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Reproductive Psychiatry: 2021 Update

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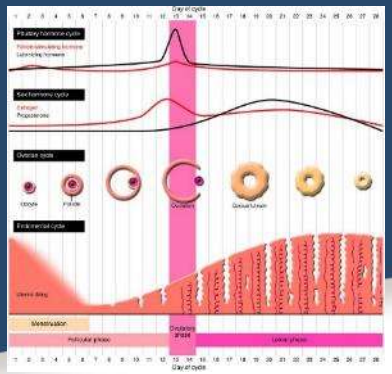
Disclosures

Scientific Advisor Sage Therapeutics 8/2020

Off label use of medications will be discussed.



Objectives

- Describe the influence of reproductive hormones on psychiatric illness in women
- Identify two scenarios in which psychotropics may treat a hormonally mediated condition
- Identify two scenarios where a hormone may treat a “psychiatric” condition.

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What is Reproductive Psychiatry?

A specialized field of psychiatry focusing on aspects of mental health that are *unique to women* from adolescence through menopause.

- Focus on hormonal shifts that women experience **premenstrually** and during **pregnancy planning/infertility**, **pregnancy**, **postpartum**, and **perimenopause** that influence mood and behavior.
- The impact of a mother's psychiatric illness and psychotropic medication on the developing child, both during pregnancy and while breastfeeding.
- The interplay between CNS agents and hormonal interventions for treating disorders of behavior and mood.

Organizations/ Training

5 fellowships, several academic centers have areas of distinction

- *Marce Society -Marce of North America (MONA)*
- *Postpartum Support International (PSI)*
- *International Society of Reproductive Psychiatrists (ISRP)*
- *North American Society of Psychosocial ObGyns (NASPOG)*

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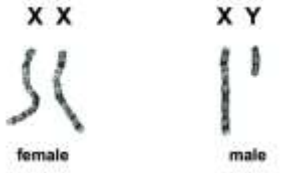
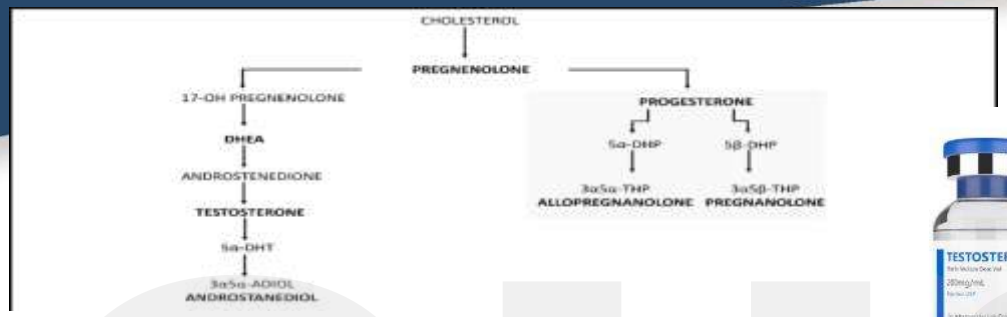
Why does sex* matter in psychiatric illness?



- Every cell has a sex
  XX or XY chromosome
- Sex influences fundamental neuroactive hormones, X dose, Y dose, female mosaicism, parental X imprinting
- Sex affects sexual behavior, neuro behavior, aging, expression of illness, etc.
- Novel therapies
  - Dissections of mechanisms that protect one sex can be harnessed to treat both sexes
  - e.g. Anxiety disorders, Alzheimer's, Schizophrenia

*Sex is defined by biologic differences between males and females based on genetics.
Gender is more loosely defined – social cultural influences, identification and role in society.

The Role of Sex Specific Neurosteroids on the CNS



- Endogenous or exogenous steroids that rapidly alter neuronal excitability through interaction with ligand-gated ion channels and other cell surface receptors.
- Synthesized in the CNS or in an endocrine gland that mediate their effects by activating nuclear steroid receptors or by directly modulating neurotransmitter receptors
- Include metabolites of **testosterone, estrogen and progesterone, oxytocin, vasopressin, cortisol**

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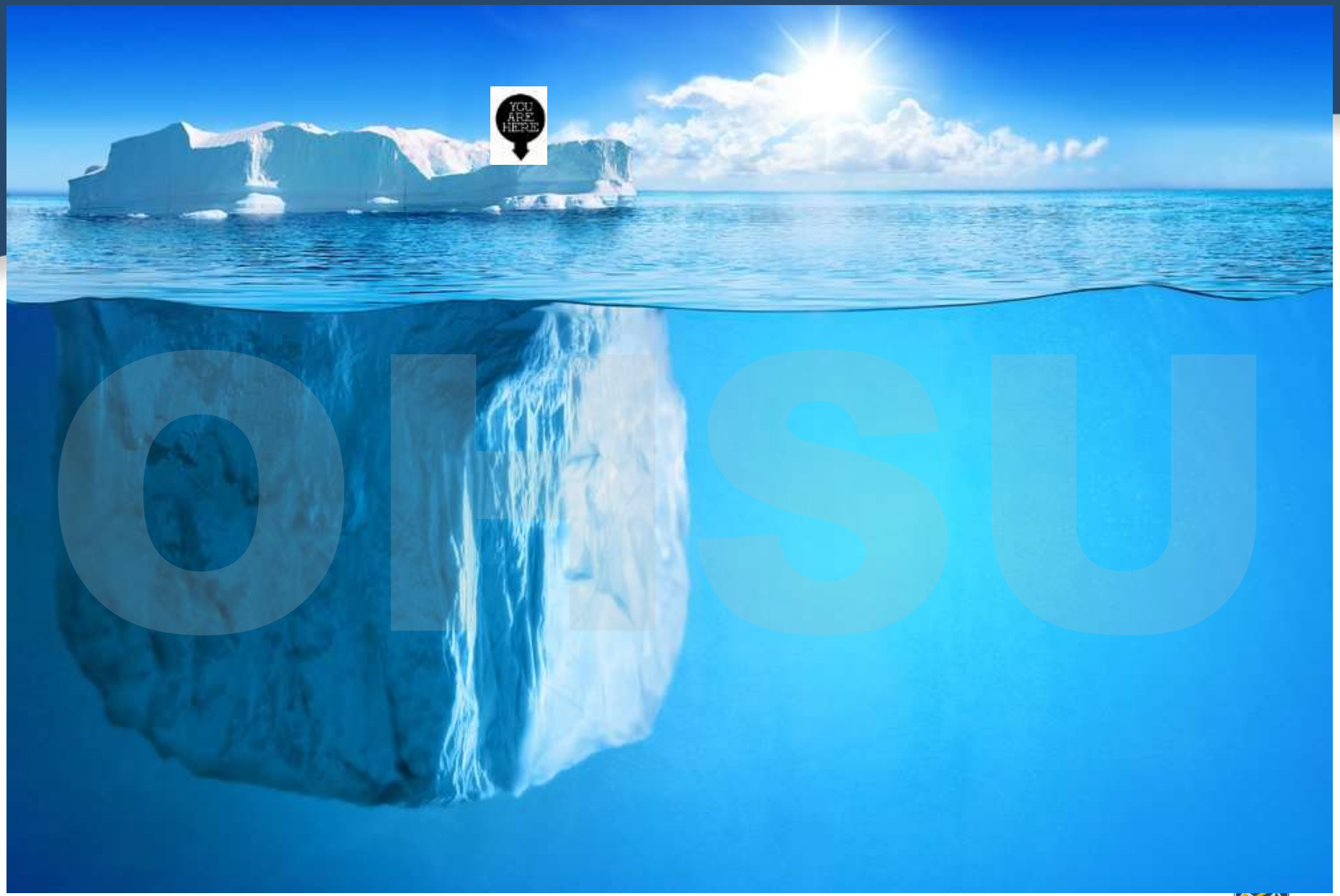

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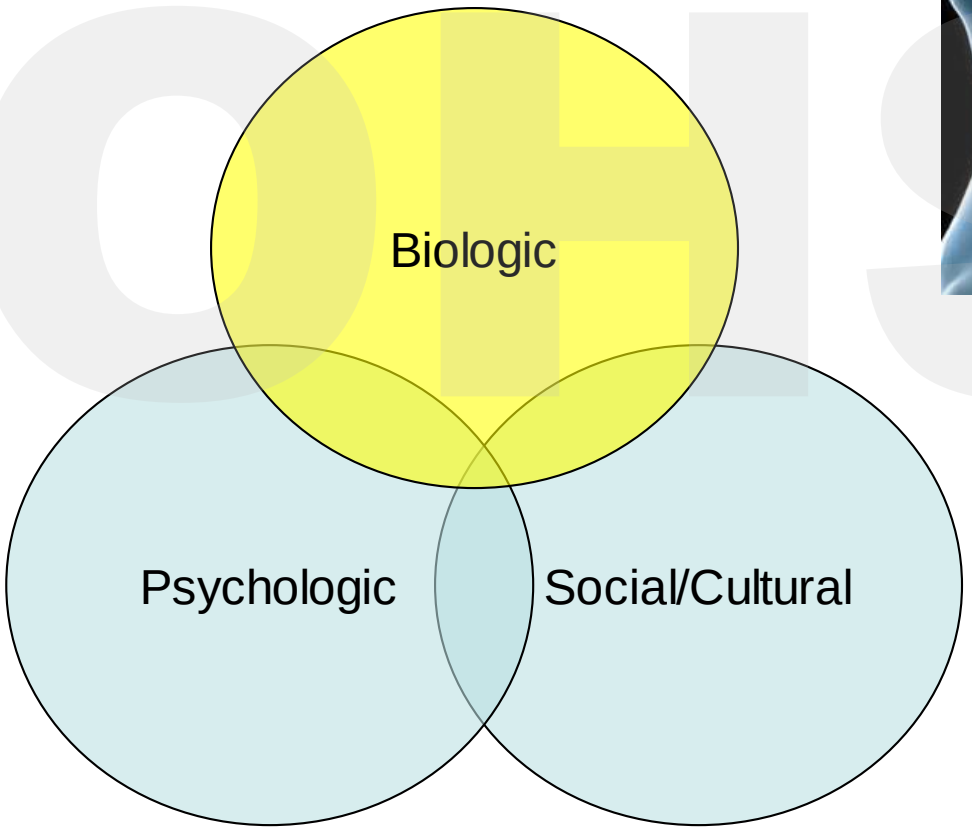
Male/Female "Sex" Brain Differences



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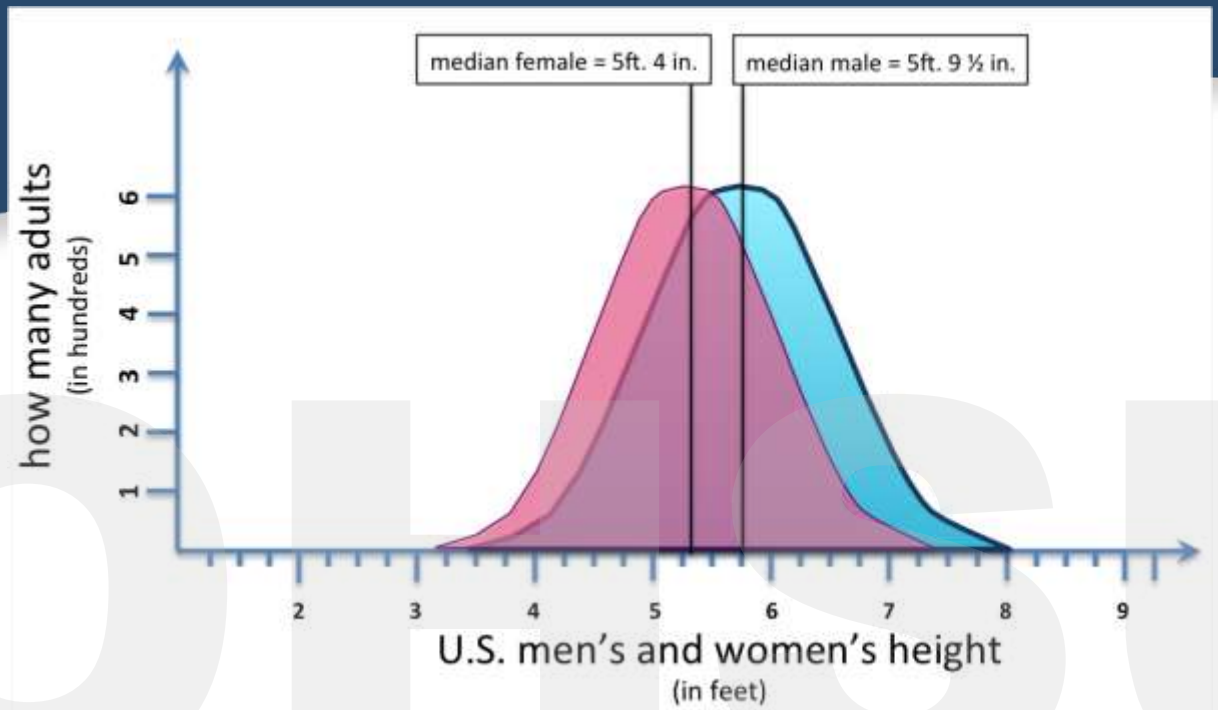
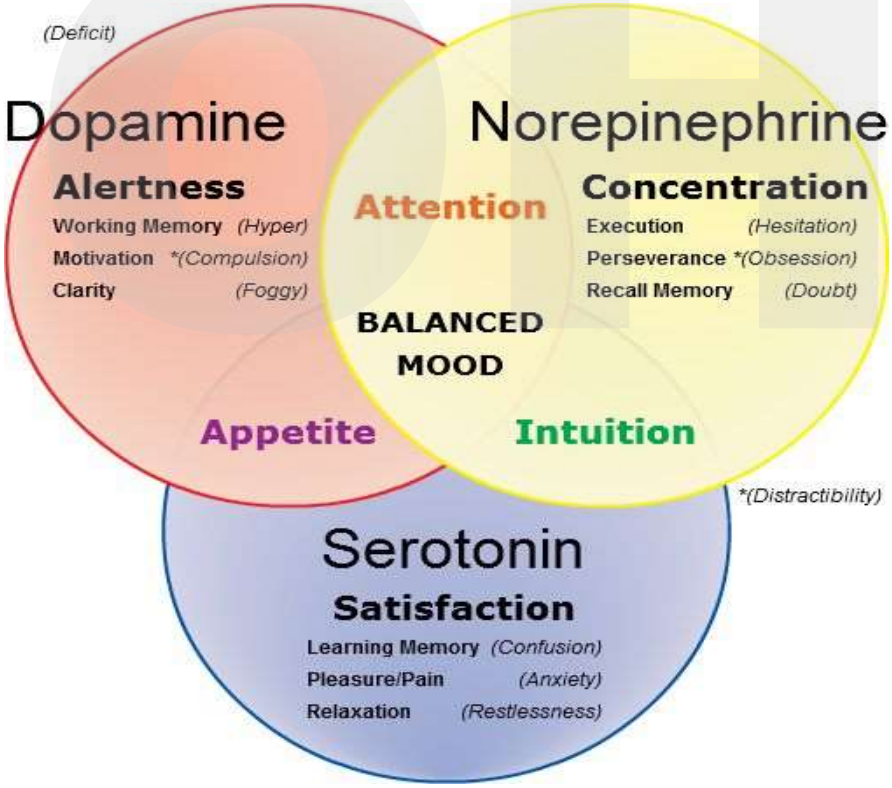
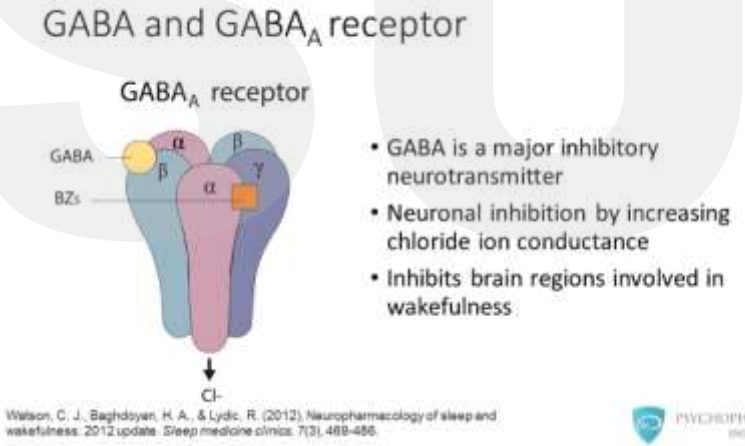

median female = 5ft. 4 in.
median male = 5ft. 9 ½ in.
how many adults
(in hundreds)
1
2
3
4
5
6
2
3
4
5
6
7
8
9
U.S. men's and women's height
(in feet)


NURTURE
NATURE

Brain Neurotransmitters Affected by Neurosteroids





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Expression of Psychiatric Illness by Sex

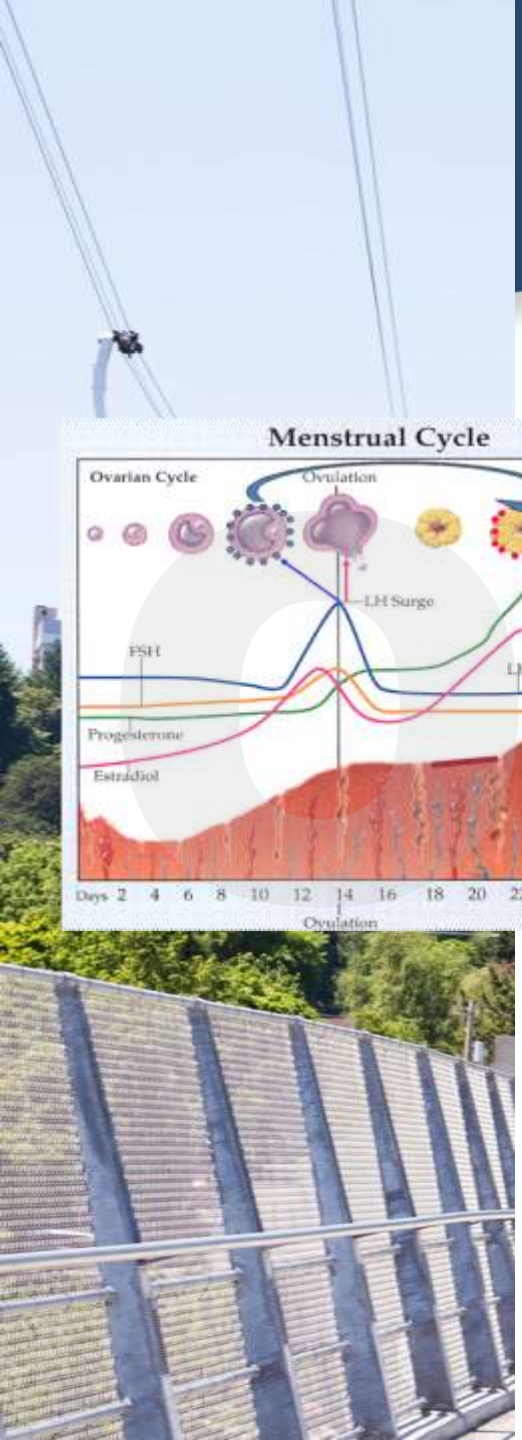
More common in Males	More common in Females
Antisocial Personality Disorder/ Aggressive Behavior	Depressive Disorders
Autism	Anxiety Disorders
Addiction	Bipolar II disorder Borderline PD
Early Onset Schizophrenia	Late Onset Schizophrenia (>45)
	Exclusively in Females
	Premenstrual Dysphoric Disorder (PMDD)
	Postpartum Psychosis
	Postpartum OCD (?)
	Perimenopausal Mood Instability

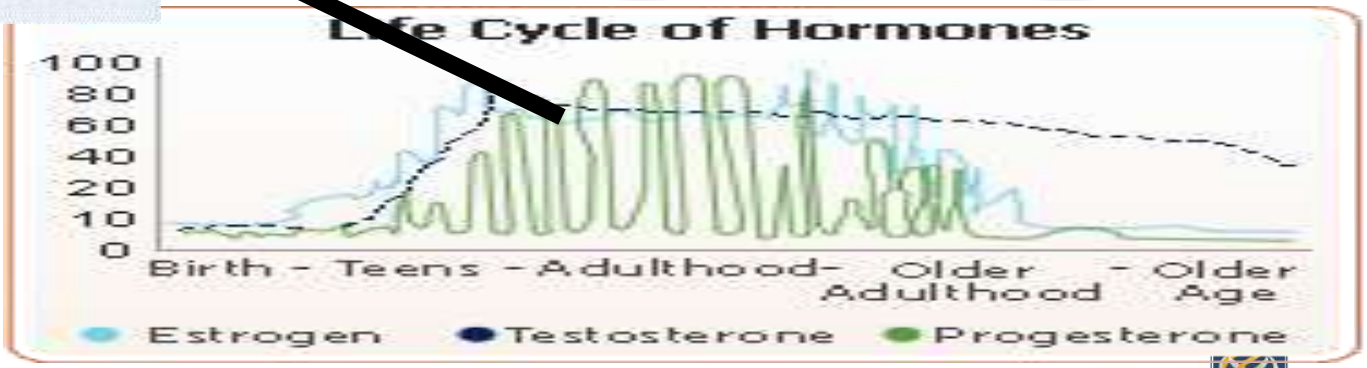
Sex Differences in Schizophrenia –Example

Females	Males
Later age of onset, second peak >45	More hospitalizations (>50%)
More affective symptoms	More substance use
More sensory hallucinations and persecutory delusions	More negative symptoms, social withdrawal
Better treatment response, lower doses (premenopausal women only)	Fewer Medication side effects (PRL, hypotension and weight gain)
Cognitive impairment in language, visuospatial, and attention	Cognitive impairment in memory - visuospatial preserved.

- **Theories**: Estrogen, testosterone and oxytocin are associated with fewer symptoms -neuroprotective
- Experimental treatment with estrogen in women **and men** have been positive
- Women have better social skills at baseline (genetically)
- Women have monthly worsening of symptoms during luteal phase when estrogen levels are lower.

Journal of Translational Neuroscience. 2016 Sep 1(1)





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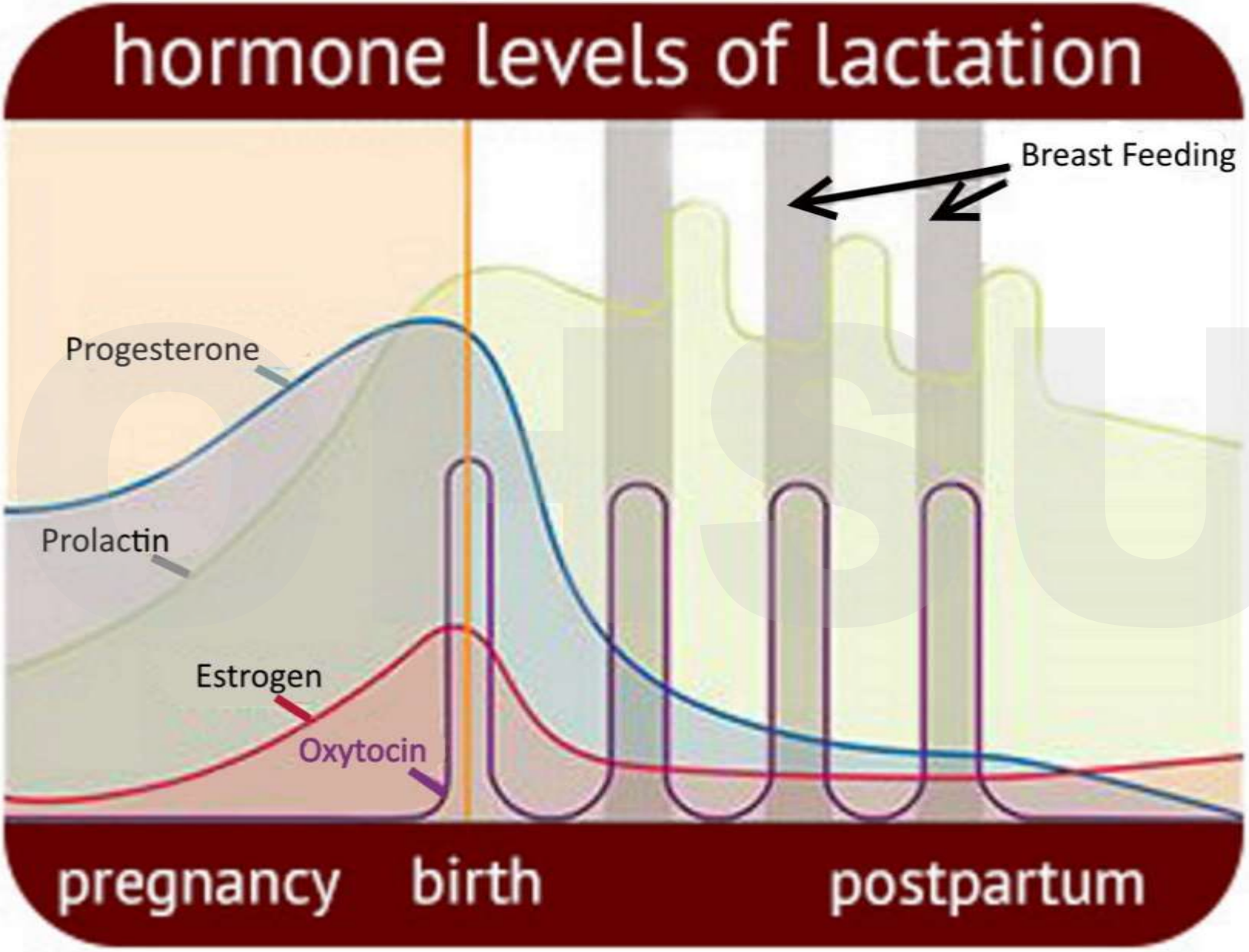
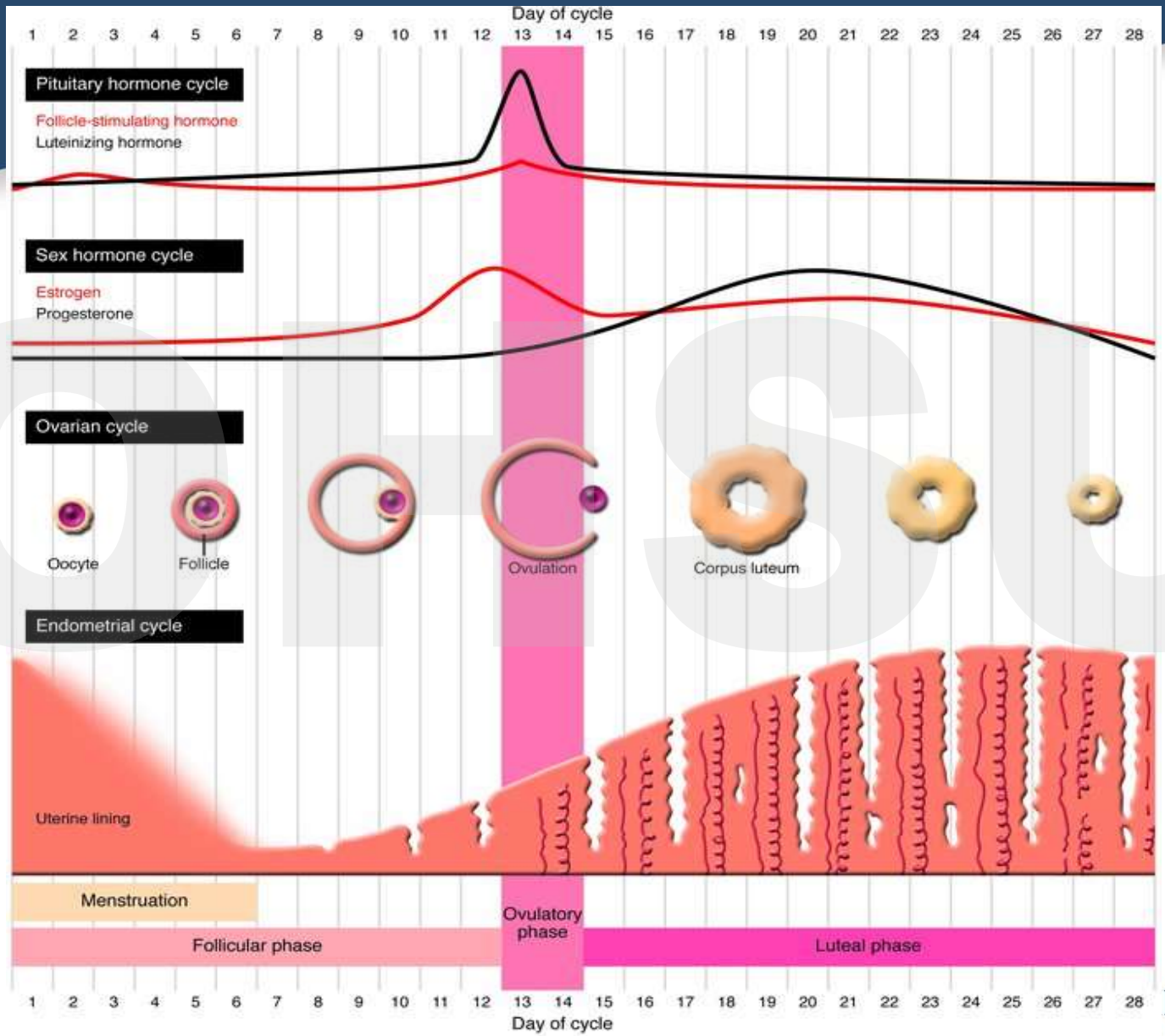

hormone levels of lactation
Breast Feeding
Progesterone
Prolactin
Estrogen
Oxytocin
pregnancy
birth
postpartum

Female Menstrual Cycle



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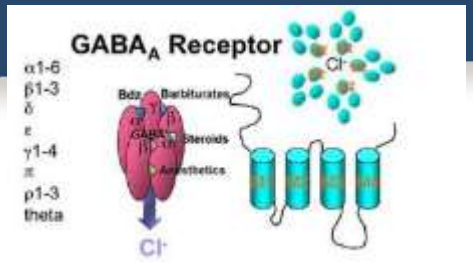
Progesterone – a Potent Neurosteroid



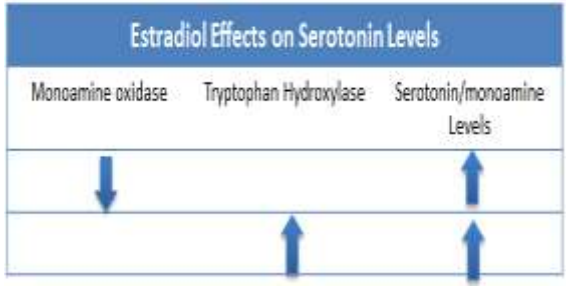
- Elevated in pregnancy with rapid drop postpartum
- Fluctuates monthly –withdrawal premenstrually
- Significant decline in menopause
- Alters binding of the serotonin 5-HT2A receptor and serotonin transporter
- Clinical studies show it can cause
  - **hypnotic and anxiolytic** effects
  - **dysphoric** effects (postmenopausal women, PMDD)
- Metabolizes into Allo (Allopregnanolone)- potent GABAa receptor modulator

Oxytocin (OT) and Attachment

- Fosters attachment b/w all mammalian mothers and infants
- Facilitates orgasm and supports testosterone
- Improves ability to interpret social situations and facilitates attending to others
- OT activates limbic structures assoc. with emotion and *attention*
- Postpartum women: Lactation suppresses physiologic response to stress.
- Lactation decreases anxiety symptoms vs. PP controls.
- Promotes amnesia during labor

Estrogen – Mood Enhancing Effects

- Documented antidepressant effects
- Neuroprotective and neurotropic effects
- Estrogen supports Serotonin
  - Increases synthesis (tryptophan)
  - Increased 5HT1 receptors in Dorsal Raphe
  - Reduces metabolism of serotonin (Decrease MAO activity)
- Estrogen supports Norepinephrine
- Antidopaminergic effects



Estrogen – Brain effects

- Facilitates gender specific behaviors in women
  - Interpersonal aptitude
  - Verbal Agility
- Inhibits Fear Response
- Decrease symptoms during the follicular phase

Psychotropics or Hormones?

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Common clinical question: Psychotropics or Hormones?

Psychotropics

- Moderate to severe psychiatric illness across the course of her lifespan
- Postpartum Depression
- PMDD
- Premenstrual Exacerbation (PME)
- Vasomotor symptoms of menopause
- Low Libido

vs. Hormone "Neurosteroid" therapy

- PP Depression – Allopregnanolone
- PMDD
- Premenstrual Exacerbation (PME)
- Perimenopause
  - Mild depression or anxiety if other symptoms are present (VMS)
  - In combination with SSRIs for severe depression in perimenopause
  - New onset depression during **perimenopause**
- Depression in surgically induced menopause
- Testosterone for Low Libido

Future

- Oxytocin for BPD or Autism
- Tamoxifen for Bipolar disorder
- Estrogen for Schizophrenia

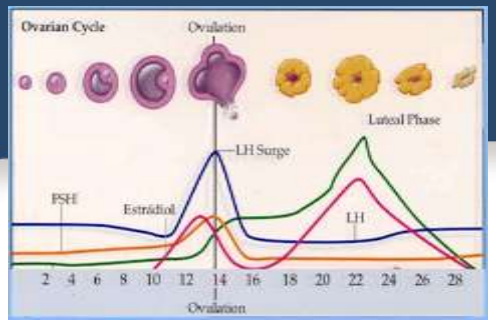
Antidepressants in Women

- Plasma levels tend to be higher in women; usually not clinically significant
- "Hyperstimulation" side effect more common in women
- Women take more psychotropic medication
- Women are twice as likely as men to report side effects
- Women take more multiple medications

Premenstrual Effects of Pharmacokinetics

- GI transit time slower
- Plasma volume increases enough to dilute water soluble drugs
- Estrogen induces liver enzymes, increases catabolism premenstrually
- Overall effect: serum levels are less predictable, usually lower if changed

Premenstrual symptom patterns: Both physical and behavioral



- PMS: mild premenstrual symptoms, not constituting a disorder (30-80% women)
- PMDD: SX severe enough to cause impairment (1.2%-6.4%)
- PME: A primary psychiatric disorder that becomes activated premenstrually (e.g 25-50% of women with depression)

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Diagnosis of PMDD - 5 symptoms, 1 must be mood

Table 1 DSM-V premenstrual dysphoric disorder symptoms[6]

Mood symptoms	Physical or behavioral symptoms
• Marked affective lability or sensitivity to rejection • Increased irritability, anger or interpersonal conflicts • Depressed mood, hopelessness or feelings of worthlessness • Anxiety, tension, feeling on edge	• Decreased interest in normal activities • Difficulty concentrating • Lethargy, low energy or easy fatigability • Overeating, cravings or change in appetite • Sleeping too much or too little • Feeling overwhelmed or out of control • Breast tenderness or swelling, pain in muscles or joints, bloating and/or weight gain

- Majority of cycles the past year
- Two prospective menstrual cycles documented
  - Daily Record of Severity of Problems (DRSP)
- Symptom free during the follicular phase
- Increase risk of developing MDD, PPD and Perimenopausal MI
- 30-70% comorbidity with MDD
- Higher concordance in twins
- Age of onset 20s

Rapkin Open Access Journal of Contraception 2019:10 27–39

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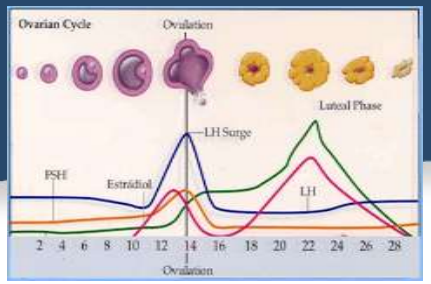
Biological basis of PMDD



- Related to exposure to progesterone (from corpus luteum)
- Levels of estrogen, progesterone and gonadotropins are normal
- Serotonin and GABA agonist abnormalities are present
- In luteal phase, Serotonin and GABA levels do not rise in PMDD women versus controls
- Abnormal paradoxical response to ALLO fluctuation

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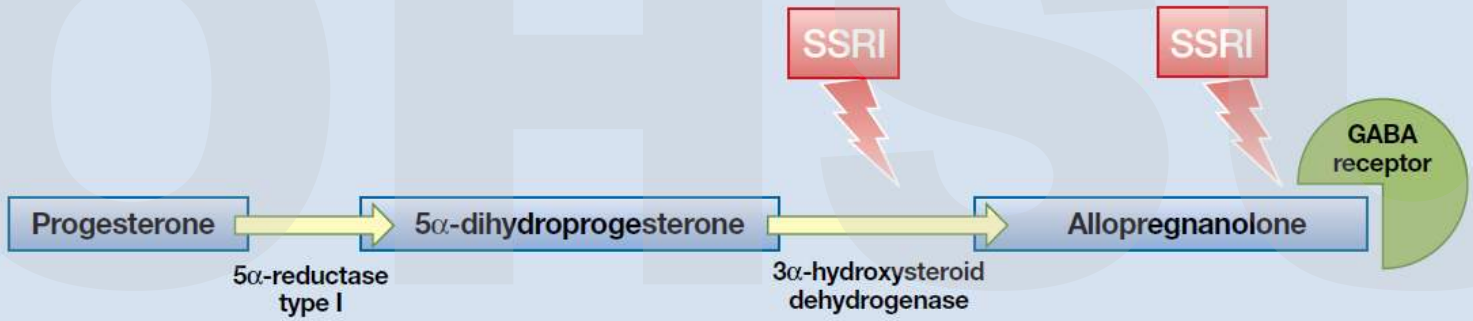
Why SSRI's work for PMDD

Figure 4

Conversion of progesterone to ALLO and the SSRI influence



SSRIs enhance the sensitivity of $GABA_A$ receptors or promote the formation of more ALLO as shown here. This is one possible mechanism by which they could be helping to alleviate PMDD symptoms.

ALLO: allopregnanolone; GABA: γ-aminobutyric acid; PMDD: premenstrual dysphoric disorder; SSRI: selective serotonin reuptake inhibitor

strogen, serotonin, and BDNF

Womensmentalhealth.org/PMDD

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Pharmacologic Treatment of PMDD Cont. – Are they requiring contraception?

- SSRIs, SNRI – continuous, luteal phase, sx onset – 60-70% response
- Luteal phase dosing psychotropics
- COCP's – Combined estrogen-progestin containing drospirenone with shorter pill free interval, then go to continuous: Yaz, Ocella, Syeda
- Leuprolide (depot) – GNRH antagonist, suppresses ovulation. +- add back E and P
- TAH/BSO (only if other indication is present)

TAH/ BSO - Indications

- PMDD confirmed with prospective symptom recording
- GNRH agonist therapy “the only medical approach that is effective” > 6 month duration
- Tolerance of estrogen progestin replacement therapy
- Childbearing complete
- Based on age several years prior to menopause.

Other Directions PMDD

- LARC – Long acting Reversible Contraceptives
- Acupuncture
- Chasteberry vitex agnus-castus– "Monks pepper" LH agonist, increases progesterone and decreased prolactin
- Ulipristal Acetate for Treatment of Premenstrual Dysphoric Disorder
  - Progesterone receptor antagonist

Disorders With Premenstrual Exacerbation (PME)

- Dysthymic Disorder
- Major depression
- Panic Disorder
- Obsessive Compulsive Disorder
- Bipolar Mood Disorder
  - (esp. rapid cycling)
- Schizophrenia

Effect of hormonal contraceptives on mood (general healthy subjects)

- Data is inconclusive– overall improvement of mood during luteal phase on HC.
  - Worsening of mood (4-10% healthy subjects)
  - 2016 prospective Danish cohort showed increase of 1st use of antidepressants
    - COC (OR 1.23)
    - CHC patch (OR 2.0)
    - LNG-IUD *Mirena* (OR 1.6)
    - Progesterone OP (OR 1.34)
- Common themes
  - Package inserts warn of risk of depression in most forms of birth control 3-5% (even with Mirena, Nexplanon)
  - Women with a history of depression more vulnerable to mood worsening
  - Mood is worse during pill free week
  - Anti androgen progesterone's associated with improved mood (drosperinone and desogestrel)

Peromaa *Acta Obstet Gyn Scand* 2012; Skovlund JAMA Psychiatry 2016:73

Laura -Case Discussion

43 y/o female physician referred by PCP for urgent appt. for suicidal ideation. Presented to PCP 6 weeks ago c/o depression, was placed on COC 6 weeks ago and buproprion 2 weeks ago.

-2 years PP from IVF, stopped breastfeeding 2 months ago

Long periods of mood stability alternating with severe episodic mood instability and episodic suicidal ideation – onset in adolescents and worse prior to menses – "literally one month was planning divorce for three days then after menses 'woke up.'".

Sx: Heavy periods. 7-10 days hopeless, fatigue, irritable, anxious, insomnia. Complete relief during pregnancy.

Past med trials: several SSRIs, mirtazapine, lamotrigine

Has tried many different oral contraceptives over the years, never found them helpful for mood (had never been on continuous dosing)

- Felt improved in pregnancy "best I have ever felt" then felt relatively okay until she stopped BF and her cycles began again.
- Fam Hx of "hormonal depression," GM completed suicide.
- Also has endometriosis.
- Uncovered suicidal ideation with plan and intent.

Laura cont.

- Etiology? What are the reproductive events happening to Laura?
- What treatments have failed? Hormonal? CNS agents?
- Next steps. Hormonal or Psychotropics? Both?

Treatment

- Change to SSRI
- Decrease all hormonal fluctuation- COC
- Leuprolide
- TAH /BSO add back E2
- Wean SSRI to off 3 years later

Perinatal Mood and Anxiety Disorders (PMADs)

Brexanolone 3/19 FDA approved for Postpartum Depression

- Synthetic Allopregnanolone
- An allosteric modulator of GABA-A receptors
- 3 days inpatient IV infusion
- Remission of depression often within 24 hours up to 30 days
- SE: Sedation effects ranged from somnolence to loss of consciousness. All resolved within 60 minutes of infusion discontinuation.
- Breastfeeding –12 women/infant dyads. Relative infant dose 1-2%.

1. *Kanes SJ, et al. Hum Psychopharmacol. 2017 Mar;32(2))*
2. *1. Hoffmann E, Wald J, Colquhoun H. Evaluation of breast milk concentrations following brexanolone iv administration to healthy lactating women. Am J Obstet Gynecol. 2019;220:S554. Abstract. DOI: doi:10.1016/j.ajog.2018.11.870*
3. *Hoffmann E, Wald J, Dray D et al. Brexanolone injection administration to lactating women: Breast milk allopregnanolone levels. Obstet Gynecol. 2019;133 (Suppl 1):115S. Abstract 30J. doi:10.1097/01.AOG.0000558846.15461.70 DOI: doi:10.1097/01.AOG.0000558846.15461.70*

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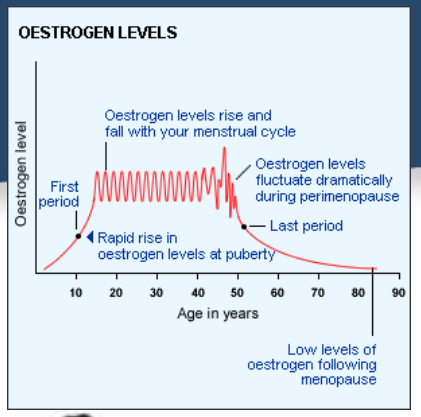
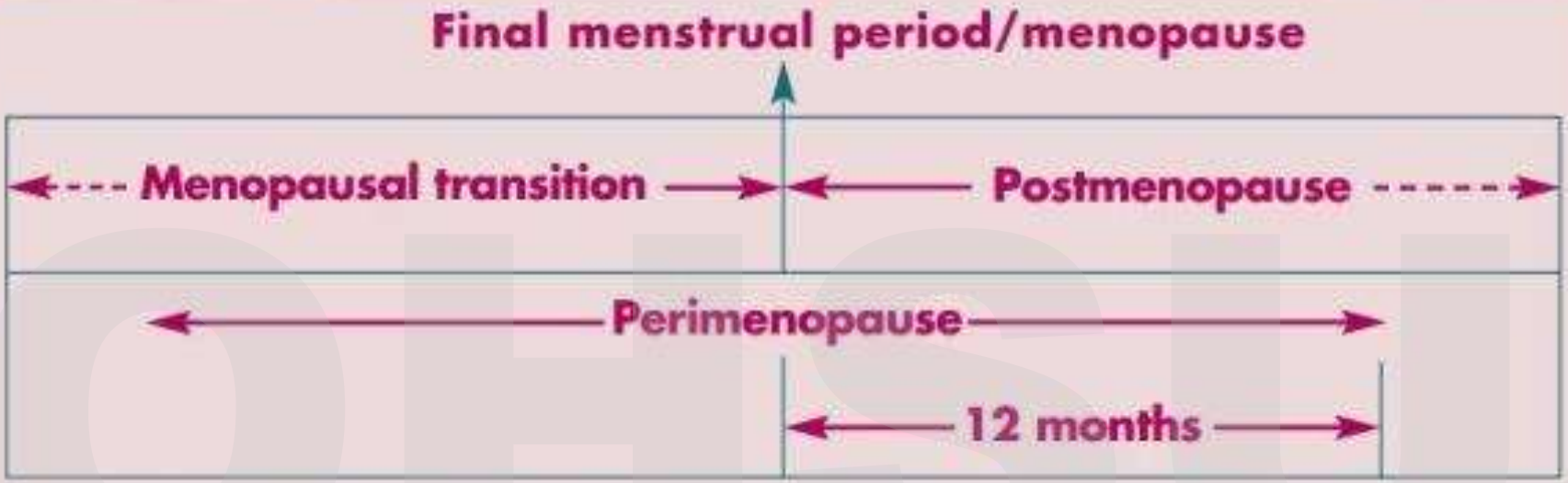
Menopausal Transition



- In 1900, average age of menopause=45
  - Life span = 49 years old
- Today, women experience menopause between 45-55
  - Average life span = 75 years
  - 20-30 years or more are post menopause


PERI
MENOPAUSE
AHEAD

Menopause timeline



World Health Organization. Research on the menopause in the 1990s: report of WHO scientific group. Geneva: WHO Technical Series 866; 1996; page 13.

FSH> 30
Estradiol <200

Reference intervals	FSH (IU/L)	LH (IU/L)	Oestradiol (pmol/L)	Progesterone (nmol/L)
Female:				
Follicular phase	2.8 - 9.3	2.8 - 7.6	46 - 607	0.6 - 4.7
Mid cycle	3.0 - 19.2	10.5 - 85	315 - 1828	2.4 - 9.4
Luteal phase (D21)	1.7 - 7.7	1.0 - 11.4	161 - 774	5.3 - 86
Postmenopausal	31 - 153	12.0 - 75	<200	0.3 - 2.5

Perimenopausal Mood Instability (PMI)

- Mood symptoms including irritability, low mood, tearfulness, decreased energy, poor concentration
- Occur intermittently during perimenopause
- 40% of women
- Do not meet criteria for clinical depression (Major Depressive disorder)

2018

First-ever guidelines for detecting, treating perimenopausal depression

by University of Illinois at Chicago

Menopause: The Journal of The North American Menopause Society
Vol. 25, No. 10, pp. 000-000
DOI: 10.1097/GME.0000000000001174
This article is being co-published in the journals *Journal of Women's Health* and *Menopause*

Consensus Recommendations

Guidelines for the evaluation and treatment of perimenopausal depression: summary and recommendations

Pauline M. Maki, PhD,[1] Susan G. Kornstein, MD,[2*] Hadine Joffe, MD, MSc,[3] Joyce T. Bromberger, PhD,[4] Ellen W. Freeman, PhD,[5] Geena Athappilly, MD,[6] William V. Bobo, MD, MPH,[7] Leah H. Rubin, PhD,[8] Hristina K. Koleva, MD,[9] Lee S. Cohen, MD,[10] Claudio N. Soares, MD, PhD, MBA,[11] on behalf of the Board of Trustees for The North American Menopause Society (NAMS) and the Women and Mood Disorders Task Force of the National Network of Depression Centers*

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Estrogen (ET) as treatment for midlife Depression?

NAMS Depression Guideline 2018 Menopause 25 (10) 2018)

- ET is shown to be effective **in depressed perimenopausal** women c/ or c/o VMS
- ET enhances mood and improves well-being in **non depressed peri- women**
- OCPs (continuous) help with Perimenopausal Mood Instability (PMI)
- There may be some benefit for ET for **prevention** of depression in perimenopausal women

- ET is not **effective in postmenopausal** women
- ET is **not FDA approved** to treat depression in women of any age
- Systemic ET is contraindicated in women with a hx of Estrogen positive CA and other oncologic conditions

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Janet – case example

- 45 year female with longstanding severe PMDD and Tobacco use presented to her PCP, referred to Center for Women's Health.
- Increase in SI premenstrually only- lasts 7 days, decreases at onset of menses. This "runs in my family."
  - Aunt and GM committed suicide – mother had severe PPD. Mother had TAH/ BSO.
- Sx: Crying, sense of devastation, headache,
- Past trials – 3 SSRIs, clonazepam PRN, duloxetine up to 90mg. Was stable on nuvaring. Was stable on SSRIs and COC, had to stop.
- Came in after she had a DVT during Covid-19 infection. **Now estrogen is contraindicated. SI returns.**

Treatment options – Hormones or CNS agents?

- Labs: FSH >30 and estradiol < 200
- Current meds: duloxetine 90 and no hormones-
- Gyn. Consult suggested options:
  - Progesterone Only Pill
  - Progesterone LARC
  - Lupron (GNRH antagonist)
  - TAH/BSO
- Psychiatry consult – added aripiprazole 2mg, prospective mood chart two months.
- Much improved. But showed breakthrough symptoms 5 days prior to cycle, “PMDD”.
- Increase duloxetine? Increase aripiprazole? Hormones?

Common clinical question: Psychotropics or Hormones?

Psychotropics

- Moderate to severe psychiatric illness across the course of her lifespan
- Postpartum Depression
- PMDD
- Premenstrual Exacerbation (PME)
- Vasomotor symptoms of menopause
- Low Libido

vs. Hormone "Neurosteroid" therapy

- Postpartum Depression – Allopregnanolone
- PMDD
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- Perimenopause
  - Mild depression or anxiety if other symptoms are present (VMS)
  - In combination with SSRIs for severe depression in perimenopause
  - New onset depression during **perimenopause**
- Depression in surgically induced menopause
- Testosterone for Low Libido

Future

- Oxytocin for BPD or Autism
- Tamoxifen for Bipolar disorder
- Estrogen for Schizophrenia

2021-Reproductive Psychiatry Consult Lines(free)

POSTPARTUM SUPPORT INTERNATIONAL

Perinatal Psychiatric Consult Line

PSI Perinatal Psychiatric Consult Line
1-800-944-4773, ext 4

Medical Providers:

Fill Out This Form to request an appointment with one of our psychiatric consultants.

The PSI perinatal psychiatric consultation line is a service provided at no cost.

The consultation line is available for medical professionals who have questions about the mental health care related to pregnant and postpartum patients and pre-conception planning. This consultation service is available for medical providers only.

The Perinatal Psychiatric Consult Line is staffed by reproductive psychiatrists who are members of PSI and specialists in the treatment of perinatal mental health disorders. The service is free and available by appointment.

Call 800-944-4773, ext 4 and we will match you with an appointment.
We will respond to your request within one business day.

Massachusetts General Hospital Postpartum Psychosis Project (MGHP3)

About Postpartum Psychosis | Resources | Survivor Stories | Case-Based Supervision

Case-Based Supervision for Providers

The MGH Postpartum Psychosis Project is pleased to announce that it will offer free "curbside case-based supervision" to providers caring for patients with acute postpartum psychosis, or those who are still suffering after an episode. Postpartum psychosis is a rare and understudied condition and we are happy to make ourselves available to providers by email and phone for brief discussions. Please read the FAQ below and submit a request to be connected with a member of our faculty. Please note that we are able to offer this service solely to care providers.

FAQ

BRINGING POSTPARTUM DEPRESSION OUT OF THE SHADOWS ACT

This federal legislation provides funding to states to create Perinatal Psychiatry Access Programs based on the MCPAP for Moms model. In 2018, 30 states and the District of Columbia applied for funding for Perinatal Psychiatry Access Programs; 7 states were each awarded 5-year grants (totaling $3.2 million per state over the lifetime of the program). This is the first-ever federal funding to address maternal mental health in the United States.

NATIONWIDE IMPACT

Citations

1 ACOG Committee Opinion 757 (2018).
2 Gavin (2005). Obstetrics & Gynecology, 106, 1071-83.
3 Fawcett (2019). Journal of Clinical Psychiatry, 80(4), 18r12527.
4 Byatt (2015). Obstetrics & Gynecology, 126(3), 1048-1058.
5 Byatt (2020). Promoting the Health of Parents & Children.

Learn more at bit.ly/mcpap-pmh

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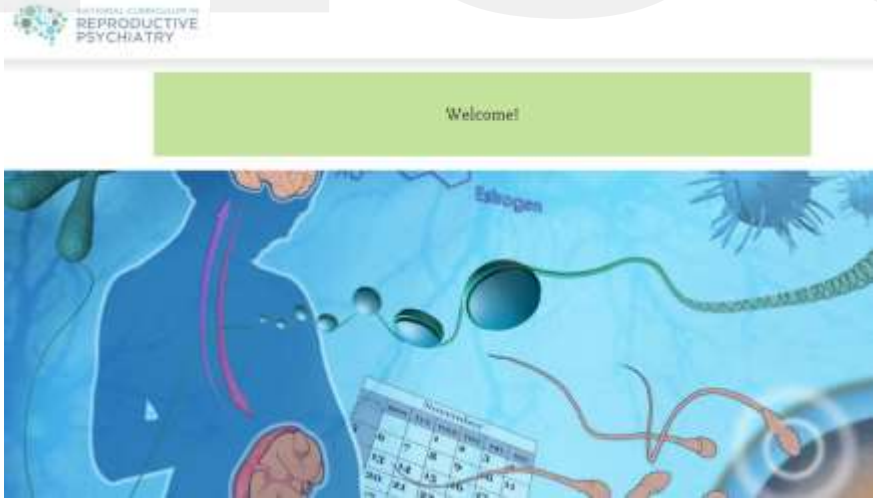
National Curriculum in Reproductive Psychiatry -Introduced in 2019

- 2019 FREE Course materials
- online at:
- **http://ncrptraining.org/**



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Questions?