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Premenstrual Syndrome
Latest Definitions, Management Guidelines & Research

Royal College of Obstetricians & Gynaecologists

Premenstrual Syndrome - History

Hippocrates' Aphorisms – (*370BC)* 'shivering, lassitude and heaviness of the head denotes onset of menstruation….'

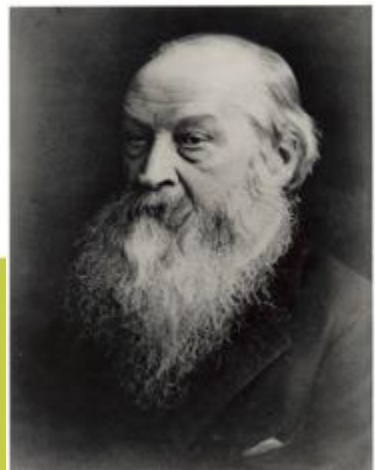
Henry Maudsley (1873) - First to make connection between PMS & cyclical ovarian activity

Frank (1931) - First use of term "Premenstrual tension"

Greene & Dalton (1953) – "Premenstrual syndrome"

Studd (1988) - Ovarian cycle syndrome –

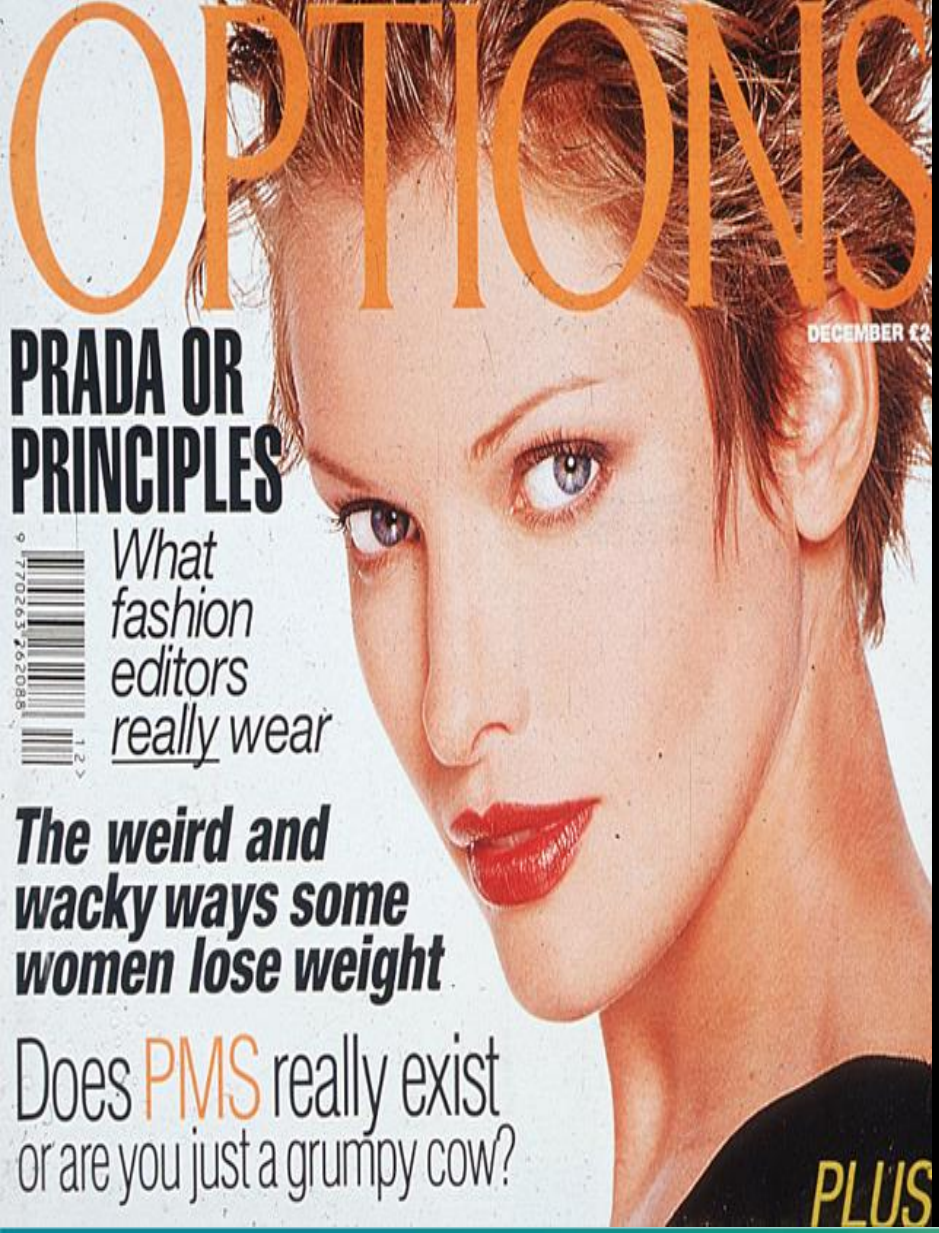
"menstruation not an essential feature of PMS"



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



Have views on PMS changed??

Up to a million British women may suffer from psychosis due to PMS, gynaecologist warns

'I got psychosis and started seeing things which weren't there. It happened just like that', one woman told The Independent

Siobhan Fenton Health Correspondent | @siobhanfenton | Wednesday 19 October 2016 | 1 comment

Dr Panay says women are being let down by a toxic mix of "poor education of the public regarding the condition; poor education of health professionals at university and postgraduate level; social stigma/taboo and prejudice that this is not a 'real' condition."

Oct 2016 The Independent

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 et al.
  - 2016 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.

Management of Premenstrual Syndrome

(NAPS Guidelines)

Nick Panay

BSc MRCOG MFSRH

www.rcog.org.uk www.pms.org.uk

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** e.g.epilepsy,migraine
  - **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.

Definitions: PMS or PMDD?

- NAPS will change its name to the National Association for Premenstrual Syndromes from "…Syndrome" to reflect the variation in definitions and severities of this disorder.

- Current PMS terminology should be maintained because PMDD refers to only one type of severe form of PMS. PMDD excludes some women with severe PMS due to the strict definition criteria.

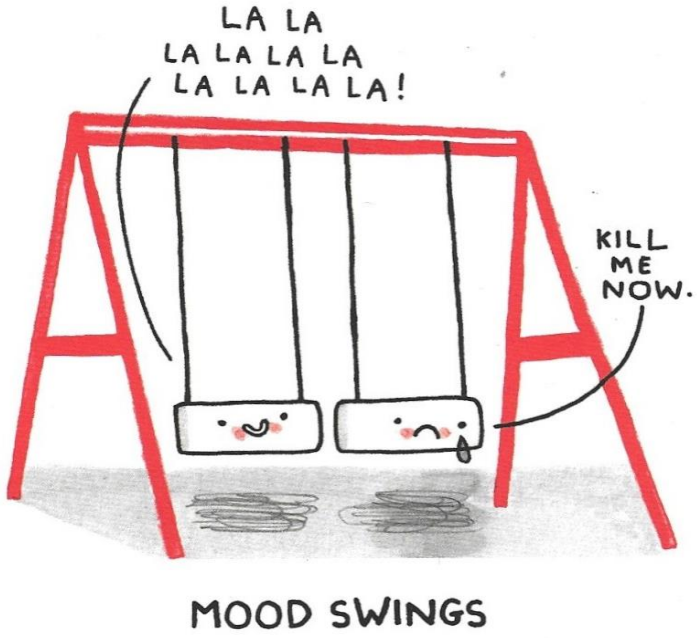
- Education of public and HCPs is the key issue going forward.

- It is vital that there is universal recognition of the severe impact that PMS can have, whatever terminology is used.

NAPS trustees' consensus statement (Sept 2017)

PMS Patient Quotes – emotional symptoms are the most distressing.

- “Jeckyll and Hyde personality”
- “My… body is taken over / mind is not my own”
- “I don’t recognise myself”
- “The mist descends”
- “The demons take over”
- “I love my husband / children but I’m about to kill him / them!”



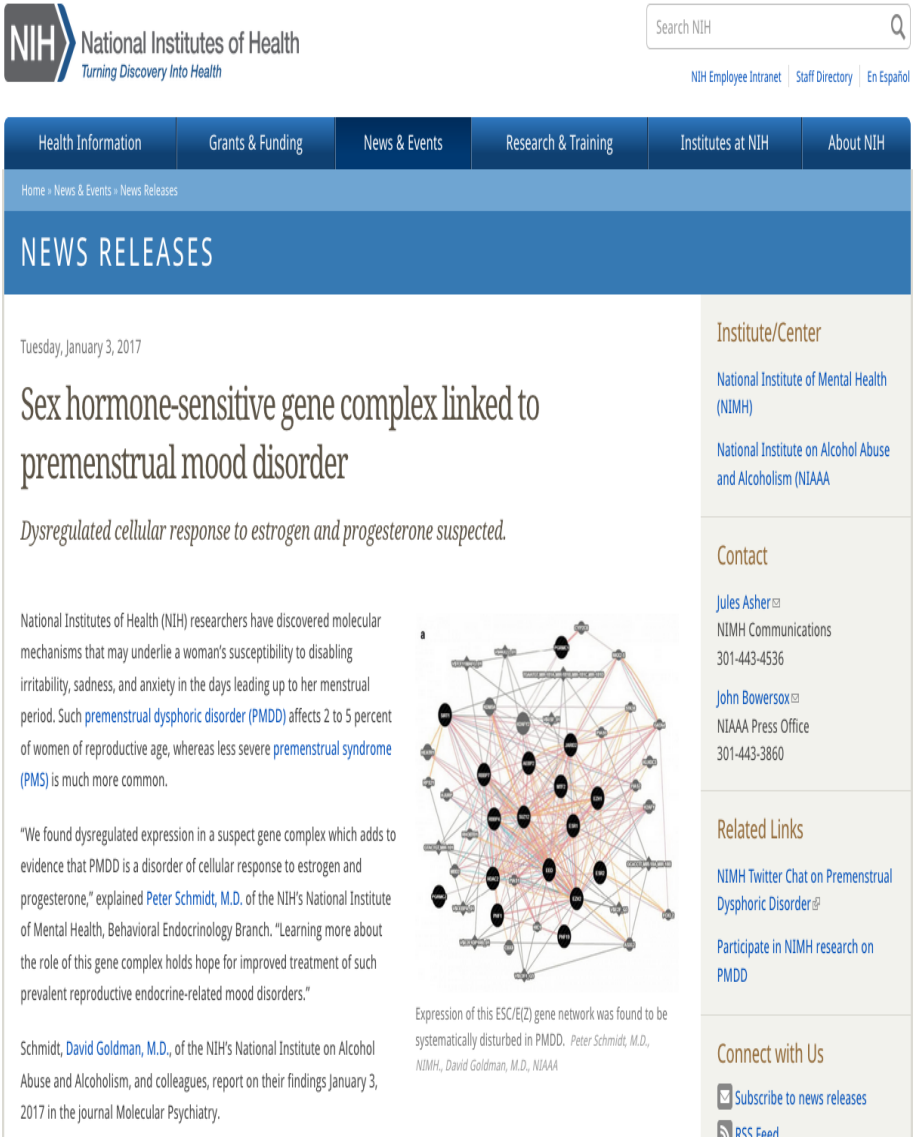
PMS 2.2 Aetiology & Prevalence

- Prevalence
  - Peak prevalence of severe PMS in 40-50y age group
  - Moderate PMS: 24% in SWS[1]
  - Severe PMS (PMDD) 5-8%[2] in general population v 23% in perimenopausal women[3]
- Aetiology
  - Likely to be multiple aetiologies (E2/serotonin, Progesterone-allopregnanolone/GABA)
  - (Cyclical) ovarian activity / hormonal fluctuations play an essential role in the genesis of symptoms, also in VMS
  - Probable genetic predisposition – unique ESR1 gene polymorphisms in PMDD sufferers v controls.[3]

1.Sadler et al JWH 2010; 2.Reid NEJM 1991; 3.Chung at al JMM 2014 4. Miller et al 2010

Tue Jan 3rd 2017

- “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 Goldman.



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Turning Discovery Into Health

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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

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NIMH Communications
301-443-4536

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NIAAA Press Office
301-443-3860

Related Links

NIMH Twitter Chat on Premenstrual Dysphoric Disorder

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Risk for Premenstrual Dysphoric Disorder is Associated with Genetic Variation in ESR1, the Estrogen Receptor Alpha Gene

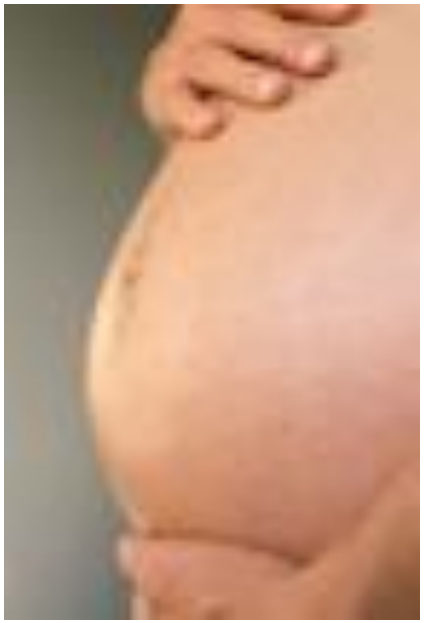
Liang Huo, M.D.[1], Richard E. Straub, Ph.D.[2], Peter J. Schmidt, M.D.[1], Kai Shi, M.D.[1], Radhakrishna Vakkalanka, Ph.D.[2], Daniel R. Weinberger, M.D.[2], and David R. Rubinow, M.D.

Proof that ovarian activity integral to PMS Aetiology

Stages with no symptoms

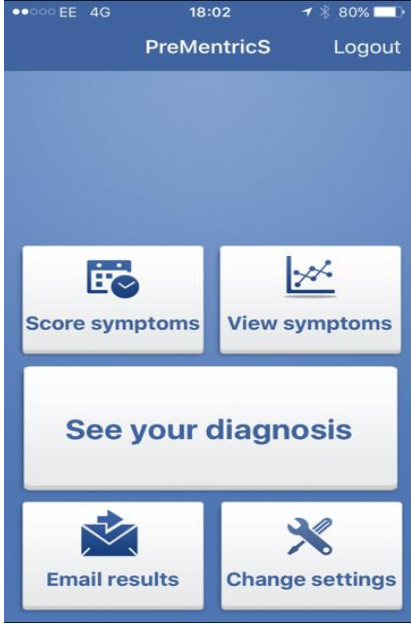
Pre-puberty

Pregnancy



Post-Menopause

PMS
4. Diagnosis



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.rcog.org.uk

www.pms.org.uk NAPS symptom diary

PMS
5.How should severe PMS be treated?

Good Practice Points

When treating women with PMS:

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

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

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

PMS
6.2 Algorithm – Management GTG

Figure1. Possible treatment regimen for the management of severe PMS

First Line	Exercise, cognitive behavioural therapy; agnus castus, red clover, calcium **Combined new-generation pill,** such as Yasmin®, Cilest®, Eloine®, (cyclically or continuously) Continuous or luteal phase (day 15-28) low-dose **SSRIs**
Second Line	**Estradiol patches** (100 micrograms) + oral/vaginal progesterone such as utrogestan 100 mg D17-D28 or Mirena® Higher-dose SSRIs continuously or luteal phase
Third Line	**GnRH analogues** + addback HRT (continuous combined estrogen + progesterone or tibolone)
Fourth Line	**Total abdominal hysterectomy and bilateral oophorectomy** + HRT (including testosterone)

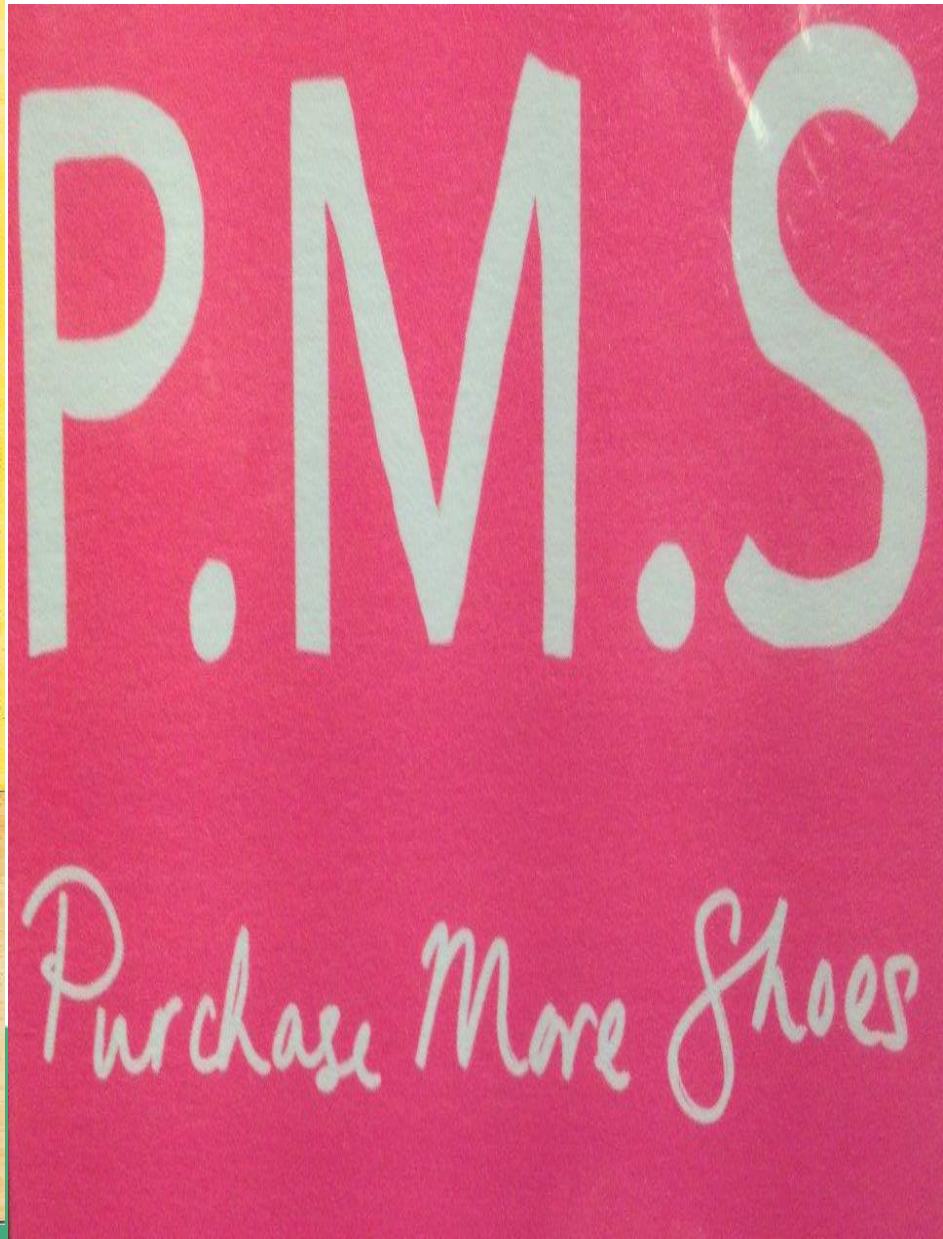
Panay N. Treatment of premenstrual syndrome: a decision-making algorithm. Menopause Int. 2012 Jun;18(2):90-2.

How do I approach a PMS patient?

- 1) **Listen**!
- 2) **Confirm the diagnosis** – charts if necessary

  …..NB: prior diagnosis of bipolar disorder!
- 3) **Judge intervention** according to
  - Patient wishes – consider all interventions
  - Previous treatments – treatment algorithm
  - Severity of PMS – may need to start with GnRHa if lives are at risk – please refer urgently.
- 4) **Review at 3 months** but remain available
- 5) **Don't place arbitrary limits** on treatment duration

“Evidence Free” Complementary Therapies for PMS



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 10 – 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.

Premenstrual Syndrome
Treatment - **SSRI's**

- Practical messages

Women should be warned of the possible adverse effects such as nausea, insomnia, fatigue and reduction in libido. [GPP]

When <u>discontinuing</u> treatment of SSRIs, therapy should be withdrawn gradually to avoid withdrawal symptoms if continuous

This is unnecessary if treatment is with low-dose luteal-phase dosing. [GPP]


PILL
TO END
PMT
'WHY WOULD I BE
INTERESTED IN THAT?'
MATT

PMS

10.Management with cycle modifying agents

10.1 The combined oral contraceptive pill

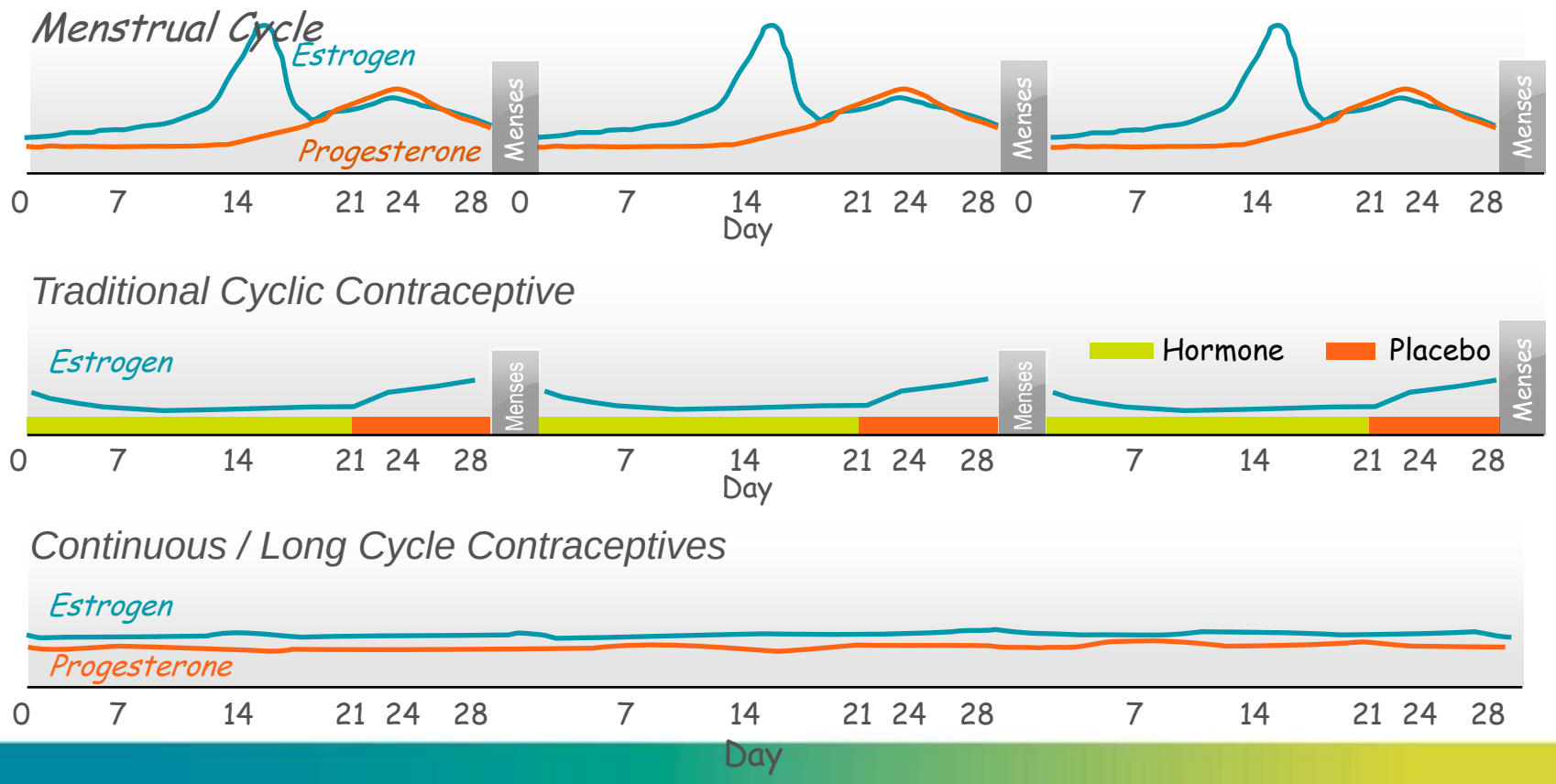
When treating women with PMS, newer contraceptive pill types may represent effective treatment for PMS and should be considered as one of the first-line pharmaceutical interventions.

10.2 Should use of combined oral contraceptive pill be continuous or cyclical?

When treating women with PMS, emerging data suggest that consideration should be given to use of the contraceptive pill continuously rather than cyclically.

Yonkers Obstet Gynecol 2005; Pearlstein Contraception 2005, Coffee Contraception 2007

Moderation of Hormonal Fluctuations



PMS

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

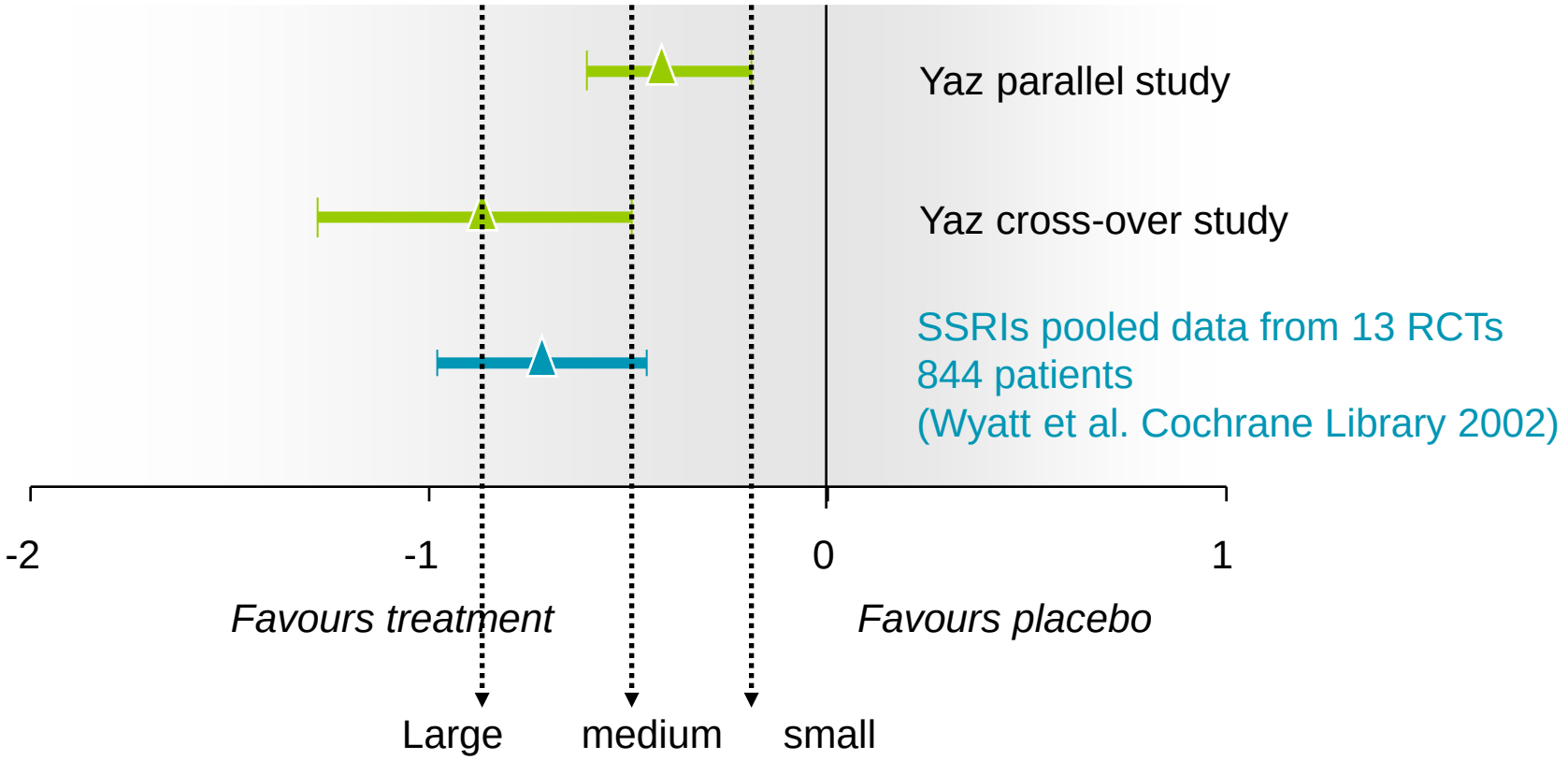
- Cochrane review of five RCTs with 1920 participants.[1]
- OCs: Drsp(3 mg)/EE v Plbo v Deso(150mcg) v Levo(150mcg)
- Drospirenone-containing OCs used for 3 months were beneficial in reducing severity of symptoms in PMDD.
  - (MD –7.92; 95% CI –11.16 to –4.67)
- **Problems with OCs in PMS: 7/7 HFI & prog. side effects**

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

Yaz vs. SSRIs in PMDD

Standardized mean difference 95% CI on overall symptoms

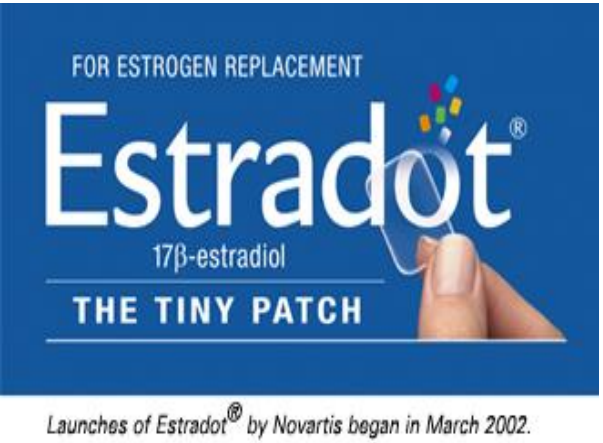
OC v SSRI for PMS –
Similar efficacy so let women decide according to preference!



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

PMS

10.Management with cycle modifying agents - HRT



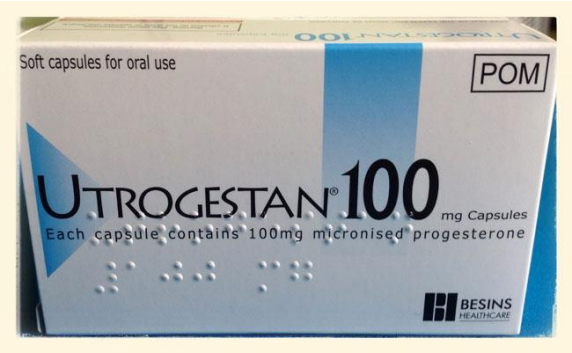
Launches of Estradot® by Novartis began in March 2002.

Estradot 75-100mcg twice weekly or..

Oestrogel 2 pumps twice daily, with

Utrogestan 100-200mg
7-12 days / cycle
pO / pV

or Mirena IUS (also contraception)



Transdermal estrogens in peri-menopausal depression

50 depressed peri-menopausal women

26 Major depressive disorder, 11 dysthymic

13 Minor depressive disease

100 µg estradiol patches in 12 week placebo controlled study

Remission of depression in 17/25 (68%) of E2 patients and in 5/25 (20%) of placebo patients

Soares et al 2001 Arch Gen Psych

Check in for a fitting!

Role of LNG IUS (Mirena®)

Rx of PMS is "off label" with or without E2

- Prog side effects / bleeding possible first 3 - 6 months
- 12mcg* system (3y) in PI women?
  - Jaydess*

Some data for use of Mirena alone – needs confirmation.[1]

1.Leminen H et al. The effect of hysterectomy or levonorgestrel-releasing intrauterine system on premenstrual symptoms in women treated for menorrhagia: secondary analysis of a randomised controlled trial. Acta Obs Gyn Scand 2012; 91: 318-25.

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 annual measurement of bone mineral density (ideally by dual energy X-ray absorptiometry). [A]**

Wyatt et al BJOG 2004

PMS
10.Management with cycle modifying agents – GnRHanalogues

- Start with nasal GnRHa if patient uncertainty re Rx
- Minimum 3 cycles to assess response
- Transdermal E2 50 / Utrogestan 100 best ccHRT
- DEXA scans baseline & annually if long term use

PMS

12.Surgical approach (Hysterectomy and BSO)

- Hysterectomy and bilateral salpingo-oophorectomy is of benefit. [C] NB: BSO alone not ideal!
- TAH BSO if on long-term GnRHa or other gynae conditions indicate surgery e.g. fibroids/bleeding. [GPP]
- Preoperative GnRH analogue test mandatory to ensure adequate efficacy / HRT is tolerated. [GPP]
- Adequate E2 +/- T essential post operatively!

Cronje et al Hum Reprod 2005

Severe PMS – 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,

PMS – Key Messages (General)

- Universal adoption of ISPMD diagnostic criteria vital to facilitate recognition and treatment of PMS (WHO-ICD 11)
- Training of Health Professionals should be addressed by Universities & Royal Colleges
- Management of severe PMS should ideally be by multidisciplinary teams with ref. to evidence based guidelines
- Best evidence thus far is for 24/4 or continuous OC, Estradiol (TD), SSRI & GnRHa.
- ?Role of Ulipristal Acetate (Esmya – promising but need data!)

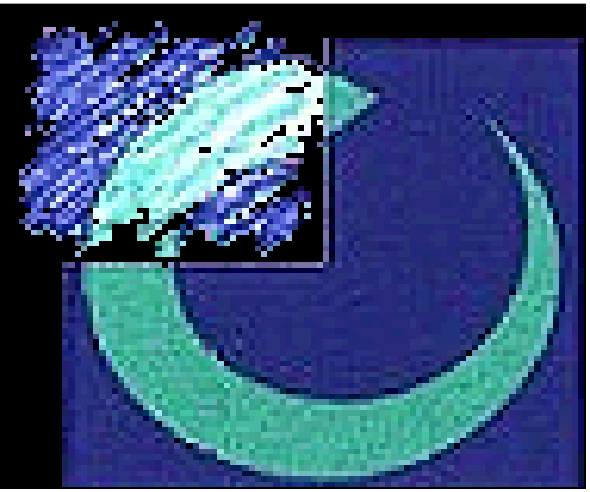
Panay N, Fenton A. Severe PMS/PMDD - is it time for a new approach? Climacteric. 2015 Jun;18(3):331-2.

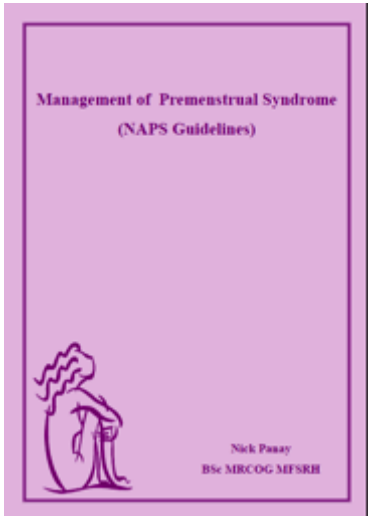
PMS – Key Messages (approach to menopause)

- PMS and VMS often coexist in perimenopause
- PMS symptoms often predict severity of VMS in perimenopause (and progestogen intolerance with HT)
- Both symptoms triggered by fluctuations in hormone levels in genetically vulnerable women
- Optimum management in perimenopause is with cycle stabilising ET + P or LNG IUS if contraception required

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

National Association for Premenstrual Syndrome **NAPS** – A Charitable Organisation for more than 30 years!





- New Website Planned www.pms.org.uk (>1000 hits per day)
- Ask the Experts
- Discussion Forum (Blog)
- PMS Guidelines
- Annual scientific meetings
- NAPS PMS awareness week

PRESS RELEASE: Overriding Messages NAPS PMS Awareness Week: Definitions 2nd – 7th October 2017

- ***If PMS symptoms affect physical, psychological, social and economic wellbeing, this should be regarded as being clinically significant PMS, warranting prompt diagnosis, appropriate recognition and evidence based medical care.***

- ***Some cases of PMS will qualify for a PMDD diagnosis, but in non-PMDD cases of severe PMS, symptoms may have an equally or even more serious impact on the sufferer.***

Thank you for listening…questions?

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