AND GABA HYPOTHESIS

Glutamate and GABA Are Widely Distributed In the Brain

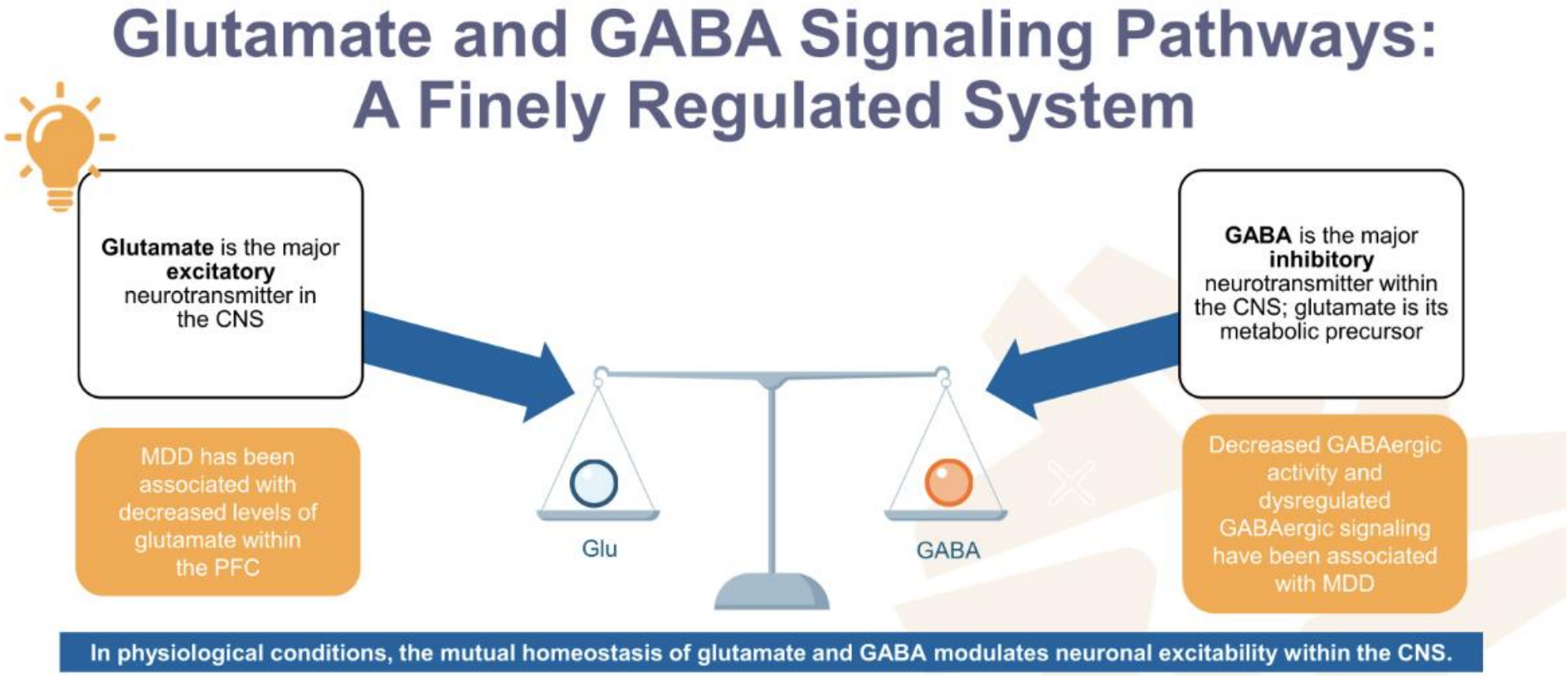
- Glutamate is the primary excitatory neurotransmitter with receptors in nearly all portions of the spinal cord and brain
- GABA is the primary inhibitory neurotransmitter and is widely found in cortical and sub-cortical structures
- These receptors are expressed by both neurons and glial cells
- Decreased levels of glutamate and GABA are linked to depression; this is consistent with the hypothesis that depression may be associated with abnormal glutamatergic neurotransmission and GABAergic neurotransmission



GABA = gamma-aminobutyric acid.

Stahl SM. *Stahl's Essential Pharmacology*. 4th ed. Cambridge University Press; 2013. Duman RS. *Dialogues Clin Neurosci*. 2014;16(1):11-27.

GLUTAMATE HYPOTHESIS AND GABA HYPOTHESIS



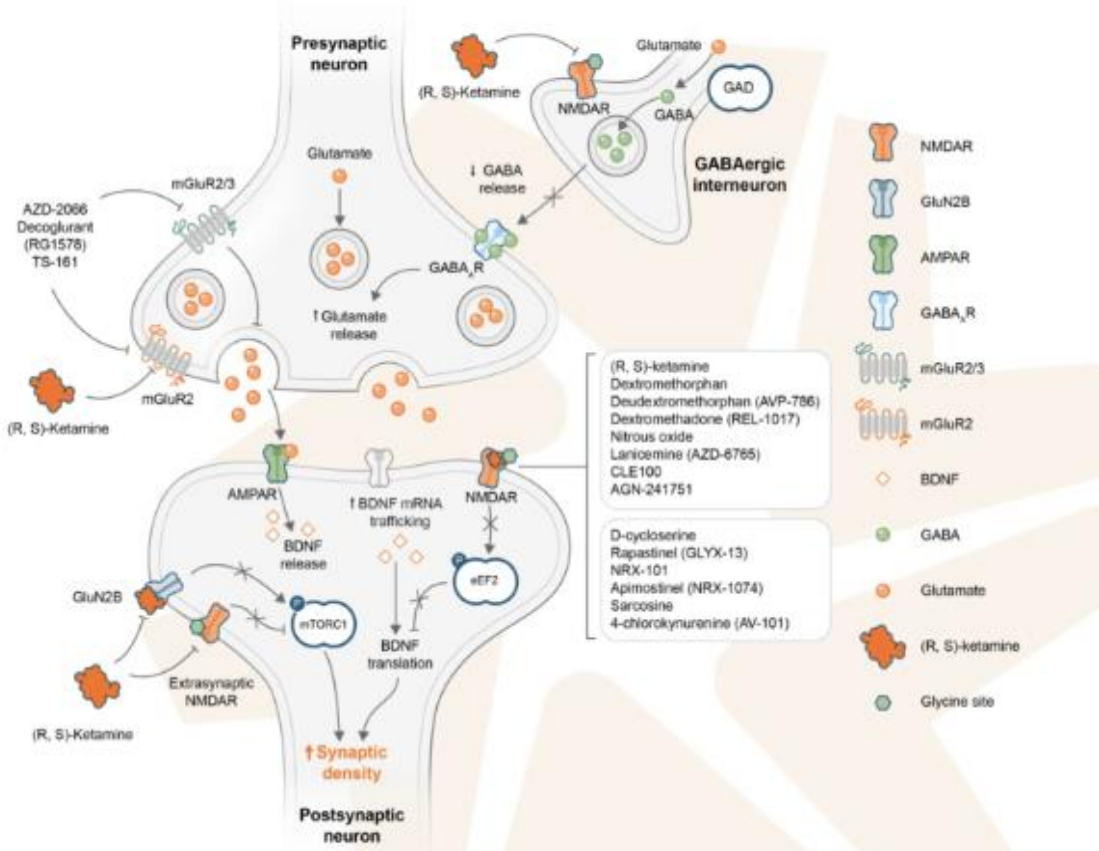
CNS = central nervous system; Glu = glutamate; PFC = prefrontal cortex.

Brosnan JT, et al. *Amino Acids*. 2013;45(3):413-418. Ionescu DF, et al. *Harv Rev Psychiatry*. 2018;26(6):320-339. Duman RS, et al. *Neuron*. 2019;102(1):75-90. Lydiard RB. *J Clin Psychiatry*. 2003;64(Suppl 3):21-27.

Glutamate-Modulating Agents via NMDA Receptor Antagonism (and Resultant AMPA Stimulation)

- Disinhibition of pyramidal neurons and enhanced glutamatergic firing by selectively blocking NMDARs
- Inhibition of spontaneous NMDAR-mediated transmission
- Inhibition of extra-synaptic NMDARs
- Activation of AMPA-R-mediated synaptic potentiation

The modulation of glutamate levels may lead to increased neuroplasticity and synaptogenesis.



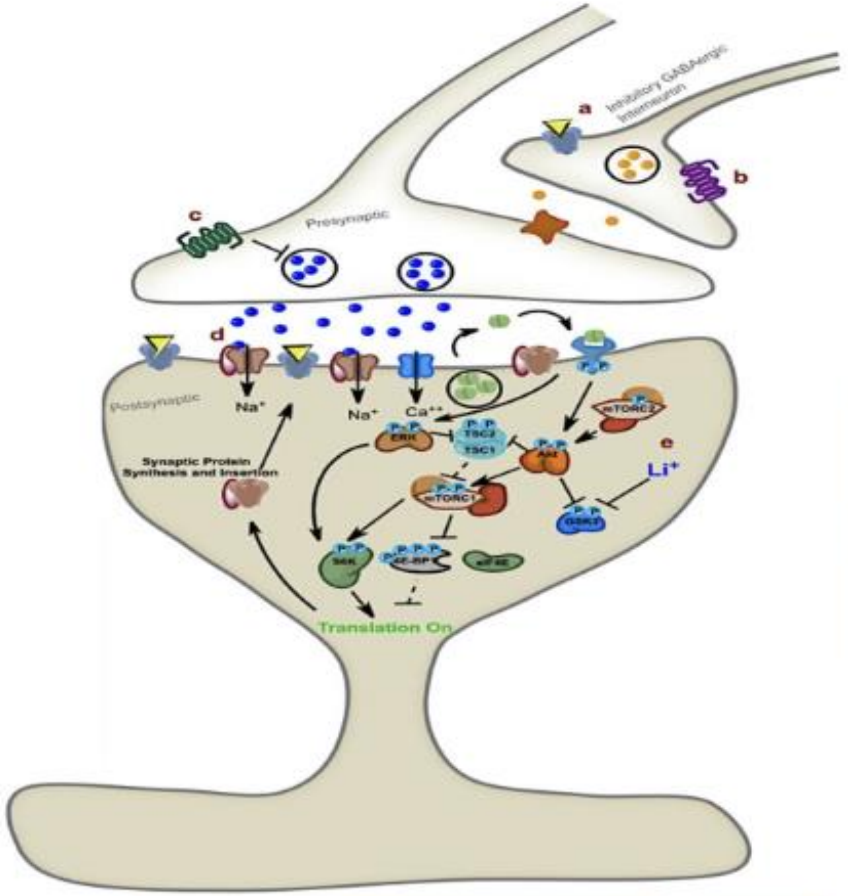
NMDA = N-methyl-D-aspartate; AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; GAD = glutamic acid decarboxylase; mRNA = messenger ribonucleic acid; BDNF = brain-derived neurotrophic factor.

Henter ID, et al. *CNS Drugs*. 2021;35(5):527-543.

How NMDA Antagonists (Esktamine, Ketamine) Work: *A Receptor and Intracellular Cascade Story*

- NMDA receptor blockade…
- Lead to increased glutamate release from pyramidal neurons
- Activation of postsynaptic AMPARs by increased glutamate transmission…
- Release of BDNF; this neurotrophic factor binds to related kinase B (TrkB) receptors, and mTOR is activated…
- Leading to transphosphorylation and downstream activation of the extracellular signal-related kinase (ERK) and suppression of glycogen synthase kinase 3 (GSK-3)

This is to illustrate that the "real action" of the pharmacologic manipulation of glutamate is intracellular. It shows the importance of the mTOR system, GSK-3, BDNF, scaffolding proteins, and synaptogenesis.



TrkB = tropomyosin receptor kinase B; mTOR = mammalian target of rapamycin; ERK = extracellular signal-regulated kinase.
Dwyer JM, et al. *Biol Psychiatry*. 2013;73(12):1189-1198

GLUTAMATE HYPOTHESIS AND GABA HYPOTHESIS

Ketamine

- Anesthetic agent
- Used intravenously primarily
- Used for chronic pain
- N-methyl-D-aspartate antagonist;
- Mu opioid agonist; stimulant (?)
- Psychotomimetic; dissociation
- Acute antidepressant efficacy not sustained

GLUTAMATE HYPOTHESIS AND GABA HYPOTHESIS

DISSOCIATIVE DRUGS WORK ON THE GLUTAMATE RECEPTORS OF THE BRAIN

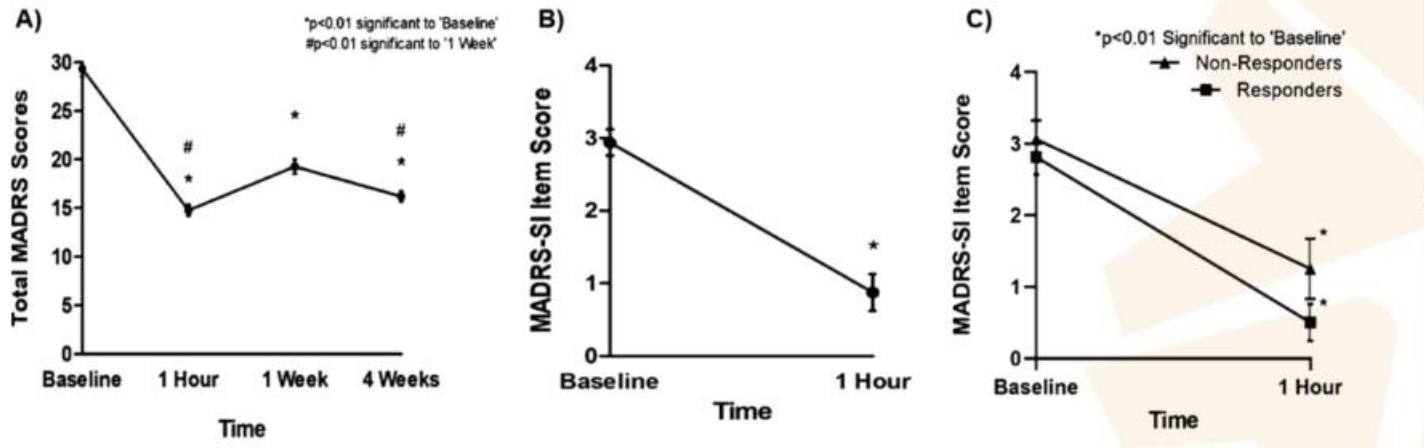
DISSOCIATIVE HALLUCINOGENIC TRANQUILIZER

- Ketamine Derivative of PCP First Synthesized in 1963 and approved by the FDA in 1970
- PCP Developed in 1950's for general Anesthesia
- DXM cause PCP-like hallucinations and confusion at higher doses

GLUTAMATE HYPOTHESIS AND GABA HYPOTHESIS

Ketamine Has a Strong, Specific Anti-Suicide Effect

Study evaluated the effects of repeated subanesthetic ketamine infusions on SI in patients with major depression. 82 participants with treatment-resistant unipolar and bipolar depression completed a 2-site open-label case-series of repeated (up to 4 weeks) infusions of ketamine (0.5 mg/kg).



Had previously failed at least 4 pharmacologic or neuro-stimulating treatments, with either unipolar or bipolar moderate to severe depression.

The observed anti-suicidal effect was independent of mood changes, as patients whose mood did not respond still exhibited significantly less SI than baseline.

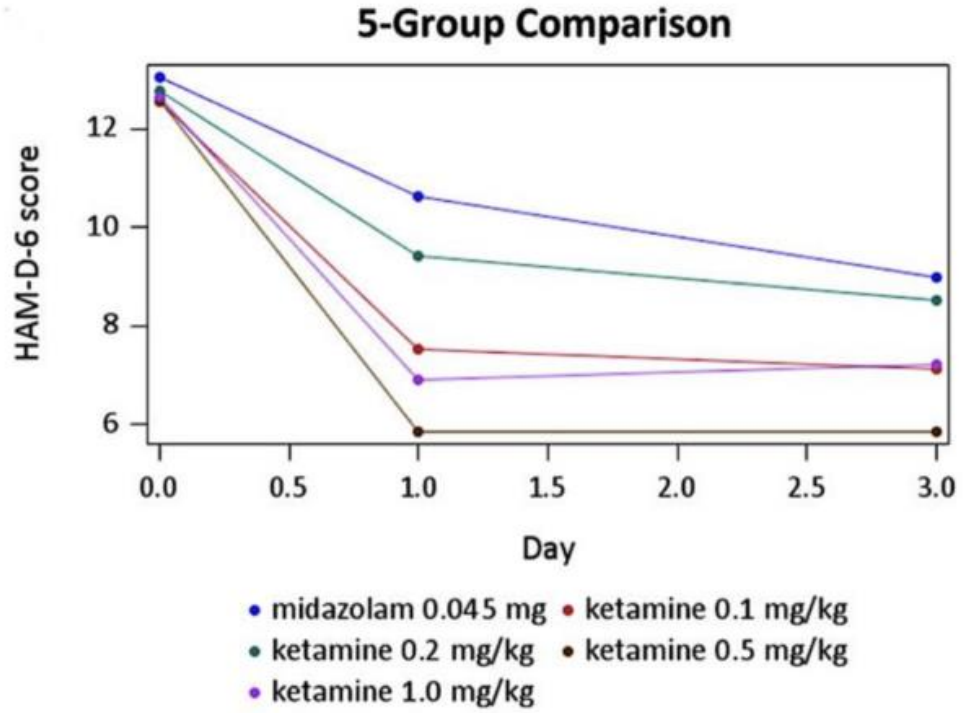
Ketamine produced a significant reduction in SI as early as 1 hour (71.1%) and up to 1-week post-infusion (60.4%).

SI = suicidal ideation.

Kang MJY, et al. *Psychiatry Res*. 2021;296:113645.

GLUTAMATE HYPOTHESIS AND GABA HYPOTHESIS

Ketamine in TRD:
Dose Finding Studies Point to Optimum Dose Range



Findings

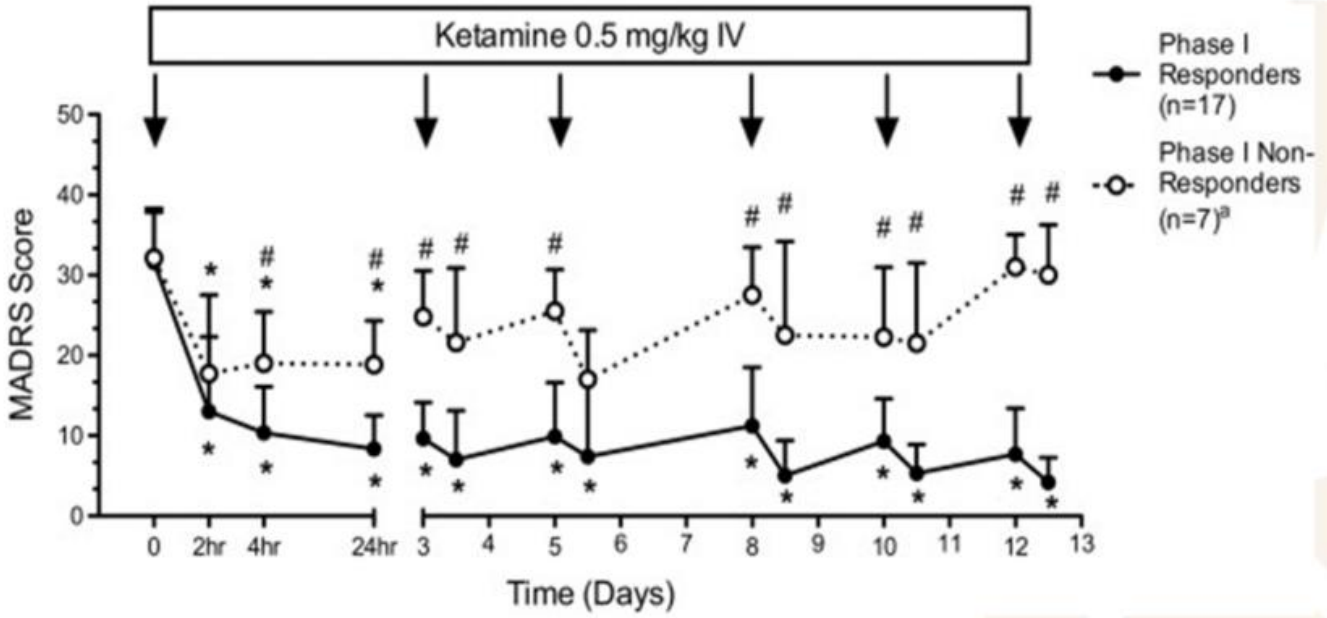
Results suggest that **there is evidence for the efficacy of the 0.5 mg/kg and 1.0 mg/kg subanesthetic doses of IV ketamine** and no clear or consistent evidence for clinically meaningful efficacy of lower doses of IV ketamine.

Most of the effect was due to differences at Day 1.

Fava M, et al. [published correction appears in Mol Psychiatry. 2019 Jan 7;:]. *Mol Psychiatry*. 2020;25(7):1592-1603.

GLUTAMATE HYPOTHESIS AND GABA HYPOTHESIS

Response to Repeated Ketamine Infusions



*p<.05

Murrough JW, et al. *Biol Psych.* 2013,70(10):1134-42.

GLUTAMATE HYPOTHESIS AND GABA HYPOTHESIS

Ketamine vs ECT in Non-Psychotic TRD

- 403 patients randomized (open label)
- 2x/week IV Ketamine or 3x/week ECT for 3 weeks
- Outcome is 50% improvement on QIDS Quick Inventory of Depressive Symptomatology (QIDS)
- 55% response in Ketamine
- 41% response ECT
- > Cognitive and musculoskeletal AEs for ECT
- > Dissociation for Ketamine

TRD = treatment-resistant depression
Anand, et al. *NEJM*. 2023;388:2315-2325.

GLUTAMATE HYPOTHESIS AND GABA HYPOTHESIS

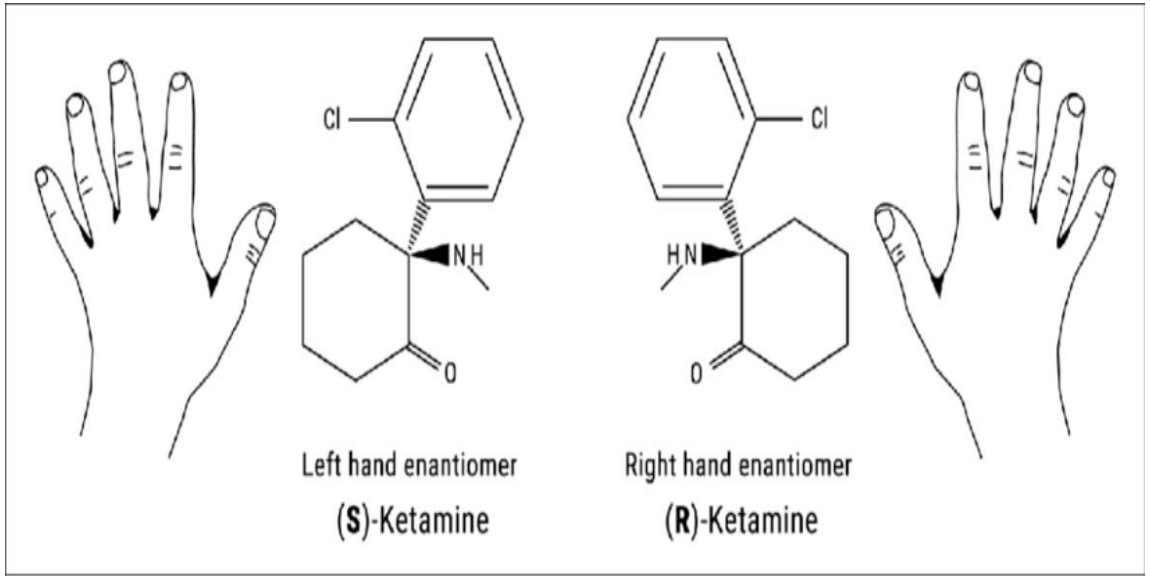
S-Ketamine is considered the active enantiomer

Isolated and packaged as Spravato

For depression, looking at concentrations of 50-100ng/ml

Loss of responsiveness at about 20 fold higher concentrations 2000ng/ml

Elimination ½ life 3 hours



OFF-LABEL USE FOR KETAMINE

DEPRESSION
ANXIETY
PTSD
PAIN CONDITIONS such as CRPS (COMPLEX REGIONAL PAIN SYNDROME)

SPRAVATO ON LABEL FDA APPROVAL FOR DEPRESSION AS ADJUNCT ONLY

OFF-LABEL USE FOR KETAMINE

What we know is useless, what we don't know can do us great harm.

THE MECHANISM FOR THE ANTIDEPRESSANT ACTION IS **UNKNOWN**!

- Numerous Theories

MECHANISM OF ACTION

- **Ketamine is what scientists call a "dirty drug," meaning it doesn't just target one system in your brain, but dozens.**
- Ketamine interacts with many binding sites such as NMDA, AMPA, opioid, monoaminergic, cholinergic, nicotinic, and muscarinic receptors.

MECHANISM OF ACTION

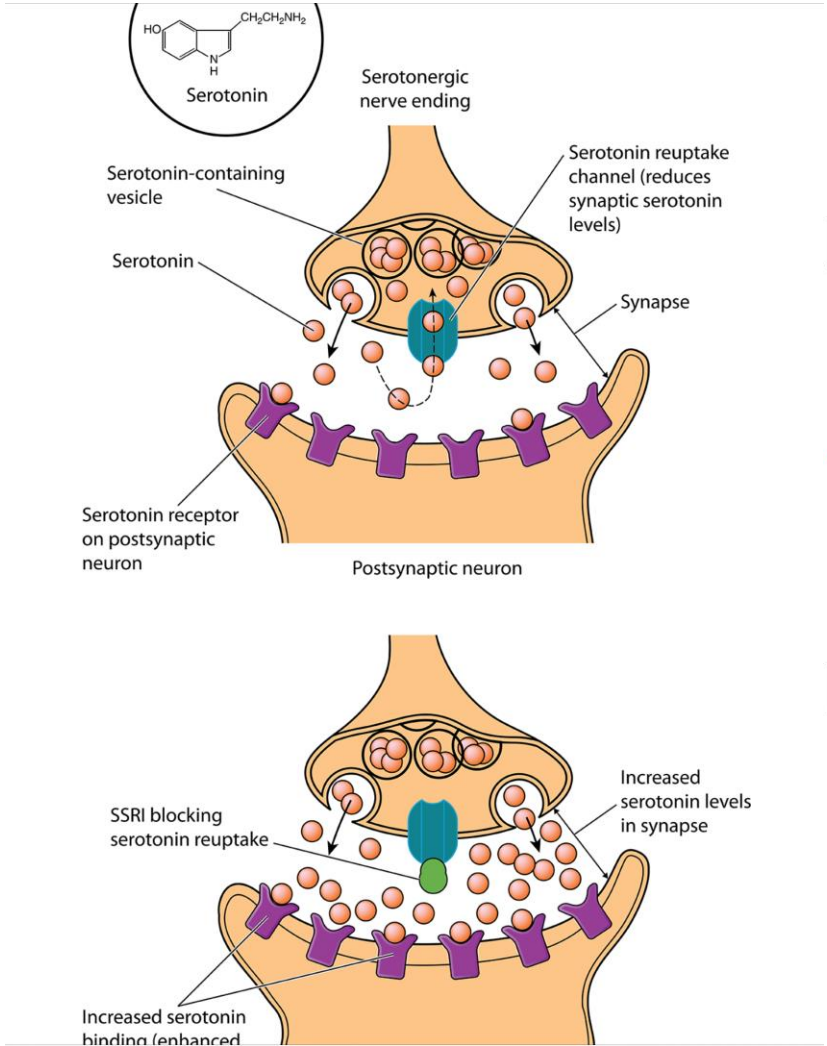
- There are two major types of glutamate receptors in the brain - NMDA receptors (N-methyl-d-aspartate) and AMPA receptors (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid).
- AMPA receptors typically eliciting a rapid response after the glutamate binds
- Experiments have confirmed that the rapid antidepressant-like effects require activation of AMPA receptors, not inhibition of NMDA receptors.
- Rasenick showed that people with depression have higher numbers of G proteins packed into lipid rafts.
  - SSRI Receptors accumulate in lipid rafts, forcing out G proteins and causing them to become active again. With Medications, this movement out of the rafts was gradual and took a days to complete.
- Ketamine moved G proteins off lipid rafts, where they were inactive, the ketamine set these proteins up to start producing more of the chemical messenger — in just 15 minutes — which could account for their rapid action.

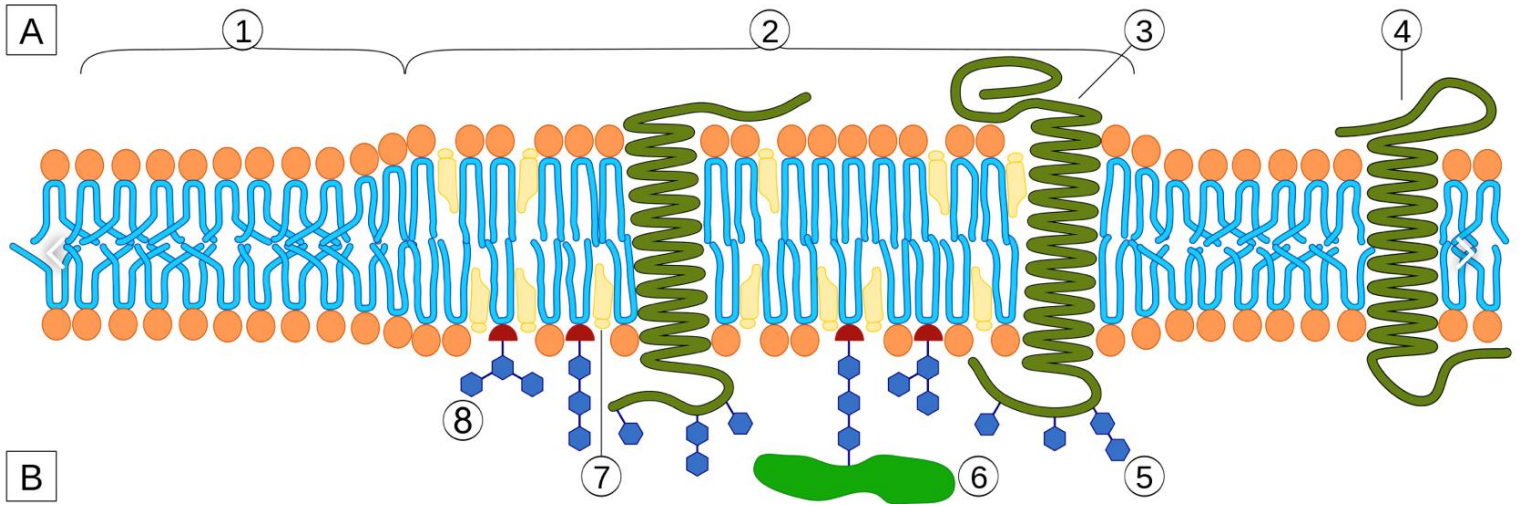
MECHANISM OF ACTION

MECHANISM OF ACTION

- A recent article points out that co-transmission of glutamate and monoamines is a very frequent phenomenon in the CNS
- This view is supported by the finding that raphe neurons, the main source of serotonergic fibers projecting to almost all brain regions, are immunopositive for glutamate
- They contain the vescicular glutamate transporter VGLUT3
- When grown in microcultures, approximately 60% of serotonergic raphe neurons evoke AMPA/kainate-mediated excitatory post synaptic potentials (EPSPs), indicating that most of these neurons in addition to 5-HT use glutamate as a co-transmitter

MECHANISM OF ACTION





MECHANISM OF ACTION

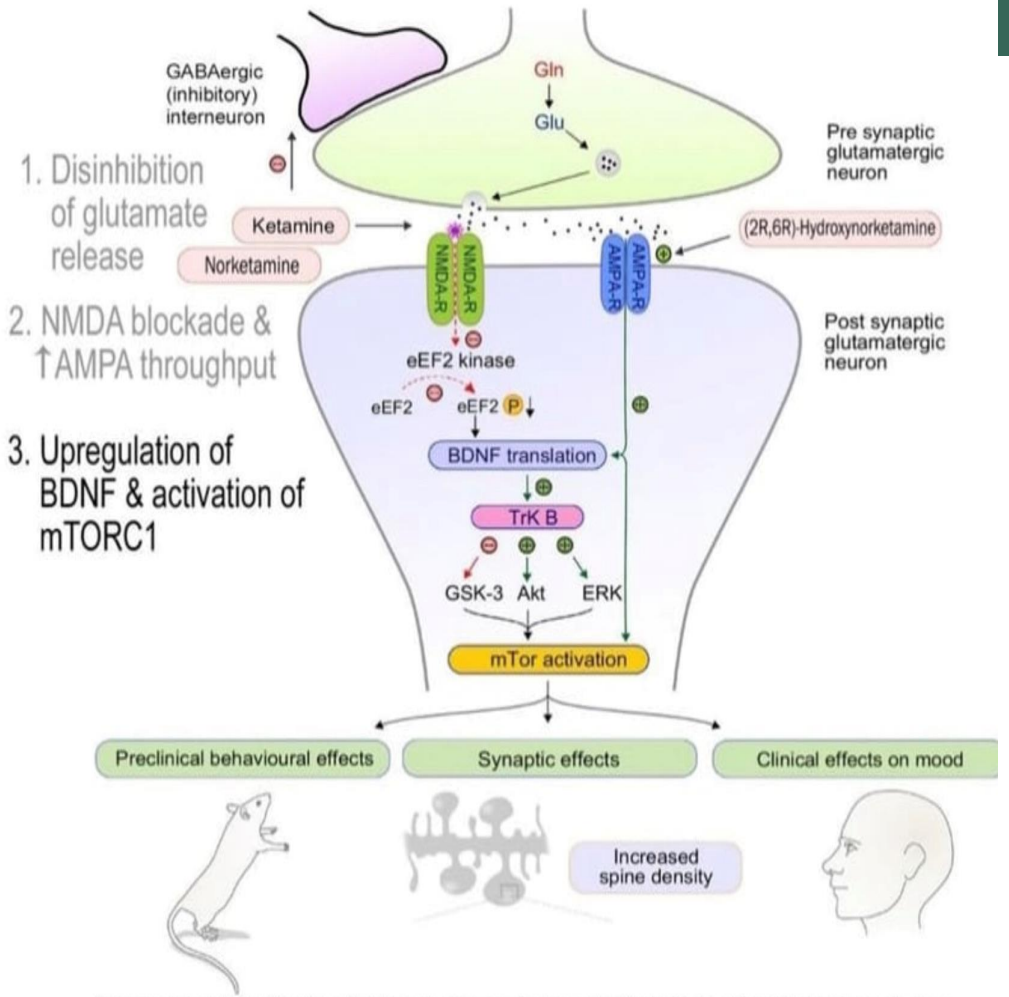


Figure adapted from: Naughton M, Clarke G, O'Leary OF, Cryan JF, Dinan TG. A review of ketamine in affective disorders: current evidence of clinical efficacy, limitations of use and pre-clinical evidence on proposed mechanisms of action. J Affect Disord. 2014 Mar;156:24-35.

Ultimately changes in critical local neuronal circuits converge via enhanced **synaptic neural plasticity and neuronal synchronization**, especially in areas involved in mood and behavior, to produce rapid antidepressant effects.

Plasticity is change through growth and reorganizations

Has a weak effect on opiate receptors and one study showed that when opiate receptors are blocked they didn't experience anti-depressive effects

Brain Derived Neurotrophic Factor- **key molecule involved in plastic changes related to learning and memory**

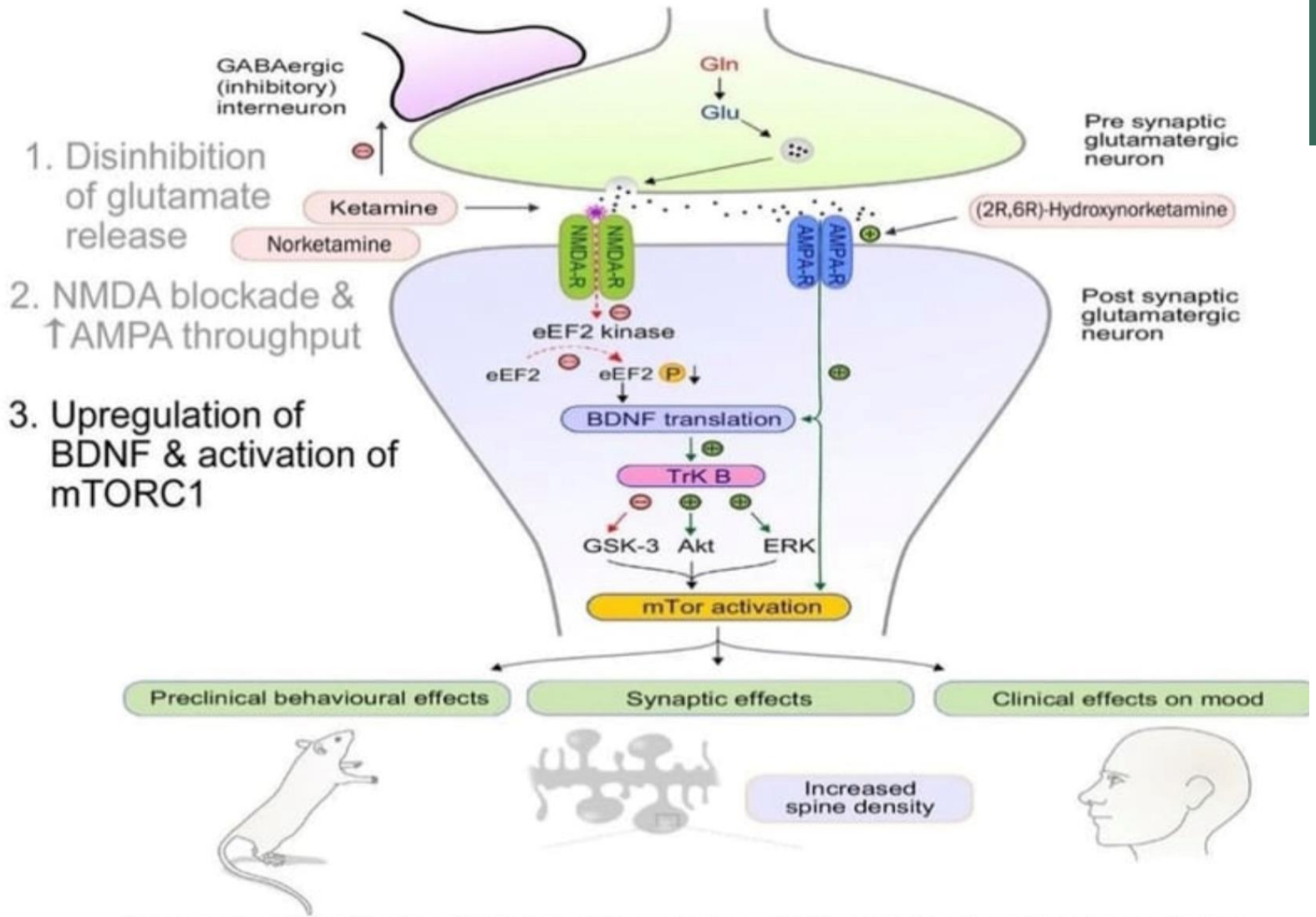
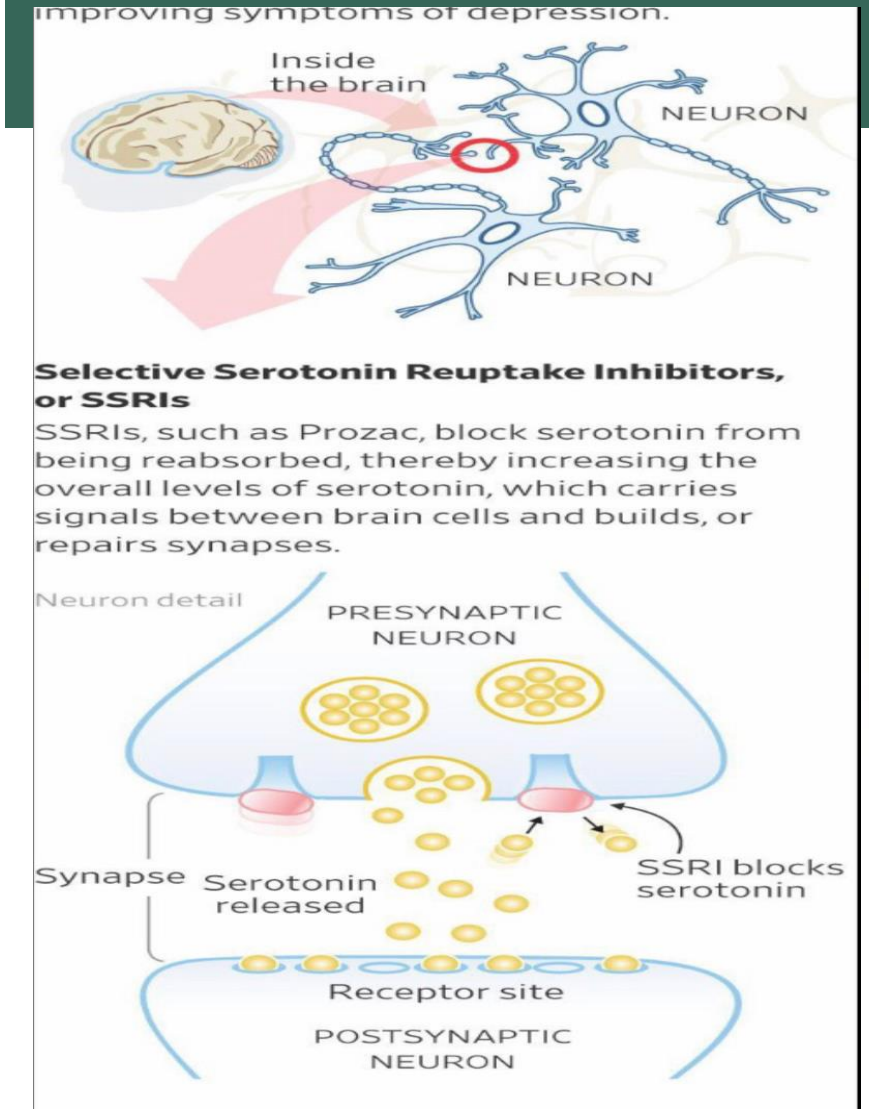
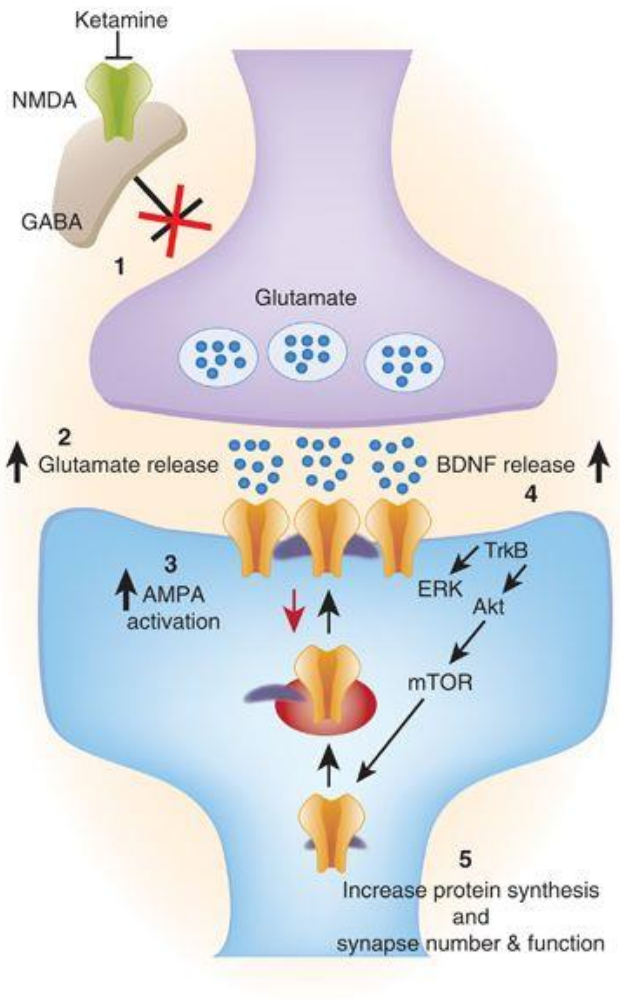


Figure adapted from: Naughton M, Clarke G, O'Leary OF, Cryan JF, Dinan TG. A review of ketamine in affective disorders: current evidence of clinical efficacy, limitations of use and pre-clinical evidence on proposed mechanisms of action. J Affect Disord. 2014 Mar;156:24-35.

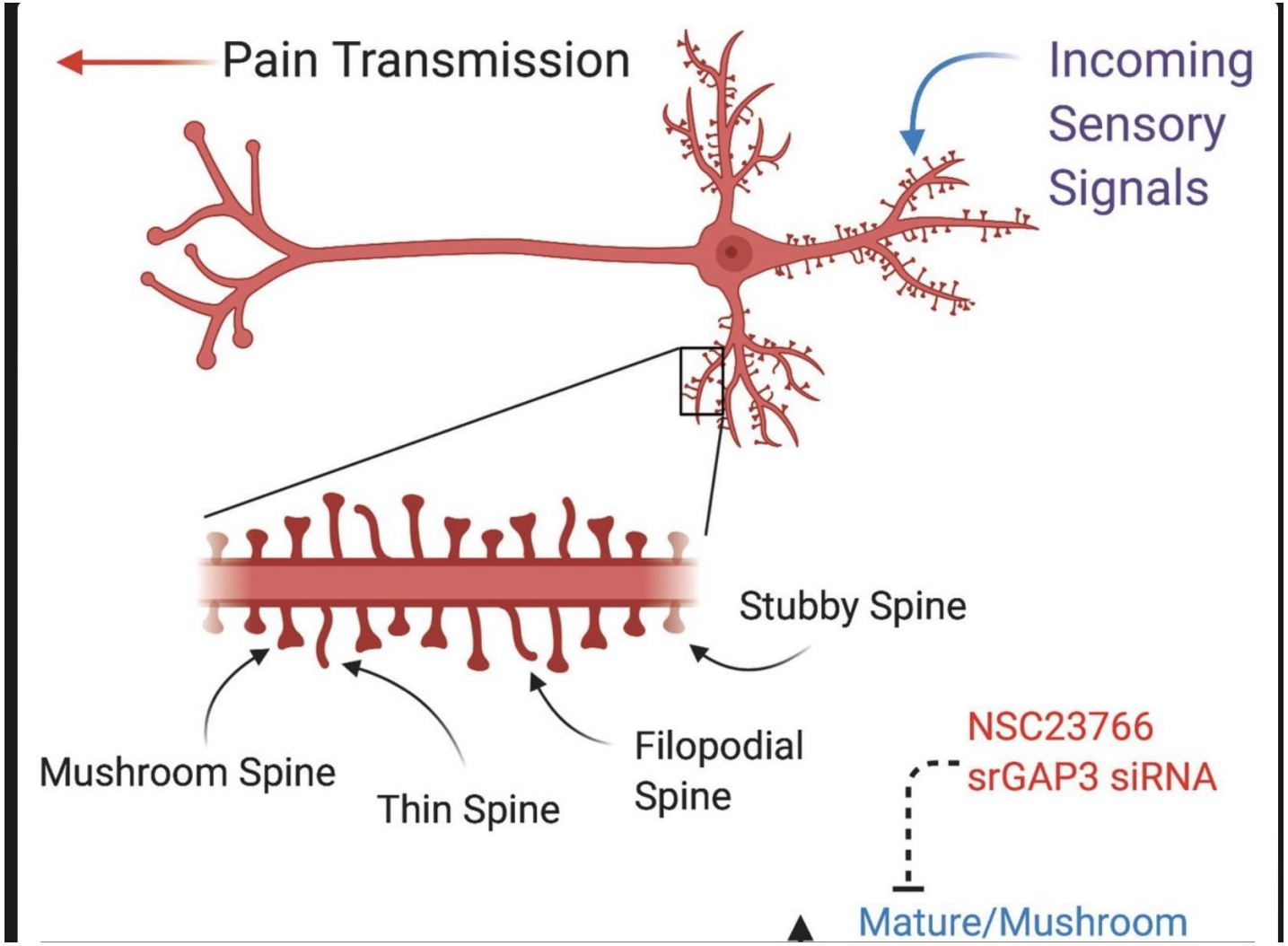
MODALITIES - **KETAMINE**





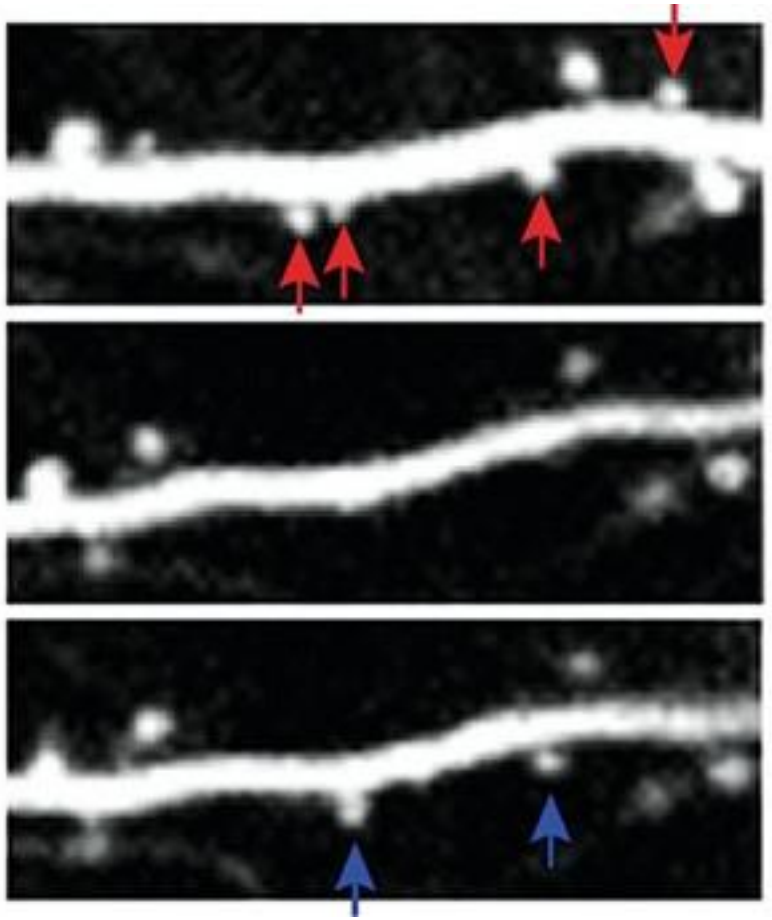
Ultimately changes in critical local neuronal circuits converge via enhanced **synaptic plasticity and neuronal synchronization**, especially in areas involved in mood and behavior, to produce rapid antidepressant effects.

MECHANISM OF ACTION



MECHANISM OF ACTION

On mouse nerve cells, dendritic spines (red arrows, top panel) disappeared after corticosterone treatment (middle panel). Some spines regrew (blue arrows, bottom panel) after the mice got a ketamine shot. Images taken at 75x magnification.



MECHANISM OF ACTION

- Ketamine IV for depression 0.5 mg/kg, but some patients may respond to doses as low as 0.1 mg/kg, and others may require up to 0.75 mg/kg. The ketamine dose is conventionally administered across 40 minutes; however, safety and efficacy have been demonstrated in sessions ranging between 2 and 100 minutes in duration

SIDE EFFECTS

- A low dose will create a mellow high with mild visual hallucinations, heightened senses, and numbness. A higher dose might cause vivid hallucinations, trouble moving, short-term memory loss, and feeling like you're having an "out-of-body" experience. This could lead to:
- Uncontrolled eye movement
- Tears
- Dilated pupils
- More saliva
- Stiffened muscles
- Nausea

CAN KETAMINE CAUSE ADDICTION

- Two clinical trials -- one looking at Cocaine addiction and the other at alcohol dependency -- showed that people who were prescribed ketamine, alongside therapy, had a better outcome than those who had therapy without ketamine treatment.
- The people who had cocaine addictions got ketamine through an IV for 5 days, in addition to 5 weeks of mindfulness relapse prevention therapy.
- The people who were dependent on alcohol got ketamine through an IV during the second week of a 5-week motivational enhancement therapy session.
- In both studies, the researchers concluded that ketamine lowered the chances of restarting or relapsing into addiction.

KETAMINE ABUSED

- When it's abused, ketamine can be an Psychologically addictive substance. But when it's administered by a professional as a form of depression treatment, ketamine does not appear to be addictive. Special care is given to the dosage, frequency, and method the ketamine is administered in so that patients are safe and protected from any possibility of addition.
- Ketamine myths are still alive and well in our culture, but as people learn more about the real benefits of the drug, perceptions are shifting. Education is the only way we can successfully inform people about the benefits of ketamine.

GLUTAMATE HYPOTHESIS AND GABA HYPOTHESIS

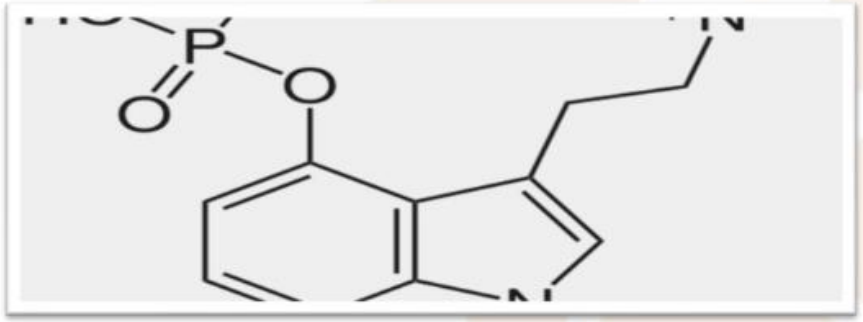
CLASSIC HALLUCINOGENS AND BEYOND-WORKS ON THE SEROTONIN RECEPTORS OF THE BRAIN

- Psilocybin
- lysergic acid diethylamide (LSD)
- Marijuana
- dimethyltryptamine (DMT)
- Mescaline
- Ayahuasca
- 251-NBOMe Synthetic hallucinogen LSD + MDMA
- Toad Venom
- Salvia

NOVEL POSSIBILITIES TO TREAT DEPRESSION

Psilocybin

- Derived from multiple species of mushrooms
- Isolated by Albert Hoffman at Sandoz in 1959
- Made available to physicians for use in psychedelic psychotherapy until the Controlled Substance Act of 1970 made it schedule 1
- Shorter half life than LSD
- Converted to psilocin



(Not FDA approved)

NOVEL POSSIBILITIES TO TREAT DEPRESSION

- Microdosing: One definition is approximately 1/5 to 1/20 of a recreational dose. (From anecdotal experience this is accurate, as a medium-strength dose of psilocybin is 2 to 3 grams of dried mushrooms, and a microdose is typically around 0.1 grams – 0.5 grams (100mg – 500mg).

NOVEL POSSIBILITIES TO TREAT DEPRESSION

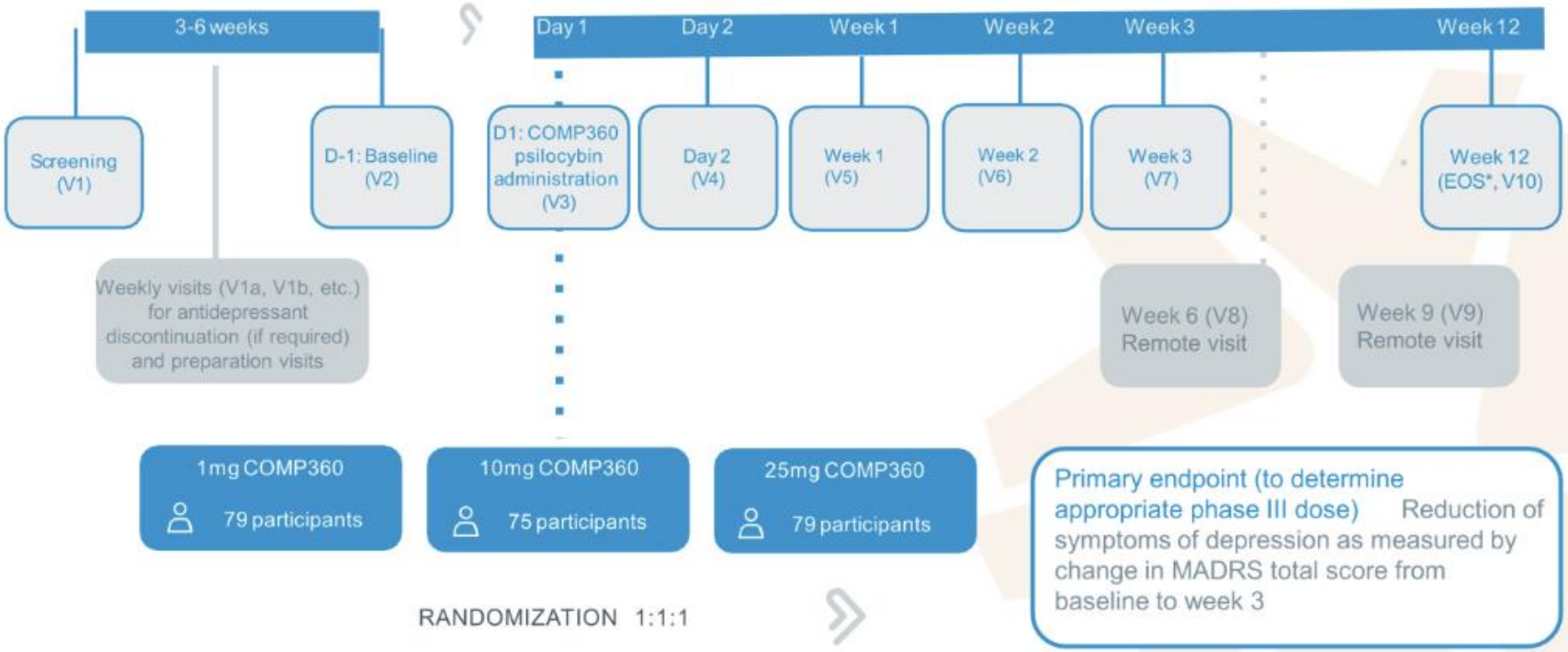
Double-blind Studies of Psilocybin in Cancer Patients with Comorbid Depression and Anxiety

- Two positive double-blind studies
- Niacin or low dose psilocybin as controls
- Full doses of psilocybin were 0.3 mg./Kg or 22 to or 30 mg./70 kg
- Both studies demonstrated sustained responses at full doses

Griffiths R, et al. *Psychopharm*. 2016;30:1181-1197. Ross S, et al. *Psychopharm*. 2016;30:1165-1180.

NOVEL POSSIBILITIES TO TREAT DEPRESSION

COMP 001 Study Design and Endpoints

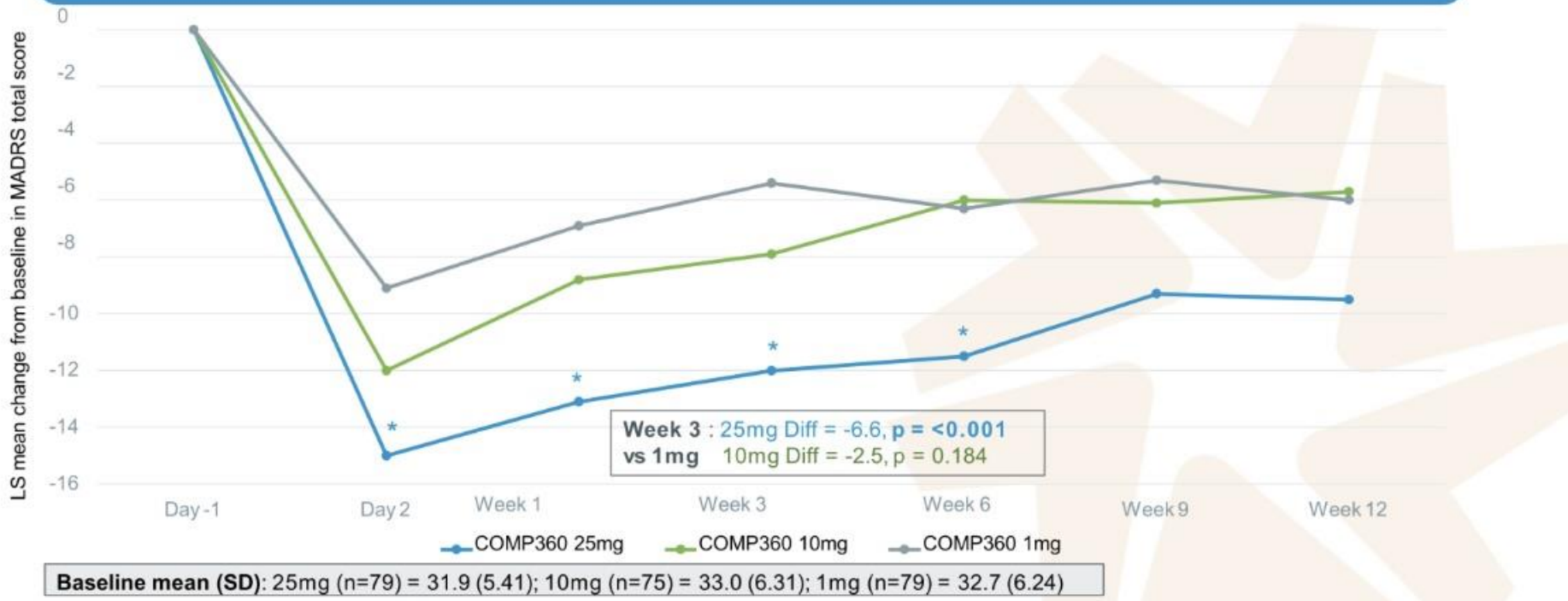


MADRS = Montgomery-Åsberg Depression Rating Scale; EOS = end of study; TRD = treatment-resistant depression; D = day; V = visit.

NOVEL POSSIBILITIES TO TREAT DEPRESSION

Primary Endpoint- Change from Baseline in MADRS Total Score

Statistically significant primary endpoint (p<0.001) at week 3 (25mg vs 1mg). There was a rapid onset of action and durable effects with treatment differences between the 25mg vs 1mg group apparent from the day after COMP360 psilocybin administration



Baseline mean (SD): 25mg (n=79) = 31.9 (5.41); 10mg (n=75) = 33.0 (6.31); 1mg (n=79) = 32.7 (6.24)

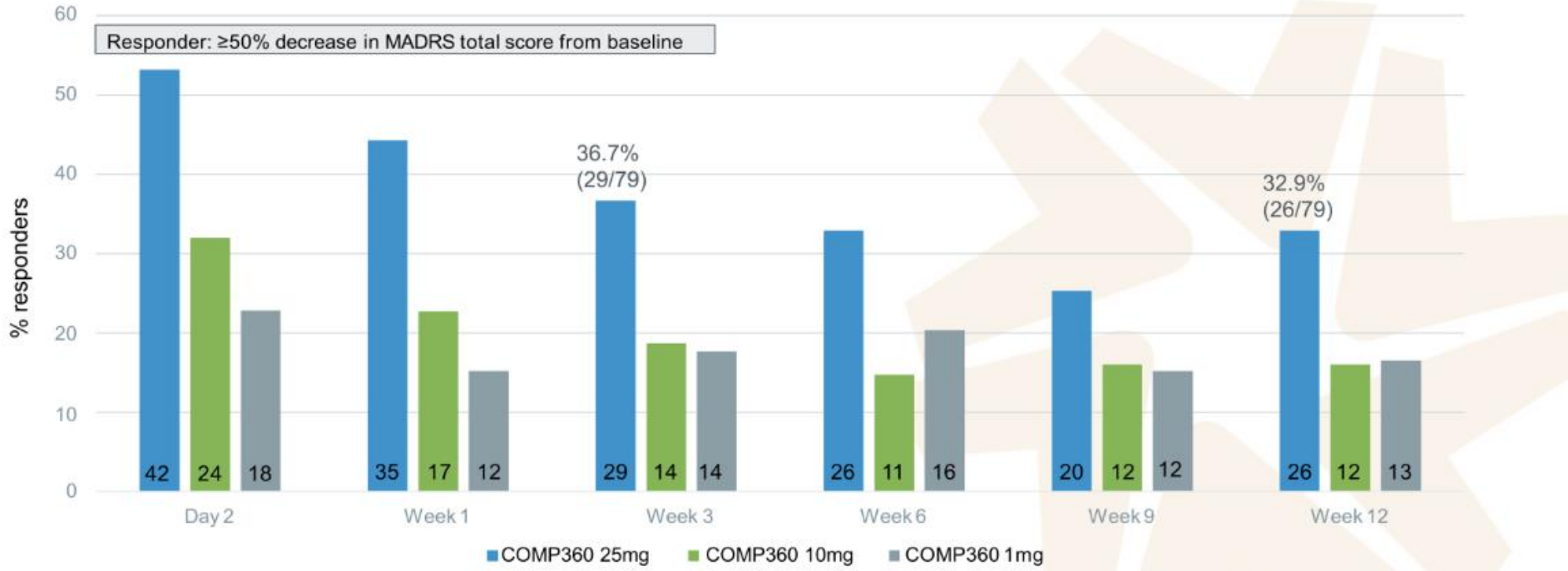
Goodwin et al, N *Eng J Med.* 2022 Nov 3;387(18):1637-1648

Note: MADRS = Montgomery-Åsberg Depression Rating Scale; n = number observed; SD = standard deviation; LS = least squares; * = statistically significant treatment difference vs 1mg at visit; p = p-value

NOVEL POSSIBILITIES TO TREAT DEPRESSION

Key Secondary Endpoint - MADRS Responders

25mg group demonstrated rapid response, with treatment differences from day 2 to week 3 compared with the 1mg group



MADRS = Montgomery-Åsberg Depression Rating Scale. Number of responders stated in bar. Goodwin et al, N Eng J Med 2022 Nov 3;387(18):1637-1648
Participants who started new treatment for depression were assumed to be non-responders, hence decreasing numbers reflecting antidepressant use over time.

RECEPTOR POTENTIAL

Potential Association Between Receptor Blockade and Efficacy

Receptor	Potential Effects of blockade
D_2	Antipsychotic, anti-manic, anti-aggression
D_3	Improve negative symptoms and cognition
a_2 adrenergic	Antidepressant, increased alertness
H_1	Anxiolytic, sleep induction, anti-EPS/akathisia
M_1	Anti-EPS/akathisia
5-HT_{1A} (partial agonism)	Anxiolytic, antidepressant, improve negative symptoms and cognition, anti-EPS/akathisia
5-HT_{2A}	Anti-EPS/akathisia, antipsychotic(?), improve cognition and mood
5-HT_{2C}	Improve cognition/mood
5-HT_7	Antidepressant

Shayegan DK, et al. *CNS Spectr.* 2004;9(10 Suppl 11):6-14.