

Neurobiologic Insights into
Major
Depressive
Disorder:

**An Update on Emerging Therapies
with Novel Mechanisms of Action**

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Faculty Disclosure

- **Dr. Thase:** Consultant—Acadia, Inc., Akili, Inc., Alkermes, Inc., Cerecor, Inc., Gerson Lehrman Group, Inc., Guidepoint Global, LLC, Janssen Pharmaceuticals, Inc., H. Lundbeck A/S, MedAvante, Inc., moksha8 Pharmaceuticals, Inc., Novartis International AG, Otsuka Pharmaceutical Co., Ltd., Pfizer Inc., Sage Pharmaceuticals, Sunovion Pharmaceuticals Inc., Takeda Pharmaceutical Company Ltd.; Employment (spouse)—Peloton Advantage (does business with several pharmaceuticals); Grant/Research Support—Acadia, Inc., Agency for Healthcare Research and Quality, Alkermes, Allergan, Inc., AssureRx Health, Inc., Axome, Inc., Intracellular Inc., Janssen Pharmaceuticals, Inc., National Institute of Mental Health, Patient Centered Outcomes Research Institute; Royalties—American Psychiatric Foundation, Guilford Publications, Herald House, W.W. Norton & Company, Inc.

Disclosure

- The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational use(s) of drugs, products, and/or devices (any use not approved by the US Food and Drug Administration).
 - The off-label and investigational use of ketamine, esketamine, rapastinel, lanicemine, ALKS 5461, celecoxib, infliximab, and AXS-05, CERC-301, MIN-117, MIN-202 (seltorexant), and NSI-189 for the treatment of major depressive disorder and treatment-resistant depression; and SAGE-547 for postpartum depression and major depressive disorder will be discussed.
- Applicable CME staff have no relationships to disclose relating to the subject matter of this activity.
- This activity has been independently reviewed for balance.

Learning Objectives

- Outline the significant prevalence and burden of major depressive disorder (MDD) and the limitations of current pharmacotherapeutic approaches to management
- Discuss the current understanding of MDD pathophysiology with respect to the neurobiologic pathways involved and potential therapeutic targets
- Evaluate the clinical and pharmacologic data surrounding MDD pharmacotherapies in late-stage development, in terms of their mechanisms of action, efficacy, and safety in treatment-resistant depression
- Discuss how these novel pharmacotherapies may expand options for evidence-based management of MDD

Depression is One of the World's Greatest Public Health Problems

- Depressive Disorders comprise the world's second greatest public health problem
 - MDD has a point prevalence of about 8% in the United States
 - Bipolar disorder (I and II) has a 3% point prevalence
- MDD is the greatest cause of workplace disability; bipolar disorder is the 8th greatest cause of disability
- Mood disorders are highly comorbid and amplify the disease burden of co-occurring conditions
- Mood disorders are implicated in three-quarters of suicides

MDD = major depressive disorder.

Kessler RC. *Psychiatr Clin North Am.* 2012;35(1):1-14. Kessler RC, et al. *Annu Rev Clin Psychol.* 2007;3:137-158.

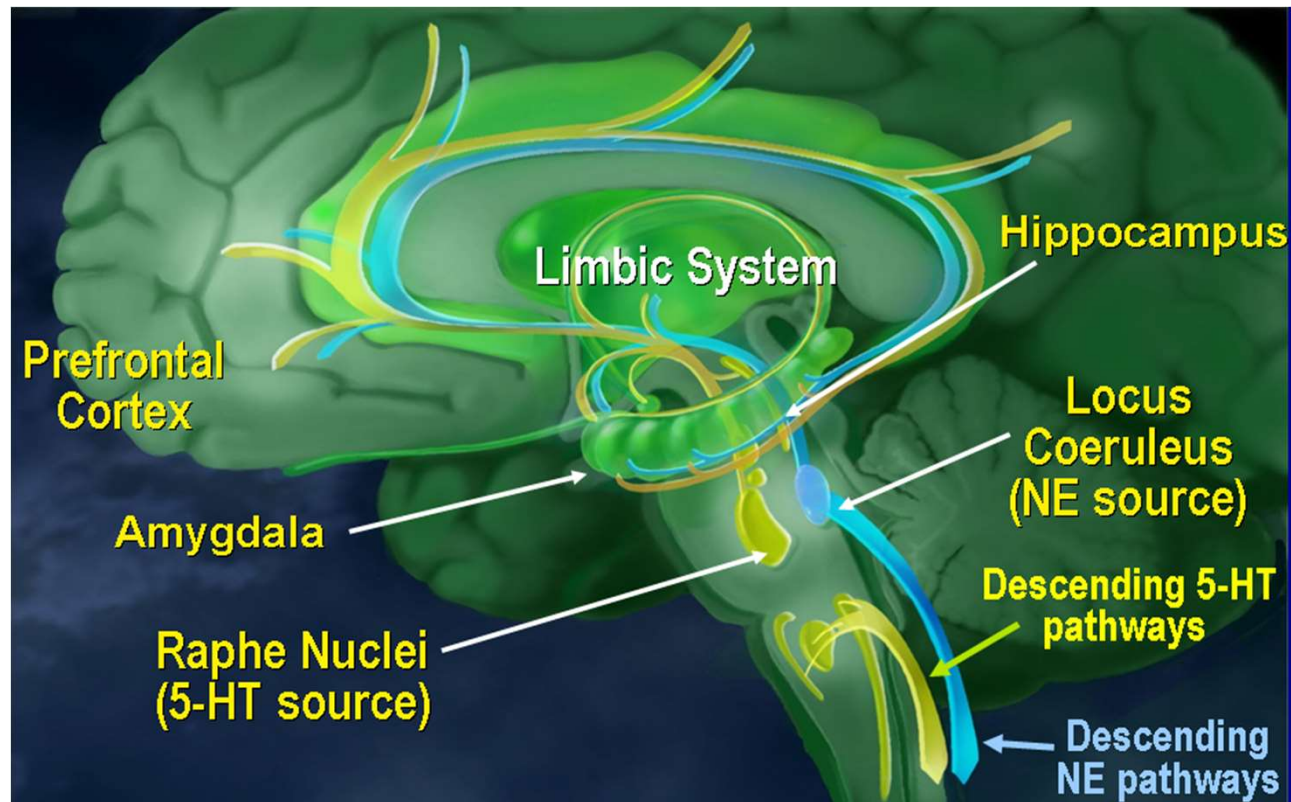
Antidepressant Drugs: Unmet Needs Circa 2018

- Limited specific efficacy (~10% to 20% advantage vs placebo in RCTs)
- Intolerable side effects for 10%
- Inconsistent effects on key symptoms (insomnia, anxiety)
- Relatively slow onset of action
- Better alternatives for nonresponders

RCT = randomized controlled trial.

Thase ME. *CNS Spectr.* 2017;22(S1):39-48.

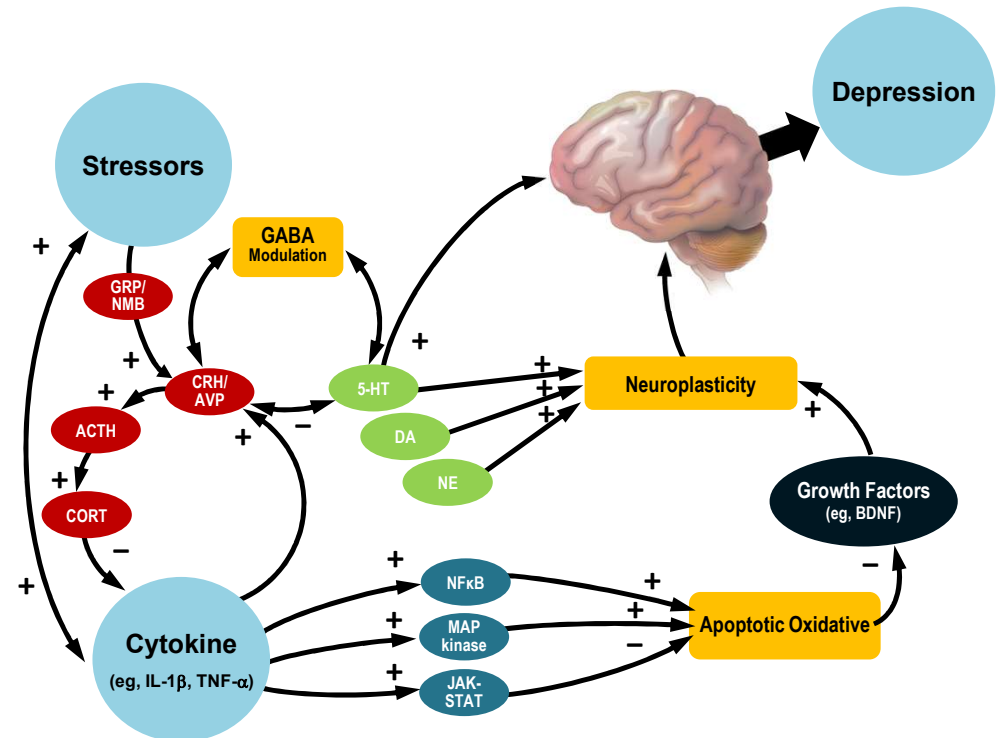
Serotonin (5-HT) and Norepinephrine (NE) Pathways in the Human Brain



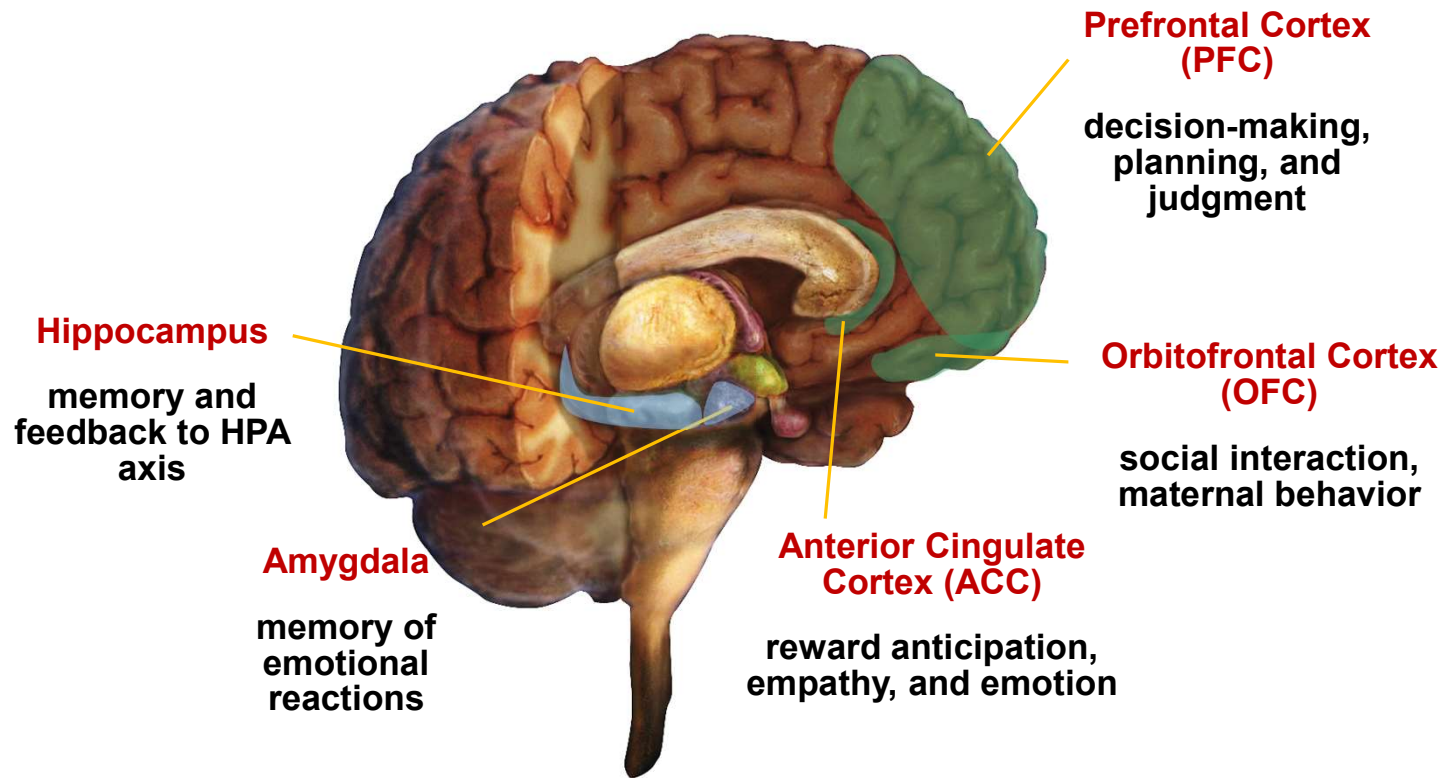
Cooper JR, et al. *The Biochemical Basis of Neuropharmacology*. Eighth Edition. New York, NY: Oxford University Press; 2003.

Neurobiology of Depression is Multidetermined and Multifactorial

- Recurrent depressive episodes may result in enduring functional and structural alterations in the sensitive brain areas
- Disruption in corticolimbic circuitry may create neuroendocrine, neuroimmune, and sympathetic dysregulation
- Inadequate monoamine and neurotrophic signaling combined with excessive glutaminergic and inflammatory cytokine transmission may precipitate a “breakdown” in vulnerable glia-neuron units
- An altered glia-neuron relationship may then further impede corticolimbic processing



Many Areas of the Brain are Implicated in Depression

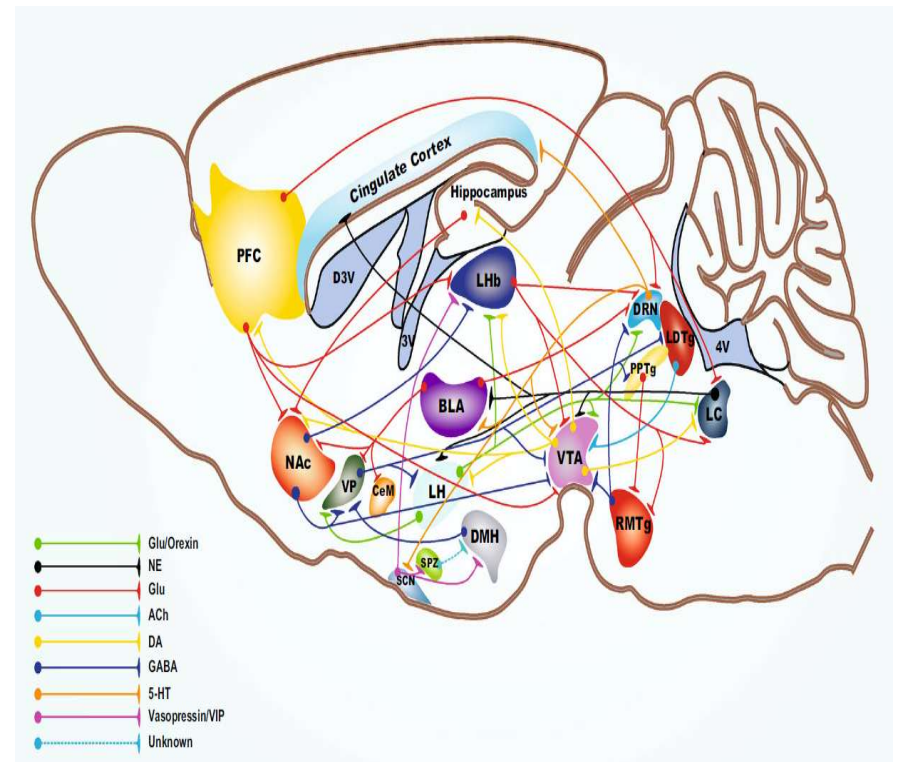


HPA = hypothalamic–pituitary–adrenal.

Charney DS, et al (Eds). *Neurobiology of Mental Illness*. Second Edition. Oxford University Press; 2004. Ongür D, et al. *Cereb Cortex*. 2000;10(3):206-219. Drevets WC. *Annu Rev Med*. 1998;49:341-361. MacDonald AW 3rd, et al. *Science*. 2000;288(5472):1835-1838. Nitschke JB, et al. *Neuroimage*. 2004;21(2):583-592. Kringelbach ML, et al. *PLoS One*. 2008;3(2):e1664.

Disruption of Functional and Structural Neural Circuits Underlie Dysregulation of Mood and Function in MDD

- Simplified schematic of brain regions and their major neural circuit connections implicated in depression-related behaviors

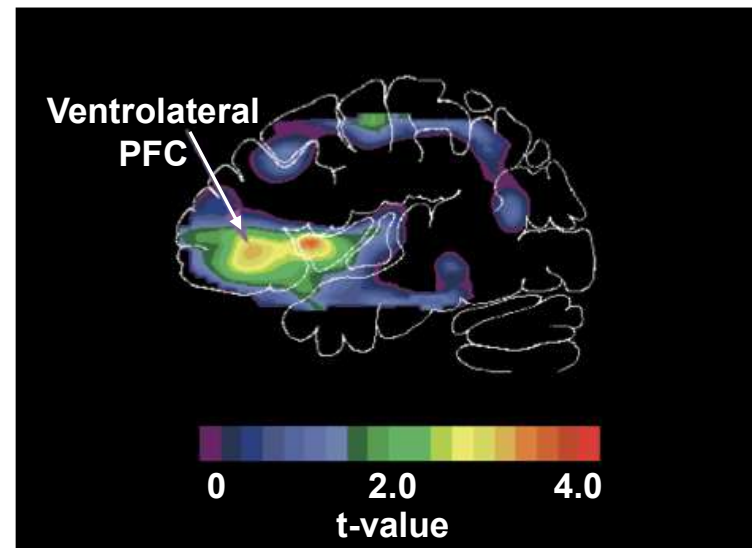
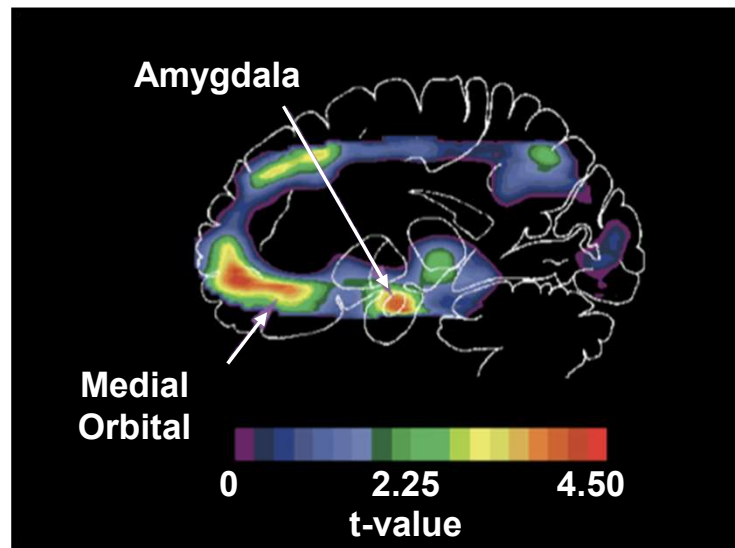


3V = third ventricle; 4V = fourth ventricle; Ach = acetylcholine; BLA = basolateral complex of the amygdala; CeM = central amygdala; D3V = dorsal third ventricle; DA = dopamine; DMH = dorsomedial nucleus of the hypothalamus; DRN = dorsal raphe nucleus; GABA = gamma-aminobutyric acid; Glu = glutamate; LC = locus coeruleus; LDTg = laterodorsal tegmental nucleus; LH = lateral hypothalamus; LHb = lateral habenula; Nac = nucleus accumbens; PPTg = pedunculopontine tegmental nucleus; RMTg = rostromedial tegmental nucleus; SCN = suprachiasmatic nucleus; SPZ = subparaventricular zone; VIP = vasoactive intestinal peptide; VP = ventral pallidum; VTA = ventral tegmental area.

Chaudhury D, et al. *Cell Mol Life Sci.* 2015;72(24):4825-4848. Duman RS, et al. *Nat Med.* 2016;22(3):238-249. Saltiel PF, et al. *Neuropsychiatr Dis Treat.* 2015;11:875-888.

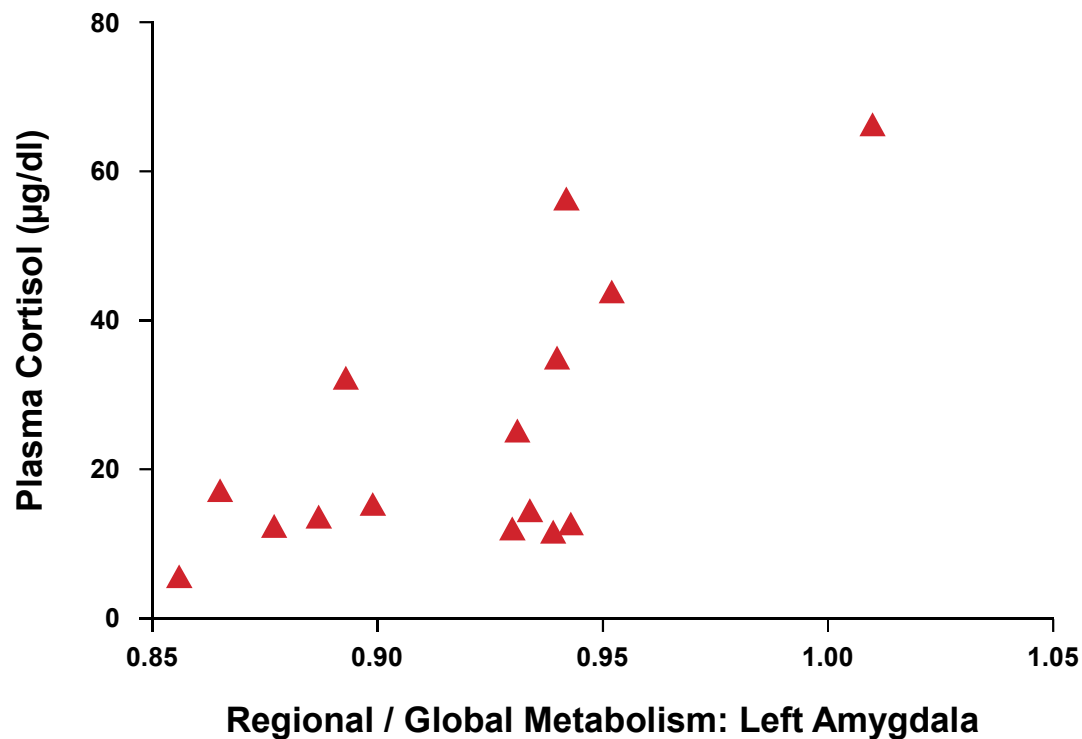
MDD Associated with Increased Blood Flow in the Amygdala and Ventrolateral PFC

Increased Blood Flow (Areas in Red) in Patients with Depression



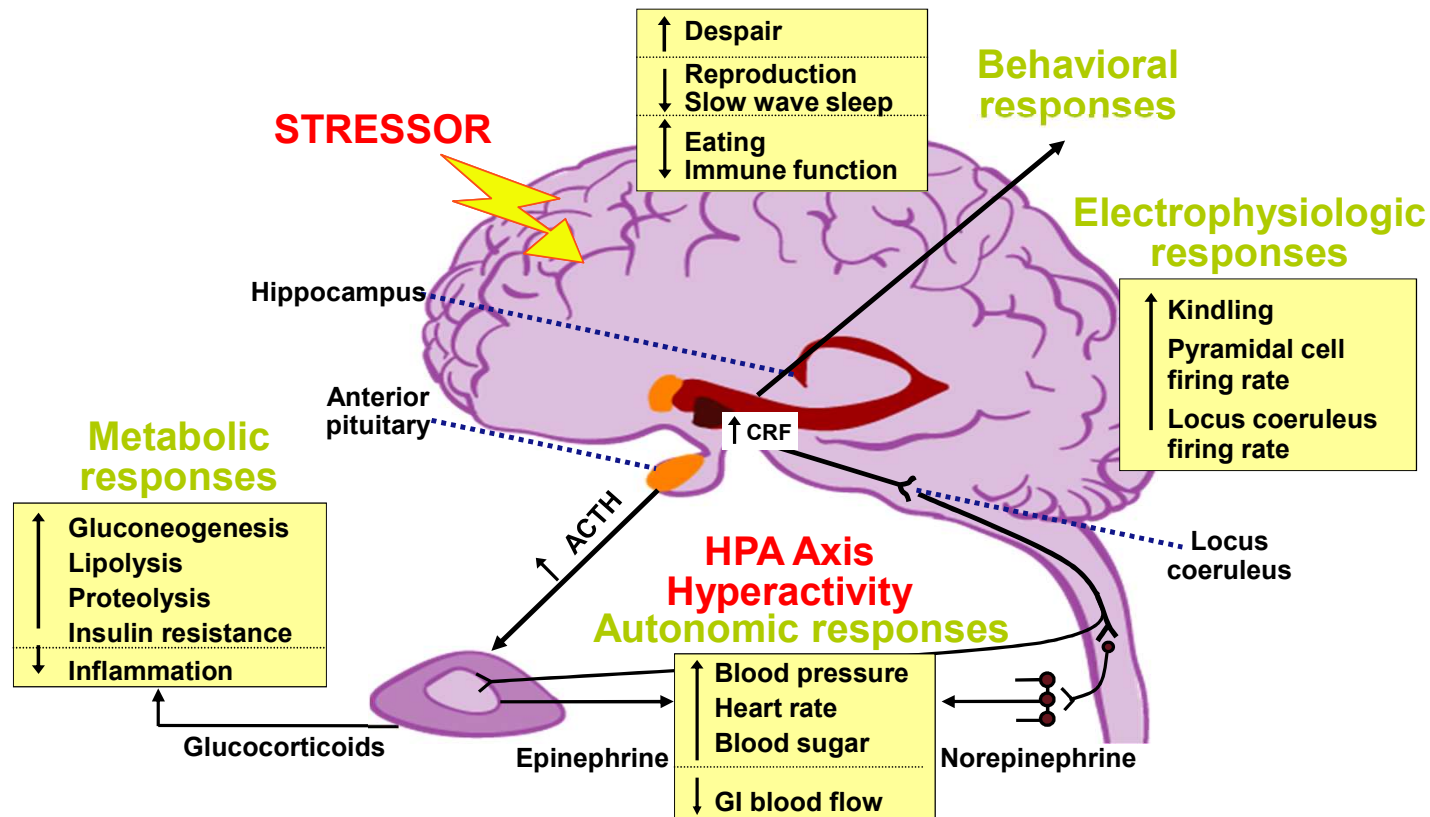
Patients with depression (n=13) had increased blood flow in the amygdala and left medial and lateral orbital cortex, extending to ventrolateral PFC, relative to healthy controls (n=33).

Increased Amygdala Metabolism Associated with Elevated Plasma Cortisol Level



Drevets WC, et al. *Pharmacol Biochem Behav.* 2002;71(3):431-447.

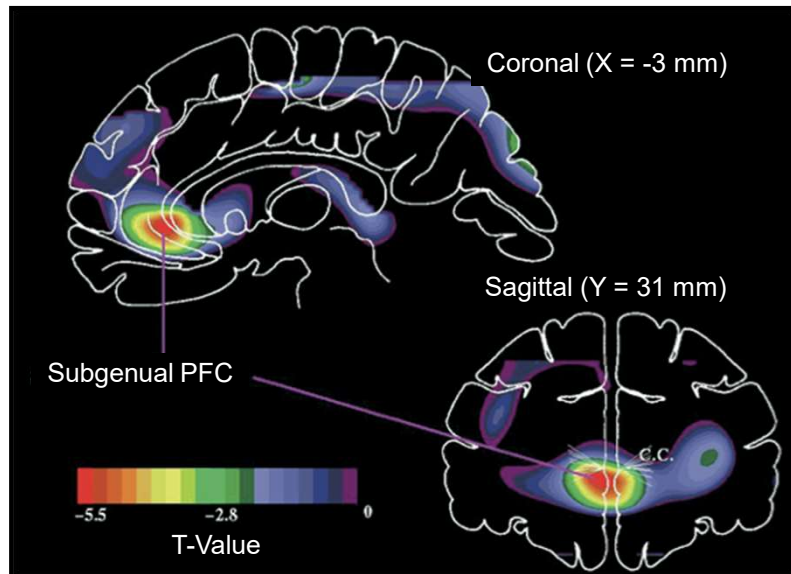
Model for Chronic Activation of Stress Responses in MDD



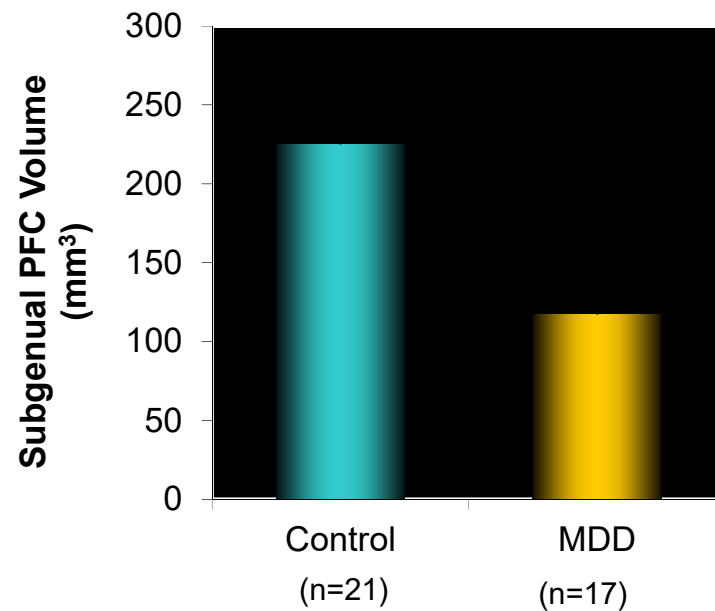
CRF = corticotropin-releasing factor; ACTH = adrenocorticotrophic hormone; GI = gastrointestinal.
 Arborelius L, et al. *J Endocrinol.* 1999;160(1):1-12.

MDD Impacts Function and Structure of the Subgenual Anterior Cingulate

Decreased Metabolism Relative to Controls



48% Less Volume in MDD



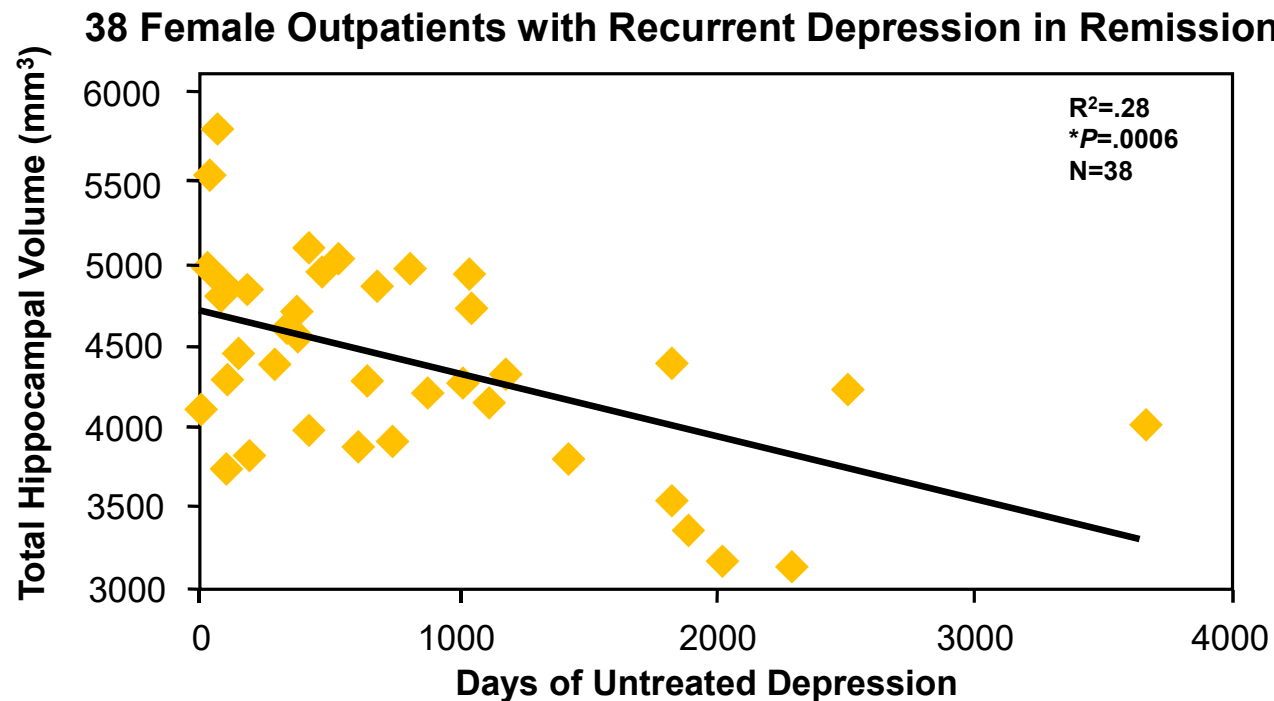
Evidence of Hippocampal Atrophy and Loss in Patients with MDD



- Compared to controls, patients with depression had smaller hippocampal volumes (n=16)
- Decreased hippocampal volume may be related to the duration of depression

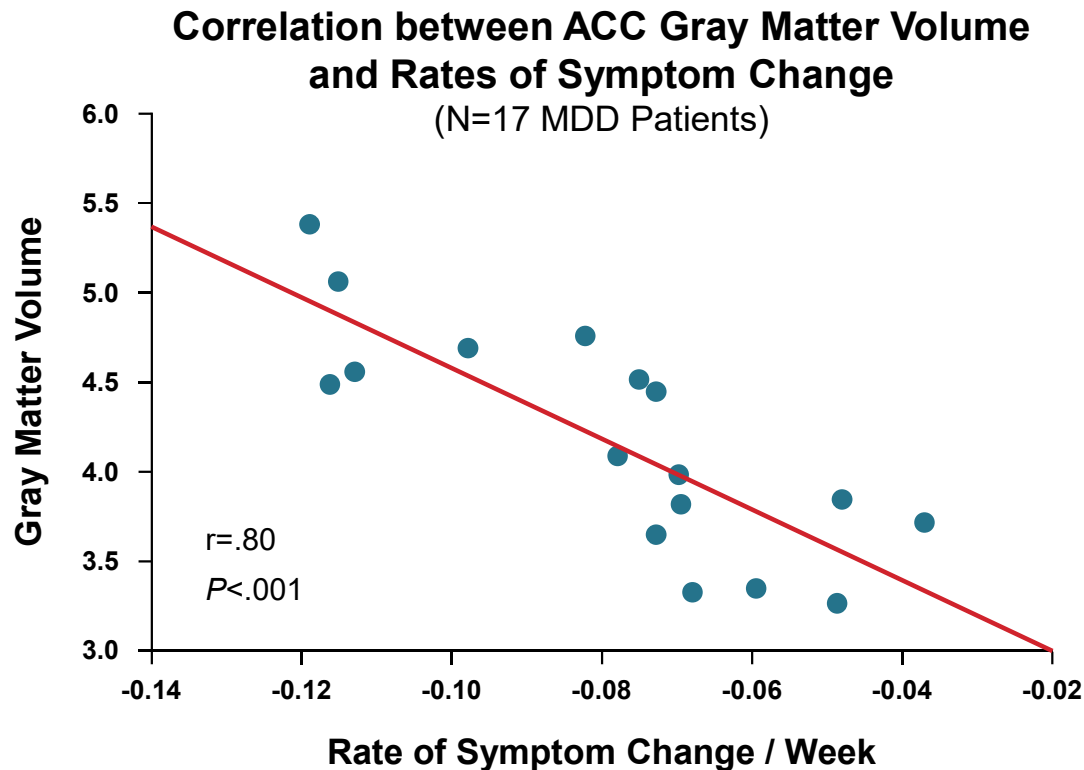
Bremner JD, et al. *Am J Psychiatry*. 2000;157(1):115-118. Sheline YI, et al. *J Neurosci*. 1999;19(12):5034-5043. *Proc Natl Acad Sci U S A*. 1996;93(9):3908-3913. Sheline YI, et al. *Am J Psychiatry*. 2003;160(8):1516-1518.

Correlation between Hippocampal Volume and Duration of Untreated Depression



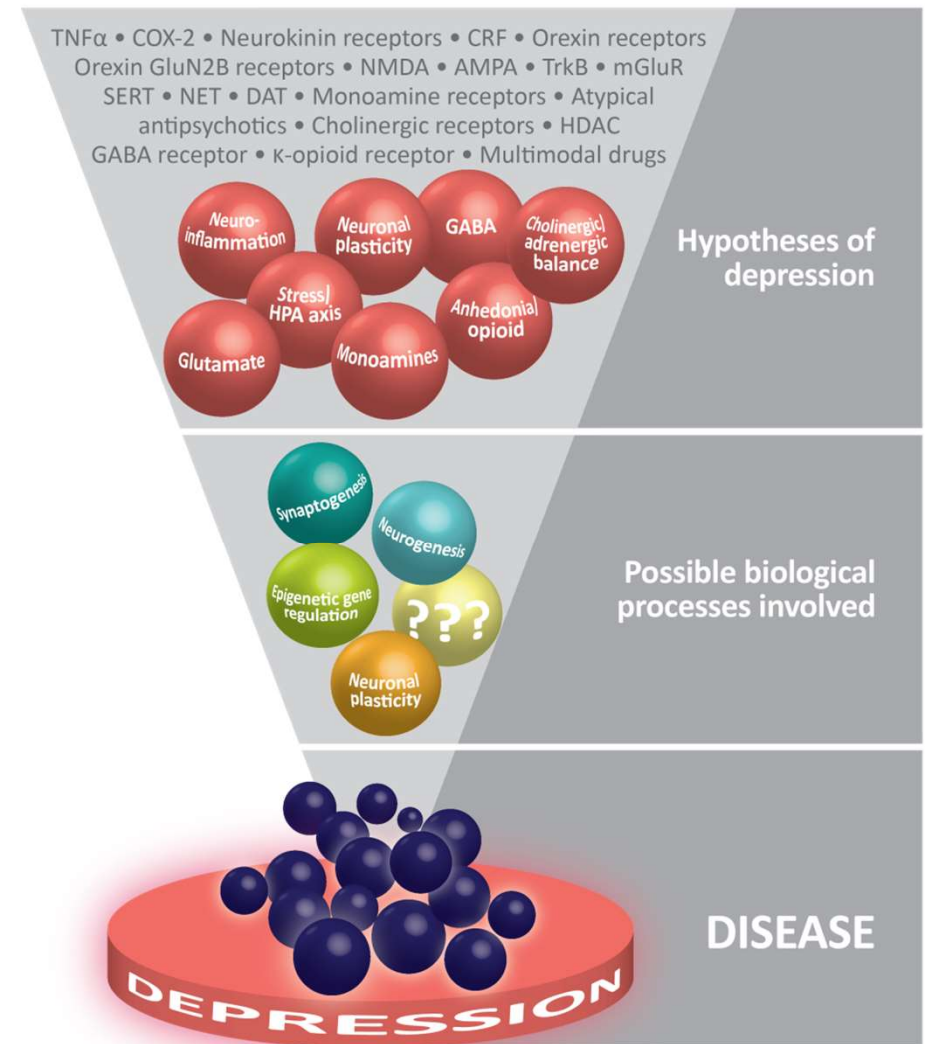
There was a significant inverse relationship between total hippocampal volume and the length of time depression went untreated

Greater Volume and Activity of ACC May Be Associated with Faster Treatment Response



- Patients with greater subgenual ACC volume had faster improvement and fewer residual symptoms

Neurobiologic Effects of MDD Extend Beyond the Monoamine Pathways

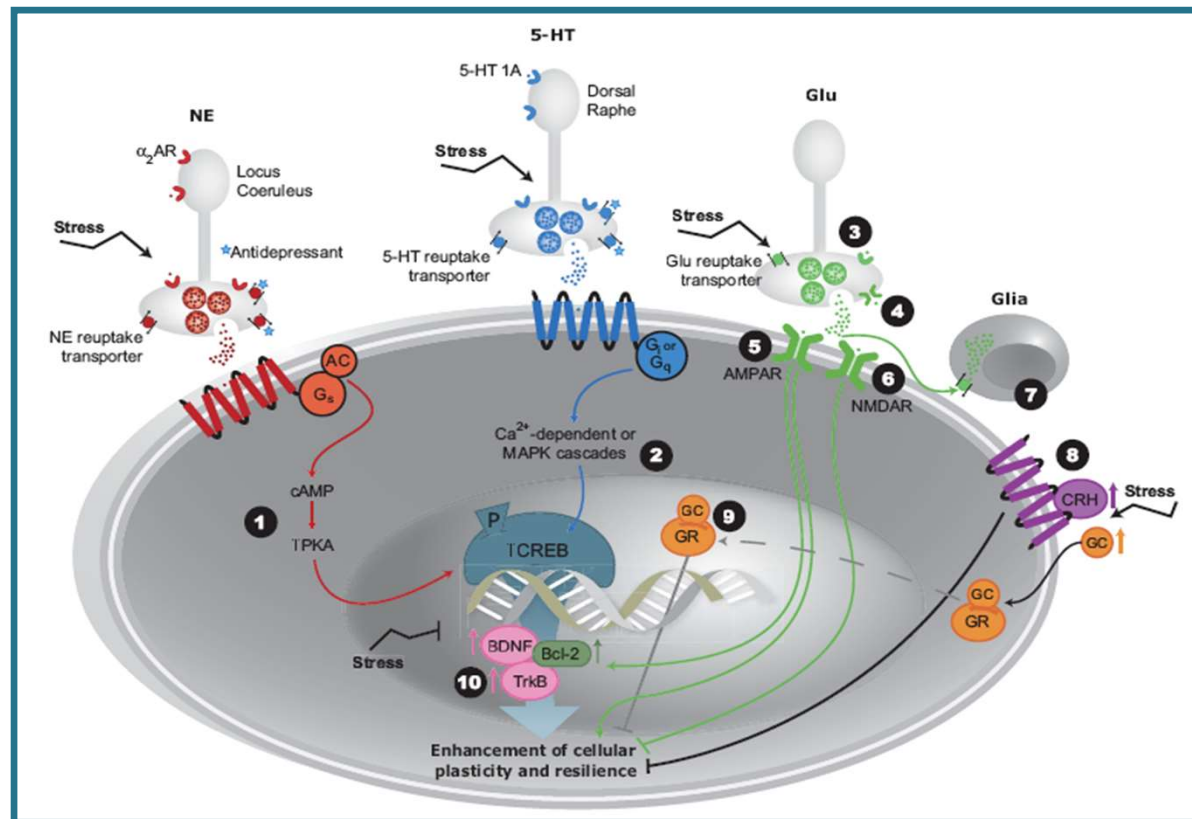


Dale E, et al. *Biochem Pharmacol*. 2015;95(2):81-97.

Other Relevant Targets for Antidepressant Interventions

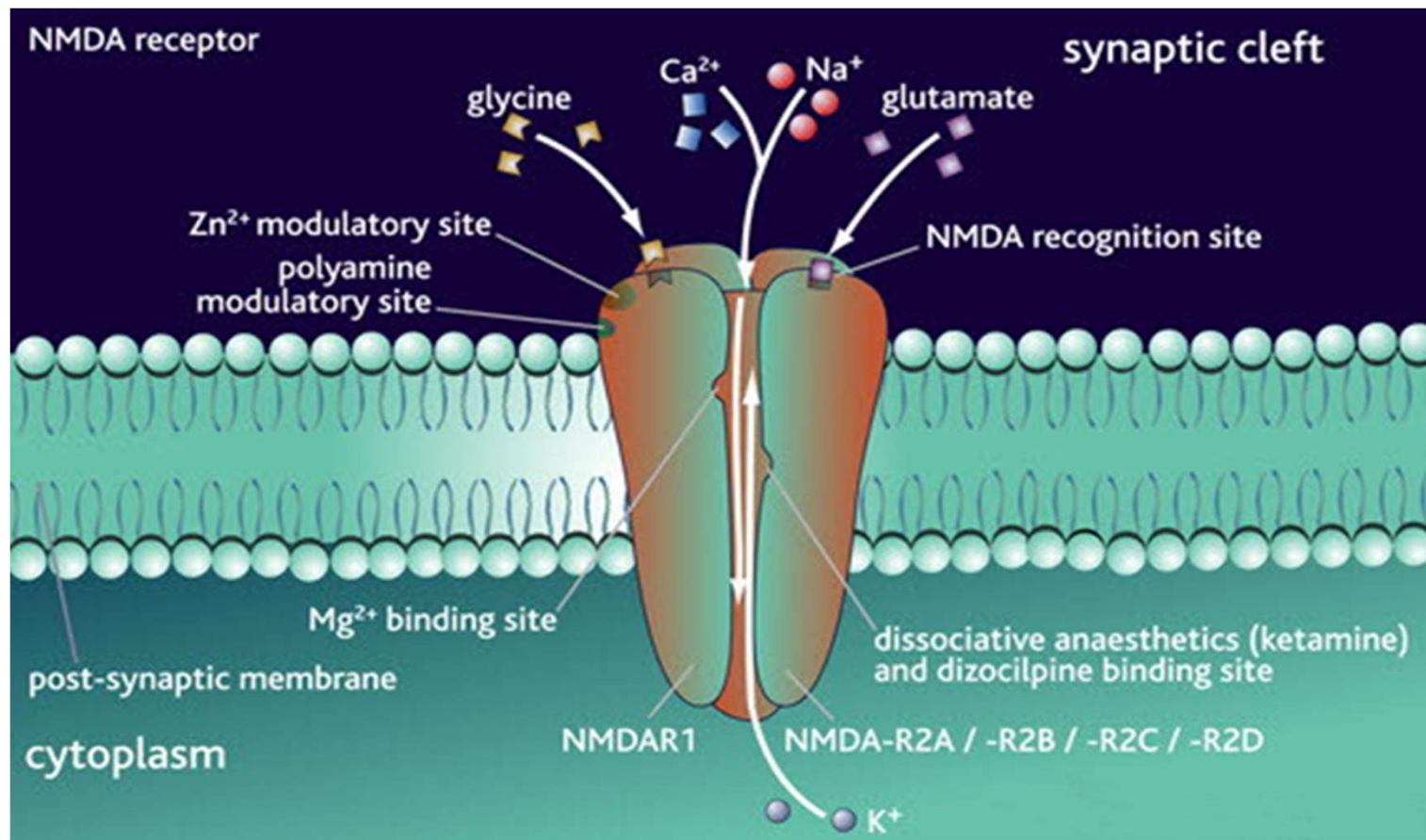
- Glutamate and Glycine
- GABA
- Endogenous Opioids
- Inflammatory Cytokines

Conventional and Several Novel Targets to Modulate Signaling Cascades



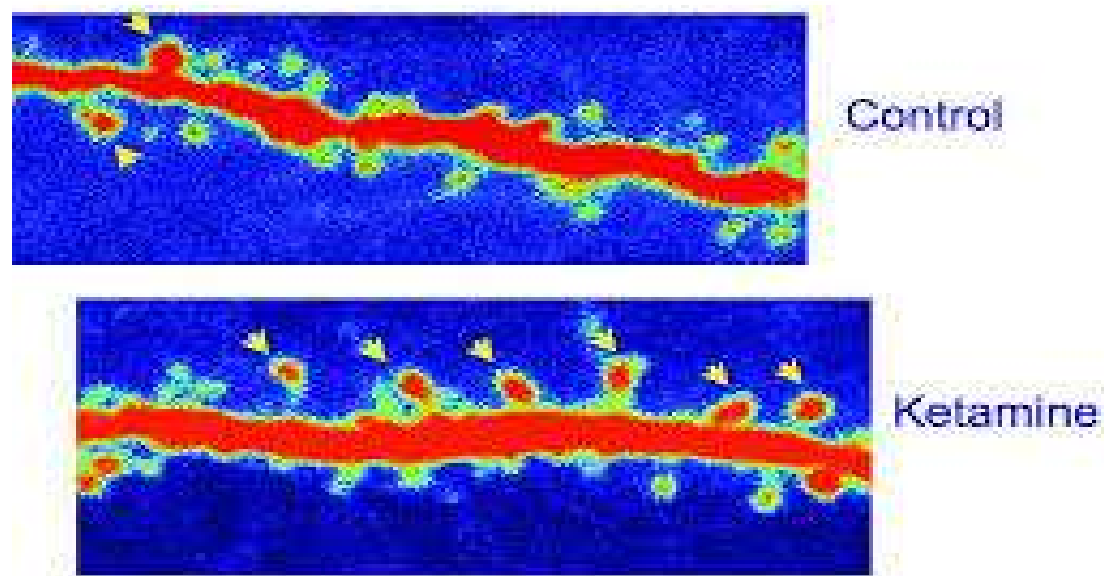
Charney DS, et al. *Sci STKE*. 2004;2004(225):re5.

NMDA Receptor: The Target of the Decade



NMDA = N-methyl-D-aspartate.

Ketamine Infusion Rapidly Enhances Neuronal Connectivity



Li N, et al. *Biol Psychiatry*. 2011;69(8):754-761.

Ketamine: The Greatest Thing for TRD Since ECT?

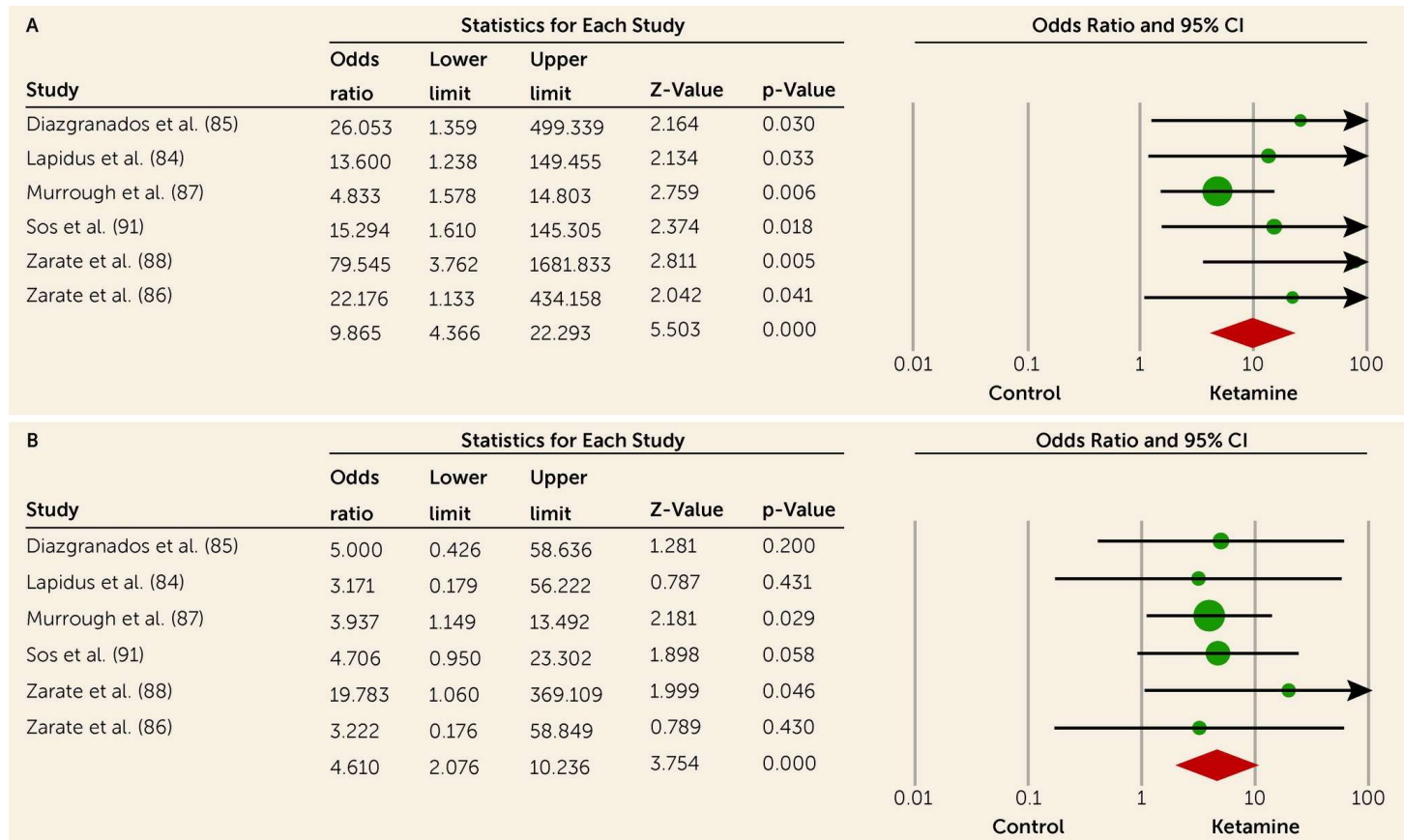
- Dissociative anesthetic with significant psychotomimetic properties
- An NMDA antagonist, related to PCP and a controlled substance because of recreational abuse potential
- Rapid and dramatic effects on depressive symptoms serendipitously observed in depressed “controls”
- Data from controlled studies progressively increasing since 2006

TRD = treatment-resistant depression; PCP = phencyclidine; ECT = electroconvulsive therapy.

Ketamine State of the Art: 2018

- Effective dose: 0.4–0.5 mg/kg infused over 40 minutes 2–3 ×/week
- Antidepressant effect typically evident within 2–3 doses; unrelated to psychotomimetic/dissociative effects
- Efficacy established across 3–4 weeks
- Clinical evidence of sustained benefit with once or twice weekly doses for months/years (Level III evidence)

IV Ketamine: Efficacy in TRD



Newport DJ, et al. *Am J Psychiatry*. 2015;172(10):950-966.

Ketamine: Important Unknowns

- Will tolerance develop with repeated doses?
- What is the risk of neurotoxicity after months/years of repeated doses?
- Can short-term treatment with ketamine restore the efficacy of standard therapies?
- Complexity of NMDA receptor suggests antidepressant effect can be uncoupled from psychotomimetic effects

Investigational Alternatives to Ketamine:

A Brief List of Glutamatergic Strategies

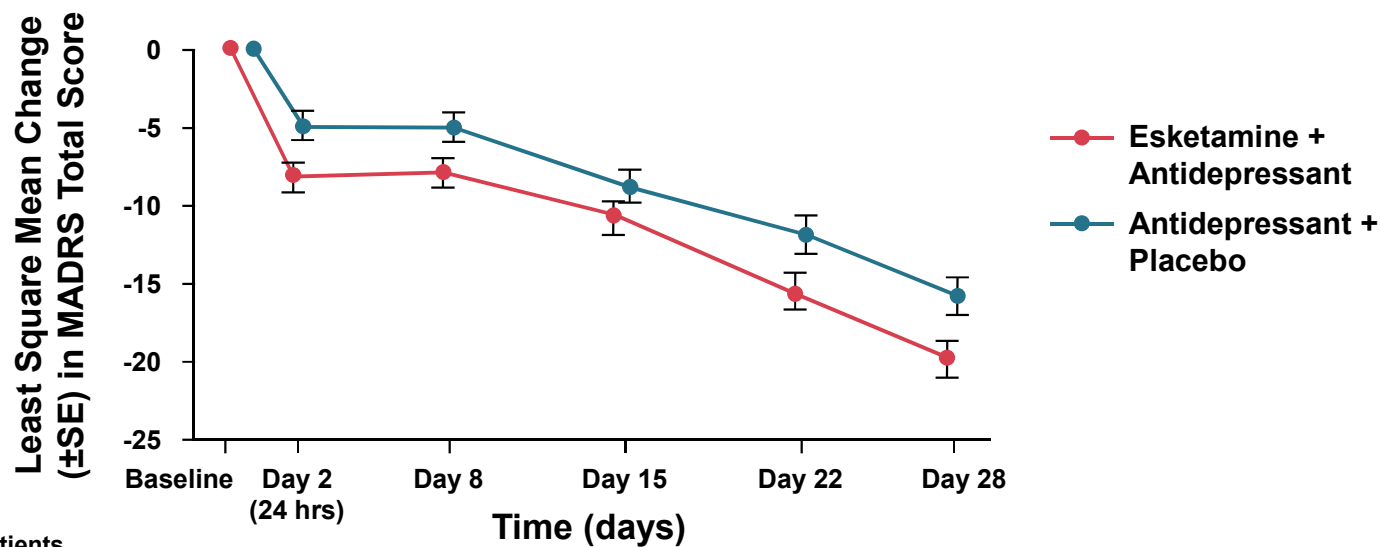
- Esketamine (intranasally delivered stereoisomer of ketamine): Multiple positive studies, Phase 3 nearing completion
- Rapastinel (allosteric modulator of NMDA receptor): Better tolerated and less abuse liability than ketamine, little dissociative effects
- Lanicemine (“low-trapping” NMDA antagonist): Potentially pivotal study failed, but evidence of problems with signal detection. A second wave of studies are planned

Esketamine:

First Descendant of Ketamine Likely to Reach the US Market

- Esketamine is a slightly more potent stereoisomer of racemic ketamine
- Developed for intranasal delivery for physician/patient convenience
- 84 mg intranasally approaches exposure of 0.4 mg/kg of IV ketamine
- Phase 3 program in TRD nearing completion; multiple positive studies
- Phase 3 program in MDD with suicidal ideation underway

Adjunctive Esketamine in TRD: MADRS Change Scores across 4 Weeks (MMRM)



Number of Patients						
Esketamine + Antidepressant	114	109	109	107	103	101
Antidepressant + Placebo	109	102	105	102	104	100
Difference of LS Means (95% CI)		-3.3 (-5.75; -0.85)	-2.9 (-5.17; -0.59)	-2.0 (-4.78; 0.82)	-3.8 (-6.87; -0.65)	-4.0 (-7.31; -0.64)

Note: Negative change in score indicates improvement *2-sided $P=0.020$.

MADRS = Montgomery-Åsberg Depression Rating Scale; MMRM = mixed-effects model repeated measures.

Popova V, et al. S111. Randomized, Double-Blind Study of Flexibly-Dosed Intranasal Esketamine Plus Oral Antidepressant Vs. Active Control in Treatment-Resistant Depression. *Biol Psychiatry*. 2018;83(9 Suppl):S390.

Adjunctive Esketamine: Safety Summary

Most adverse events were mild to moderate and resolved by ~1–1.5 hours post-dose.

Discontinuation due to TEAEs: 7.8% (9/116) and 0.96% (1/111), respectively

TEAEs with incidence $\geq 10\%$		
Adverse Event	Esketamine + Antidepressant (N=114)	Antidepressant + Nasal Placebo (N=109)
Nausea	30 (26.1%)	7 (6.4%)
Vertigo	30 (26.1%)	3 (2.8%)
Dysgeusia	28 (24.3%)	13 (11.9%)
Dissociation	27 (23.5%)	3 (2.8%)
Dizziness	24 (20.9%)	5 (4.6%)
Headache	23 (20.0%)	19 (17.4%)
Somnolence	15 (13.0%)	7 (6.4%)
Vision Blurred	14 (12.2%)	3 (2.8%)
Paresthesia	13 (11.3%)	1 (0.9%)
Anxiety	12 (10.4%)	5 (4.6%)

TEAE = treatment-emergent adverse events.

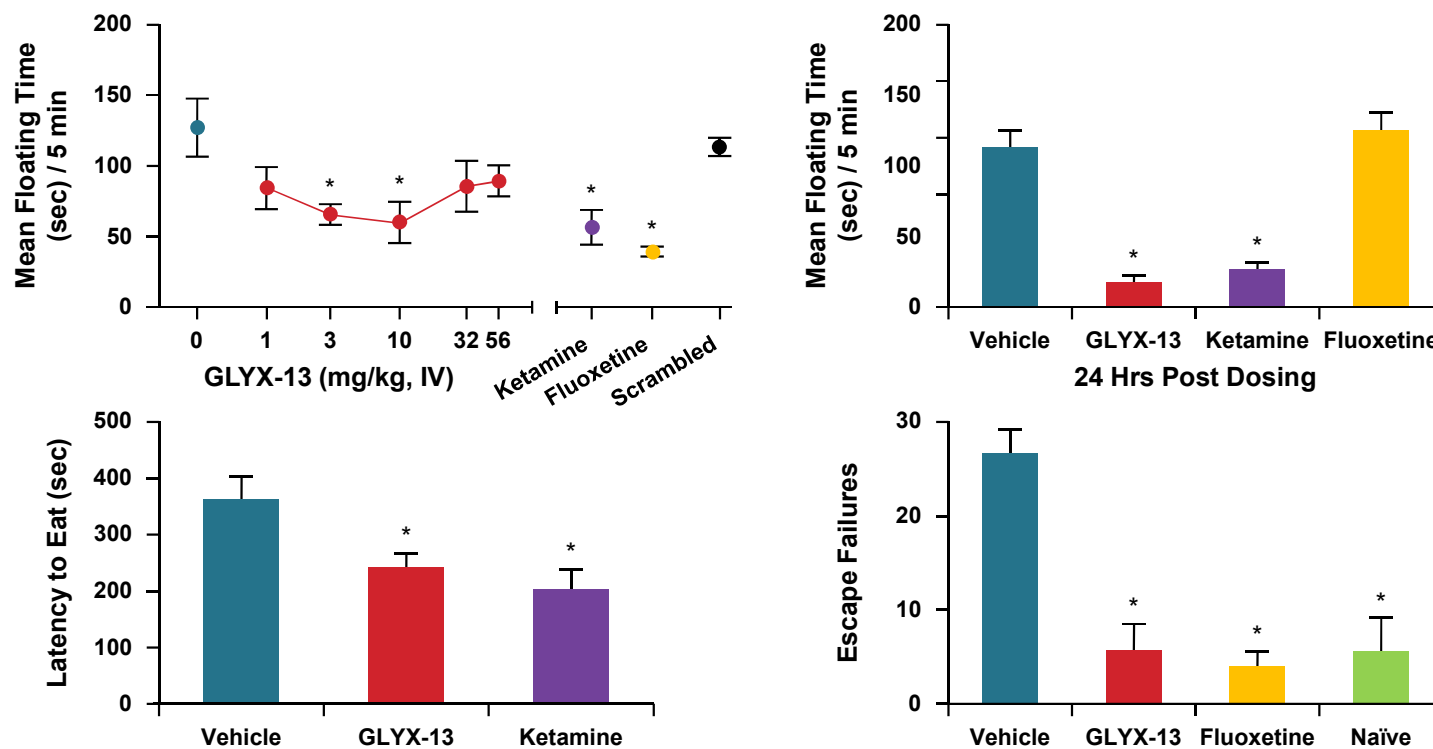
Popova V, et al. S111. Randomized, Double-Blind Study of Flexibly-Dosed Intranasal Esketamine Plus Oral Antidepressant Vs. Active Control in Treatment-Resistant Depression. *Biol Psychiatry*. 2018;83(9 Suppl):S390.

Rapastinel:

NMDA Receptor Modulator Unrelated to Ketamine

- Delivered by IV infusion
- Rapid effects comparable to ketamine in animal models
- One positive Phase 2 study in MDD
- Minimal dissociative or psychoactive side effects
- Phase 3 programs in TRD and MDD with suicidal ideation underway

Rapastinel Has Ketamine-Like Effects in Several Animal Models of Depression



Neuropsychopharmacology

* $P < .05$ Fisher's PLSD *post hoc* test vs vehicle.

Burgdorf J, et al. *Neuropsychopharmacology*. 2013;38(5):729-742.

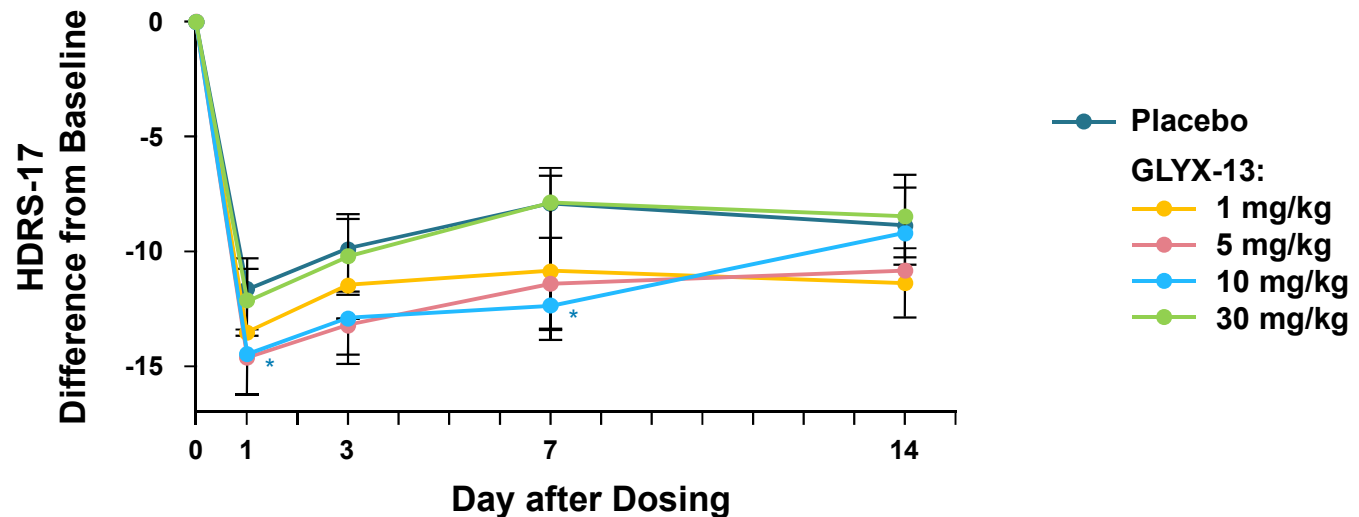
Rapastinel Phase 2a Single-Dose Study

GLYX-13 at 5 and 10 mg/kg:

Drug Effect $P < .05$

Time Effect $P < .0001$

Drug $\times$ Time $P < .0001$



Effect size of GLYX-13 after a single dose was roughly double that of SSRIs after weeks of repeated dosing

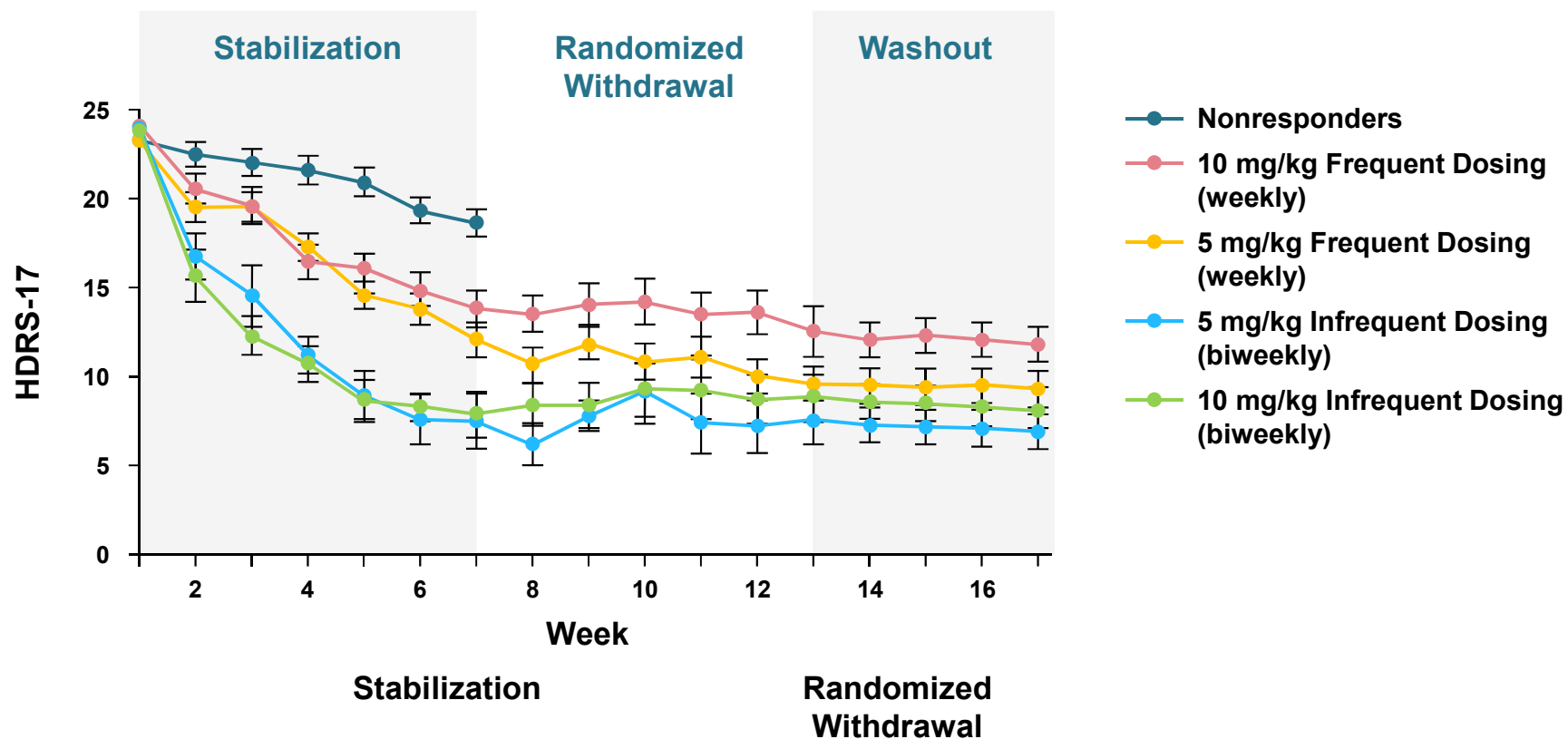
GLYX-13 (one 5 mg/kg dose) = 0.41–0.49

GLYX-13 (one 10 mg/kg dose) = 0.43–0.58

Aripiprazole (6 wks daily dosing) = 0.36

SSRIs (6–8 wks daily dosing) = 0.20–0.25

Rapastinel Phase 2b Study in TRD

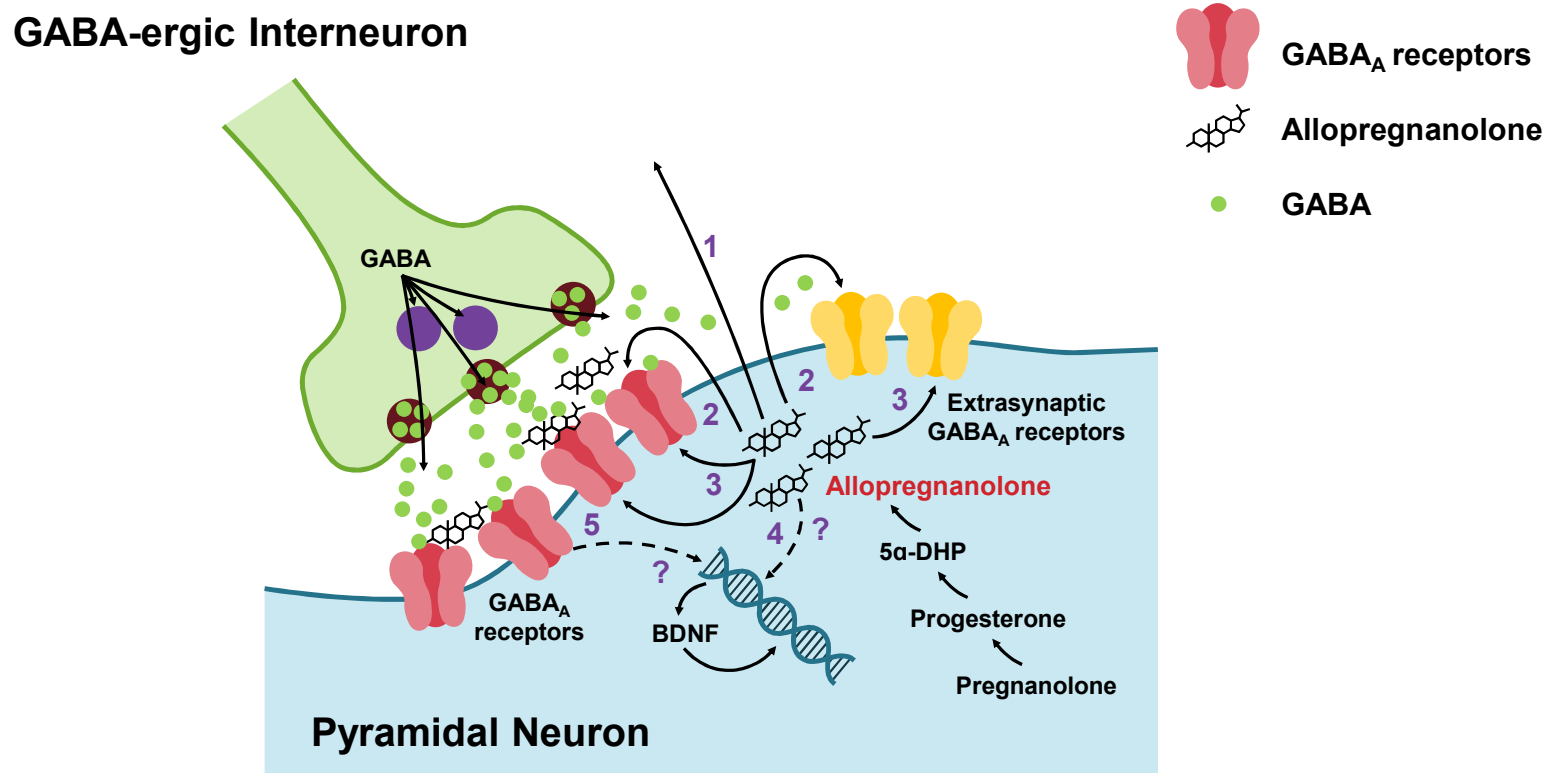


GABA-ergic Antidepressants:

Background

- Antidepressant effects documented for more than 40 years for several benzodiazepines, including alprazolam and adinazolam
- Potential therapeutic benefits diminished by:
 - Risks of misuse, abuse, and dependence
 - Concerns about tolerance to therapeutic effects
 - Pharmacoepidemiologic evidence of relationships with chronicity, falls/fractures, and dementia

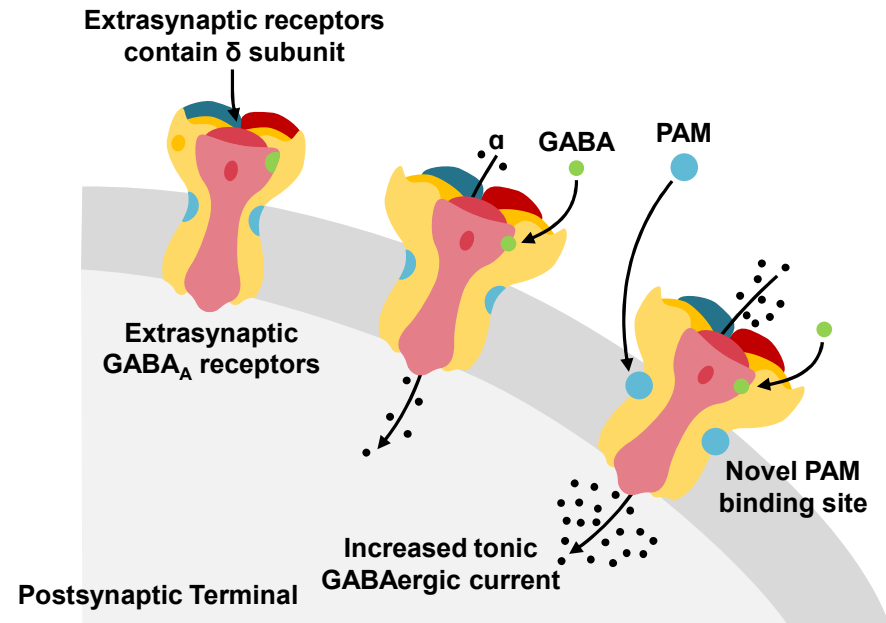
Schematic of GABA-ergic Neurotransmission



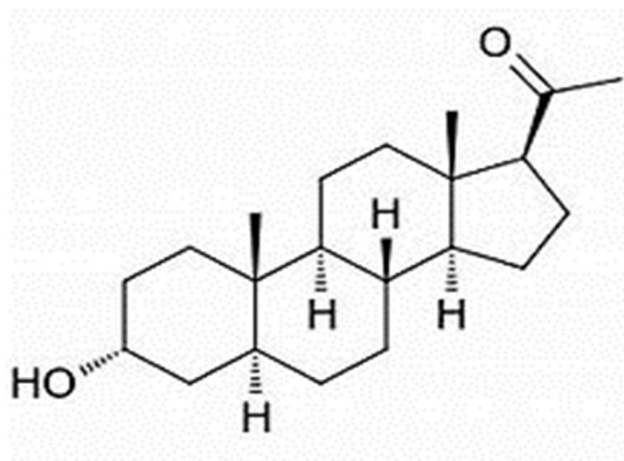
Allosteric Modulation May Increase Receptor Activity without Overstimulation

Allosteric Modulation of Extrasynaptic GABA_A Receptors

- **Positive allosteric modulation (PAM)** increases receptor efficacy and/or potency
- Fine tunes receptor activity without overstimulation
 - Direct gating compounds can't do this



Chemical Structure of Allopregnanolone



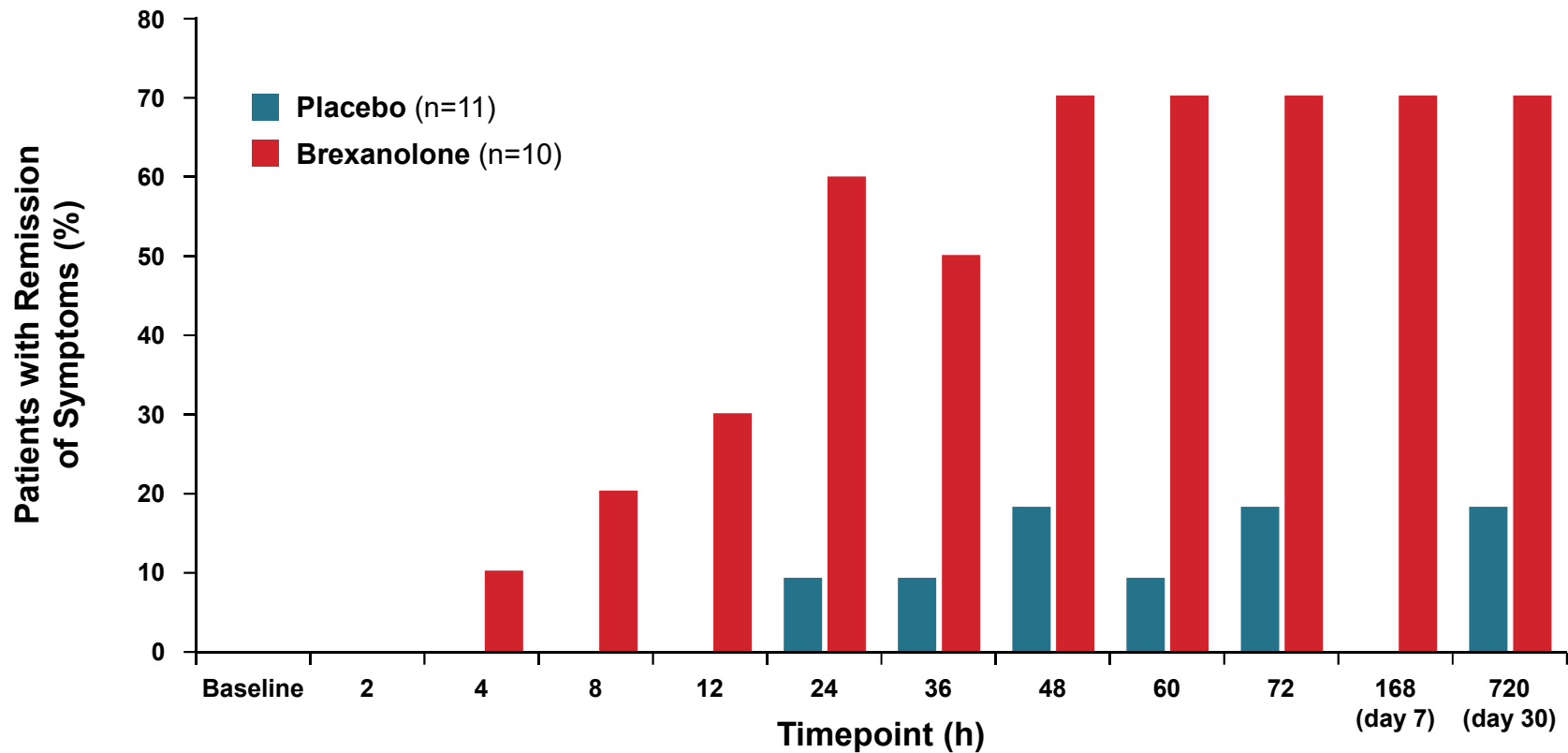
Martinez Botella G, et al. *J Med Chem.* 2017;60(18):7810-7819.

Introduction to Neurosteroids:

The Allopregnanolone Story

- Also known brexanolone and SAGE-547, allopregnanolone (3 α ,5 α -tetrahydroprogesterone ([THP])) is:
 - an endogenous inhibitory pregnane neurosteroid
 - synthesized from progesterone
 - a positive allosteric modulator of GABA_A receptors
- Originally investigated for treatment of epilepsy, brexanolone has shown efficacy as an infusion therapy for severe postpartum depression and MDD

Initial Proof of Concept Study of Brexanolone in Postpartum Depression



Kanes S, et al. *Lancet*. 2017;390(10093):480-489.

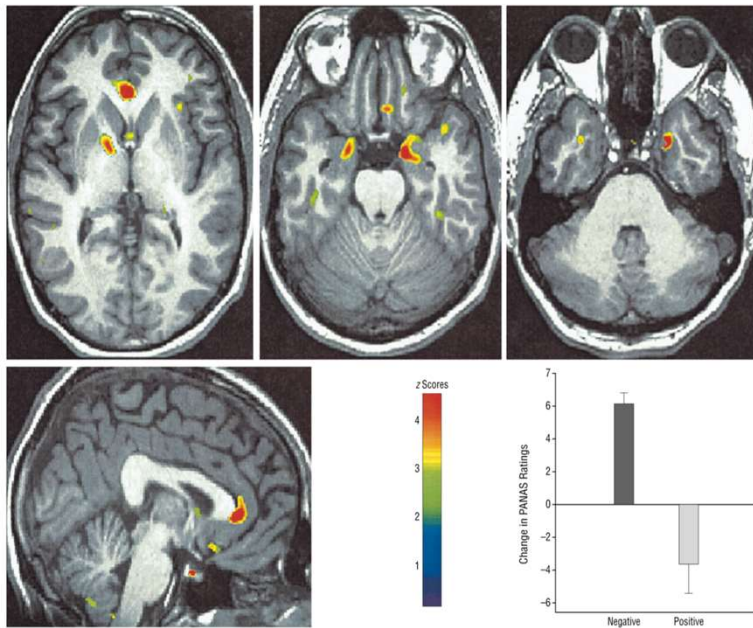
Fast Forward: *Neurosteroids as Antidepressants*

- Phase 3 study of SAGE-547 infusion therapy positive in postpartum depression
- SAGE-217, which can be orally delivered, shows positive results in MDD
- Both drugs given FDA “fast track” designation
- SAGE-547 currently under FDA review for postpartum depression

Modulating the Endogenous Opioid System to Treat Depression

- Long history of the “opium cure” for treatment of melancholic states
- High comorbidity between depression and opioid dependence
- Evidence of role of endogenous opioid system in modulating mood and reward
- Open-label experience with buprenorphine and tramadol in TRD

Endogenous Opioids and Their Receptors: *Abnormal in MDD*



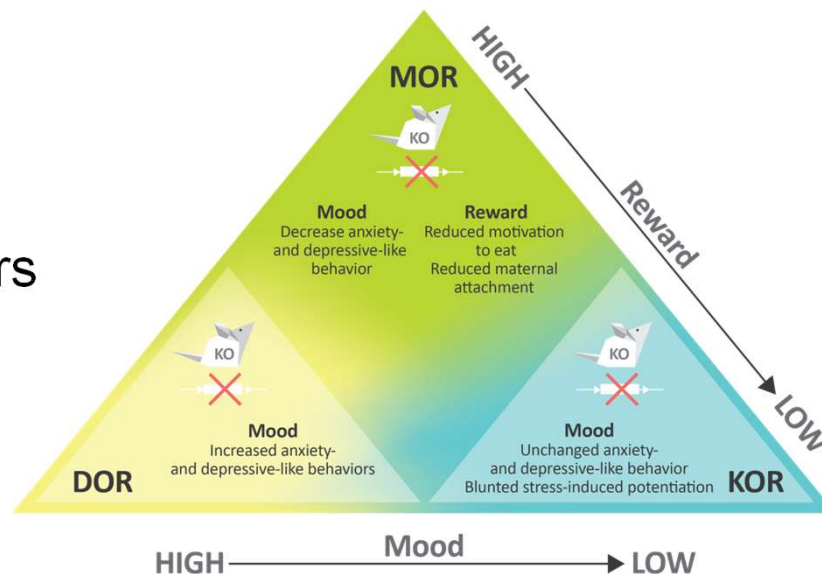
Reductions in μ -opioid receptor-mediated neurotransmission during a sustained sadness state

- Sadness and chronic stress lead to alterations in opioid receptors neurotransmission
- **The Opioid System:** mu-, delta-, and kappa-receptors (G protein-coupled)
- **μ -receptors:** Analgesia, reward, and dependence
- **δ -receptors:** Antidepressant and anti-anxiety-like behavior
- **κ -receptors:** anti-reward, dysphoria, pro-depression

Zubieta JK, et al. *Arch Gen Psychiatry*. 2003;60(11):1145-1153. Moles A, et al. *Science*. 2004;304(5679):1983-1986. Filliol D, et al. *Nat Genet*. 2000;25(2):195-200. Lutz PE, et al. *Trends Neurosci*. 2013;36(3):195-206.

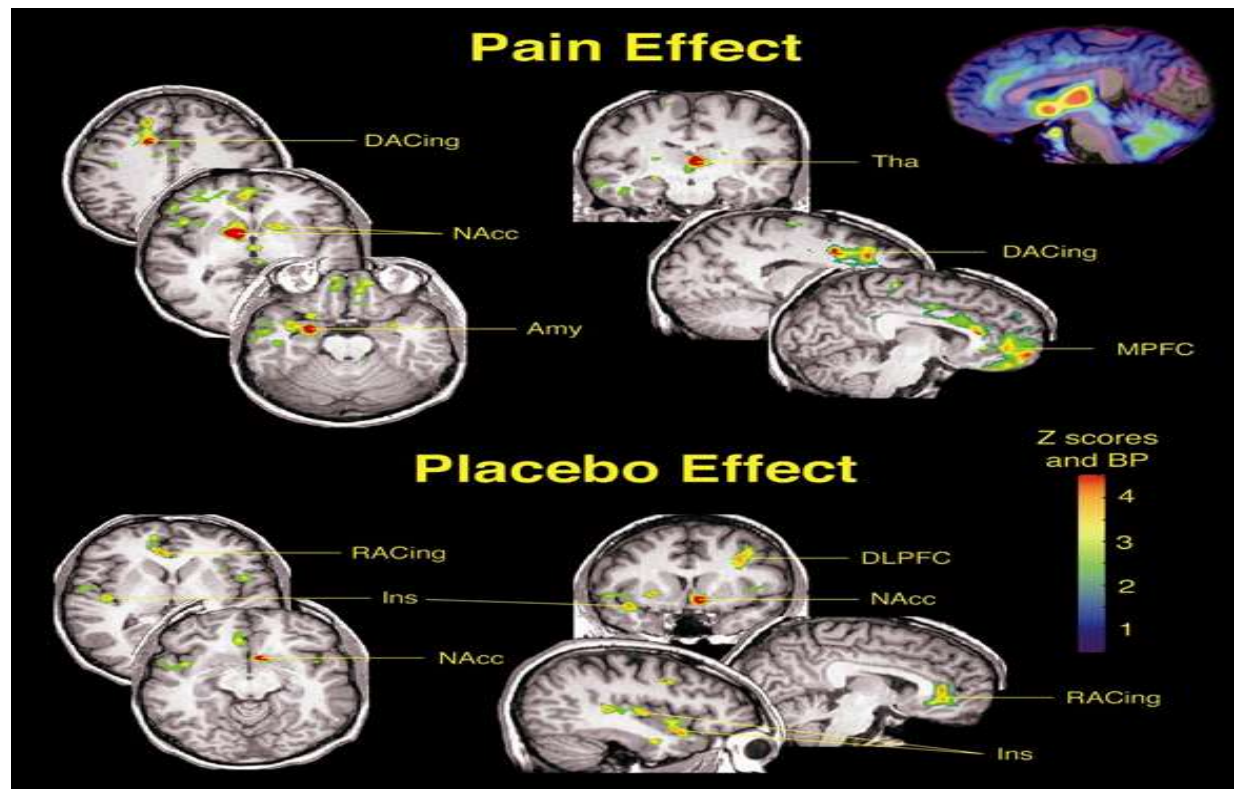
Dysregulation of the Endorphin System May Be the Mechanism for Impaired Emotion Regulation and Reward Processing in MDD

Opioid receptor KO mice phenotypes in models of addiction and mood disorders



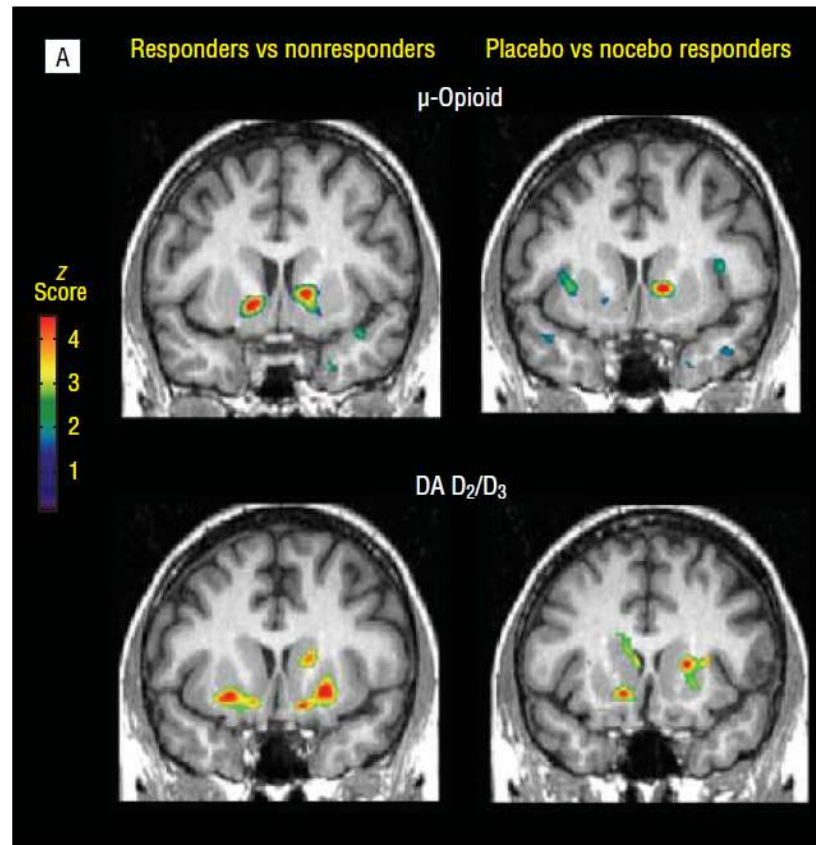
DOR = δ -opioid receptor; KO = knockout; KOR = κ -opioid receptor; MOR = μ -opioid receptor.
Lutz PE, et al. *Trends Neurosci.* 2013;36(3):195-206.

Placebos Reduce Pain Through Effects on Opioid Circuitry



Zubieta JK, et al. *J Neurosci*. 2005;25(34):7754-7762.

Nocebo Effect Mediated by Failure to Engage Endogenous Opioid System



Scott DJ, et al. *Arch Gen Psychiatry*. 2008;65(2):220-231.

Antidepressant Effects of Buprenorphine

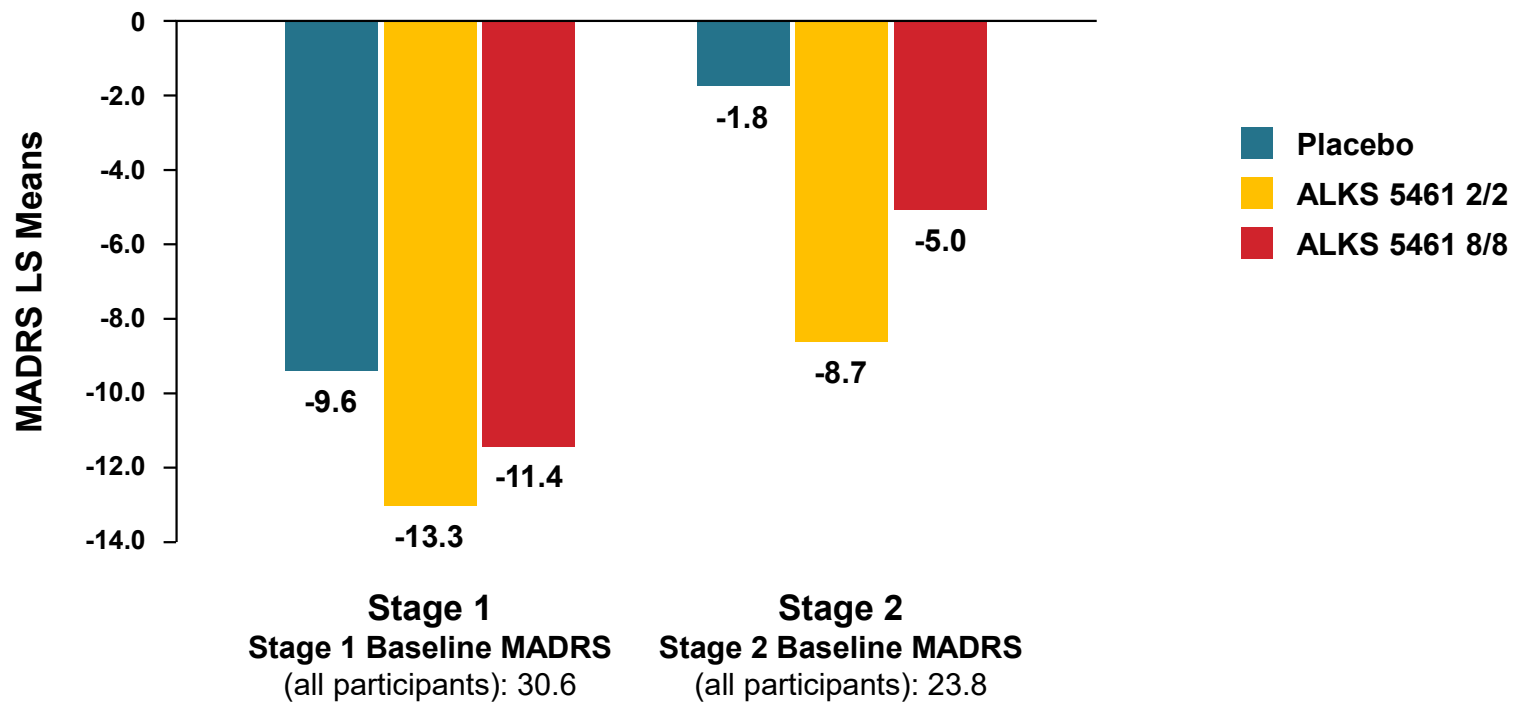
- κ antagonist and μ -opioid partial agonist
- Used in addiction treatment
- Open-label, positive data in refractory depression
- RCT of low dose buprenorphine for suicidal ideation
 - N=88 patients with clinically significant suicidal ideation
 - Buprenorphine 0.1–0.8 mg/day (mean 0.44 mg/day) or placebo for 4 weeks
 - Buprenorphine superior to placebo for reducing suicidal ideation at 2 and 4 weeks
 - No withdrawal symptoms after treatment discontinuation

ALKS 5461 (Buprenorphine + Samidorphan): *Mixed Opioid System Modulator Developed for MDD*

- A fixed-dose combination of buprenorphine (predominantly a κ -receptor antagonist) and samidorphan (a preferential μ -receptor antagonist)
- In a 2 mg/2 mg combination, ALKS 5461 has the mood elevating/reward enhancing effects of opioids without euphorogenic or intoxicating effects
- Positive findings in some animal models of antidepressant action
- Studies of highly experienced opioid users, healthy controls, and people with depression have confirmed that the drug is not “liked” for its psychoactive properties and is not associated with withdrawal/discontinuation properties

Proof of Concept Study: ALKS 5461 in TRD

MADRS Change from Baseline at Week 4



ALKS 5461 (BUP/SAM sublingual tablet): FORWARD-4

Patient population was failing an antidepressant, had HAM-D-17 > 18 and were still on an antidepressant

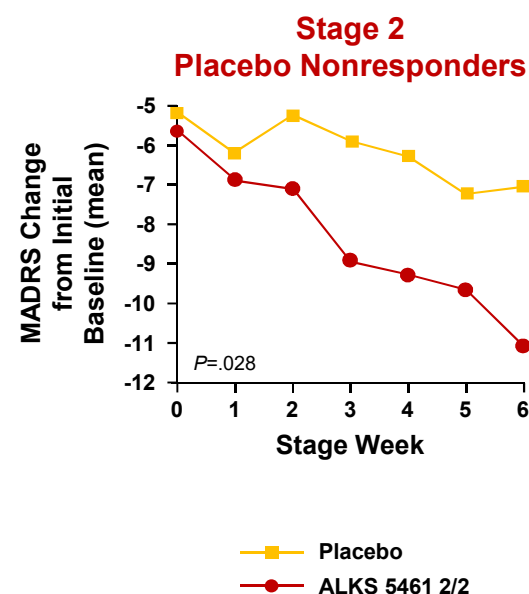
	Stage 1			Stage 2		
	PBO (n=265)	0.5/0.5 (n=59)	2/2 (n=60)	PBO (n=56)	0.5/0.5 (n=56)	2/2 (n=56)
Age, Mean (SD)	45.8 (11.5)	45.0 (13.9)	46.2 (12.1)	45.8 (10.4)	45.5 (12.0)	49.1 (10.2)
Female, n (%)	182 (69)	38 (64)	40 (67)	40 (71)	33 (59)	42 (75)
Race, n (%)	White	42 (71)	42 (70)	35 (63)	35 (63)	41 (73)
	Black	77 (29)	16 (27)	20 (36)	19 (34)	15 (27)
	Other	6 (2)	1 (2)	1 (2)	2 (4)	0
MADRS Total Score Mean (SD)	31.9 (5.0)	32.7 (4.7)	32.0 (5.7)	27.5 (7.5)	26.6 (7.1)	26.2 (7.5)

MADRS baseline score for Stage 2 population reflects score at Stage 2 randomization

Event / Preferred Term, n (%)	Stage 1		
	PBO (n=265)	0.5/0.5 (n=59)	2/2 (n=60)
Any AE	142 (53.6)	34 (57.6)	41 (68.3)
SAE	1 (0.4)	0	0
Nausea	17 (6.4)	14 (23.7)	17 (28.3)
Constipation	4 (1.5)	4 (6.8)	10 (16.7)
Dizziness	9 (3.4)	4 (6.8)	8 (13.3)
Somnolence	7 (2.6)	5 (8.5)	6 (10.0)
Vomiting	4 (1.5)	4 (6.8)	6 (10.0)
Headache	22 (8.3)	7 (11.9)	5 (8.3)

Event / Preferred Term, n (%)	Stage 2		
	PBO (n=56)	0.5/0.5 (n=56)	2/2 (n=56)
Any AE	29 (51.8)	27 (48.2)	29 (51.8)
SAE	0	0	0
Nausea	1 (1.8)	5 (8.9)	8 (14.3)

- There were no SAEs with ALKS 5461.
- There was no evidence of withdrawal.
- No pattern of AEs indicative of abuse potential.



Ehrich EW, et al. Evaluation of the Efficacy and Safety of ALKS 5461 as Adjunctive Therapy in MDD: Results of FORWARD-3 and FORWARD-4 Studies. Poster presented at: 56th Annual Meeting of the American Society of Clinical Psychopharmacology; May 2016; Scottsdale, AZ.

ALKS 5461: Summary to Date

- Two positive Phase 2 studies
- FORWARD-4 showed efficacy of ALKS 5461 2/2 in adjunctive treatment of MDD; FORWARD-3 did not show efficacy
- Both studies demonstrated similar reductions in MADRS for ALKS 5461 2/2; the difference between studies was placebo response rate
- Forward-5 ALKS 5461 2 mg/2 mg met the prespecified primary endpoint of significantly reducing depression scores compared to placebo, as measured by 6-item MADRS scores ($P=.018$), it also demonstrated statistically significant reductions in 10-item MADRS scores compared to placebo ($P=.026$)
- ALKS 5461 2/2 appears to be safe and generally well tolerated without evidence of abuse potential (Controlled Substance classification uncertain)
- Currently under review by FDA; if approved it may provide an alternate option for adjunctive therapy with better tolerability than atypical antipsychotics

Ehrich EW, et al. Evaluation of the Efficacy and Safety of ALKS 5461 as Adjunctive Therapy in MDD: Results of FORWARD-3 and FORWARD-4 Studies. Poster presented at: 56th Annual Meeting of the American Society of Clinical Psychopharmacology; May 2016; Scottsdale, AZ. ClinicalTrials.gov Identifier: NCT02218008. www.drugs.com/clinical_trials/alkermes-announces-positive-topline-results-forward-5-pivotal-phase-3-study-alks-5461-major-17214.html. Accessed September 5, 2018.

Evidence that Inflammation Plays a Role in the Pathophysiology and Treatment of Depression

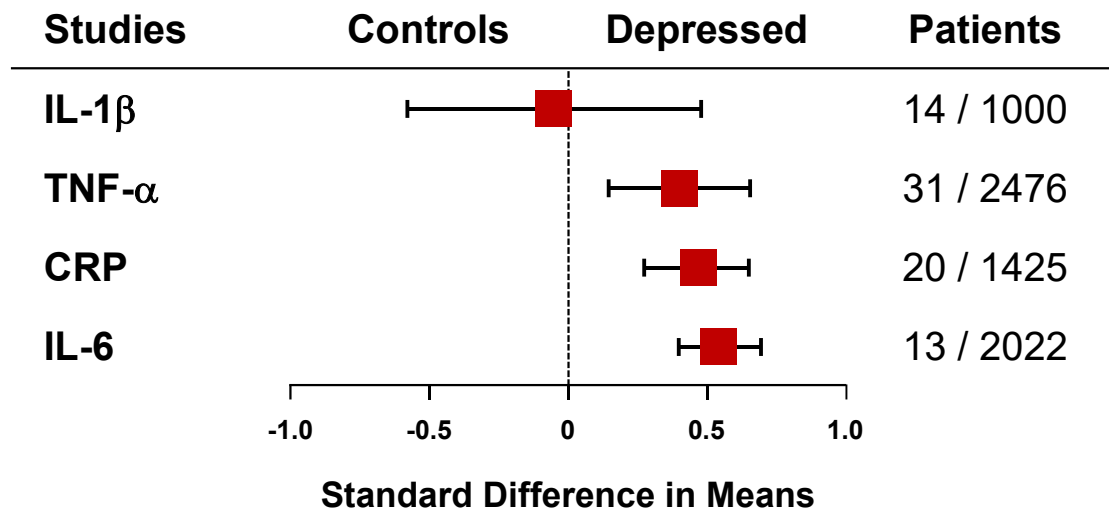
- Positive correlation between depressive symptom severity and innate immune cytokines
- Treatment of depression tends to reverse these abnormalities
- Elevated innate immune cytokines predict poor response to antidepressant therapies and are elevated in patients with treatment resistance. Cytokine gene polymorphisms (IL-1, TNF) predict antidepressant treatment response
- Administration of innate immune cytokines (eg, IL-1, TNF- α , and IL-6) produce depressive behaviors in laboratory animals and humans
- Inhibition of cytokine signaling has been found to alleviate depressive and anxiety behaviors in patients with inflammatory disorders and in laboratory animals

IL = interleukin; TNF = tumor necrosis factor.

Köhler O, et al. *JAMA Psychiatry*. 2014;71(12):1381-1391.

High Prevalence of Inflammation in Depression

Meta-Analysis of Cytokine Levels in MDD

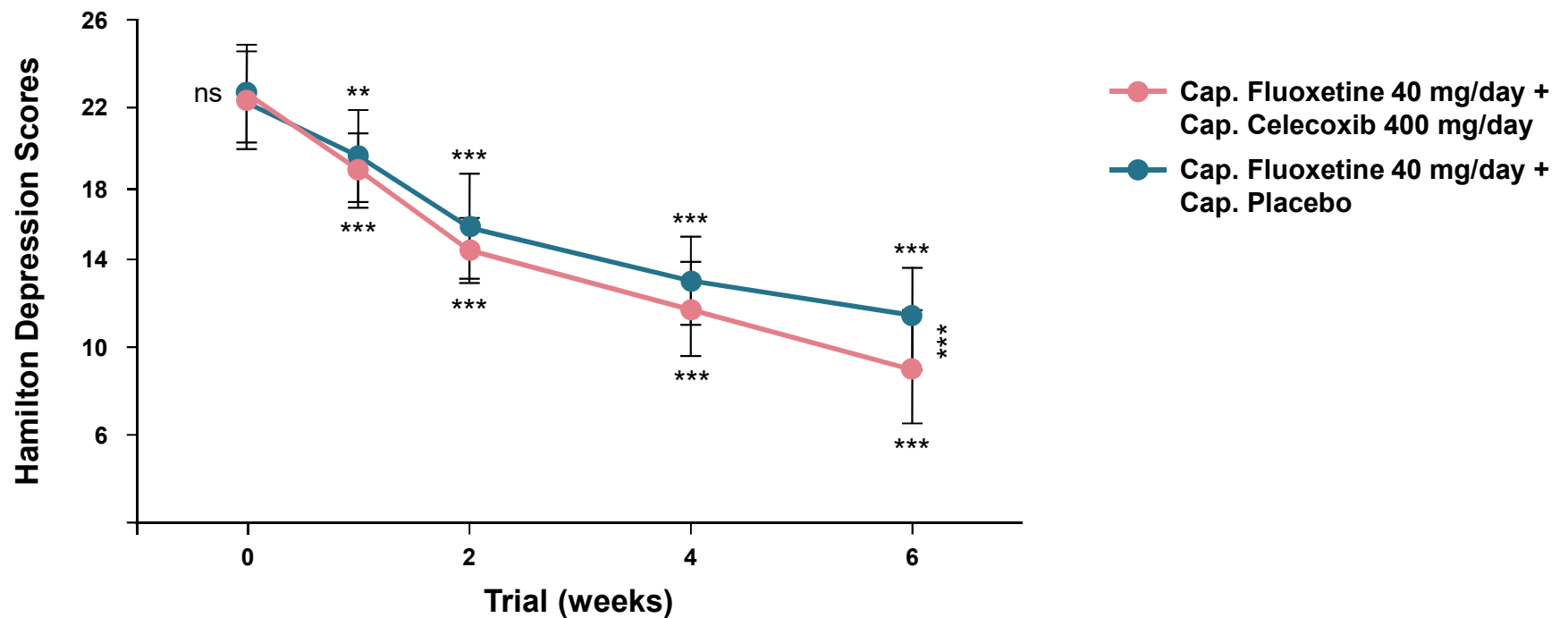


- Cytokines = non-antibody proteins released by cells on contact with antigens
- Cytokines induce depressive symptoms and HPA axis activation
- Patients with depression have high levels of cytokines

CRP = C-reactive protein.

Dunn AJ, et al. *Neurosci Biobehav Rev.* 2005;29(4-5):891-909. Yirmiya R, et al. *Ann N Y Acad Sci.* 2000;917:478-487. Haapakoski R, et al. *Brain Behav Immun.* 2015;49:206-215.

RCT of Adjunctive Cyclooxygenase-2 Inhibitor Celecoxib in MDD

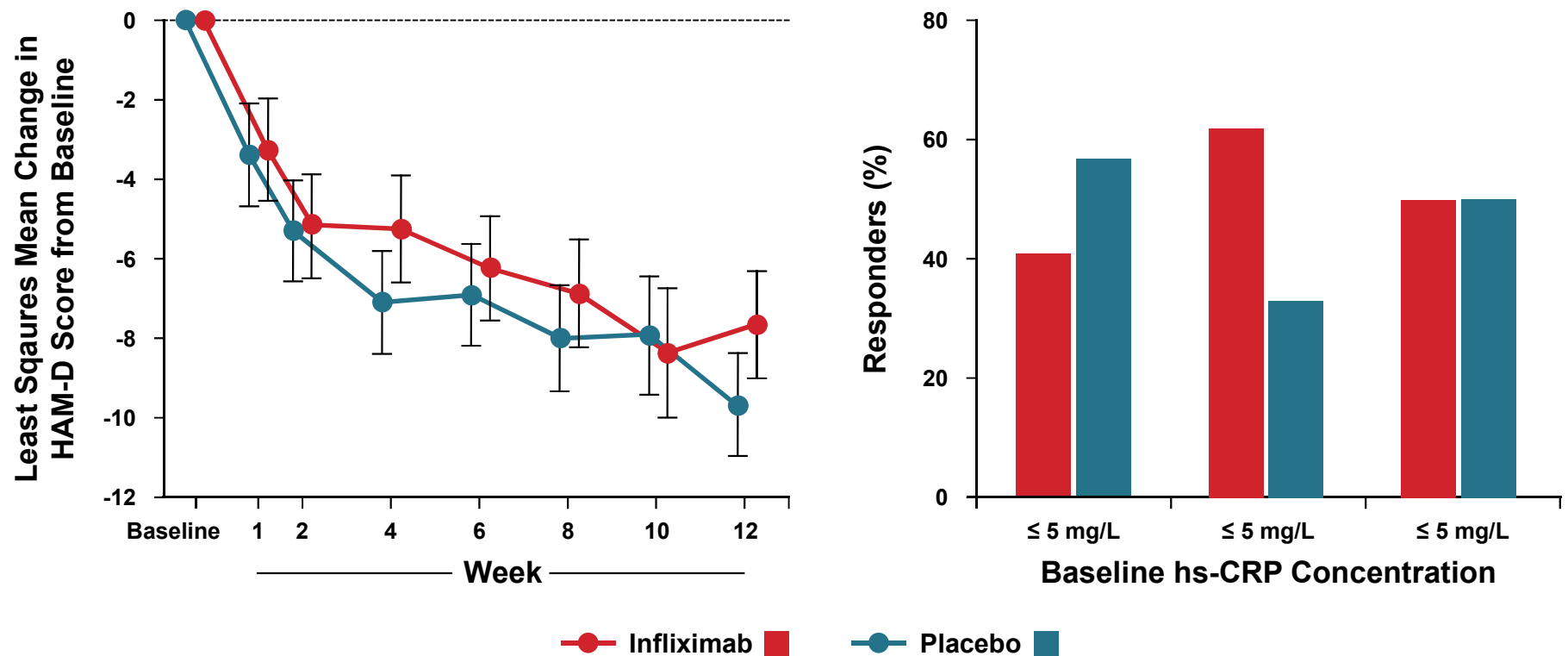


Mean $\pm$ SD of the 2 protocols the Hamilton Depression Rating Scales scores.

** $P \leq .01$, *** $P \leq .001$. ns = nonsignificant.

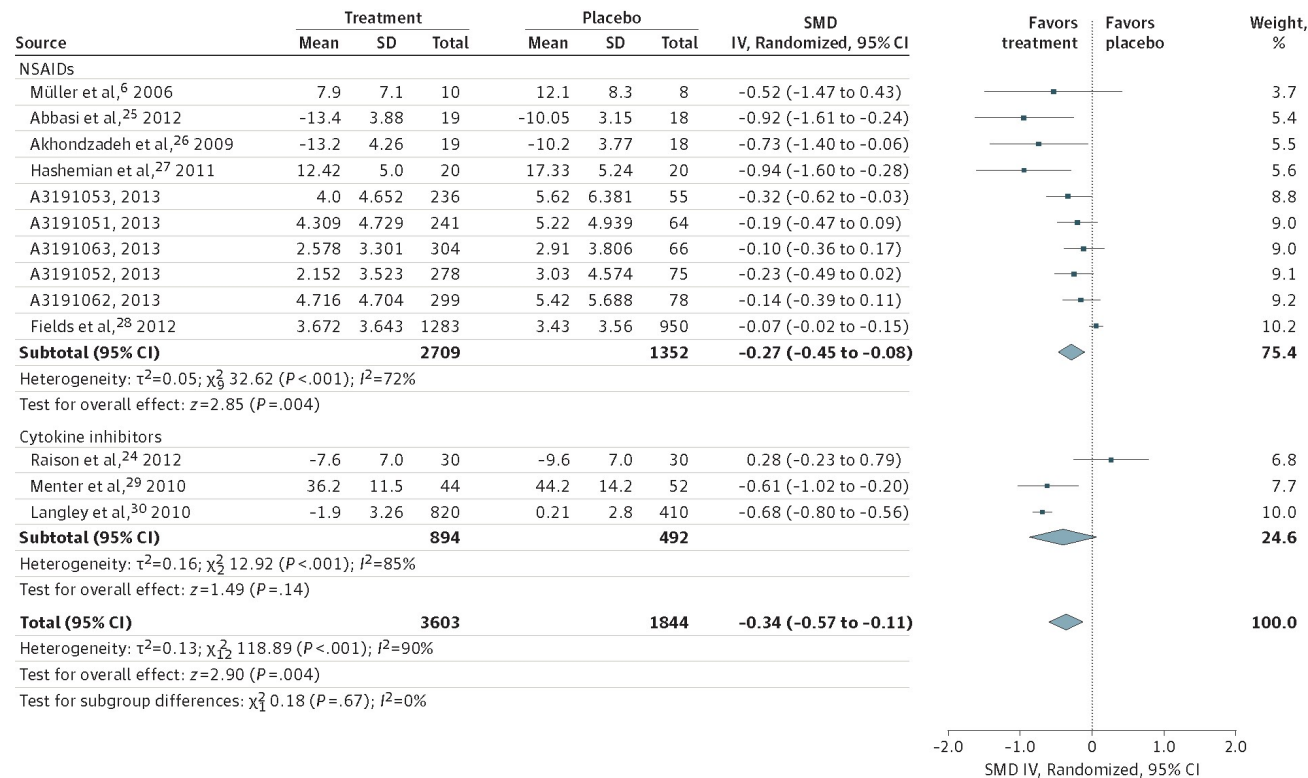
Akhondzadeh S, et al. *Depress Anxiety*. 2009;26(7):607-611.

TNF- α Antagonist Infliximab: *Effective Only for TRD Participants with Pre-existing Inflammation (high CRP)*



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

Meta-Analysis of Studies of Anti-inflammatory Strategies



Köhler O, et al. *JAMA Psychiatry*. 2014;71(12):1381-1391.

Other Novel Compounds Recently Under Investigation as Antidepressants

- Lanicemine: “Low-trapping” NMDA channel blocker
- AXS-05: Combination formulation of bupropion and dextromethorphan, a sigma-1 receptor agonist and NMDA receptor antagonist
- CERC-301: A selective NR2B specific NMDA receptor antagonist
- MIN-117: 5-HT_{1A} and 5-HT_{2A} receptor antagonist and inhibitor of serotonin and dopamine reuptake
- MIN-202 (seltorexant): Small-molecule antagonist of the OX₂ receptor
- NSI-189: Promotes neurogenesis via an unknown mechanism

Summary

- Traditional focus on monoamines now expanded by research on other modes of neurotransmission
- Recognition of roles of glutamate and glycine in neuronal responses to stress and resilience set stage for serendipitous discovery of ketamine's rapid antidepressant effect and subsequent research on alternate novel medications
- Modulation of endogenous opioid receptors has permitted assessment of effects on mood and behavior while minimizing risks of abuse/tolerance
- Discovery of neurosteroid modulation of GABA_A receptor activity may open yet another pathway to rapid antidepressant effects