Mood Disorders in Women: PMS, PMDD and Depression

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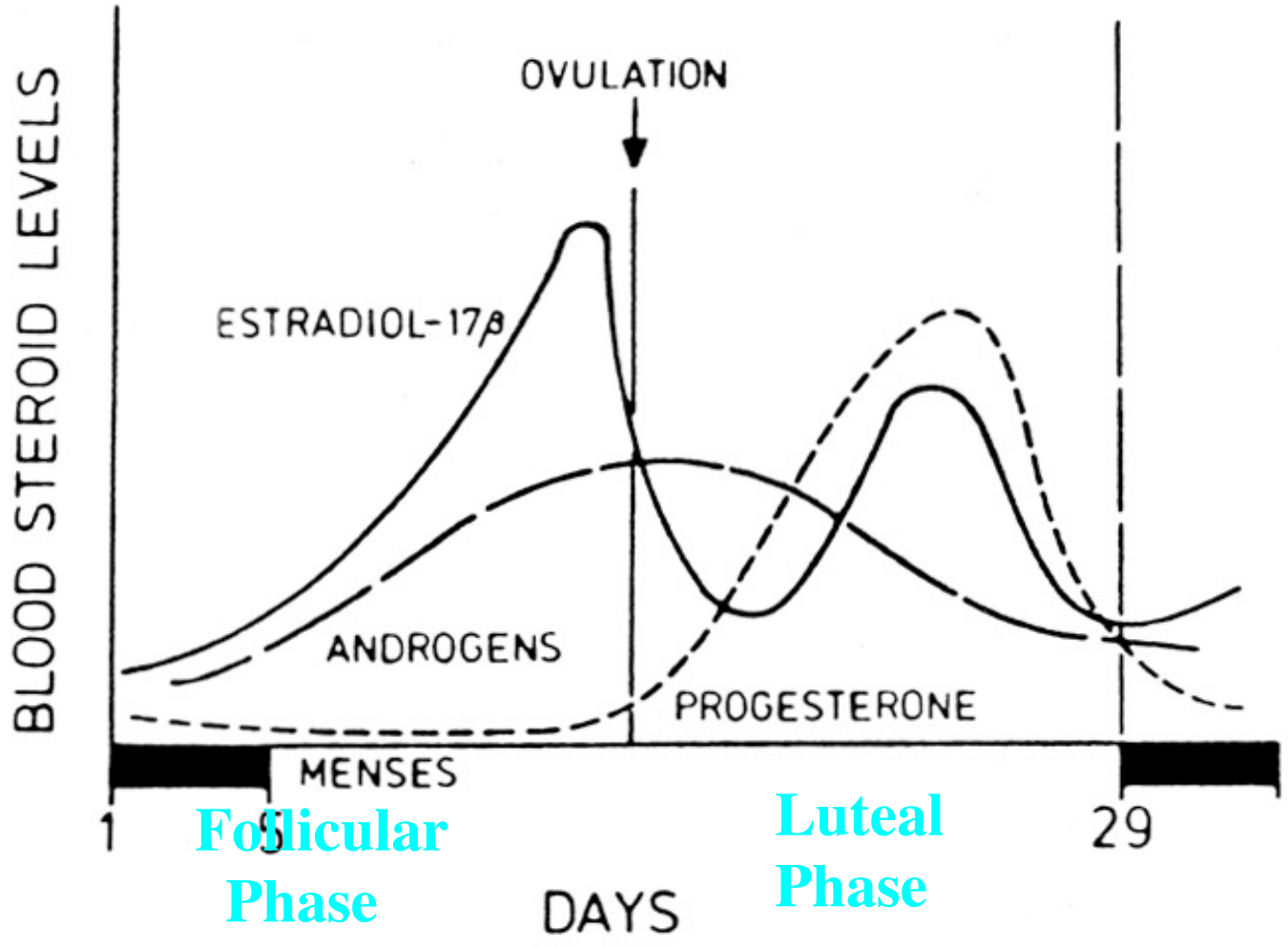
How the king of beasts handles PMS:

Menstrual Cycle



Sex steroid changes in human menstrual cycle.

Mood

- **80%** of women acknowledge some increased emotional sensitivity before their period starts
- **8-10%** have severe ‘hell-on-earth’ mood changes the 2 weeks before their period

What is going on here?

- The female brain experiences hormonally determined emotional fluctuations
- Not a big deal for 80%
- A VERY big deal for 8-10%

PMDD vs Normal PMS

Normal PMS (Premenstrual Syndrome):

- 80% of women
- Mild to moderate emotional fluctuations

PMDD (Premenstrual Dysphoric Disorder):

- 8-10% of women
- In most menstrual cycles during the past year, symptoms (severe moods swings, depressed mood, irritability, anxiety, physical symptoms) occurring exclusively during the luteal phase (weeks 3-4) and remitting within a few days of the onset of menses. These symptoms must be severe enough to interfere with work, school or usual activities and be entirely absent for at least 1 week postmenses.

DSM-IV Research Criteria For PMDD

-It is considered “Depression NOS”

A. In most menstrual cycles during the past year, five (or more) of the following symptoms were present for most of the time during the last week of the luteal phase, began to remit within a few days after the onset of the follicular phase, and were absent in the week postmenses, with at least one of the symptoms being either (1), (2), (3), or (4):
   1. Markedly depressed mood, feelings of hopelessness, or self-deprecating thoughts
   2. Marked anxiety, tension, feelings of being "keyed up" or "on edge"
   3. Marked affective lability (e.g., feeling suddenly sad or tearful)
   4. Persistent and marked anger or irritability or increased interpersonal conflicts
   5. Decreased interest in usual activities (e.g., work, school, friends, hobbies)
   6. Subjective sense of difficulty in concentrating
   7. Lethargy, easy fatigability, or marked lack of energy
   8. Marked change in appetite, overeating, or specific food cravings
   9. Hypersomnia or insomnia
   10. A subjective sense of being overwhelmed or out of control
   11. Other physical symptoms, such as breast tenderness or swelling, headaches, joint or muscle pain, a sensation of "bloating," or weight gain

B. The disturbance markedly interferes with work or school or with usual social activities and relationships with others

C. The disturbance is not merely an exacerbation of the symptoms of another disorder (although it may be superimposed on any of these disorders).

D. Criteria A, B, and C must be confirmed by prospective daily ratings during at least two consecutive symptomatic cycles.

Daily Record of Symptoms

Mild  Moderate  Severe 

Circle the dates of your period.

MONTH:

Symptom:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31

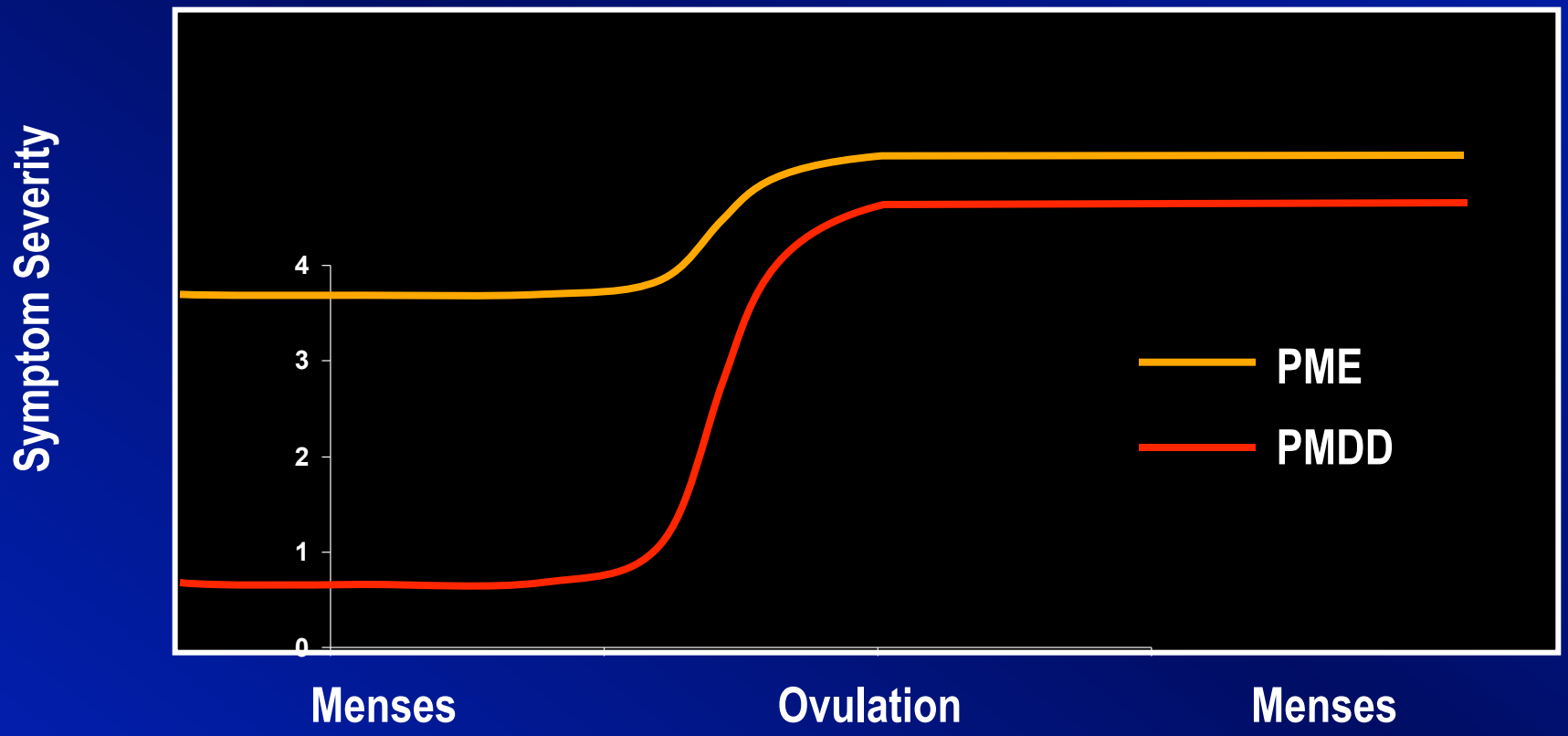
MONTH:

Symptom	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31

MONTH:

Symptom	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31

PMDD vs Premenstrual Exacerbation

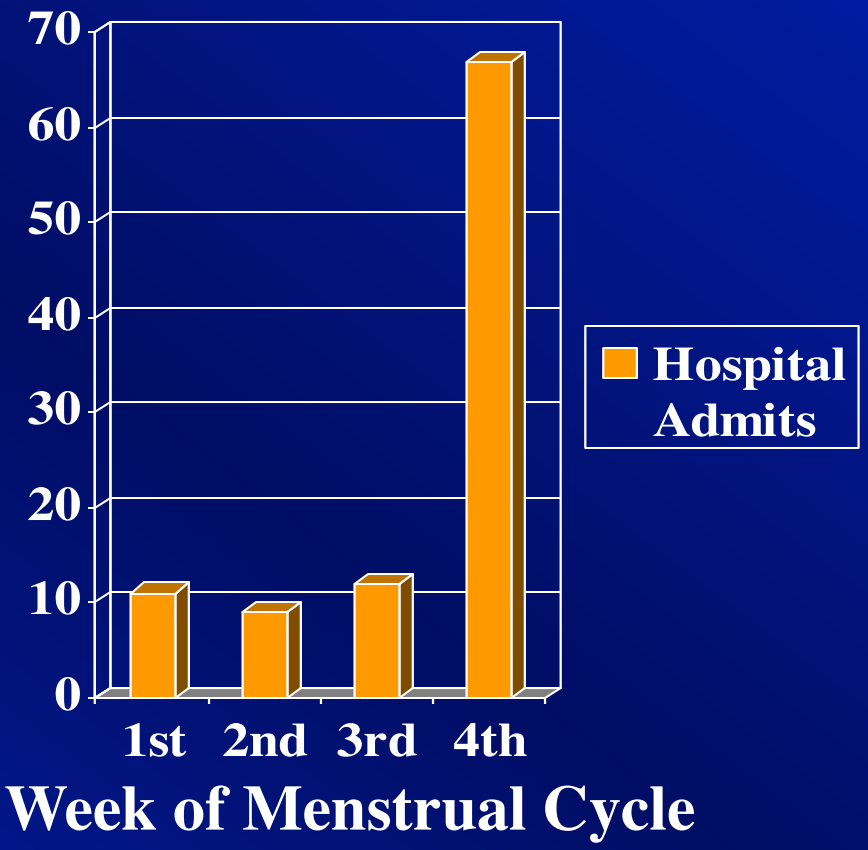


Disorders with Premenstrual Exacerbation (PME)

- Affective disorders
- Anxiety disorders
- Psychotic disorders
- Eating disorders
- Personality disorders
- Substance abuse
- Migraine
- Allergies
- Asthma
- Seizures

Menstrual Cycle Week and All Psychiatric Admissions

- If random, admissions of women to psychiatric hospitals for all psychiatric diagnoses would be 25% on each week of the menstrual cycle



How does estrogen and progesterone effect the brain?

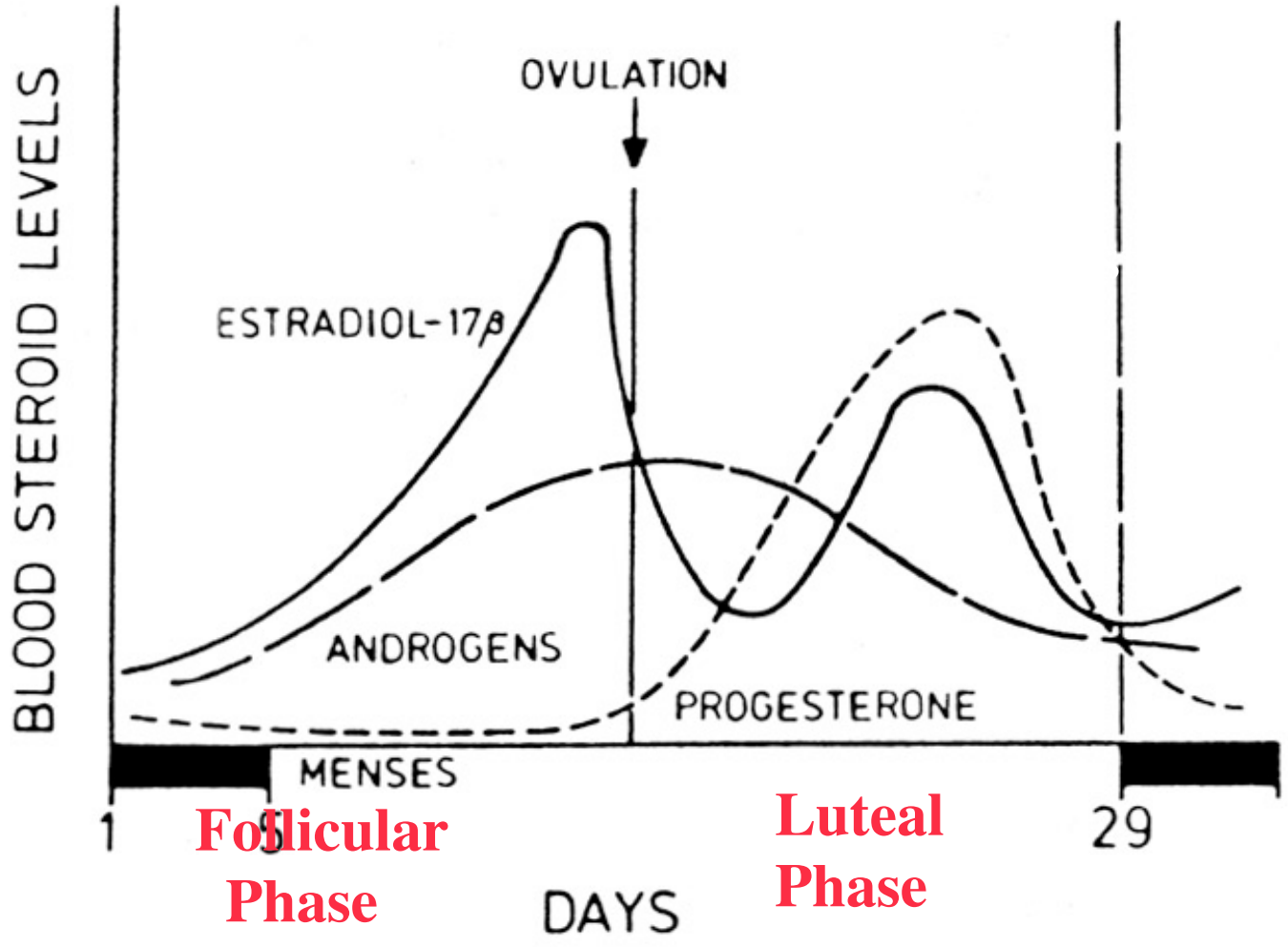
- Estrogen acts to increase neuronal excitability thus producing a brain stimulant-like effect.

- The progesterone metabolite, **allopregnanolone** (ALLO), produces a sedating/calming Valium-like effect.

Hypotheses of **Key Factor(s) in Dysphoric Mood in Cycling Women**

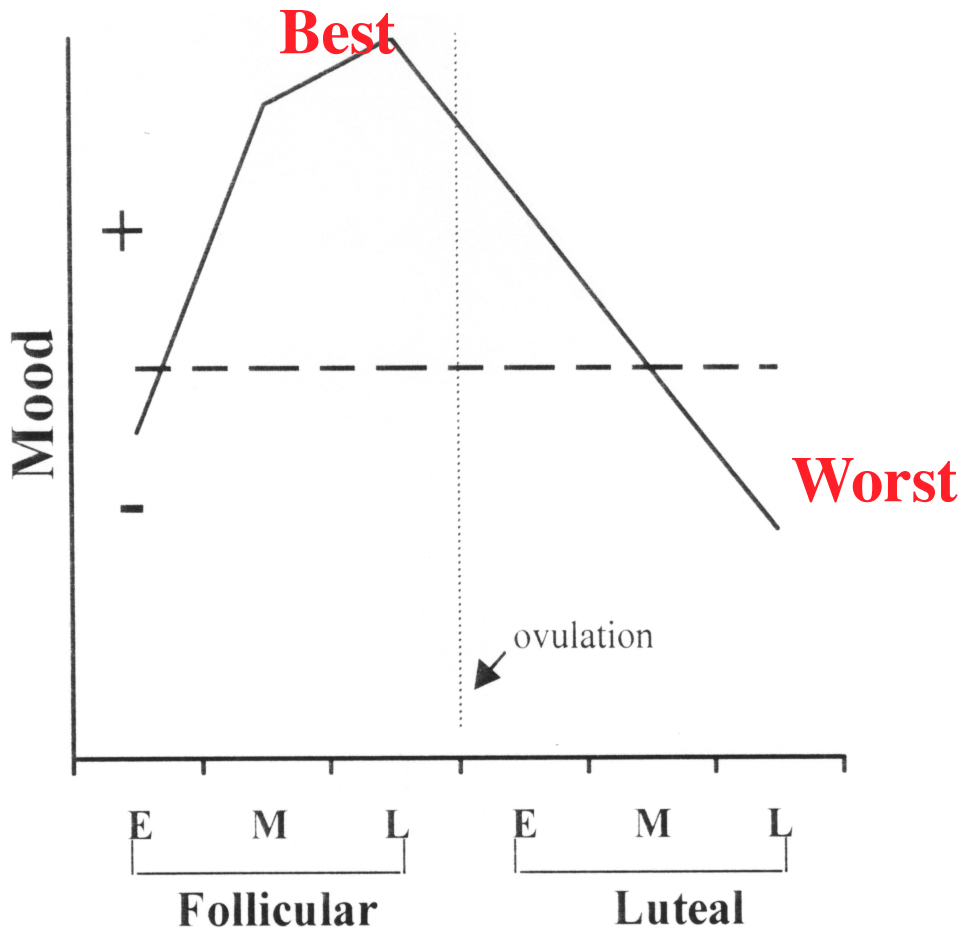
- Estrogen deficiency
- Progesterone effects
- Repeated fluctuations in hormones during menstrual cycles

Menstrual Cycle



Sex steroid changes in human menstrual cycle.

Mood Changes Across the Menstrual Cycle



week 1 2 3 4

-Morales, 1986

PMDD

Progesterone → Allopregnanolone (ALLO)

soothing, like Valium

- -ALLO= a neuroactive metabolite of progesterone and works on GABA (gamma-aminobutyric acid) receptors in the brain
- -Hence, ALLO is a powerful anxiolytic, anticonvulsant, and anesthetic agent which decreases anxiety and depression.
- -Barbituates, benzodiazepines and EtOH also work at this receptor.

-Griffin, 1999

PMDD

Progesterone → Allopregnanolone (ALLO)

soothing, like Valium

-Prozac, Paxil and Zoloft were found not only to increase Serotonin, but also to increase ALLO production by activating 2 enzymes (lowering their Km, activation of energy) that convert progesterone to ALLO

-Imipramine (Tofranil) had no effect on ALLO production

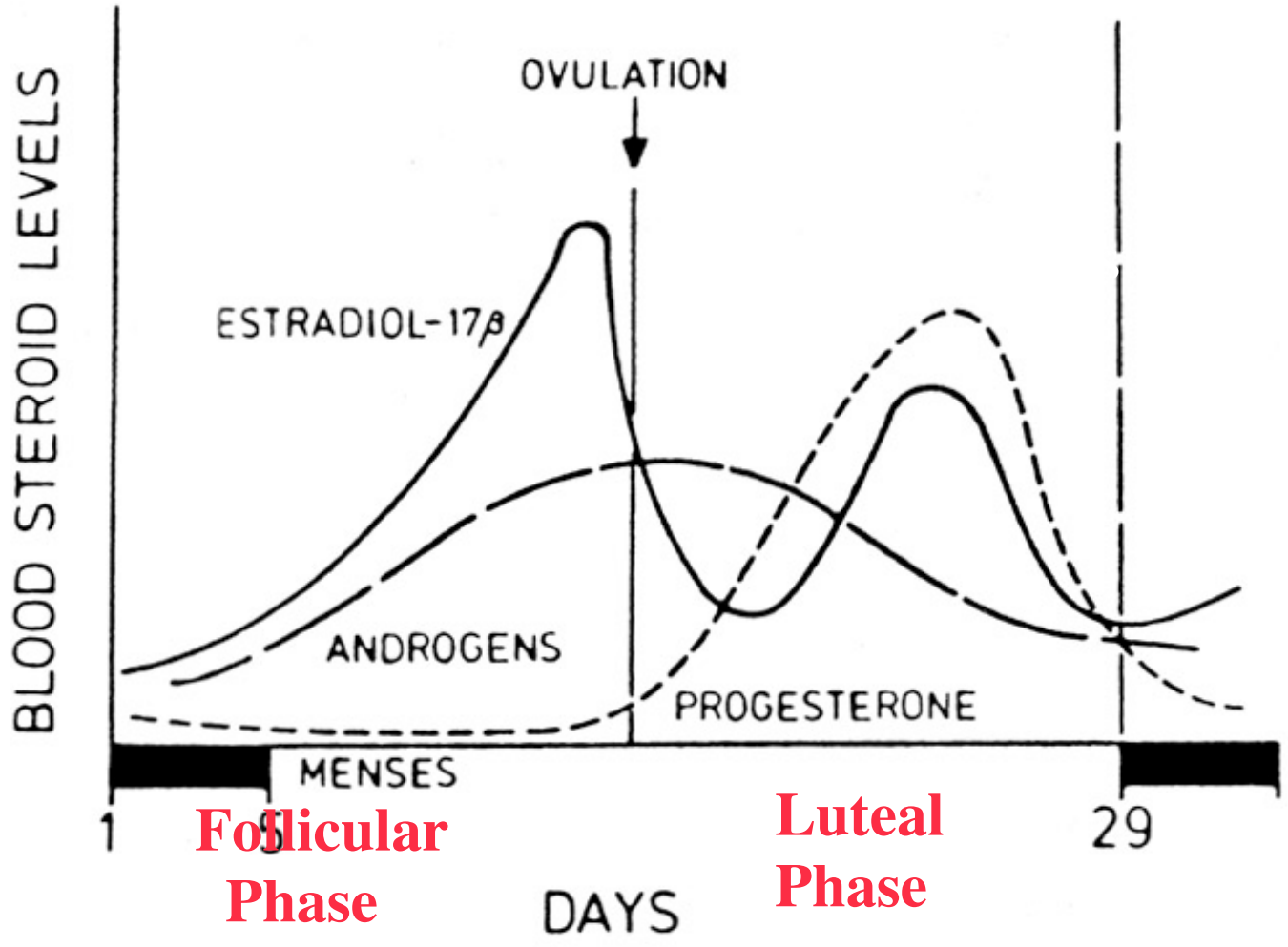
Journal:

-Lisa Griffin, MD, PhD and Synthia Mellon, PhD.

Selective serotonin reuptake inhibitors directly alter activity of neurosteroidogenic enzymes.

Proc Natl Acad Sci U S A. 1999 Nov 9;96(23):13512-7.

Menstrual Cycle



Sex steroid changes in human menstrual cycle.

PMDD

Main Treatments

- **Hormones:**
  - Start an OCP, or change to one with a progesterone good for mood
  - Take OCP continuously
    - Women are sensitive to hormones in different ways – some to the hormone fluctuation, some to the amount, and some to the progestin type

- **SSRI's:**
  - Either 7-10 days before menses to help boost ALLO, or daily
  - Works immediately, in the first 1-2 weeks, unlike the mechanism with depression

All Possible PMDD Treatments

Antidepressants

-SSRI*

-SNRI*

-Clomipramine**

Ovulation Suppression

-OCP's*

-GnRH Agonists (Lupron)**

-Danazol (inhibits LH/FSH)

-Oophorectomy

Anxiolytics

-BZD**

-Buspar**

Other

-Exercise

-Calcium**

-CBT*

-Chasteberry
(may reduce FSH or Prolactin)

-Vit B6

-NSAIDS

-Diet

*Efficacy in double-blind studies of PMDD

**Efficacy in double-blind studies of PMS

-Teri Pearlstein, M.D. Warren Alpert Medical School of Brown University, APA Conference 2008

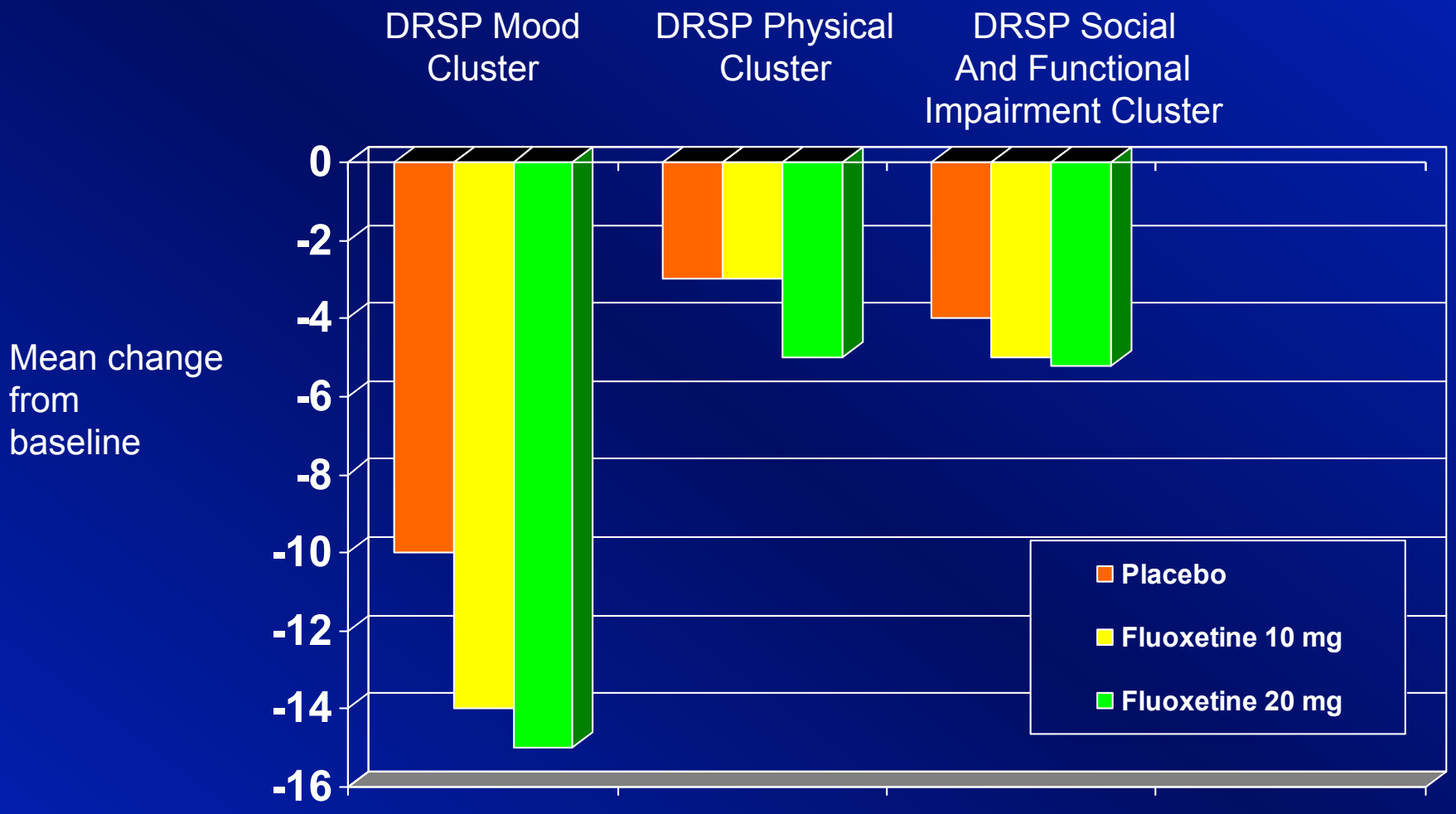
Advantages of SSRI's

- Fluoxetine, Sertraline and Paroxetine CR each FDA approved for PMDD
- Both continuous and intermittent dosing is effective in multiple trials
- Although intermittent Fluoxetine is effective for mood symptoms at both 10 and 20 mg, 20 mg is more effective for physical symptoms than 10 mg, as shown in a trial by Cohen et al, looking at intermittent Fluoxetine dosing for PMDD*
- No discontinuation symptoms with intermittent dosing
- Dosing strategies can be tailored to a woman's preferences

*Cohen LS, et al. *Obstet Gynecol.* 2002; 100: 435-444.

-Teri Pearlstein, M.D. Warren Alpert Medical School of Brown University, APA Conference 2008

Intermittent Fluoxetine in PMDD



DRSP = Daily Record of Severity of Problems

Cohen LS, et al. *Obstet Gynecol.* 2002; 100: 435-444.

Concerns With SSRI's

- Potential long-term effects of weight gain and sexual dysfunction
- Lower doses are less effective for physical symptoms than for mood/ anxiety symptoms
- Tolerance to dose over time?
- Recurrence of symptoms after dose discontinuation?
- Pregnancy during treatment (may not want to choose Paroxetine CR if pregnancy is a possibility)

-Teri Pearlstein, M.D. Warren Alpert Medical School of Brown University, APA Conference 2008

Add-Back Hormones in PMDD

- If you stop ovulation, you stop the trigger and you will not have PMS
- **Problem**: With GnRH agonists, you induce a medical menopause, and you need add-back hormones for bone/ cardiac health
- Add-back estrogen and progesterone may reduce the effectiveness of the GnRH agonist treatment of PMS because of reinduction of mood/ anxiety symptoms

Leather AT, et al. *Gynecol Endocrinol. 1999; 13: 49-55.*

Other Luteal Phase Treatments

- Alprazolam up to 0.25 mg po tid (taper at menses)
- Spironolactone 100 mg for edema
- Bromocriptine 2.5 mg for breast pain/ tenderness (mastalgia)
- NSAIDS for cramps/ leg pain

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Which birth control pill is good for mood?

- Lower progestin potency:

Ortho Evra patch	Necon 1/35
Ovcon 35	Alesse
Ortho-TriCyclen	Levlite
Othro-Cyclen	Tri-Levlen
Brevicon	Triphasil
Modicon	Trivora

Which birth control pill is good for mood?

- Women are sensitive to hormones in different ways – some to the progestin, some to the amount and some to the hormonal fluctuation.
- Seasonale, or any monophasic oral contraceptive pill (OCP) taken continuously (having only 1 period every 3 months) can also help stabilize mood.
- Of note, YAZ® is the only OCP given an indication for PMDD. However, it has a high progestin potency and may not be ideal for every woman.
- YAZ shortens the placebo week from the regular 7 days to 4 days – to minimize the time of hormonal fluctuation.
- Women who are sensitive to hormonal fluctuation should avoid triphasic OCP's.

YAZ®

- Contains:
  - Drospirenone 3 mg
  - Ethinyl estradiol 20 µg (Yasmine has 30 µg)
- Shortened hormone-free interval:
  - 24 active pills, 4 inactive pills (Yasmine has 21 active/ 7 inactive pills)
- Efficacy was expected for physical symptoms. But, surprisingly, efficacy in mood and irritability with YAZ was also seen.

-Yonkers KA, Brown C, Pearlstein TB, et al. "Efficacy of a new low-dose oral contraceptive with drospirenone in premenstrual dysphoric disorder." Obstet Gynecol. 2005;106:492-501.

Drospirenone

- Derived from 17 alpha spirolactone
- Analogue of spironolactone
- Has antimineralocorticoid activity (leads to water diuresis)
- Has antiandrogenic activity
- Increases K+ retention, Na+ and water excretion

PMDD In Summary

- PMDD effects 8-10% of women
- The current hypothesis is that women who experience PMDD are sensitive to the change in estrogen and progesterone, and experience progesterone (and ALLO) withdrawal
- SSRI's are clearly effective treatments with either daily or luteal phase dosing, but higher doses are more effective for physical vs. mood symptoms
- YAZ® has similar efficacy to SSRI's, both for physical and mood symptoms
- The big question: should women with PMDD be treated with OCP's or SSRI's first?

Which birth control pill is good for mood?

- **Bottom line:** Treatment needs to be individualized for each patient and trial and error may be necessary. It takes about 2 cycles to see if a certain OCP will work for a woman or not. Evidence based studies comparing one OCP to another are lacking.

The End

Thank You!

A special thank you to Dr. Louann Brizendine