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PMDD & the DUTCH Test: Understanding Neurotransmitters, Stress & Inflammation

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A NOTE ON VERBIAGE: This lecture and the cited scientific literature, when referring to women/females, are referring to individuals born biological females.

Today's Objectives

- Review epidemiology and diagnostic criteria for PMDD
- Discuss role of hormone fluctuations and impact on neuroactive steroids and neurotransmitters in disorder
- Discuss roles of stress and inflammation in disorder
- Examine patterns on the DUTCH test that may be helpful to assess in individuals with PMDD
- Review established and emerging conventional and natural approaches to treatment and symptom management

Epidemiology of PMDD

- PMDD is a serious mood disorder that impacts women of reproductive age
- It impacts 3-8% of menstruating individuals worldwide
  - This range may include confirmed and provisional diagnoses
- According to IAPMD's Facts and Figures:
  - It takes on average 12 years and 6 different healthcare providers for patients with PMDD to finally receive a diagnosis
  - More than 75% of those diagnosed with PMDD cycle through multiple treatments before finding any sort of relief
  - 90% of individuals with PMDD are misdiagnosed with another condition with 25% being misdiagnosed with Bipolar Disorder
  - PMDD causes major economic and relational distress with 40% of individuals with PMDD being more likely to miss work, 27% more likely to be unemployed, and 22% more likely to get divorced
  - Sadly, only 10% of medical providers are comfortable treating PMDD, which is why we need to be talking more about it

PMDD: DSM-V TR (2022) Diagnostic Criteria

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.

B. One (or more) of the following symptoms must be present:

1. Marked affective lability (e.g., mood swings; feeling suddenly sad or tearful, or increased sensitivity to rejection).
2. Marked irritability or anger or increased interpersonal conflicts.
3. Marked depressed mood, feelings of hopelessness, or self-deprecating thoughts.
4. Marked anxiety, tension, and/or feelings of being keyed up or on edge.

C. One (or more) of the following symptoms must additionally be present, to reach a total of five symptoms when combined with symptoms from Criterion B above:

1. Decreased interest in usual activities (e.g., work, school, friends, hobbies).
2. Subjective difficulty in concentration.
3. Lethargy, easy fatigability, or marked lack of energy.
4. Marked change in appetite; overeating; or specific food cravings.
5. Hypersomnia or insomnia.
6. A sense of being overwhelmed or out of control.
7. Physical symptoms such as breast tenderness or swelling, joint or muscle pain, a sensation of “bloating,” or weight gain.

Note: The symptoms in Criteria A–C must have been met for most menstrual cycles that occurred in the preceding year.

PMDD: DSM-V TR (2022) Diagnostic Criteria (Continued)

D. The symptoms cause clinically significant distress or interference with work, school, usual social activities, or relationships with others (e.g., avoidance of social activities; decreased productivity and efficiency at work, school, or home).

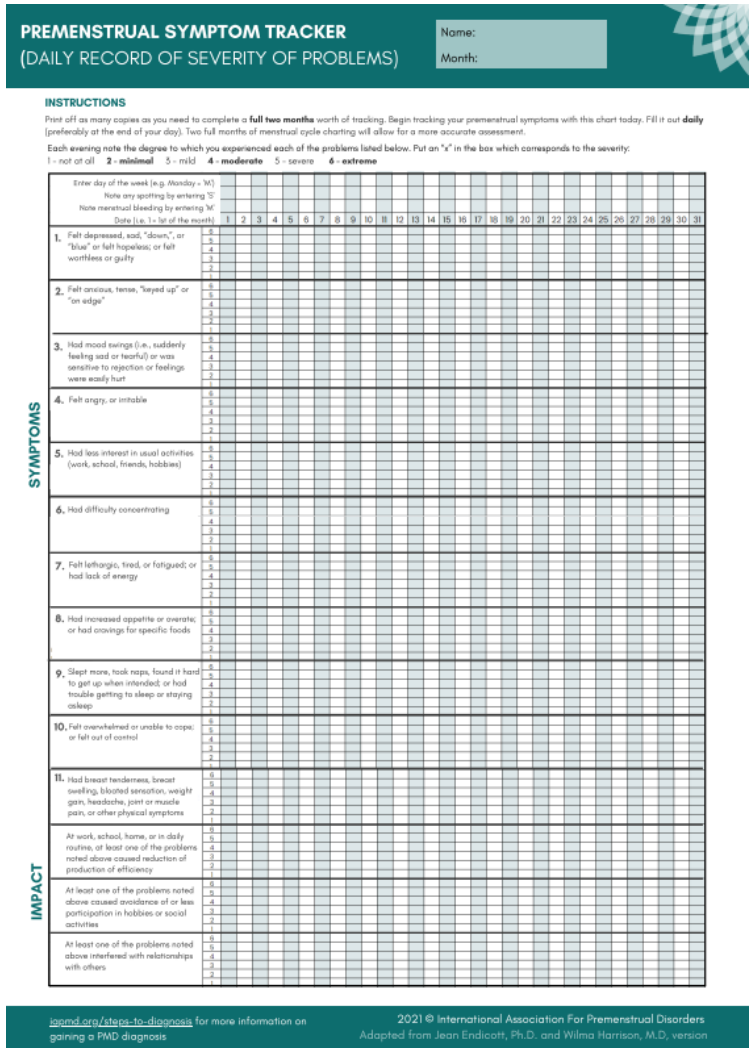
E. The disturbance is not merely an exacerbation of the symptoms of another disorder, such as major depressive disorder, panic disorder, persistent depressive disorder, or a personality disorder (although it may co-occur with any of these disorders).

F. Criterion A should be confirmed by **prospective** daily ratings during at least two symptomatic cycles. *(Note: The diagnosis may be made provisionally prior to this confirmation.)*

G. The symptoms are not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication, other treatment) or another medical condition (e.g., hyperthyroidism).

Symptom Tracking

- There are no lab tests via blood, saliva, urine, or imaging that can diagnose PMDD
  - We can rule out other issues with these tests though
    - Ex: low thyroid function → depression
    - Ex: low luteal progesterone → increased anxiety
- Symptom tracking is key!
  - The Daily Record of Severity of Problems is a gold standard, clinically validated tracking tool patients can use to document symptoms over 2 menstrual cycles
  - The International Association of Premenstrual Disorders (IAPMD.org) is a great resource for free tracking tools and resources in general around PMDD



PREMENSTRUAL SYMPTOM TRACKER
(DAILY RECORD OF SEVERITY OF PROBLEMS)

Name:
Month:

INSTRUCTIONS

Print off as many copies as you need to complete a **full two months** worth of tracking. Begin tracking your premenstrual symptoms with this chart today. Fill it out **daily** (preferably at the end of your day). Two full months of menstrual cycle charting will allow for a more accurate assessment.

Each evening note the degree to which you experienced each of the problems listed below. Put an "x" in the box which corresponds to the severity:

1 - not at all **2 - minimal** 3 - mild **4 - moderate** 5 - severe **6 - extreme**

Enter day of the week (e.g. Monday = 'M')
Note any spotting by entering 'S'
Note menstrual bleeding by entering 'M'
Date (i.e. 1 = 1st of the month) 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

SYMPTOMS

1. Felt depressed, sad, "down," or "blue" or felt hopeless; or felt worthless or guilty
2. Felt anxious, tense, "keyed up" or "on edge"
3. Had mood swings (i.e., suddenly feeling sad or tearful) or was sensitive to rejection or feelings were easily hurt
4. Felt angry, or irritable
5. Had less interest in usual activities (work, school, friends, hobbies)
6. Had difficulty concentrating
7. Felt lethargic, tired, or fatigued; or had lack of energy
8. Had increased appetite or overate; or had cravings for specific foods
9. Slept more, took naps, found it hard to get up when intended; or had trouble getting to sleep or staying asleep
10. Felt overwhelmed or unable to cope; or felt out of control
11. Had breast tenderness, breast swelling, bloated sensation, weight gain, headache, joint or muscle pain, or other physical symptoms

IMPACT

At work, school, home, or in daily routine, at least one of the problems noted above caused reduction of production of efficiency
At least one of the problems noted above caused avoidance of or less participation in hobbies or social activities
At least one of the problems noted above interfered with relationships with others

iapmd.org/steps-to-diagnosis for more information on gaining a PMD diagnosis

Adapted from Jean Endicott, Ph.D. and Wilma Harrison, M.D. version

International Association for Premenstrual Disorders. PMDs symptom tracker. IAPMD. Accessed June 2, 2026.

PMDD Diagnosis Key Points

- PMDD is differentiated from other mental health issues by its temporal relationship to the menstrual cycle
- The symptoms arise in the luteal phase and are resolved in the follicular phase
- Symptoms that are present in the follicular phase but worsen in the luteal phase should be treated as chronic mental health issues and not cyclical to avoid undertreating the patient
  - Worsening of an established underlying mental health issue during the luteal phase is known as a Premenstrual Exacerbation (PME) and should still be evaluated and addressed
  - If the patient experiences symptoms different enough from the underlying mental health disorder during the luteal phase, they may have a comorbidity of PMDD

PMDD Key Points

- **PMDD is characterized by an increased sensitivity to normal levels of fluctuating sex hormones**
- Those with and without PMDD are indistinguishable based on aggregate levels of peripheral sex hormones
- If you find a true hormonal imbalance such as low progesterone relative to estrogen, correcting such an imbalance may be beneficial but may not address the underlying PMDD if the patient is sensitive to normal levels

PMDD Experiences

- “I don’t believe in hell but if there was one, PMDD definitely fits the description.”
- “It doesn’t even feel like me anymore. It’s like a psychotic version of myself. Then afterwards I’m completely fine and normal.”
- “I’m generally not an angry person and it takes me a lot to feel enraged, but anything triggers me during that week.”
- “My PMDD makes me feel like everything is bleak, nothing matters, and I’m worthless.”
- “I had the intense wish to die every two weeks like clockwork. I could be the happiest person and then be completely depressed.”

A Note on Suicidal Ideation in PMDD

When the Cycle Hurts Too Much: Talking About Self-Harm and Suicidal Thoughts

Up to 72%

Experience suicidal thoughts or ideation during symptomatic times.[1]

51%

Engage in self-harming behaviors (cutting, hitting, burning, etc.) as a coping mechanism and report non-suicidal self-injury (NSSI) during the luteal phase.[2]

Up to 34%

Attempt suicide at some point in their lives.[2]

7x

More likely to attempt suicide compared to those without PMDD.

PMDD is associated with disproportionately high rates of suicidal ideation, self-harm, and suicide attempts. Research and community-reported data reveal a troubling prevalence. Below is a summary of what we currently know:

International Association for Premenstrual Disorders. Self-harm & suicidality. IAPMD. Accessed June 1, 2026.

What Adds to Susceptibility for Developing or Worsening PMDD

- Genetics/Epigenetic factors
  - The sensitivity to normal levels of fluctuating hormones may lie in genetically driven differences in molecular mechanisms, receptors
- Stress
- Inflammation/Immune Dysfunction
- Trauma/ Adverse Childhood Events (ACEs)
- Neurodivergence
  - Prevalence of PMDD is significantly increased in females with Autism and ADHD
- Major reproductive events can worsen PMDD symptoms
  - Menarche, postpartum, perimenopausal transition
- MCAS and histamine intolerance
  - Histamine can exacerbate symptoms of PMDD

Important Papers in Understanding PMDD

The New England
Journal of Medicine

VOLUME 338 JANUARY 22, 1998 NUMBER 4

DIFFERENTIAL BEHAVIORAL EFFECTS OF GONADAL STEROIDS IN WOMEN WITH AND IN THOSE WITHOUT PREMENSTRUAL SYNDROME

PETER J. SCHMIDT, M.D., LYNNETTE K. NIEMAN, M.D., MERRY A. DANACEAU, R.N., LINDA F. ADAMS, B.A., AND DAVID R. RUBINOW, M.D.

ABSTRACT

Background The symptoms of women with menstrual syndrome improve in response to pression of ovarian function, although these wo have no evidence of ovarian dysfunction. We ur took a study to determine the role of estrogen progesterone in this syndrome.

Methods We first studied the effect of ovarian pression with leuprolide, an agonist analogue of nadotropin-releasing hormone, or placebo on sy toms in 20 women with premenstrual syndrome. women whose symptoms improved during leu lide treatment were given estradiol and progeste in a double-blind, crossover design, each for weeks, during continued leuprolide administra Women without premenstrual syndrome (no women) participated in a similar protocol. Outco were assessed on the basis of daily self-report the patients and biweekly rater-administered sy tom-rating scales.

Results The 10 women with premenstrual drome who were given leuprolide had a signifi decrease in symptoms as compared with base values and with values for the 10 women who given placebo. The 10 women with premenstrual drome who were given leuprolide plus estradi progesterone had a significant recurrence of sy toms, but no changes in mood occurred in 15 no women who received the same regimen or in 5 w en with premenstrual syndrome who were given cebo hormone during continued leuprolide adm tration.

Conclusions In women with premenstrual drome, the occurrence of symptoms represent abnormal response to normal hormonal chan (N Engl J Med 1998;338:209-16.)

Premenstrual Dysphoric Disorder Symptoms Following Ovarian Suppression: Triggered by Change in Ovarian Steroid Levels But Not Continuous Stable Levels

Peter J. Schmidt, M.D., Pedro E. Martinez, M.D., Lynnette K. Nieman, M.D., Deloris E. Koziol, Ph.D., Karla D. Thompson, R.N., Linda Schenkel, B.S., Paul G. Wakim, Ph.D., David R. Rubinow, M.D.

Objective: Premenstrual dysphoric disorder (PMDD) symptoms are eliminated by ovarian suppression and stimulated by administration of ovarian steroids, yet they appear with ovarian steroid levels indistinguishable from those in women without PMDD. Thus, symptoms could be precipitated either by an acute change in ovarian steroid levels or by stable levels above a critical threshold playing a permissive role in expression of an underlying infradian affective "pacemaker." The authors attempted to determine which condition triggers PMDD symptoms.

Method: The study included 22 women with PMDD, ages 30 to 50 years. Twelve women who experienced symptom remission after 2–3 months of GnRH agonist-induced ovarian suppression (leuprolide) then received 1 month of single-blind (participant only) placebo and then 3 months of continuous combined estradiol/progesterone. Primary outcome measures were the Rating for Premenstrual Tension observer and self-ratings completed every 2 weeks during clinic visits. Multivariate repeated-measure ANOVA for mixed models was employed.

Results: Both self- and observer-rated scores on the Rating for Premenstrual Tension were significantly increased (more symptomatic) during the first month of combined estradiol/progesterone compared with the last month of leuprolide alone, the placebo month, and the second and third months of estradiol/progesterone. There were no significant differences in symptom severity between the last month of leuprolide alone, placebo month, or second and third months of estradiol/progesterone. Finally, the Rating for Premenstrual Tension scores in the second and third estradiol/progesterone months did not significantly differ.

Conclusions: The findings demonstrate that the change in estradiol/progesterone levels from low to high, and not the steady-state level, was associated with onset of PMDD symptoms. Therapeutic efforts to modulate the change in steroid levels proximate to ovulation merit further study.

Am J Psychiatry 2017; 174:980–989; doi: 10.1176/appi.ajp.2017.16101113

Original Article | Published: 03 January 2017

The ESC/E(Z) complex, an effector of response to ovarian steroids, manifests an intrinsic difference in cells from women with premenstrual dysphoric disorder

N Dubey, J F Hoffman, K Schuebel, Q Yuan, P E Martinez, L K Nieman, D R Rubinow, P J Schmidt ✉ & D Goldman

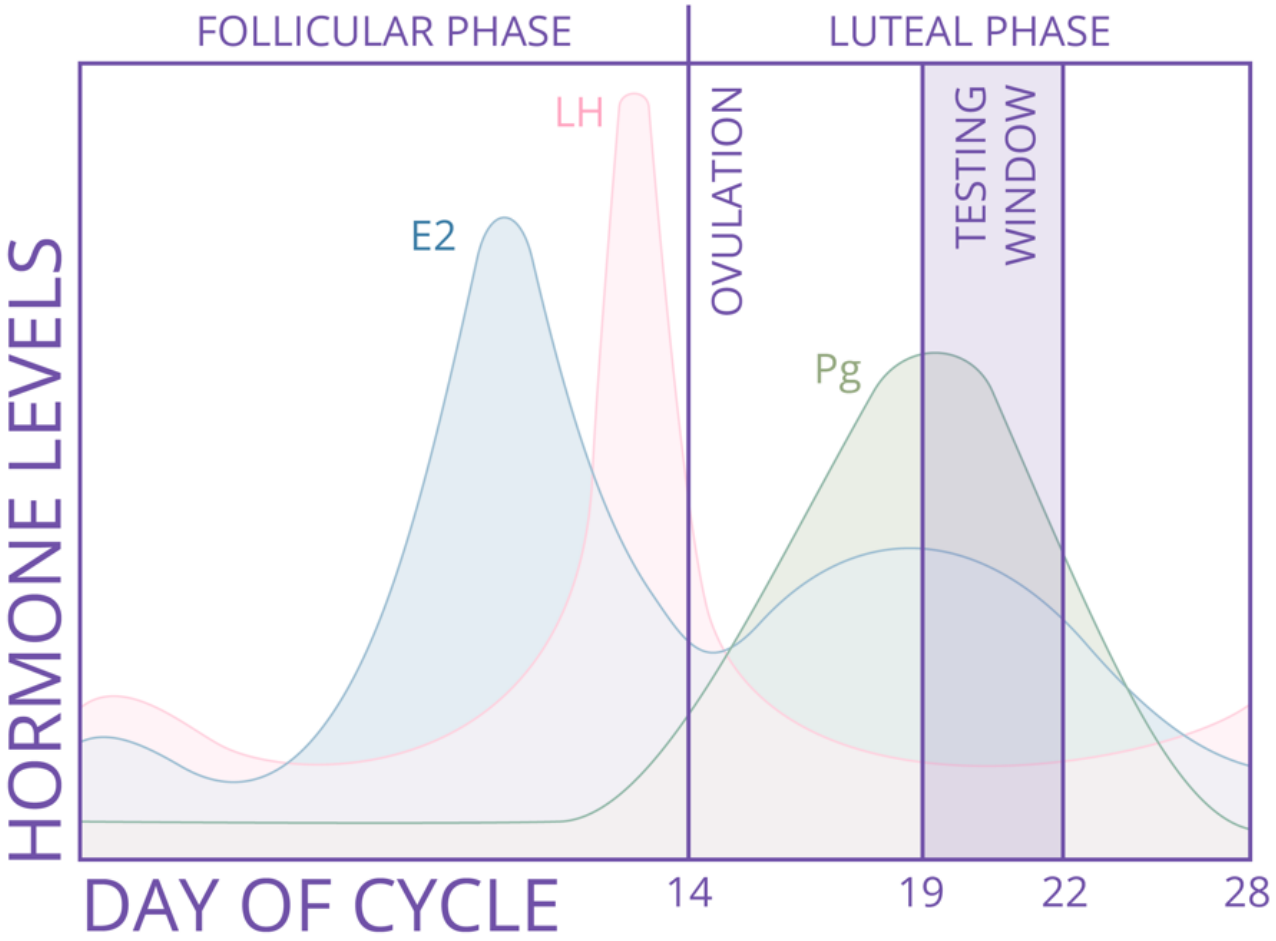
Molecular Psychiatry **22**, 1172–1184 (2017) | Cite this article

4718 Accesses | **91** Citations | **458** Altmetric | Metrics

Abstract

Clinical evidence suggests that mood and behavioral symptoms in premenstrual dysphoric disorder (PMDD), a common, recently recognized, psychiatric condition among women, reflect abnormal responsivity to ovarian steroids. This differential sensitivity could be due to an unrecognized aspect of hormonal signaling or a difference in cellular response. In this study, lymphoblastoid cell line cultures (LCLs) from women with PMDD and asymptomatic controls were compared via whole-transcriptome sequencing (RNA-seq) during untreated (ovarian steroid-free) conditions and following hormone treatment. The women with PMDD manifested ovarian steroid-triggered behavioral sensitivity during a hormone suppression and addback clinical trial, and controls did not, leading us to hypothesize that women with PMDD might differ in their cellular response to ovarian steroids. In untreated LCLs, our results overall suggest a divergence between mRNA (for example, gene transcription) and protein (for example, RNA translation in proteins) for the same genes. Pathway analysis of the LCL

The Menstrual Cycle



Proposed Players in PMDD

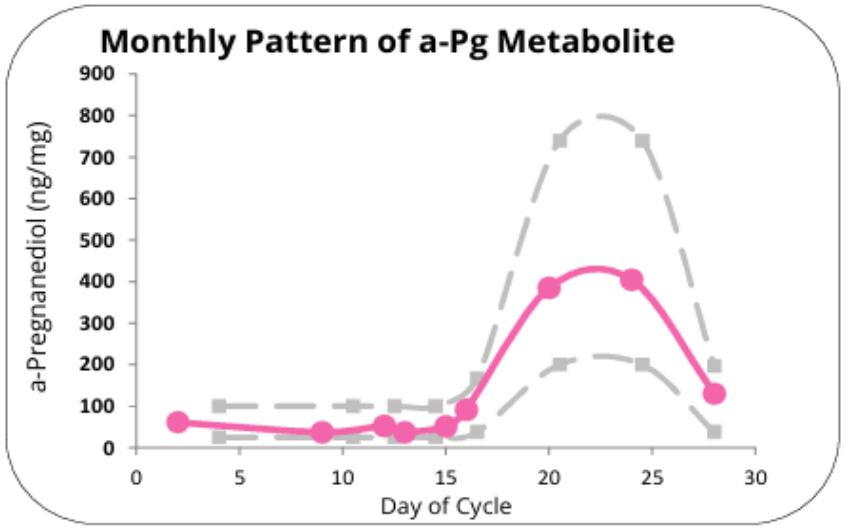
Proposed Players in PMDD

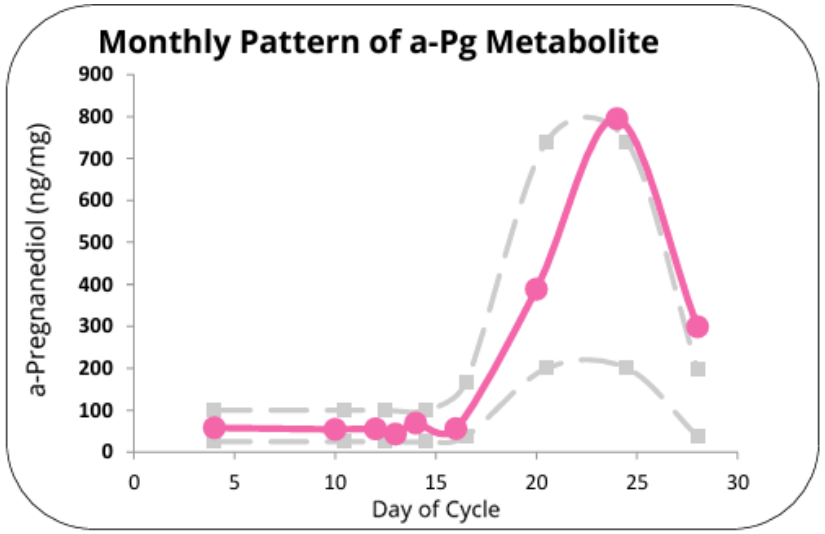
- Allopregnanolone
  - GABA
  - GABA-A Receptor
- Estrogen
  - Serotonin
  - Histamine
  - ESR1 Polymorphisms
- Inflammation
- Stress/Trauma
  - HPA Axis Dysfunction

Allopregnanolone's Role in PMDD

The Role of Allopregnanolone (ALLO) in PMDD

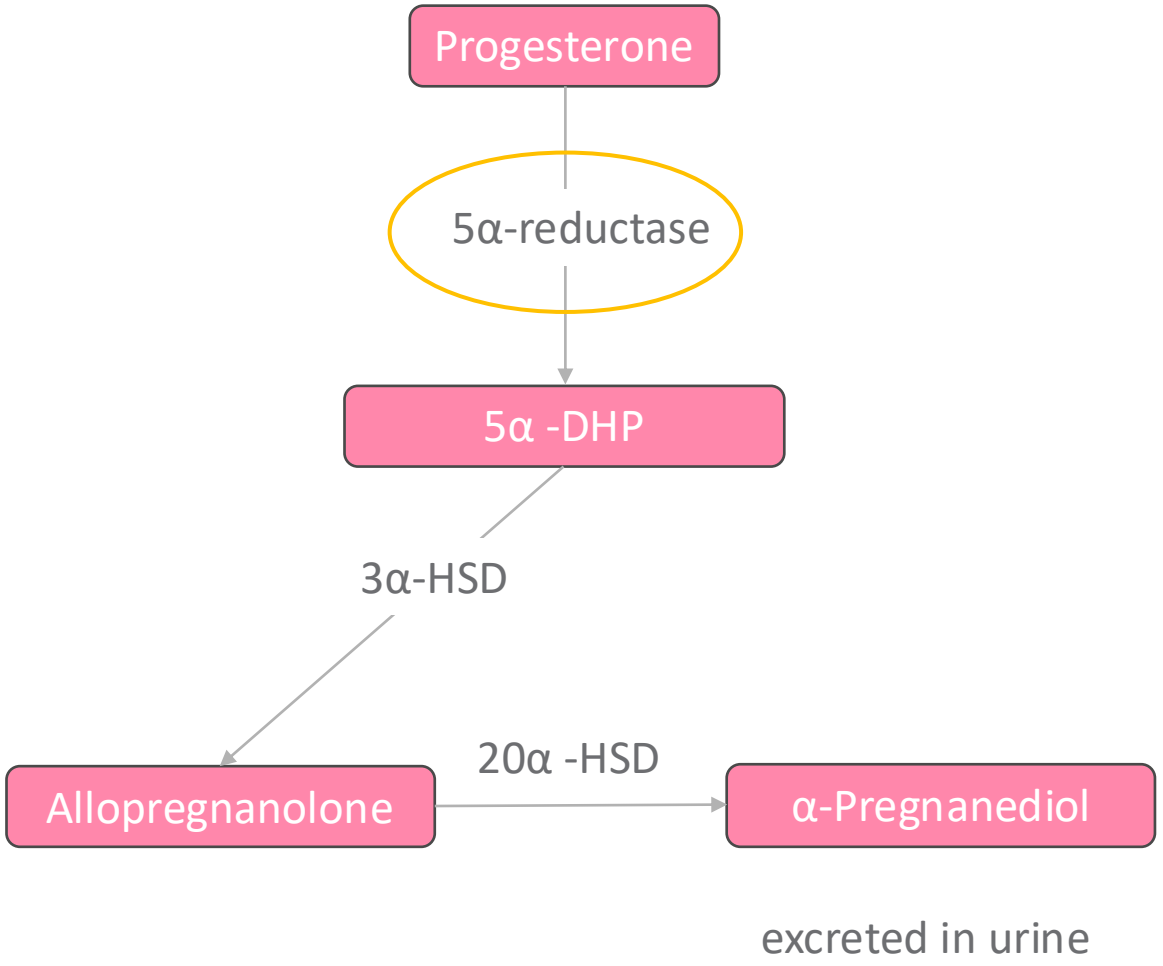
- Allopregnanolone is a neuroactive steroid (NAS) derived from progesterone, which rises then subsequently falls during the luteal phase of an ovulatory cycle if pregnancy does not occur
- ALLO acts as a positive allosteric modulator of the GABA-A Receptor- similar to benzodiazepines, alcohol, and many herbal components
- Typically, ALLO has anxiolytic and calming effects, but in PMDD, a paradoxical response to ALLO arises, leading to mood lability, irritability, and increased anxiety





*ALLO levels can be indirectly observed via the a-pregnanediol metabolite with the DUTCH test

What We Measure on the DUTCH Test



- Progesterone is converted to allopregnanolone in a two-step process:
  - Step 1: progesterone to 5a-dihydroprogesterone (5a-DHP) via **5a-reductase (5aR)**
  - Step 2: 5α-DHP to allopregnanolone via 3a-hydroxysteroid-deyhydrogenase (3a-HSD)
- We measure 5a-pregnanediol on the DUTCH test which gives us an idea of progesterone metabolism through 5aR

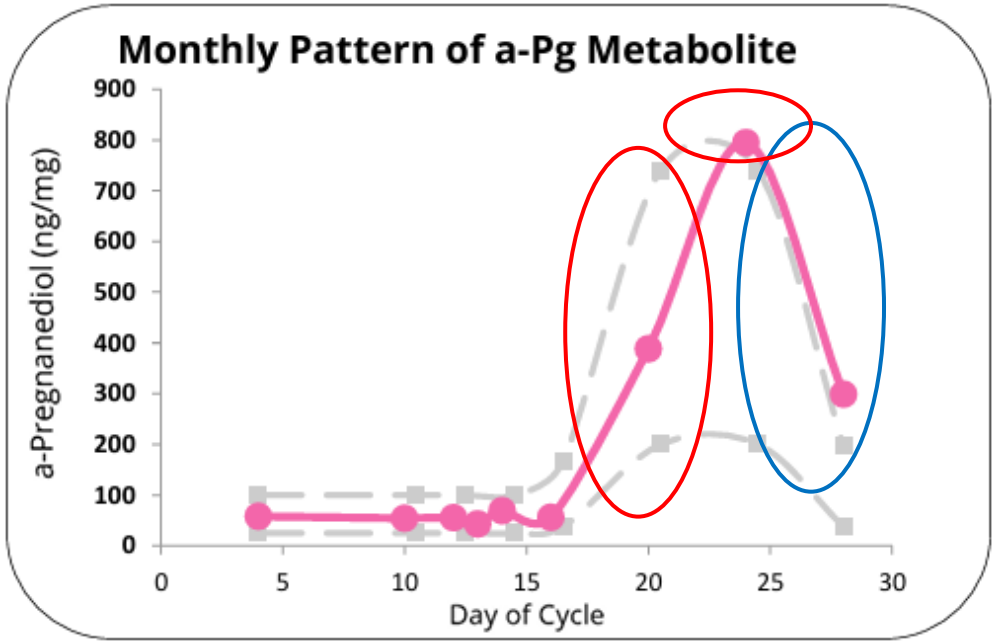
ALLO Mechanisms in PMDD

The main theories behind ALLO's role in PMDD:

- GABA withdrawal
  - Some PMDD may be triggered by a drop in allopregnanolone in the late luteal phase
- Paradoxical GABA response
  - Some PMDD may be triggered by normal luteal levels of allopregnanolone
- Low allopregnanolone
  - Some women with low progesterone may not make enough allopregnanolone to gain its calming benefits
  - *Test, don't guess- correct an imbalance first*

Is it an ALLO/GABA Withdrawal Issue?

- ALLO has been implicated in PMDD as it mirrors progesterone's rise and fall in the luteal phase and is a neuroactive steroid
- Animal studies exposing them to ALLO followed by a rapid withdrawal replicated symptoms of social withdrawal and anhedonia similar to PMDD ☹
- In human studies, women whose progesterone levels were steady then dropped *sharply* over the final 3 days into menses experienced premenstrual mood changes as opposed to asymptomatic controls whose progesterone gradually waned over several days into menses
- A 2016 RCT saw that blocking 5aR with Dutasteride to prevent ALLO production without impacting progesterone production reduced symptoms of PMDD
  - Complete inhibition of ALLO production, therefore, was the key to PMDD reduction

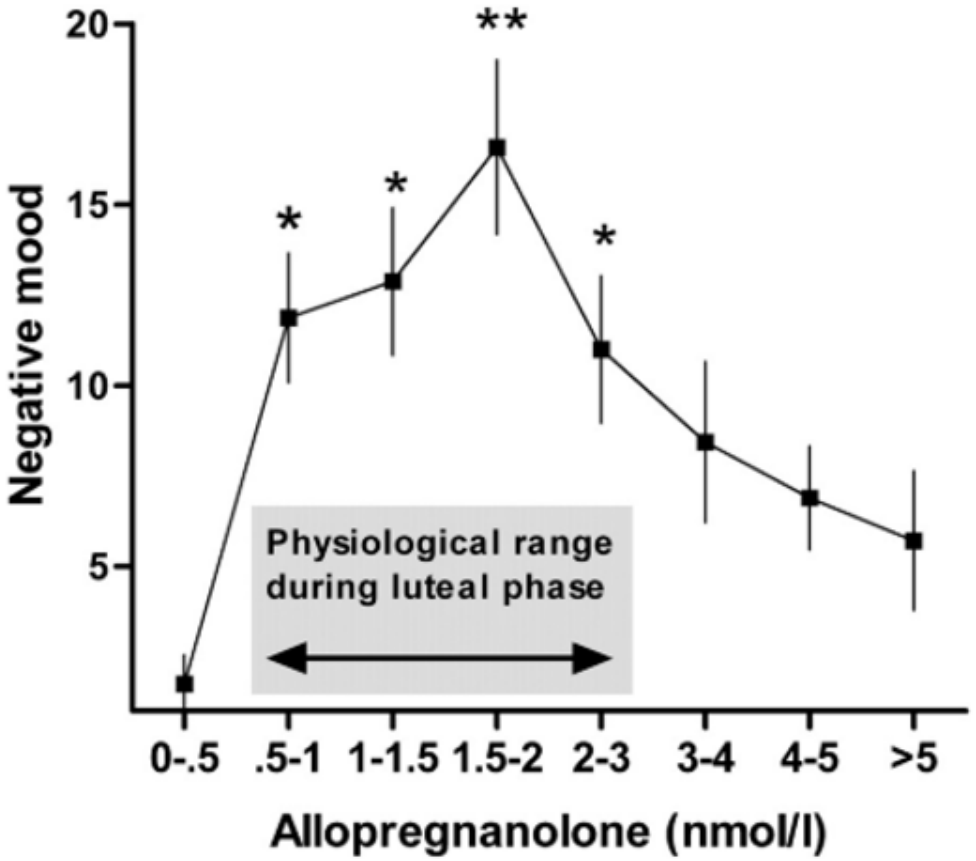


CM of patient with known diagnosis of PMDD. We see here a rapid fall of a-preg over 4 days prior to menses that may explain late luteal symptoms.

But what about patients whose symptoms are worse at the beginning or in the middle of their luteal phase?

ALLO's Bimodal Response

- ALLO concentration shows a bimodal response in PMDD
  - Low levels (follicular phase, suppression by OCP/ GnRH agonist/dutasteride) → minimal negative mood
  - **Mid-range levels (endogenous luteal range level) → maximal negative mood**
  - High levels (supraphysiological range, bioidentical progesterone supplementation) → sedative, anxiolytic, calming



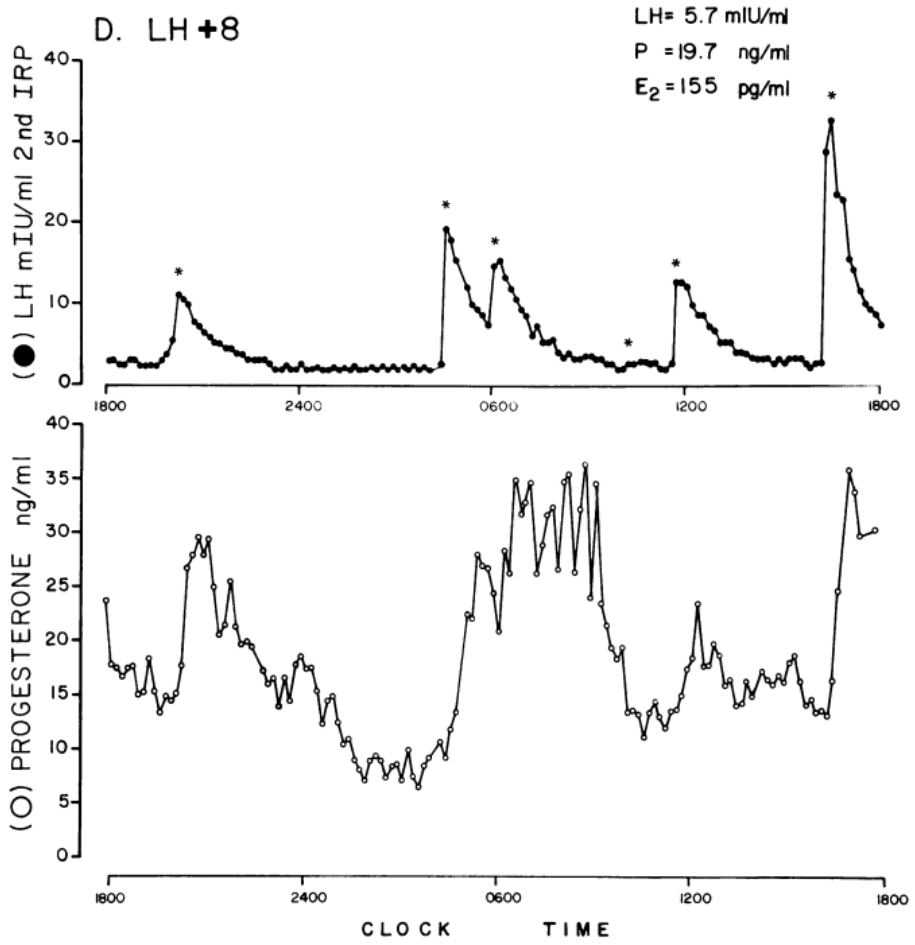
Andreen L, et al. Psychopharmacology (Berl). 2006; 187(2): 209-221

A Paradoxical Response: Maladaptive GABA-A Receptor

- So why are normal fluctuating levels of allopregnanolone during the luteal phase so aggravating for women with PMDD?
  - **It may be more of a GABA-A receptor plasticity issue**
- GABA-A receptors are comprised of 5 different subunits that are remodeled or shuffled as a result of neurosteroid fluctuations during the menstrual cycle
  - Allopregnanolone has highest affinity for δ-containing extra-synaptic GABA-A receptors, which have a role in tonic inhibition
  - The delta subunits are regulated by ALLO: upregulating with higher levels, downregulation at chronically high levels of ALLO and upregulation when ALLO declines to compensate and maintain tonic inhibitory state
- Animal PMDD models have shown increases in non-inhibitory a4 subunits after ALLO withdrawal leading to more agitation
- **A recent 2025 study by Stiernman et al**. examined the mRNA expression of these subunits in 29 women with PMDD and 27 asymptomatic controls in the mid follicular (+5-+11) and late luteal phase (-8 to -1 days prior to menses)
  - Through RT-qPCR of human PBMCs they saw a decrease in inhibitory δ subunits in women with PMDD in the luteal phase compared to asymptomatic follicular phase while the controls showed no decrease in these subunits
  - Additionally, the decreased δ subunit mRNA expression correlated with higher amygdala activation on fMRI in women with PMDD as well
    - Increased amygdala activity during the luteal phase is consistent among PMDD neuroimaging studies
- *Without adequate δ-mediated tonic inhibition, there is limited buffer against the fluctuation of ALLO during the luteal phase*
- *The loss of plasticity of the GABA-A receptor may be what contributes to the paradoxical ALLO response*

THEREFORE, promoting a steady state of GABA
to buffer against fluctuations in ALLO may provide relief

Progesterone's Pulsatile Release



- It's important to remember that progesterone is secreted in pulses under the control of luteinizing hormone (LH). **Progesterone levels may fluctuate up to eightfold within 90 minutes.**
- Allopregnanolone is therefore also behaving in this pulsatile nature
- This may be helpful to visualize in the context of fluctuation sensitivity in PMDD
- DUTCH Testing shows average hormone levels over hours of time in a pooled hormone perspective which smooths out these pulses
- Serum shows hormone levels at one point in time.

Filicori M, et al. J Clin Invest. 1984;73(6):1638-1647.

Summary of ALLO's and GABA- A Receptor's role

To summarize, women with PMDD:

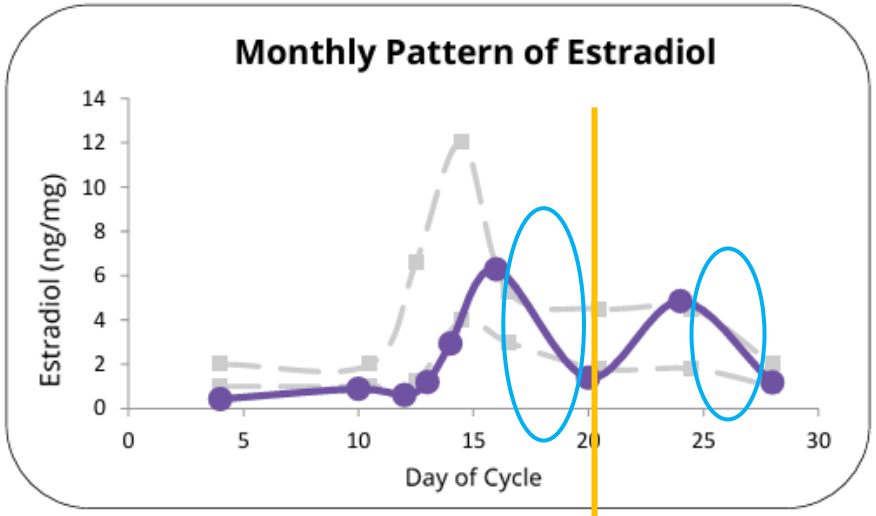
- May be sensitive to normal levels of fluctuating neuroactive steroid during the menstrual cycle
- May be sensitive to the drop in ALLO in the late luteal phase
- May have a loss of plasticity of the GABA-A receptor subunits to normally fluctuating neuroactive steroid leading to overall excitability, not inhibition
- Genetics, epi-genetics, early life stress/trauma, inflammation/neuroinflammation may all play a role in this loss of adaptation during neurosteroid changes during the luteal phase
    - We will review the role of stress and inflammation in PMDD in later slides
- Treatment approaches include:
    - Suppressing ALLO
    - Increasing ALLO to levels that relieve symptoms during the luteal phase
    - Stabilize GABA through consistent GABA supports

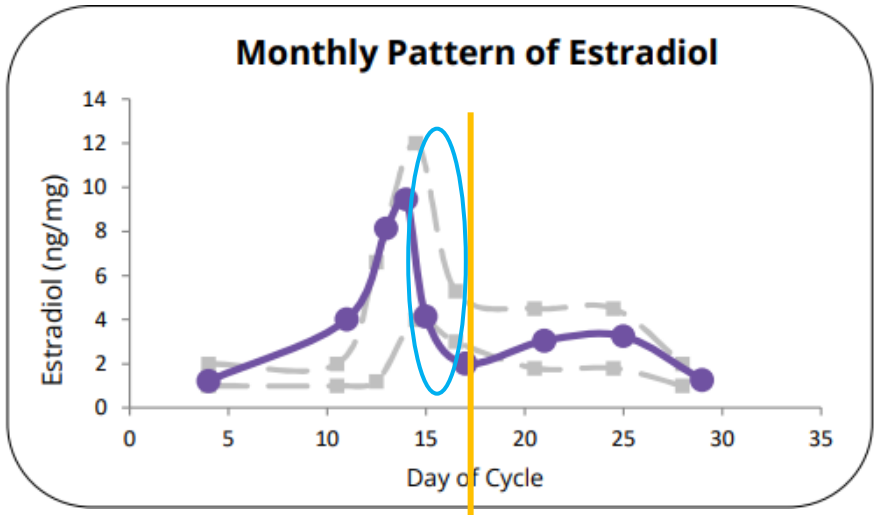
Estradiol's Role in PMDD

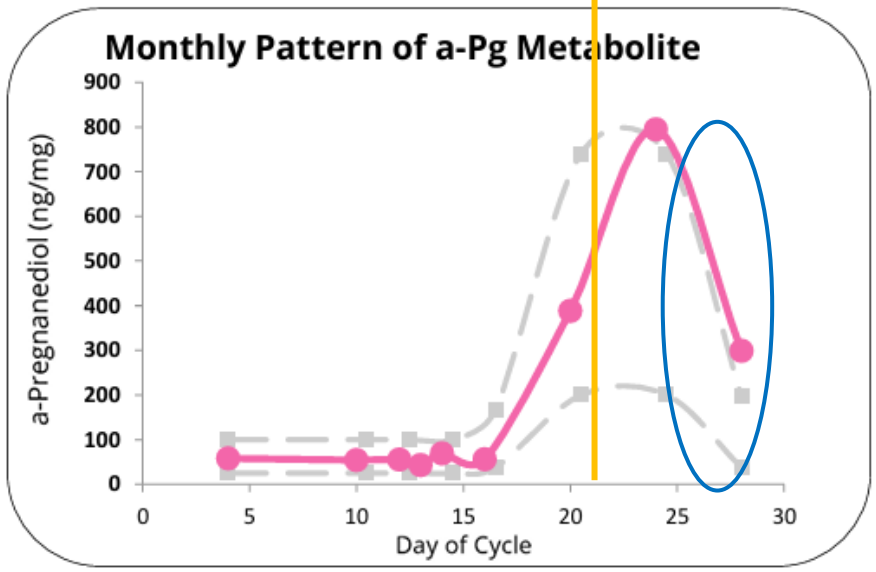
The Role of Estradiol in PMDD

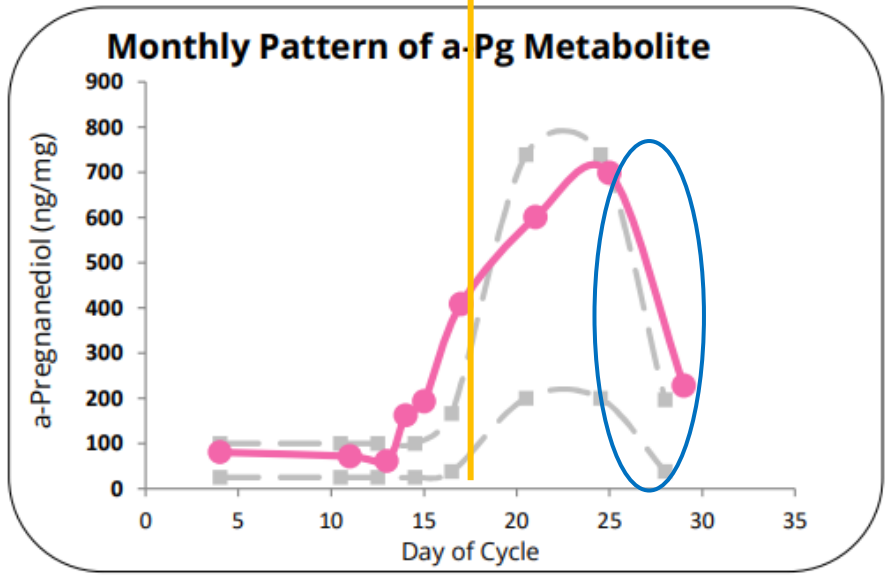
- Estrogen is strongly tied to our serotonin system (as well as dopamine, oxytocin, BDNF)
  - The net effect of estrogen is to increase serotonin availability and decrease serotonin breakdown via MAO-A
- Late luteal estrogen decline and subsequent decline in serotonin, is implicated in PMDD mood changes prior to menses
  - This drop in addition to ALLO/GABA withdrawal may contribute to PMDD symptoms
- Post-ovulatory estrogen decline into the luteal phase should be a consideration for early luteal phase PMDD symptoms as well
  - This drop in addition to the rise of ALLO may be a feature in PMDD
    - Yen et al. showed that women with PMDD have significantly lower early luteal phase (EL) estrogen levels than controls; additionally, women with PMDD with lower EL estrogen levels had higher EL progesterone levels than controls (the ratio of EL P to EL E is key here, not levels)
- A study by Huo et al. showed a significant association between genetic SNPs in the ESR1 gene and PMDD compared to those without PMDD
  - This gene encodes ER alpha and SNPs impact estrogen function and potentially downstream serotonin transport activity and dopamine pathways depending on the polymorphism
  - These SNPs make the receptor more sensitive to normal levels of estrogen leading to physical and psychiatric symptoms of PMDD
  - Again, these polymorphisms may increase risk but are not a single cause

Examples of Estradiol and Progesterone Behavior in PMDD









What's the Deal with Histamine and PMDD?

- A social media movement (driven by women for women) has popularized the use of antihistamines during the luteal phase to help with severe PMDD symptoms
- Although the research has not caught up to the movement, the proposed theory behind the reduction of symptoms in some individuals may be as follows:
- Histamine is not just an immune mediator but functions as a major neurotransmitter
  - For example, histamine acts as a wake promoting NT, which can drive hyperarousal and insomnia
- Estradiol drives up histamine through mast cell degranulation and downregulates DAO
- Progesterone stabilizes mast cells and upregulates DAO production
- In cases where histamine is elevated relative to DAO availability (like MCAS or in functional or overt DAO deficiency) cognitive/psychiatric symptoms like anxiety, panic attacks, brain fog, insomnia, restlessness, sensory sensitivities, mood swings may arise
  - Physical symptoms of flushing, sneezing, nasal congestion, headaches/migraines, digestive issues may also arise
- A popular combination in the PMDD community is to use an H1 (allergy) Blocker such as cetirizine or loratadine in combination with an H2 (stomach acid) Blocker like famotidine to manage luteal phase symptoms
- *More research is needed in this department!*

Addressing Estradiol's Role in PMDD

To summarize Estrogen's role:

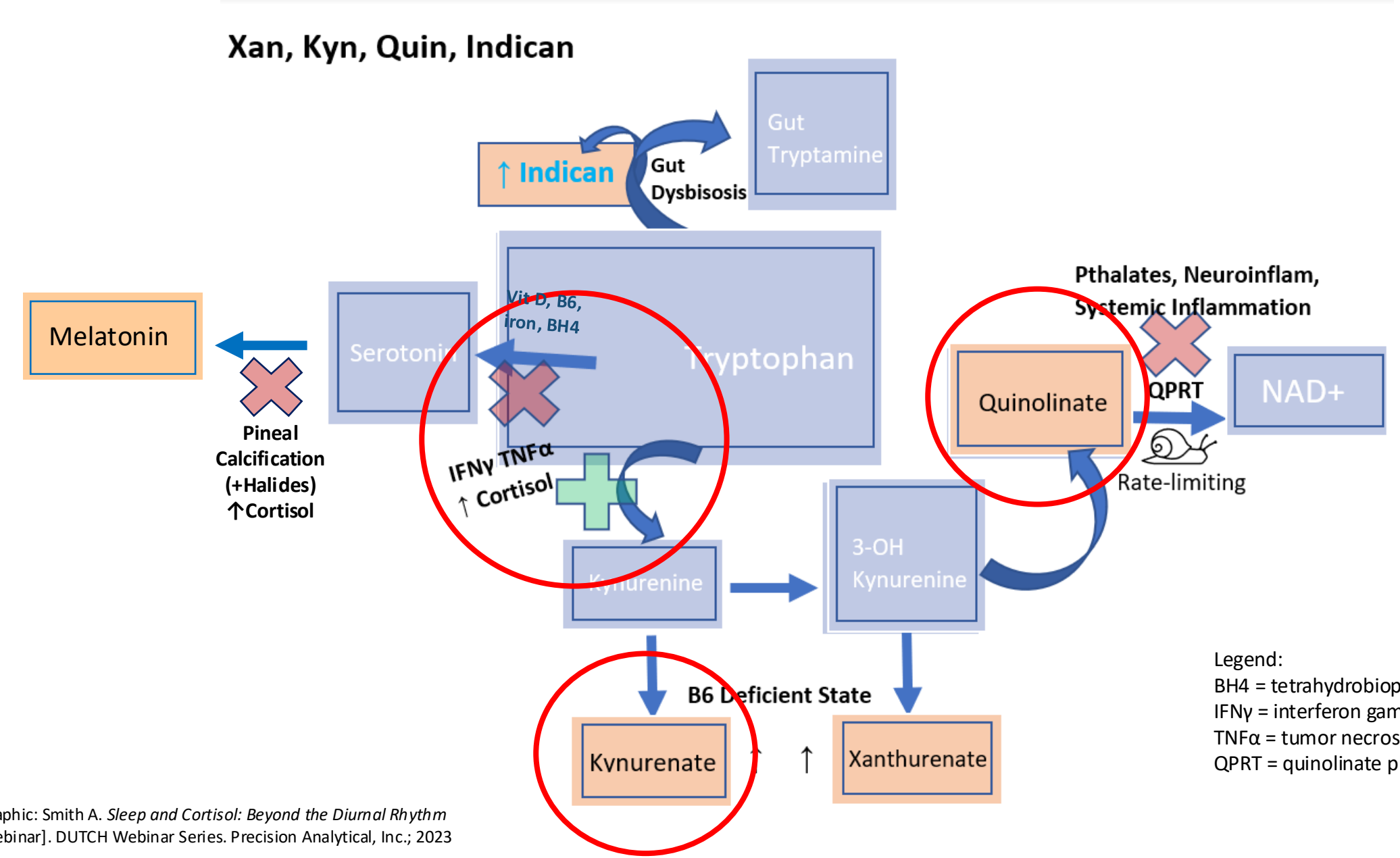
- Estradiol's post-ovulatory and late luteal decline may contribute to PMDD through the drop in serotonin support
  - Stabilizing serotonin may be a helpful strategy via serotonergic and BDNF supports
  - Modulating estrogen levels with phytoestrogen support or DIM to modulate peaks may be helpful
- ESR1 polymorphisms are more common in women with PMDD than those without and may increase risk of developing the condition
- Estradiol may exacerbate histamine related issues that may contribute to PMDD symptoms (research still catching up)
  - Consider antihistamine support for histamine relief
  - Support progesterone if low to support DAO production or support DAO directly

How Stress and Inflammation Impact PMDD

The Role of Stress and Inflammation in PMDD

- It has been shown that those with PMDD are about twice as likely as their control counterparts to have a history of trauma
- Early life trauma especially involving emotional abuse and Adverse Childhood Events (ACEs) are directly associated with PMDD development
  - Trauma can impact brain structures, central nervous system, neurotransmitters, and HPA axis response
- Elevated serum hs-CRP has been found to be positively correlated with increased severity of premenstrual symptoms, including mood sxs
- Inflammation may directly alter GABA-A receptor function
- Inflammation and stress can also shift tryptophan metabolism down the kynurenine and quinolinate pathway as opposed to the serotonin pathway- more on next slide

The Kynurenine Pathway: How Serotonin Can Get Hijacked



Legend:
BH4 = tetrahydrobiopterin
IFNγ = interferon gamma
TNFα = tumor necrosis factor alpha
QPRT = quinolinate phosphoribosyltransferase

Graphic: Smith A. *Sleep and Cortisol: Beyond the Diurnal Rhythm* [webinar]. DUTCH Webinar Series. Precision Analytical, Inc.; 2023

Evaluate the DUTCH OATs

Organic Acid Tests (OATs)

TEST		RESULT	UNITS	NORMAL RANGE
Nutritional Organic Acids (Urine)				
Vitamin B12 Marker - May be deficient if high				
Methylmalonate (MMA)	Above range	4.9	ug/mg	0 - 2.5
Vitamin B6 Markers - May be deficient if high				
Xanthurenate	Above range	1.23	ug/mg	0.12 - 1.2
Kynurenate	Above range	5.4	ug/mg	0.8 - 4.5
Biotin Marker - May be deficient if high				
b-Hydroxyisovalerate	Within range	7.9	ug/mg	0 - 12.5
Glutathione Marker - May be deficient if high				
Pyroglutamate	Within range	42.0	ug/mg	28 - 58
Gut Marker - Potential gut putrefaction or dysbiosis if high				
Indican	Above range	114.0	ug/mg	0 - 100
Neuro-Related Markers (Urine)				
Dopamine Metabolite				
Homovanillate (HVA)	Within range	4.4	ug/mg	3 - 11
Norepinephrine/Epinephrine Metabolite				
Vanilmandelate (VMA)	Within range	4.3	ug/mg	2.2 - 5.5
Neuroinflammation Marker				
Quinolinate	Above range	13.2	ug/mg	0 - 9.6
Additional Markers (Urine)				
Melatonin - Waking				
6-OH-Melatonin-Sulfate	Below range	5.3	ng/mg	10 - 85
Oxidative Stress / DNA Damage				
8-Hydroxy-2-deoxyguanosine (8-OHdG)	Within range	2.6	ng/mg	0 - 5.2

Blunted Cortisol Response

Blunted Cortisol Response to Acute Psychosocial Stress in Women With Premenstrual Dysphoric Disorder

Ajna Hamidovic, John Davis, Fatimata Soumare

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Correspondence: Ajna Hamidovic, 833 South Wood Street 117A PHARM, MC 886 Chicago, IL, USA 60612 (ahamidov@uic.edu).

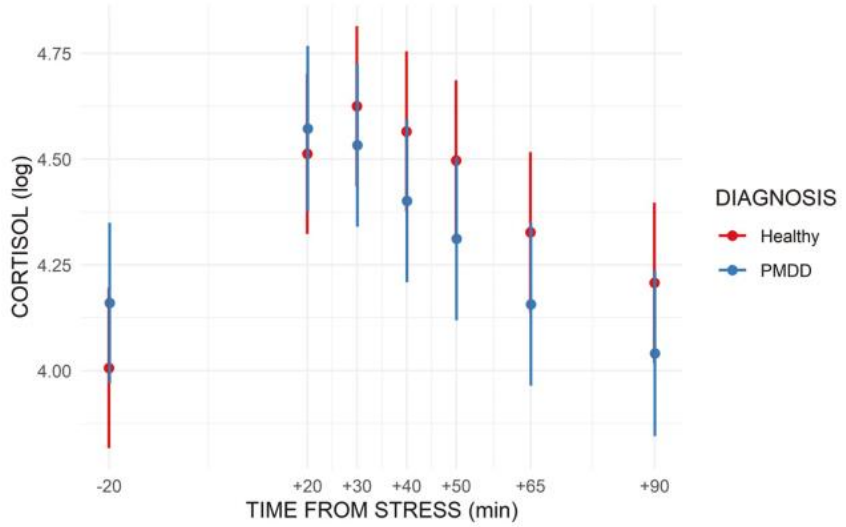
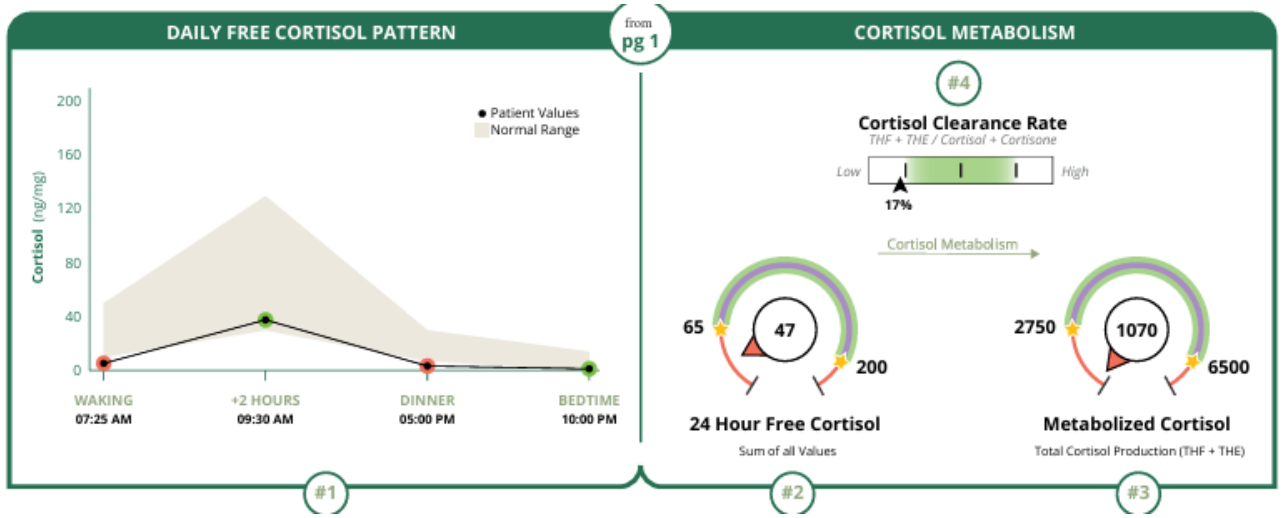
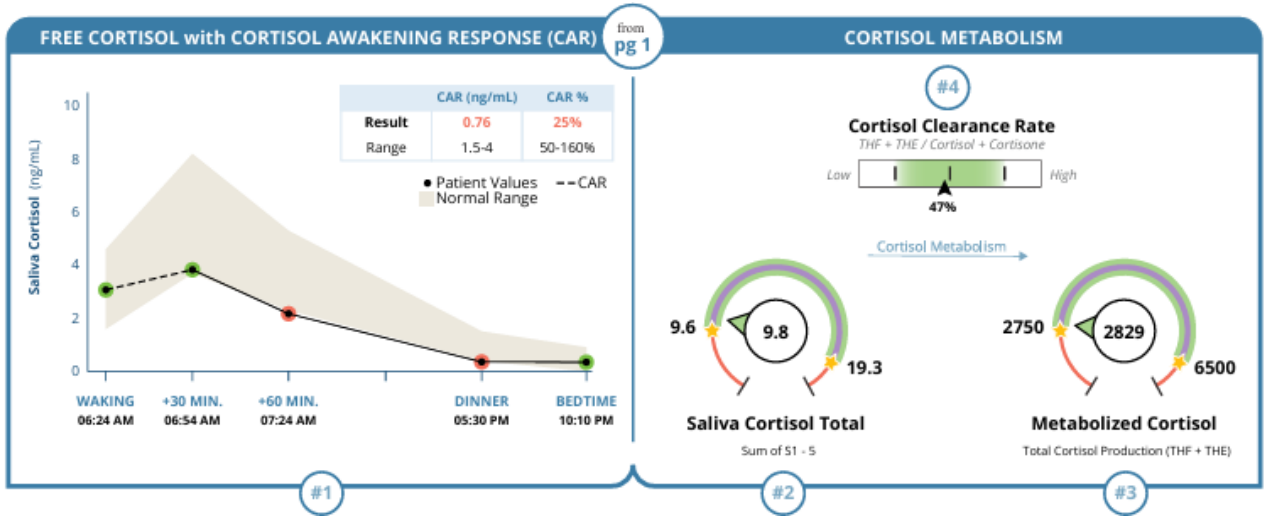


Figure 1. The effect of time and diagnosis on serum cortisol. Considering the baseline, PMDD participants had lower cortisol levels at +40 ($P \leq .01$), +50 ($P \leq .01$), +65 ($P \leq .01$), and +90 ($P \leq .01$) minutes from the start of TSST relative to the healthy controls. The intervals represent confidence intervals for the predicted values. PMMD, premenstrual dysphoric disorder; TSST, Trier Social Stress Test.

Hamidovic A, et al. Int J Neuropsychopharmacol. 2024;27(3):pyae015

Cortisol on the DUTCH Test





Examples of blunted urinary (top) and salivary cortisol graphs on the DUTCH test

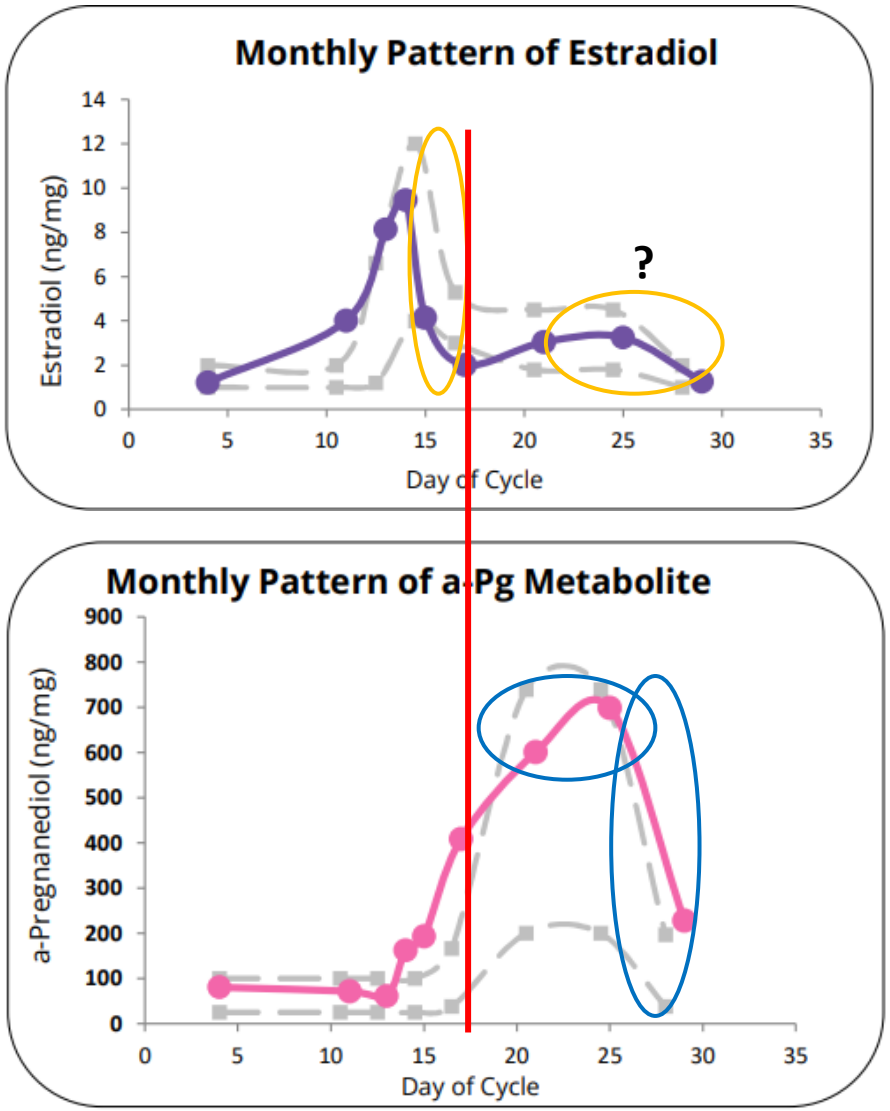
Blunted cortisol responses can indicate HPA axis dysregulation and poor adaptability. We need a proper cortisol response to manage stress and inflammation.

How Can DUTCH Support Your Patient with PMDD?

How DUTCH Helps

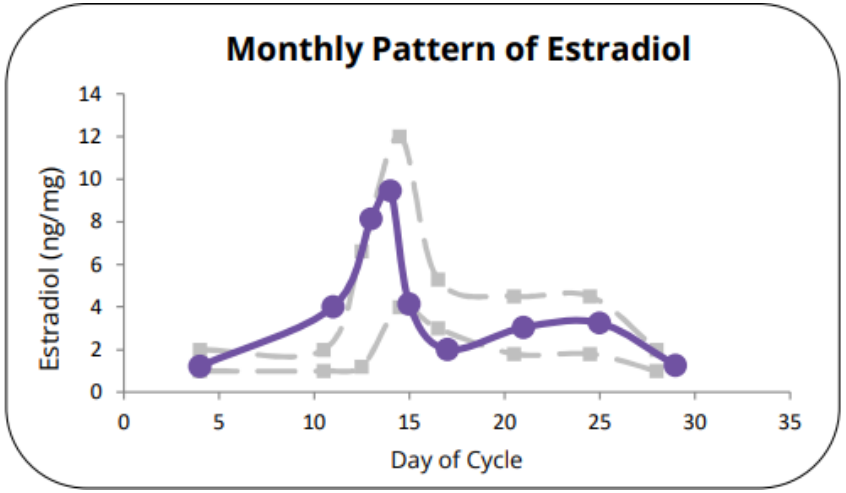
- Cycle Map
  - Track symptoms during entire collection to find patterns
    - Are symptoms worst post-ovulation, mid luteal, late luteal or throughout the entire phase
    - Is there *enough* progesterone to balance estrogen in the luteal phase
      - Need to rule out an actual hormonal imbalance- if progesterone is low, the patient may not be getting enough calming support from ALLO
- Hormone balance
  - Check estrogen dial compared to progesterone dial (progesterone should be leading the way)
- Enzyme patterns
  - Evaluate 5aR preference:
    - if low, may not get enough ALLO for calming effects
    - If normal or high, may be aggravating at luteal levels due to paradoxical response
- Cortisol assessment
  - High cortisol may indicate high stress or inflammation that can exacerbate symptoms of PMDD as well as impact ovulation and progesterone response
  - Low cortisol may indicate long term stress/ glucocorticoid resistance/ blunting of HPA axis resulting in low overall resilience to stress and dysregulation
  - Assess for optimal diurnal pattern to track any sleep disturbances
- Inflammation
  - Can show up in metabolism patterns such as high 5aR, high 4OHE1, high cortisol, and high quinolinate and kynurenate in OATs

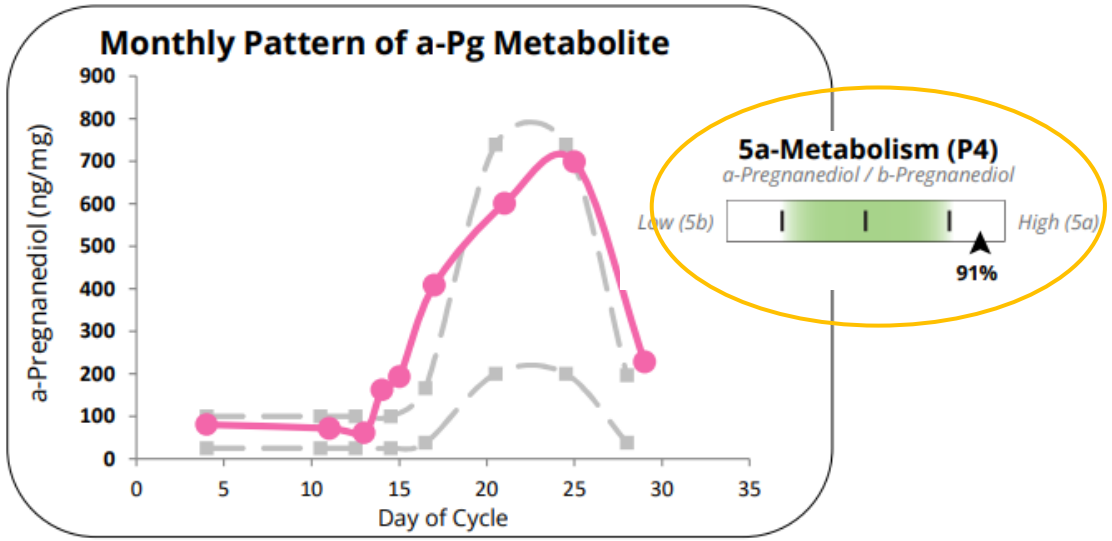
PMDD Case



- This 31 yo F patient diagnosed with PMDD presents with severe symptoms post-ovulation and throughout her entire luteal phase with anxiety and depression marked as severe (3) on her requisition
- She also marks frequent migraines (unsure if cyclical) and a tentative diagnosis of endometriosis from her ob-gyn based on her history
- She has heavy, prolonged menstrual bleeding every menses with severe dysmenorrhea
- This patient also complains of mild acne, hair loss, hirsutism
- She takes a multivitamin, omega 3 FA, and magnesium citrate

PMDD Case: DUTCH Results





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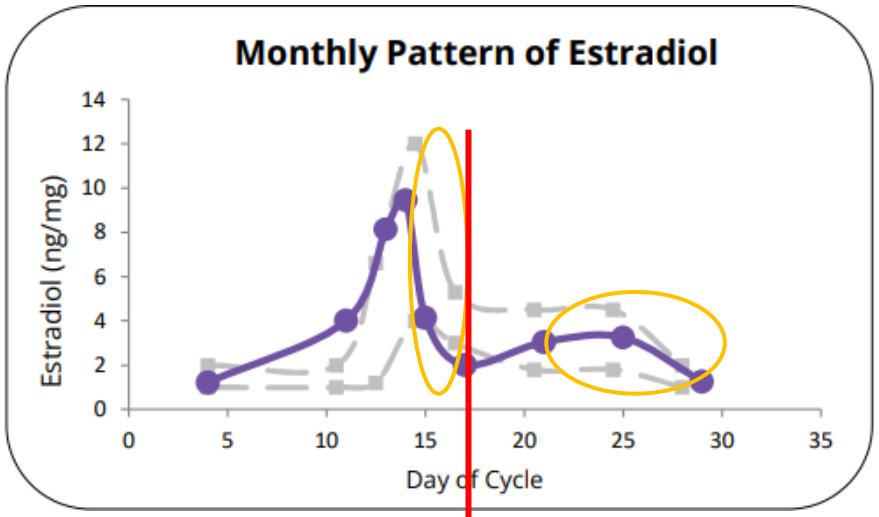
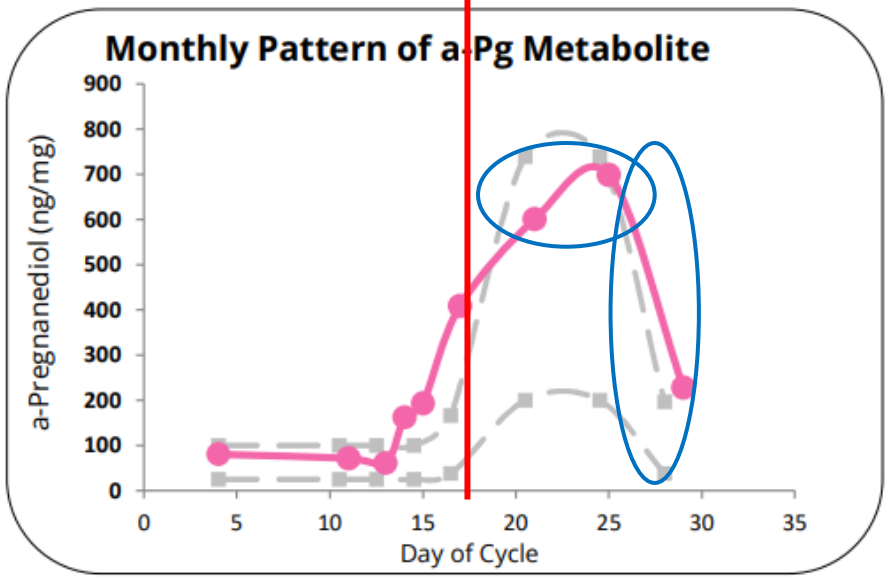
PMDD Case: Treatment Considerations





- Check iron, ferritin, thyroid due to heavy bleeding
  - Deficiencies/imbalances here can exacerbate mood issues
- Post-ovulatory estrogen drop:
  - Boost serotonin supports: black cohosh, St. John's Wort, or saffron (can inhibit serotonin reuptake)
  - Provide estrogen modulation during peri-ovulatory phase with DIM to mitigate drop off
    - Support methylation further since COMT at 31% and DIM will increase estrogen load (B vitamins, magnesium, choline, TMG…)
- Paradoxical GABA response?
  - Consider GABA support like l-theanine or honokiol/magnolol throughout luteal phase or cycle to buffer against ALLO fluctuations
  - 5aR is increased by insulin and inflammation so consider looking into those issues and treating if present
  - Natural 5aR inhibitors like reishi, a grounding adaptogen, may reduce ALLO production and help with androgen symptoms.
- Consider Histamine as a player here due to migraine and endometriosis picture
  - Get more information around migraines timing- are they at random times or do they follow the cyclical estrogen drops? If more cyclical, could be serotonin related.
  - Check for any other histamine symptoms: allergies, flushing, runny nose, etc.
  - Trial antihistamines like Loratidine and Pepcid during the luteal phase if strong suspicion of histamine role

Treatments

Conventional Treatment Options

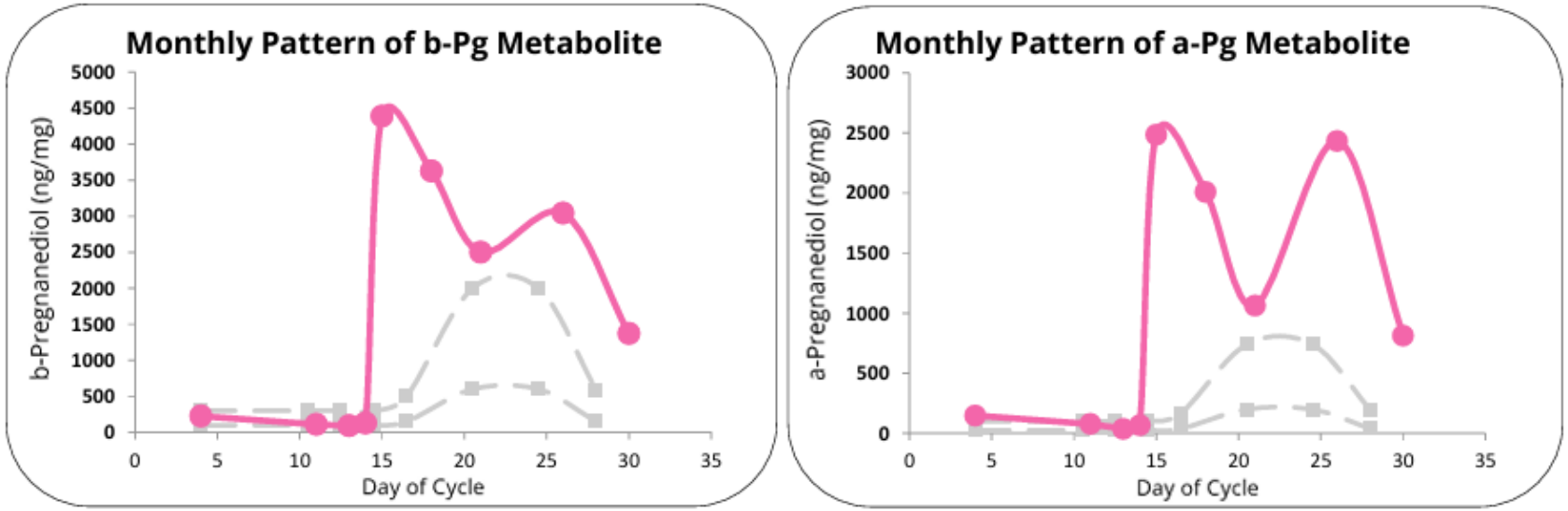
- SSRIs (1st line treatment)
  - FDA Approved for PMDD: Fluoxetine, Sertraline, Paroxetine CR
  - Effects for PMDD start much more quickly- within hours or days as opposed to weeks for MDD
  - Given at low doses for PMDD and can be prescribed intermittently from day 14 or day of ovulation to start of next menses to manage PMDD. Continuous use recommended as next step if intermittent dosing is not adequate.
  - SSRIs not only increase serotonin levels/activity in the brain through selective reuptake inhibition, they act as Brain Steroidogenic Stimulants (SBSS) and can normalize ALLO levels and GABA-A receptor activity (remember it is the rapid *fluctuations* in ALLO that negatively impact GABA-A receptor switching to a more excitable form)
  - SSRIs can also increase BDNF in the brain
  - Response rate in PMDD is 60-70%
- Combination OCP (2nd line treatment unless actively seeking contraception, then 1st line)
  - FDA approved: Drospirenone/Ethinyl Estradiol 20 µg (24/4 Regimen)- ie. Yaz
    - The anti-mineralocorticoid/anti-androgenic activity of drospirenone help reduce physical and emotional symptoms of PMDD.
    - Number needed to treat: 8
  - Other progestins combined with ethinyl estradiol may still be beneficial as ovulation suppression is key
  - Progestin only contraceptives (POPs, Mirena IUD) may not suppress cycling estrogen or ovulation, so these types of contraception are not currently recommended for management of PMDD

Conventional Treatments

- GnRH Agonists with combined hormonal add-back therapy (3rd line treatment for severe, refractory cases)
  - GnRH agonists like leuprolide induce a chemical menopause to suppress ovarian function and cycling hormones
  - Add back therapy is necessary to protect bone and cardiovascular health and prevent symptoms of menopause
  - Please refer to ACOG's 2023 Clinical Practice Guideline regarding Management of Premenstrual Disorders for more information on the approach here
    - They specifically reference a 2009 paper by Segebladh et. al. looking at daily transdermal estradiol with cyclical 14-day vaginal progesterone
- Bilateral Oophorectomy with or without hysterectomy (last resort)
  - A trial of chemically induced menopause with a GnRH agonist prior to surgically induced menopause to ensure that ovarian suppression truly stops PMDD symptoms is advised prior to surgery
  - Hormone therapy should be a consideration after
- Cognitive Behavioral Therapy (CBT) – great adjunctive support
  - Has been well studied in PMDD and is helpful in identifying and reframing negative or irrational thoughts
  - Dialectical Behavioral Therapy (DBT) and Mindfulness Based Cognitive Therapy (MBCT) may be helpful as well
    - DBT may be specifically more helpful for extreme emotional dysregulation
  - EMDR (with EMDR trained practitioners) is helpful to process trauma and reduce its effects on the nervous system

Hormone Therapy

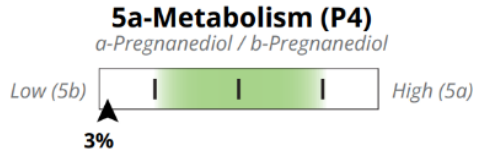
- Bioidentical progesterone
  - OMP: 50-400mg taken at bedtime in the luteal phase, days 16-26 in a 28-day cycle to stabilize GABA
  - When it comes to MHT, continuous dosing is typically best to avoid fluctuations
  - **Clinical data comparing oral and vaginal progesterone in PMDD is limited



CM of cycling patient with PMDD taking 100 mg OMP days 15-25 of her cycle.

Emerging and Experimental Treatments

- Sepranolone
  - First-in-class neurosteroid and GABA-A modulating steroid antagonist (GAMSA)
  - Works to block the effects of Allopregnanolone via subcutaneous injection during the luteal phase
  - Despite showing promising Phase 2a results, the Phase 2b clinical trial showed higher placebo effect
  - Further research regarding this medication for PMDD has essentially stalled
- Dutasteride
  - Dual 5aR Inhibitor (blocks type 1 and 2) so blocks ALLO production
  - Experimental treatment for PMDD based on 2015 study by Martinez et. al.
    - 2.5 mg daily shown to significantly decrease irritability, anxiety, and sadness and some physical symptoms like bloating and food cravings with few side effects over short term (2 menstrual cycles)
    - Long term use of Dutasteride, however, impairs cortisol metabolism and can contribute to fatty liver and metabolic syndrome
    - May be a temporary tool if weighing risks and benefits in cases of suicidality
  - This paper was really designed to test a hypothesis about neurosteroids in PMDD, so again, this is experimental and requires further research at this time
- Antihistamines (?)
  - As discussed on a previous slide, OTC H1 and/or H2 blockers may be helpful for targeting histamine related mood issues



The Potential of Oxaloacetate

Oxaloacetate reduces emotional symptoms in premenstrual syndrome (PMS): results of a placebo-controlled, cross-over clinical trial

Lisa Tully, PhD[1], John Humiston, MD[2], Alan Cash, MS[3]

[1]Nutritional Supplements Division, Energy Medicine Research Institute, Boulder, CO; [2]The Center for Health and Wellbeing; [3]Terra Biological LLC, San Diego, CA, USA

- A very compelling study looking at oxaloacetate stabilized with ascorbic acid and its effect on depression, anxiety, perceived stress, and aggression in PMS (official PMDD diagnoses were excluded due to FDA reasons)
- Oxaloacetate is a metabolite in the Kreb's Cycle and is crucial for gluconeogenesis. Not only can oxaloacetate make glucose more available, but it may help drive glucose directly into the cell as found in a previous study of patients with diabetes mellitus
- The cerebellum is the part of the brain that is important for motor coordination but also emotional regulation and response
  - It has been shown to require more glucose in conditions like bipolar disorder and in individuals with severe premenstrual mood swings
- The hypothesis was that by making glucose more available to the brain, these patients may experience fewer premenstrual mood issues
- This cross-over clinical trial showed a statistically significant improvement in the measured outcomes after 2 menstrual cycles
- Name of the product on the market that contains this combination is Jubilance
- *This brings to mind the importance of blood sugar regulation in a condition like PMDD – treat the whole person!*

Natural Therapies: Herbs, Nutraceutical, Lifestyle Supports

- Vitex
  - Shown in systematic reviews to be an efficacious alternative treatment for PMDD in some women
- GABAergic supports
  - Ashwagandha, Lemon balm, Passionflower, Honokiol/Magnolol, L-Theanine, Taurine, Magnesium, B6, GABA, Lactium, Fermented foods
- Serotonergic supports
  - Saffron, St. John's Wort, Black Cohosh, 5-HTP, BDNF supports
- BDNF supports
  - Aerobic exercise (super powerful), Bacopa monnieri, Saffron, Lion's mane mushroom
- Antihistamine supports
  - Stinging nettle (leaf), Butterbur, Quercetin, Vitamin C, Consider limiting high histamine foods
  - Support DAO with appropriate co-factors, adequate progesterone production in the luteal phase
  - Consider environmental factors that may drive histamine
- Estrogen modulating therapies
  - DIM around periovulatory surge to modulate slope of postovulatory estrogen drop, can used DIM in luteal phase as well if not too low (check metabolism pathways with DUTCH test)
  - Phytoestrogen modulators around estrogen drops- post ovulation and late luteal- like ground flaxseed, soy, red clover
- Calming adaptogens
  - Ashwagandha, Reishi mushroom, Holy basil
- Natural 5aR inhibitors (?)
  - Stinging nettle (root), Reshi mushroom, Saw palmetto, EGCG
    - These supports will mildly inhibit compared to pharmacological intervention

DUTCH Treatment Guide: Inflammation Support

Inflammation Support

Anti-inflammatories

- Herbal anti-inflammatories:
  - Boswellia
  - Ginger
  - Green tea (EGCG)
  - Maitake
  - Reishi
  - Rosemary (Rosemarinic acid)
  - Shiitake
  - Turmeric
- Fish oil (EPA/DHA)
- Quercetin
- Systemic enzyme therapies (bromelain, etc. on an empty stomach)
- Rx: Low-dose naltrexone (LDN), if appropriate

Antioxidants

(If oxidative damage is contributing)

- Alpha lipoic acid (ALA)
- Flavonoids
- Lycopene
- Melatonin
- NAC
- Resveratrol
- SOD, catalase
- Sulforaphane
- Support glutathione - see "Pyroglutamate" on **page 45**
- Vitamins A, E, C
- Herbal antioxidants:
  - Astragalus
  - Ginger
  - Ginkgo
  - Green tea
  - Korean ginseng
  - Milk thistle
  - Propolis
  - Rosemary
  - Schisandra
  - Shilajit
  - Siberian ginseng
  - Thyme
  - Turmeric

If Poor Detoxification is Contributing

- Avoid or limit things that impede detox pathways: alcohol, smoking, toxic chemical compounds, sugar, refined carbohydrates, additives, etc. See "EDCs" on **page 51**.
- See Section 2 Estrogen Detoxification.
- See "Liver Support" on **page 55**.

Diet and Exercise

- Aerobic exercise regularly to reduce CRP, TNF-α, and IL-6.
- Choose unprocessed, whole foods.
- Correct insulin resistance. See **page 54**.
- Eat vegetables with every meal.
- Encourage exercise and movement in moderation.
- Encourage weight loss, if appropriate.
  See "Obesity" on **page 58**.
- Improve omega 3: omega 6 ratio with diet choices. Foods rich in omega 3 fatty acids include:
  - Anchovies
  - Chia seeds
  - Cod liver oil
  - Flaxseeds
  - Herring
  - Mackerel
  - Oysters
  - Salmon
  - Sardines
  - Soybeans
  - Walnuts
- Increase fiber intake.
- Increase intake of foods and/or supplements high in polyphenols and bioflavonoids.
- Optimize diet – consider an anti-inflammatory diet, autoimmune protocol (AIP) diet, or Mediterranean diet.

Treat the Whole Person

- Treat nutrient deficiencies: iron, vitamin D, B12
- Treat thyroid dysfunction if present
- Support the gut-brain axis
- Incorporate regular exercise, which increases BDNF and helps regulate mood
- Eat to support stable blood sugar, which is important for mood regulation
  - Focus on healthy fats, fiber, protein, resistant starches, complex over simple carbs
- Meditation and mindfulness practices
  - After consistent practice can reduce amygdala activity
- Prioritize sleep hygiene and healthy circadian rhythm
- Get enough sunlight
- Drink enough water
- Reduce or eliminate alcohol intake
  - Alcohol can exacerbate symptoms of anxiety, depression, and irritability in PMDD
- Spend time in nature
  - Can lower stress, regulate mood, sleep, and decrease negative thought loops and rumination
- Create a supportive community
  - Communicating needs and prepping for the luteal phase, tracking cycles with loved ones, find a PMDD support group

DUTCH Mini Guide: PMDD

Premenstrual Dysphoric Disorder (PMDD)

SIGNS AND SYMPTOMS

PMDD is distinguished by the presence of at least one moderate to severe affective symptom in the luteal phase:

- Mood swings
- Irritability
- Anger
- Depression or feelings of hopelessness
- Anxiety or tension
- Decreased interest in usual activities

In addition to emotional symptoms, PMDD often includes physical symptoms such as breast tenderness or swelling, joint or muscle pain, bloating, and weight gain.

WHAT IS PMDD?

Premenstrual Dysphoric Disorder (PMDD) is a severe and sometimes disabling set of emotional and physical symptoms occurring in the luteal phase of the cycle and resolving with menses. It is distinguished from PMS in its intense psychological symptoms, increased severity, and its impact on a woman's life, including work and social relationships.

PATHOPHYSIOLOGY & DIAGNOSIS

Pathophysiology

The exact pathophysiology of PMDD is not fully understood, but sensitivity to the normal fluctuations of estrogen and progesterone is thought to trigger changes in brain chemicals like serotonin and GABA, which could explain the mood disturbances. This atypical response to these hormonal changes could be influenced by genetic factors, history of other mood disorders, or environmental stressors.

Diagnosis

The diagnosis of PMDD is clinical, typically made by tracking symptoms across at least two menstrual cycles. The presence of five or more symptoms (see list to the left) that interfere with daily functioning, with at least one being an affective symptom, is required for the diagnosis.

Differential Diagnosis

- Premenstrual syndrome (PMS)
- Psychiatric disorders that are worse in the luteal phase

DUTCH CHECKLIST

Test patterns and markers associated with PMDD

- ☐ **DUTCH Cycle mapping findings:**
  - ☐ **Estrogen rapidly increases or decreases**
    - ☐ Estrogen on the DUTCH Cycle Mapping Test may show rapid changes, sharp inclines or declines, which can impact mood
- ☐ **Alpha progesterone metabolites (a-pregnanediol)** within the luteal range: In some women, the alpha progesterone metabolites exert a paradoxical effect on the GABA receptors and instead of promoting a sense of calm, they promote anxiety and irritability. This paradoxical effect has been associated with PMDD. If mood changes coincide with the increase in progesterone during the luteal phase, consider this as a potential cause.
- ☐ **Low progesterone:** Progesterone has a calming effect on the brain, and low levels during the luteal phase may be associated with PMDD symptoms
- ☐ **Estrogen excess or low progesterone/estrogen (P/E) ratio:** can contribute to mood swings and irritability, which are hallmark signs of PMDD
- ☐ **Sluggish phase 2 estrogen methylation:** impaired methylation can lead to an accumulation of estrogen, which might contribute to PMDD symptoms
- ☐ **Elevated androgens:** have not been linked to PMDD but they can contribute to overall hormonal imbalance and have been associated with mood disorders
- ☐ **Any abnormal cortisol findings:** dysregulated cortisol may exacerbate symptoms of anxiety and depression associated with PMDD
- ☐ **High or low HVA (dopamine metabolite) and VMA (norepinephrine and epinephrine metabolite):** imbalances in these neurotransmitters can be associated with mood disorders, although their link to PMDD specifically is not well established
- ☐ **High MMA:** may be seen with vitamin B12 deficiency which could influence serotonin and GABA synthesis, potentially affecting mood and contributing to PMDD symptoms

POTENTIAL SUPPORT CONSIDERATIONS

Review the DUTCH Interpretative Guide for patterns identified on the DUTCH checklist above.

Other support may include, but is not limited to:

- Herbal support: chaste tree, black cohosh
- Nutrient support: magnesium, vitamin B6, vitamin C
- Daily Oxaloacetate
- Exercise
- Medications: selective serotonin reuptake inhibitors (SSRIs), combined oral contraceptives (COCs), GnRH agonists, hormone suppressing treatments
- Bioidentical hormone therapy: Oral progesterone
- Cognitive behavioral therapy (CBT)

Goals of Functional Medicine Treatment

- Improve symptoms
- Refer when appropriate

DUTCH Resources on PMDD

Case Study: "PMDD: Premenstrual Dysphoric Disorder" with Hilary Miller, ND

Find more DUTCH Education at: https://dutchtest.com/education/

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