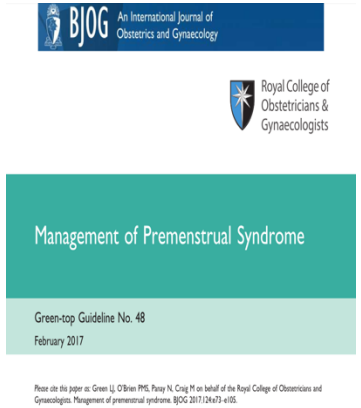
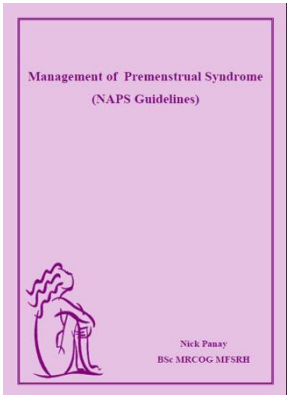


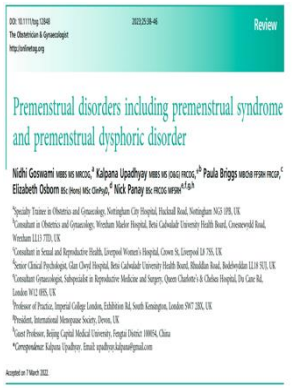
NAPS
National Association for Premenstrual Syndromes



PMS/PMDD : An Update

Nick Panay

Professor of Practice, Imperial College London
President, International Menopause Society



Key Disclosures

Pharma:

- Lecturer/Advisory: Abbott, Astellas, Besins, Gedeon Richter, Mithra, Novo, Se Cur, Theramex, Viatris
- Research Grants: Viatris, Yes company

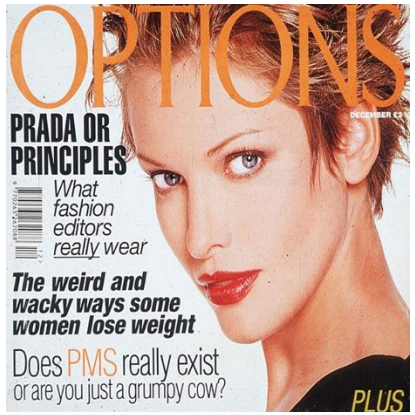
Professional:

- President: International Menopause Society
- Board Member BMS
- Patron Daisy Network
- Chair NAPS (PMS Society UK)
- Clinical Advisory Board Member (IAPMD)

Fashionable 19th.
Century Disorders in Women

- Neurasthenia
- Insanity
- **Menstrual madness**
- Nymphomania
- Masturbation
- Moral insanity
- Hysteria

all often due to
reading serious
books or playing music



Do not underestimate impact of PMS on women's mental health, government told

Ministers urged to take treatment for premenstrual syndrome seriously as report claims women's health concerns are dismissed

By Laura Donnelly, HEALTH EDITOR

15 April 2022 • 6:00pm

Dr Panay, who is also the chairman of the National Association for Premenstrual Syndromes, said that he hoped the strategy would mean more research into menstrual health and better information and education, both for women and healthcare professionals.

The Telegraph, April 2022

Department of Health & Social Care

WOMEN'S HEALTH
Let's take action

Our Vision for the **Women's Health Strategy for England**

Published December 2021

Topics highlighted were:

- menstrual health and gynaecological conditions, including the impact of premenstrual syndrome on someone's quality of life
- fertility, pregnancy, pregnancy loss, and maternal health, including women not feeling listened to during and after pregnancy and the provision of bereavement support services
- menopause, including suggestions for improvements in training and guidelines for healthcare professionals
- gynaecological and other cancers, including barriers to accessing high-quality, up-to-date information on risk factors for female cancers
- mental health, including its interaction with other health conditions across women's lives
- healthy ageing, including the need to increase focus on the health needs of older women and emphasise that women may experience the same conditions as men in different ways
- violence against women and girls, including the complications associated with hymenoplasty and barriers to accessing healthcare support for those who have been subject to years of violence and abuse.

Psychological symptoms

- Irritability
- Nervousness
- Lack of control
- Agitation
- Anger
- Insomnia
- Difficulty in concentrating
- Depression
- Severe fatigue
- Anxiety
- Confusion
- Forgetfulness
- Poor self-image
- Paranoia
- Emotional sensitivity
- Crying spells
- Moodiness
- Trouble sleeping

Fluid retention

- Swelling of the ankles, hands, and feet
- Periodic weight gain
- Diminished urine output
- Breast fullness and pain

Respiratory problems

- Allergies
- Infections

Eye complaints

- Vision changes
- Eye infection

Gastrointestinal symptoms

- Abdominal cramps
- Bloating
- Constipation
- Nausea
- Vomiting
- Pelvic heaviness or pressure
- Backache

Skin problems

- Acne
- Skin inflammation with itching
- Aggravation of other skin disorders, including cold sores

Neurologic and vascular symptoms

- Headache
- Dizziness
- Fainting
- Numbness, prickling, tingling, or heightened sensitivity of arms and/or legs
- Easy bruising
- Heart palpitations
- Muscle spasms

Other

- Decreased coordination
- Painful menstruation
- Diminished sex drive
- Appetite changes
- Food cravings
- Hot flashes

PMDD – A SEVERE FORM OF PREMENSTRUAL SYNDROME

APA definition of a type of severe premenstrual disorder

- Over the course of a year, during most menstrual cycles, 5 or more of the following symptoms must be present:
  - Depressed mood
  - Anger or irritability
  - Trouble concentrating
  - Lack of interest in activities once enjoyed
  - Moodiness
  - Increased appetite
  - Insomnia or the need for more sleep
  - Feeling overwhelmed or out of control
  - Other physical symptoms, the most common being belly bloating, breast tenderness, and headache
- Symptoms that disturb your ability to function in social, work, or other situations
- Symptoms that are not related to, or exaggerated by, another medical condition

Freeman EW. Premenstrual syndrome and premenstrual dysphoric disorder: definitions and diagnosis Psychoneuroendocrinology. 2003 Aug;28 Suppl 3:25-37.

International Society for PreMenstrual Disorders (ISPMD) Consensus on Definitions, Diagnosis and Management

- **Core Premenstrual Disorders (PMDs):**
  - Classic PMS: Ovulatory cycles, functional impairment, post menstrual resolution

- **Variants**
  - **Premenstrual Exacerbation (PME)** e.g. epilepsy, migraine, asthma, psychosis
  - **Non-Ovulatory PMDs:** ovarian activity(perimenopause)
  - **Progestogen Induced:** side effects of OCP / HRT
  - **PMDs without Menstruation:** post TAH / ablation

O'Brien PMS, Backstrom T, Brown C, Dennerstein L, Endicott J, Epperson CN, Eriksson E, Freeman E, Halbreich, Ismail KMK, Panay N, Pearlstein T, Rapkin A, Reid R, Schmidt P, Steiner M, Studd J, Yonkers K. Arch Women's Ment Health 2011; 14: 13-21.
Women's Ment Health 2013; 16 (4) 279 – 291.

- **Premenstrual Exacerbation (PME)**
  - Preliminary evidence suggests ovarian hormones may exert strong effects on Borderline Personality Disorder symptom expression and possibly ADHD
  - Background symptomatology with premenstrual exacerbation due to hormonal fluctuation
  - Further research is warranted examining mechanisms and developing interventions for PME of neurodiversity

Published in final edited form as:
Curr Psychiatry Rep. ; 21(11): 109. doi:10.1007/s11920-019-1096-y.

Ovarian Hormones as a Source of Fluctuating Biological Vulnerability in Borderline Personality Disorder

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Abstract

Purpose of Review: To examine the potential role of ovarian hormones in biological vulnerability to borderline personality disorder (BPD). The review focuses primarily on research examining the menstrual cycle as a source of short-term lability of BPD symptom expression, while discussing the currently understudied possibility of ovarian hormone influence in the developmental course of BPD.

Findings: Several patterns of menstrual cycle effects on BPD symptoms and relevant features in non-clinical samples have been observed in empirical studies. Most symptoms demonstrated patterns consistent with peri-menstrual exacerbation; however, timing varied between high and low arousal symptoms, potentially reflecting differing mechanisms. Symptoms are typically lowest around ovulation, with an exception for proactive aggression and some forms of impulsive behaviors.

Summary: Preliminary evidence suggests ovarian hormones may exert strong effects on BPD symptom expression, and further research is warranted examining mechanisms and developing interventions. Recommendations for researchers and clinicians working with BPD are provided.

Keywords

Menstrual Cycle; Estradiol; Progesterone; Borderline Personality Disorder; Premenstrual Exacerbation; Premenstrual Dysphoric Disorder

Peters JR, Eisenlohr-Moul TA. Ovarian Hormones as a Source of Fluctuating Biological Vulnerability in Borderline Personality Disorder. Curr Psychiatry Rep. 2019 Oct 17;21(11):109.

Lin J, Nunez C, Susser L, Gershengoren L. Understanding premenstrual exacerbation: navigating the intersection of the menstrual cycle and psychiatric illnesses. Front Psychiatry. 2024 Aug 8;15:1410813.

RCOG Guidelines for Premenstrual Syndrome www.rcog.org.uk

- Development of consensus and guidelines on PMS essential to encourage acceptance of condition by patients/health professionals and regulatory authorities

- "Management of Premenstrual Syndrome"
  - 2007 RCOG Green-Top Guideline No 48
    - Panay N et al.
  - 2017 RCOG Green-Top Guideline No 48 (pending further review)
    - Baker L, Panay N, Craig M, O'Brien PMS
- *guidelines systematically developed using standardised evidence-based methodology

BJOG An International Journal of Obstetrics and Gynaecology

Royal College of Obstetricians & Gynaecologists

Management of Premenstrual Syndrome

Green-top Guideline No. 48

February 2017

Please cite this paper as: Green LJ, O'Brien PMS, Panay N, Craig M on behalf of the Royal College of Obstetricians and Gynaecologists. Management of premenstrual syndrome. BJOG 2017;124:e73–e105.

www.rcog.org.uk

Management of Premenstrual Syndrome

(NAPS Guidelines)

Nick Panay

BSc MRCOG MFSRH

www.pms.org.uk

DOI: 10.1111/tog.12848 2023;25:38–46

The Obstetrician & Gynaecologist

http://onlinetog.org

Review

Premenstrual disorders including premenstrual syndrome and premenstrual dysphoric disorder

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*Correspondence: Kalpana Upadhyay. Email: upadhyay.kalpana@gmail.com

Accepted on 7 March 2022.

www.onlinetog.org

PMS/PMDD 2.2a Prevalence

- Prevalence
  - Peak prevalence of severe PMS in 35-45y age group
  - Moderate PMS: 24% in SWS[1]
  - Severe PMS (PMDD) 5-8%[2] general population
    - NB: 23% in one perimenopause study[3]
  - Asian countries slightly lower compared to Europe and the United States.[4]
  - PMS/PMDD higher prevalence if prior emotional and physical abuse.[5-6]

1.Sadler et al JWH 2010; 2.Reid NEJM 1991; 3.Chung at al JMM 2014 4. Cunningham J Harv Rev Psychiatry 2009
5.Bertone-Johnson ER et al J Womens Health 2014; 6. Eisenlohr-Moul et al 2016 Psychoneuroendocrinology

PMS/PMDD 2.2b Etiology

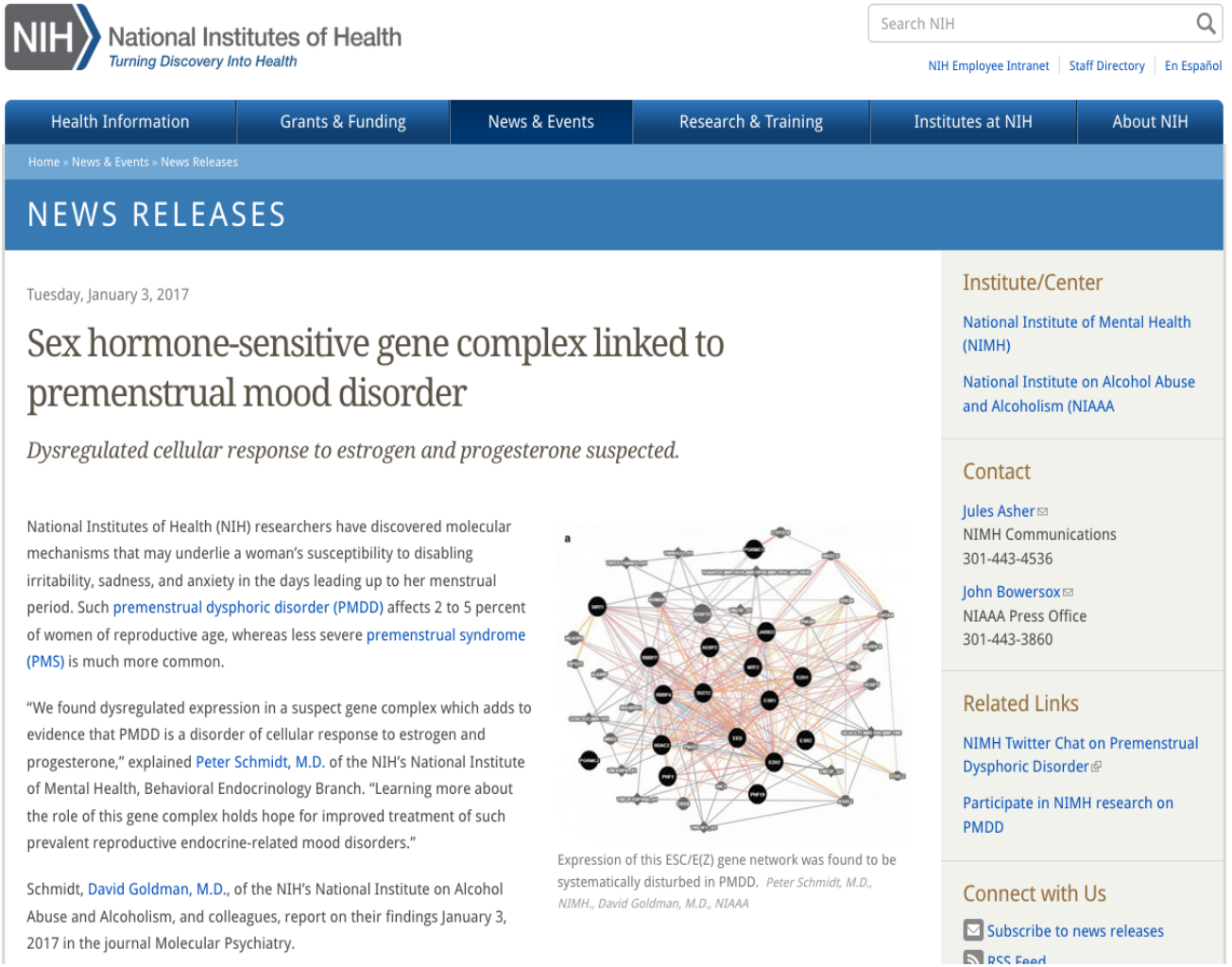
- Etiology
  - Probably multiple etiologies (E2/serotonin, Progesterone/allopregnanolone/GABA)
    - **(Cyclic) ovarian activity / hormonal fluctuations essential in genesis of symptoms**
  - Abnormalities demonstrated by fMRI.[1]
    - **Brain imaging studies of task-related activation during fMRI have identified several regions of abnormal function in women with PMDD especially in amygdala during luteal phase.**
  - Probable genetic predisposition with increased sensitivity to hormonal fluctuations
    - ESR1 gene polymorphisms in PMDD sufferers v controls.[2]

1. Comasco E, Sundström-Poromaa I. Neuroimaging the Menstrual Cycle and Premenstrual Dysphoric Disorder. Curr Psychiatry Rep. 2015 Oct;17(10):77

2. Huo L, Straub RE, Roca C, Schmidt PJ, Shi K, Vakkalanka R, Weinberger DR, Rubinow DR. Risk for premenstrual dysphoric disorder is associated with genetic variation in ESR1, the estrogen receptor alpha gene. Biol Psychiatry. 2007 Oct 15;62(8):925-33.

- Sensitivity is attributed to dysregulation and overexpression of the ESC/E(Z)] gene complex (ER alpha) in PMDD. [1]

- “This is a big moment for women’s health, because it establishes that women with PMDD have an intrinsic difference in their molecular apparatus for response to sex hormones – not just emotional behaviors they should be able to voluntarily control,” said Prof Goldman.



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NEWS RELEASES

Tuesday, January 3, 2017

Sex hormone-sensitive gene complex linked to premenstrual mood disorder

Dysregulated cellular response to estrogen and progesterone suspected.

National Institutes of Health (NIH) researchers have discovered molecular mechanisms that may underlie a woman’s susceptibility to disabling irritability, sadness, and anxiety in the days leading up to her menstrual period. Such premenstrual dysphoric disorder (PMDD) affects 2 to 5 percent of women of reproductive age, whereas less severe premenstrual syndrome (PMS) is much more common.

“We found dysregulated expression in a suspect gene complex which adds to evidence that PMDD is a disorder of cellular response to estrogen and progesterone,” explained Peter Schmidt, M.D. of the NIH’s National Institute of Mental Health, Behavioral Endocrinology Branch. “Learning more about the role of this gene complex holds hope for improved treatment of such prevalent reproductive endocrine-related mood disorders.”

Schmidt, David Goldman, M.D., of the NIH’s National Institute on Alcohol Abuse and Alcoholism, and colleagues, report on their findings January 3, 2017 in the journal Molecular Psychiatry.

Expression of this ESC/E(Z) gene network was found to be systematically disturbed in PMDD. *Peter Schmidt, M.D., NIMH., David Goldman, M.D., NIAAA*

Institute/Center

National Institute of Mental Health (NIMH)

National Institute on Alcohol Abuse and Alcoholism (NIAAA

Contact

Jules Asher
NIMH Communications
301-443-4536

John Bowersox
NIAAA Press Office
301-443-3860

Related Links

NIMH Twitter Chat on Premenstrual Dysphoric Disorder

Participate in NIMH research on PMDD

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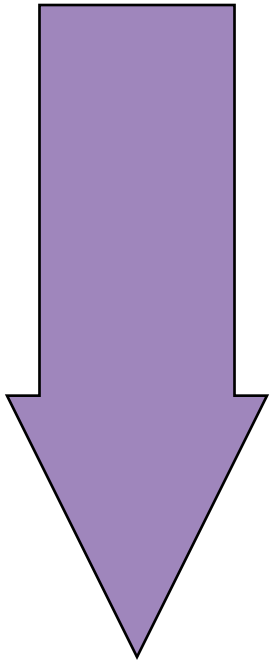
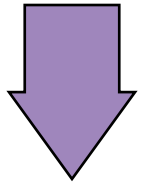
1. Dubey N The ESC/E (Z) complex, an effector of response to ovarian steroids, manifests an intrinsic difference in cells from women with premenstrual dysphoric disorder. *Mol Psychiatry* 2017; **22**: 1172-84.

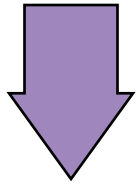
The triad of estrogen responsive depressive disorders



Postnatal depression



Premenstrual depression



Climacteric depression

NB: Worsening PMS could be a sign of imminent POI / menopause due to hormonal fluctuations.
D2/3 HP may be helpful.

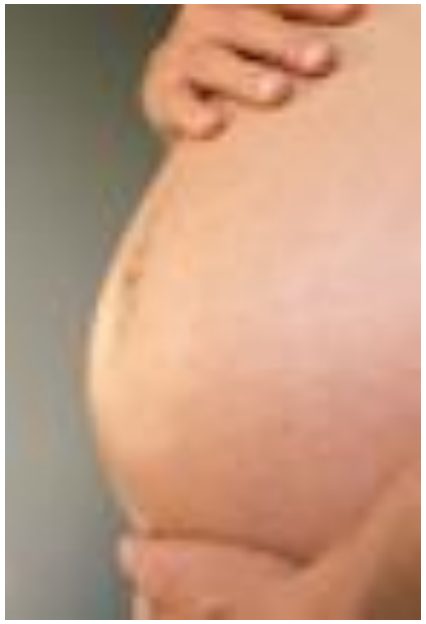
Studd J, Panay N. Hormones and depression in women. Climacteric. 2004 Dec;7(4):338-46.

Proof that ovarian activity integral to PMS Etiology

Stages with no symptoms

Pre-puberty

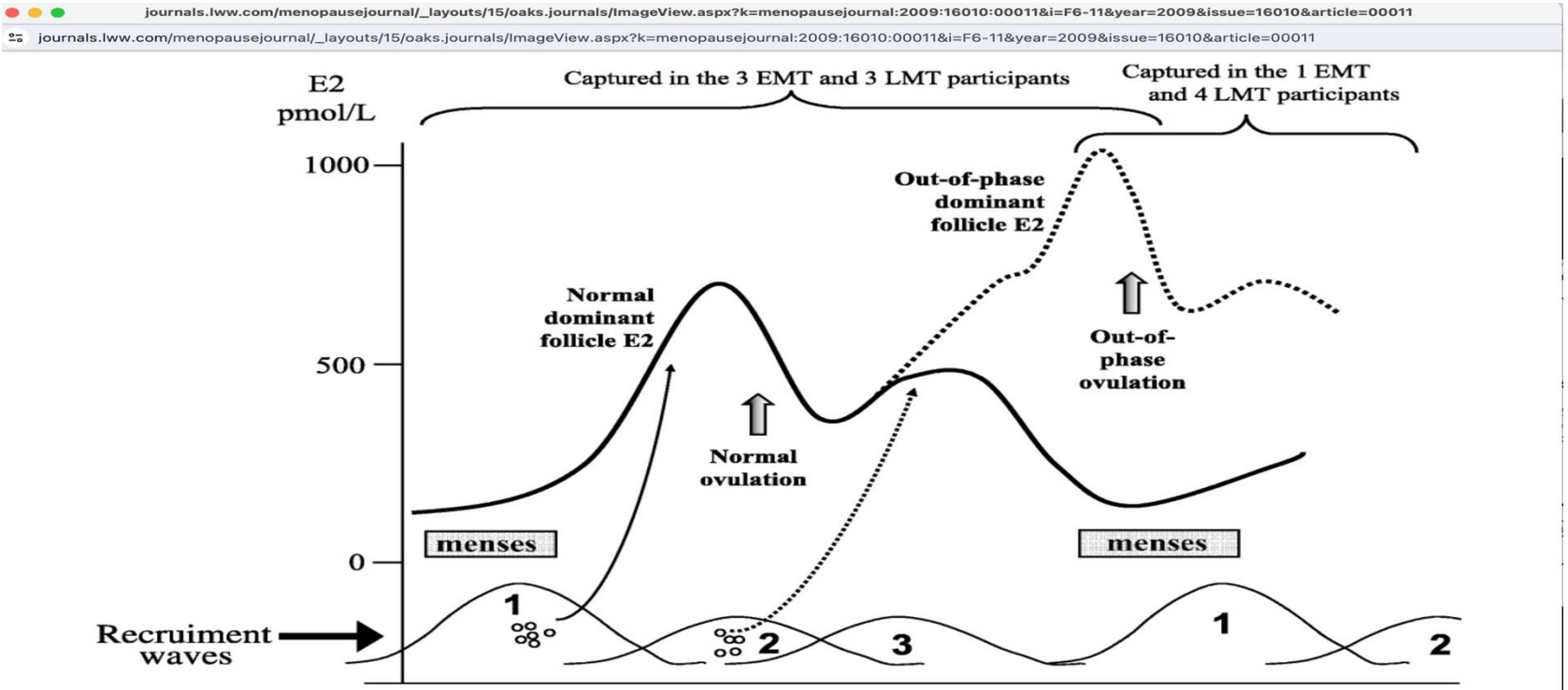
Pregnancy



Post-Menopause

Atypical estradiol secretion and ovulation patterns caused by luteal out-of-phase (LOOP) events underlying irregular ovulatory menstrual cycles in the perimenopause

journals.lww.com/menopausejournal/_layouts/15/oaks.journals/ImageView.aspx?k=menopausejournal:2009:16010:00011&i=F6-11&year=2009&issue=16010&article=00011



Schematic diagram adapted from estradiol (E_2) data in the current study and ultrasonography data from Baerwald et al.[42] In six cycles, a luteal-out-of-phase (LOOP) event was fully captured. In five others, the tail end of a LOOP event was captured. Evidence for these cycle patterns representing the tall-end of a LOOP includes: (1) cycle-1 menstrual phase E_2 secretion pattern very similar to the cycle-2 E_2 secretion pattern in the cycles with a fully captured LOOP, (2) where basal body temperature (BBT) data were available (in three of the five cycles), they indicated that the menstrual cycle before cycle 1 was ovulatory. Ovarian follicle recruitment waves 1, 2, and 3 are illustrated at the bottom of the figure, where wave 1 is normally ovulatory and waves 2 and wave 3 do not normally result in ovulation.[42] Wave 1 occurs during the early follicular phase and normally provides the reservoir of developing antral follicles that result in a dominant follicle, which causes the normal increase in E_2 during the follicular phase (solid line) and a normal mid-cycle ovulatory episode. Wave 2 occurs around mid-cycle and may be the source of a dominant follicle that causes the steep increase in E_2 during the mid-luteal phase (heralding the onset of the LOOP event, represented above by the dotted line) and triggers ovulation early in the subsequent cycle. Wave 3 occurs in some women during the late luteal phase and may be responsible for the advancement of dominant follicle selection and decreased cycle length observed in late reproductive age.[25] EMT, early menopause transition; LMT, late menopause transition.

Conclusion: Many marked increases in ovulatory cycle E2 and cycle irregularities during MT may be due to LOOP events and appear to be triggered by prolonged high follicular phase FSH levels with recruitment of multiple follicles simultaneously.

Hale GE, Hughes CL, Burger HG, Robertson DM, Fraser IS. Menopause. 2009 Jan-Feb;16(1):50-9.

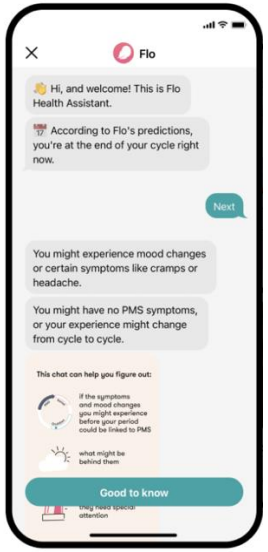
How do I approach a PMS/PMDD patient?

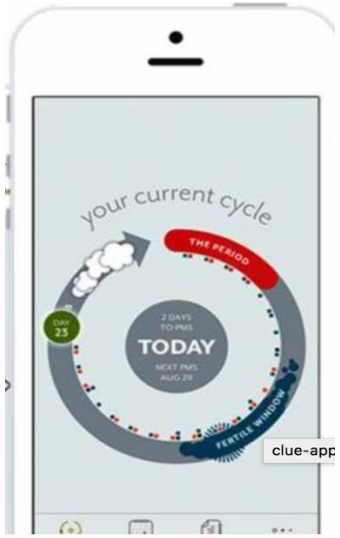
- **Listen Carefully & Confirm the diagnosis** – symptom charts NB: beware misdiagnosis of bipolar disorder due to missed cyclicity!
- **Judge intervention** according to….
  - Patient wishes – consider all interventions
  - Previous treatments – use treatment algorithm
  - Severity of PMS – may need to start with GnRHa if lives are at risk
- **Review at 3 months** but remain available
- **Don't place arbitrary limits** on treatment duration
- **Co-manage patients with background psychopathology with Mental Health Services**

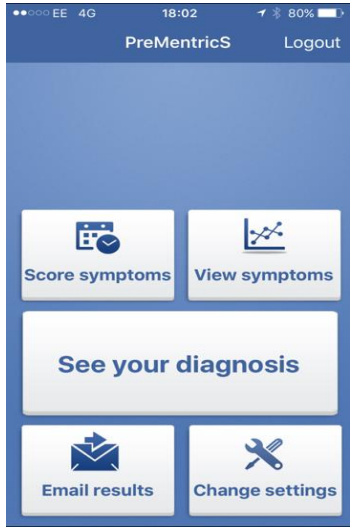
Brown D, Smith DM, Osborn E, Wittkowski A. The experiences and psychological impact of living with premenstrual disorders: a systematic review and thematic synthesis. Front Psychiatry. 2024 Sep 2;15:1440690.

PMS
4. Diagnosis

“There are no diagnostic laboratory tests/investigations to make the diagnosis of PMS/PMDD.”







4. How is PMS diagnosed?

When assessing women with PMS, symptoms should be recorded prospectively, over two cycles using a symptom diary, as retrospective recall of symptoms is unreliable. ✓

There are many symptom diaries available but the Daily Record of Severity of Problems (DRSP) is well-established and simple for patients to use (See Appendix 1).[4]

www.pms.org.uk NAPS symptom diary

PMS/PMDD
5.How should severe PMS be treated? (1)

Good Practice Points

When treating women with PMS:

- ☑ General advice about exercise, diet and stress reduction should be considered before starting treatment

- ☑ The most efficacious treatments for PMS are evidence based but unlicensed for that indication

- Women with underlying psychopathology as well as PMS should be referred to a psychiatrist (ideally in a MDT)….

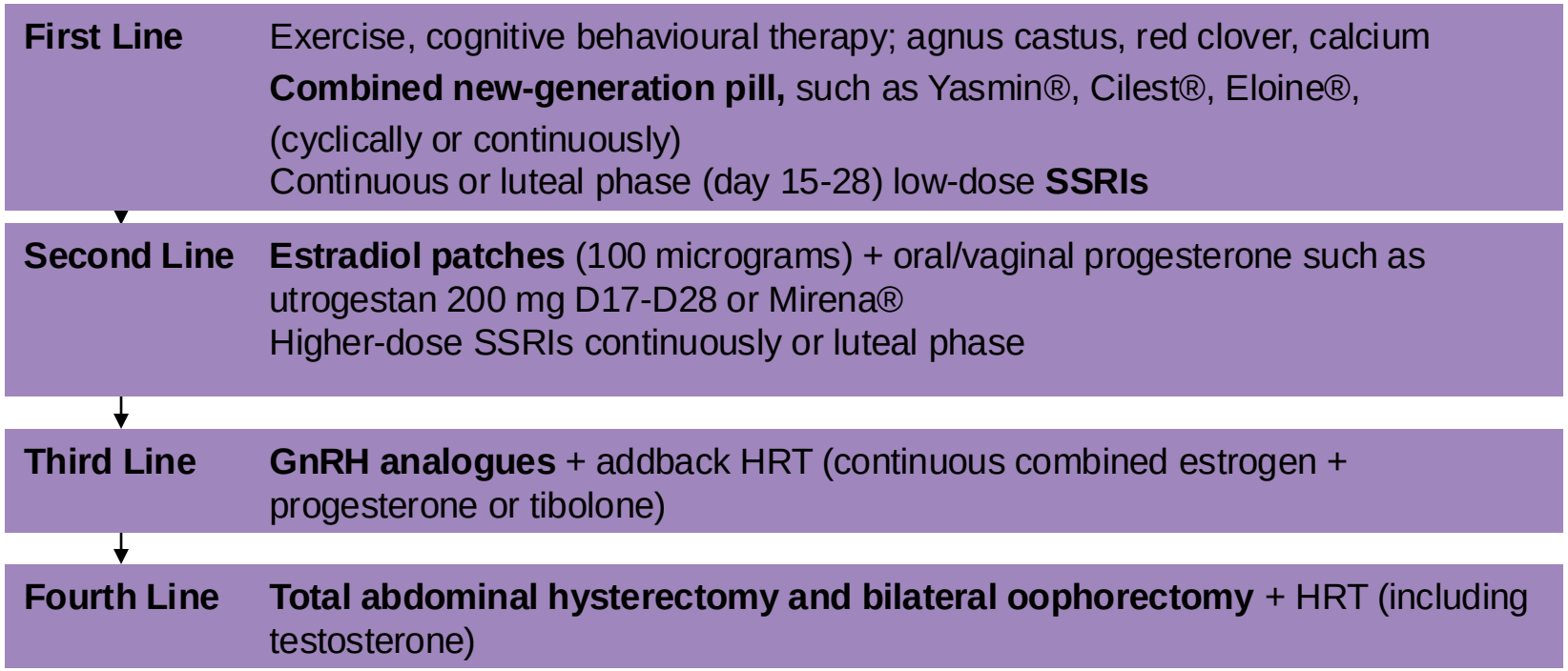
PMS/PMDD
5.How should severe PMS be treated? (2)

- Survey by IAPMD (Int Assoc for Premenstrual Disorders) published on 'World Suicide Day 2021' - 86% of women with PMDD considered suicide and 30% reported at least one attempt during their lifetime.
- Suicidal thoughts, ideation, plans and attempts are strongly associated with PMDD, and all PMDs should be considered risk categories for suicidality.[1-2]
- **It is vital that hormonal management is coordinated closely with mental health teams with plans in place for times when there is suicidal ideation and intent.**

1. Saunders KE, Hawton K. Suicidal behaviour and the menstrual cycle. *Psychol Med* 2006; **36**: 901-12.
2. Osborn E, Brooks J, O'Brien PMS, Wittkowski, A. Suicidality in women with premenstrual dysphoric disorder: a systematic literature review. *Arch Womens Ment Health* 2021; **24:** 173-184.
3. Gordon JL, Chenji S, Di Florio A, Hantsoo L, MacDonald S, Peters JR, Ross JM, Schmalenberger K, Eisenlohr-Moul TA. Suicidality should be considered for inclusion in the diagnostic criteria for PMDD. Lancet Psychiatry. 2024 Sep 19:S2215-

PMS/PMDD
6.2 Algorithm – Management GTG

Figure1. Possible treatment regimen for the management of severe PMS



Panay N. Treatment of premenstrual syndrome: a decision-making algorithm. Menopause Int. 2012 Jun;18(2):90-2.

PMS/PMDD – Complementary therapies

Summary of best evidence for complementary therapies

Complementary therapy	Benefit	Type of studies	Number in the studies	Note
Vitamin B6	No	Meta-analysis	1067 (13 trials)	10 – 50 mg max/d PN at higher doses
Calcium	Yes	2 RCTs crossover	499	Consistent evidence of benefit
Isoflavones	Yes	2 Double-blind randomised studies	72	May benefit menstrual migraine
Agnus castus	Yes	7/8 RCTs showed benefit	560	Effective but lack of standard preparations
St John‘s Wort	Unknown	RCT double blind	125	Significant interactions

Whelan et al 2009; Dante et al 2011; Van Die et al 2013

PMS/PMDD
8.Cognitive therapy

8. Managing severe PMS with cognitive behavioural therapy

When treating women with severe PMS, cognitive behavioural therapy should be considered routinely as a treatment option. A

A clinical psychology service should be available for this patient group. ✓

RCT: Fluoxetine 20mg v CBT v combined therapy – no significant diff. between groups.[1]

Meta analysis of 5 CBT studies and RCT of iCBT showed benefit.[2-3]

1. Hunter et al J Psychosom Obstet Gynecol 2002;
2. Busse et al; Psychotherapy & Psychosom 2009
3. Weise C, Kaiser G, Janda C, Kues JN, Andersson G, Strahler J, Kleinstäuber M. Internet-Based Cognitive-Behavioural Intervention for Women with Premenstrual Dysphoric Disorder: A Randomized Controlled Trial. Psychother Psychosom. 2019;88(1):16-29.

PMS/PMDD
9.Management with SSRIs/SNRIs

- Modulating serotonin with SSRIs improves psychological PMS symptoms. [A]

- When treating women with PMS, both luteal and continuous dosing with SSRIs can be recommended - continuous may be more effective according to recent systematic review. [B][1-2]
    - Well tolerated: Escitalopram 5 – 20mg in luteal phase or even symptom phase dosing [Personal Experience] NB: 1 mg drops

- In perimenopause, should only be used for short term treatment of symptoms until cycle stabilisation achieved hormonally [Personal view]

1. Marjoribanks J, Brown J, O'Brien PMS, Wyatt K. Selective serotonin reuptake inhibitors for premenstual syndrome (review). Cochrane Database Syst Rev 2013; (6): CD001396.
2. Jespersen C, Lauritsen MP, Frokjaer VG, Schroll JB. Selective serotonin reuptake inhibitors for premenstrual syndrome and premenstrual dysphoric disorder. Cochrane Database Syst Rev. 2024 Aug 14;8(8):CD001396.
3. Gröndal M, Näslund J, Englund C, Luke TJ, Ask K, Eriksson E, Winblad S. Intermittent escitalopram treatment and reactive aggression in women with premenstrual irritability and anger: A crossover study. J Affect Disord. 2024 Oct 10;369:599-607.

PMS/PMDD

10.Management with cycle modifying agents – COC cyclical regimens

- ***Problems with COC in PMS due to HFI & PMS-type AEs of some progs.***

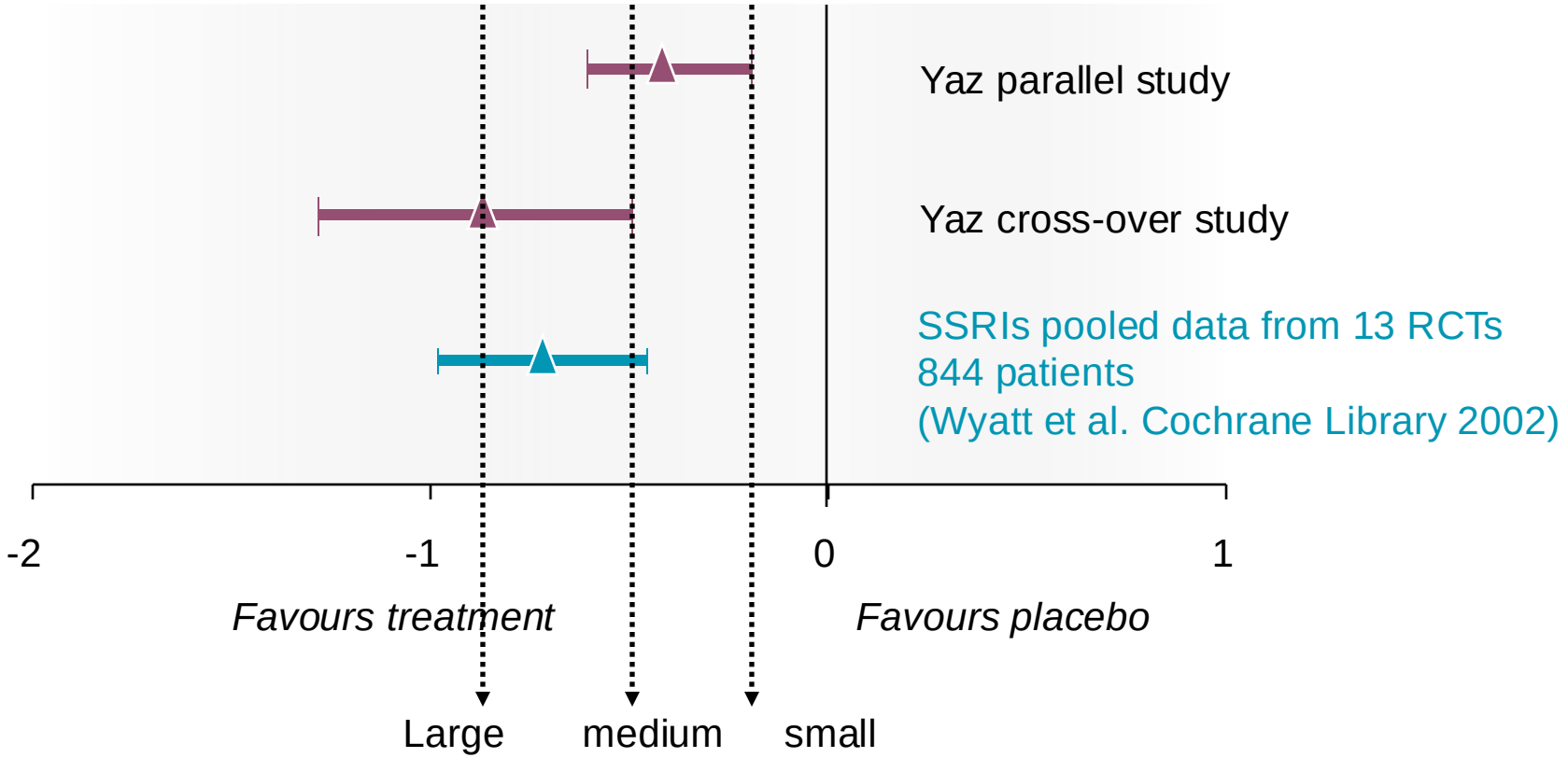
- Cochrane review of five RCTs with 1920 participants.[1]
- EE COCs: Drsp(3 mg) v Plbo v Deso(150mcg) v Levo(150mcg)
- Drospirenone - containing COCs for 3/12 beneficial in reducing PMDD.
  - (MD –7.92; 95% CI –11.16 to –4.67)

- *Role of estradiol and estetrol COCs still to be established but recent pilot study with E2/nomegestrol pill showed benefit in PMDD*

1. Lopez LM, Kaptein AA, Helmerhorst FM. Oral contraceptives containing drospirenone for premenstrual syndrome. Cochrane Database of Systematic Reviews 2012 (2):CD006586.
2. Robertson E, Thew C, Thomas N, Karimi L, Kulkarni J. Pilot Data on the Feasibility And Clinical Outcomes of a Nomegestrol Acetate Oral Contraceptive Pill in Women With Premenstrual Dysphoric Disorder. Front Endocrinol (Lausanne). 2021 Sep 24;12:704488.

EE 20mcg/DRSP 3mg 24/4(Yaz) vs. SSRIs in PMDD

Standardized mean difference 95% CI on overall symptoms



COC v SSRI for PMS

Similar efficacy so let women decide according to preference!

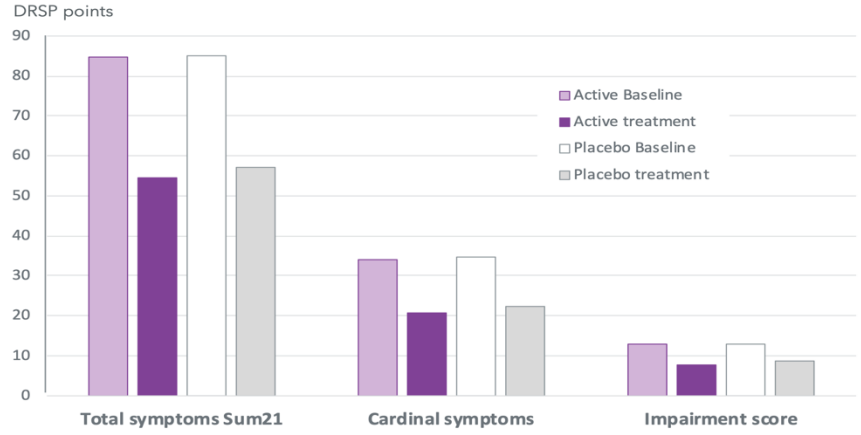
Yonkers et al Obstet Gynecol 2005; Pearlstein et al Contraception 2005; NB: Marr et al Int J O & G 2011 – further study confirming benefit of Yaz v Placebo

Sepranolone* PMDD study (*GABA receptor modulator which regulates effects of allopregnanolone)

Phase IIb Clinical Study
Treatment effect

ASARINA PHARMA

- Late luteal phase symptom scores in the ITT population (N=192)



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Phase IIb Clinical Study
In Conclusion

ASARINA PHARMA

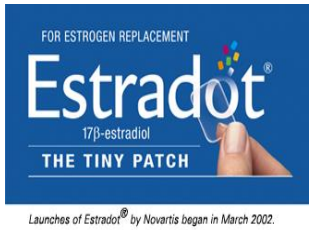
- The baseline data show that the intended patient population was recruited
  - Stricter inclusion criteria produced a well defined patient population
- Sepranolone did not met the primary or secondary end-points
  - Placebo effect high and with large variance
  - The change from baseline in the Sepranolone also with larger variance than expected
  - Numerically, reduction was larger for the Sepranolone group than the placebo group for all symptoms and end-points, but not statistically significantly
- Sepranolone was well tolerated with no safety signals observed

"Symptom reduction was greater for the Sepranolone group than for placebo but the difference between the groups was not statistically significant"

Bäckström T, Ekberg K, Hirschberg AL, Bixo M, Epperson CN, Briggs P, Panay N, O'Brien S. A randomized, double-blind study on efficacy and safety of sepranolone in premenstrual dysphoric disorder. Psychoneuroendocrinology. 2021 Nov;133:105426.

PMS

10.Management with cycle modifying agents - HRT



Estradot 100mcg twice weekly or..
Oestrogel 2 pumps twice daily, with

Utrogestan 100-300mg 7-12 days / cycle
pO / pV (depending on tolerance)

or Mirena IUS (also contraception)

NB: Role of Jaydess/Kyleena being evaluated in PI women with USS ET

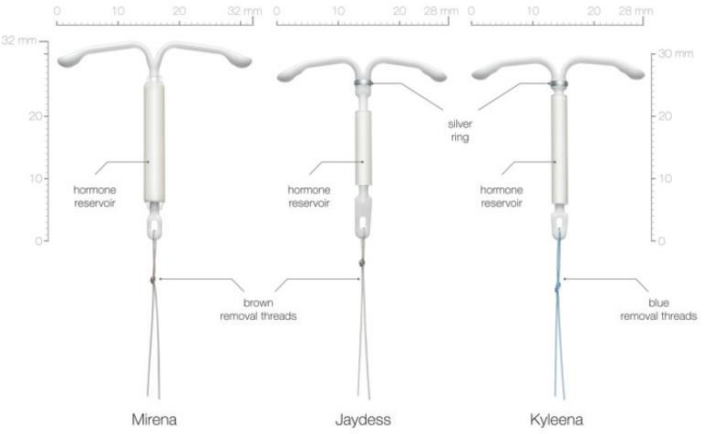
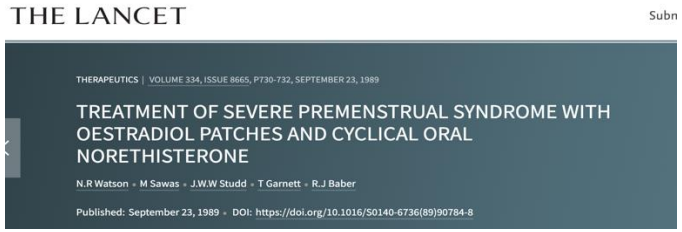


Figure 1: Physical appearance of Mirena, Jaydess and Kyleena.

Table 1: Average *in vivo* LNG release rates (µg/day) of the 3 LNG-IUS

	Mirena	Jaydess	Kyleena
Initial Release*	20	14	17.5
2 months	n/c	10	15
1 year	n/c	6	10
End of indicated period of use**	10	5	7


THE LANCET

THERAPEUTICS | VOLUME 334, ISSUE 8665, P730-732, SEPTEMBER 23, 1989

TREATMENT OF SEVERE PREMENSTRUAL SYNDROME WITH OESTRADIOL PATCHES AND CYCLICAL ORAL NORETHISTERONE

N.R Watson • M Sawas • J.W.W Studd • T Garnett • R.J Baber

Published: September 23, 1989 • DOI: https://doi.org/10.1016/S0140-6736(89)90784-8


BJOG An International Journal of Obstetrics and Gynaecology

Royal College of Obstetricians & Gynaecologists

A randomised comparison over 8 months of 100 µg and 200 µg twice weekly doses of transdermal oestradiol in the treatment of severe premenstrual syndrome

Roger N. J. Smith, John W. W. Studd, Dante Zamblera, E. F. Nigel Holland

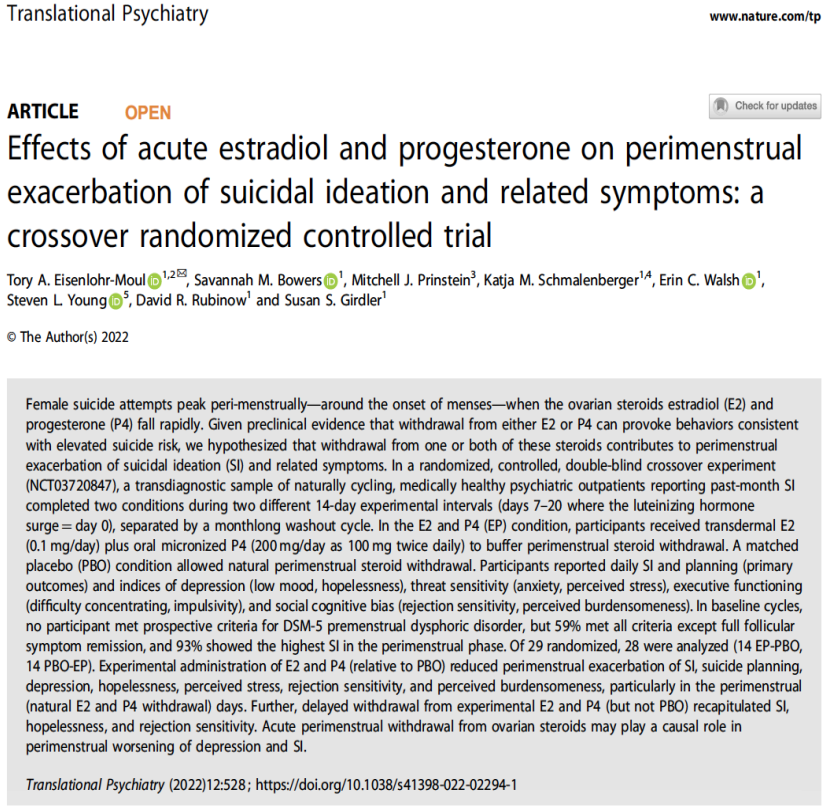
First published: June 1995 | https://doi.org/10.1111/j.1471-0528.1995.tb11321.x | Citations: 61

Management of Perimenstrual suicidal ideation and related symptoms with estradiol / progesterone

- Admin of E2 / P4 (relative to PBO) reduced perimenstrual exacerbation of SI, suicide planning, depression, hopelessness, perceived stress and rejection sensitivity, esp in perimenstrual (natural E2 and P4 withdrawal) days.

- Delayed withdrawal from experimental E2 and P4 (but not PBO) recapitulated symptoms such as SI, hopelessness, and rejection sensitivity.

- **Conclusion: Acute perimenstrual withdrawal from ovarian steroids may play a causal role in perimenstrual worsening of depression and SI.**



Translational Psychiatry www.nature.com/tp

ARTICLE OPEN

Check for updates

Effects of acute estradiol and progesterone on perimenstrual exacerbation of suicidal ideation and related symptoms: a crossover randomized controlled trial

Tory A. Eisenlohr-Moul[1,2✉], Savannah M. Bowers[1], Mitchell J. Prinstein[3], Katja M. Schmalenberger[1,4], Erin C. Walsh[1], Steven L. Young[5], David R. Rubinow[1] and Susan S. Girdler[1]

Female suicide attempts peak peri-menstrually—around the onset of menses—when the ovarian steroids estradiol (E2) and progesterone (P4) fall rapidly. Given preclinical evidence that withdrawal from either E2 or P4 can provoke behaviors consistent with elevated suicide risk, we hypothesized that withdrawal from one or both of these steroids contributes to perimenstrual exacerbation of suicidal ideation (SI) and related symptoms. In a randomized, controlled, double-blind crossover experiment (NCT03720847), a transdiagnostic sample of naturally cycling, medically healthy psychiatric outpatients reporting past-month SI completed two conditions during two different 14-day experimental intervals (days 7–20 where the luteinizing hormone surge = day 0), separated by a monthlong washout cycle. In the E2 and P4 (EP) condition, participants received transdermal E2 (0.1 mg/day) plus oral micronized P4 (200 mg/day as 100 mg twice daily) to buffer perimenstrual steroid withdrawal. A matched placebo (PBO) condition allowed natural perimenstrual steroid withdrawal. Participants reported daily SI and planning (primary outcomes) and indices of depression (low mood, hopelessness), threat sensitivity (anxiety, perceived stress), executive functioning (difficulty concentrating, impulsivity), and social cognitive bias (rejection sensitivity, perceived burdensomeness). In baseline cycles, no participant met prospective criteria for DSM-5 premenstrual dysphoric disorder, but 59% met all criteria except full follicular symptom remission, and 93% showed the highest SI in the perimenstrual phase. Of 29 randomized, 28 were analyzed (14 EP-PBO, 14 PBO-EP). Experimental administration of E2 and P4 (relative to PBO) reduced perimenstrual exacerbation of SI, suicide planning, depression, hopelessness, perceived stress, rejection sensitivity, and perceived burdensomeness, particularly in the perimenstrual (natural E2 and P4 withdrawal) days. Further, delayed withdrawal from experimental E2 and P4 (but not PBO) recapitulated SI, hopelessness, and rejection sensitivity. Acute perimenstrual withdrawal from ovarian steroids may play a causal role in perimenstrual worsening of depression and SI.

Translational Psychiatry (2022)12:528; https://doi.org/10.1038/s41398-022-02294-1

Eisenlohr-Moul TA, Bowers SM, Prinstein MJ, Schmalenberger KM, Walsh EC, Young SL, Rubinow DR, Girdler SS. Effects of acute estradiol and progesterone on perimenstrual exacerbation of suicidal ideation and related symptoms: a crossover randomized controlled trial. Transl Psychiatry. 2022 Dec 30;12(1):528.

Novel hormonal approaches to PMS/PMDD

Ulipristal Acetate for Treatment of Premenstrual Dysphoric Disorder: A Proof-of-Concept Randomized Controlled Trial

Erika Comasco, Ph.D., Helena Kopp Kallner, M.D., Ph.D., Marie Bixo, M.D., Ph.D., Angelica L. Hirschberg, M.D., Ph.D., Sara Nyback, R.N., Haro de Grauw, M.Sc., C. Neill Epperson, M.D., Inger Sundström-Poromaa, M.D., Ph.D.

Objective: Premenstrual dysphoric disorder (PMDD) is a common mood disorder, characterized by distressing affective, behavioral, and somatic symptoms in the late luteal phase of the menstrual cycle. The authors investigated continuous treatment with a selective progesterone receptor modulator, ulipristal acetate (UPA), as a potential treatment for PMDD.

Methods: The authors conducted an investigator-initiated, multicenter, double-blind, randomized, parallel-group clinical trial in which women with PMDD (N=95) were treated with either 5 mg/day of UPA or placebo during three 28-day treatment cycles. The primary outcome was the change in premenstrual total score on the Daily Record of Severity of Problems (DRSP) from baseline to end of treatment. DRSP scores were captured by daily ratings using a smartphone application and were analyzed with linear mixed models for repeated measures.

Results: The mean improvement in DRSP score after 3 months was 41% (SD=18) in the UPA group, compared with 22% (SD=27) in the placebo group (mean difference −18%; 95% CI=−29, −8). Treatment effects were also noted for the DRSP depressive symptom subscale (42% [SD=22] compared with 22% [SD=32]) and the DRSP anger/irritability subscale (47% [SD=21] compared with 23% [SD=35]), but not for the DRSP physical symptom subscale. Remission based on DRSP score was attained by 20 women in the UPA group (50.0%) and eight women in the placebo group (21.1%) (a statistically significant difference).

Conclusions: If these results are replicated, UPA could be a useful treatment for PMDD, particularly for the psychological symptoms associated with the disorder.

Am J Psychiatry 2021; 178:256–265; doi: 10.1176/appi.ajp.2020.20030286

- Double-blind, randomized, parallel-group clinical trial in which women with PMDD (N=95) were treated with either 5 mg/day of UPA or placebo during three 28-day treatment cycles.

- The mean improvement in DRSP score after 3 months was 41% (SD=18) in the UPA group, compared with 22% (SD=27) in the placebo group (mean difference -18%; 95% CI=-29, -8).

Comasco E, Kopp Kallner H, Bixo M, Hirschberg AL, Nyback S, de Grauw H, Epperson CN, Sundström-Poromaa I. Ulipristal Acetate for Treatment of Premenstrual Dysphoric Disorder: A Proof-of-Concept Randomized Controlled Trial. Am J Psychiatry. 2021 Mar 1;178(3):256-265.

PMS/PMDD

10.Management with cycle modifying agents – GnRHa

- **If GnRH analogue therapy does not result in elimination of premenstrual symptoms, this suggests a questionable diagnosis rather than limitation of therapy.**
  - ***Evidence level 1++***
- **When treating women with severe PMS using GnRH analogues for > 6 months, add-back hormone therapy should be used. [A]**
- **Women on long-term treatment should have measurement of bone mineral density (ideally by dual energy X-ray absorptiometry). [A]**

TOP TIPS

- Start with nasal GnRHa if patient uncertainty re Rx
- Minimum 3 cycles to assess response
- Transdermal E2 50-100 / Utrogestan 100-200, best ccHRT

Original Article

The treatment of severe premenstrual syndrome with goserelin with and without 'add-back' estrogen therapy: A placebo-controlled study

A. T. Leather, J. W. W. Studd, N. R. Watson & E. F. N. Holland

Pages 48-55 | Published online: 28 Aug 2009

Download citation https://doi.org/10.1080/09513599909167531

PMS/PMDD

12.Surgical approach (Hysterectomy and BSO)

- Hysterectomy and bilateral salpingo-oophorectomy is of benefit. [C]
  - NB: BSO alone not ideal as endometrial protection still required!

- TAH BSO if long-term GnRHa / gynae conditions indicate surgery e.g. fibroids/bleeding. [GPP]

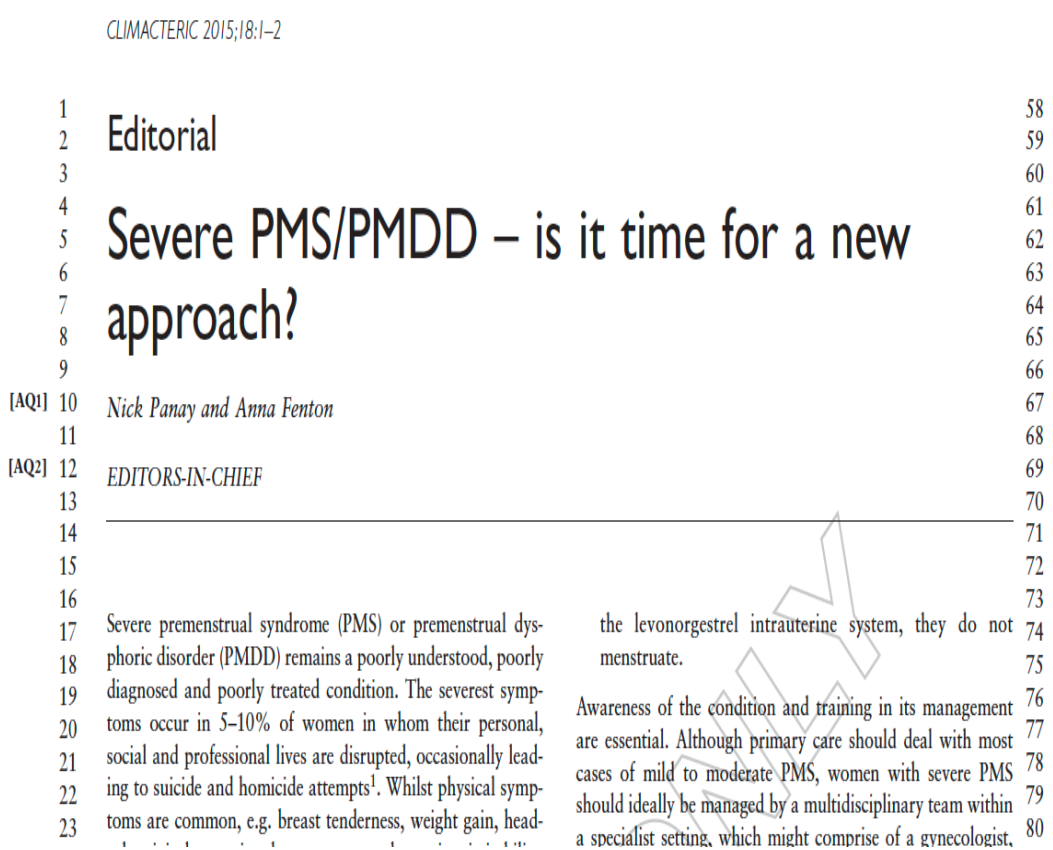
- Pre-operative GnRH analogue test mandatory to ensure adequate efficacy / HT tolerance. [GPP]

- Adequate add back HRT with E2 +/- T essential post operatively!

- NB: Residual “CRS” in some women – possibly related to hormonal fluctuations esp with gels; implanted pellets may be a better option but unlicensed.

Cronje et al Hum Reprod 2005

Severe PMS/PMDD – time for a new approach!



CLIMACTERIC 2015;18:1–2

Editorial

Severe PMS/PMDD – is it time for a new approach?

Nick Panay and Anna Fenton

EDITORS-IN-CHIEF

Severe premenstrual syndrome (PMS) or premenstrual dysphoric disorder (PMDD) remains a poorly understood, poorly diagnosed and poorly treated condition. The severest symptoms occur in 5–10% of women in whom their personal, social and professional lives are disrupted, occasionally leading to suicide and homicide attempts[1]. Whilst physical symptoms are common, e.g. breast tenderness, weight gain, headache, the levonorgestrel intrauterine system, they do not menstruate.

Awareness of the condition and training in its management are essential. Although primary care should deal with most cases of mild to moderate PMS, women with severe PMS should ideally be managed by a multidisciplinary team within a specialist setting, which might comprise of a gynecologist,

WHO states, "Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity".

"We must continue to strive to improve recognition and provide appropriate treatment to women affected by premenstrual disorders". NP

Panay N, Fenton A. Severe PMS/PMDD - is it time for a new approach? Climacteric. 2015 Jun;18(3):331-2

PMS/PMDD – an Update
Key Messages

- In a landmark decision in 2019, WHO added (**PMDD**) to International Statistical Classification of Diseases, **Eleventh** Revision (**ICD-11**). **PMDD** has its own **ICD** code (GA34).
- Training of Health Professionals should be addressed urgently by academic bodies
- Management of severe PMS/PMDD ideally by MDTs, with shared care protocols with primary care, gynaecology, mental health services and evidence-based guidelines
- Adequately resourced women's health strategies for PMS/PMDD required globally!

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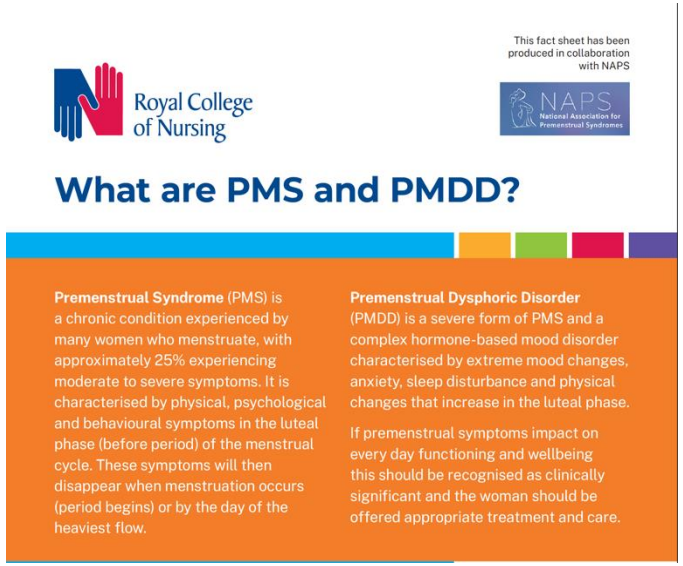
PEER SUPPORT GROUPS
(When 'I' is replaced by 'We', 'Illness' becomes 'Wellness')

NAPS (National Association for Premenstrual Syndromes)

- Website https://pms.org.uk
- Ask the Experts
- Scientific Meetings / Webinars
- PMS Guidelines
- Collaboration with RCN / HH



IAPMD (International Association for Premenstrual Disorders)

- Website https://iapmd.org
- Lifeline of support for sufferers
- Information & Educational Resources
- PCORI (Patient Centred Outcomes Research Institute Grant – PMDD/PME)

Van Gogh and the menstrual cycle!
THANK YOU FOR YOUR ATTENTION