

#CHAIR2020

12TH ANNUAL
CHAIR SUMMIT

CME
Outfitters

Master Class for Neuroscience Professional Development

February 27-29, 2020 | The LINQ | Las Vegas, Nevada

Provided by
CME
Outfitters



GABA-enhancing Neurosteroids as New Treatments in Psychiatry

Charles F. Zorumski, MD

Samuel B. Guze Professor and Head of Psychiatry
Professor of Neuroscience
Director, Taylor Family Institute for Innovative
Psychiatric Research
Washington University School of Medicine
St. Louis, MO



Charles F. Zorumski, MD

Disclosures



- **Research/Grants:** Bantly Foundation; National Institute of Mental Health (NIMH) and Sage Therapeutics
- **Consultant:** Sage Therapeutics, Inc. and Takeda Pharmaceuticals U.S.A., Inc.
- **Stockholder (directly purchased):** Sage Therapeutics, Inc.
- **Patents:** Neurosteroid analogs & GABA receptors; redox reagents & T-channels; oxysterols as neuroprotectants

Learning Objective 1

Evaluate the latest clinical evidence on the safety and efficacy of neurosteroids in treating mood disorders.



Psychiatry Needs New Treatments!



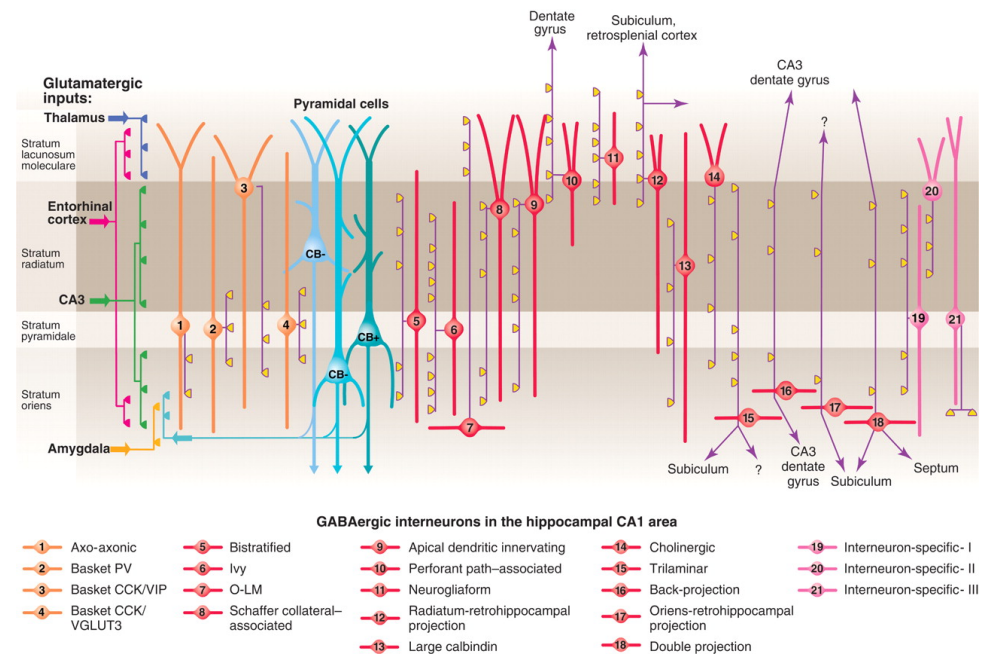
- Psychiatric illnesses cause much disability & death
- Current treatments are good...not great
 - Fair response & remission rates...high relapse
 - Same targets (monoamines)...same results
- Are GABA receptors & neurosteroids viable targets?

GABA = gamma-aminobutyric acid.

GABA as a Neurotransmitter



- Major fast inhibitory transmitter in brain
 - Usually acts within local brain circuits
 - Released from interneurons...21 types in CA1 hippocampus
 - Regulates excitatory/inhibitory (E/I) balance
 - Required for fine-tuning neural circuits & regulating cell firing and neural oscillations



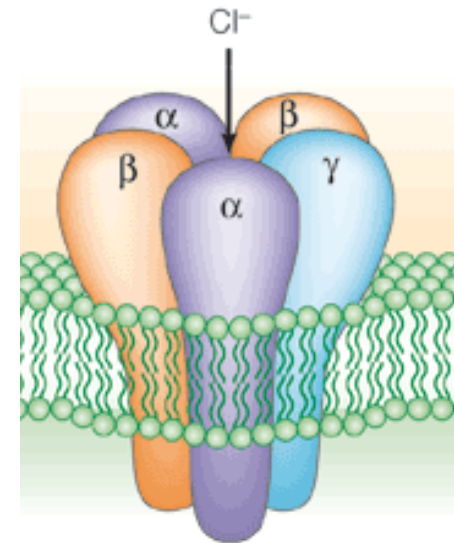
E/I = excitation/inhibition.

Zorumski CF, et al. *Neurobiol Stress*. 2019;11:100196. Klausberger T, et al. *Science*. 2008;321(5885):53-57.

GABA as a Neurotransmitter (cont.)

● GABA Receptors

- GABA_ARs: ligand-gated chloride channels – fast (ms)
 - 19 different subunits (α 1-6, β 1-3, γ 1-3, δ , ϵ , ρ 1-3, π , θ)
 - Pentamers typically with 2 α , 2 β , + γ/δ subunits...20-30 subtypes in brain
 - Act at synaptic (γ 2 subunits) & extrasynaptic sites (δ subunits) → to mediate phasic & tonic inhibition
 - Sites of action of BDZs, barbs, certain anesthetics
- GABA_BRs: G-protein coupled receptors – slow (sec)
 - Site of action of baclofen



GABA_ARs = γ -Aminobutyric acid type A receptors; G-protein = guanine nucleotide-binding proteins;
ms = millisecond; BDZ = benzodiazepine; barb = barbiturates.

Zorumski CF, et al. *Neurobiol Stress*. 2019;11:100196. Belelli D, Lambert JJ. *Nature Rev Neurosci*. 2005; 6: 565-575.

GABA & Depression



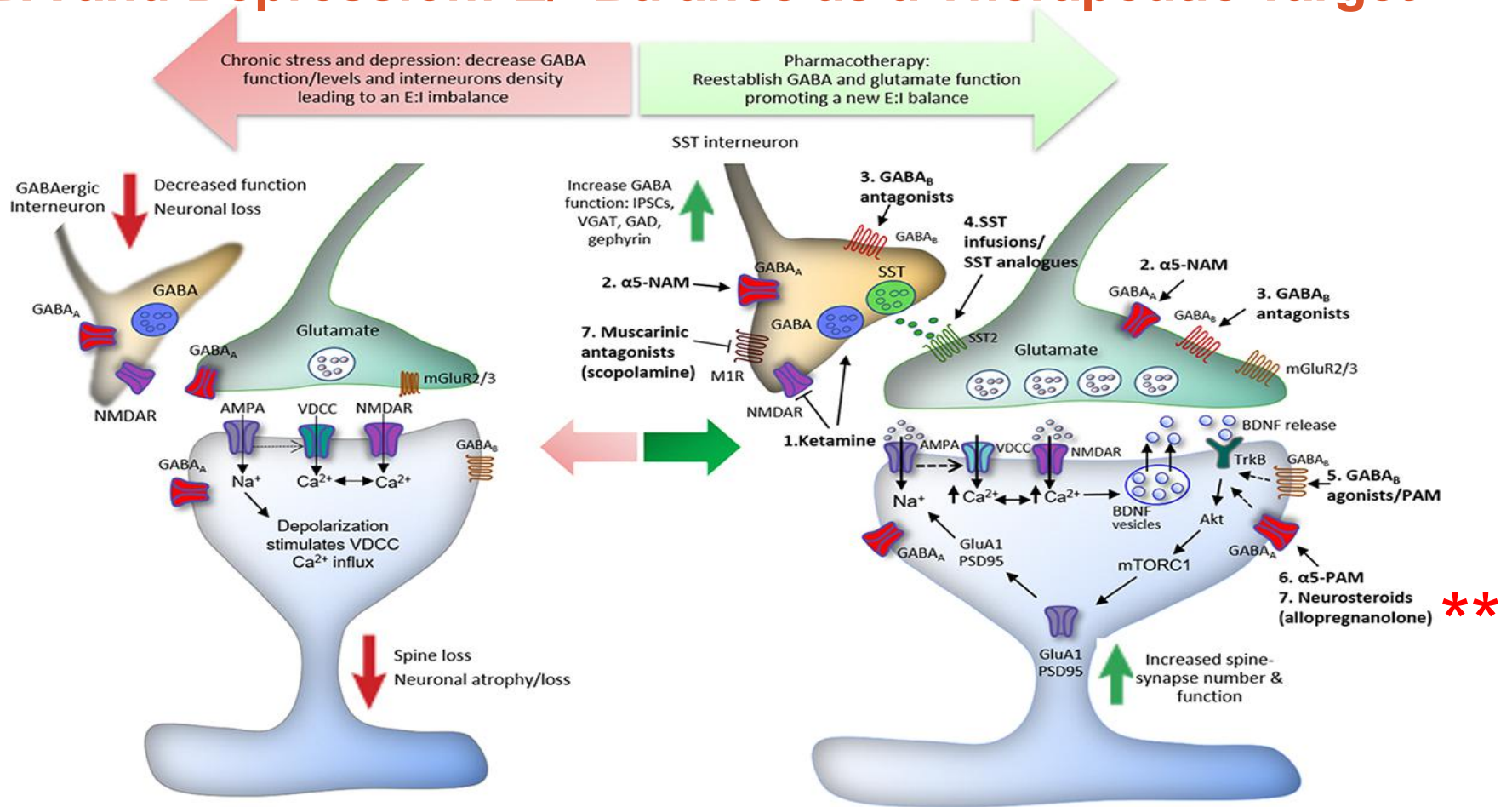
Human Studies

- ↓ GABA levels in plasma, CSF & resected neocortex
- ↓ GABA in cortex by MR spectroscopy
- ↓ Calbindin⁺ (SST⁺) interneurons in PFC/HC
- Genetic associations with $\alpha 4$, $\alpha 5$, $\beta 1$, $\beta 3$ GABA_AR subunits

CSF = cerebrospinal fluid; HC = hippocampus; PFC = prefrontal cortex;
MR = magnetic resonance; SST = somatostatin.

Fogaca MV, et al. *Front Cell Neurosci.* 2019;13:87; Luscher B, et al. *Mol Psychiatry.* 2011;16:383-406.

GABA and Depression: E/I Balance as a Therapeutic Target



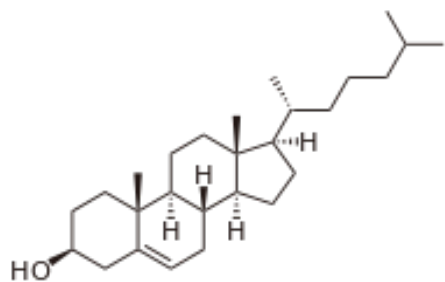
Targeting GABA_ARs for Novel Psychiatric Treatments

Neurosteroids and Neuroactive
Steroids

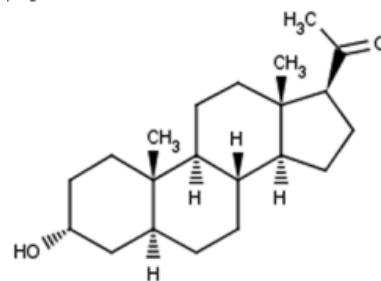


Neurosteroids and Neuroactive Steroids

- **Neurosteroids** – endogenous steroids that are synthesized in the nervous system from cholesterol or sterol precursors
- **Neuroactive steroids** - endogenous and exogenous steroids that modulate nervous system function

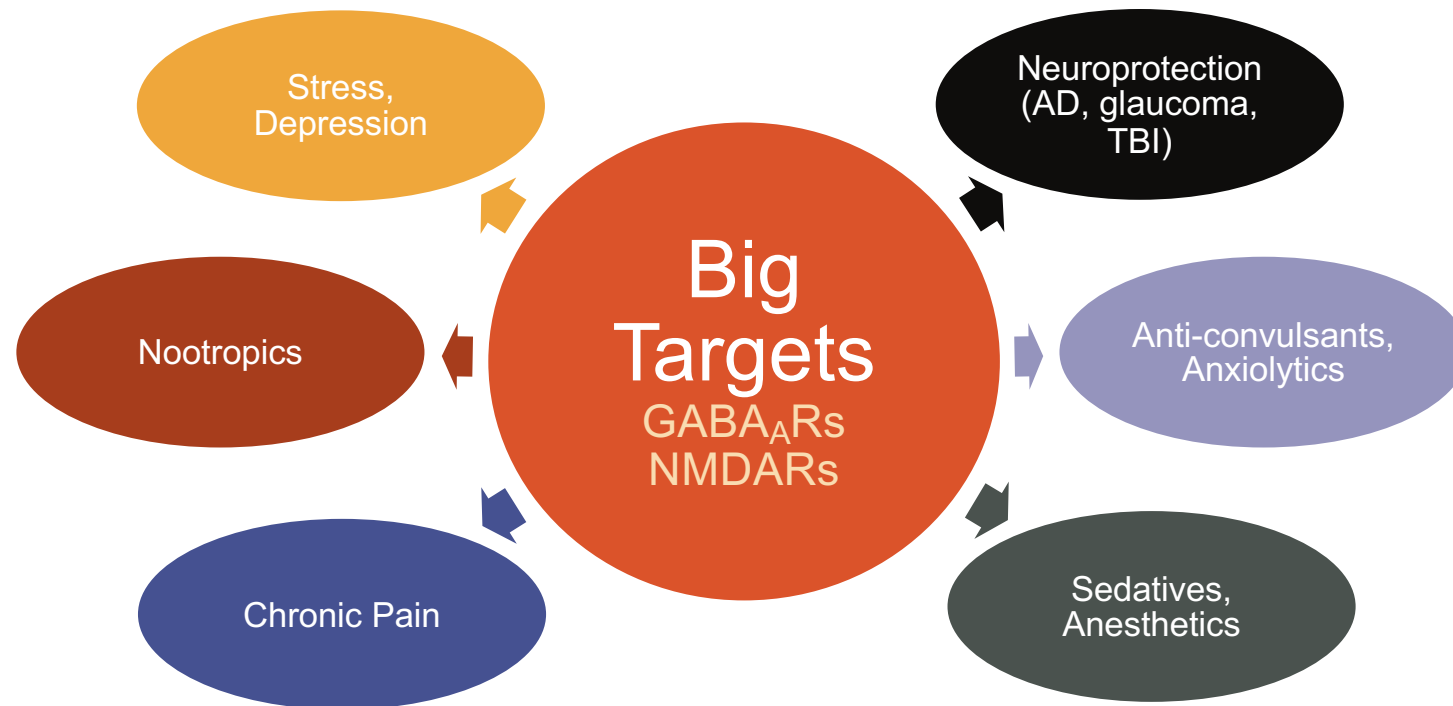


Cholesterol



Allopregnanolone, 3 α 5 α P
Brexanolone

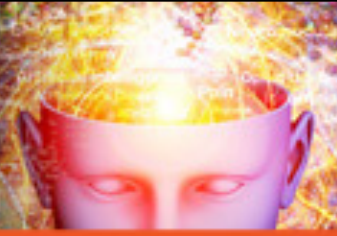
Why Neurosteroids?



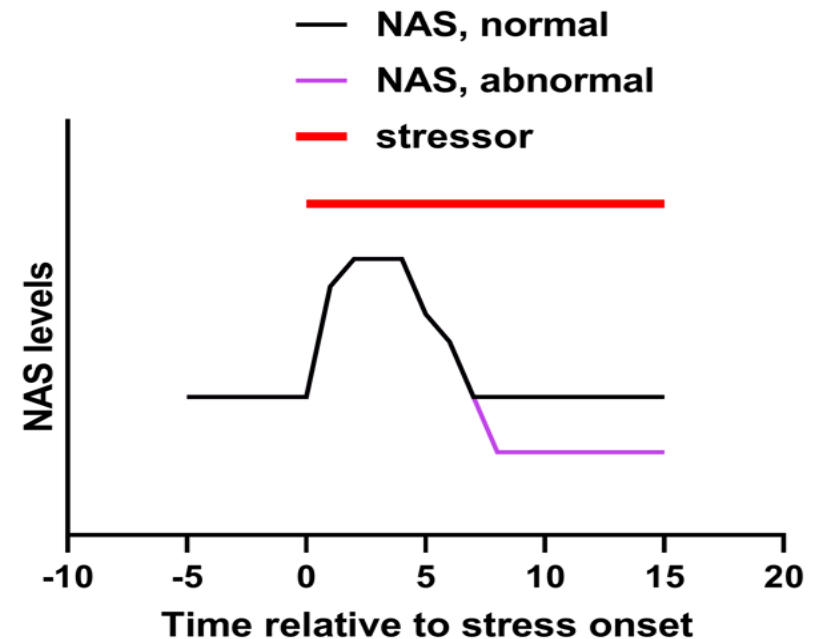
AD = Alzheimer's Disease; TBI = traumatic brain injury.

Zorumski CF, et al. *Neurosci Biobehav Rev.* 2013;37:109-122; Zorumski CF, et al. *Neurobiol Stress.* 2019;11:100196.

Why GABAergic Neurosteroids?



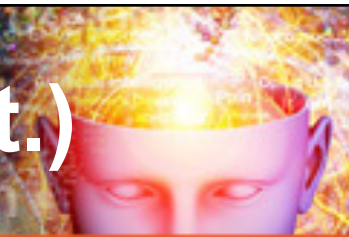
- Acute “on-demand” modulators of neuronal stress
 - Made in excitatory (glutamate) neurons + other cells
- Chronic stress depletes neurosteroids
 - Animal models & humans



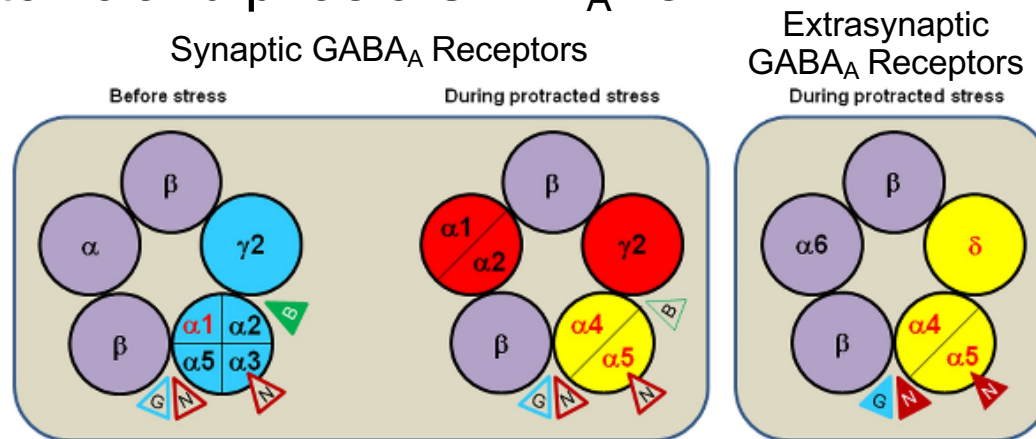
NAS = neuroactive steroids.

Zorumski CF, et al. *Neurosci Biobehav Rev.* 2013;37:109-122; Zorumski CF, et al. *Neurobiol Stress.* 2019;11:100196; Luscher B, et al. *Mol Psychiatry.* 2011;16:383-406; Locci A, et al. *Br J Pharmacol.* 2017;174:3226-3241; Pinna G. *Front. Behav. Neurosci.* 2019;13:114.

Why GABAergic Neurosteroids? (cont.)



- Chronic stress alters expression of GABA_AR subunits favoring effects of neurosteroid GABA PAMs
 - ↓ $\gamma 2$ (phasic inhibition) + ↑ δ (tonic inhibition)
- Neurosteroids correct E/I balance in networks under stress by acting at BOTH tonic and phasic GABA_ARs



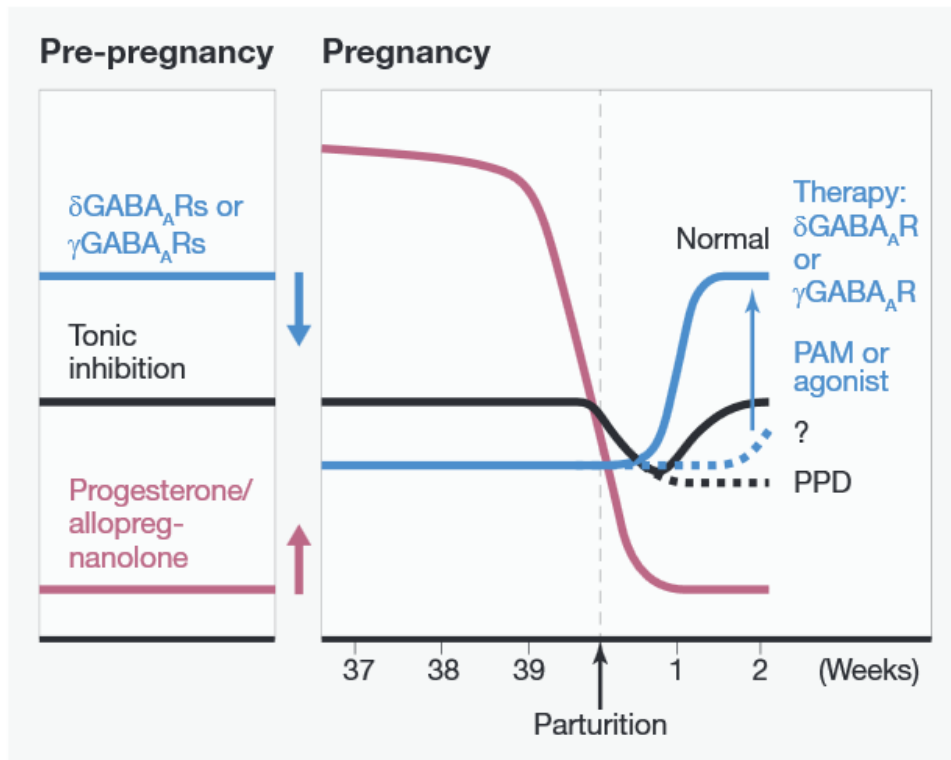
Stress
 Red = ↓ expression
 Yellow = ↑ expression

NAS ↑ function + expression of GABA_ARs

Zorumski CF, et al. *Neurosci Biobehav Rev.* 2013;37:109-122; Zorumski CF, et al. *Neurobiol Stress.* 2019;11:100196; Luscher B, et al. *Mol Psychiatry.* 2011;16:383-406; Locci A, et al. *Br J Pharmacol.* 2017;174:3226-3241; Pinna G. *Front. Behav. Neurosci.* 2019;13:114.

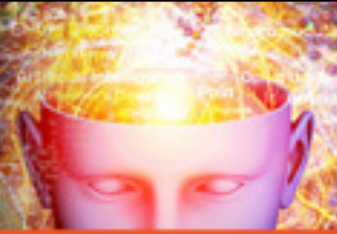
Neurosteroids as Novel Treatments

Rationale for Postpartum Depression



- During the postpartum period, the brain's inhibitory GABA_A receptors may not recover in time following their reduced numbers during pregnancy.
- This may be the cause of postpartum depression prevalent in ~12% of childbearing women.
- A new therapy for this condition consists of administering a synthetic neurosteroid during the postpartum period to alleviate the mood disorder.

Postpartum Depression: Brexanolone ~ Dosing & Side Effects



Dosing

- 60 h IV infusion at 60 vs. 90 $\mu\text{g}/\text{kg}/\text{h}$
- Dose ramped over 24 h \rightarrow maintain to 52 h
- \rightarrow taper over final 8 hours
- Doses selected to mimic pregnancy (~ 100 nM)

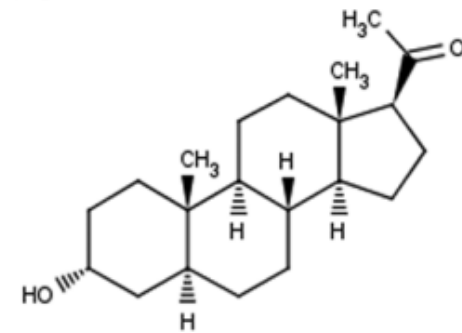
Side Effects

- Headache, dizziness, somnolence

Serious / Severe Adverse Effects

- Suicidal ideation + overdose (N = 1)
- Altered consciousness + syncope, excess sedation (N = 5)

Brexanolone =
IV allopregnanolone in CDX
FDA approved, March 2019



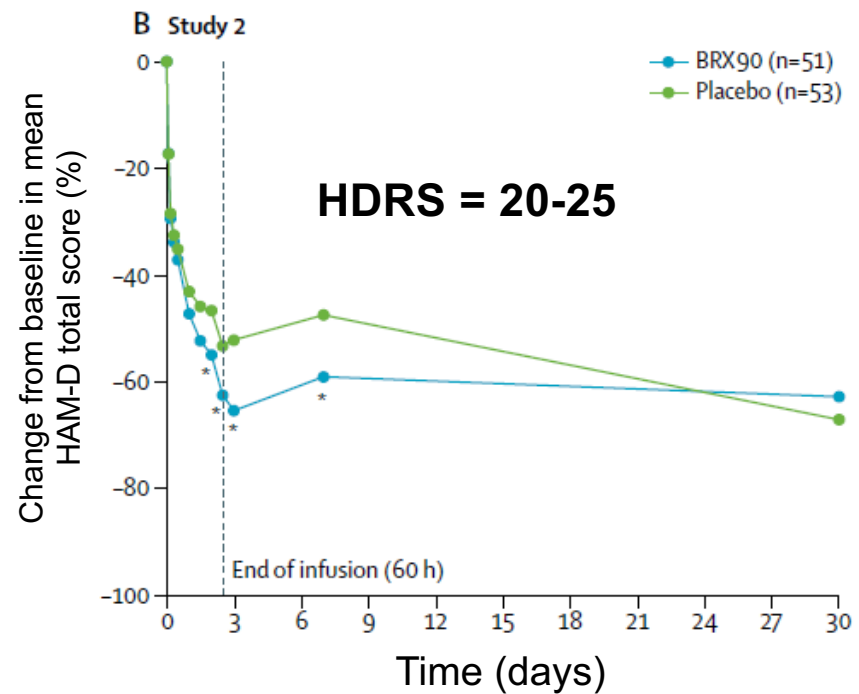
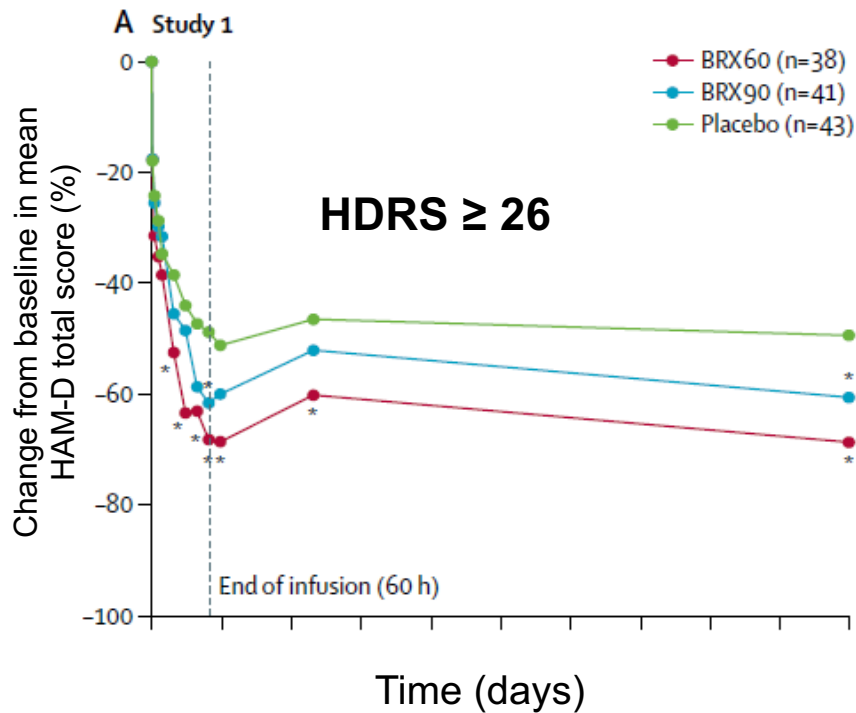
CDX = Captisol (polyanionic beta cyclodextrin)

Kanes S, et al. *Lancet*. 2017;390:480-489; Meltzer-Brody S, et al. *Lancet*. 2018;392:1058-1070.

Postpartum Depression



Brexanolone: Phase 3 Clinical Trials



BRX90 = brexanolone 90 $\mu\text{g}/\text{kg}$ per hour; HDRS = Hamilton Depression Rating Scale.

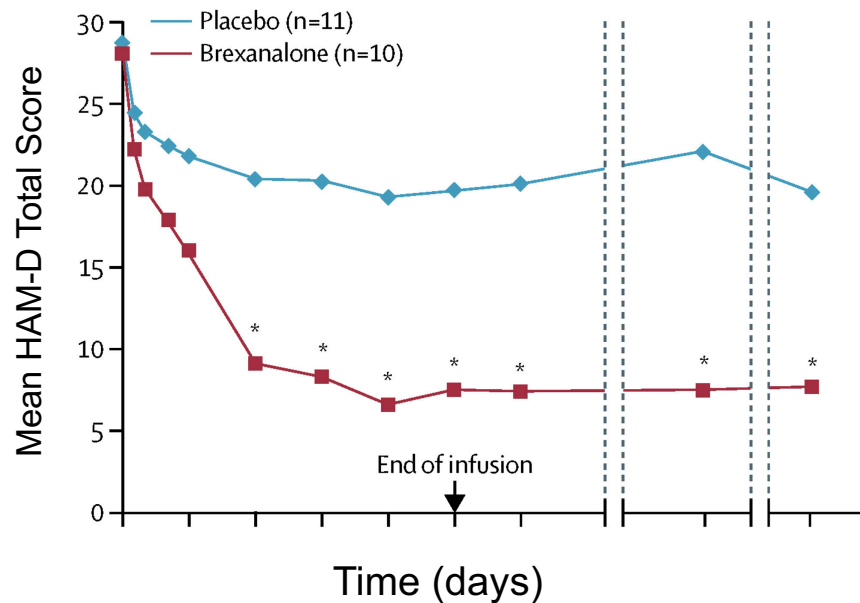
Kanes S, et al. *Lancet*. 2017;390:480-489; Meltzer-Brody S, et al. *Lancet*. 2018;392:1058-1070.

Postpartum Depression

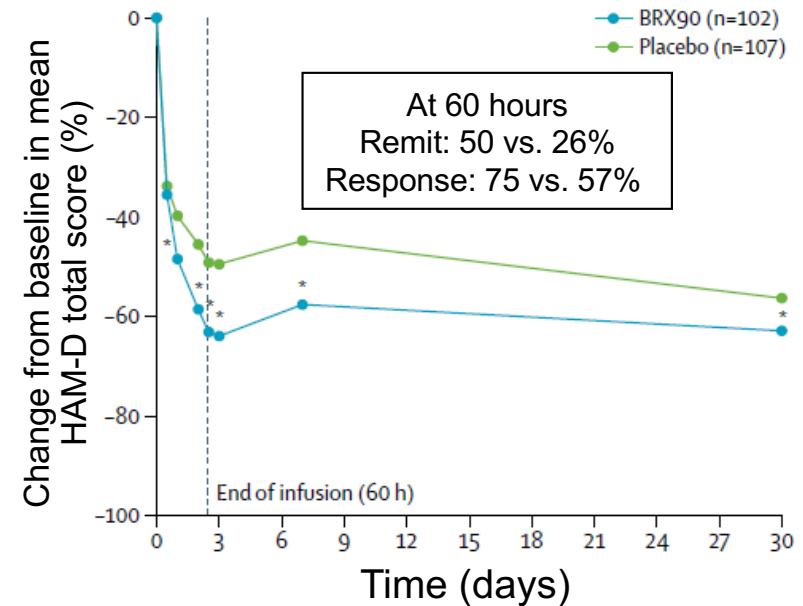


Brexanolone: Phase 2B & 3 Clinical Trials

Phase 2B



BRX90 Combined



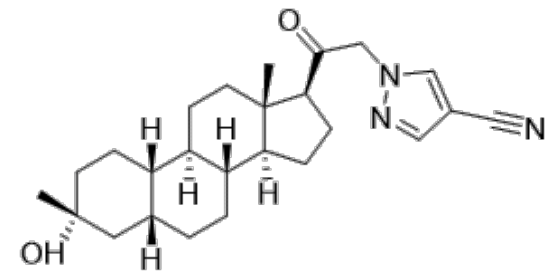
Kanes S, et al. *Lancet*. 2017;390:480-489; Meltzer-Brody S, et al. *Lancet*. 2018;392:1058-1070.

What About an Oral Drug?



Positive Phase 3 trial of Zuranolone

- Women with severe PPD (HRSD \geq 26; N=151)
 - SAGE-217: 1x/day at 30 mg x 2 weeks
- Response at 2 weeks: 72% vs. 48%
 - Remission at 2 weeks: 45% vs. 23%
- Response at 4 weeks: 75% vs. 57%
 - 53% vs. 30% remission
- Side effects: 60% vs. 52%
 - Somnolence: 12.8% vs. 8.2%



PPD = postpartum depression; SAGE-217 = zuranolone.

Lasser R, et al. *Eur Neuropsychopharmacol.* 2019;29(Suppl 6):S219; Vieta E. 32nd European College of Neuropsychopharmacology (ECNP) Congress; 2019. Presentation No. S.0808.

What About Major Depression?

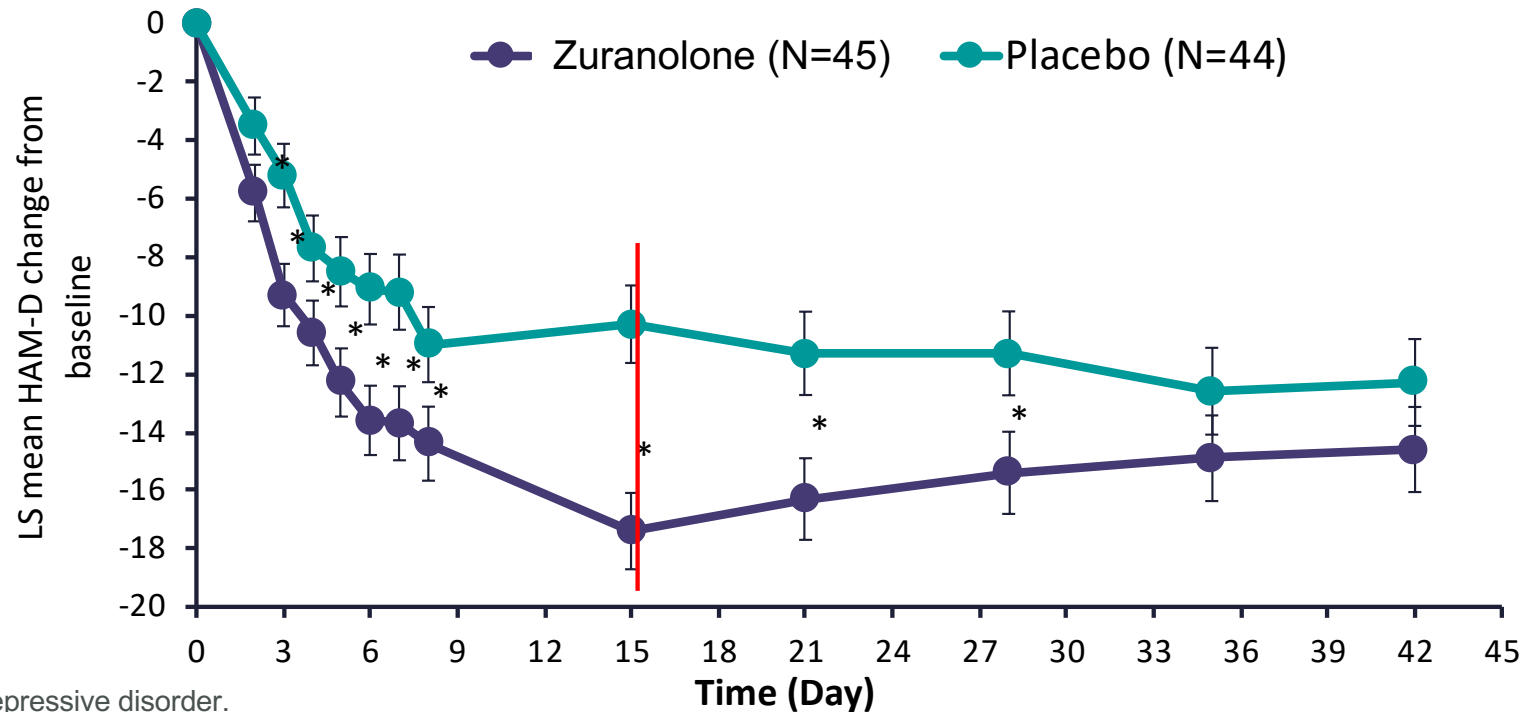


- ↓ Plasma & CSF AlloP in depression
 - Reverses with antidepressants
 - Correlates with outcome
- ↑ CSF/plasma AlloP with fluoxetine, paroxetine, fluvoxamine & sertraline
 - Also seen with many BDZs, clozapine, olanzepine
 - ...not all antidepressants increase steroids (rTMS, mirtazepine)

AlloP = allopregnanolone; BDZs = benzodiazepines; rTMS = repetitive transcranial magnetic stimulation.
Strohle A, et al. *Biol Psychiatry*. 1999;45(3):274-277; . Uzunova V, et al. *Proc Natl Acad Sci U*. 1998;95(6):3239-3244;
Hellgren C, et al. *Neuropsychobiology*. 2014;69(3):147-153); Nin MS, et al. *Front Endocrinol Lausanne*. 2011;2:73.

Zuranolone & MDD: Phase 2B Trial

- Moderate to severe MDD (HAM-D ≥ 22); N = 89 women & men
- Once daily, 30 mg oral dose x 14 days
- Sustained effect after discontinuation?



MDD = major depressive disorder.
Gunduz-Bruce H, et al. *New Engl J Med.* 2019; 381:2178-2179.

Summary



- GABA is the major fast inhibitory transmitter in brain & is critical for regulating E/I balance
- Neurosteroids may offer unique ways to modulate brain networks
 - Modulate major neurotransmitter systems (GABA)
 - May modulate defects across “stress-related” disorders?
 - IV drug approved for PPD; oral drug in development
- May open broad therapeutic avenues...risks?

SMART Goal

Specific, Measurable, Attainable, Relevant, Timely



- Begin considering the role of neurosteroids in treatment paradigms for mood disorders

Questions & Answers

Don't forget to fill out your evaluations to collect your credit.



Additional Abbreviations



Akt = Protein kinase B

AMPA = α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor

BDNF = Brain-derived neurotrophic factor

GAD = generalized anxiety disorder

GluA1 = glutamate receptor 1

IPSCs = Induced pluripotent stem cells

mGluR2/3 = metabotropic glutamate receptors

M1R = muscarinic acetylcholine receptor

mTORC1 = mammalian target of rapamycin

NAM = nucleus ambiguus

NMDAR = N-methyl-D-aspartate receptor

PAM = positive allosteric modulator

TrkB = Tropomyosin receptor kinase B

VDCC = Voltage-gated calcium channels

VGAT = vesicular GABA transporter