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Staying in Your Lane? Practical Guide to Use of Hormones in Everyday Practice

C. Neill Epperson, MD

Robert Freedman Endowed Professor and Chair
Department of Psychiatry
University of Colorado School of Medicine -
Anschutz Medical Campus
Aurora, CO



C. Neill Epperson, MD

Disclosures



- **Research/Grants:** Sage Therapeutics, Inc.
- **Speakers Bureau:** Sage Therapeutics, Inc.
- **Consultant:** Asarina Pharma, Sage Therapeutics, Inc.
- **Advisory Board:** Asarina Pharma

Learning Objective 1

Describe two reasons why psychiatrists should understand when and how to consider hormonal strategies.



Reason 1: Sex as a Biological Variable



Reason 1: Sex as a Biological Variable



Sex differences in years of life lost due to disability:
Burden of unipolar depression is **50% higher in females compared to males**

MALES				FEMALES			
	Cause	YLD (millions)	% of Total YLD		Cause	YLD (millions)	% of Total YLD
1	Unipolar depressive disorders	24.3	8.3	1	Unipolar depressive disorders	41.0	13.4
2	Alcohol use disorder	19.9	6.8	2	Refractive errors	14.0	4.6
3	Hearing loss, adult onset	14.1	4.8	3	Hearing loss, adult onset	13.3	4.3
4	Refractive errors	13.8	4.7	4	Cataracts	9.9	3.2
5	Schizophrenia	8.3	2.8	5	Osteoarthritis	9.5	3.1
6	Cataracts	7.9	2.7	6	Schizophrenia	8.0	2.6
7	Bipolar disorder	7.3	2.5	7	Anemia	7.4	2.4
8	COPD	6.9	2.4	8	Bipolar disorder	7.1	2.3
9	Asthma	6.6	2.2	9	Birth asphyxia/trauma	6.9	2.3
10	Falls	6.3	2.2	10	AD and other dementias	5.8	1.9

Men > Women
Alcohol use disorders

Women > Men
Unipolar depression
AD and other dementias

COPD = chronic obstructive pulmonary disease; YLD = years lost due to disability.
World Health Organization Website. 2020. https://www.who.int/gho/mortality_burden_disease/daly_rates/text/en/.

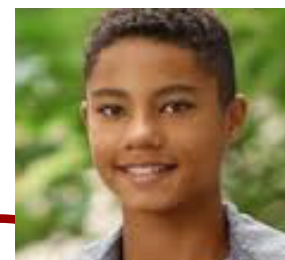
Emerging View of Infant Development



(genetics)



(environment)
(epigenetics)

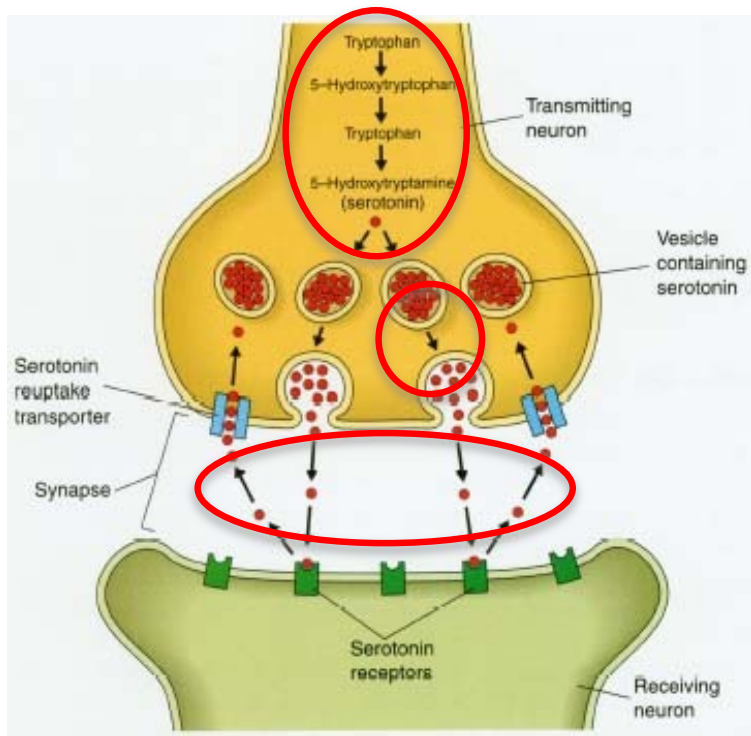


INTRAUTERINE PROGRAMMING

Sex Differences: Impact of Hormones?



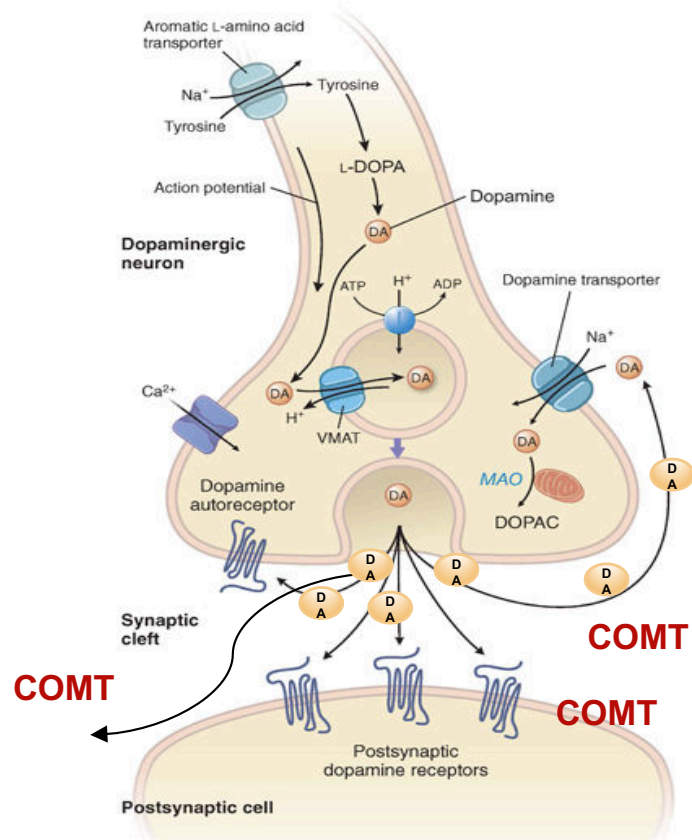
Reason 2: Powerful Impact of Hormones



- ↑ Tryptophan hydroxylase
- ↓ Clearance of 5-HT by monoamine oxidase activity
- ↑ 5HT-2A receptor density
- ↓ Potency of estradiol on *TPH2* gene expression
- ↓ 5HT1A receptor binding⁵

Sanchez RL, et al. *Mol Brain Res.* 2005;135:194-203. Benmansour S, et al. *Neuropsychopharm.* 2009;34:555-564. Kugaya A, et al. *Am J Psychiatry.* 2003;160:1522-1524. Shively CA, et al. *Pharmacogenomics J.* 2003;3(2):114-121. Murrough JW, et al. *Arch Gen Psychiatry.* 2011;68(9):892-900.

Reason 2: Powerful Impact of Hormones

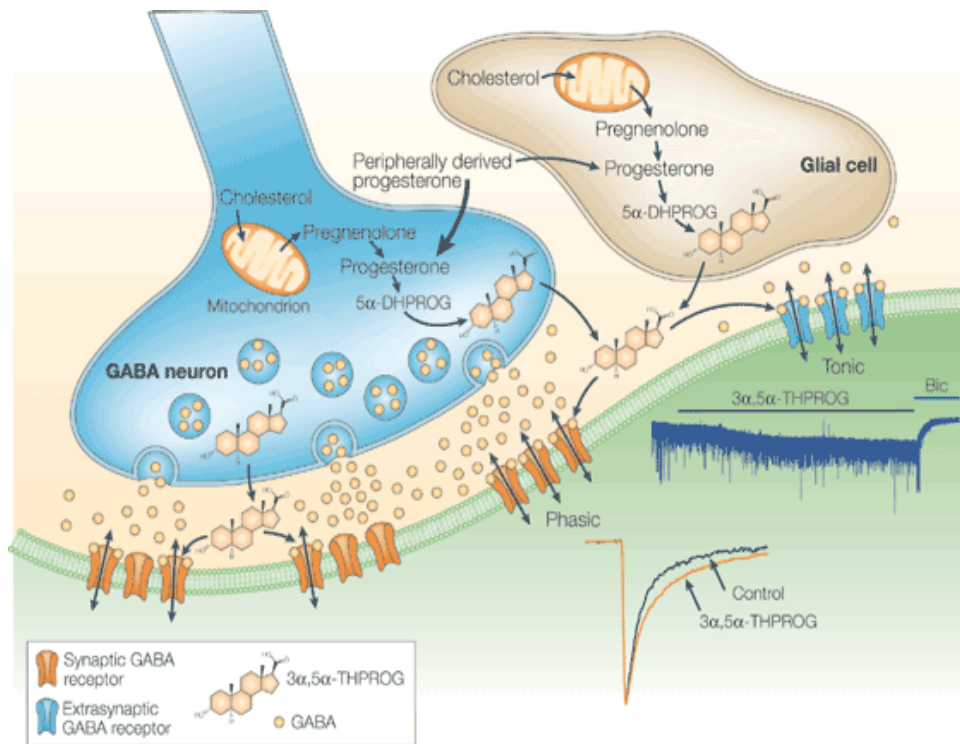


- Methionine substitute for valine at codon 158 is associated with 2- to 4-fold decrease in COMT activity
 - Met allele: higher prefrontal cortex (PFC) dopamine
 - Val allele: lower PFC dopamine

DA = dopamine.

Jacobs E, D'Esposito M. *J Neurosci*. 2011;31:5286-5293. Standaert DG, Sung VW. Pharmacology of dopaminergic neurotransmission. Basicmedical Key Website. https://basicmedicalkey.com/pharmacology-of-dopaminergic-neurotransmission/#ch014_fig002. Published August 3, 2016. Accessed February 25, 2020.

Reason 2: Powerful Impact of Hormones



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Belelli D, Lambert JJ. *Nat Rev Neurosci.* 2005;6(7):565-575. Pinna G, et al. *Curr Opin Pharm.* 2009;9:24-30.

- Prolonged exposure and withdrawal of allopregnanolone alters GABAA sub-unit configuration and receptor sensitivity to agonists
- Implicated in premenstrual dysphoric disorder, post-traumatic stress disorder and...
- **Postpartum depression**

Flexible Female Brain



PRENATAL

PUBERTY



PREGNANCY



MENOPAUSE



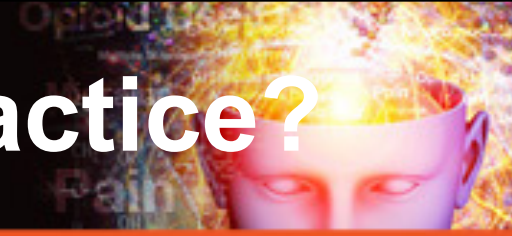
PRE-PUBERTY



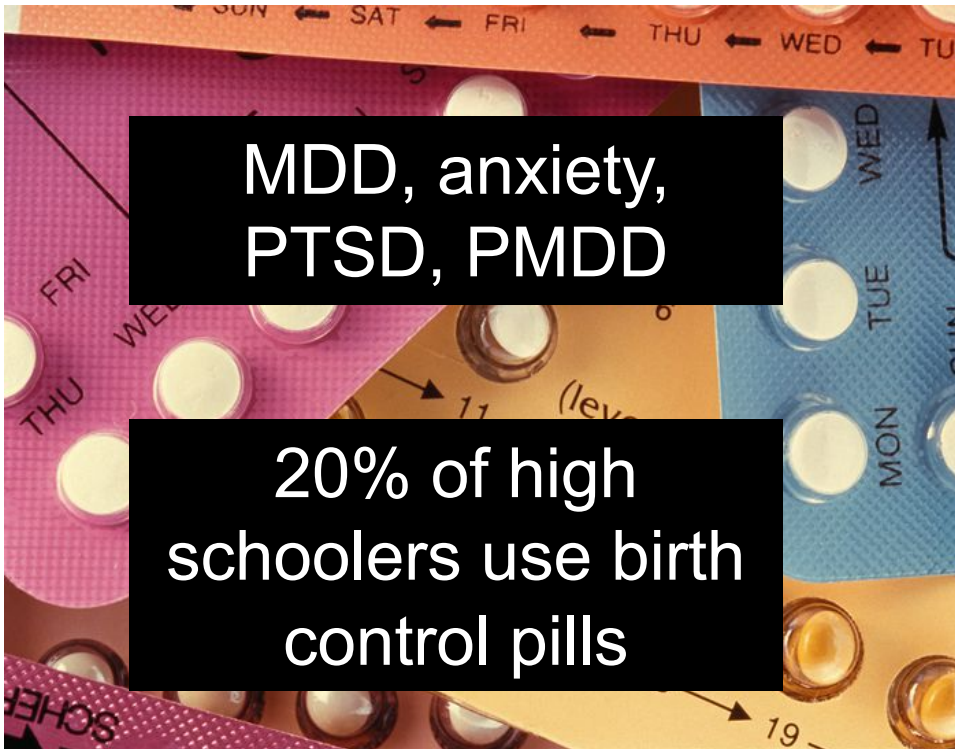
ANDROPAUSE



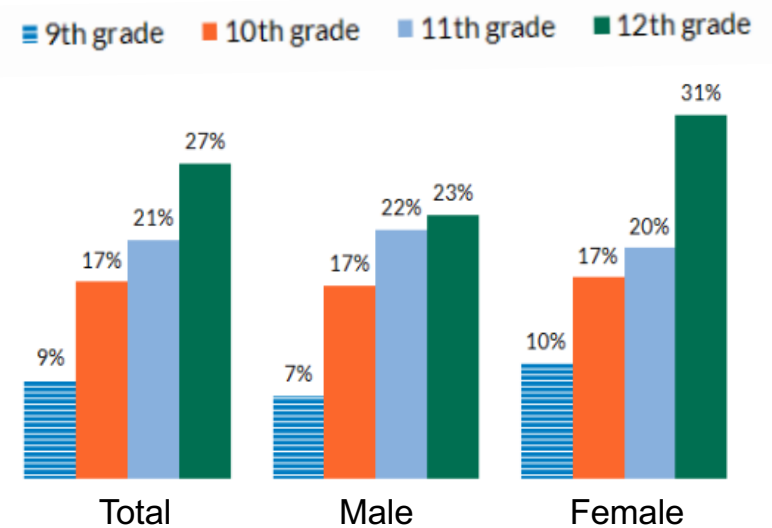
How Does This Affect Your Practice?



Youth



Percentage of Sexually Active* High School Students Who Reported Using Birth Control Pills at Most Recent Intercourse, by Grade and Gender: 2017

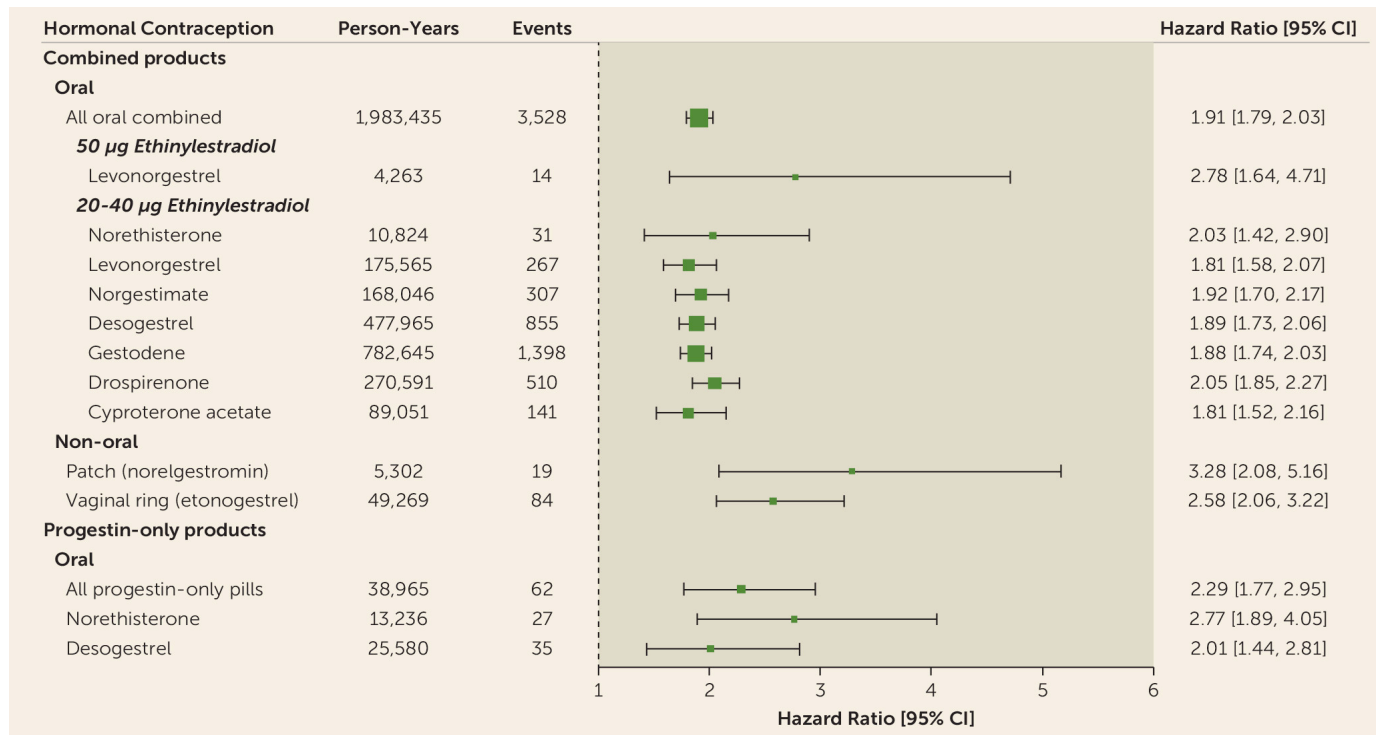


¹ Students who had sexual intercourse in the three months preceding this survey.
Source: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention. (2018). YRBS Youth Online Data Analysis Tool [Data tool]. Retrieved from <https://nccd.cdc.gov/youthonline/App/Default.aspx>.

MDD = major depressive disorder; PTSD = post-traumatic stress disorder.

Hormonal Contraceptives and Suicide

Relative Risk of a First Suicide Attempt, by Type of Hormonal Contraceptive Currently Used, Compared to Never-Users*



*Age as underlying time, and adjusted for calendar year, education, polycystic ovary syndrome and endometriosis.
 Skovlund CW, et al. *Am J Psychiatry*. 2018;175(4):336-342; Dokras A, et al. *Fertil Steril*. 2018;109(5):888-899.

Hormonal Contraceptives and Depression



- 4,765 female adolescents were assessed using structured interview assessments
- **No relationship** was established between oral contraceptives (OCPs) and either current or lifetime depressive disorder
- OCP use is **not associated** with an increased risk for depression

Recommendations



- If contraception is needed, contact patient's PCP or Ob/Gyn; recommend a combined pill with lower estrogen and non-levonorgestrel progestin
- Inform patient that steroid contraceptives may trigger or worsen depression; in relatively rare cases it could increase suicidal thinking
- If patient presents with depression and is using steroid contraceptive, convince yourself that the two are not related

Reproductive Years

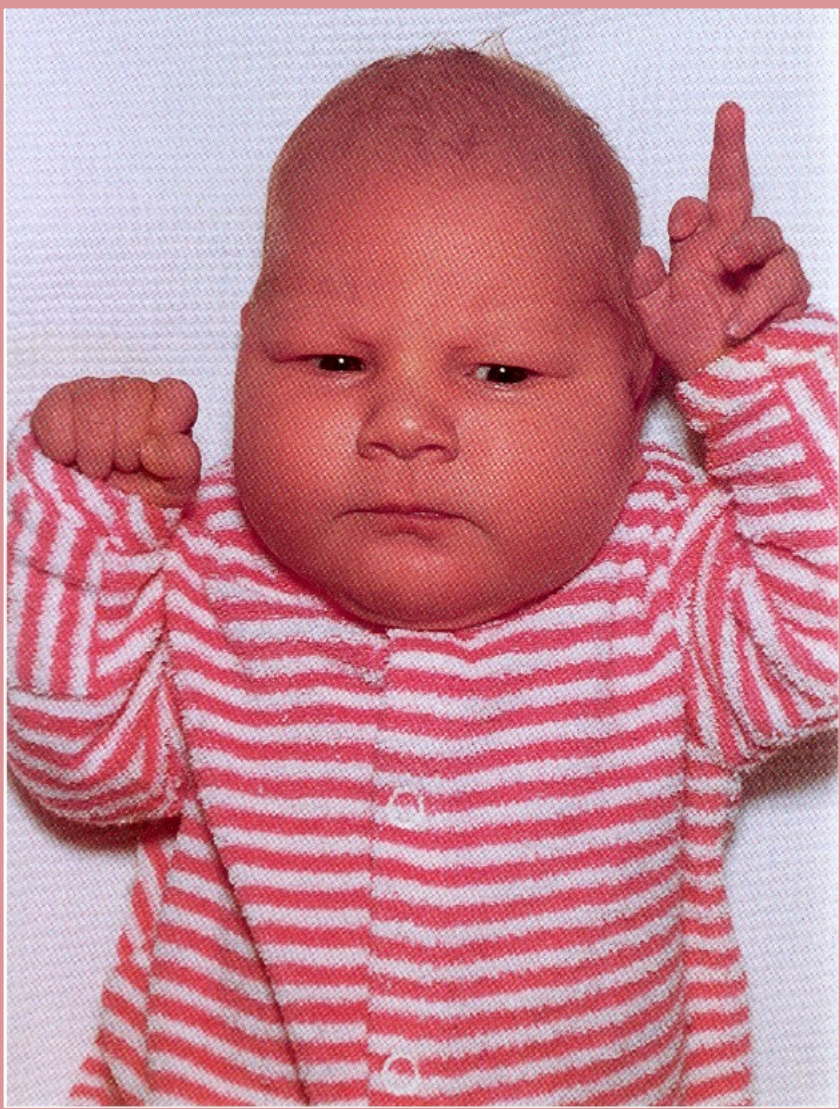


MDD and PMDD

- If PMDD or premenstrual exacerbation of depression is expected, one must use daily ratings to confirm
- OCPs can exacerbate PMDD symptoms
- OCPs can be safely used in women with depression
- Take care when prescribing to teens

Perinatal Illness

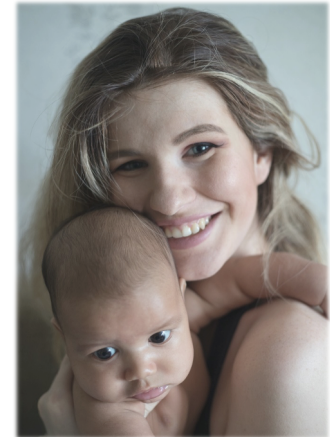
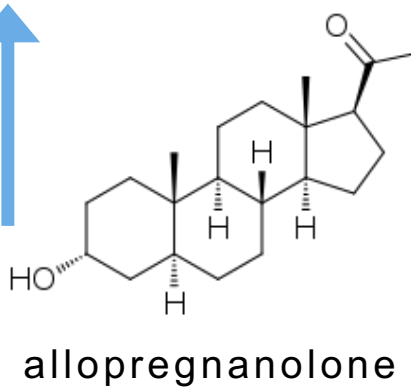
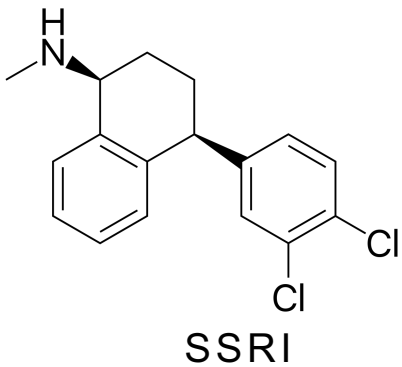
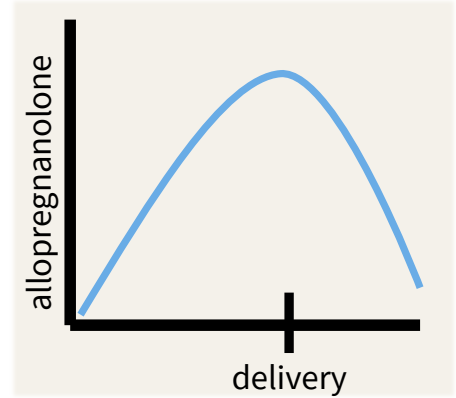
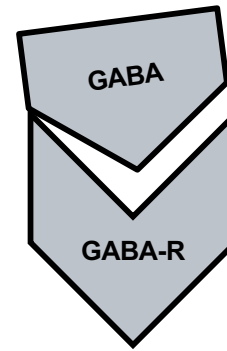
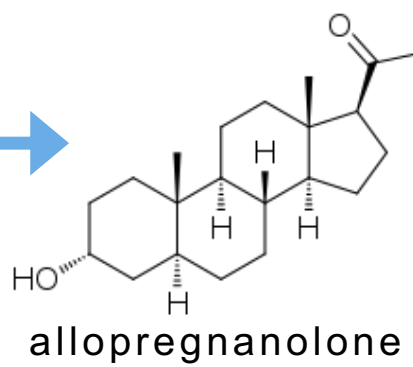
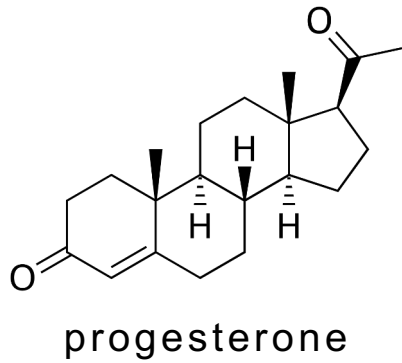
- Postpartum depression (PPD) is the most common undiagnosed complication of childbirth... 10%-20%
- Approximately 40% of women with depression after delivery were depressed during pregnancy
- Brexanolone vs. standard oral antidepressants



Brexanolone for PPD

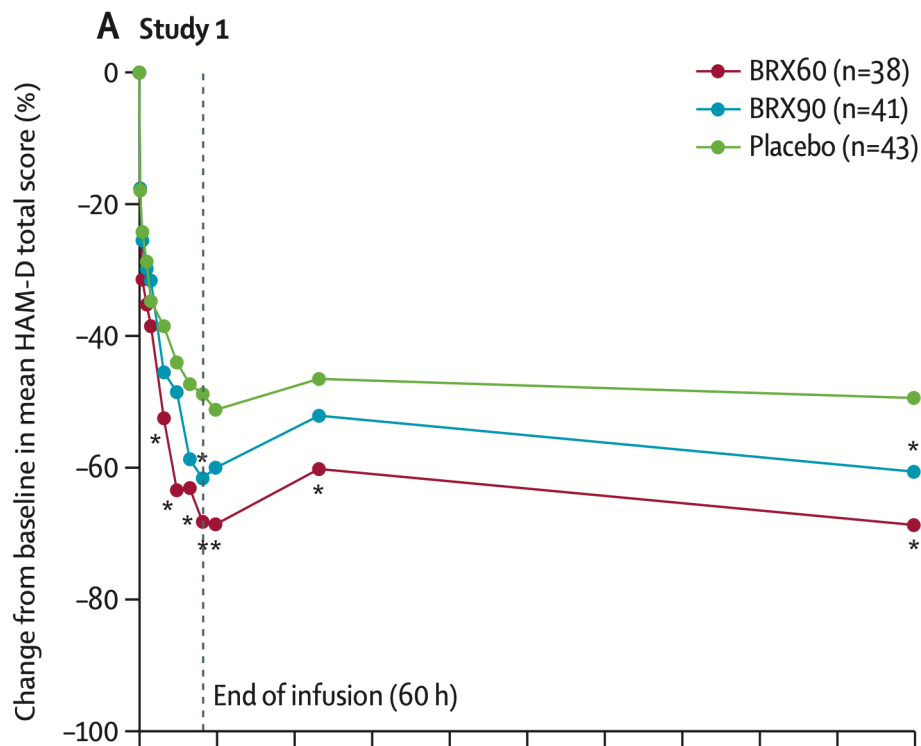
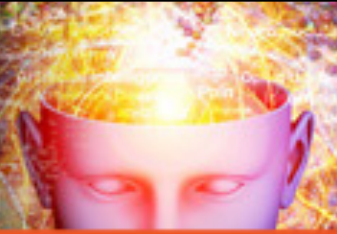


Formulation of allopregnanolone for intravenous infusion



SSRI = selective serotonin reuptake inhibitor.
Melón L, et al. *Front Endocrinol.* 2018;9:703.

Brexanolone: Results and REMS



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

REMS Criteria

- First treatment approved by the U.S. Food and Drug Administration (FDA) for PPD
- Every-2-hour checks for excessive sedation
- All clinicians REMS trained
- Additional documentation and oversight
- Onset of PPD within 4 weeks of delivery
- Moderate-severe MDD
- Standardized rating
- Infusion within 6 months post-delivery
- No suicide attempt during index episode

Peri-/Postmenopausal Adult Women



- Women will live a third of their lives in the postmenopausal hypoestrogenic state
 - Loss of estradiol impacts many body tissues, including the brain
 - Symptoms include: depression, insomnia, decreased libido, vulvovaginal atrophy, osteoporosis, weight changes, vasomotor symptoms, cognitive complaints
- **How do you know if your patient is peri- or postmenopausal?**
- **Why does this matter?**

Older Women



- More likely to outlive their spouses
 - Increased risk of dementia, particularly AD
- Epidemiologic studies show that early estrogen use reduces the risk of AD
- However, it is not recommended that women who are “many” years past their final menstrual period start hormone therapy (HT)
- What to do about women who have used HT for more than 5 years?

Recommendations



- Always ask female patients about their menstrual cycles
 - Determine reproductive stage
 - Relationship between cyclicity and mood
- If patient may benefit from hormone therapy, discuss pros and cons with patient and contact his/her PCP
- The decision to use hormone therapy should be made on a case-by-case basis

SMART Goals

Specific, Measurable, Attainable, Relevant, Timely



- Know how to discuss hormone status and options with patients and when to consult their PCP, oncologist, or Ob/Gyn.
- Document hormonal/reproductive considerations.
- Apply knowledge to all female patients.
- Conduct one hormone discussion/consideration this month.

Questions & Answers

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

