Next Generation Neurosteroids for the Treatment of Major Depressive Disorder: *Neurobiology and Pathophysiology*

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Faculty Disclosure

- **Dr. Maletic**: Consultant—Alkermes, Inc., Allergan, Eisai-Purdue, Janssen, Lundbeck A/S, Otsuka America Pharmaceutical, Inc., Shire, Sunovion Pharmaceuticals Inc., Supernus Pharmaceuticals, Inc., Takeda Pharmaceutical Company Limited, Teva Pharmaceutical Industries Ltd.; Speakers Bureau—Alkermes, Inc., Allergan, Janssen, H. Lundbeck A/S, Otsuka America Pharmaceutical, Inc., Sunovion Pharmaceuticals Inc., Takeda Pharmaceutical Company Limited, Teva; Speakers Bureau (spouse)—Otsuka.
- **Dr. Montano**: Consultant—Allergan, Shire/Takeda Pharmaceutical Company Ltd., Sunovion Pharmaceuticals Inc., Arbor Pharmaceuticals Ltd.; Research Support—Allergan, Avanir, Sunovion Pharmaceuticals Inc., Tonix, BioHaven, Axsome Therapeutics Arbor Pharmaceuticals Ltd.; Speakers Bureau—Allergan, Shire/Takeda Pharmaceutical Company Ltd., Arbor Pharmaceutical Ltd.

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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 investigational use of SAGE-217 for the treatment of major depressive disorder and postpartum depression 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

- Identify the risk factors and symptomology associated with postpartum depression (PPD) and major depressive disorder (MDD) to improve accurate diagnosis
- Discuss the diverse pathophysiologic mechanisms that may contribute to MDD and PPD and resultant implications for therapeutic targeting
- Summarize the role of the GABAergic signaling pathway in the neurobiology of MDD and PPD
- Translate the mechanisms of action and available efficacy and safety data surrounding next generation neurosteroids to informed therapeutic decisions in MDD and PPD

Recognizing Major Depressive Disorder and Postpartum Depression Prevalence and Burden

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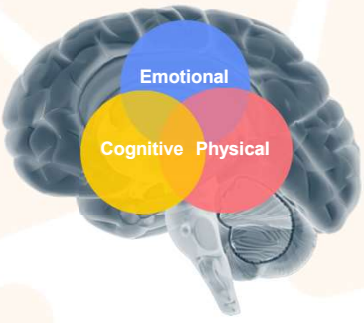
Postpartum Depression vs Major Depressive Disorder: **One in the Same?**

***DSM-5* diagnostic criteria for PPD are identical to MDD, with the exception of the Postpartum Onset Specifier:**

In *DSM-5* the specifier has changed to include "with peripartum onset"

The "with peripartum onset" specifier is used if the onset of mood symptoms occurs during pregnancy or within the 4 weeks following delivery.



MDD = major depressive disorder; PPD = postpartum depression.

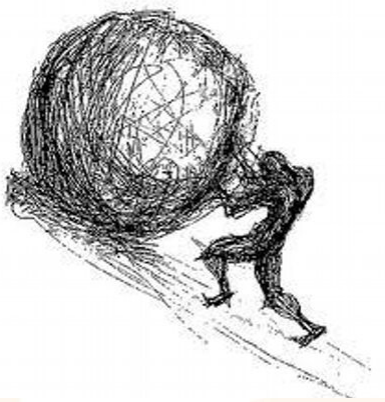
American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.* Arlington, VA: American Psychiatric Association Publishing; 2013. World Health Organization. *ICD-10 Classification of Mental and Behavioral Disorders*. Geneva, Switzerland: World Health Organization; 1992.

Postpartum Depression Risk Factors

Emotional lability during the early postpartum was the most important predictor of later PPD

Low educational level, marital status, comorbid physical illnesses, low socioeconomic status, unemployment, and unintended pregnancy

History of depression (including PPD)
History of anxiety (including during pregnancy)
Family history of PPD – heritability 44% to 54%
Post Partum insomnia
Inadequate social supports
Difficult infant temperament
Stressful life events
Child care stress
Low self-esteem



One of the predominant risk factors for the development of PPD is stress and previous adverse life events, which lead to epigenetic changes

Hapgood CC, et al. *Aust N Z J Psychiatry*. 1988;22(3):299-306. Dunn C, et al. *Arch Womens Ment Health*. 2012;15(2):139-143.

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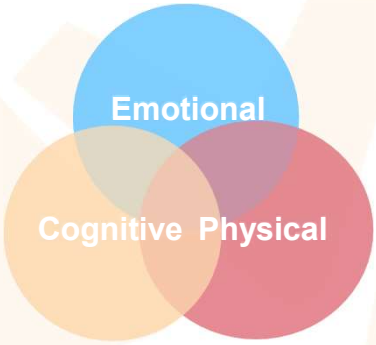
Identifying At-Risk Patients

- **Depressed mood**
- **Loss of interest or pleasure**
- **Diminished ability to think/concentrate or indecisiveness**
- **Significant change in weight or appetite**
- **Insomnia or hypersomnia**
- **Psychomotor agitation or retardation**
- **Fatigue or loss of energy**
- **Feelings of worthlessness or excessive guilt**
- **Suicidal ideation**



1. Depressed mood, loss of interest, or pleasure must be present
2. ≥ 5 of these symptoms must be present for at least 2 weeks
3. Clinically significant distress or impairment in social, occupational, or other functioning

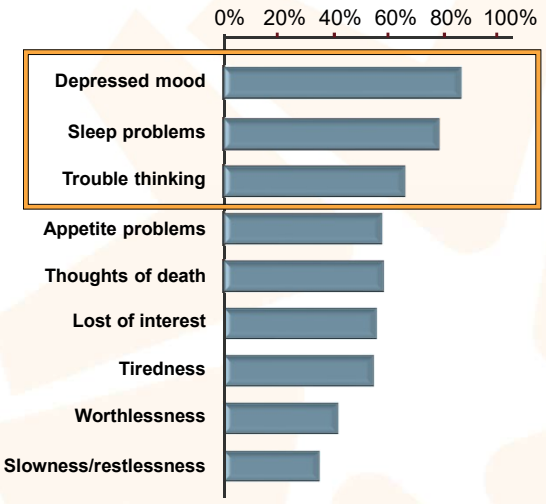
American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.* Arlington, VA: American Psychiatric Association Publishing; 2013.

8

Top 3: Sleep, Mood, and Concentration

Prevalence of Symptoms during Major Depressive Disorder Episodes

13-year NIMH study of 1920 individuals in the Baltimore Epidemiologic Catchment Area



Chen LS, et al. *Am J Psychiatry*. 2000;157(4):573-580.

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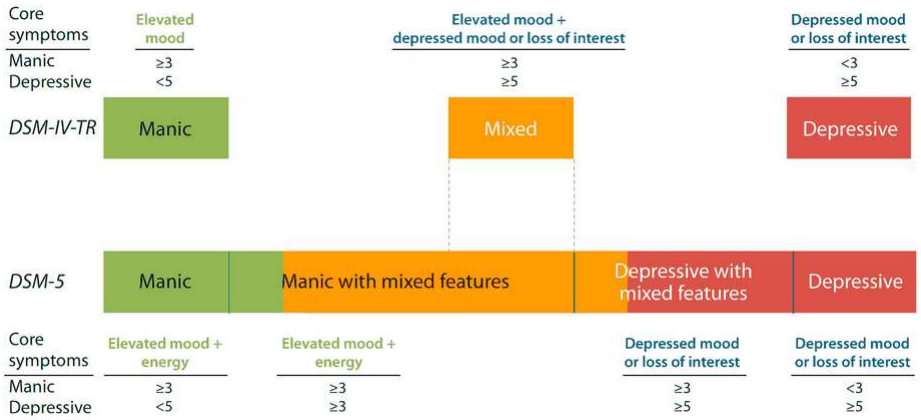
Current Challenges in MDD/PPD Management



Softer presentations of hypomania and mixed features are often seen in primary care, but not properly diagnosed or treated.

Hu J, et al. *Prim Care Companion CNS Disord*. 2014;16(2).

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Differential Diagnosis: Bipolar Disorder

21.4% to 54% of women with PPD have a diagnosis of bipolar disorder

Women with PPD in particular should be routinely screened for mania and hypomania

1. **Family History**
   - Higher rates of psychiatric illness
   - Positive for bipolar disorder
2. **Course of Illness**
   - Age of first mania/depression
   - Duration of episodes
   - Frequency of episodes
   - Seasonality
3. **Treatment Response**
   - Multiple treatment failures
   - Nonresponse or erratic response to antidepressants
4. **Mania Symptoms**
   - Distractibility
   - Insomnia
   - Grandiosity
   - Flight of ideas
   - Activities
   - Pressured speech
   - Thoughtlessness
5. **Associated Features**
   - Unevenness in intimate relationships
   - Frequent career changes
   - Substance use disorders

Key Elements

Sharma V, et al. *J Affect Disord*. 2017;219:105-111.

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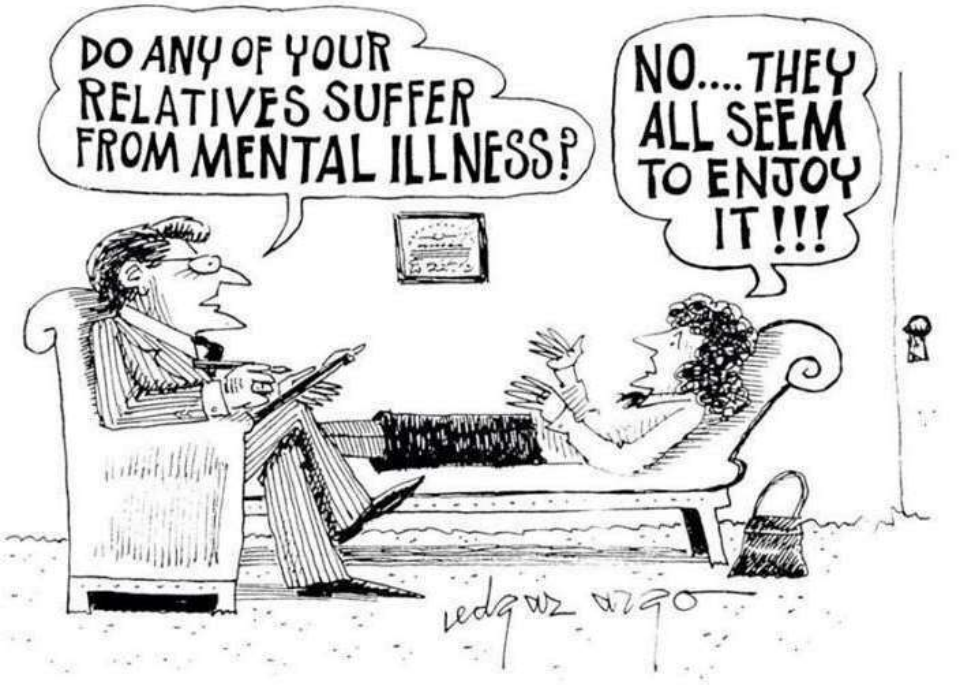

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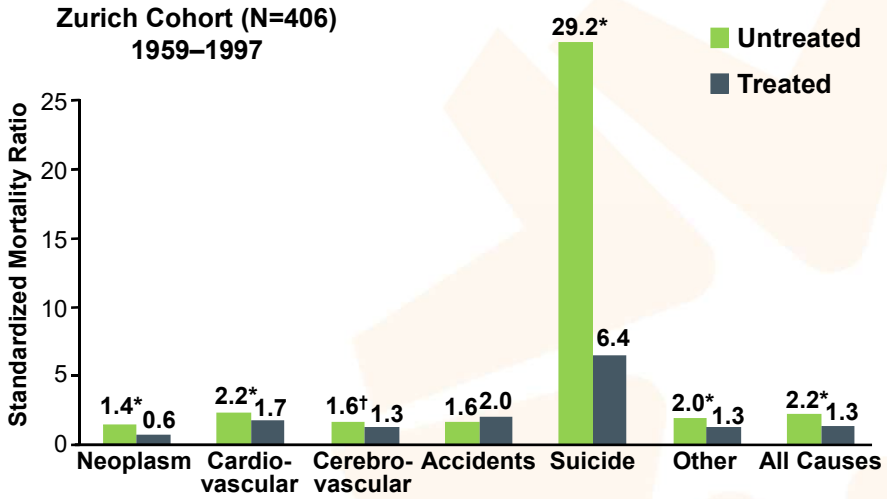
Bipolar Disorder:
Untreated vs Treated Standardized Mortality Ratios



******P*<.001; **†***P*<.05.

Angst F, et al. *J Affect Disord.* 2002;68(2-3):167-181.

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Available Assessment Tools: *PHQ-9*

The Patient Health Questionnaire (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems?	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite—being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

If you circled **any** problems on this questionnaire so far, mark how **difficult** these problems have made it for you to do your work, take care of things at home, or get along with other people.

- ☐ Not difficult at all
- ☐ Somewhat difficult
- ☐ Very difficult
- ☐ Extremely difficult

ADD COLUMNS ____ + ____ + ____

TOTAL ____

For healthcare professionals: Because this questionnaire relies on patient self-report, all responses should be verified by the clinician. A definitive diagnosis should be made on clinical grounds, taking into account how well the patient understood the questionnaire, as well as other relevant information from the patient. Be sure to exclude response to a significant loss, substance abuse, or other medical condition.

Total PHQ-9 Score	Depression Severity
1–4	Minimal
5–9	Mild
10–14	Moderate
15–19	Moderate–Severe
20–27	Severe

Kroenke K, et al. *J Gen Intern Med.* 2001;16(9):606-613.

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Available Assessment Tools: *MDQ*

1	Has there ever been a period of time when you were not your usual self and…	Y	N
	…you felt so good or so hyper that other people thought you were not your normal self or you were so hyper that you got into trouble?		
	…you were so irritable that you shouted at people or started fights or arguments?		
	…you felt much more self-confident than usual?		
	…you got much less sleep than usual and found you didn't really miss it?		
	…you were much more talkative or spoke faster than usual?		
	…thoughts raced through your head or you couldn't slow your mind down?		
	…you were so easily distracted by things around you that you had trouble concentrating or staying on track?		
	…you had much more energy than usual?		
	…you were much more active or did many more things than usual?		
	…you were much more social or outgoing than usual, for example, you telephoned friends in the middle of the night?		
	…you were much more interested in sex than usual?		
	…you did things that were unusual for you or that other people might have thought were excessive, foolish, or risky?		
	…spending money got you or your family into trouble?		
2	If you checked YES to more than one of the above, have several of these ever happened during the same period of time? *Please circle one response only.* YES NO		
3	How much of a problem did any of these cause you—like being unable to work; having family, money, or legal troubles; getting into arguments or fights? *Please circle one response only.* No problem Minor problem Moderate problem Serious problem		

A positive screen requires:

1. ≥ 7 "yes" on 13 items
2. ≥ 2 co-occurring symptoms
3. The level of functional impairment must be "moderate problem" to "serious problem"

Sensitivity (0.73)
Specificity (0.90)

Hirschfeld RM, et al. *Am J Psychiatry*. 2000;157(11):1873-1875. Hirschfeld RM, et al. *Am J Psychiatry*. 2003;160(1):178-180.

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Available Assessment Tools: *EPDS*

Edinburgh Postnatal Depression Scale[1] (EPDS)

Name: _____ Address: _____

Your Date of Birth: _____ _____

Baby's Date of Birth: _____ Phone: _____

As you are pregnant or have recently had a baby, we would like to know how you are feeling. Please check the answer that comes closest to how you have felt **IN THE PAST 7 DAYS**, not just how you feel today.

Here is an example, already completed.

I have felt happy:
☐ Yes, all the time
☒ Yes, most of the time — This would mean: "I have felt happy most of the time" during the past week.
☐ No, not very often — Please complete the other questions in the same way.
☐ No, not at all

In the past 7 days:

1. I have been able to laugh and see the funny side of things
☐ As much as I always could
☐ Not quite so much now
☐ Definitely not so much now
☐ Not at all

2. I have looked forward with enjoyment to things
☐ As much as I ever did
☐ Rather less than I used to
☐ Definitely less than I used to
☐ Hardly at all

*3. I have blamed myself unnecessarily when things went wrong
☐ Yes, most of the time
☐ Yes, some of the time
☐ Not very often
☐ No, never

4. I have been anxious or worried for no good reason
☐ No, not at all
☐ Hardly ever
☐ Yes, sometimes
☐ Yes, very often

*5. I have felt scared or panicky for no very good reason
☐ Yes, quite a lot
☐ Yes, sometimes
☐ No, not much
☐ No, not at all

*6. Things have been getting on top of me
☐ Yes, most of the time I haven't been able to cope at all
☐ Yes, sometimes I haven't been coping as well as usual
☐ No, most of the time I have coped quite well
☐ No, I have been coping as well as ever

*7. I have been so unhappy that I have had difficulty sleeping
☐ Yes, most of the time
☐ Yes, sometimes
☐ Not very often
☐ No, not at all

*8. I have felt sad or miserable
☐ Yes, most of the time
☐ Yes, quite often
☐ Not very often
☐ No, not at all

*9. I have been so unhappy that I have been crying
☐ Yes, most of the time
☐ Yes, quite often
☐ Only occasionally
☐ No, never

*10. The thought of harming myself has occurred to me
☐ Yes, quite often
☐ Sometimes
☐ Hardly ever
☐ Never

SCORING

- **Questions 1, 2, and 4** (without an *) are scored 0, 1, 2, or 3 with top box scored as 0 and the bottom box scored as 3
- **Questions 3, 5, and 10** (marked with an *) are reverse scored, with the top box scored as a 3 and the bottom box scored as 0
- **Maximum score**: 30 = Possible Depression: > 10 *always* look at item 10 (suicidal thoughts)

Sensitivity (0.90)
Specificity (> 0.85)

Cox JL, et al. *Br J Psychiatry*. 1987;150:782-786.

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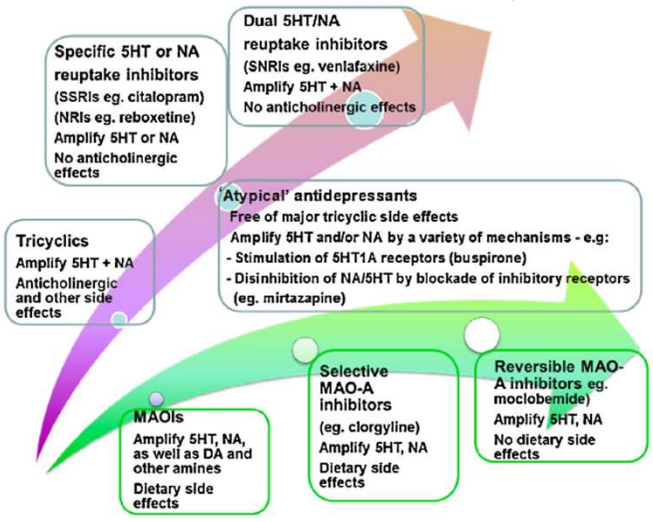
Nonpharmacologic Treatment Options

- Psychotherapy should be the initial treatment for mild-to-moderate depression. However, in the setting of moderate-to-severe illness or a past history of depression responding to medication, antidepressant medication should be considered first-line treatment
- Evidence-based psychotherapies that have demonstrated efficacy in peripartum women include CBT and interpersonal psychotherapy when administered by a psychotherapist trained in these treatments
- Pregnant and breastfeeding women often express preference for psychotherapy and complementary and alternative treatments as a means of avoiding fetal and infant exposure to antidepressants
- For mild-to-moderate depression, complementary therapies such as exercise, yoga, bright light therapy, and acupuncture have shown efficacy and can be used alone or adjunctively

CBT = cognitive-behavioral therapy.

Byatt N, et al. *Acta Psychiatr Scand*. 2013;127(2):94-114. Battle CL, et al. *J Psychiatr Pract*. 2013;19(6):443-453. Stuart S, et al. *Best Pract Res Clin Obstet Gynaecol*. 2014;28(1):61-70. Deligiannidis KM, et al. *Best Pract Res Clin Obstet Gynaecol*. 2014;28(1):85-95.

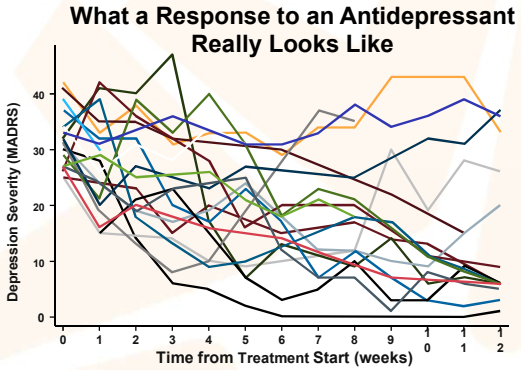
Evolution of Major Depressive Disorder Pharmacotherapy



Willner P, et al. *Neurosci Biobehav Rev*. 2013;37(10 Pt 1):2331-2371.

Candidates for Consultation or Referral

- Diagnostic uncertainty or dilemma
- Treatment refractory
- Acuity/severity
  - Danger to self/others mandating inpatient status
  - Need for intensive outpatient therapy
- Patient-provider mismatch
  - Clinician or patient preference



MADRS = Montgomery–Åsberg Depression Rating Scale.
Jackson WC. *Drug Benefit Trends*. 2005;17(Suppl A):17-22. Uher R. *Harv Rev Psychiatry*. 2011;19(3):109-124.

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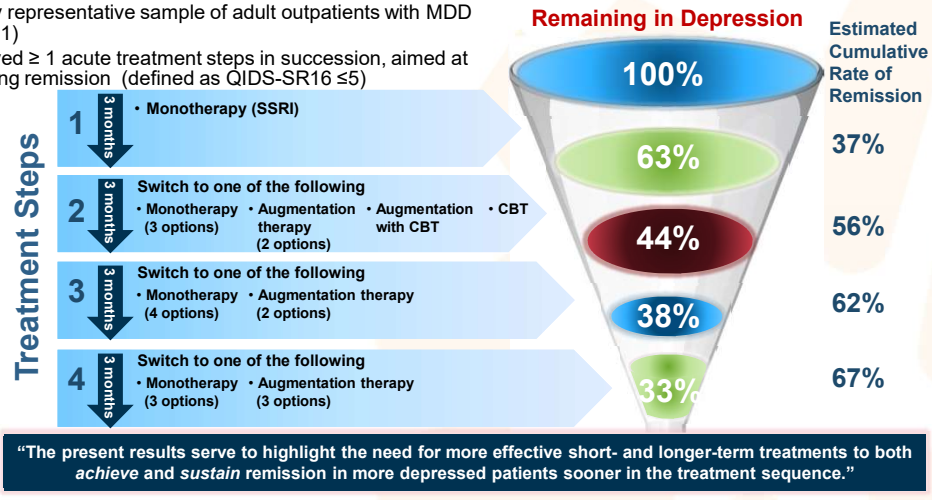
STAR*D Trial: 33% of Patients Remained Depressed after 4 Treatment Steps

- Broadly representative sample of adult outpatients with MDD (N=3671)
- Employed ≥ 1 acute treatment steps in succession, aimed at achieving remission (defined as QIDS-SR16 ≤5)



"The present results serve to highlight the need for more effective short- and longer-term treatments to both *achieve* and *sustain* remission in more depressed patients sooner in the treatment sequence."

QIDS-SR16 = 16-item Quick Inventory of Depressive Symptomatology.
Rush AJ, et al. *Am J Psychiatry*. 2006;163(11):1905-1917.

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GABA, Neurosteroids, Stress, and Major Depressive Disorder

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University of South Carolina School of Medicine
Greenville, South Carolina

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Crossing the Pharmacologic Equator
What in the world just happened?

MONOAMINES

GABA, GLUTAMATE,
Neurosteroids

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Subtypes of $GABA_A$ Receptors

- There are ~ 20 to 30 different $GABA_AR$ isoforms within the mammalian CNS
- **$GABA_ARs$** possess a **pentameric structure**, surrounding a central anion conducting pore. To date, 19 subunits have been identified (α1–6, β1–3, γ1–3, δ, ε, θ, π, ρ1–3)
- $GABA_AR$ isoforms incorporating the **γ2 subunit**, in combination with α and β subunits are ubiquitously expressed throughout the brain and are predominantly **located within the synapse**, where they are responsible for mediating **"phasic" GABAergic inhibition**
- **δ-subunit containing $GABA_ARs$** are primarily prevalent in the cerebellum, dentate gyrus, thalamus, striatum, and cortex where they are expressed only at **peri- and extrasynaptic** locations and mediate a **"tonic" form of GABAergic inhibition**

CNS = central nervous system; GABA = gamma-aminobutyric acid.
Gunn BG, et al. *Front Neurosci.* 2011;5:131.

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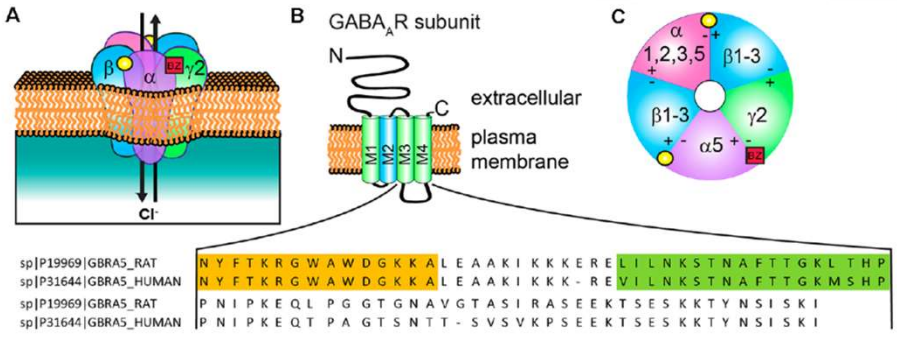
Generic $GABA_A$ Synaptic Heteropentamer



α5 $GABA_AR$ signaling can be altered in neurodevelopmental disorders including autism and developmental neurocognitive disability, and by inflammation in CNS injury and disease. Modulators of these receptors are being targeted and tested as treatments for neurodevelopmental disorders, mild cognitive impairment, depression, and schizophrenia

Jacob TC. *Front Mol Neurosci.* 2019;12:179.

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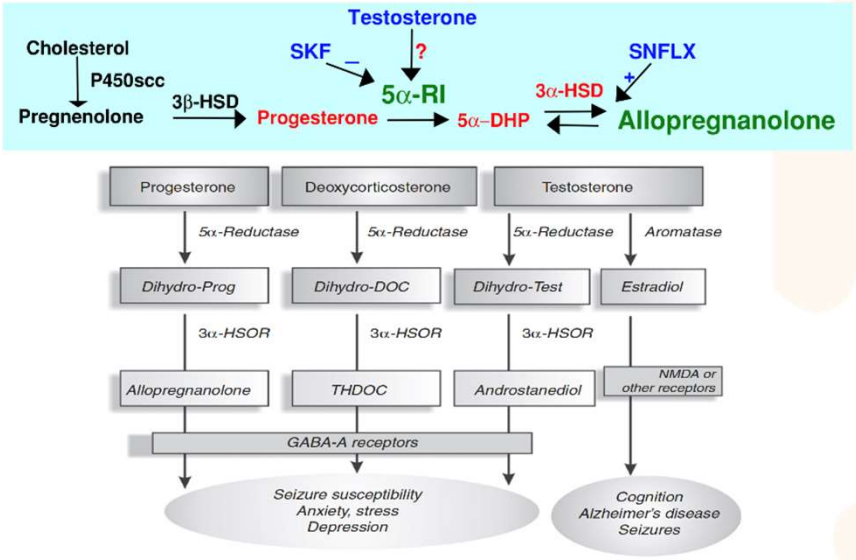
Neuroactive Steroids: *Neurosteroids*

- Central and peripheral nervous system has capacity to synthesize steroids from cholesterol
- *De novo* synthesis of steroids in the brain is conserved across vertebrate species
- Neurosteroids synthesized in the brain: **pregnenolone**, epiallopregnanolone, epipregnanolone, tetrahydrodeoxycorticosterone (THDOC), androsterone, pregnenolone sulfate, 7α-hydroxypregnenolone, dehydroepiandrosterone (DHEA), progesterone, corticosterone, **allopregnanolone**, androstenedione, testosterone, and estradiol-17β
- Brain cells and sites involved in producing neurosteroids: **oligodendrocytes**, **astrocytes** and **neurons**, cerebellum, pyramidal neurons in hippocampus, sensory neurons in the dorsal root ganglia, and motor neurons in the spinal cord, pineal gland neurons
- Positive and negative allosteric modulators of $GABA_A$Rs (epiallopregnanolone and epipregnanolone are negative allosteric modulators of $GABA_A$Rs)
- Neurosteroids are endogenous regulators of $GABA_A$ signaling in the brain

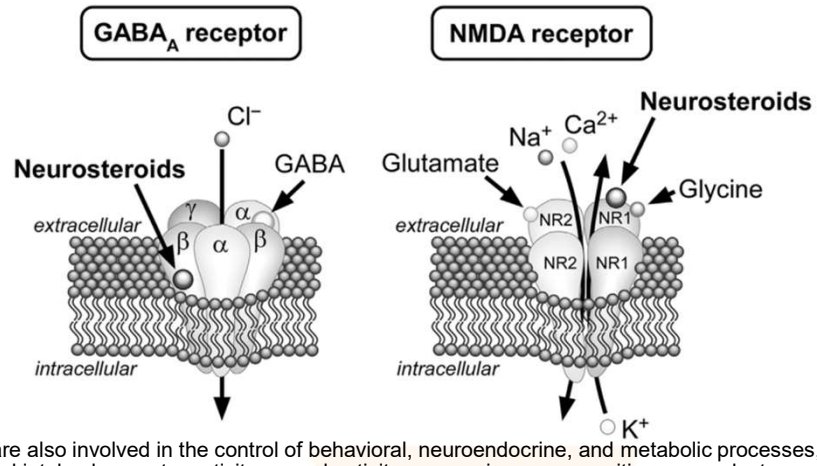
Tsatsui K, et al. Neurosteroids. In: Takei Y, et al (Eds). *Handbook of Hormones: Comparative Endocrinology for Basic and Clinical Research*. 2016:537-539. Cruz DA, et al. *Chronic Stress*. 2019 Apr 18; Epub.

Roles of Endogenous Neurosteroids



Reddy DS. *Prog Brain Res*. 2010;186:113-137. Pinna G, et al. *Neurochem Res*. 2008;33(10):1990-2007.

Neurosteroid Activities are Mediated by $GABA_A$ and NMDA Glutamate Receptors



Neurosteroids are also involved in the control of behavioral, neuroendocrine, and metabolic processes, such as regulation of food intake, locomotor activity, sexual activity, aggressiveness, cognition, arousal, stress, depression, anxiety, sleep, and blood pressure.

NMDA = N-methyl-D-aspartate.

Tsatsui K, et al. Neurosteroids. In: Takei Y, et al (Eds). *Handbook of Hormones: Comparative Endocrinology for Basic and Clinical Research*. 2016:537-539.

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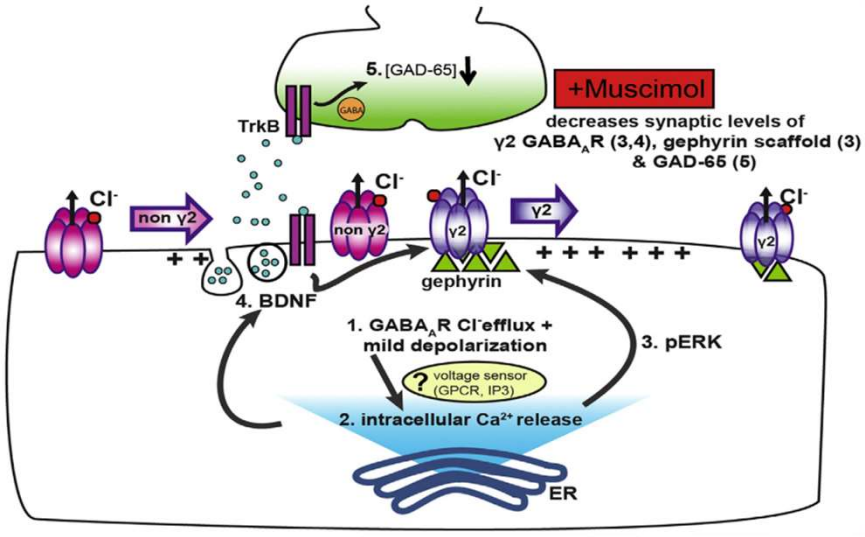
GABA Signaling Regulates Neuroplasticity



Brady ML, et al. *Neuropharmacology*. 2018;128:324-339.

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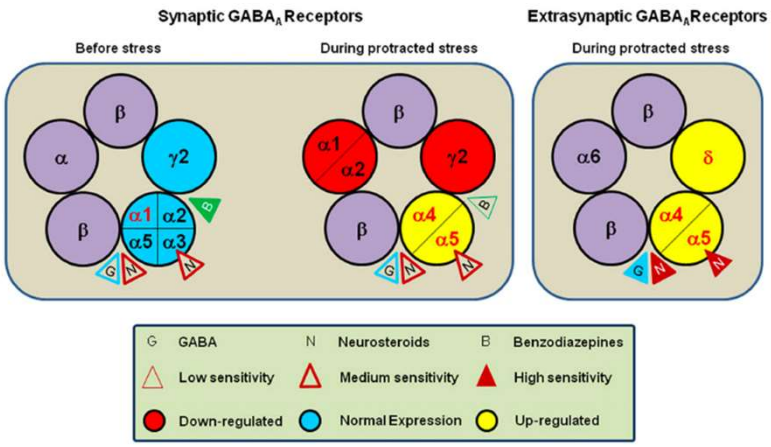
Benefits of Neurosteroids in Chronically Stressful Situations



Allo enhances extrasynaptic and postsynaptic inhibition by directly binding at GABA$_A$Rs, and thus, positively and allosterically modulates the function of GABA. Stress favors a GABA$_A$R subunit composition with higher sensitivity for Allo, which by inhibiting NMDA tonic neurotransmission, provides neuroprotection and cognitive benefits.

Allo = allopregnanolone.

Locci A, et al. *Br J Pharmacol.* 2017;174(19):3226-3241.

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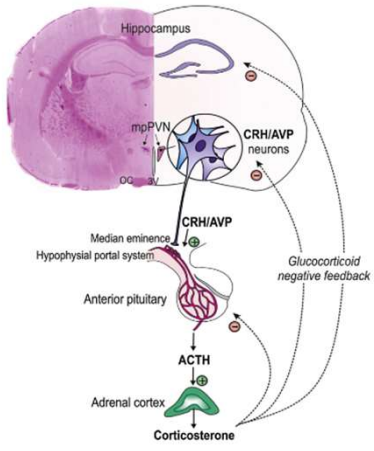
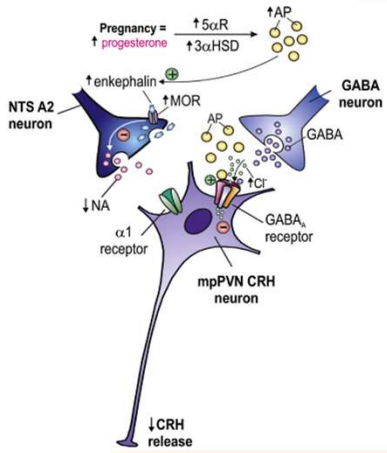
Neurosteroids are Involved in Regulation of Stress Response





Noradrenergic A2 neurons in the brainstem NTS project to parvocellular CRH neurons in the mpPVN. Increased levels of progesterone result in increased brain and circulating levels of AP in pregnancy. AP increases mRNA expression for pENK-A and MOR in the NTS neurons in pregnancy. Additionally, AP may also inhibit CRH neurons by positively modulating GABA inputs to the mpPVN via actions on GABA$_A$Rs.

AP = allopregnanolone; CRH = corticotropin-releasing hormone; mpPVN = medial parvocellular paraventricular nucleus; MOR = μ-opioid receptor; NTS = nucleus tractus solitarii; pENK-A = proenkephalin-A.

Brunton PJ. *J Steroid Biochem Mol Biol.* 2016;160:160-168.

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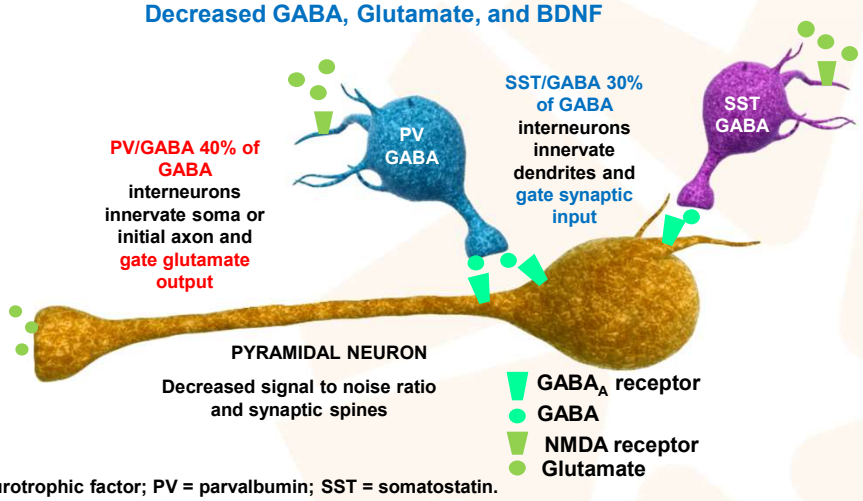
GABA and Glutamate Transmission in Major Depressive Disorder

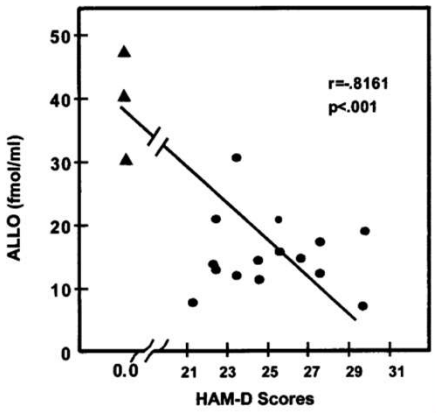
Chronic Stress/Depression
Decreased GABA, Glutamate, and BDNF



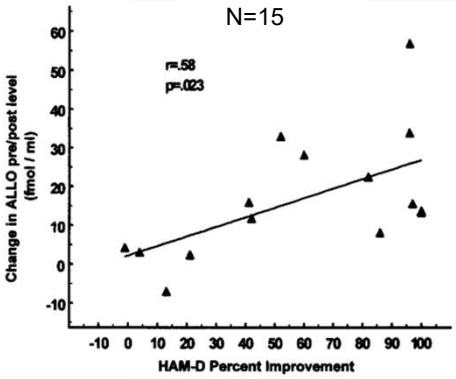
BDNF = brain-derived neurotrophic factor; PV = parvalbumin; SST = somatostatin.
Adapted from: Duman RS, et al. *Neuron*. 2019;102(1):75-90.

31

Depression is Associated with Reduced Cerebrospinal Fluid Allopregnanolone Levels



Negative correlation between the severity of depression (HAM-D) and ALLO levels in CSF at baseline [*r*=.081; *P*=.01]

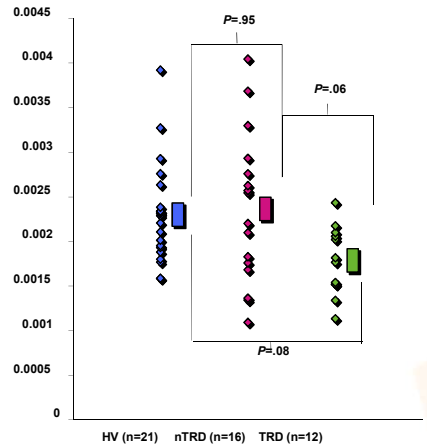


Fluoxetine or fluvoxamine related increase in ALLO content of CSF correlates with the improvement in the HAM-D score [*r*=.58; *P*=.023]

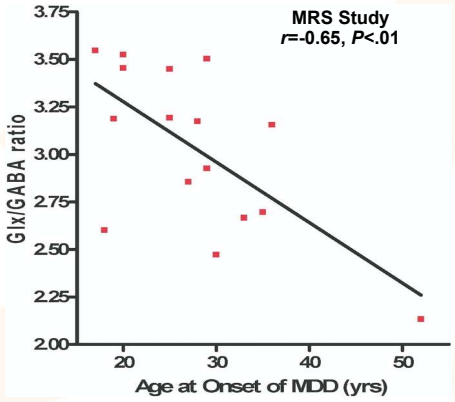
ALLO = allopregnanolone; CSF = cerebrospinal; HAM-D = Hamilton Rating Scale for Depression.
Uzunova V, et al. *Proc Natl Acad Sci U S A*. 1998;95(6):3239-3244.

32

GABA in Major Depressive Disorder



GABA/W ratios (arbitrary units [a.u.]) in the ACC of HV, patients with nTRD, and patients with TRD.



Correlation of age of onset of major depression and Glx/GABA ratio in vmPFC in participants with MDD in full remission (N=16).

ACC = anterior cingulate cortex; Glx = glutamate/glutamine; HV = healthy volunteers; MRS = magnetic resonance spectroscopy; nTRD = non-treatment-resistant major depression; TRD = treatment-resistant depression; vmPFC = ventromedial prefrontal cortex.

Price RB, et al. *Biol Psychiatry*. 2009;65(9):792-800. Hasler G, et al. *Biol Psychiatry*. 2005;58(12):969-973.

Key Learning Points

- Neurosteroids are synthesized in central and peripheral nervous system
- Neurosteroids are positive and negative modulators of $GABA_AR$ mediated signaling
- Neuroactive steroids participate in regulation of *stress response, aggression and anxiety, sleep, memory, mood, neuroplasticity, and pain threshold*
- Allopregnanolone and GABA signaling are altered in MDD

Neurons, Glia, GABA, and Inflammation in Major Depressive Disorder

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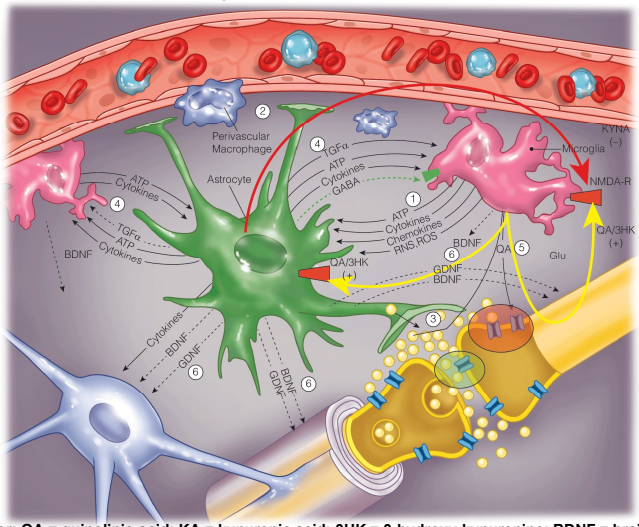
Interactions at the Glia–Synaptic Junction in Bipolar Disorder

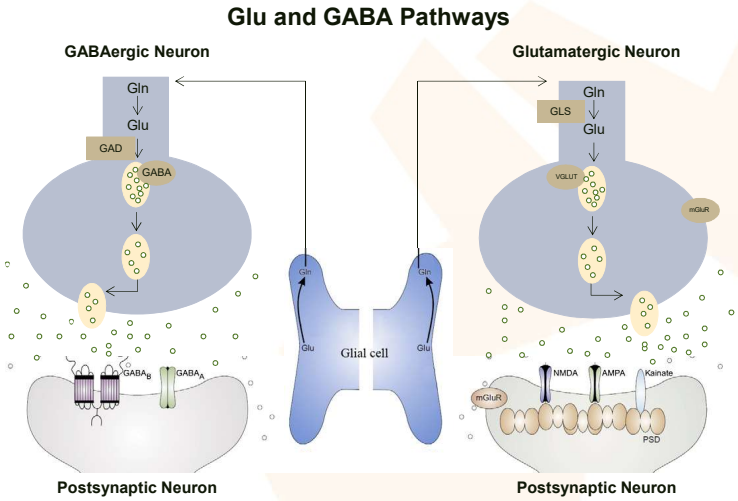


NMDA-R = N-methyl-D-aspartate receptor; QA = quinolinic acid; KA = kynurenic acid; 3HK = 3-hydroxy-kynurenine; BDNF = brain-derived neurotrophic factor; GDNF = glial-derived neurotrophic factor; TGF = transforming growth factor; ATP = adenosine triphosphate; Glu = glutamate; GABA = gamma-aminobutyric acid.

Modified from: Maletic V, DeMuri-Maletic B. Bipolar Disorders and Their Clinical Management, Part I: Epidemiology, Etiology, Genetics, and Neurobiology. In: Black DW (Ed). *Scientific American Psychiatry*. Decker; 2018.

36

Do glial cells regulate Glutamate/GABA balance?



GAD = glutamic acid decarboxylase; GLS = glutaminase; Gln = glutamine; Glu = glutamate; VGLUT = vesicular Glu transporters.
Zhao J, et al. *J Affect Disord*. 2012;138(3):494-502.

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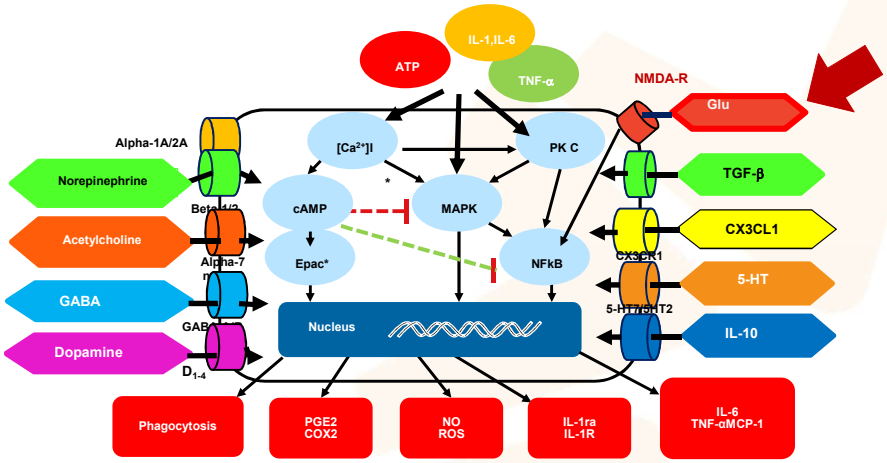
Regulation of Microglial Activation



Microglia are activated by proinflammatory cytokines (eg, IL-1β), endogenous antigens (eg, Aβ), exogenous antigens (eg, LPS), or ATP. Norepinephrine has properties to inhibit microglial inflammatory reactions through the activation of cAMP and suppression of downstream MAPK and/or NFkB.

Adapted from: Maletic V, Raison CL. *The New Mind-Body Science of Depression*. New York, NY: WW Norton; 2017. Liu H, et al. *Stroke Vasc Neurol*. 2016;1(2):52-58.

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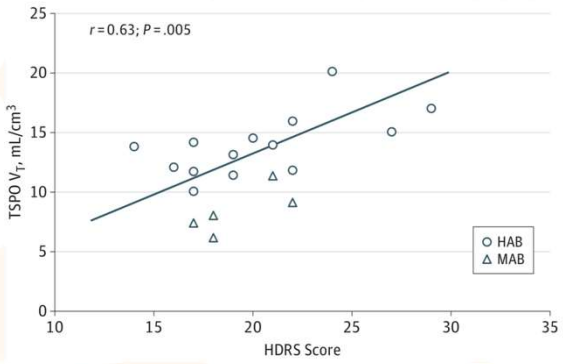
Major Depressive Disorder Symptom Severity Correlates with Microglial Activation (TSPO)

- HDRS

0–7 no depression
8–15 mild symptom level
16–20 substantial level of symptoms
> 20 moderate–to–severe depression

- Differential binding according to the single-nucleotide polymorphism rs6971 of the TSPO gene, resulting in HAB and MAB



HAB = high affinity binders; HDRS = Hamilton Rating Scale for Depression; MAB = mixed affinity binders; TSPO = translocator protein; TSPO vT = translocator protein total distribution volume.
Setiawan E, et al. *JAMA Psychiatry*. 2015;72(3):268-275.

Key Learning Points

- GABA has a role in regulation of microglia function and neuroinflammation
- Astrocytes are important GABA producers in the CNS
- Astrocytes are involved in regulation of GABA / Glutamate balance
- Severity of MDD correlates with microglial activation

GABA, Neurosteroids, and Neural Networks in Major Depressive Disorder

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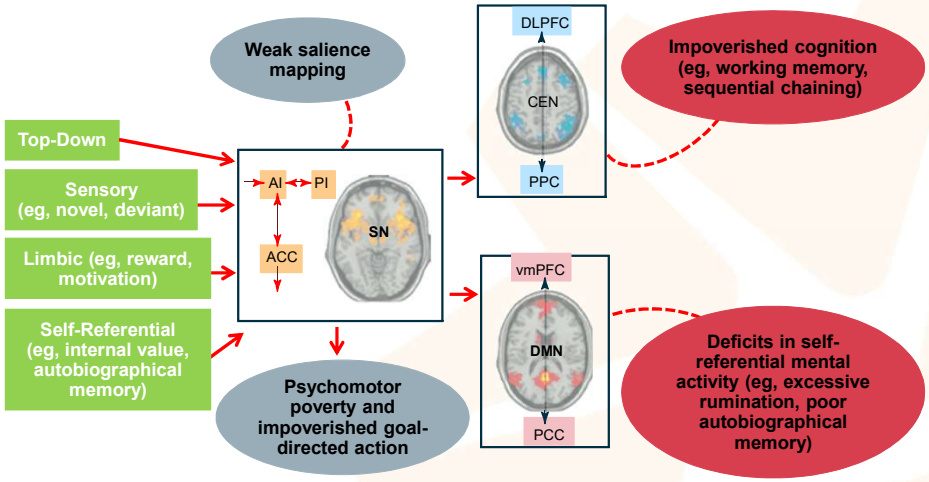
The 3 Network Theory of Mood Disorders



ACC = anterior cingulate cortex; AI = anterior insular; CEN = central executive network; DLPFC = dorsolateral prefrontal cortex; DMN = default mode network; PCC = posterior cingulate cortex; PI = posterior insular; PPC = posterior parietal cortex; SN = substantia nigra; vmPFC = ventromedial prefrontal cortex.

Menon V. *Trends Cogn Sci*. 2011;15(10):483-506.

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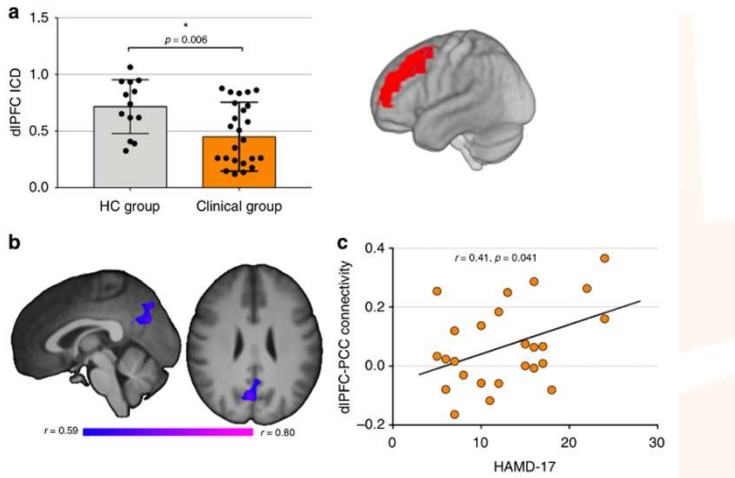
Aberrant Default Mode Network–dlPFC Connectivity is Associated with Severity of Major Depressive Disorder

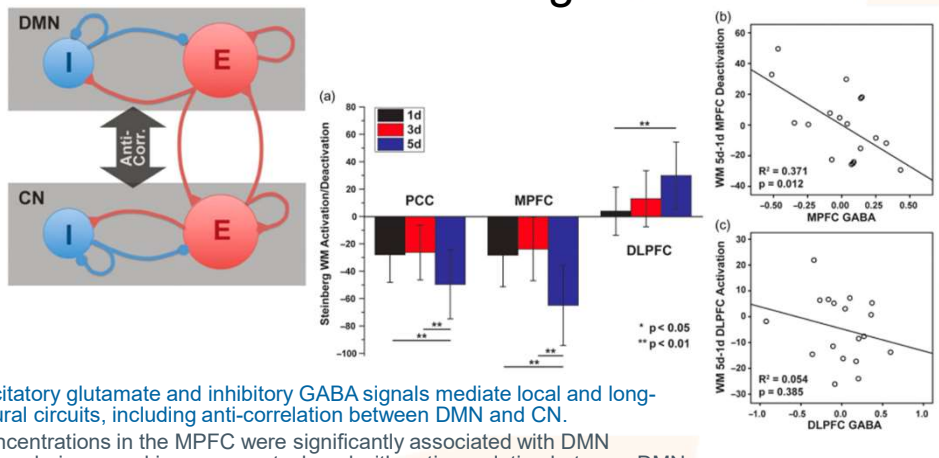
Positive correlation between dlPFC–PCC connectivity and severity of depressive symptoms



dlPFC = dorsolateral prefrontal cortex; HC = healthy comparison; ICD = intrinsic connectivity distribution; PCC = posterior cingulate cortex.
Holmes SE, et al. *Nat Commun*. 2019;10(1):1529.

43

GABA Regulates Connectivity between Default Mode Network and Cognitive Control Network



Rapid excitatory glutamate and inhibitory GABA signals mediate local and long-range neural circuits, including anti-correlation between DMN and CN.

GABA concentrations in the MPFC were significantly associated with DMN deactivation during a working memory task and with anti-correlation between DMN and CN at rest and during task performance.

CN = control network; DMN = default mode network; DLPFC = dorsolateral prefrontal cortex; E = excitatory; I = inhibitory; MPFC = medial prefrontal cortex; PCC = posterior cingulate cortex.
Chen X, et al. *Cereb Cortex*. 2019;29(4):1607-1618.

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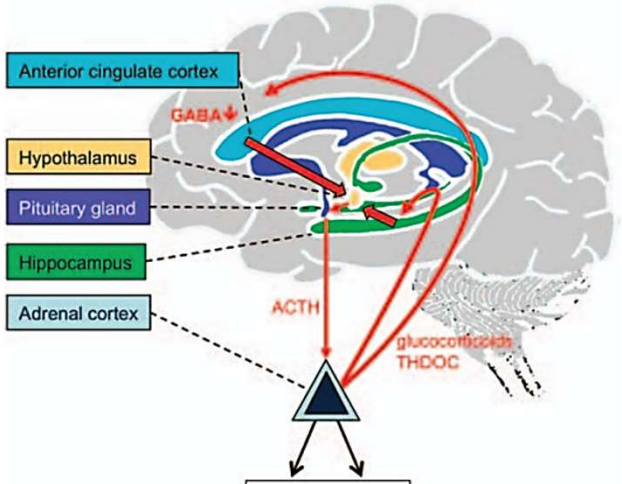
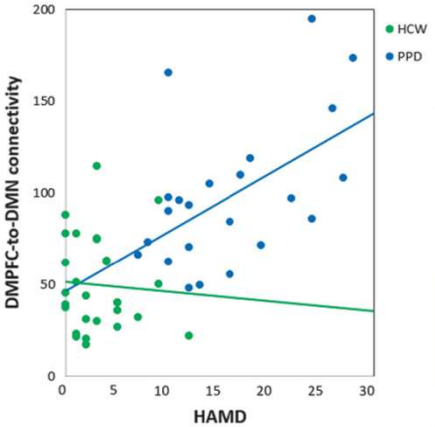
Decreased GABA Signaling in ACC May Precipitate Aberrant Stress Response



ACC = anterior cingulate cortex; ACTH = adrenocorticotropic hormone; THDOC = [allo]tetrahydrodeoxycorticosterone.
Luscher B, et al. *Mol Psychiatry*. 2011;16(4):383-406.

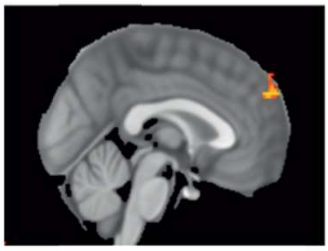
45

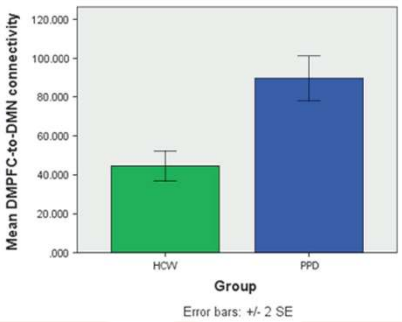
Increased Default Mode Network Activity in Peripartum Depression



DMN component connectivity of DMPFC to the rest of the network was related to PPD.

HCW (n=28)
PPD (n=23)





DMN = default mode network; DMPFC = dorsomedial prefrontal cortex; HCW = healthy comparison women.
Deligiannidis KM, et al. *Neuropsychopharmacology*. 2019;44(3):546-554.

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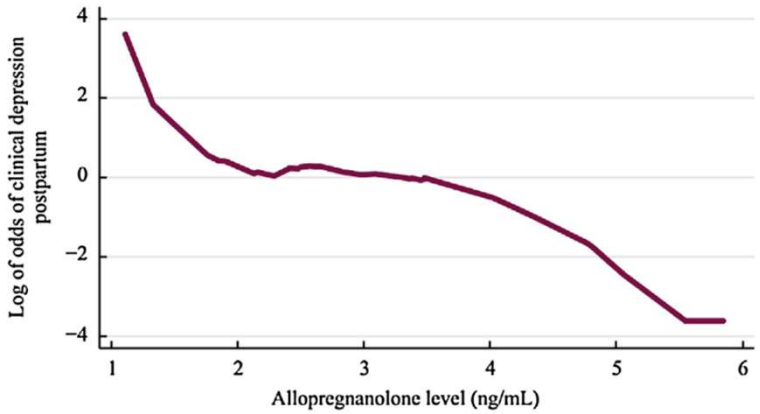
Lower Allopregnanolone Levels Predict the Risk of Postpartum Depression



N=60 pregnant women with a prior diagnosis of a mood disorder.

Osborne LM, et al. *Psychoneuroendocrinology*. 2017;79:116-121.

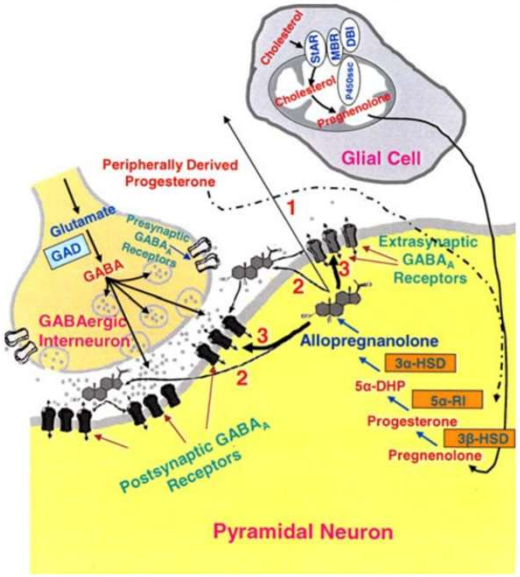
Key Learning Points

- MDD is associated with dysfunction of major functional networks
- GABA regulates connectivity between major functional networks
- Functional networks and GABA signaling are altered in peripartum depression
- Allopregnanolone signaling predicts the risk of PPD

GABA and Neurosteroids in Treatment of Major Depressive Disorder

Mode of Allopregnanolone Action

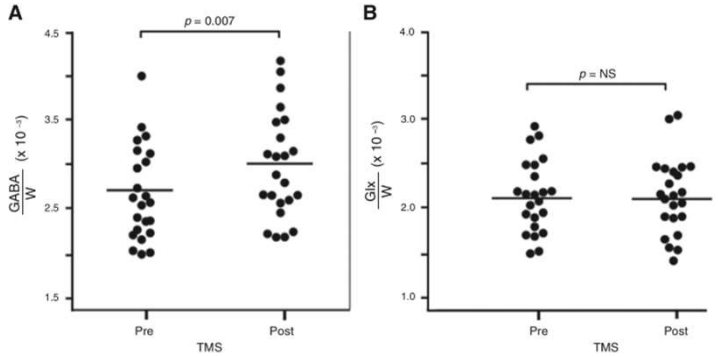
Allopregnanolone facilitates the synaptic inhibitory action of GABA at postsynaptic and extrasynaptic $GABA_A$Rs by a paracrine (**arrow 1**) or autocrine (**arrow 2**) mechanism or may access $GABA_A$Rs by acting at the intracellular sites (**arrow 3**) of the $GABA_A$R.



DBI = diazepam binding inhibitor; GAD = glutamic acid decarboxylase; MBR = mitochondria benzodiazepine receptor; StAR = steroidogenic acute regulatory protein.

Pinna G, et al. *Neurochem Res*. 2008;33(10):1990-2007.

Successful TMS Treatment Elevates GABA in MPFC of Patients with Treatment-Resistant Depression



GABA/unsuppressed voxel water signal (GABA/W) levels in the MPFC in patients with depression before and after a 25-session treatment with TMS over the left DLPFC. Subgroup of TMS responders. GABA/W increases by 17.4% post-TMS compared with baseline (*P*=.07). In the subgroup of TMS nonresponders there was an 11.9% change in GABA/W post-TMS compared with baseline (*P*=.10). N=25 patients with TRD.

DLPFC = dorsolateral prefrontal cortex; Glx = combined resonance of glutamate and glutamine; MPFC = medial prefrontal cortex; NS = nonsignificant; TMS = transcranial magnetic stimulation; TRD = treatment-resistant depression.

Dubin MJ, et al. *J Psychiatry Neurosci*. 2016;41(3):E37-E45.

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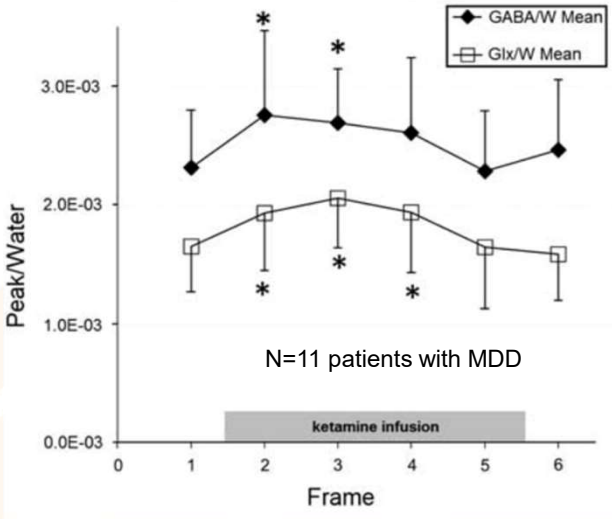
Ketamine Increases GABA and Glutamate in mPFC of Patients with Major Depressive Disorder

MRS measurement of GABA/water and Glx/water concentrations in mPFC in MDD before (baseline frame), during (frame 1–4) and after (frame 5–6) an intravenous ketamine infusion (40-minute duration). Frame duration was 13:20 minutes.

Mean areas under the curve for Glx/W (*P*=.025) and GABA/W (*P*=.005) increased and correlated (*r*=.796; *P*=.018)



N=11 patients with MDD

***Statistically significant group increases in GABA and Glx concentrations relative to pre-ketamine baseline levels.**

Milak MS, et al. *Mol Psychiatry*. 2016;21(3):320-327.

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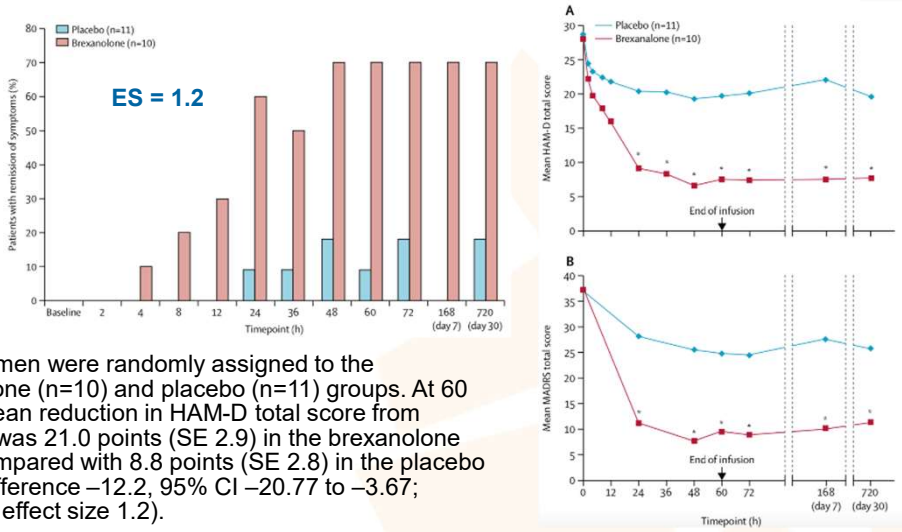
Brexanolone in Postpartum Depression



N=21 women were randomly assigned to the brexanolone (n=10) and placebo (n=11) groups. At 60 hours, mean reduction in HAM-D total score from baseline was 21.0 points (SE 2.9) in the brexanolone group compared with 8.8 points (SE 2.8) in the placebo group (difference –12.2, 95% CI –20.77 to –3.67; *P*=.0075; effect size 1.2).

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

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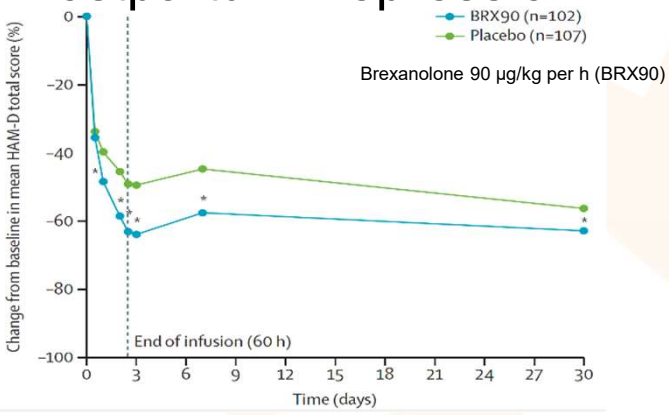
Brexanolone Injection as Treatment for Postpartum Depression



In study 1, at 60 hours, the LS mean reduction in HAM-D total score from baseline was 19.5 points (SE 1.2) in the BRX60 group and 17.7 points (1.2) in the BRX90 group compared with 14.0 points (1.1) in the placebo group (difference –5.5 [95% CI –8.8 to –2.2], *P*=.0013 for the BRX60 group; –3.7 [95% CI –6.9 to –0.5], *P*=.0252 for the BRX90 group). In study 2, at 60 hour, the LS mean reduction in HAM-D total score from baseline was 14.6 points (SE 0.8) in the BRX90 group compared with 12.1 points (SE 0.8) for the placebo group (difference –2.5 [95% CI –4.5 to –0.5], *P*=.0160).

Meltzer-Brody S, et al. *Lancet.* 2018;392(10152):1058-1070.

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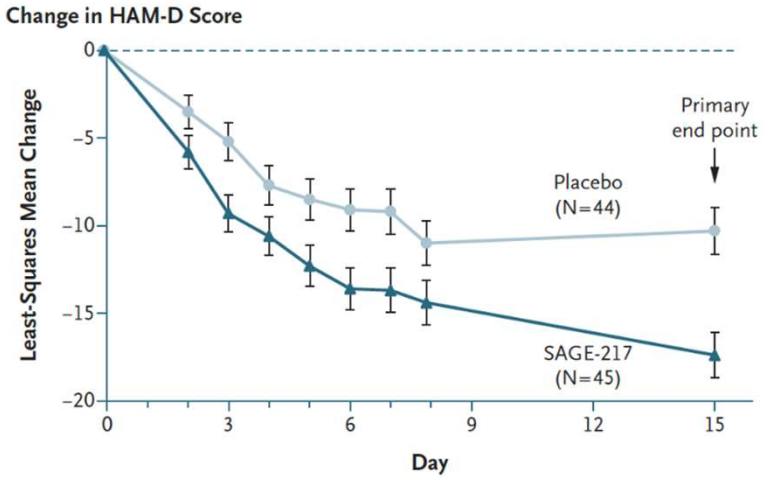
Positive $GABA_A$ Receptor Modulator in Major Depressive Disorder



N=45 patients were assigned to the SAGE-217 group, and 44 to the placebo group. Baseline HAM-D scores 25.2 ± 2.6 and 25.7 ± 2.4, respectively. Use of antidepressants at baseline — no. (%) SAGE 217: 12 (27%); PBO: 10 (23%).

Gunduz-Bruce H, et al. *N Engl J Med*. 2019;381(10):903-911.

Key Learning Points

- Several antidepressant treatments including rTMS and ketamine ameliorate GABA signaling in patients with MDD
- Neurosteroid brexanolone has established efficacy in treatment of PPD
- Positive allosteric modulator of $GABA_A$ receptors, SAGE-217, has preliminary evidence of efficacy in MDD treatment studies

Anna

Presentation | Past Psychiatric History | Treatment | Follow-Up

- 32-year-old married female, 3 weeks postpartum
- OB/GYN referral for treatment of depression, which started during the last 6 weeks of gestation
- Feeling sad and tired most of the days. She is waking up often during the night
- Anhedonia; loss of interest for work and hobbies
- Anna has to “make” herself play with her child
- She and her husband have had marital problems in the past. They believed that another child would bring them closer together
- Anna is concerned that she is not losing her “baby weight”
- She is very anxious and irritable

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Anna

Presentation | Past Psychiatric History | Treatment | Follow-Up

- Anna has had 3 previous depressive episodes, including 1 after her previous pregnancy. Her daughter is 5 years old now
- Past episodes responded to a combination of SSRIs and psychotherapy. Treatment was cut short in the past by emergence of sexual side effects and weight gain
- She is currently ruminating about her weight gain and the risk of losing her job. Anna fears that unless she can “get it together” her husband may eventually divorce her
- PHQ-9 = 21; MDQ = negative; EPDS = 18

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Anna

Presentation | Past Psychiatric History | Treatment | Follow-Up

- Pregnancy was unremarkable aside from pronounced first trimester "morning" sickness
- She is overweight (BMI = 28)
- Physical exam and vital signs were wnl
- Anna was treated with appropriate dose of an SNRI for 6 weeks
- Despite initial partial improvement her depression has worsened now, and she is beginning to feel hopeless and has developed passive suicidal ideation
- Most recent T3, T4, and TSH were wnl
- After thorough discussion of potential risk and benefits, decision was made to initiate treatment with a 60-hour neurosteroid IV infusion

BMI = body mass index; SNRI = serotonin–norepinephrine reuptake inhibitor; TSH = thyroid stimulating hormone.

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Anna

Presentation | Past Psychiatric History | Treatment | Follow-Up

- Anna has returned for a 2-week follow-up visit
- SNRI treatment was tapered and then discontinued
- Her affect is much brighter and she reports substantially improved mood, energy, sleep, sexual response, and enthusiasm
- Anna is still on maternity leave so she is able to enjoy her time with children
- First 2 days of treatment, Anna experienced somnolence in the morning hours, dizziness, and transient nausea. These side effects at first abated and then completely stopped
- PHQ-9 = 21 → 7; EPDS = 18 → 6

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Summary

- Significant number of patients suffering from MDD and PPD do not achieve clinical and functional remission with currently available treatments
- MDD is clinically and biologically heterogeneous condition
- GABA and neurosteroid signaling are compromised in a portion of individuals suffering from MDD and PPD
- Novel treatments modulating GABA transmission, including neurosteroid derivatives may be very effective in a subcategory of patients with depression

Psych Congress

Q&A