
# The Menstrual Cycle and Mental Health: *Progress, Gaps, and Barriers*

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- My laboratory's logo indicates findings from my group.
  - www.clearlabresearch.com

# Overview

Epidemiology

Pathophysiology

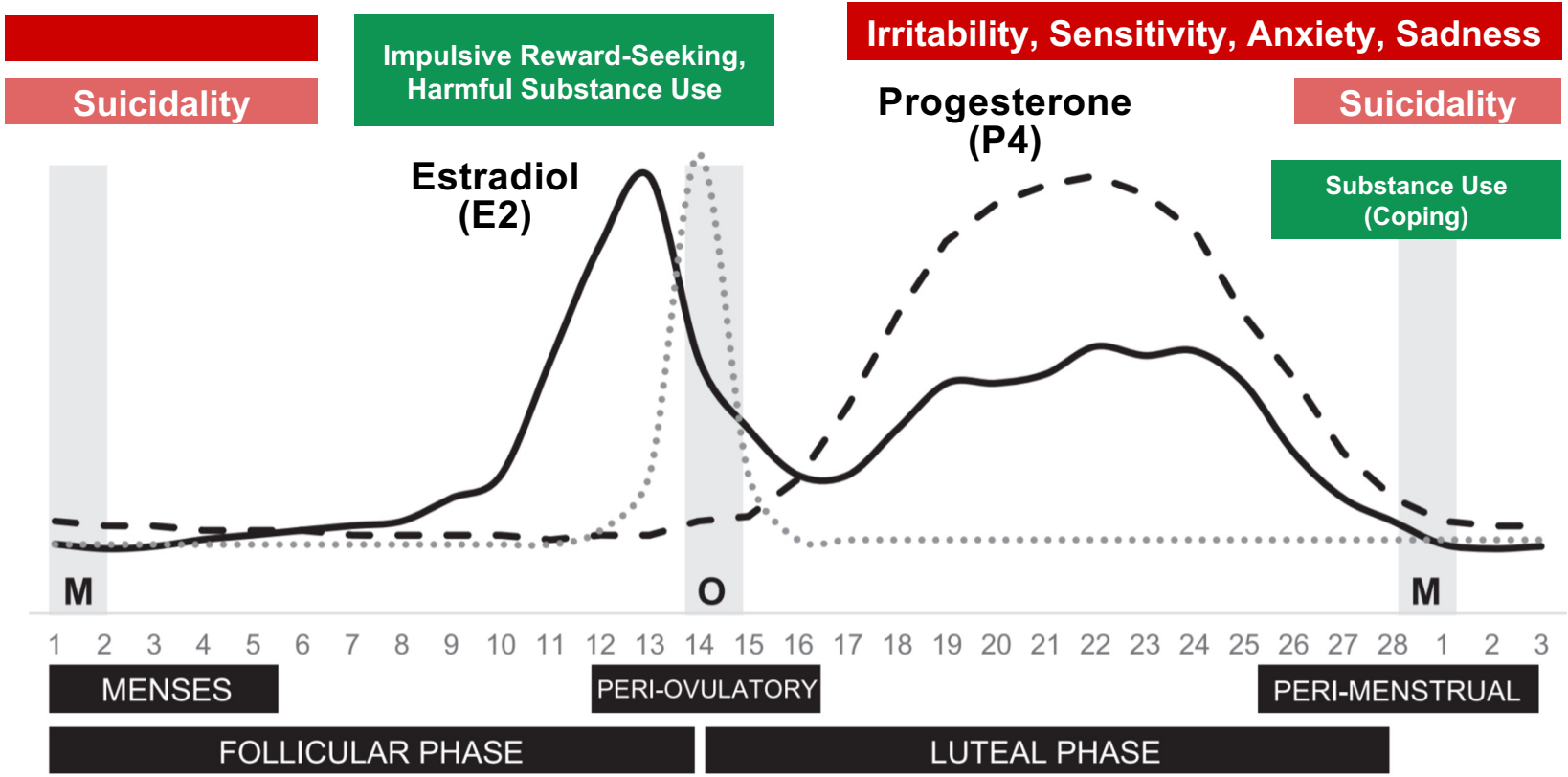
Treatment

Barriers

# EPIDEMIOLOGY

## PROGRESS TO DATE

# The cycle triggers significant changes in emotion and behavior *in some people, but not all*



EPIDEMIOLOGY

# Premenstrual Dysphoric Disorder (PMDD) is the sole diagnostic entity

*Added to DSM-5 in 2013… added to ICD-11 in 2022*

***At least 5 (at least one emotional) of the symptoms below must be present in the week before menses AND minimal or absent in the week post-menses:***

1. Marked affective lability
2. Marked irritability, anger, or conflicts
3. Marked depressed mood *(least common)*
4. Marked anxiety

1. Decreased interest in usual activities
2. Difficulty concentrating
3. Lethargy, fatigability, lack of energy
4. Marked change in appetite
5. Hypersomnia or Insomnia
6. Feeling overwhelmed or out of control
7. Physical symptoms (swelling, pain, bloating)

Excludes **premenstrual exacerbation (PME)** of chronic emotional disorders, even if the degree of change is the same

Does not capture **periovulatory changes** in impulsive reward-seeking or substance use

*PMID:* 22764360

# Daily ratings are required for valid diagnosis, but few use them

**~60% false positives**

## Structured Interviews

| *PREMENSTRUAL DYSPHORIC DISORDER* (PAST 12 MONTHS) | PREMENSTRUAL DYSPHORIC DISORDER CRITERIA | | |
|---|---|---|---|
| *IF SUBJECT IS A BIOLOGICAL MALE, POST-MENOPAUSAL FEMALE, PREGNANT FEMALE, OR FEMALE WITH HYSTERECTOMY PLUS OOPHORECTOMY, CHECK HERE ___ AND SKIP TO NEXT MODULE.* | | | A172 |
| **Looking back over your menstrual cycles for the past 12 months, since** (1 YEAR AGO), **have you had mood symptoms such as anger, irritability, anxiety, or depression that developed before your period and then went away during the week after your period?**<br>*IF YES*: **After your period began, did the problems disappear for at least a week?** | A. In the majority of menstrual cycles, at least five symptoms must be present in the final week before the onset of menses, start to improve within a few days after the onset of menses, and become minimal or absent in the week postmenses.<br>NOTE: If number of days of symptoms is 20 per month or greater, recheck symptom-free and symptom present intervals. | ? 1 2 3<br>GO TO NEXT MODULE | A173 |

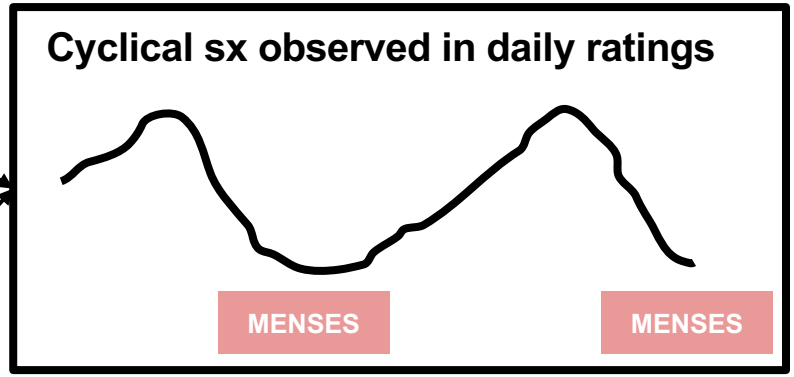
## Single Timepoint Survey

**The premenstrual symptoms screening tool (PSST)**

(please mark an "X" in the appropriate box)

**Do you experience some or any of the following premenstrual symptoms which *start before* your period and *stop* within a few days of bleeding?**

| Symptom | Not at all | Mild | Moderate | Severe |
|---|---|---|---|---|
| 1. Anger/irritability | | | | |
| 2. Anxiety/tension | | | | |




***… Prospective ratings used by only ~12% of clinicians who routinely diagnose PMDD***

*PMIDs:* 27523500, 33651443

EPIDEMIOLOGY

# Standardized scoring for daily ratings is available, but still not clinically feasible

## Toward the Reliable Diagnosis of DSM-5 Premenstrual Dysphoric Disorder: The Carolina Premenstrual Assessment Scoring System (C-PASS)

Tory A. Eisenlohr-Moul, Ph.D., Susan S. Girdler, Ph.D., Katja M. Schmalenberger, M.S., Danyelle N. Dawson, M.A., Pallavi Surana, B.S., Jacqueline L. Johnson, Dr.P.H., David R. Rubinow, M.D.

**Objective:** Despite evidence for the validity of premenstrual dysphoric disorder (PMDD) and the inclusion of the disorder in DSM-5, variable diagnostic practices compromise the construct validity of the diagnosis and threaten the clarity of efforts to understand and treat its underlying pathophysiology. In an effort to hasten and streamline the translation of the DSM-5 criteria for PMDD into terms compatible with existing research practices, the authors present the development and initial validation of the Carolina Premenstrual Assessment Scoring System (C-PASS). The C-PASS (available as a worksheet, Excel macro, and SAS macro) is a standardized scoring system for making DSM-5 PMDD diagnoses using two or more months of daily symptom ratings with the Daily Record of Severity of Problems (DRSP).

**Method:** Two hundred women recruited for retrospectively reported premenstrual emotional symptoms provided two to four months of daily symptom ratings on the DRSP. Diagnoses made by expert clinician and by the C-PASS were compared.

**Results:** Agreement of C-PASS diagnosis with expert clinical diagnosis was excellent; overall correct classification by the C-PASS was estimated at 98%. Consistent with previous evidence, retrospective reports of premenstrual symptom increases were a poor predictor of prospective C-PASS diagnosis.

**Conclusions:** The C-PASS is a reliable and valid companion protocol to the DRSP that standardizes and streamlines the complex, multilevel diagnosis of DSM-5 PMDD. Consistent use of this robust diagnostic method would result in more clearly defined, homogeneous samples of women with PMDD, thereby improving the clarity of studies seeking to characterize and treat the underlying pathophysiology of the disorder.

*Am J Psychiatry 2016; 00:1–9; doi: 10.1176/appi.ajp.2016.15121510*

**cpass package**

**GAP**

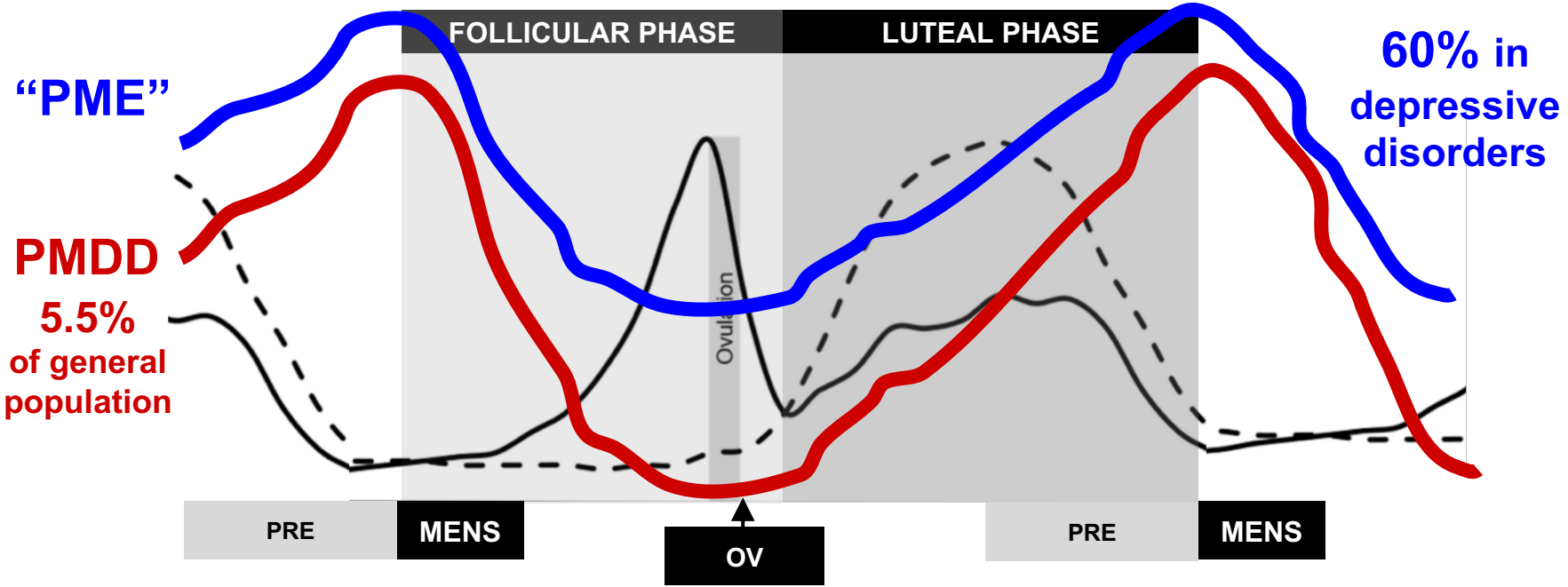
Poor clinical feasibility of daily ratings and standardized scoring

PMID: 27523500

EPIDEMIOLOGY

# PMDD is prevalent, and PME is even more prevalent

*PME accounts for the majority of clinical referrals, transdiagnostic*




*PMIDs:* 15385694, 18366818, 35936817, 35867164

EPIDEMIOLOGY

# Cyclical emotional changes are linked with suicidality

In 599 patients recruited for PMDD:

**87%** reported lifetime suicidal ideation

**34%** **reported** lifetime suicide attempt

In 128 patients recruited for suicidal ideation:

**62%** demonstrated PME *(>=30% change)*

**History of suicide attempt** (vs. ideation only) predicted greater premenstrual worsening

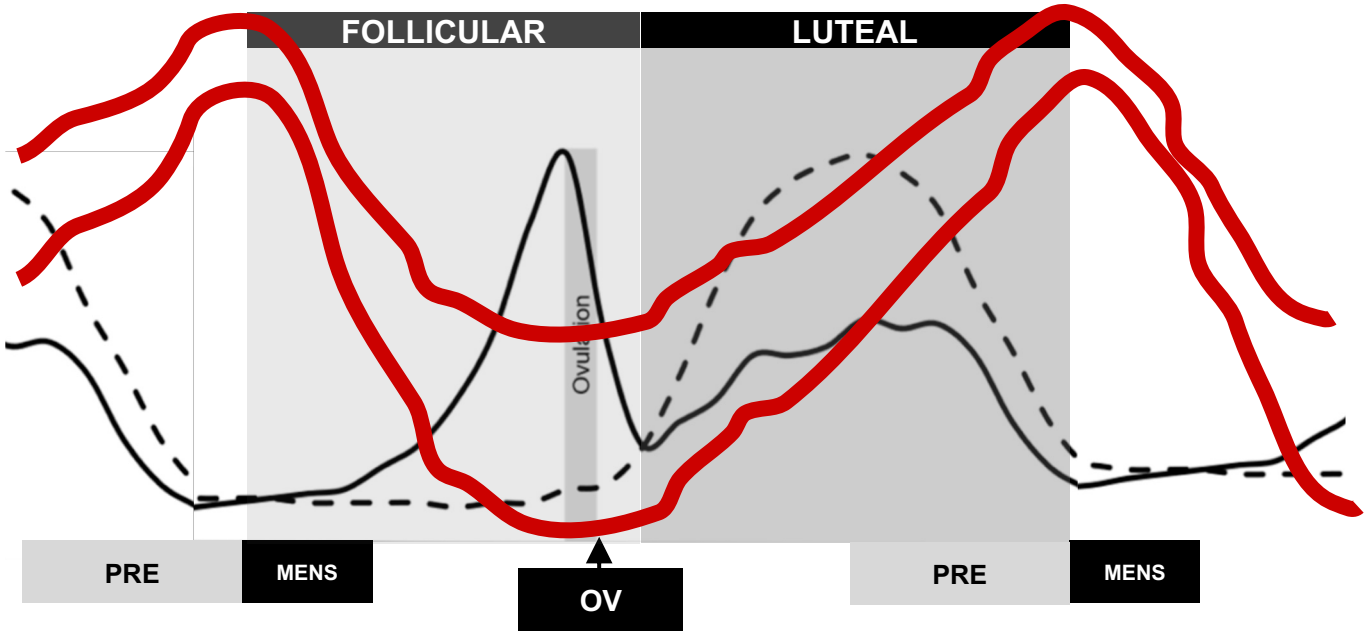
… and risk of **hospitalization for suicide attempt** peaks during menses

PMIDs: 35303811, 38093647, 16573848

# MAJOR RESEARCH GAP: Discriminant validity of PME

EPIDEMIOLOGY

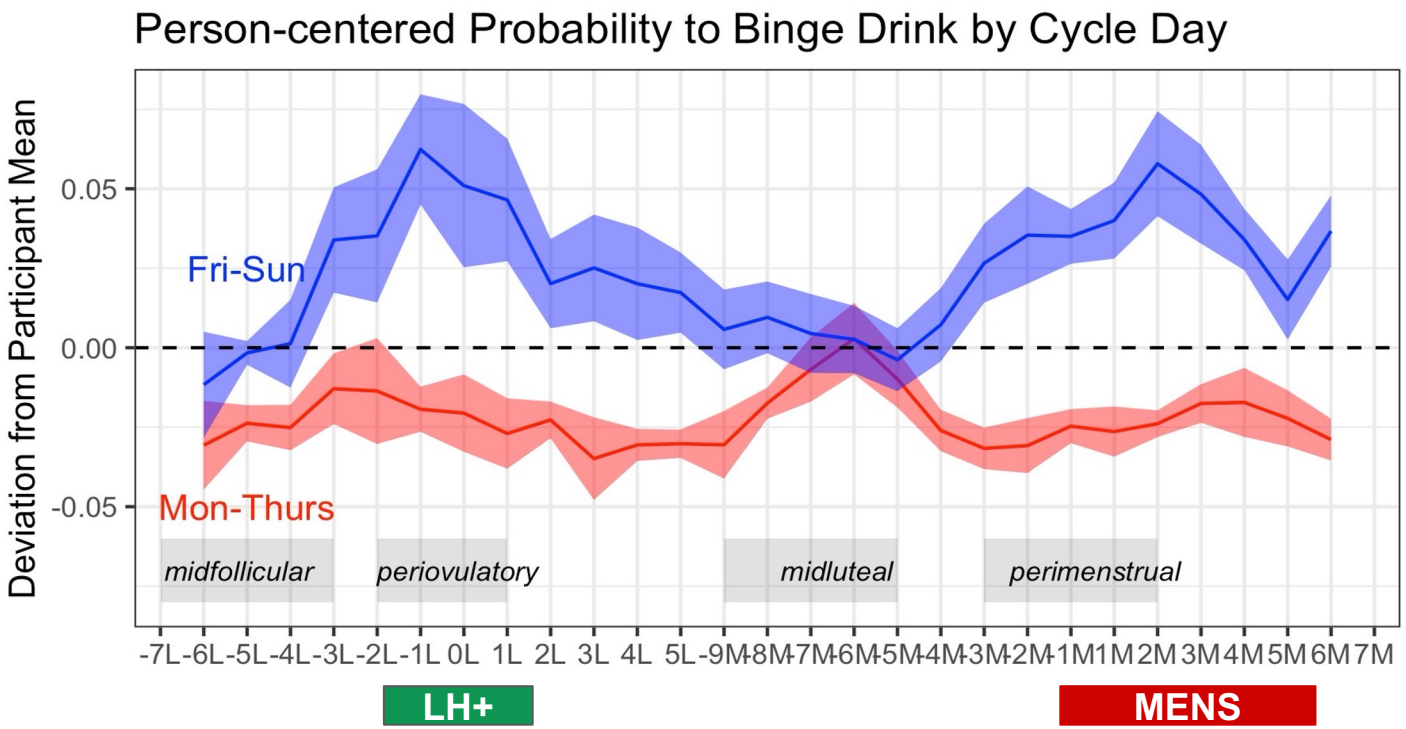
**Are PMDD and PME always different? Can we identify patients with PME who would benefit from diagnosis and treatment?**



EPIDEMIOLOGY

# Harmful Alcohol Use Peaks at Ovulation and Menses

*Observed across multiple cohorts, explained by daily E2 surges*



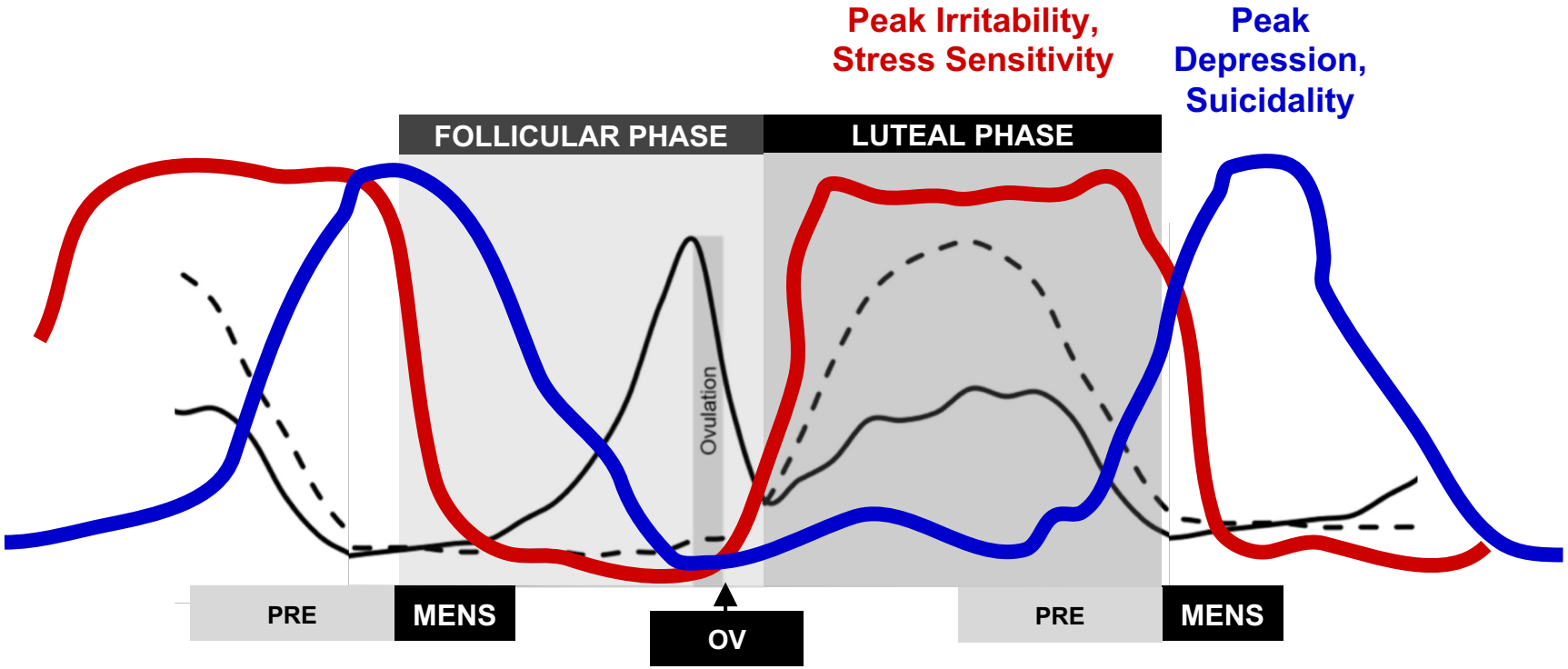

**GAP**

Need large-scale studies in patients with SUD

*PMIDs:* 36661851, 29154570, 38413577

# Evidence for temporal and content heterogeneity

*Repeatedly observed in our PMDD and PME cohorts*




*PMIDs:* 12892990, 31010447, 31624929

# MAJOR RESEARCH GAP: Longitudinal Cohort Studies

EPIDEMIOLOGY

- Longitudinal daily ratings data needed to estimate the prevalence, reliability, and validity of different potential subtypes, develop markers for personalized medicine
- What are the long-term developmental trajectories of PMDD/PME, and how do they relate to the development of comorbidities and PME?
- Does early intervention reduce a progression from PMDD→ PME or PMDD + psychiatric comorbidity?
- How do other reproductive changes like pregnancy, hormonal contraceptive use, and the menopause transition intersect with PMDD/PME?

# PATHOPHYSIOLOGY

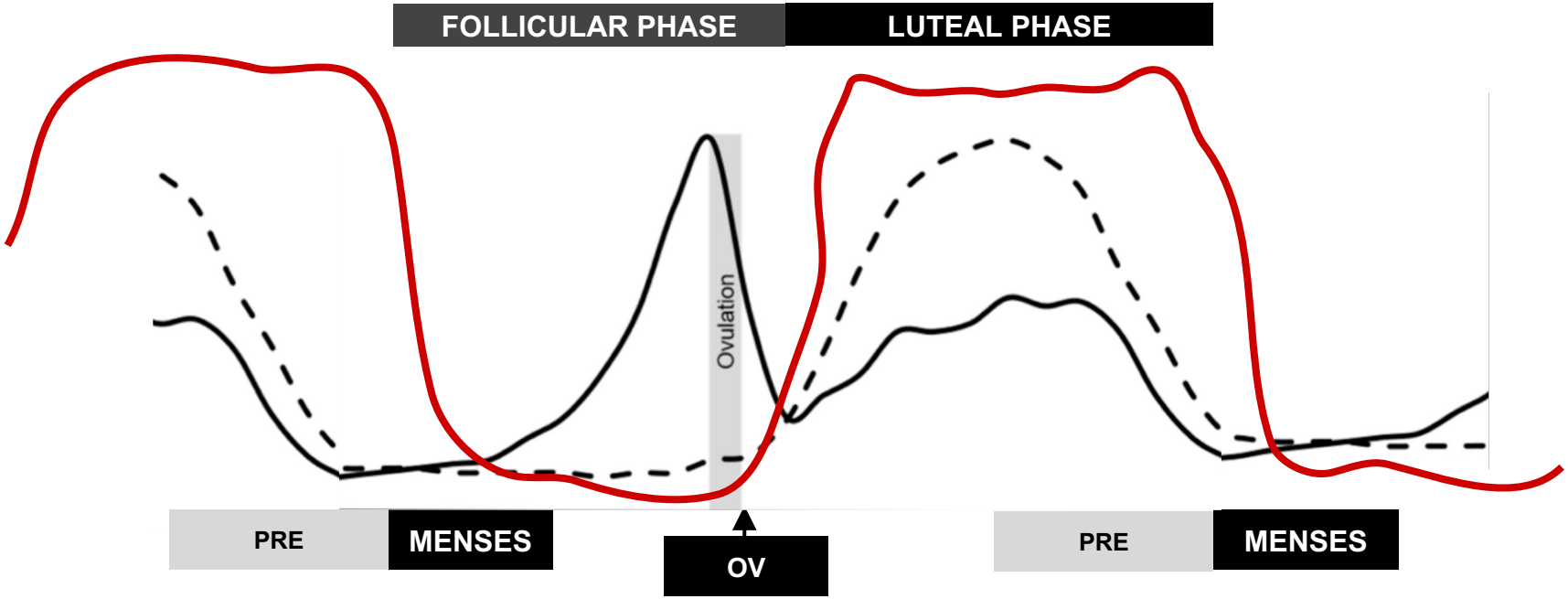
## PROGRESS TO DATE

PATHOPHYSIOLOGY

## Mounting evidence for multiple hormonal triggers/sensitivities

**PROGESTERONE METABOLITE SENSITIVITY**

**Peak Irritability, Stress Sensitivity**




*Illustrative PMIDs: 29154570, 26272051, 36585408, 32399989, https://osf.io/x5h9y/*

PATHOPHYSIOLOGY

# (Steroid Surge) Pathophysiology of Luteally-Confined PMDD

- ➔ Extensive evidence for luteal **serotonergic** dysfunction
  - ◆ Rapid benefit of SSRIs (24h), first-line treatment

- ➔ Beneficial effects of **ovarian suppression**
  - ◆ Drospirenone-containing COCs (second-line), GnRHa (third-line)

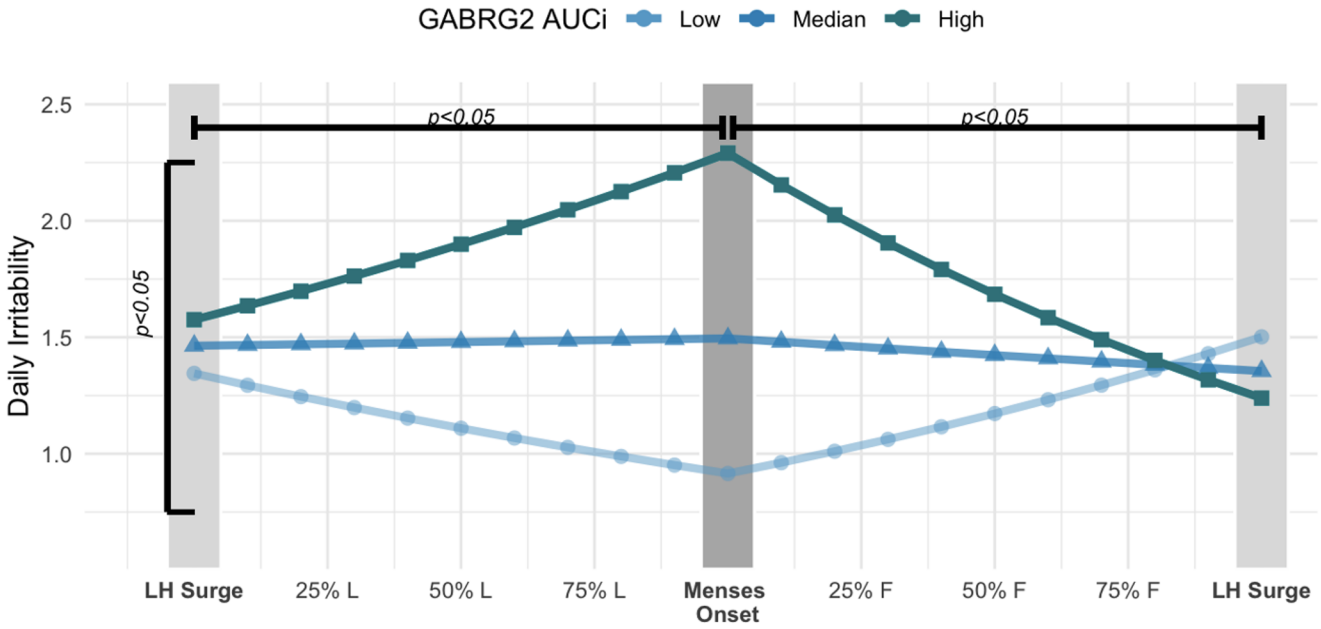
- ➔ Abnormal *sensitivity* to **addback of normal luteal surges in E2 or P4**, mediated by 5α-reduced P4 metabolites (ALLO)

- ➔ Abnormal sensitivity of GABA-A receptor to ALLO?
  - ◆ Hypothesized aberrant expression of subunits

PMIDs: 37171547, 28427285, 26272051, 26377947, 27347888, 23770328

PATHOPHYSIOLOGY

# Peripheral Whole-Blood Expression of GABRG2 AUCi Predicts Perimenstrual Irritability




Specific to irritability--

No effect on depression

***Effect size:***

**27%** increase in irritability across luteal phase at +2 SD

**42%** increase in irritability across luteal phase at +3 SD

N=112; 75 Transdiagnostic Outpatients, 37 Controls

Unpublished Data, Jordan Barone dissertation (Defended March 1)

PATHOPHYSIOLOGY

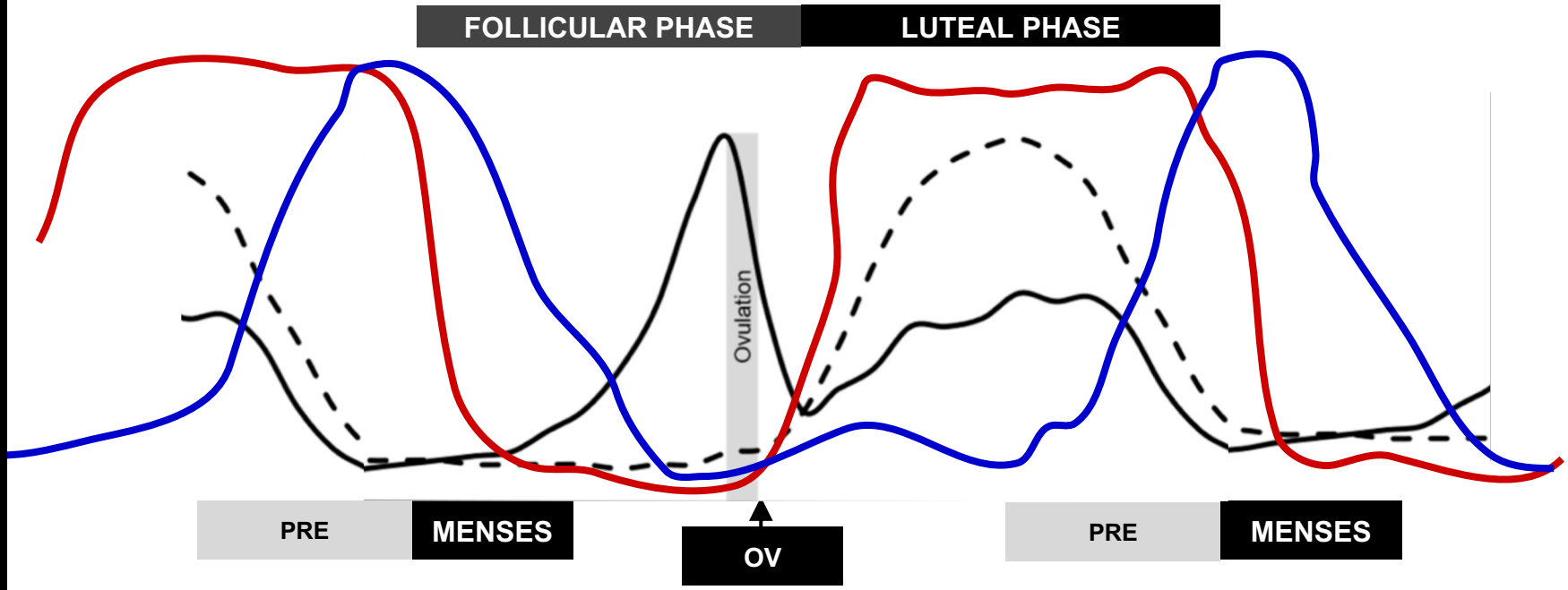
## Mounting evidence for multiple hormonal triggers/sensitivities

**PROGESTERONE METABOLITE SENSITIVITY**

Peak Irritability, Stress Sensitivity

**WITHDRAWAL?**

Peak Depression, Suicidal Ideation

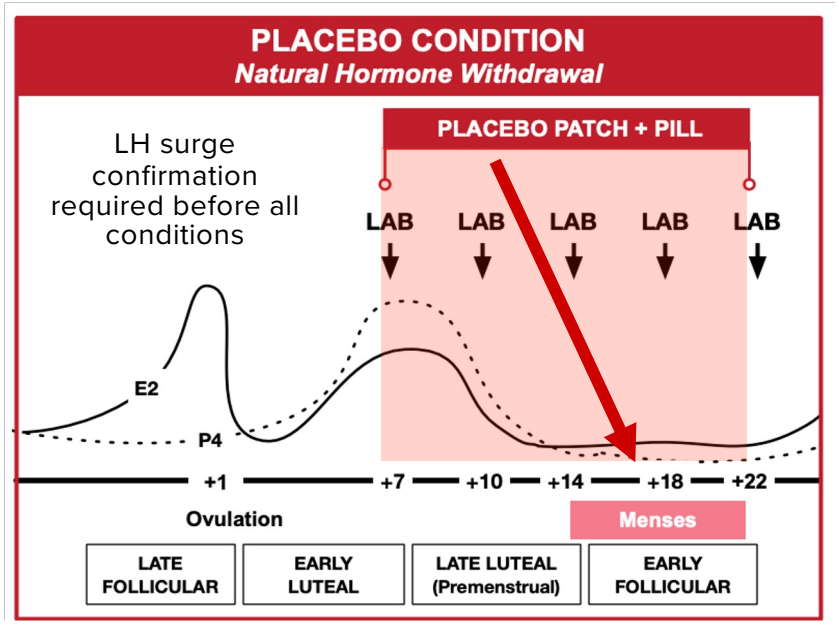



*Illustrative PMIDs: 29154570, 26272051, 36585408, 32399989, https://osf.io/x5h9y/*

# CLEAR-1 Crossover RCT Design

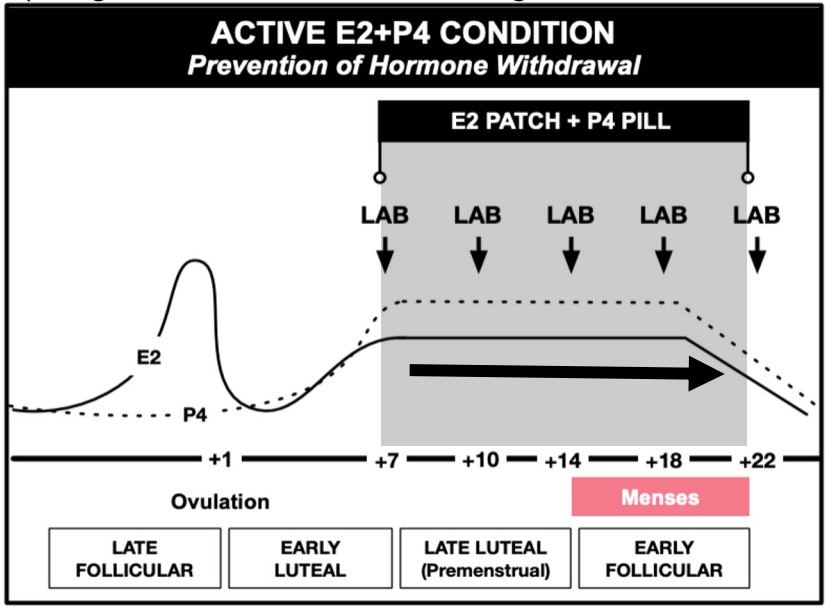
*(N=30 female patients recruited for past-month suicidal ideation)*

**Placebo:** Allow E2+P4 withdrawal




**E2 + P4:** Prevent withdrawal

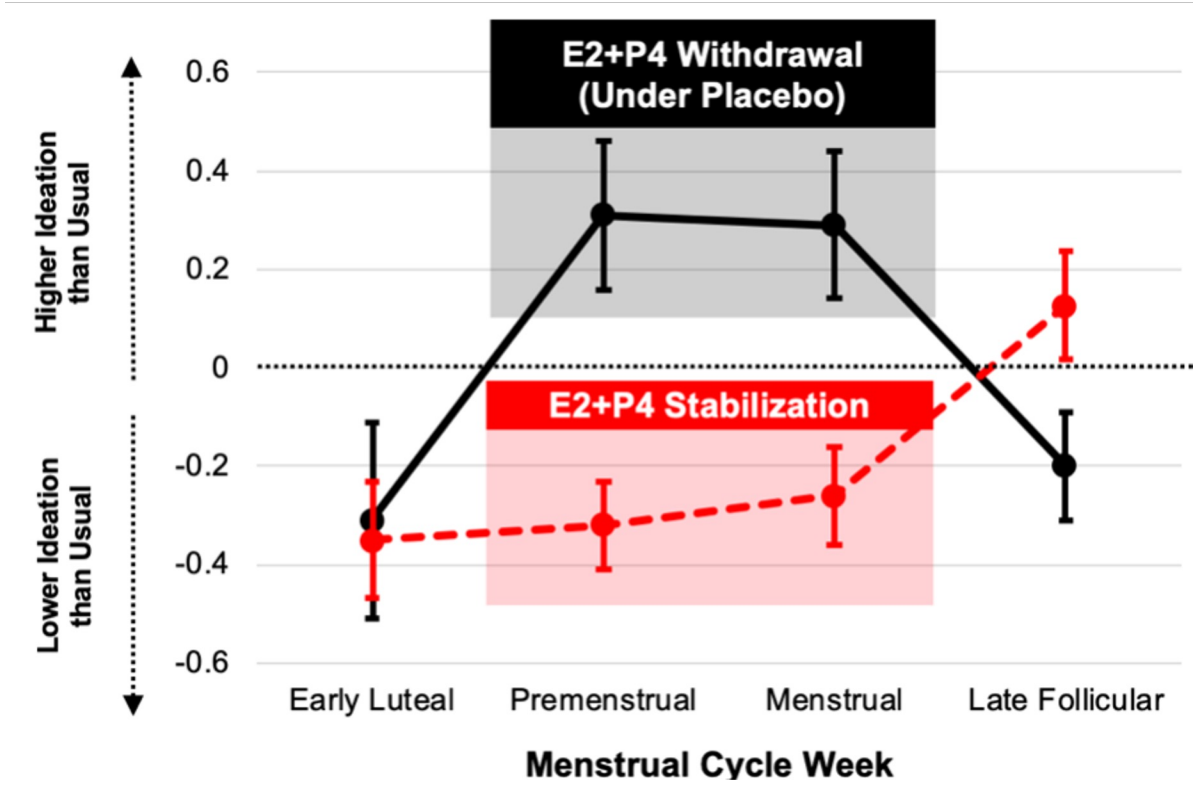
(.1mg/d transdermal E2 + 200mg oral micronized




*Eisenlohr-Moul et al., 2018;* ***NIMH K99/R00109667***

PATHOPHYSIOLOGY

# PME of SI & Depression Triggered by Steroid Withdrawal




Specific to depression--

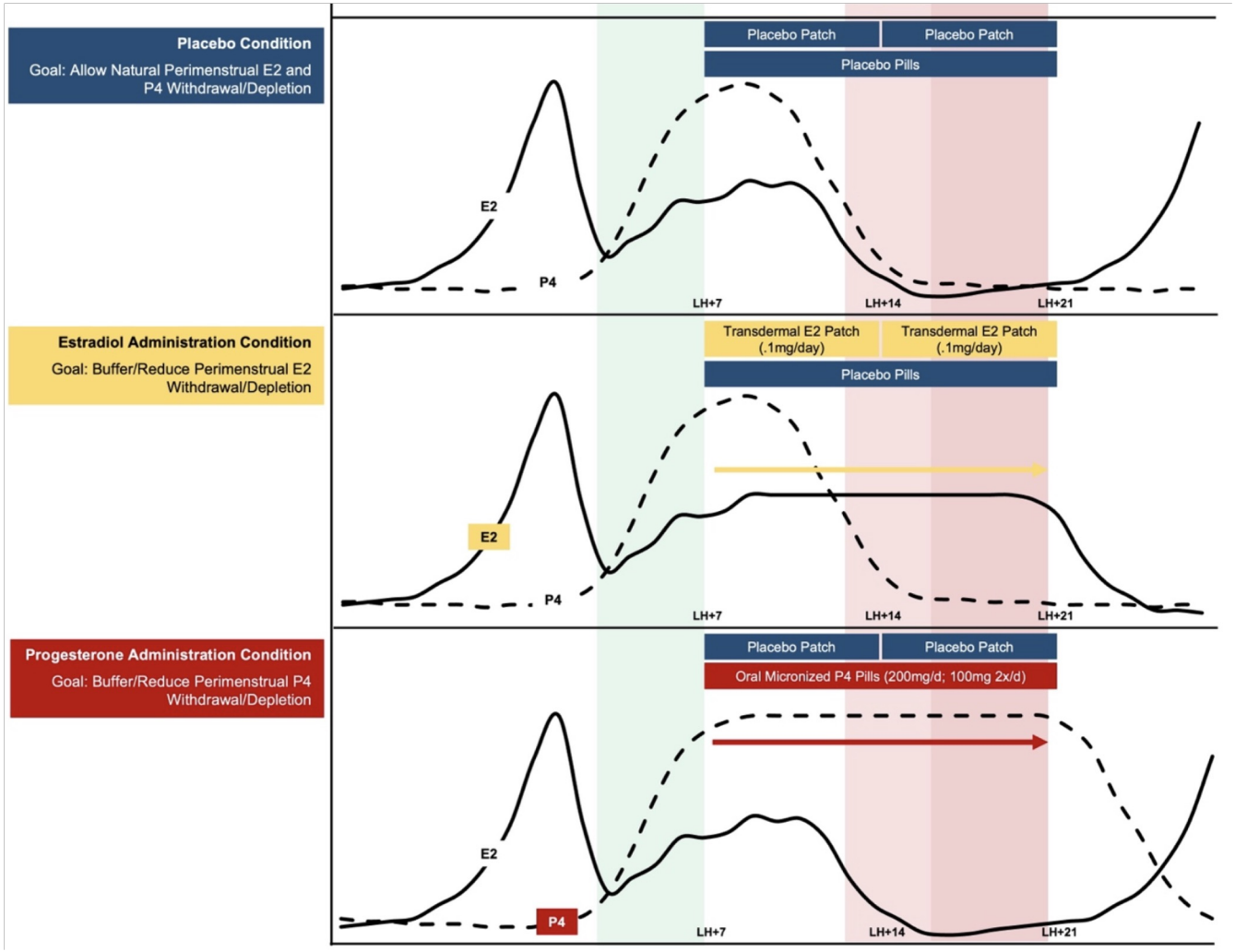
No effect on irritability

*Eisenlohr-Moul et al., 2022;* ***NIMH K99/R00109667***

PATHOPHYSIOLOGY

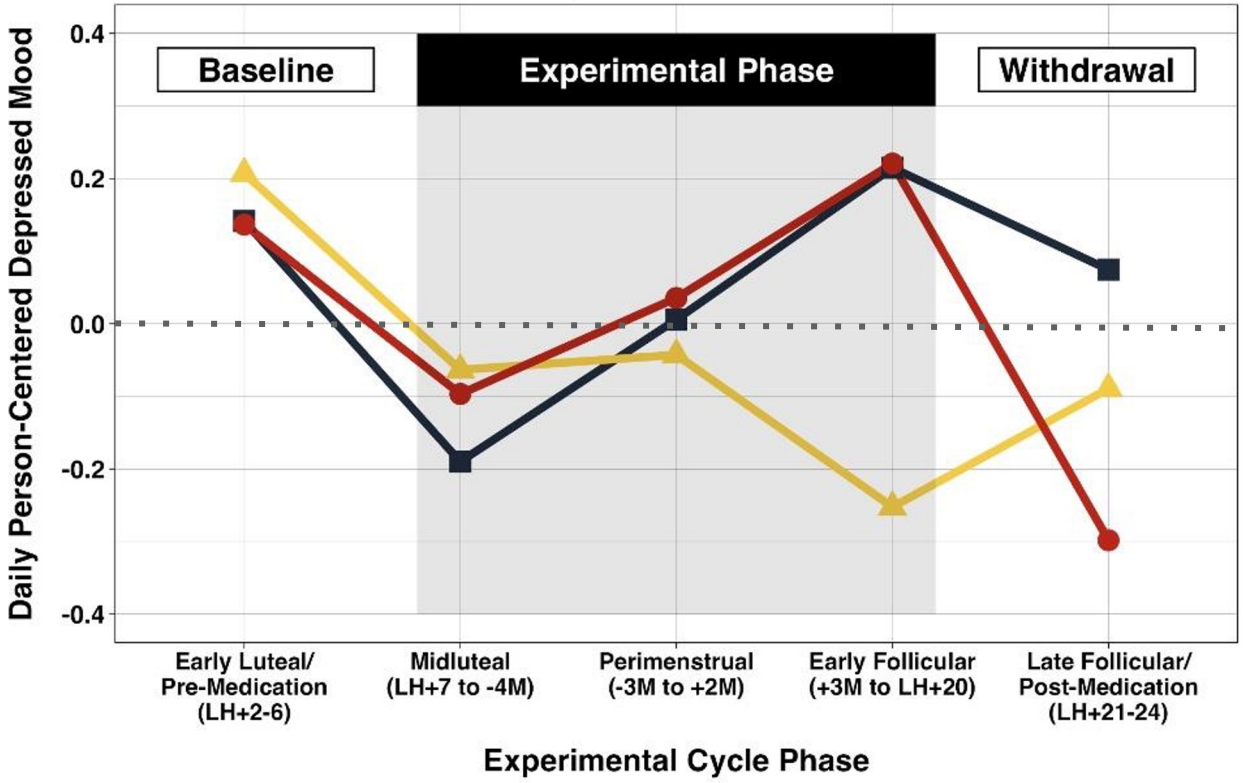
# CLEAR-2 Crossover RCT Design

*(N=44 recruited for past-month suicidal ideation)*



PATHOPHYSIOLOGY

# PME of SI and Depression Triggered by E2 Withdrawal




Specific to depression--

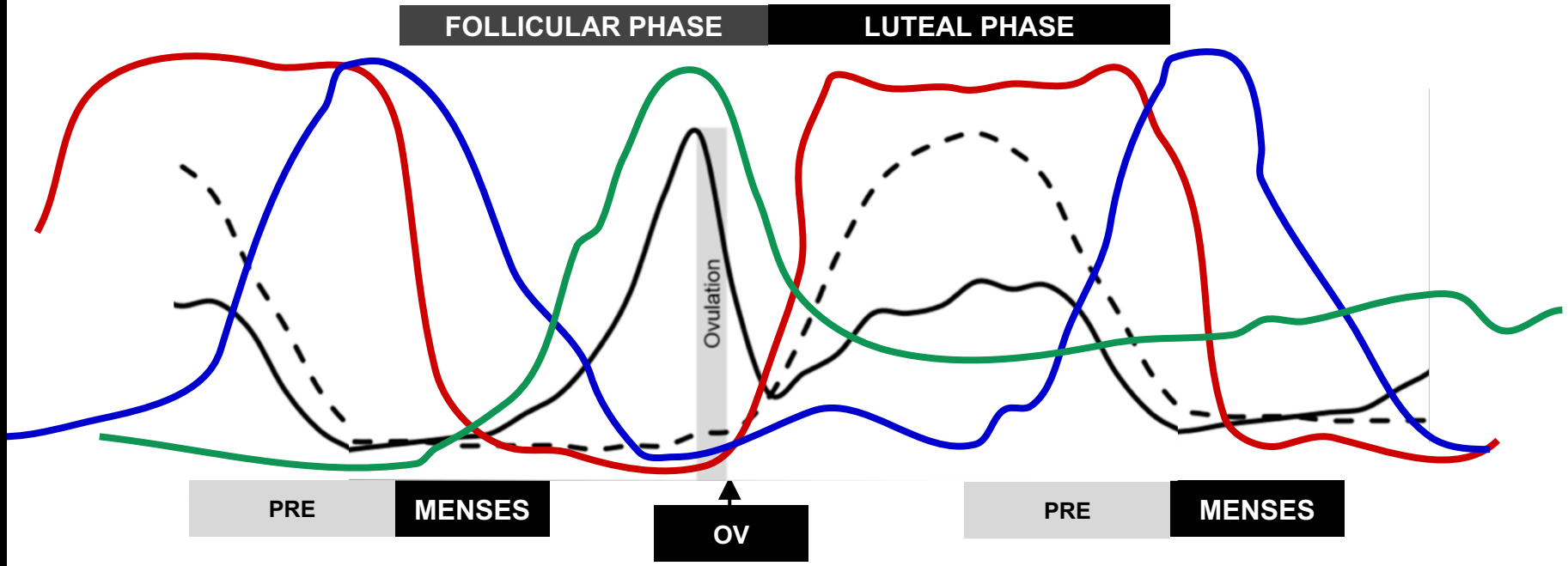
No effect on irritability

*R00 MH 109667*

PATHOPHYSIOLOGY

# Dimensional Affective Sensitivity to Hormones

| ESTRADIOL SURGE SENSITIVITY | PROGESTERONE METABOLITE SENSITIVITY | ESTRADIOL WITHDRAWAL SENSITIVITY |
|---|---|---|
| Impulsive Reward-Seeking | Negative Emotion (peak Irritability) | Negative Emotion (peak depression, SI) |




*Illustrative PMIDs: 29154570, 26272051, 36585408, 32399989, https://osf.io/x5h9y/*

# TREATMENT

## PROGRESS TO DATE

TREATMENT

# Evidence-Based Treatment Algorithm

(1) **SSRIs in luteal phase only or continuously**

(1) **Drospirenone-Containing Combined Oral Contraceptives**

(1) **GnRH Agonist + Stable E2/P4 addback** (Chemical Menopause)

(1) **Surgical Menopause** (Removal of Ovaries, Stable E2 addback)

**GAP**

Limited Treatment Options

**GAP**

Few predictors of treatment response

**GAP**

Lack of Behavioral Treatments

**GAP**

Limited access to chemical and surgical menopause

*PMID: 37341478*

# Recently Emerging Treatments with Emerging Evidence

TREATMENT

**Ulipristal Acetate** (SPRM) *potential liver toxicity*
- Suppresses ovulation, maintains moderate E2

One trial ✅

**Dutasteride** *teratogenicity*
- 5α Reductase Inhibitor (blocks PROG→ ALLO)

One trial ✅

***Asarina Pharma's Sepranolone* (Isoallopregnanolone)** *abandoned*
- Isomer of ALLO that antagonizes its effects at GABAAR
- Phase IIb Failure - Beats placebo in re-analysis of luteal subtype only

Phase IIa ✅
Phase IIb ❌

**MAJOR GAP: No pharma-sponsored trials currently underway per clinicaltrials.gov**

*PMID: 37171547*

# MOST IMPORTANT BARRIERS TO PROGRESS

- **Very small number of laboratories**, mentors in this area; leaky pipeline
- Single diagnostic entity (PMDD) for a **heterogeneous population**
- **Lack of back-translation** of human experiments to animal work
  - 28-day temporal dynamics, hormone *sensitivity*
- **Pharmaceutical company disengagement** (Sepranolone failure, PBO response)
- Lack of funding options for a **clinically feasible diagnostic platform** (need automated daily ratings collection with automated, standardized scoring systems)
  - Grants cannot support software/apps long-term, lack of interest from “femtech” companies
- Lack of diagnostic entities for (highly-prevalent) **PME**, or for **peri-ovulatory** phenotypes

CLOSING

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Clinical Psychology

Medicine


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NIMH R01-122446
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