Nick Panay BSc FRCOG MFSRH
Professor of Practice, Imperial College London
Chair: National Association for Premenstrual Syndromes
Clinical Advisory Board: International Association for Premenstrual Disorders
President: International Menopause Society

The modern management of PMS/PMDD - Latest Definitions, Guidelines, Management & Research (based on RCOG / NAPS / TOG Guidelines)

vv

NATIONAL ASSOCIATION FOR PREMENSTRUAL SYNDROMES (NAPS)

STUDY DAY ON WOMEN'S HEALTH

Friday 17th November 2023
Gleeson Lecture Theatre, Chelsea and Westminster Hospital
369 Fulham Rd. London SW10 9NH
9.00am – 4.45pm

Key Disclosures

Pharma:

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

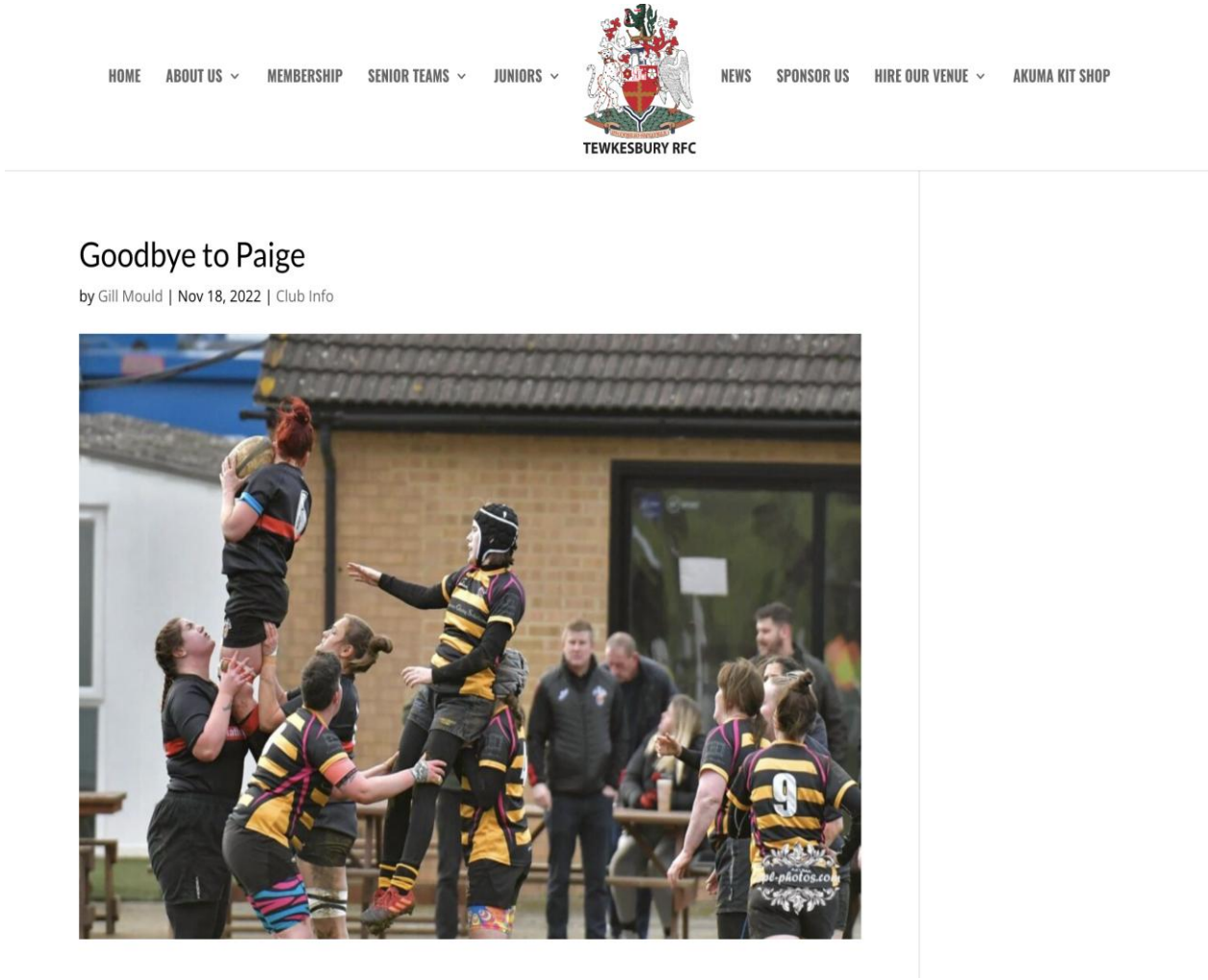
Professional:

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

Too many precious lives are being lost!

We dedicate this NAPS meeting as a tribute to Paige

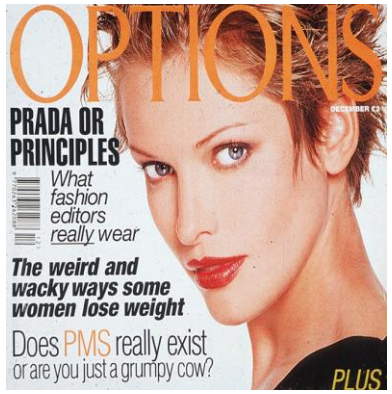
- TRIBUTE BY TEWKESBURY RFC NOV 18, 2022
- Today we say goodbye to one of our own, Paige McCormack. The most kind-hearted, calm and considerate person with the fastest legs and the most ruthless tackles.
- Our thoughts are with all of Paige's family, friends and teammates.
- In memory of Paige the club will be making donations to the following charities National Association for Premenstrual Syndromes (PMS) NAPS and Great Western Air Ambulance Charity Please visit the links below if you would like to make a donation.
- NAPS – National Association For premenstrual Syndromes – https://www.pms.org.uk/donate/



Fashionable 19th.
Century Disorders in Women

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

all often due to reading serious



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.

Definitions: Premenstrual Syndrome (PMS) or premenstrual dysphoric disorder (PMDD)?

- NAPS changed its name to the National Association for Premenstrual Syndromes from "…Syndrome" to reflect the variation in definitions and severities of premenstrual disorders.
- Current PMS terminology should be maintained because PMDD refers to only one type of severe form of PMS.
- It is vital that there is universal recognition of the severe impact that PMS can have, whatever terminology is used.
- Education of public and HCPs is the key issue going forward.

NAPS trustees' consensus statement (Sept 2017)

International Society for PreMenstrual Disorders (ISPMD) Consensus on Definitions, Diagnosis and Management – best way forward?

- **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

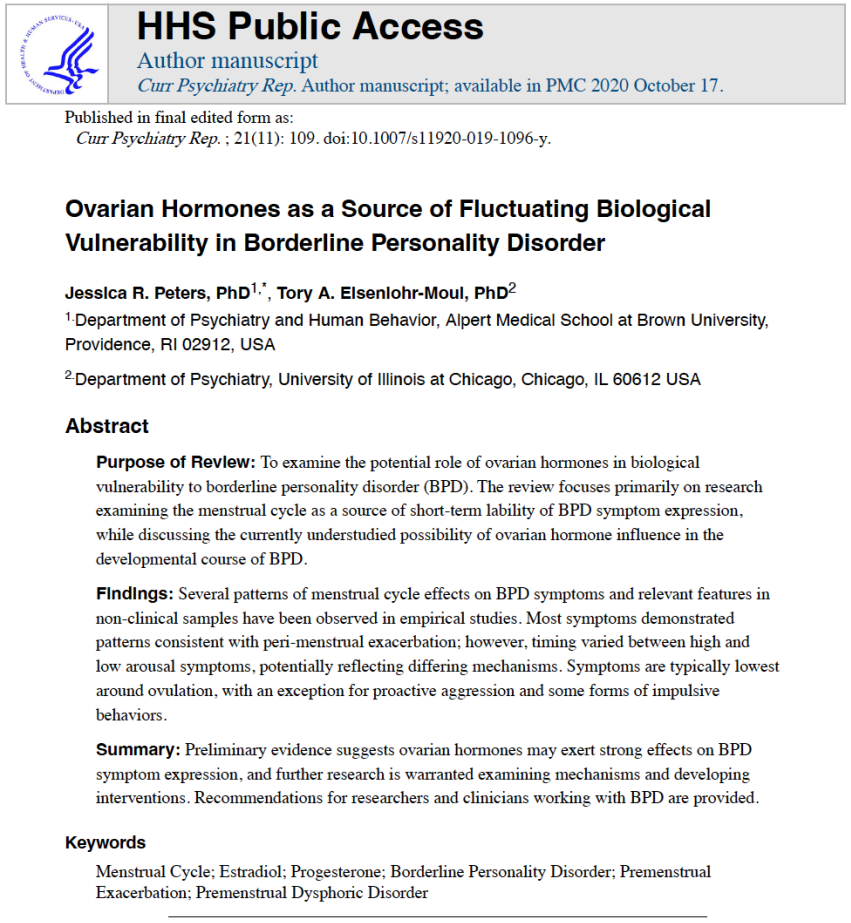
O'Brien PMS, Backstrom T, Brown C, Dennerstein L, Endicott J, Epperson CN, Eriksson E, Freeman E, Halbreich, Ismail KMK, Panay N, Pearlstein T, Rapkin A, Reid R, Schmidt P, Steiner M, Studd J, Yonkers K. Arch Women's Ment Health 2011; 14: 13-21.
Women's Ment Health 2013; 16 (4) 279 – 291.

- **Variants**
  - **Premenstrual Exacerbation (PME)**

- Preliminary evidence suggests ovarian hormones may exert strong effects on Borderline Personality Disorder symptom expression (also ?ADHD)

- Background symptomatology with premenstrual exacerbation due to hormonal fluctuation

- Further research is warranted examining mechanisms and developing interventions.



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.

RCOG Guidelines for Premenstrual Syndrome

www.rcog.org.uk

Royal College of Obstetricians & Gynaecologists

- 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
    - 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

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www.pms.org.uk

DOI: 10.1111/tog.12848 2023;25:38–46 Review

The Obstetrician & Gynaecologist

http://onlinetog.org

Premenstrual disorders including premenstrual syndrome and premenstrual dysphoric disorder

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Accepted on 7 March 2022.

http://onlinetog.org

PMS 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 v 23% perimenopause[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 2.2b Etiology

- Etiology
  - May be multiple etiologies (E2/serotonin, Progesterone/allopregnanolone/GABA)
  - Abnormalities have been demonstrated by fMRI.[1]
    - **Brain imaging studies of task-related activation during fMRI have identified several regions of abnormal function in women with PMDD esp in amygdala during luteal phase.**
  - (Cyclic) ovarian activity / hormonal fluctuations essential in genesis of symptoms.
  - Probable genetic predisposition / 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

- Sensitivity may be attributed to dysregulation and overexpression of the ESC/E(Z)] gene complex 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

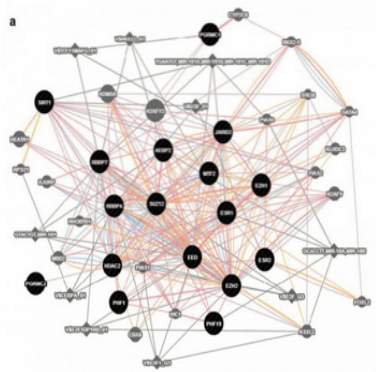
Sex hormone-sensitive gene complex linked to premenstrual mood disorder

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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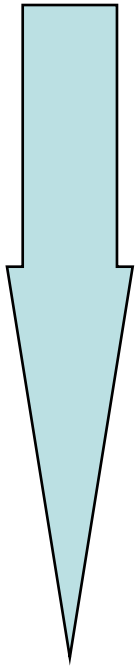
RSS Feed

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.

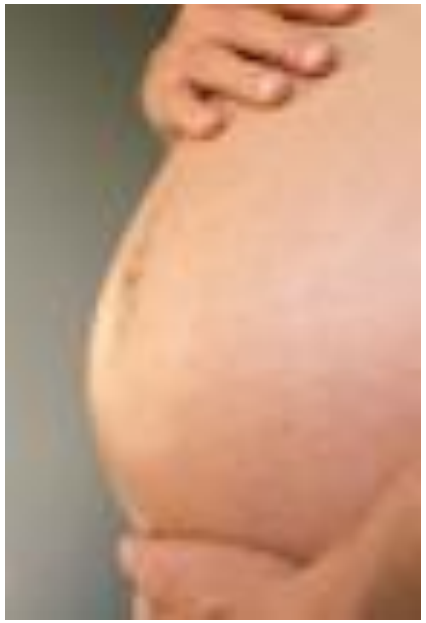
Studd J, Panay N. Hormones and depression in women. Climacteric. 2004 Dec;7(4):338-46.

Proof that ovarian activity integral to PMS Aetiology

Stages with no symptoms

Pre-puberty

Pregnancy



Post-Menopause

How do I approach a PMS/PMDD patient?

- **Listen Carefully**!

- **Confirm the diagnosis** – charts NB: beware prior misdiagnosis of bipolar disorder!

- **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

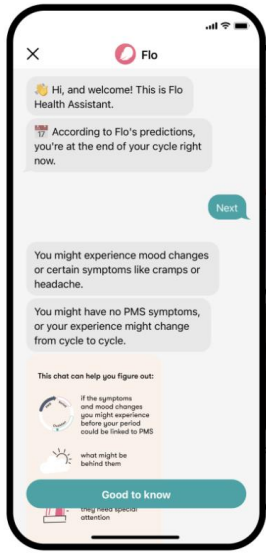
- **Review at 3 months** but remain available

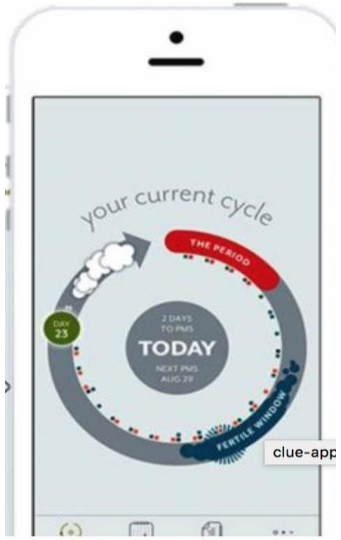
- **Don't place arbitrary limits** on treatment duration

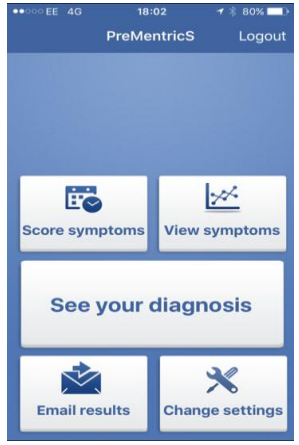
- **Co-manage patients with background psychopathology with Mental Health Services**

PMS
4. Diagnosis

“There are no diagnostic laboratory tests/investigations to make a 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
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
5.How should severe PMS be treated? (2)

- Survey by IAPMD (International Association for Premenstrual Disorders) published on ‘World Suicide Day 2021’ showed that 86% of women with PMDD considered suicide and 30% report at least one attempt during their lifetime.

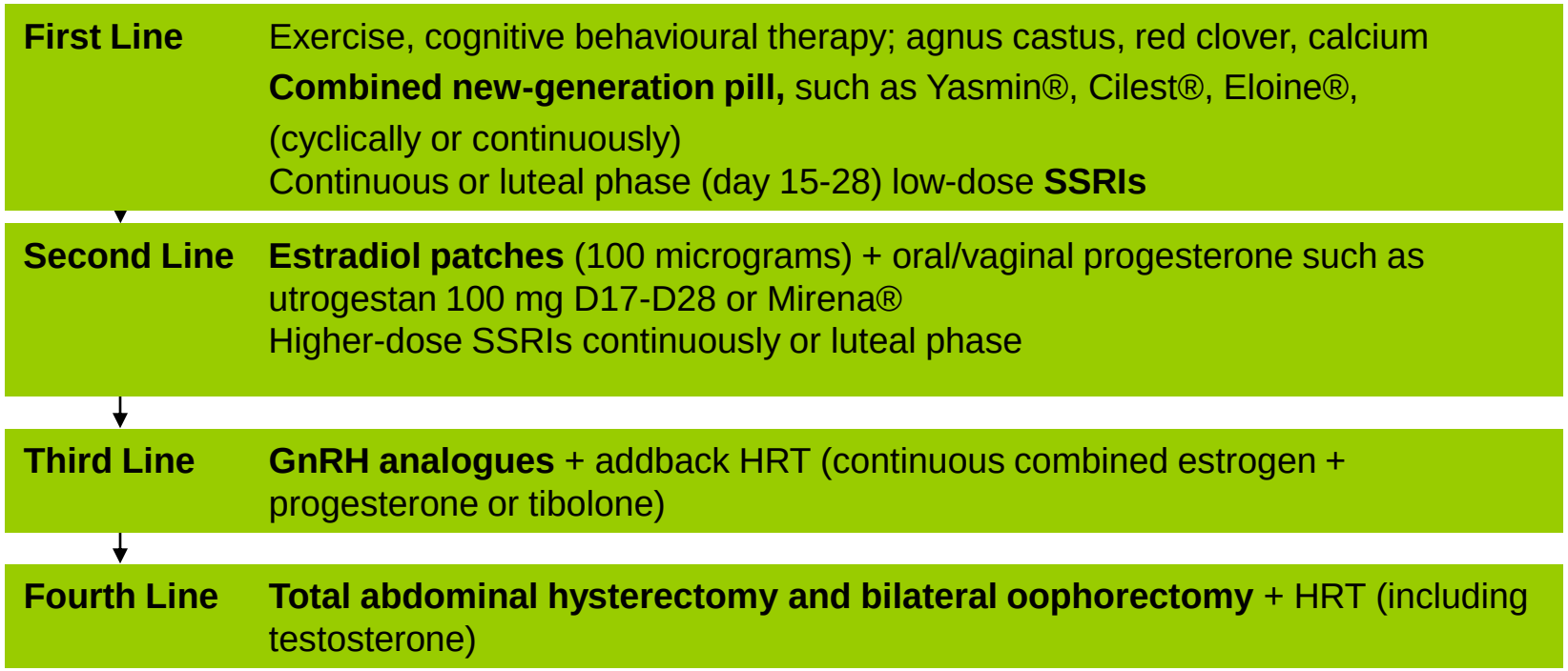
- Suicidal thoughts, ideation, plans and attempts are strongly associated with PMDD, and all PMDs should be considered risk categories for suicidality.[1-2]

- It is therefore vital that hormonal management is coordinated closely with mental health teams with plans in place for times when the woman has 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.

PMS
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 – 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
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 showed benefit.[2]

1. Hunter et al J Psychosom Obstet Gynecol 2002; 2. Busse et al; Psychother & Psychosom 2009

PMS
9.Management with SSRIs/SNRIs

- Modulating levels of serotonin with SSRIs improves psychological PMS symptoms. [A]
- When treating women with PMS, both luteal and continuous dosing with SSRIs can be recommended. [B]
- Well tolerated: Escitalopram 5 – 20mg in luteal phase or even symptom phase dosing [Personal Experience]
- In perimenopause, short term treatment of symptoms until cycle stabilisation achieved hormonally [Personal view]

Marjoribanks J, Brown J, O'Brien PMS, Wyatt K. Selective serotonin reuptake inhibitors for premenstual syndrome (review). Cochrane Database Syst Rev 2013; (6): CD001396.

PMS

10.Management with cycle modifying agents – **COC cyclical regimens**

- **Problems with COC in PMS: 7/7 HFI & PMS side effects of some progs.**
- **?Role of E2/E4 pills**

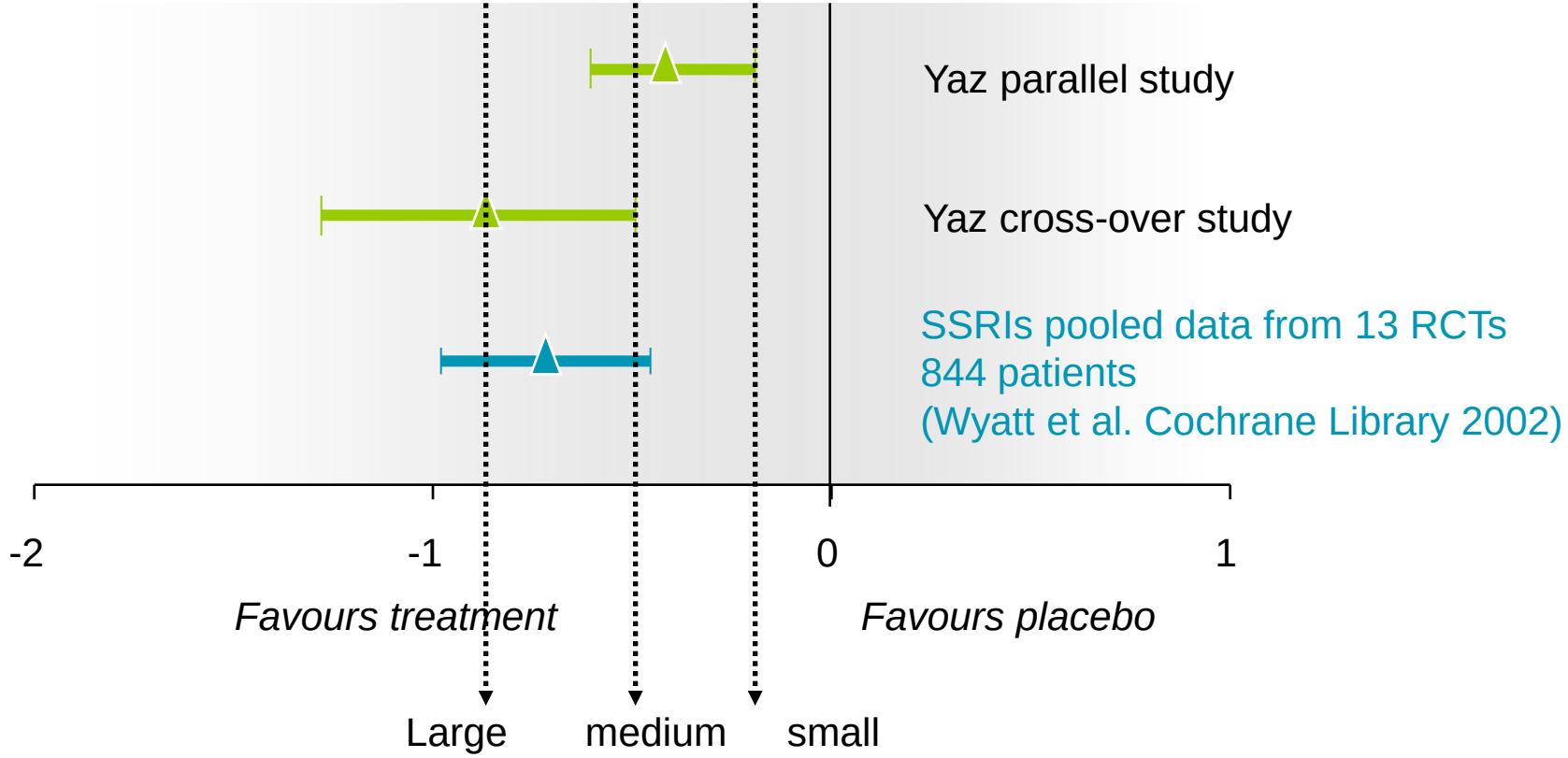
- Cochrane review of five RCTs with 1920 participants.[1]
- EE COCs: Drsp(3 mg) v Plbo v Deso(150mcg) v Levo(150mcg)
- Drospirenone - containing COCs for 3/12 beneficial in reducing severity of PMDD.
  - (MD –7.92; 95% CI –11.16 to –4.67)

1. Lopez LM, Kaptein AA, Helmerhorst FM. Oral contraceptives containing drospirenone for premenstrual syndrome. Cochrane Database of Systematic Reviews 2012 (2):CD006586.

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

Standardized mean difference 95% CI on overall symptoms

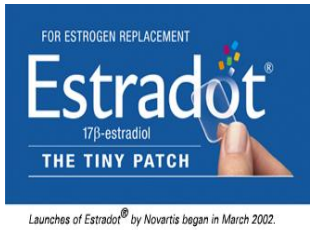
<u>OC v SSRI for PMS</u>
Similar efficacy so let women decide according to preference!



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

PMS

10.Management with cycle modifying agents - HRT



Launches of Estradot® by Novartis began in March 2002.

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 monitoring of ET

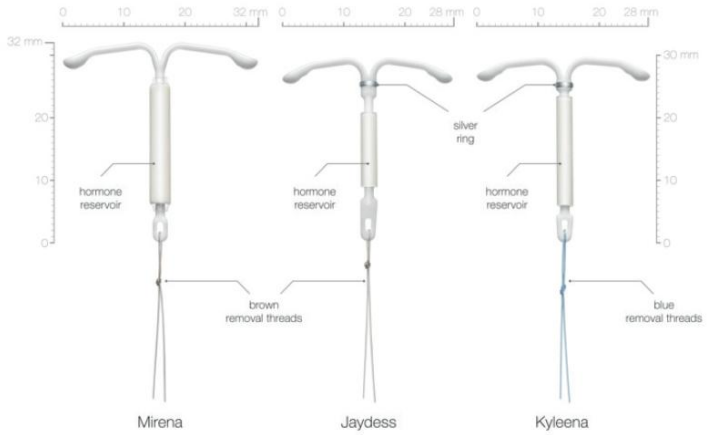


Figure 1: Physical appearance of Mirena, Jaydess and Kyleena.

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

PMS

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

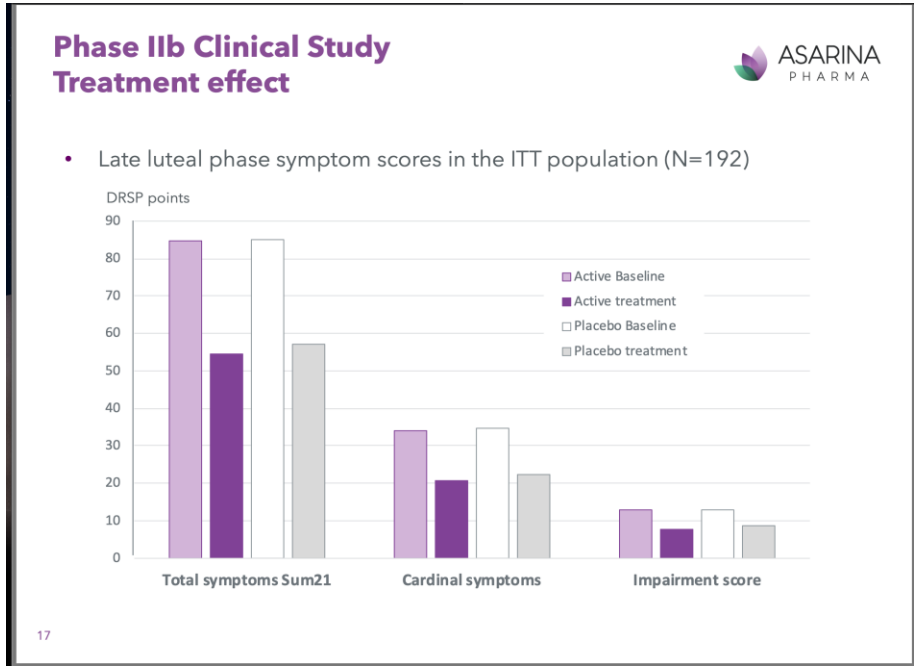
PMS

12.Surgical approach (Hysterectomy and BSO)

- Hysterectomy and bilateral salpingo-oophorectomy is of benefit. [C]
  - NB: BSO alone not ideal as EP still required!
- TAH BSO if long-term GnRHa or other gynae conditions indicate surgery e.g. fibroids/bleeding. [GPP]
- Pre-operative GnRH analogue test mandatory to ensure adequate efficacy / HT tolerance. [GPP]
- Adequate E2 +/- T essential post operatively!
- NB: Residual “CRS” in some women – possibly related to hormonal fluctuations esp with gels

Cronje et al Hum Reprod 2005

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



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. doi: 10.1016/j.psyneuen.2021.105426. Epub 2021 Sep 23. PMID: 34597899.

A new era of collaboration?

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A scoping review of hormonal clinical trials in menstrual cycle-related brain disorders: Studies in premenstrual mood disorder, menstrual migraine, and catamenial epilepsy

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Catamenial epilepsy
Menstrual migraine

ABSTRACT

Cyclic variations in hormones during the normal menstrual cycle underlie multiple central nervous system (CNS)-linked disorders, including premenstrual mood disorder (PMD), menstrual migraine (MM), and catamenial epilepsy (CE). Despite this foundational mechanistic link, these three fields operate independently of each other. In this scoping review (N = 85 studies), we survey existing human research studies in PMD, MM, and CE to outline the exogenous experimental hormone manipulation trials conducted in these fields. We examine a broad range of literature across these disorders in order to summarize existing diagnostic practices and research methods, highlight gaps in the experimental human literature, and elucidate future research opportunities within each field. While no individual treatment or study design can fit every disease, there is immense overlap in study design and established neuroendocrine-based hormone sensitivity among the menstrual cycle-related disorders PMD, MM, and CE.

Scoping review structured summary: Background. The menstrual cycle can be a biological trigger of symptoms in certain brain disorders, leading to specific, menstrual cycle-linked phenomena such as premenstrual mood disorders (PMD), menstrual migraine (MM), and catamenial epilepsy (CE). Despite the overlap in chronicity and hormonal provocation, these fields have historically operated independently, without any systematic communication about methods or mechanisms.

Objective. Online databases were used to identify articles published between 1950 and 2021 that studied hormonal manipulations in reproductive-aged females with either PMD, MM, or CE. We selected N = 85 studies that met the following criteria: 1) included a study population of females with natural menstrual cycles (e.g., not perimenopausal, pregnant, or using hormonal medications that were not the primary study variable); 2) involved an exogenous hormone manipulation; 3) involved a repeated measurement across at least two cycle phases as the primary outcome variable.

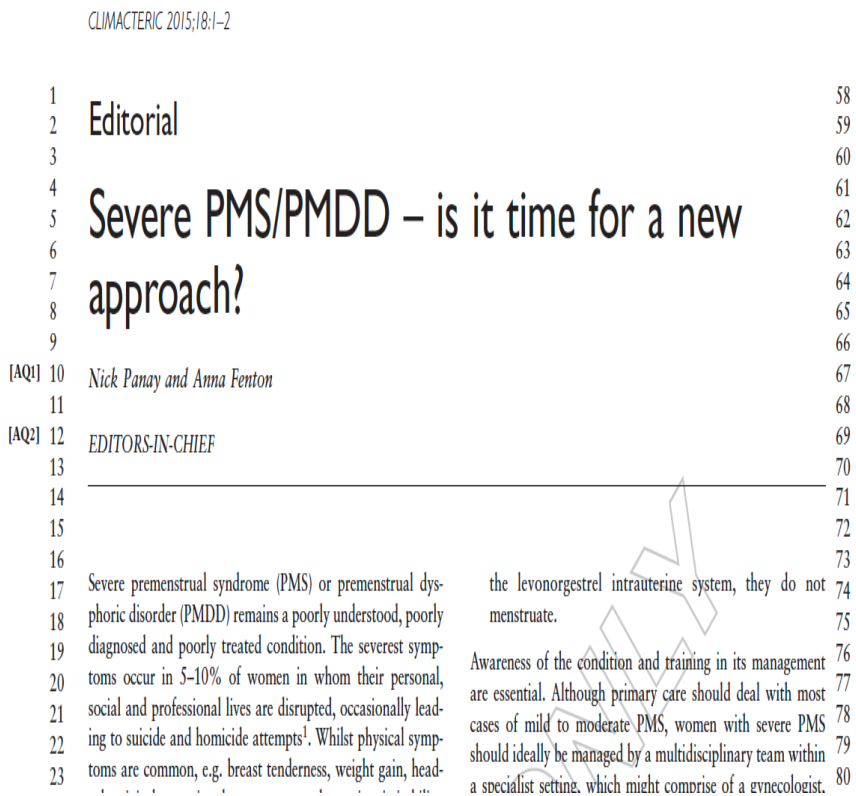
Charting methods. After exporting online database query results, authors extracted sample size, clinical diagnosis of sample population, study design, experimental hormone manipulation, cyclical outcome measure, and results from each trial. Charting was completed manually, with two authors reviewing each trial.

Results. Exogenous hormone manipulations have been tested as treatment options for PMD (N = 56 trials) more frequently than MM (N = 21) or CE (N = 8). Combined oral contraceptive (COC) trials, specifically those containing drospirenone as the progestin, are a well-studied area with promising results for treating both PMDD and MM. We found no trials of COCs in CE. Many trials test ovulation suppression using gonadotropin-releasing hormone agonists (GnRHa), and a *meta*-analysis supports their efficacy in PMD; GnRHa have been tested in two MM-related trials, and one CE open-label case series. Finally, we found that non-contraceptive hormone manipulations, including but not limited to short-term transdermal estradiol, progesterone supplementation, and progesterone antagonism, have been used across all three disorders.

- Across PMD, MM, and CE, various exogenous hormone manipulations have been tested to treat symptoms,
- While no individual treatment or study design treats all three menstrual cycle-linked CNS disorders, it is clear that there is overlap in study design and neuroendocrine-based hormone sensitivity.
- In the current scientific landscape that promotes open science, reproducibility, and translational collaboration, there are massive opportunities for collaboration and education among menstrual cycle researchers across psychiatric and neurologic fields.

Barone JC, Butler MP, Ross A, Patterson A, Wagner-Schuman M, Eisenlohr-Moul TA. A scoping review of hormonal clinical trials in menstrual cycle-related brain disorders: Studies in premenstrual mood disorder, menstrual migraine, and catamenial epilepsy. Front Neuroendocrinol. 2023 Aug 22;71:101098.

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.

Key take home messages…….

The modern management of PMS/PMDD – Key Messages

- Universal adoption of ISPMD diagnostic criteria would be helpful to facilitate recognition and treatment of PMS/PMDD
  - *In a landmark decision in May 2019, the World Health Organization (WHO) added (**PMDD**) to the International Statistical Classification of Diseases, **Eleventh** Revision (**ICD-11**). **PMDD** now has its own **ICD** code (GA34).*
- Best evidence thus far is for 24/4 or continuous OCs, Estradiol (TD), SSRIs & GnRHa
- Training of Health Professionals should be addressed by Universities & Royal Colleges
- Management of severe PMS/PMDD ideally by MDTs with evidence-based guidelines
- Adequately resourced women's health strategies for PMS/PMDD required globally!

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

Further Information

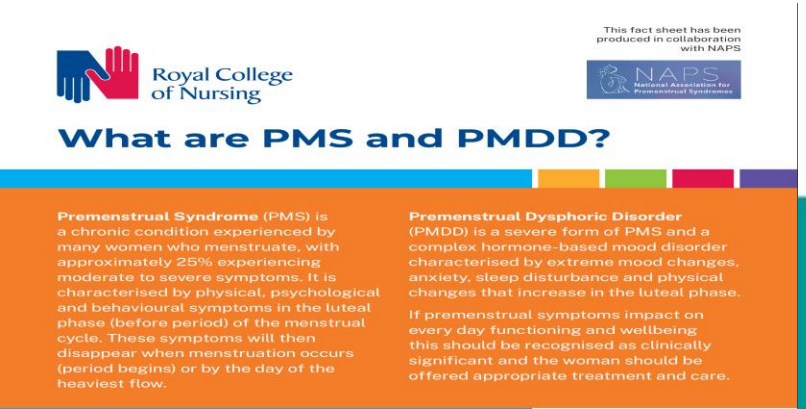
PEER SUPPORT GROUPS (When 'I' is replaced by 'We', 'illness' becomes 'Wellness')

NAPS (National Association for Premenstrual Syndromes)

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

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)



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