

Psychopharmacology of Depression: Beyond Monoamines



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Disclosures:

Research support:

- NeoSync
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- Neuropace

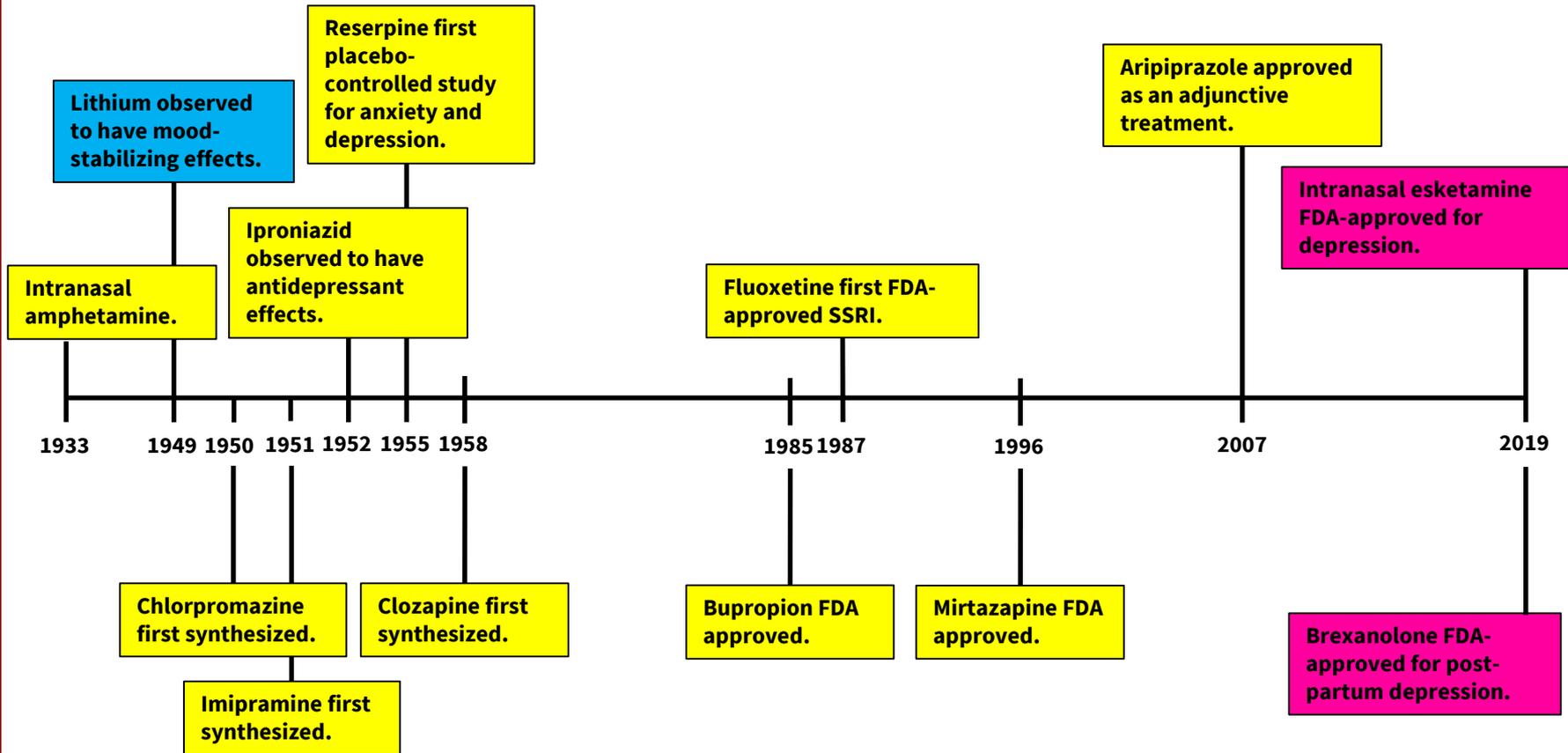
Objectives:

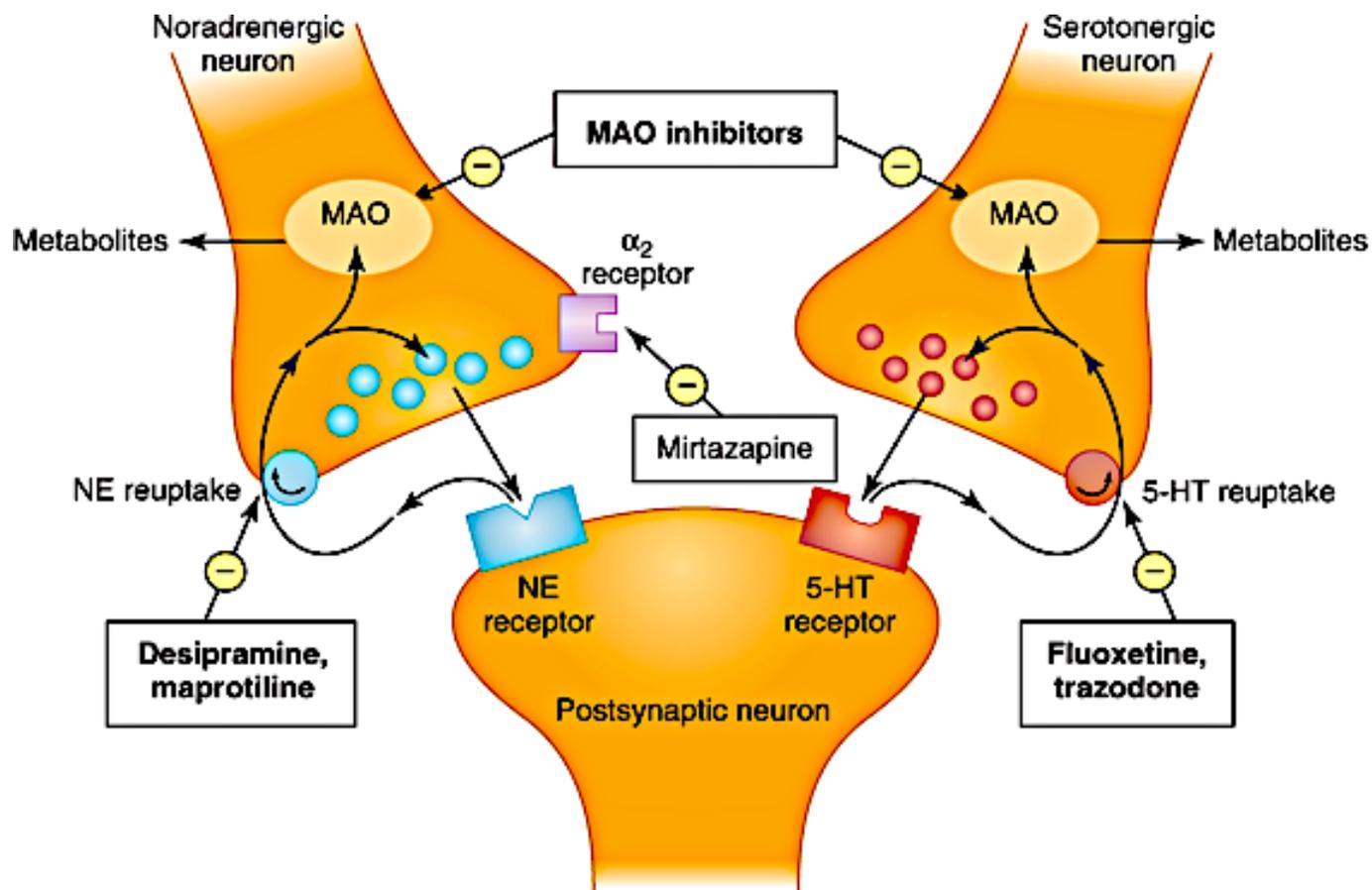
- Understand the monoamine hypothesis of depression and its relevance to modern psychopharmacology.
- Appreciate depression as more than a disturbance in monoamines.
- Learn about novel pharmacological treatments for depression.
- Understand the use of brexanolone and esketamine.
- Appreciate the placebo effect as a way to find novel psychiatric treatments.

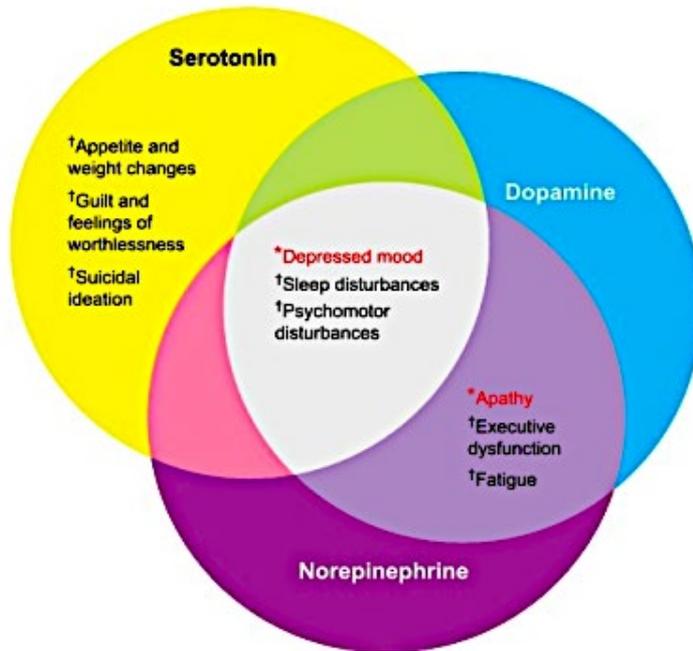
Introduction:

- Psychopharmacology is the study of drug-induced changes in mood, sensation, thinking, and behavior.
- Medications are an important treatment for many psychiatric disorders and some of the most commonly prescribed (and profitable).
- Most psychiatric medications were discovered by serendipity, and their complete mechanism of action remains unknown.
- Most psychiatric medications target monoamine neurotransmitters (serotonin, norepinephrine, dopamine, histamine).
- Psychiatric medications have limited effectiveness.

History:





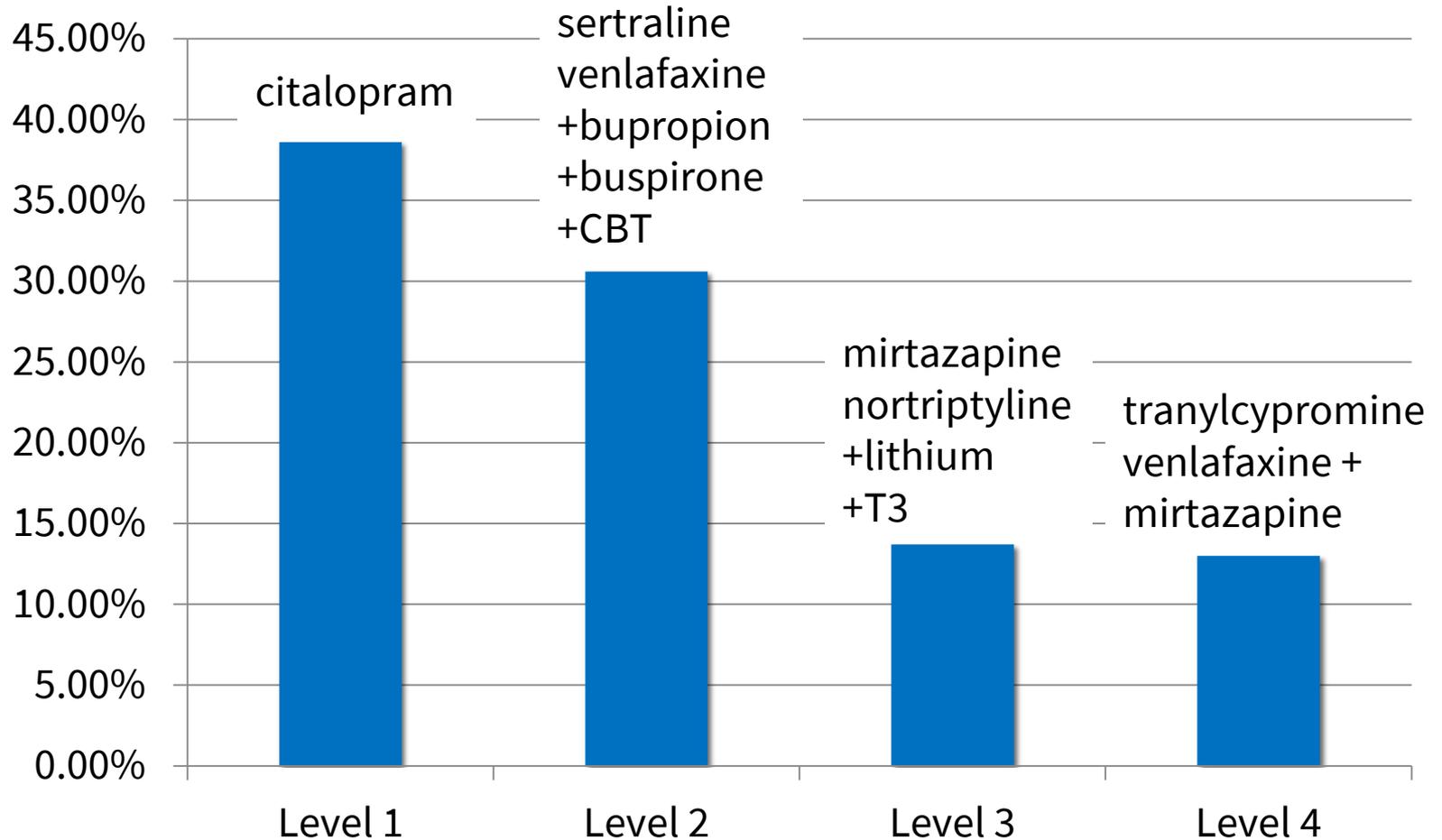


Depression:

- Depression is a heterogeneous group of disorders involving multiple neurotransmitter systems.
- Conventional antidepressant medications primarily modulate monoaminergic neurotransmitters.
- Antidepressants have marginal benefit (10-20%) over placebo.
- 30-40% of depressed patients do not respond to conventional antidepressants.
- One-third of patients have treatment-resistant depression (failure to respond to two or more antidepressant medications).

STAR*D:

Depression Remission Rates



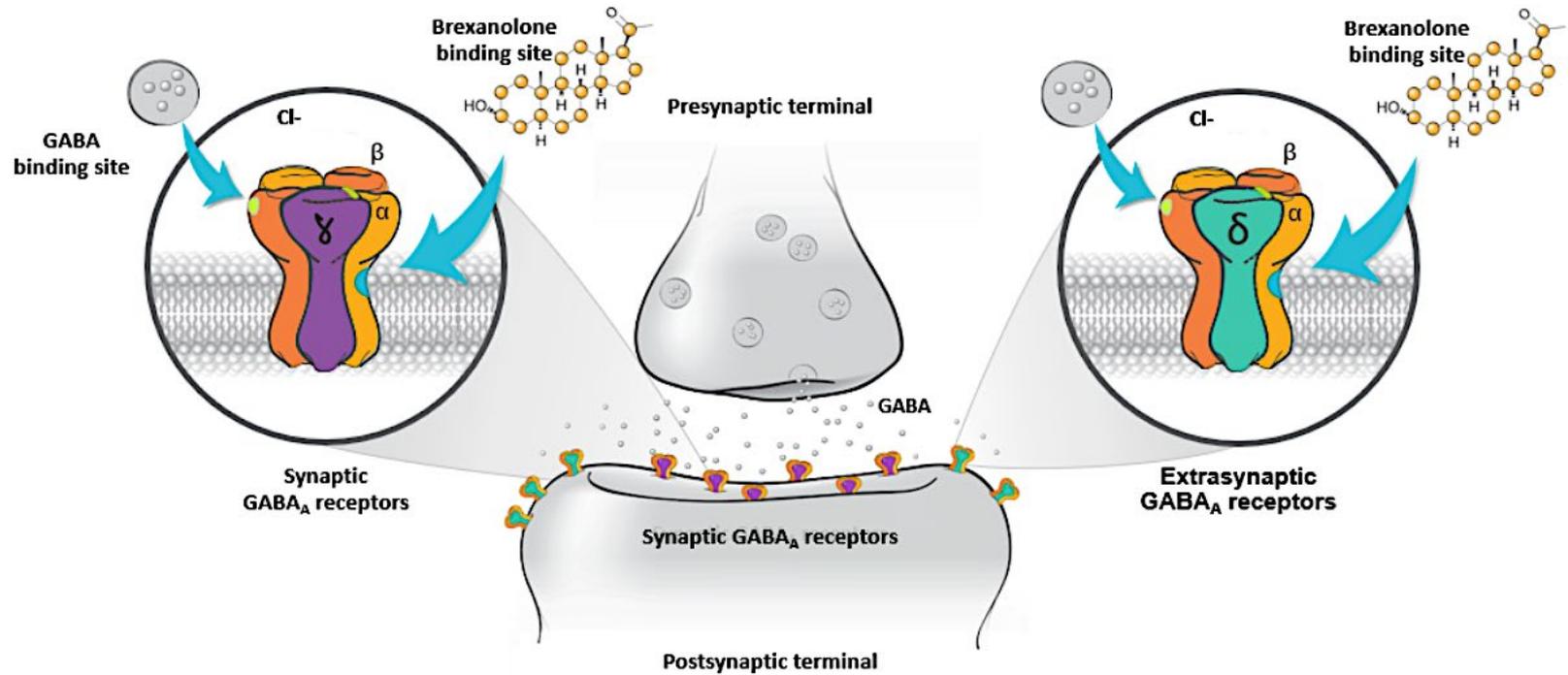
Beyond monoamines:

- Amino acids (GABA, glutamate)
- Acetylcholine
- Amines
- Corticotrophins
- Galanins
- Lipids (cannabinoids)
- Melanocortins
- Neurohypophyseals
- Neuromedins
- Neuropeptides
- Opioids
- Orexins
- Purines
- Secretins
- Somatostatins
- Tachykinins

Brexanolone:

- Brexanolone (allopregnanolone, Zulresso™) FDA-approved for postpartum depression 2019.
- Allopregnanolone is a neurosteroid reduced postpartum and in depression, anxiety, and other psychiatric disorders.
- Repeated and chronic stress leads to a significant reduction in serum concentrations of allopregnanolone.
- Allopregnanolone is a potent allosteric modulator of the GABA_A receptor.
- Additional effects via enhancement of neurogenesis, myelination, neuroprotection, and effects on the HPA axis.
- SSRIs, SNRIs, mirtazapine, TCAs, olanzapine increase allopregnanolone levels.

Brexanolone:



Brexanolone:

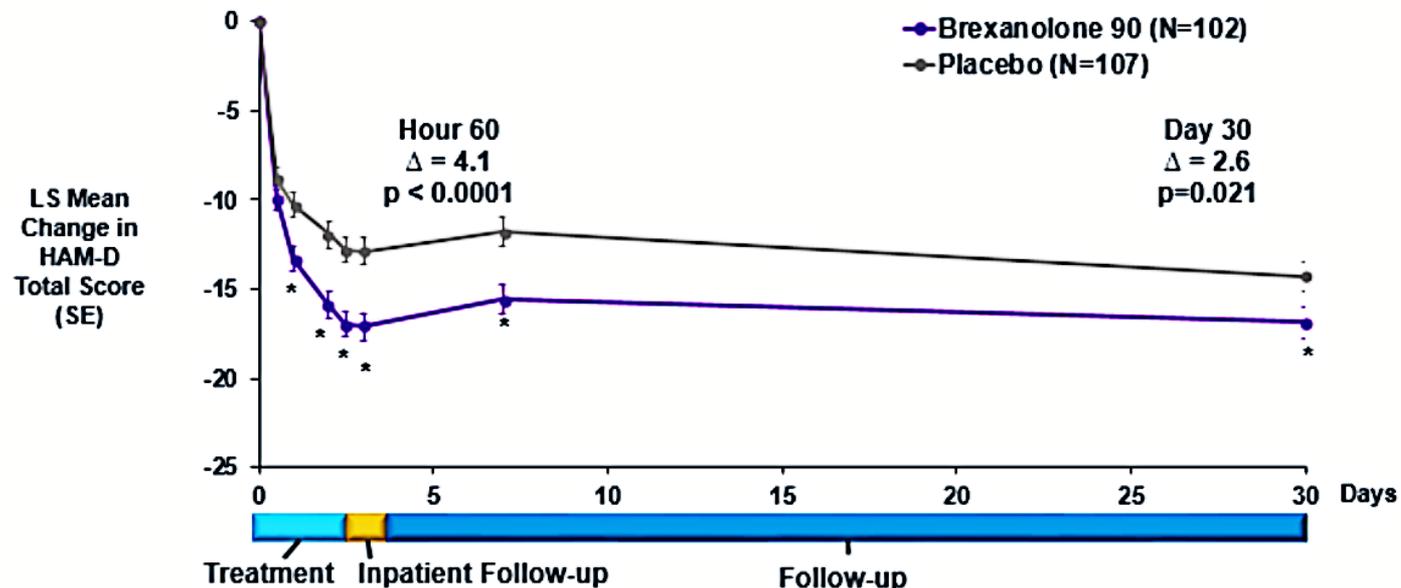
- Dose given by infusion and started at 30 $\mu\text{g}/\text{kg}/\text{hr}$ and increased to 60-90 $\mu\text{g}/\text{kg}/\text{hour}$ for a 60 hour infusion.
- Three placebo-controlled trials showed a rapid antidepressant effect with ~65% reduction in depression symptoms observed after 60 hour infusion.
- Durable antidepressant effect out to 30 days.



Brexanolone injection in post-partum depression: two multicentre, double-blind, randomised, placebo-controlled, phase 3 trials

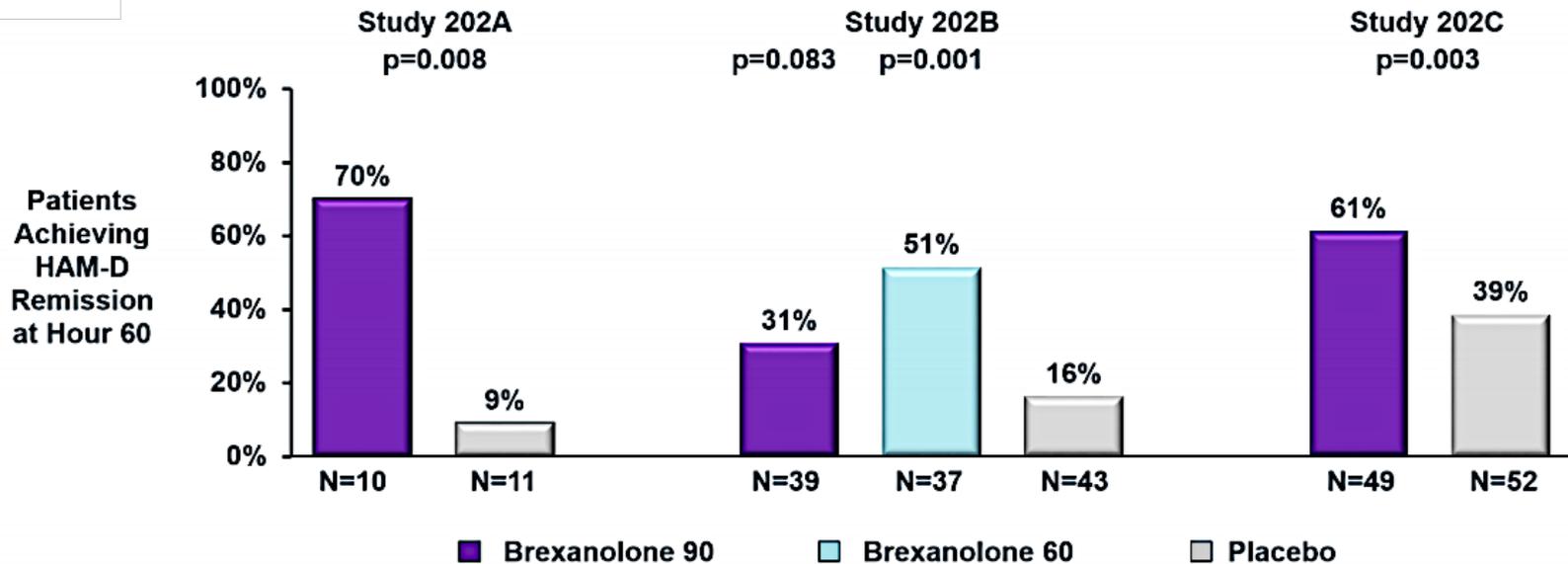
Samantha Meltzer-Brody, Helen Colquhoun, Robert Riesenberg, C Neill Epperson, Kristina M Deligiannidis, David R Rubinow, Haihong Li, Abdul J Sankoh, Christine Clemson, Amy Schacterle, Jeffrey Jonas, Stephen Kaness

Least Squares Mean Change in HAM-D Total Score Over Time for Pooled Key Studies (Full Analysis Set)



Brexanolone:

HAM-D Remission at Hour 60 for Individual Key Studies (Full Analysis Set)



Brexanolone:

- Most common side effects: headache, dizziness, somnolence (~30% patients).
- Used restricted to facilities with estimated cost per treatment: \$34,000.
- Oral version under development (SAGE-217) with antidepressant effects most observed in women. Studies underway in unipolar and bipolar disorder.



SpravatoTM
(esketamine) 
nasal spray 

SPRAVATOTM is
Now Approved

SPRAVATOTM is a prescription medicine, used along with an antidepressant taken by mouth, for treatment-resistant depression (TRD) in adults.

Esketamine:

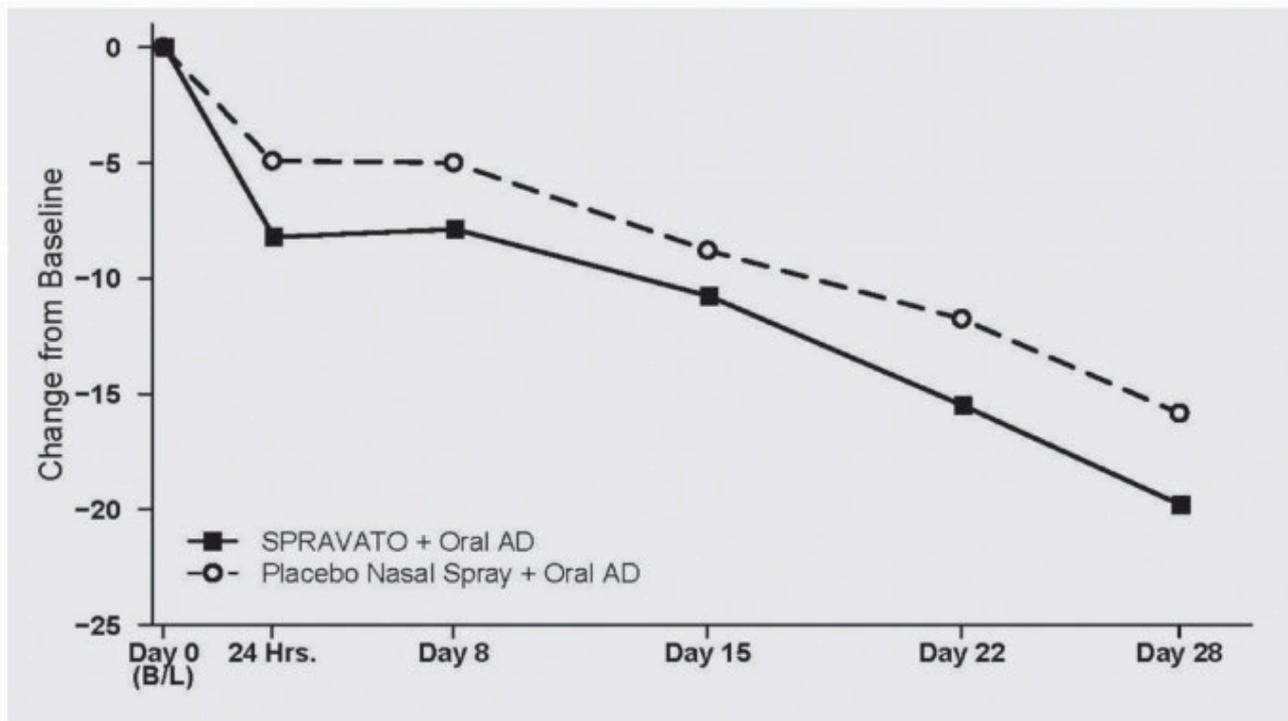
- Esketamine (Spravato™) FDA-approved 2019 for treatment-resistant depression when used in conjunction with an oral antidepressant.
- Used as an anesthetic and acts as a N-methyl-D-aspartate (NMDA) receptor antagonist.
- Intranasally administered (rapid-acting, 28 mg/device). Dosage 56-84 mg starting twice/week for 4 weeks followed by weekly for 4 weeks then biweekly thereafter.
- Potential for abuse (interaction with opiate and dopamine receptors).
- Only available through a restricted distribution system due to sedation and dissociation two hours post-administration.
- Estimated cost of treatment: \$5000/month.

Esketamine:

- Efficacy evaluated in three 4-week placebo controlled trials and a longer maintenance trial with esketamine used in combination with a newly started oral antidepressant.
- 1 of 3 placebo-controlled trials showed statistically significant effect compared to placebo when used in patients with treatment-resistant depression (failure to respond to 2 or more antidepressants).
- Patients who continued treatment with esketamine and an oral antidepressant had a statistically longer time to relapse than patients on placebo.
- Most common side effects were dissociation, dizziness, nausea, sedation, vertigo, decreased feeling or sensitivity (hypoesthesia), anxiety, lethargy, increased blood pressure, vomiting, and feeling drunk.

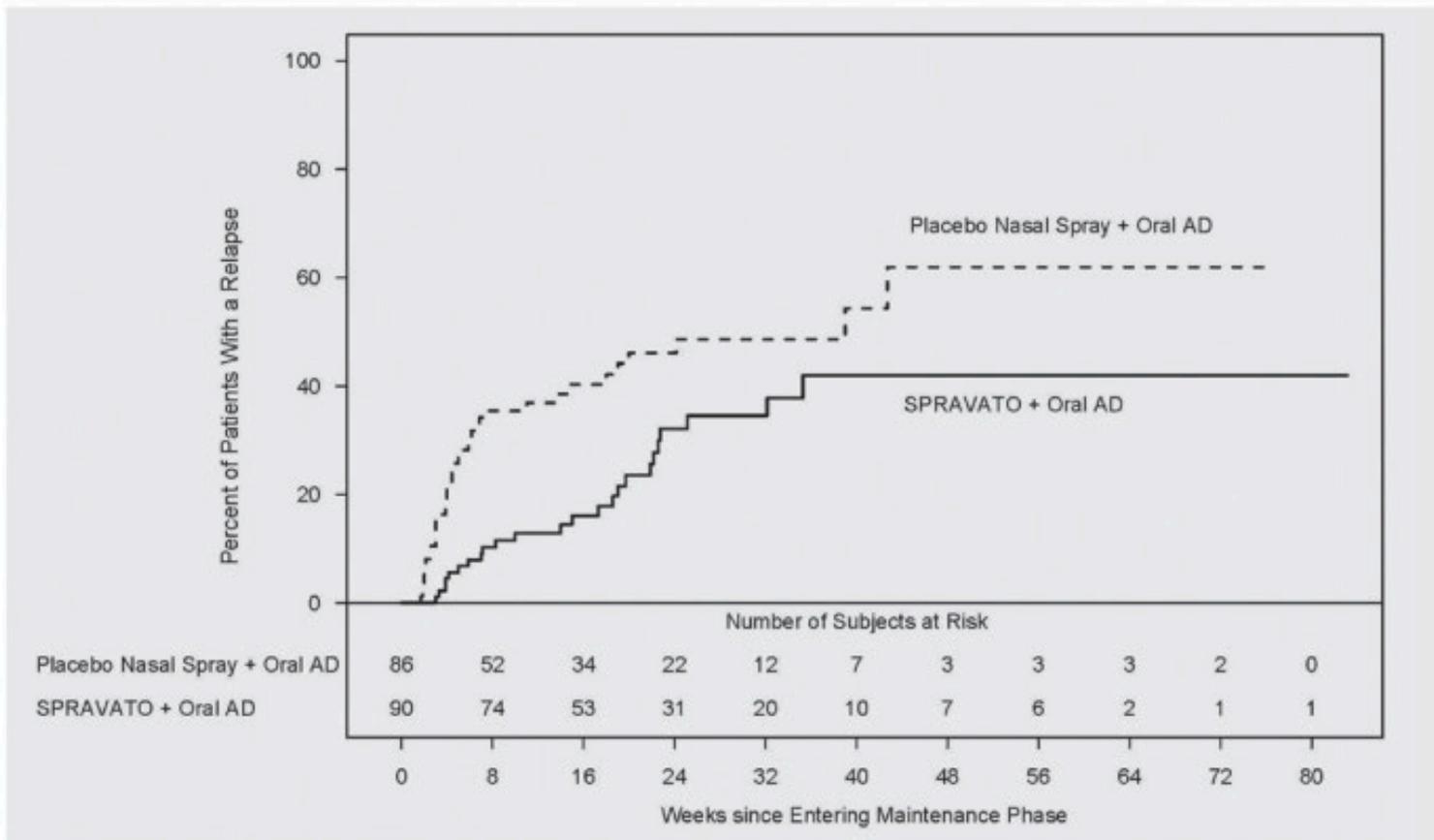
Esketamine:

Treatment Group	Number of Patients	Mean Baseline Score (SD)	LS Mean (SE) Change from Baseline to end of Week 4	LS Mean Difference (95% CI)*
SPRAVATO (56 mg or 84 mg) + Oral AD [†]	114	37.0 (5.7)	-19.8 (1.3)	-4.0 (-7.3; -0.6)
Placebo nasal spray + Oral AD	109	37.3 (5.7)	-15.8 (1.3)	-



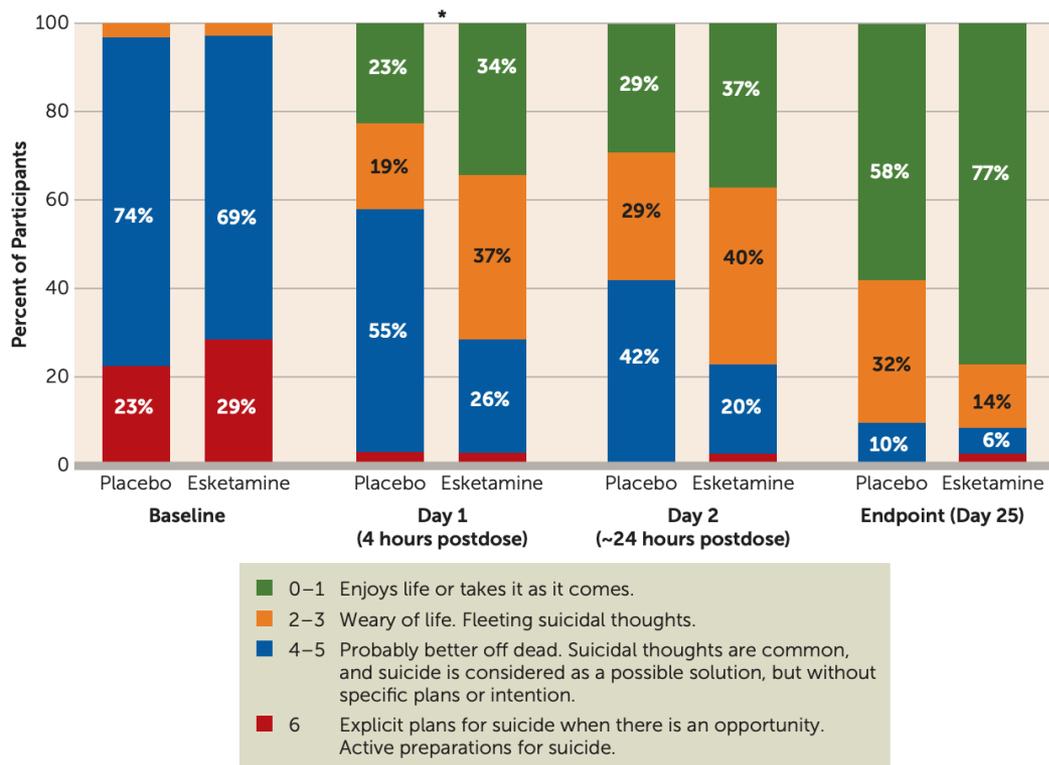
Esketamine:

Figure 5: Time to Relapse in Patients with TRD in Stable Remission in Study 2* (Full Analysis Set)



Efficacy and Safety of Intranasal Esketamine for the Rapid Reduction of Symptoms of Depression and Suicidality in Patients at Imminent Risk for Suicide: Results of a Double-Blind, Randomized, Placebo-Controlled Study

Carla M. Canuso, M.D., Jaskaran B. Singh, M.D., Maggie Fedgchin, Pharm.D., Larry Alphas, M.D., Ph.D., Rosanne Lane, M.A.S., Pilar Lim, Ph.D., Christine Pinter, M.S., David Hough, M.D., Gerard Sanacora, M.D., Ph.D., Husseini Manji, M.D., Wayne C. Drevets, M.D.

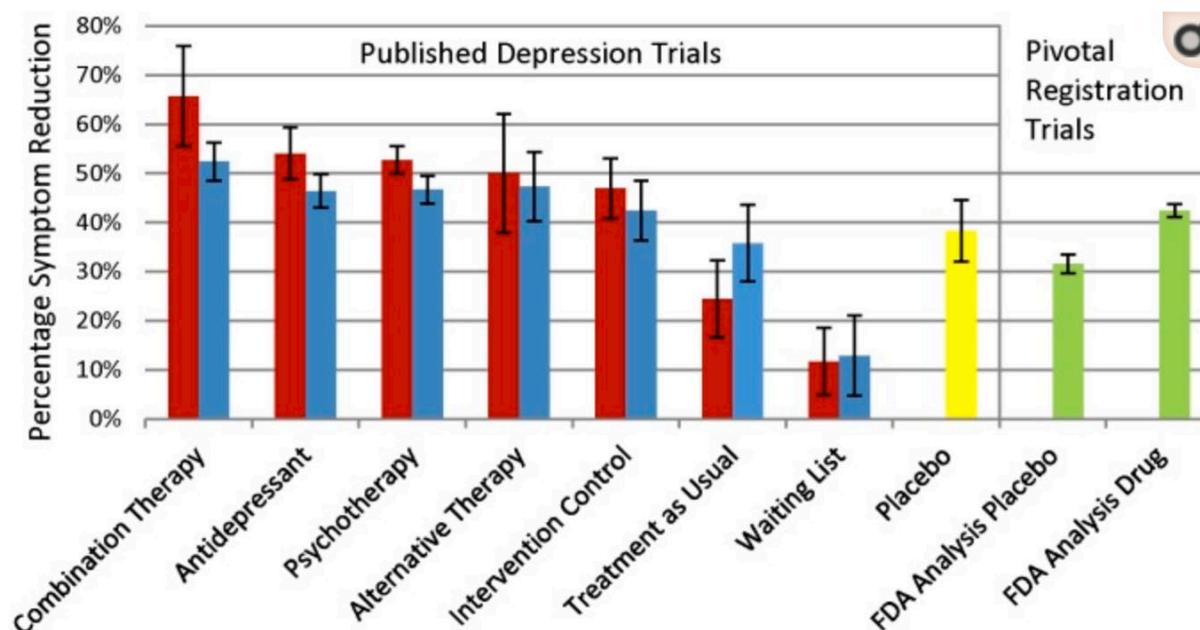


Placebo effects:

- Placebo effects have complicated the development of antidepressants.
- Response to placebos in antidepressant trials are large and consistent observations (with 40-50% responses).
- Antidepressants are marginally (10-20%) more effective than placebos.

A Systematic Review of Comparative Efficacy of Treatments and Controls for Depression

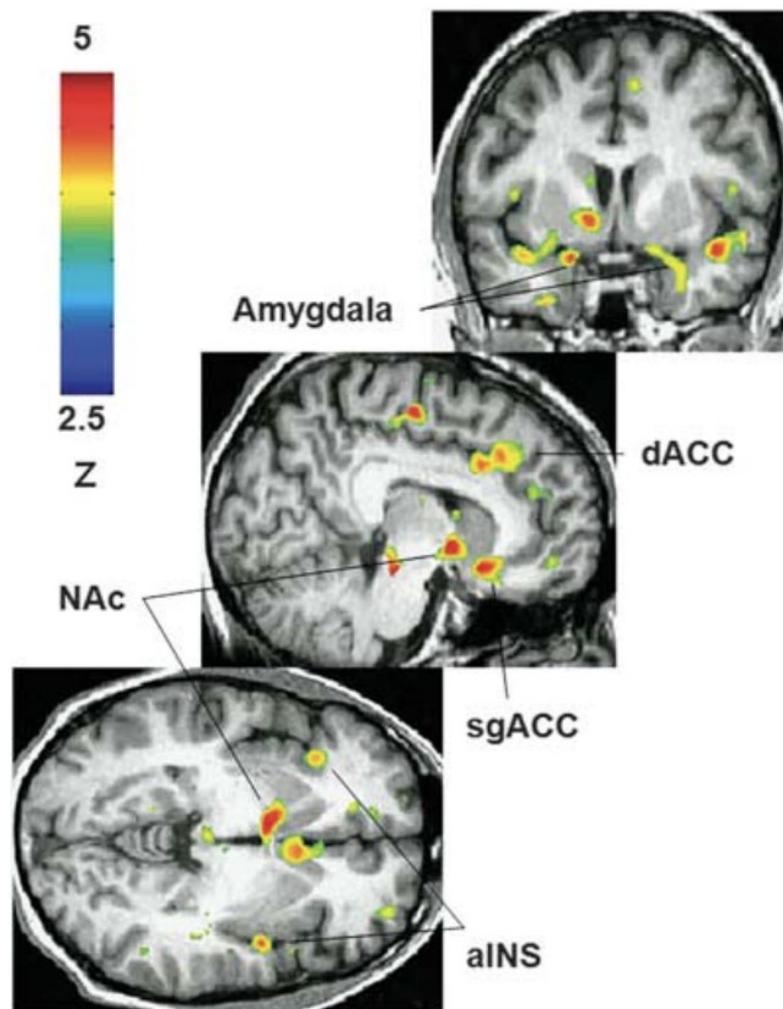
Arif Khan^{1,2*}, James Faucett¹, Pesach Lichtenberg³, Irving Kirsch^{4,5}, Walter A. Brown^{6,7}



Mean Percentage Symptom Reduction from Un-blinded and Blinded Treatment Arms from Published Depression Trials Compared to Data from Pivotal Registration Depression Trials as Reported by the FDA.

Placebo effects:

- Placebo responses are associated with endogenous opioid and non-opioid (dopamine, endocannabinoid) neurotransmitter changes.
- Better understanding the neural basis of the placebo response could lead to potential psychiatric treatments.



(M.Peciña, *Molecular Psychiatry*, 2015)

Conclusions:

- The monoamine hypothesis of depression is an incomplete explanation for understanding and treating depression.
- Conventional psychiatric medications for depression target monoaminergic neurotransmitters with limited benefit.
- Novel medications targeting non-monoaminergic neurotransmitters offer the hope of improved treatments.
- Placebo effects complicate the discovery of new antidepressants, and a better understanding of placebo effects may help develop treatments.