

Premenstrual Syndrome

Management Options

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Premenstrual Syndrome

History

Hippocrates - '....shivering, lassitude and heaviness of the head denotes the onset of menstruation....'

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

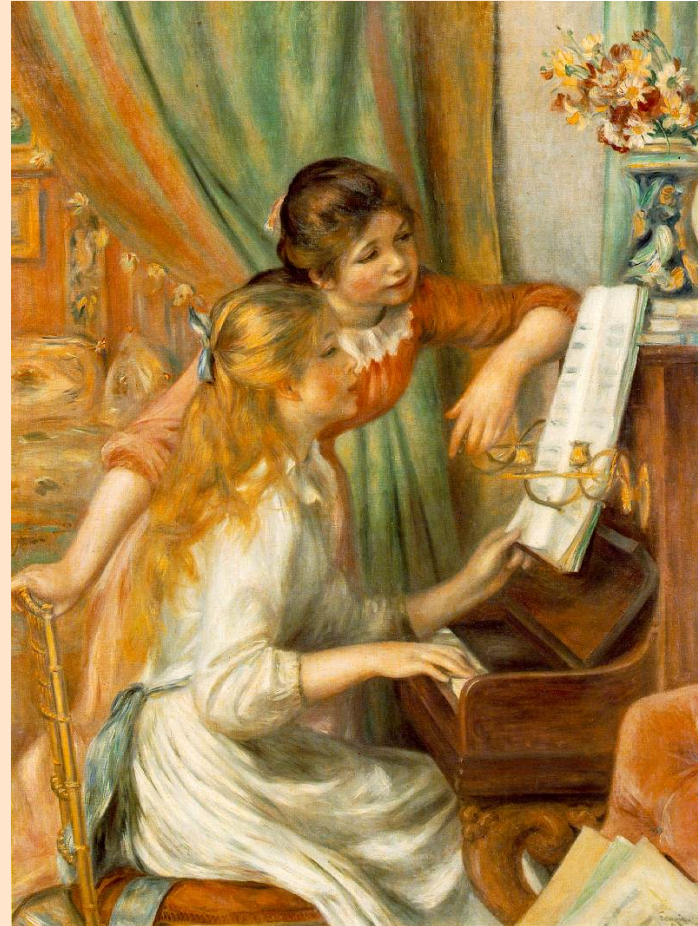
Greene & Dalton (1953) - Introduced the term "premenstrual syndrome"

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*



Maudsley

“...The monthly activity of the ovaries which marks the advent of puberty in women has a notable effect upon the mind and body; wherefore it may become an important cause of mental and physical derangement ...”

Premenstrual Syndrome

Modern Definition

Distressing physical, psychological and behavioural symptoms, not caused by organic disease, which regularly recur during the same phase of the menstrual (ovarian) cycle and which significantly regress or disappear during the remainder of the cycle

Magos & Studd (1984)

PMDD Definition

(DSM IV - Diagnostic and Statistical Manual of Mental Diseases)

(4th edn. American Psychiatric Association, 1994)

- ◆ Five or more of the following present premenstrually (one must be a core* symptom):
 - Markedly depressed mood *
 - Marked anxiety/tension*
 - Marked affective lability
 - Marked anger/irritability*
 - Decreased interest in usual activities*
 - Difficulty concentrating
 - Lethargy/fatigue
 - Appetite change/food cravings
 - Sleep disturbance
 - Feeling overwhelmed
 - Physical symptoms (e.g. breast tenderness, bloating)
- ◆ Symptoms in most menstrual cycles during the last year (retrospective confirmation) and in at least two cycles as prospective confirmation
- ◆ Occur the last week before menses and remit within a few days of onset of menses
- ◆ Marked interference with work, social activities, relationship

Premenstrual Syndrome Symptoms – Prevalence

SWS 2007 Sadler Inskip Panay (Submitted)

- ▶ >25 000 Women Surveyed
- ▶ 30% stated that PMS severely affected their quality of life (cf PMDD 3-8%)
- ▶ Positive correlation of PMS with obesity / less exercise / less qualifications
- ▶ Less PMS with increasing hormonal contraceptive use

Premenstrual Syndrome

Symptoms

Over 160 PMS related symptoms Moos (1968)

- ▶ **Physical** e.g. breast tenderness, headache, bloating
- ▶ **Psychological** e.g. mood swings, irritability, depression
- ▶ **Behavioural** e.g. lowered cognitive performance, accidents, suicide attempts

Premenstrual Syndrome Diagnosis

▶ History

- **Primary PMS:** Complete resolution of symptoms at onset of menstruation Dalton (1977)
- **Secondary PMS:** Improvement of symptoms following menstruation, even if only for a few days

Premenstrual Syndrome Diagnosis

- ▶ Validated Prospective symptom diaries
 - Confirm diagnosis more accurately than retrospective recall
 - Moos Menstrual Distress Questionnaire (MDQ/PDQ)
 - » Moos 1968, Magos/Studd 1987 (Oestradiol trials)
 - Daily Record of Severity of Problems (DRSP)
 - » Endicott & Harrison NY State Psych Inst 1990, Arch Women's Mental Health 2006 (Yaz trials)
 - Premenstrual Symptoms Screening Tool (PSST)
 - Steiner et al Arch Womens Ment Health 2003 (SSRI trials)

Premenstrual Syndrome

Proposed Pathophysiology in PMS

▶ Biological

Glucocorticoids
Androgens
Prolactin
Fluid retention
Vitamin deficiency

- A
- B6

Antidiuretic hormone
Reactive hypoglycaemia
Prostaglandins

- excess
- deficiency
- prolactin hypersensitivity

Endogenous opiate peptides

- mid luteal increase
- premenstrual withdrawal

Endogenous hormone allergy

Menstrual toxin
Magnesium deficiency

Neurotransmitters

- cholinergic
- catecholamines
- serotonin

Melatonin

▶ Psychological

▶ Social & evolutionary

▶ Genetic

Premenstrual Syndrome

Aetiology

- ▶ No convincing evidence for any of the postulated biological or psychological mechanisms
- ▶ May be multiple aetiologies (E2/serotonin, Progesterone-allopregnanolone/GABA)
- ▶ Ovarian function appears to play an essential role in the genesis of symptoms Studd (1979)

Premenstrual Syndrome

Aetiology

▶ Serotonin

- Lower platelet concentrations
- Lower luteal phase levels
- Enhanced sensitivity to progesterone
- Levels elevated by oestradiol
- SSRIs effective for PMDD

Premenstrual Syndrome

Aetiology

▶ GABA

- Major inhibitory system in CNS
- Low levels of GABA in mood disorders
- Low levels in women with PMDD during late luteal phase

Premenstrual Syndrome

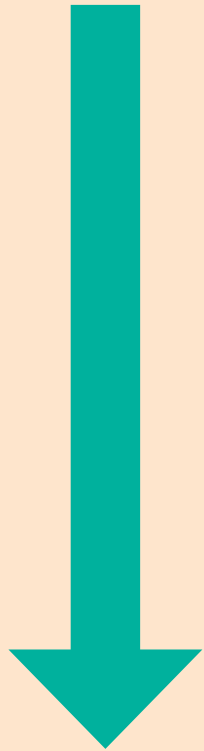
Aetiology

Rapidly changing oestradiol and progesterone levels in vulnerable women can lead to the triad of hormone responsive depressive disorders

Pisa 2006 – 6th IMS Workshop

Schmidt P – “Short arm of serotonin transporter gene affected in vulnerable women”

The triad of Oestrogen Responsive Depressive Disorders



Postnatal depression

Premenstrual depression

Climacteric depression

Premenstrual Syndrome

Proposed Treatments for PMS

► Pharmacological

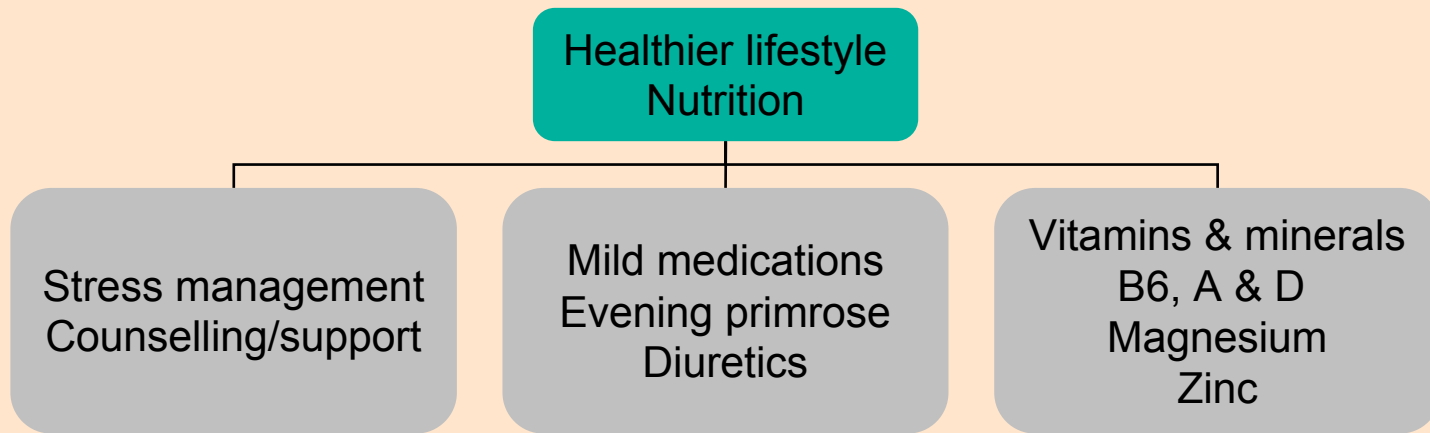
- Diuretics
- Bromocriptine
- Magnesium
- Desensitization
- GnRH analogues
- Psychoactive drugs
 - SSRI inhibitors
 - tranquillizers
 - lithium
- Prostaglandin mediators
 - PG synthetase inhibitors, g linolenic acid
- Vitamins
 - B6, A, E
- Sex hormones
 - progesterone
 - progestogens
 - combined pill
 - danazol
 - LHRH analogues
 - oestradiol implants and patches
 - androgens

► Psychological & Social Support

► Miscellaneous

- Physical Activity
- Diet
- Hypnosis
- Meditation
- Yoga
- Acupuncture
- Bilateral oophorectomy
- Radiation menopause

Management of Mild / Moderate PMS



Vitex Agnus Castus

Chaste Tree berry

- Progesterone type effects
?opiod effect

BMJ 2001

- Schellenberg et al
- RCT study
- Agnus castus v placebo
- $P < 0.001$ active group



Calcium & Vit D

Bertone-Johnson et al. Ca and Vit D Intake & Risk of Premenstrual Syndrome Arch Intern Med. 2005

The intake of calcium from food sources was inversely related to PMS

Participants with the highest intake (median, 1283 mg/d) had a relative risk of 0.70

- (95% confidence interval, 0.50-0.97)

New developments in complementary therapies for PMS

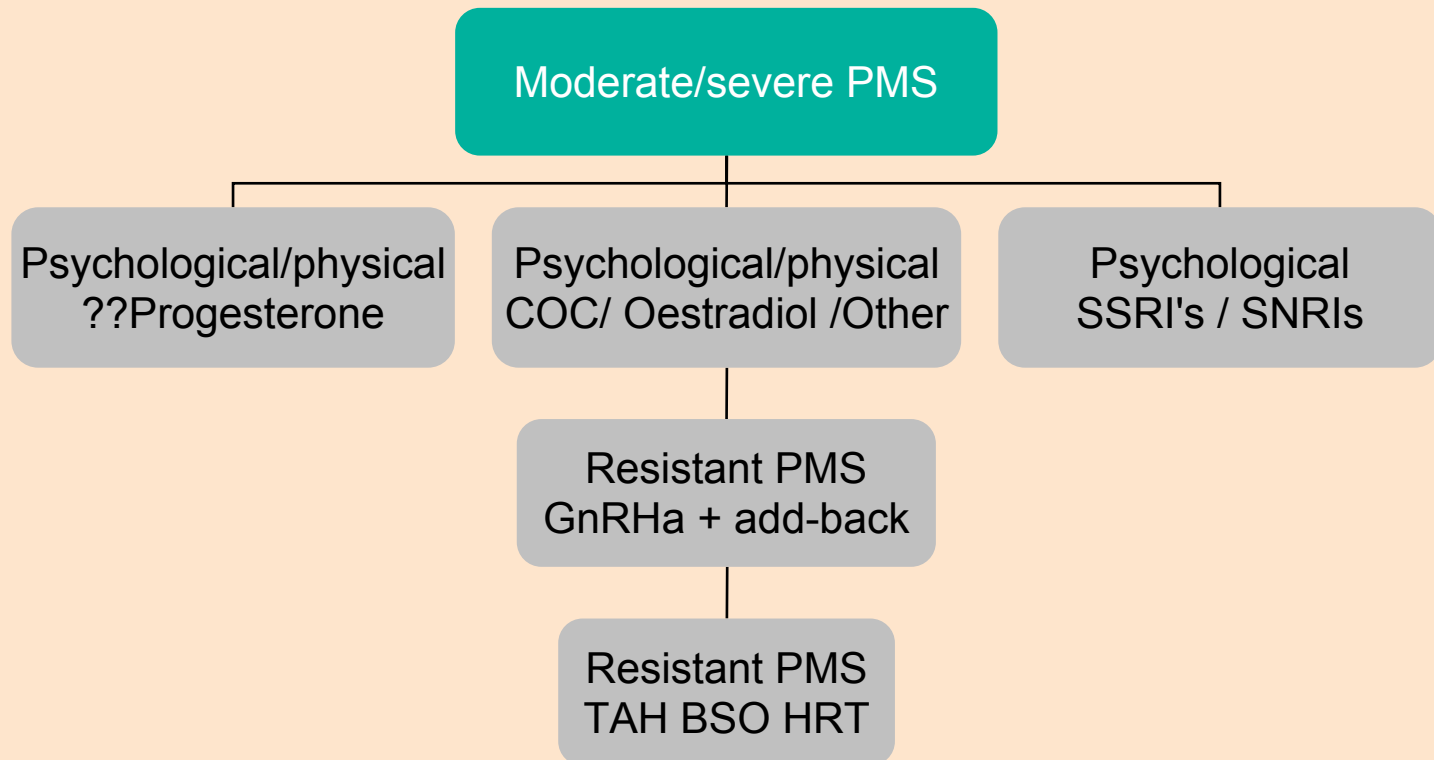
Prospective RCTs:

Vit D & Calcium supplementation (Nigel Denby & BBC) – approx 30% improvement

Static magnet therapy for dysmenorrhoea and PMS symptoms (Adroit)

Red clover isoflavones (Novogen)

Moderate / Severe PMS



Premenstrual Syndrome

Progesterone – Causative or Therapeutic?

- ▶ Magill et al Br J Gen Pract 1995
- ▶ Cyclogest pessaries, 400mg bd for 14/7 in 93 patients (141 randomised)
- ▶ Significant improvement in both physical & psychological PMS symptoms V placebo
- ▶ Not supported by O'Brien RCT meta-analysis data but...
 - 4 progesterone and 10 progestogen studies

Premenstrual Syndrome

Treatment - Ovulation Suppression Agents

- ▶ COC / POP / progestogens
- ▶ Levonorgestrel intrauterine system
- ▶ Depot progestogens / Implanon[®] / Cerazette[®]
- ▶ Danazol
- ▶ Oestradiol implants / patches
- ▶ GnRH analogues +/- add-back HRT

Premenstrual Syndrome Treatment - Ovulation Suppression Agents

COCP

- ▶ Graham & Sherwin (1992) J Psych Res
- ▶ Little benefit with COCP despite ovulation suppression.
 - *progestogenic PMS-like side effect & pill free week*
- ▶ Rapkin (2003) Psychoneuroendocrinol
 - *anti-androgenic, anti-mineralocorticoid progestogen, drospirinone – Yasmin COCP showing promise*



Premenstrual Syndrome Treatment – Yaz®

- ▶ Yonkers K. (Yale) et al Obstet Gynecol 2005
- ▶ EE 20mcg / Drospirenone 3mg, 24 active/4 inactive
- ▶ RCT 2 month run in 3 treatment cycles in 450 women PMDD
- ▶ Response (50% reduction in daily symptoms): 48% active v 36% placebo p = 0.015

Premenstrual Syndrome Treatment – Yaz[®]

- ▶ Pearlstein T. (Rhode Island) et al Obstet Gynecol 2005
- ▶ RCT 2/12 run in, 6 treatment cycles with crossover at 3 months
- ▶ 511 women screened – only 25 completed study!!
- ▶ Symptom Scores (DRSP) -12.5 (active) v -6.5 (placebo) (P<0.001)

Premenstrual Syndrome

Treatment - Ovulation Suppression Agents

COCP

Take home messages

1) Use bicycling/tricycling or long cycle regimens

2) Extended cycle regimens on the way

Premenstrual Syndrome Treatment - Progestogens

- ▶ AVOID! “Model for premenstrual syndrome”
 - Magos & Studd BJOG (1986)
 - Wyatt et al BMJ Meta analysis (2001)

- ▶ POP
 - Replaces cyclical with continuous progestogenic SE's
 - Especially androgenic POP's

Role of LNG IUS (Mirena®) in PMS



- ▶ Small benefit shown in some studies
- ▶ Progestogenic side effects
 - *Physical*
 - *Psychological*
- ▶ SE's usually in 1st 3 months
 - *LNG IUS Working Group (inc. Panay N) JFPRH 2007)*

Premenstrual Syndrome

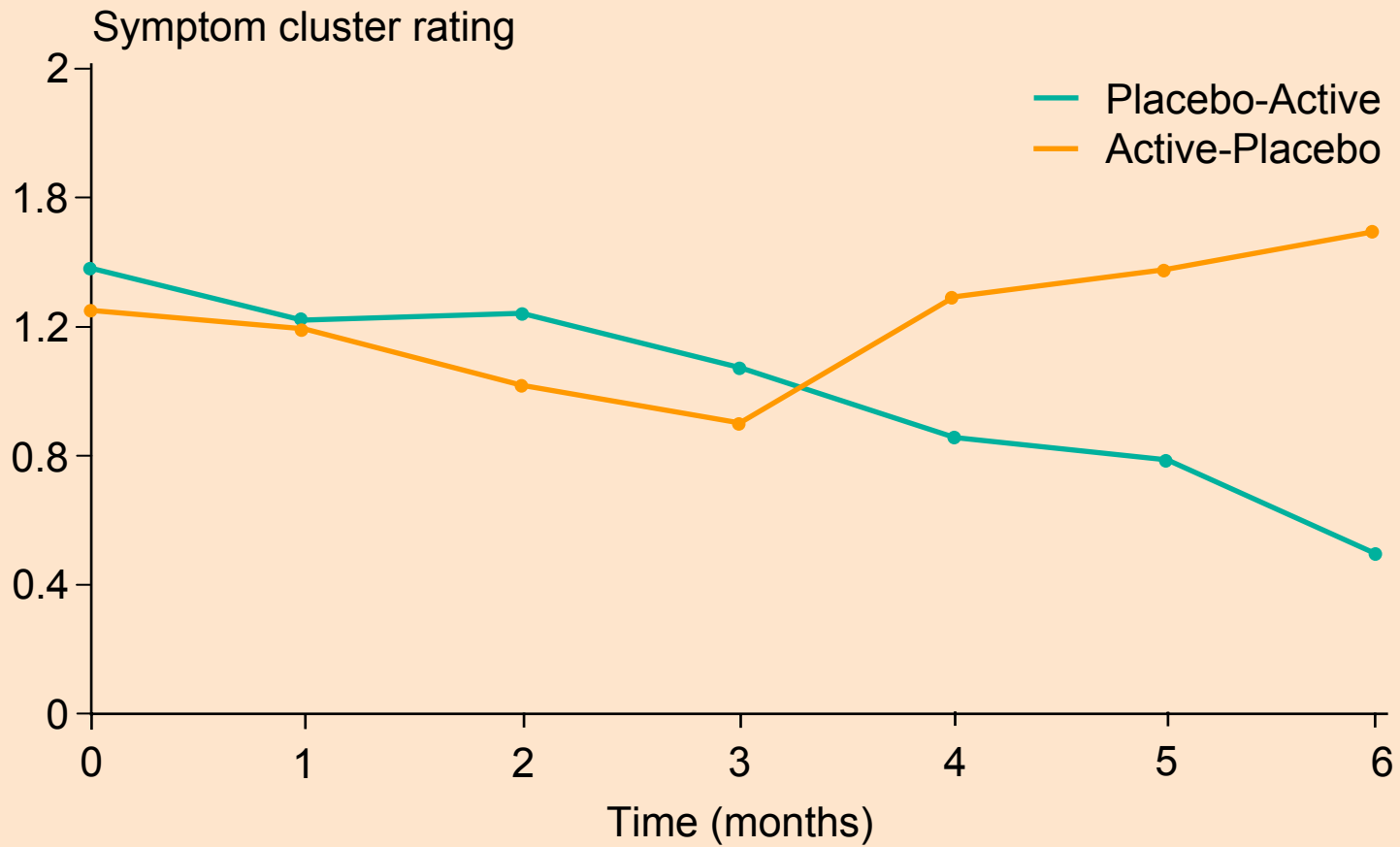
Treatment - Ovulation Suppression Agents

- ▶ Depo Provera / Implanon[®] / Cerazette[®]
 - Some report improvement in PMS due to ovulation suppression.
 - Those with continuing cycle may have background in addition to cyclical PMS
 - PMS SE's less common with Implanon[®] (acne reported)

Premenstrual Syndrome Treatment - Oestradiol Patches

- ▶ 40 patients with PMS confirmed by PDQ and MDQ
- ▶ Randomised double blind placebo controlled with 3 month cross-over
 - Active treatment: 200mcg patches + Oral NET D19-26
 - Placebo treatment: Placebo patches + Oral NET D19-26
 - Gp1: Active treatment -> Placebo
 - Gp2: Placebo -> Active treatment

Mood Swings



Oestrogen Therapy

- ▶ 100µg patches tried subsequently
 - As effective
 - Fewer symptoms of breast discomfort and bloating
 - Less anxiety about high dose oestrogen therapy

Is 100 µg – or 200 µg- Oestradiol Patch Anovulatory?

Important information for young women who need treatment for PMS and contraception.

But totally unproven - so don't risk it!!

Randomised, Prospective, Placebo Controlled, Multicentre Study of Women with Severe PMS, Treated with 100 µg Transdermal Oestradiol (2006)

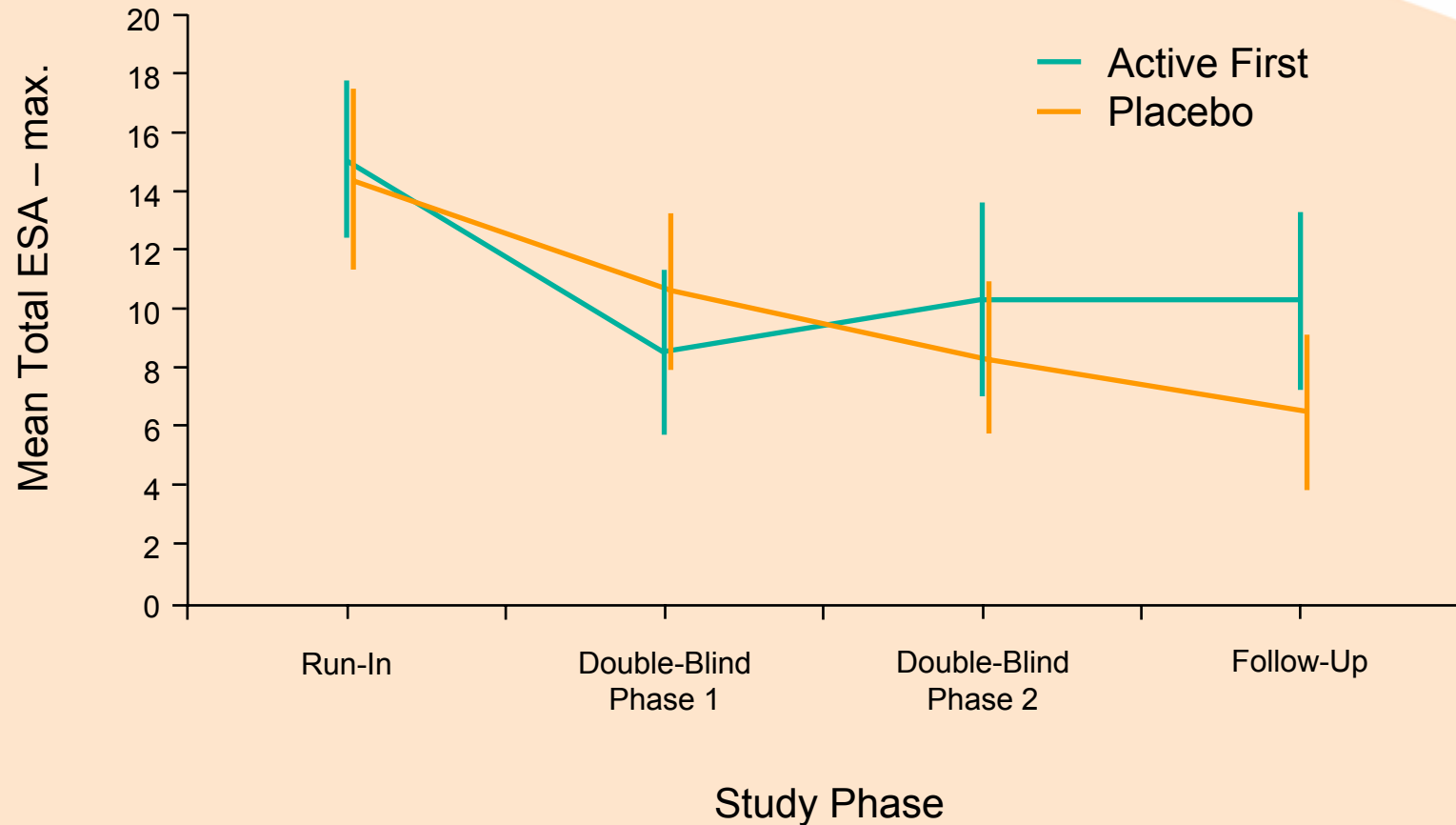
Panay N*, Rees M**, Domoney C*, Zakaria F*,
Guilford S***, Studd JWW*

*Chelsea & Westminster Hospital

**John Radcliffe Hospital, Oxford

***Janssen Cilag, Saunderton, Bucks

Randomised, Prospective, Placebo Controlled, Multicentre Study of women with Severe PMS, treated with 100 µg Transdermal Oestradiol (2006)



Premenstrual Syndrome

Treatment - SSRI's

- ▶ PMDD (premenstrual dysphoric disorder)
 - Premenstrual depression partly due to serotonin deficiency
 - SSRI's increase serotonin levels
 - Fluoxetine was licensed in UK for Rx of PMDD
 - not renewed by company

Premenstrual Syndrome Treatment - SSRI's

- ▶ Steiner M. et al 1995 NEJM
 - Fluoxetine in treatment of premenstrual dysphoria
 - 405 women in 2 month placebo washout phase
 - 313 women randomised to fluoxetine 20mg, 60mg or placebo
 - Both doses significantly superior to placebo in reducing tension & irritability by VAS

Premenstrual Syndrome Treatment - SSRI's

- ▶ Luteal phase fluoxetine as effective with fewer side-effects

Dimmock et al Lancet 2000

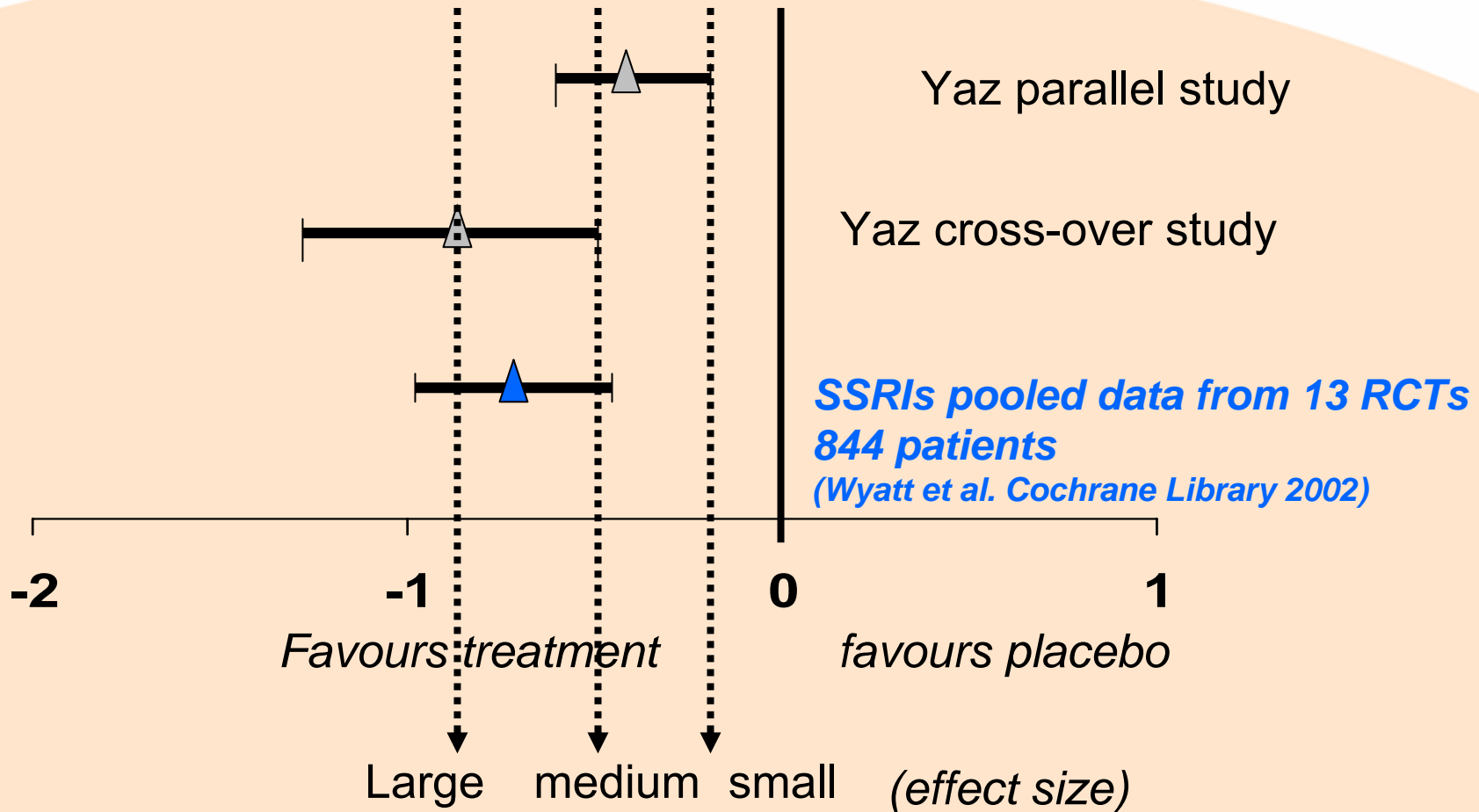
Efficacy of selective serotonin-reuptake inhibitors in premenstrual syndrome: a systematic review.

- ▶ **Take home tip:**
Mildest SSRI therapy

*Citalopram 10 – 20mg luteal phase
(D15 – D28)*

Effect size of Yaz vs. SSRIs in PMDD

Standardized mean difference 95% CI
on overall symptoms

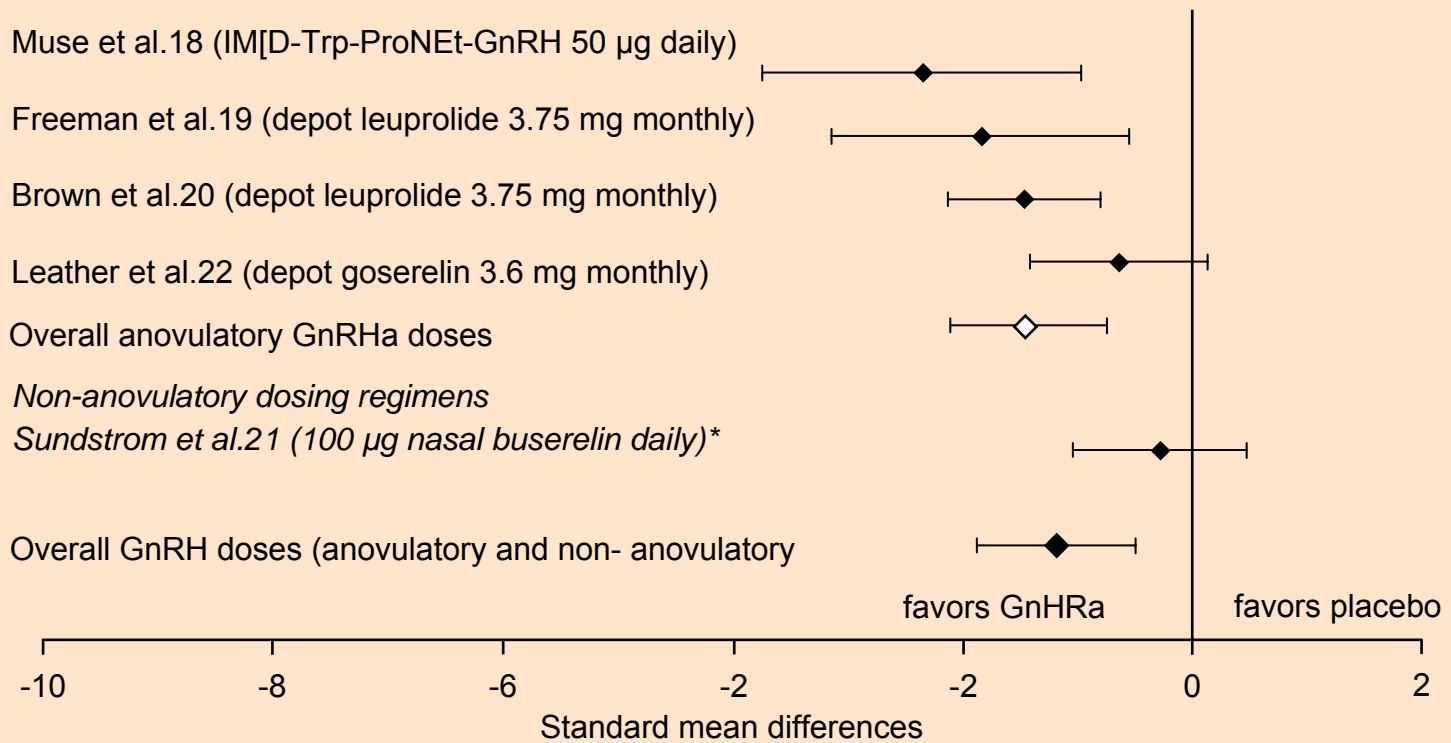


Premenstrual Syndrome

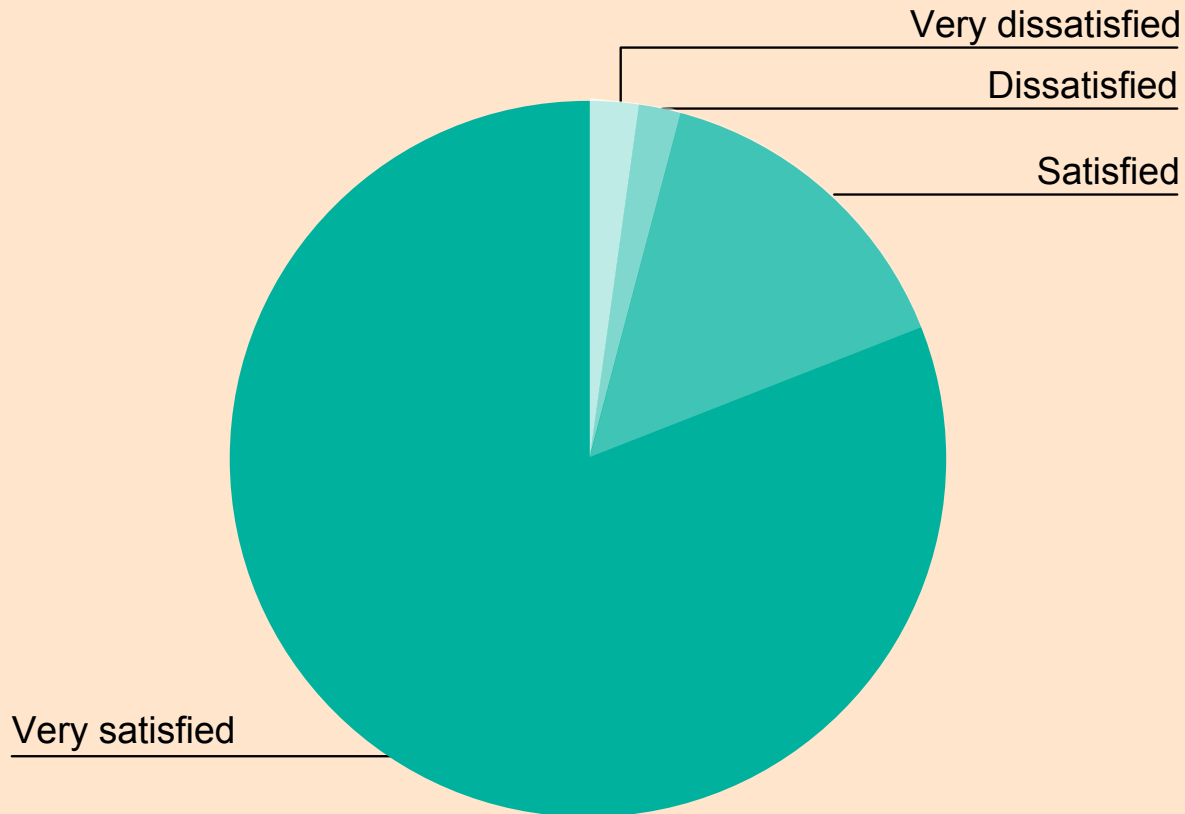
Treatment - GnRH Analogues

- ▶ Very effective for PMS - also diagnostic
- ▶ Unsuitable for long term use alone
- ▶ HRT add back to prevent menopausal symptoms and bone loss

Meta Analysis of RCTs (GnRHa vs placebo)



Total Abdominal Hysterectomy and Bilateral Salpingo-Oophorectomy for Premenstrual Syndrome Cronje Studd 2002



Premenstrual Syndrome: Pathophysiology, Definition of the Disease and Treatment Options

Summary

- ▶ Prevalence of severe PMS/PMDD 10 – 30%
- ▶ E2/serotonin and Prog/GABA most plausible aetiologies in genetically vulnerable women
- ▶ Confirmation of severe PMS/PMDD by validated rating scales essential

Premenstrual Syndrome: Pathophysiology, Definition of the Disease and Treatment Options

Summary

- ▶ Training of Health Professionals of paramount importance to aid recognition of condition
- ▶ Management ideally should be by multidisciplinary teams
- ▶ Moderate/severe PMS usually needs medical intervention - sooner rather than later to avoid unnecessary suffering

Premenstrual Syndrome

Future Aims

- ▶ Confirmation of benefits of new COCPs/ long cycle COCPs
- ▶ Licensing of
 - Yaz[®] for PMS/PMDD
 - Long Cycle COCPs
 - Transdermal oestradiol
 - GnRHa + add-back for severe PMS

Premenstrual Syndrome

Future Aims

- ▶ Training of GPs in women's health
 - ?funding from PCT's / PBC
- ▶ "Evidence based treatment options for PMS"
 - Panay N RCOG Green Top Guidelines 2007
 - www.rcog.org.uk

National Association for Premenstrual Syndrome – NAPS A Registered Charity



Website www.pms.org.uk

(>10000 hits per day)

Help-line

Monthly e Newsletter (Once a Month)

Annual scientific meetings

Policy planning for PMS

Liaison with media

PMS Database

Thank you for your attention!

*British Menopause Society Meeting
Bournemouth June 28th – 29th 2007*