BJPsych The British Journal of Psychiatry (2013)
202, 9–13. doi: 10.1192/bjp.bp.111.102855

Reappraisal

Should psychiatrists be prescribing oestrogen therapy to their female patients?

Michael C. Craig

Summary
Some studies have indicated that oestrogen therapy may be beneficial in the treatment of a number of neuropsychiatric disorders. However, it has been suggested that psychiatrists fail to prescribe oestrogen therapy to their patients, as they are 'not aware of' or 'do not believe' studies supporting their use. This paper reappraises the putative role of hormone treatments, particularly oestrogen therapy, in psychiatry.

Declaration of interest
M.C.C. is the clinical lead of the Female Hormone Clinic, Maudsley Hospital, London. This is part of the NHS National Services Directory that accepts NHS and private referrals for the assessment and treatment of women with mental health problems at times of hormonal fluctuation.

There are gender differences in the incidence of a variety of neuropsychiatric disorders. For example, males are at increased risk of neurodevelopmental disorders (e.g. autism, attention-deficit hyperactivity disorder) and alcohol dependence, whereas females are at increased risk for developing Alzheimer's disease, anxiety disorder and depression. The biological basis for these gender differences is still poorly understood but probably involves a complex interaction between genes, the environment and sex hormones on the brain. It has been reported that a subgroup of women are at especially high risk for developing depressive symptoms at times of sex hormone fluctuation.[1–4] Some clinicians have proposed that individuals in this group have a discreet nosological entity, sometimes referred to as reproductive depression.[5] It has also been suggested that these women are particularly responsive to oestrogen therapy and that it should be offered as a first-line treatment in this group.[6] Further, other neuropsychiatric disorders, including Alzheimer's disease[7] and schizophrenia,[8] have also been reported to be responsive to oestrogen therapy. It has recently been suggested that psychiatrists fail to prescribe oestrogen therapy to these women as they are 'not aware of' or 'do not believe' studies supporting their use.[6] This paper therefore reappraises the putative role of hormone treatments, particularly oestrogen therapy, in psychiatry, focusing on women with reproductive depression.

Does reproductive depression exist?

Family[9] and twin studies[10–12] have reported that the heritability of premenstrual dysphoric disorder (PMDD) is over 50%,[13] and that PMDD is associated with significant differences in single nucleotide polymorphisms modulating the alpha oestrogen receptor.[14] Likewise, unipolar, non-psychotic depression has a heritability of 40%[15] and a significant familial aggregation (especially when narrowly defined as developing within 6–8 weeks postpartum).[16] Iatrogenic induction of acute hormonal fluctuation has also been reported to trigger a recurrence of symptoms in vulnerable women. For example, following ovarian suppression (i.e. with a gonadotropin-releasing hormone analogue) and subsequent treatment with high doses of oestrogen and progesterone, women with a history of postnatal depression had a recurrence of depressive symptoms post acute sex hormone withdrawal (i.e. modelling postnatal hormonal changes).[1] Importantly, these mood changes were not found in women without a history of postnatal depression, suggesting that acute hormonal fluctuation may only trigger depressive symptoms in a specific subgroup of women. This study was, however, small and needs to be replicated. Despite the purported risk of depression in some women, early controlled studies reported that the incidence of depression did not increase in the postpartum period.[17–20] Also, many studies included women that did not have postpartum onset of depression. However, after controlling for relevant risk factors and comparing with appropriate control groups, the incidence for unipolar depressive episodes has been reported to double[21] and the rate of in-patient admissions to triple[22] postpartum. Further support for the concept of reproductive depression is derived from the observation in some studies that women with vulnerability to depressed mood associated with one period of hormonal fluctuation (e.g. PMDD) are particularly vulnerable to depression at other times of hormonal fluctuation (e.g. postnatal and perimenopausal depression).[1–4] Also, two of these studies suggest that it is the same women that experience all three conditions,[3,4] but these findings need to be confirmed by larger studies.

Types of oestrogen

In women there are three major naturally occurring oestrogens: oestrone (E_1), oestradiol (E_2 or 17β-oestradiol) and oestriol (E_3). Oestrogen therapy prescribed to postmenopausal women provides low dosages of one or more oestrogens. In the past, the most commonly prescribed form of oral oestrogen therapy was a compound containing conjugated equine oestrogens, predominantly E_1. Prior to being absorbed, oral oestrogens pass through the liver where, in addition to a large proportion being metabolised, it activates blood coagulation and increases the risk of venous thromboembolism. This can be avoided by prescribing oestrogen via methods of administration that enter the blood-stream directly (e.g. implants, patches, creams, vaginal rings, gels). Currently, the most common method is via transdermal E_2/17β-oestradiol skin patches. High-dose E_2/17β-oestradiol is also used in the combined oral contraceptive pill. However, in order to make it more resistant to de-activation in the liver, an ethinyl group is substituted at C_{17}, leading to the production of ethinylestradiol.

Should oestrogen therapy be prescribed in women with reproductive depression?

Postnatal unipolar depression

Research into the effects of oestrogen therapy in postpartum unipolar depression remains limited. An open-label study of 17β-oestradiol treatment in women with postnatal depression reported a significant sustained reduction in depressive symptoms, measured using the Montgomery–Åsberg Rating Scale, over an 8-week period.[23] Furthermore, a randomised controlled trial (RCT) of 61 women with postpartum depression reported a significantly larger reduction in Edinburgh Postnatal Depression Scale scores when randomised to oestrogen therapy compared with placebo, at 3 and 6 months.[24] Women allocated to oestrogen therapy received 17β-oestradiol skin patches for 6 months (plus additional dydrogesterone tablets for 12 days each month) and those in the placebo group received non-hormonal patches and tablets.

In summary, there is preliminary support for the use of oestrogen therapy to treat postpartum depression but there is still insufficient evidence available to justify the widespread use of hormone treatment for postnatal depression in clinical practice.[25] More definitive recommendations may, however, be available following analysis of a phase II RCT of 17β-oestradiol treatment (*v.* sertraline and placebo) at the National Institute of Mental Health, USA (trial registration: NCT00059228).

Peri- and postmenopausal depression

Oestrogen therapy has been reported to be associated with improvement in psychological 'well-being' in postmenopausal women without depression.[26,27] However, this improvement has been reported to be no greater than placebo after 4 months.[27,28] In women with clear depressive symptoms, studies have reported mixed results. Several studies of oestrogen therapy have failed to demonstrate superiority over placebo in menopausal women with depression.[29–32] However, these studies included longer-term postmenopausal women and the benefits of oestrogen therapy may be limited to perimenopausal women. This is supported by a 4-week pilot study of 22 menopausal women with depression, which reported improvement in mood in 6/10 perimenopausal but only 2/12 postmenopausal women with 17β-oestradiol (100 µg/day) therapy.[33] Also, a 6-week RCT of 34 women with perimenopausal depression (major and minor) reported that 17β-oestradiol (50 µg) was associated with a significant improvement in mood compared with placebo.[34] These findings were replicated in a 12-week double-blind RCT of 17β-oestradiol (100 µg) in 50 women with perimenopausal depression (major/minor) or dysthymic disorder.[35] These results were still significant at the 4-week follow-up, but it remains unclear whether improvements extended beyond this time. Larger clinical trials, with longer treatment follow-up, are still needed before recommending widespread clinical use of oestrogen therapy in this patient population.

What about premenstrual syndrome/dysphoric disorder?

Premenstrual syndrome (PMS) has been defined as:

> 'a condition which manifests with distressing physical, behavioural and psychological symptoms, in the absence of organic or underlying psychiatric disease, which regularly recurs during the luteal phase of each menstrual (ovarian) cycle and which disappears or significantly regresses by the end of menstruation'.[36]

In DSM-IV, women with severe dysphoric symptoms may also fulfil criteria for PMDD, where it is classified as a 'depressive disorder not otherwise specified'.[37] The main difference between PMDD and major depressive disorder is that the affective symptoms associated with PMDD are cyclical and subside with onset of menses.

Until relatively recently the predominant theory to explain the biological basis for dysphoric symptoms associated with PMS was the 'ovarian hormone hypothesis'.[38] This proposed that the symptoms of premenstrual dysphoria were caused by an imbalance in the ratio of oestrogen to progesterone, with a relative deficiency in progesterone.[39,40] Despite an absence of evidence to support this theory,[41] it became widely accepted and led to progestogens and progesterone becoming the most commonly prescribed treatment for PMS from 1993 to 1998 in the UK.[42] However, a meta-analysis of all RCTs from 1966 to 2000[42] reported that, although there was a *statistically* significant improvement for women taking progesterone or progestogens compared with placebo, this was *clinically* insignificant. This publication contributed to the more recent decline in prescription of progestogens and progesterone in the UK and the Royal College of Obstetricians and Gynaecologists have confirmed that there is 'insufficient evidence to recommend the routine use of progesterone or progestogens for women with PMS'.[43]

Although the Royal College of Obstetricians and Gynaecologists still supports the use of hormonal treatments for PMS/PMDD, these treatments are based on the simple principle that premenstrual symptoms may be eliminated by ovulation suppression.[43] This principle was, perhaps surprisingly, poorly supported by early RCTs using the combined oral contraceptive pill. However, this may have been due to intolerance to the type of progesterone (i.e. levonorgestrel or norethisterone) contained in second-generation contraceptive pills studied.[44] More recent observational and small randomised trials have suggested that a third-generation contraceptive pill may be effective in some women with PMS[45] (particularly when prescribed continuously, with fewer pill-free breaks[46]). This pill contains a progesterone with anti-mineralocorticoid and low androgenic properties (i.e. drospirenone). Further, a lower-dose version may be even more effective,[47] but it is still not licensed for use in the UK.

Other methods for ovulation suppression recommended for women with severe PMS/PMDD include the use of percutaneous oestradiol, either as an implant or as a patch. This requires the addition of cyclical progestogen (10–12 days) or a levonorgestrel intrauterine system, to avoid endometrial hyperplasia in women who have a uterus. Ovulation suppression can be achieved by the unlicensed use of gonadotropin-releasing analogues (with oestrogen add-back) or, as a last resort, hysterectomy with bilateral salpingo-oophorectomy.

The clear association between PMS and the cyclical fluctuation in ovarian sex hormones has contributed to the virtual absence of mental health professionals being involved in treating the depressive symptoms associated with this disorder in the UK. Instead, patients are predominantly managed by their general practitioner or, in more severe cases, by a gynaecologist. However, mental health professionals should perhaps be taking a more active role in treating women with PMS/PMDD in the UK. This argument is supported by the robust finding that selective serotonin (and noradrenaline) reuptake inhibitors (SSRI/SNRIs) significantly improve symptoms in 60–90%[48] of women with PMS/PMDD. Also, a recent RCT reported that although SSRIs significantly improved PMDD symptoms, 10 sessions of cognitive–behavioural therapy (CBT) was associated with an even better outcome at 1-year follow-up.[49] However, the study needs replicating as the sample size was small and the drop-out rate was high. Although mental health professionals are more likely to be able to identify women with the capacity to engage and

https://doi.org/10.1192/bjp.bp.111.102855 Published online by Cambridge University Press

benefit from CBT, they are still rarely involved in guiding such decisions or providing treatment to this group of women in the UK.

Should oestrogen therapy be used in women with postnatal bipolar episodes/psychosis?

It has been estimated that women with bipolar disorder have a greater than one in four risk of relapse during the postpartum period,[50] with most episodes occurring within the first 2 weeks.[51] This risk doubles in women with a history of severe postpartum psychosis or in women with bipolar disorder and a family history of postpartum psychosis.[50,52] Familial (probably genetic) factors have been implicated in this postpartum susceptibility[50] and linkage studies have reported the location of possible susceptibility genes.[53]

To date there have been three open-label pilot studies into the efficacy of oestrogen therapy in the prevention or treatment of postpartum psychosis. In the first preventive study, only one out of seven women with histories of puerperal psychosis experienced a postpartum psychotic episode after treatment with a reducing regime of oestrogen following a subsequent birth (intravenous oestradiol for 2 days, then oral premarin 5 mg twice daily to 0.625 mg daily over 26 days).[54] Further, partial non-adherence was reported in one woman who had a relapse. In a subsequent treatment study of ten women with postpartum psychosis, a significant reduction of symptoms was reported following sublingual oestrogen therapy (1 mg three to six times daily).[55] Also, psychiatric symptoms resumed within 1 week in one patient who discontinued the treatment. However, the largest preventive study to date reported no significant reduction in the postpartum relapse rate in an open trial of transdermal 17β-oestradiol in 29 women with a history of postpartum affective psychotic episodes. Although women who had been prescribed the highest dose of oestradiol (800 µg/day) required less antipsychotic medication, and were discharged sooner than women prescribed lower doses, it was concluded that the use of prophylactic oestrogen therapy in such circumstances is 'highly questionable'.[56] In summary, wider prescribing of oestrogen therapy to women with postpartum psychosis cannot be supported at the present time.

Is there a role for oestrogen therapy in the treatment of schizophrenia?

Women with schizophrenia have been reported to have a later onset and require less antipsychotic medication than men. However, they also have an increased vulnerability to relapse around the time of menopause and postpartum.[57] It has been suggested that these factors are modulated by oestrogen and that women are protected from psychotic illness when oestrogen levels are high. This hypothesis was supported by several preliminary studies into the therapeutic effects of oestrogen therapy in schizophrenia. However, a meta-analysis of four RCTs ($n = 108$) published up to 2003 concluded that, overall, oestrogen therapy did not have a significant beneficial effect as a sole treatment or adjunctive therapy. Further, those studies that reported a positive effect were too weak to draw any firm conclusions, highlighting the need for larger RCTs.[58] A subsequent 28-day RCT in 100 women with acute psychosis reported that 100 µg of transdermal 17β-oestradiol significantly reduced positive and general psychopathological symptoms compared with women receiving antipsychotic medication alone.[8] Although it was concluded that these results were 'promising', the absence of follow-up beyond 28 days prohibits support for wider change in current prescribing practice in this patient population.

Is there a role for oestrogen therapy in the treatment of Alzheimer's disease?

Early studies reported that oestrogen therapy improved cognitive function in postmenopausal women with Alzheimer's disease. However, interpretation of these findings was limited by the absence of standardised diagnostic criteria for Alzheimer's disease, small sample size, brief follow-up and poor study design. A meta-analysis of seven double-blind RCTs (n=351) reported that, although oestrogen therapy was associated with a statistically significant improvement in verbal episodic memory and Mini-Mental State Examination scores at 2 months, these effects were not evident at 3 months (or longer) and are probably not clinically significant.[59] Therefore, current evidence suggests that oestrogen therapy does not have a significant beneficial effect in treating Alzheimer's disease.

Our current understanding of the role of oestrogen therapy in preventing Alzheimer's disease remains less clear but can be summarised as follows: oestrogen therapy prescribed to older women may have a neutral or negative effect, particularly if it is combined with a progestagen.[60] However, oestrogen therapy prescribed at a 'critical period' around the time of menopause (particularly postsurgical menopause in younger premenopausal women) may reduce the risk of Alzheimer's disease in later life.[7] However, further studies are currently needed to test the 'critical period' hypothesis further and widespread prescription of oestrogen therapy cannot be supported based on current evidence.

Conclusions

Studies to date suggest that:

(a) PMDD responds positively to the prescription of certain agents that suppress ovulation (e.g. oestrogen therapy);

(b) there is preliminary support for the use of oestrogen therapy to treat postpartum and peri- (not post-) menopausal depression, but the definitive work has not yet been completed and oestrogen therapy cannot be recommended as a first-line treatment;

(c) there is limited support for the prescription of E_2, in conjunction with antipsychotic medication, to treat women with postnatal psychosis or schizophrenia, but the current evidence does not support a wider change in current prescribing practice;

(d) oestrogen therapy prescribed at a 'critical period' around the time of menopause (particularly postsurgical menopause in younger premenopausal women) may reduce the risk of Alzheimer's disease in later life but current evidence suggests that oestrogen therapy does not have a significant beneficial effect in treating Alzheimer's disease.

In those situations where it is considered appropriate to prescribe oestrogen therapy, it is important for physicians to be familiar with specific side-effects and risks associated with this form of therapy in different patient populations.[61] It has been suggested that 'coping' with the minor problems of hormone therapy, such as irregular bleeding or breast discomfort, 'will be outside the experience and training of psychiatrists'.[6] Although this may be accurate in many cases, this could be overcome locally via liaison with gynaecology colleagues or, in more complex

https://doi.org/10.1192/bjp.bp.111.102855 Published online by Cambridge University Press

cases, by referral to a tertiary referral service (e.g. www.national.slam.nhs.uk/services/adult-services/femalehormoneclinic/).

In addition to the need for larger RCTs, further research is also required to help understand the biological basis of oestrogen therapy in neuropsychiatric disorders in women. Preliminary brain imaging studies in women with a vulnerability to reproductive depression have, for example, reported differences in limbic brain function (e.g. within the amygdala and orbitofrontal cortex). However, it is unknown whether these findings are specific to women vulnerable to reproductive depression (i.e. as opposed to other forms of depression), and/or how sex hormones differentially modulate brain function (e.g. whether this involves differential modulation of neurochemical systems[62]).

Despite the significant health burden there remains a paucity of industrial or government support for psychiatric research into women's mental health. It is hoped that this reappraisal will contribute to a renewed interest in this area and stimulate further research.

Michael C. Craig, MRCOG, MRCPsych, PhD, Department of Forensic and Neurodevelopmental Sciences, Institute of Psychiatry, Kings College London, 16 De Crespigny Park, London SE5 8AF, UK. Email: michael.c.craig@kcl.ac.uk

First received 13 Sep 2011, final revision 18 Jun 2012, accepted 23 Jul 2012

References

1 Bloch M, Schmidt PJ, Danaceau M, Murphy J, Nieman L, Rubinow DR. Effects of gonadal steroids in women with a history of postpartum depression. *Am J Psychiatry* 2000; **157**: 924–30.

2 Rubinow DR, Schmidt PJ, Roca CA. Estrogen-serotonin interactions: implications for affective regulation. *Biol Psychiatry* 1998; **44**: 839–50.

3 Payne JL, Roy PS, Murphy-Eberenz K, Weismann MM, Swartz KL, McInnis MG, et al. Reproductive cycle-associated mood symptoms in women with major depression and bipolar disorder. *J Affect Disord* 2007; **99**: 221–9.

4 Stewart DE, Boydell KM. Psychologic distress during menopause: associations across the reproductive life cycle. *Int J Psychiatry Med* 1993; **23**: 157–62.

5 Payne JL, Palmer JT, Joffe H. A reproductive subtype of depression: conceptualizing models and moving toward etiology. *Harv Rev Psychiatry* 2009; **17**: 72–86.

6 Studd JW. A guide to the treatment of depression in women by estrogens. *Climacteric* 2011; **14**: 637–42.

7 Craig MC, Murphy DG. Estrogen therapy and Alzheimer's dementia. *Ann N Y Acad Sci* 2010; **1205**: 245–53.

8 Kulkarni J, de Castella A, Fitzgerald PB, Gurvich CT, Bailey M, Bartholomeusz C, et al. Estrogen in severe mental illness: a potential new treatment approach. *Arch Gen Psychiatry* 2008; **65**: 955–60.

9 Widholm O, Kantero RL. A statistical analysis of the menstrual patterns of 8,000 Finnish girls and their mothers. *Acta Obstet Gynecol Scand* 1971; **14** (suppl 14): 1–36.

10 Dalton K, Dalton ME, Guthrie K. Incidence of the premenstrual syndrome in twins. *BMJ (Clin Res Ed)* 1987; **295**: 1027–8.

11 Kendler KS, Silberg JL, Neale MC, Kessler RC, Heath AC, Eaves LJ. Genetic and environmental factors in the aetiology of menstrual, premenstrual and neurotic symptoms: a population-based twin study. *Psychol Med* 1992; **22**: 85–100.

12 Condon JT. The premenstrual syndrome: a twin study. *Br J Psychiatry* 1993; **162**: 481–6.

13 Kendler KS, Karkowski LM, Corey LA, Neale MC. Longitudinal population-based twin study of retrospectively reported premenstrual symptoms and lifetime major depression. *Am J Psychiatry* 1998; **155**: 1234–40.

14 Huo L, Straub RE, Roca C, Schmidt PJ, Shi K, Vakkalanka R, et al. Risk for premenstrual dysphoric disorder is associated with genetic variation in ESR1, the estrogen receptor alpha gene. *Biol Psychiatry* 2007; **62**: 925–33.

15 Treloar SA, Martin NG, Bucholz KK, Madden PA, Heath AC. Genetic influences on post-natal depressive symptoms: findings from an Australian twin sample. *Psychol Med* 1999; **29**: 645–54.

16 Forty L, Jones L, Macgregor S, Caesar S, Cooper C, Hough A, et al. Familiality of postpartum depression in unipolar disorder: results of a family study. *Am J Psychiatry* 2006; **163**: 1549–53.

17 Cooper PJ, Campbell EA, Day A, Kennerley H, Bond A. Non-psychotic psychiatric disorder after childbirth. A prospective study of prevalence, incidence, course and nature. *Br J Psychiatry* 1988; **152**: 799–806.

18 O'Hara MW, Zekoski EM, Philipps LH, Wright EJ. Controlled prospective study of postpartum mood disorders: comparison of childbearing and nonchildbearing women. *J Abnorm Psychol* 1990; **99**: 3–15.

19 Cox JL, Murray D, Chapman G. A controlled study of the onset, duration and prevalence of postnatal depression. *Br J Psychiatry* 1993; **163**: 27–31.

20 Gaynes BN, Gavin N, Meltzer-Brody S, Lohr KN, Swinson T, Gartlehner G, et al. Perinatal depression: prevalence, screening accuracy, and screening outcomes. *Evid Rep Technol Assess (Summ)* 2005; **119**: 1–8.

21 Eberhard-Gran M, Eskild A, Tambs K, Samuelsen SO, Opjordsmoen S. Depression in postpartum and non-postpartum women: prevalence and risk factors. *Acta Psychiatr Scand* 2002; **106**: 426–33.

22 Munk-Olsen T, Laursen TM, Pedersen CB, Mors O, Mortensen PB. New parents and mental disorders: a population-based register study. *JAMA* 2006; **296**: 2582–9.

23 Ahokas A, Kaukoranta J, Wahlbeck K, Aito M. Estrogen deficiency in severe postpartum depression: successful treatment with sublingual physiologic 17beta-estradiol: a preliminary study. *J Clin Psychiatry* 2001; **62**: 332–6.

24. Gregoire AJ, Kumar R, Everitt B, Henderson AF, Studd JW. Transdermal oestrogen for treatment of severe postnatal depression. *Lancet* 1996; **347**: 930–3.

25 Craig M, Howard L. Postnatal depression. *Clin Evid (Online)* 2009; **1**: 1407.

26 Sherwin BB, Suranyi-Cadotte BE. Up-regulatory effect of estrogen on platelet 3H-imipramine binding sites in surgically menopausal women. *Biol Psychiatry* 1990; **28**: 339–48.

27 Montgomery JC, Appleby L, Brincat M, Versi E, Tapp A, Fenwick PB, et al. Effect of oestrogen and testosterone implants on psychological disorders in the climacteric. *Lancet* 1987; **1**: 297–9.

28 Welton AJ, Vickers MR, Kim J, Ford D, Lawton BA, MacLennan AH, et al. Health related quality of life after combined hormone replacement therapy: randomised controlled trial. *BMJ* 2008; **337**: a1190.

29 Coope J. Is oestrogen therapy effective in the treatment of menopausal depression? *J R Coll Gen Pract* 1981; **31**: 134–40.

30 Campbell S, Whitehead M. Oestrogen therapy and the menopausal syndrome. *Clin Obstet Gynaecol* 1977; **4**: 31–47.

31 Pearce J, Hawton K, Blake F, Barlow D, Rees M, Fagg J, et al. Psychological effects of continuation versus discontinuation of hormone replacement therapy by estrogen implants: a placebo-controlled study. *J Psychosom Res* 1997; **42**: 177–86.

32 Morrison MF, Kallan MJ, Ten Have T, Katz I, Tweedy K, Battistini M. Lack of efficacy of estradiol for depression in postmenopausal women: a randomized, controlled trial. *Biol Psychiatry* 2004; **55**: 406–12.

33 Cohen LS, Soares CN, Poitras JR, Prouty J, Alexander AB, Shifren JL. Short-term use of estradiol for depression in perimenopausal and postmenopausal women: a preliminary report. *Am J Psychiatry* 2003; **160**: 1519–22.

34 Schmidt PJ, Nieman L, Danaceau MA, Tobin MB, Roca CA, Murphy JH, et al. Estrogen replacement in perimenopause-related depression: a preliminary report. *Am J Obstet Gynecol* 2000; **183**: 414–20.

35 Soares CN, Almeida OP, Joffe H, Cohen LS. Efficacy of estradiol for the treatment of depressive disorders in perimenopausal women: a double-blind, randomized, placebo-controlled trial. *Arch Gen Psychiatry* 2001; **58**: 529–34.

36 Magos AL, Studd JWW. The premenstrual syndrome. In *Progress in Obstetrics and Gynaecology* (ed. J Studd): 334–50. Churchill Livingstone, 1984.

37 American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (4th edn) (DSM-IV)*. APA, 1994

38 Klock SC. Premenstrual dysphoric disorder. In *Kistner's Gynecology and Women's Health* (7th edn) (ed. KJ Ryan): 520–4. Mosby, 1999.

39 Dalton K. *The Premenstrual Syndrome and Progesterone Therapy* (2nd edn). Year Book Medical Publisher, 1984.

40 Dalton K. Comparative trials of new oral progestogenic compounds in treatment of premenstrual syndrome. *Br Med J (Clin Res Ed)* 1959; **2**: 1307–9.

41 Redei E, Freeman EW. Daily plasma estradiol and progesterone levels over the menstrual cycle and their relation to premenstrual symptoms. *Psychoneuroendocrinology* 1995; **20**: 259–67.

42 Wyatt K, Dimmock P, Jones P, Obhrai M, O'Brien S. Efficacy of progesterone and progestogens in management of premenstrual syndrome: systematic review. *BMJ* 2001; **323**: 776–80.

https://doi.org/10.1192/bjp.bp.111.102855 Published online by Cambridge University Press

43 Royal College of Obstetricians and Gynaecologists. *Management of Premenstrual Syndrome (Green-top Guideline No. 48)*. RCOG, 2007.

44 Graham CA, Sherwin BB. A prospective treatment study of premenstrual symptoms using a triphasic oral contraceptive. *J Psychosom Res* 1992; **36**: 257–66.

45 Freeman EW, Kroll R, Rapkin A, Pearlstein T, Brown C, Parsey K, et al. Evaluation of a unique oral contraceptive in the treatment of premenstrual dysphoric disorder. *J Womens Health Gend Based Med* 2001; **10**: 561–9.

46 Coffee AL, Kuehl TJ, Willis S, Sulak PJ. Oral contraceptives and premenstrual symptoms: comparison of a 21/7 and extended regimen. *Am J Obstet Gynecol* 2006; **195**: 1311–9.

47 Pearlstein TB, Bachmann GA, Zacur HA, Yonkers KA. Treatment of premenstrual dysphoric disorder with a new drospirenone-containing oral contraceptive formulation. *Contraception* 2005; **72**: 414–21.

48 Yonkers KA, O'Brien PM, Eriksson E. Premenstrual syndrome. *Lancet* 2008; **371**: 1200–10.

49 Hunter MS, Ussher JM, Browne SJ, Cariss M, Jelley R, Katz M. A randomized comparison of psychological (cognitive behavior therapy), medical (fluoxetine) and combined treatment for women with premenstrual dysphoric disorder. *J Psychosom Obstet Gynaecol* 2002; **23**: 193–9.

50 Jones I, Craddock N. Familiality of the puerperal trigger in bipolar disorder: results of a family study. *Am J Psychiatry* 2001; **158**: 913–7.

51 Heron J, Robertson Blackmore E, McGuinness M, Craddock N, Jones I. No 'latent period' in the onset of bipolar affective puerperal psychosis. *Arch Womens Ment Health* 2007; **10**: 79–81.

52 Robertson E, Jones I, Haque S, Holder R, Craddock N. Risk of puerperal and non-puerperal recurrence of illness following bipolar affective puerperal (post-partum) psychosis. *Br J Psychiatry* 2005; **186**: 258–9.

53 Jones I, Craddock N. Searching for the puerperal trigger: molecular genetic studies of bipolar affective puerperal psychosis. *Psychopharmacol Bull* 2007; **40**: 115–28.

54 Sichel DA, Cohen LS, Robertson LM, Ruttenberg A, Rosenbaum JF. Prophylactic estrogen in recurrent postpartum affective disorder. *Biol Psychiatry* 1995; **38**: 814–8.

55 Ahokas A, Aito M, Rimon R. Positive treatment effect of estradiol in postpartum psychosis: a pilot study. *J Clin Psychiatry* 2000; **61**: 166–9.

56 Kumar C, McIvor RJ, Davies T, Brown N, Papadopoulos A, Wieck A, et al. Estrogen administration does not reduce the rate of recurrence of affective psychosis after childbirth. *J Clin Psychiatry* 2003; **64**: 112–8.

57 Craig MC, Cutter WJ, Norbury R, Murphy DGM. X chromosome, estrogen and brain development: implications for schizophrenia. In *Neurodevelopment and Schizophrenia* (eds M Keshavan, JL Kennedy, R Murray): 330–46. Cambridge University Press, 2005.

58 Chua WL, de Izquierdo SA, Kulkarni J, Mortimer A. Estrogen for schizophrenia. *Cochrane Database Syst Rev* 2005; **4**: CD004719.

59 Hogervorst E, Yaffe K, Richards M, Huppert FA. Hormone replacement therapy to maintain cognitive function in women with dementia. *Cochrane Database Syst Rev* 2009; **1**: CD003799.

60 Craig MC, Maki PM, Murphy DGM. The Women's Health Initiative Memory Study: findings and implications for treatment. *Lancet Neurol* 2005; **4**: 1–5.

61 British Medical Association & Royal Pharmaceutical Society. 6.4.1.1 Oestrogens and HRT. In *British National Formulary 63 (March 2012)*: 470–7. British Pharmaceutical Press, 2012.

62 Craig MC, Brammer M, Maki PM, Fletcher PC, Daly EM, Rymer J, et al. The interactive effect of acute ovarian suppression and the cholinergic system on visuospatial working memory in young women. *Psychoneuroendocrinology* 2010; **35**: 987–1000.

poem

Wilhelmina and Manfreda at the Balcony (XIII century)

Dino Campana

Here we are alone before the nocturnal mystery. The moon
May shine over mankind's sad loves,
She's veiled with mist and tears like Venus rising
From the sea on the first morning of the world
The world still smoking in primal chaos as she laughs
With so much tender sorrow
Since then much time has flown, and still that sorrow
Is weighing on the tender breast of Venus
Yet it is infinitely sweet to feel the tiredness
Of our hearts exhausted but still burning
Through immemorial time
Towards the soul of the world that none can slake.

This poem is from Dino Campana's (1885–1932) *Selected Works*, translated by Cristina Viti and published by Survivors' Poetry in 2006. Dino Campana was admitted to San Salvi, an asylum in Florence at the age of 32 years and transferred to Castel Pulci, a place designated for those regarded as incurable in April 1918 where he remained until his death. Another of his poems, *Easy Listening*, was published in the *Journal* in August 2012.

Chosen by Femi Oyebode.

The British Journal of Psychiatry (2013) 202, 13. doi: 10.1192/bjp.bp.111.102004

https://doi.org/10.1192/bjp.bp.111.102855 Published online by Cambridge University Press