

Special Issues in the Management of Depression in Women

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Depression is more prevalent in women than in men, which may be related to biological, hormonal, and psychosocial factors. Four depressive conditions are specific to women: premenstrual dysphoric disorder (PMDD), depression in pregnancy, postpartum depression, and depression related to perimenopause or menopause. Antidepressant therapy with selective serotonin reuptake inhibitors and venlafaxine has demonstrated efficacy in PMDD. Both continuous and intermittent dosing regimens were effective at usual but not at low dosages. Despite reluctance of some women to take medication for depression during pregnancy and breastfeeding, substantial evidence suggests that antidepressants are safe and efficacious during these periods, while untreated depression has negative consequences for both mother and child. In peri- or postmenopausal women with depression, estrogen may enhance the effects of antidepressant medications, although a pooled analysis of data in women aged 50 years or over treated with venlafaxine found that remission rates were similar in those who were taking estrogen and those who were not. The management of women with depression can be done safely and effectively using antidepressants and alternative interventions throughout the life cycle.

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Clinical Implications

- Women are susceptible to depression during the reproductive cycle from menarche, pregnancy, and postpartum to menopause.
- The etiopathophysiology of depression during the reproductive life cycle in women is largely unknown but encompasses a complex interplay among circulating hormones and neurotransmitters, psychosocial response, and genetic risk factors.
- There are effective and essentially safe somatic and psychological therapies available to treat women with depression.

Limitations

- Safety data for the newer antidepressants during pregnancy, postpartum, and lactation are limited and lack the rigour of placebo-controlled trials (level 1 evidence).
- Maintenance and prophylaxis data regarding the use of antidepressants in women are poor.
- There is a paucity of research addressing the effectiveness of psychological therapies to treat women with depression.

Key Words: *depression, women, reproductive cycle, hormones, premenstrual, pregnancy, postpartum, lactation, menopause, antidepressants, cognitive therapy*

The lifetime rate of major depression is 1.7 to 2.7 times higher for women than for men (1–3); in the National Comorbidity Survey, the lifetime prevalence for major depressive disorder (MDD) was 21.3% for women and 12.7% for men (1). Three factors have been proposed to explain the higher prevalence of depression in women than men (3). The first factor suggests that the difference in prevalence is primarily an artifact of diagnostic bias, a function of the possibility that women seek help for depression more often than men

do or that women are more likely to report past or current depression in response to questioning about the illness. A second set of proposed factors include biological theories that consider differences in brain structure and function, which may relate to different reproductive hormones in women, compared with men. The third area considers psychosocial factors such as differences in socialization, stress, and coping mechanisms and styles. It is likely that each of these factors

contributes to the difference in depression rates between women and men.

Sex differences are also reported for clinical features of depression. Women appear to be more seriously affected by depression than men, with earlier age of onset, greater family history of affective disorders, greater severity of illness, poorer social adjustment, and poorer quality of life (4). Women may have a more chronic and recurrent course of illness, with more frequent and longer episodes, than men (5–8). Women may derive greater psychological benefit from positive social relationships, but the effects of marital conflict on depression do not seem to vary by sex (9).

The profile of depressive symptoms varies between men and women. In one study, women experienced more sleep changes, psychomotor retardation, and anxiety or somatization than men (4). In another study of older individuals, men and women with MDD presented with distinct profiles of symptoms that could not be explained by psychosocial factors: women with depression presented with more appetite disturbances and men with depression had more agitation (10). Some studies have suggested that premenopausal women are less responsive to tricyclic antidepressants (TCAs), compared with selective serotonin reuptake inhibitors (SSRIs) (11–13). However, in a retrospective analysis of data for 1746 patients aged 18 to 65 years, men and women younger and older than age 50 years had equivalent response rates to TCAs and fluoxetine (14). This study concluded that, overall, neither sex nor menopausal status was relevant in antidepressant treatment of adult patients with depression up to age 65 years. Similarly, no differences in outcome with venlafaxine therapy were seen between men and women in an analysis of data from 8 trials (15). Men and women receiving venlafaxine exhibited comparable rates of remission (men 45%, women 45%) that were higher than those seen with SSRIs (men 36%, women 34%; $P \leq 0.04$) or placebo (men 26%, women 24%; $P \leq 0.001$). Women younger and older than age 50 years had similar responses (16). At this time, the data are not sufficient to suggest that clinicians who are treating depression in women must consider menopausal status when selecting medications.

Sex may influence discontinuation rates: women taking TCAs and men taking SSRIs appear more likely to withdraw from treatment (11,12). This may be related to the fact that some drugs may have higher bioavailability and slower renal clearance in women than in men (17), resulting in higher drug levels and a greater potential for side effects (18).

US consensus guidelines on the treatment of depression in women addressed 4 depressive conditions specific to women: premenstrual dysphoric disorder (PMDD), depression in pregnancy, postpartum depression in a mother choosing to

Table 1 DSM-IV criteria for the diagnosis of premenstrual dysphoric disorder (26)

- Cyclical relation to luteal phase of menstrual cycle
- Symptoms cause functional impairment
- Not an exacerbation of an underlying disorder
- Diagnosis confirmed by 2 cycles of daily ratings
- 5 of the following, including at least 1 mood symptom:
 - Low mood
 - Irritability
 - Anxiety and (or) tension
 - Sleep changes
 - Difficulty concentrating
 - Physical symptoms (bloating, breast tenderness)
 - Mood swings
 - Fatigue
 - Decreased interest
 - Appetite changes
 - Feeling overwhelmed

breastfeed, and depression related to perimenopause or menopause (19). These areas are each briefly reviewed below.

Premenstrual Dysphoric Disorder

Approximately 3% to 8% of women experience premenstrual symptoms that meet the DSM-IV criteria for PMDD (20,21). In a community sample of 1488 women, the 12-month prevalence rate of PMDD was 5.8%, and an additional 18.6% were “near threshold cases” who experienced symptoms but failed to meet the criteria of functional impairment (22). The likelihood of a past depression in women with PMDD is reported to be 30% to 97% (23–25), and 29% of women with PMDD also experience postpartum depression (25).

The DSM-IV criteria for PMDD include a cyclical relation to the luteal phase of the menstrual cycle and symptoms that cause functional impairment and are not an exacerbation of an underlying disorder (Table 1) (26). The diagnosis is confirmed by 2 cycles of daily ratings, and patients must demonstrate at least 5 symptoms, including at least 1 mood symptom.

Several structured tools are available to assess the severity of symptoms and response to treatment. The Daily Record of Severity of Problems (DSRP) consists of 21 numbered items that assess the 11 DSM-IV–defined symptoms of PMDD, rated on 6-point scales (27). The Calendar of Premenstrual Experiences (COPE) diary measure is a prospective inventory of 22 items (12 psychological and 10 physical) rated on 3-point scales (28). The 17-item Daily Symptom Report (DSR) is relatively brief and appropriate for clinical and primary care settings (29). A new tool has recently been developed in primary care, the Premenstrual Symptoms Screening Tool (PSST) (30). It does not require multiple months of daily record keeping as do most currently available measures. This tool was developed in a large sample of women in primary

care (over 500 participants) and may provide a very practical measure of PMDD in the primary care setting, although it likely requires validation in other settings.

Patients with PMDD are at increased risk for depressive episodes, including postpartum depression (31,32). PMDD is associated with an increased risk of developing MDD, above and beyond a family history of depression and a personal history of depression (32).

Management of PMDD

Alterations in serotonin and hypothalamic–pituitary–gonadal axis dysregulation may be important in PMDD (33). The SSRIs and the serotonin norepinephrine reuptake inhibitors (SNRIs) have demonstrated efficacy in the management of this disorder. Dimmock and colleagues conducted a metaanalysis on the efficacy of SSRIs in PMDD that included 15 randomized placebo-controlled trials performed in the 1990s (34). The primary analysis included data on 570 women assigned to active treatment and 435 assigned to placebo. The 2 most-studied SSRIs were fluoxetine (7 trials, 398 participants) and sertraline (5 trials, 364 participants). The odds ratio for a reduction in premenstrual symptoms was 6.91 (95%CI, 3.90 to 12.2) in favour of SSRIs. SSRIs were effective for both physical and behavioural symptoms, with no significant variation in the overall mean differences ($P = 0.386$). However, most of the trials (13/15) enrolled patients presenting with a classification of premenstrual syndrome that predominantly assessed behavioural symptoms. There were no differences in intermittent or semiintermittent (continuous but with lower dosages during the follicular phases) dosing regimens, compared with continuous dosing.

Studies published following the Dimmock metaanalysis have further explored the role of intermittent SSRI therapy in the luteal phase and provided information on the use of agents with a combined mechanism of action, such as venlafaxine and nefazodone (Table 2). In 2 studies, one with sertraline and the other with fluoxetine, women with PMDD received treatment during the luteal phase only for 3 cycles (35,36). Mean improvements in DRSP were about 9% to 13% greater with SSRI therapy, compared with placebo. Response rates (CGI-I of 1 or 2 [“much” or “very much” improved, respectively]) were significantly greater with sertraline, compared with placebo (58% vs 45%; $P = 0.036$) (35). There were no significant differences between the treatment groups in physical symptoms. Fluoxetine showed significant improvement over placebo when used at a dosage of 20 mg daily, but not at 10 mg daily, for both mood symptoms and physical symptoms (36). Miner and colleagues evaluated the efficacy and tolerability of enteric-coated fluoxetine 90 mg given once or twice on day 7 or on days 14 and 7 before expected menses during the luteal phase of 3 menstrual cycles, compared with placebo (37). At

the end of the study, women receiving the 2 dosages of fluoxetine had statistically significant improvements in mean DSRP change (about 6% greater than those seen with placebo). The single dose of fluoxetine given 7 days before menses was not significantly better than placebo.

Freeman and colleagues assessed treatment with venlafaxine over 4 cycles in women with PMDD (Table 2) (38). Venlafaxine resulted in significant improvements in the mean change in DSR (26% greater than those seen with placebo). Response rates ($\geq 50\%$ reduction in DSR score) were almost double those seen with placebo (60% vs 35%; $P = 0.003$). Similarly, remission rates (reduction in DSR scores to the premenstrual level) were significantly higher among women treated with venlafaxine, compared with those receiving placebo (43% vs 25%; $P = 0.034$). Patients experienced less pain and fewer physical symptoms, including cramps, aches, headache, breast tenderness, and swelling. The mean dosage of venlafaxine was 50 mg daily in the first cycle and 130 mg daily in the fourth cycle, demonstrating the need to optimize dosing in PMDD.

In a small study, the efficacy of nefazodone, which acts primarily as a serotonergic 5-HT₂ receptor antagonist as well as a weaker SSRI, was compared with that of buspirone, a partial 5-HT_{1A} receptor agonist, and placebo (Table 2) (39). Treatment was given in the luteal phase only for the first 2 cycles and daily for an additional 2 cycles. Buspirone ($P < 0.001$) but not nefazodone was significantly superior to placebo on self-rated global improvement. The differences with buspirone appeared to be primarily due to improvement in irritability.

Response to antidepressant medications in PMDD generally appears to be very rapid. In studies with sertraline and fluoxetine, improvement was reported within the first treatment cycle (35,36). Eighty percent of symptom reduction with venlafaxine was experienced in the first treatment cycle (38).

In a study comparing pharmacotherapy to psychotherapy for PMDD, fluoxetine was compared with cognitive-behavioural therapy (CBT, 10 sessions) and combined therapy (CBT plus fluoxetine) in 108 women with PMDD, of whom 60 completed 6 months of treatment (40). Significant improvement occurred in all 3 treatment groups at endpoint, as assessed by the COPE scores. Fluoxetine was associated with more rapid symptom improvement. At 1-year follow-up, CBT was associated with better maintenance of treatment effects. There was no additional benefit of combination treatment.

In summary, the serotonergic agents, including venlafaxine at serotonergic dosages, appear effective in PMDD. For the roughly 5% of women who are significantly impaired by premenstrual symptoms, these agents can reduce acute symptoms and are safe (41). This combination of efficacy and

Table 2 Antidepressant therapy for premenstrual dysphoric disorder

Study details	Treatment and dosage, mg	Number completed/enrolled (%)	Primary outcome, change vs baseline (%)	SE
Dimmock and others (34) Metaanalysis	FLX (7 trials) SER (5 trials) PRX (1 trial) CIT (1 trial) FLV (1 trial)	NR/398 NR/364 NR/53 NR/69 NR/20	SSRI > PBO OR 6.9, psychological and physical symptoms	SSRI > PBO most common insomnia, gastrointestinal disturbances, and fatigue Withdrawal OR 2-42
Halbreich (35) <i>n</i> = 281; DRSP 72/33; luteal, 3 cycles	SER, 48–74 daily PBO	115/142 (81) 106/139 (76)	DRSP –26.1 (36.0)** ^a –16.4 (23.0)	SER > PBO nausea (12.5 vs 3.1; <i>P</i> = 0.006), dry mouth (10.3 vs 3.1; <i>P</i> = 0.02), sexual SE (7 vs 0 patients)
Cohen (36) <i>n</i> = 260; DRSP 79/27; luteal, 3 cycles	FLX, 10 daily FLX, 20 daily PBO	77/86 (90) 64/86 (74) 75/88 (85)	DRSP –27.5 (34.9), ns –31.3 (38.7)** –23.2 (29.7)	FLX20 > FLX10 > PBO: sexual SE (9.3 vs 5.8 vs 0, <i>P</i> = 0.007). PBO > FLX: accidental injury
Miner and others (37) <i>n</i> = 257; DRSP 77/28; luteal, 3 cycles, administered days 14 + 7 (twice) or day 7 (once) premenstrual	FLX, 90 twice FLX, 90 once PBO, twice	NR/86 NR/86 NR/85	DRSP –30.4 (39.3)* –25.3 (33.0), ns –25.9 (33.1)	FLX twice vs FLX once vs PBO: nausea (15.1 vs 14.0 vs 2.4, <i>P</i> = 0.006); diarrhea (7 vs 7 vs 0, <i>P</i> = 0.027); infection (0 vs 3.5 vs 8.2, <i>P</i> = 0.012)
Freeman and others (38) <i>n</i> = 164, DSR 176/33; daily, 4 cycles	VEN, 50–130 daily PBO	50/77 (65) 51/80 (64)	DSR –100 (56.8)** –54 (30.7)	VEN > PBO: nausea (45 vs 13; <i>P</i> < 0.001); insomnia (34 vs 16; <i>P</i> < 0.05); dizziness (32 vs 5; <i>P</i> < 0.001); sexual SE (16 vs 0; <i>P</i> < 0.001)
Hunter and others (40) <i>n</i> = 108, COPE 18.7/3.32; daily FLX; 10 CBT sessions; 6 months	FLX, 20 daily CBT CBT + FLX	19/35 (54) 22/37 (59) 19/36 (53)	COPE at 3 months –9.78 (49.7), ns –4.12 (24.8), ns –7.31 (36.8), ns	FLX: GI symptoms, sexual SE 25%, insomnia
Landen and others (39) <i>n</i> = 63; luteal, 2 cycles; daily, 2 cycles	BSP, 21–27 daily NEF 228–304 daily PBO	15/23 (65) 20/23 (87) 19/23 (83)	VAS irritability <u>Cycle 2</u> (72) <u>Cycle 4</u> (83) ^{a,b} (52) (47) (47) (54)	BSP, NEF > PBO: dizziness, disturbed balance, blurred vision, abnormal dreams, flu-like symptoms; NEF > PBO: nausea, memory disturbance, insomnia, somnolence

^aAsterisks indicate significant difference from PBO: **P* ≤ 0.05; ***P* ≤ 0.01; ****P* ≤ 0.001; ns = not significant (*P* > 0.05).

BSP = buspirone; CBT = cognitive-behavioural therapy; CGI-S = Clinical Global Impression-Severity; CGI-I = CGI-Improvement; CIT = citalopram; COPE = Calendar of Premenstrual Experiences; DRSP = Daily Record of Severity of Problems; DSR = Daily Symptom Report; FLV = fluvoxamine; FLX = fluoxetine; NEF = nefazodone; NR = not reported; PBO = placebo; PRX = paroxetine; SE = side effects; SER = sertraline; VEN = venlafaxine

tolerability may underlie the finding of reduced occupational impairment for women with PMDD treated with fluoxetine (42).

Pregnancy

Pregnancy does not protect women from experiencing episodes of depression (43). In fact, the rate of depression increases during late pregnancy and the early puerperium period (44), and a longitudinal study of 1558 pregnant women found the prevalence of depressive symptoms was 17% during late pregnancy, 18% in the maternity ward, and 13% at both 6 to 8 weeks and 6 months postnatally (45). A history of a mood disorder increases the risk for depression during

pregnancy (46,47); other risk factors include lack of education, being unmarried or unemployed, marital discord or dissatisfaction, inadequate psychosocial supports, unwanted pregnancy, and being in a second or subsequent pregnancy (43,46–48).

Fifty percent of pregnancies may be unplanned; most pregnancies are first documented at 6 to 8 weeks' gestation (49). Therefore, many pregnant women will have several weeks' exposure to antidepressant therapy. With that in mind, it is important to balance the risks of antidepressant therapy to the fetus and the risks of persistent or recurrent depression to both the fetus and the mother. Data suggest that the rate of relapse of major depression in women who have discontinued

medication at conception or early in the pregnancy is as high as 75% (50). Adverse neonatal outcomes that have been associated with depression in pregnancy include low birth weight (≤ 2500 g) (51) and preterm delivery (51,52). In addition, depression during pregnancy can lead to decreased appetite and consequent lower-than-normal weight gain, a factor associated with negative pregnancy outcomes (53). Depressive symptoms may lead to self-medication with cigarettes, alcohol, or other drugs (54–58) and the consequent problems associated with these substances (59).

Management of Depression During Pregnancy

Potential risks to the fetus from medication exposure include organ malformation (teratogenicity), neonatal toxicity (perinatal syndromes), and postnatal behavioural sequelae (behavioural teratogenicity) (19). Organ malformation is associated with fetal drug exposure during the first 12 weeks of gestation, when organ formation occurs (60,61). The baseline incidence of major congenital malformations in the US is 2.0% to 4.0% (61) and has been estimated to be as high as 7% to 10% if minor malformations are included (62). According to the FDA, most of the data currently available would classify the antidepressants as category C agents (63). The category C rating is “risk cannot be ruled out.” Adequate, well-controlled studies are lacking; there is a chance of fetal harm, but the potential benefits may outweigh the potential risks.

Table 3 reviews some of the larger studies evaluating the effect of antidepressant use during pregnancy on neonatal outcomes (64–76). There are few data on the use of mirtazapine and bupropion in pregnant women (77,78).

The antidepressants with the largest cohort analyses, including citalopram, fluoxetine, paroxetine, sertraline, nefazodone, and venlafaxine, as well as the TCAs, have demonstrated no increase in the incidence of major congenital malformations (64–76). SSRI exposure during pregnancy, particularly during the third trimester, has been associated with earlier delivery and consequent lower birth weight in some studies (66,72) but not in others (64,70). Third-trimester exposure to SSRIs but not TCAs was also associated with lower Apgar scores (72). The antidepressant most extensively studied in pregnant women is fluoxetine (65–69), and a 7-year follow-up study of children exposed in utero found no evidence of behavioural teratogenicity (79).

Cases of neonatal withdrawal syndrome have been reported after third-trimester in utero exposure with the SSRIs paroxetine, citalopram, and fluoxetine (80–82). Withdrawal symptoms occurred within a few days after birth and lasted up to 1 month. Symptoms were irritability, crying, shivering, increased tonus, eating and sleeping difficulties, and convulsions. Poor neonatal adaptation, including respiratory difficulty, cyanosis on feeding, jitteriness, hypoglycemia, and

jaundice has been reported in studies with fluoxetine and paroxetine, which the authors attributed to possible withdrawal symptoms (66,74).

In summary, the literature does not currently suggest that there are long-term adverse consequences of in utero exposure to SSRIs, the SNRI venlafaxine, or the traditional tricyclic agents. It appears that infants exposed to SSRIs shortly prior to birth are at risk of experiencing serotonergic symptoms in the several days following delivery, but no studies report sustained adverse outcomes in exposed infants.

Postpartum Depression

Mood symptoms in the postpartum period fall into 3 broad categories: postpartum blues, postpartum MDD, and psychoses. Postpartum blues are experienced by 50% to 70% of women (83): symptoms are transient irritability and mood lability that generally dissipate by day 10 to 14 after birth (84). Puerperal psychosis, an acute delusional state that can include altered consciousness, is often a medical emergency (84) and occurs in 1 to 2 per 1000 births (85).

Postpartum depression is strictly defined as a depressive episode that occurs within 4 weeks after delivery (26). Studies indicate a prevalence of postpartum depression of 11% to 15% (45,86,87). However, 20% to 25% of women will experience some depressive symptoms during the postpartum period (48,87). Postpartum depression can lead to impaired functioning in the mother, family distress, disrupted parent–infant bonding, and altered neurological behaviour in infants (88–92). In more severe forms of postpartum depression, there is a risk of suicide or infanticide. Thus, rapid attention and treatment are imperative.

The Edinburgh Postnatal Depression Scale (EPDS) (Table 4) (93), a self-report screening tool, can significantly increase the detection of postpartum depression, compared with routine clinical evaluation (35.4% vs 6.3%; $P = 0.001$) (94). The negative predictive value is high for the EPDS (0.97 in one study); this is a more important consideration for a screening instrument as it describes the probability with which a condition can be safely ruled out if the screening test is negative (95). These and other data support the use of the EPDS as a valid, reliable, and easy-to-administer screening questionnaire.

The risk of postpartum depression is higher in women with a history of prior depression (25% risk), a history of a prior postpartum depression (50% to 62% risk), or depressive symptomatology during pregnancy (96–98). Women with past postpartum depression are at particularly high risk in subsequent pregnancies and should be monitored carefully for depressive symptoms throughout the pregnancy as well as the postpartum period. Marital discord, stressful life events,

Table 3 Studies evaluating the use of antidepressants during pregnancy

Drug and study	Malformations, %	Premature delivery	Neonatal complications
Fluoxetine			
Goldstein and others (65) <i>n</i> = 796, first trimester	5.0	Premature: 3.3% SA: 13.8%	—
Chambers and others (66) <i>n</i> = 228, FLX vs control subjects	5.5 vs 4.0, ns ^a	Premature: RR 4.8 SA: 10.5% vs 9.1%, ns	RR 2.6: admission to special-care nurseries RR 8.7: poor neonatal adaptation, including respiratory difficulty, cyanosis on feeding, and jitteriness; birth weight and length lower
Loebstein and Koren (67) <i>n</i> = 55, First-trimester FLX vs TCA vs control drugs	3.4 vs 0 vs 3.0	ns	—
Cohen and others (68) <i>n</i> = 64	—	4.8%	—
Addis and Koren (69)	2.6	—	—
Nefazodone <i>n</i> = 89 Trazodone <i>n</i> = 58			
Einarson and others (76) First trimester; drug vs other antidepressants vs control subjects	1.6 vs 2.4 vs 3.0, ns	SA: 13.4 vs 11.2 vs 8, ns	Mean 38 vs 39 weeks, 3306 vs 3418 g, ns
Paroxetine			
Costei and others (74) <i>n</i> = 55, third-trimester PRX vs first- or second-trimester PRX or no exposure	—	—	21.8% vs 5.6% complications necessitating intensive treatment and prolonged hospitalization: respiratory distress, hypoglycemia, jaundice
Venlafaxine			
Einarson and others (71) <i>n</i> = 150	1.3, ns	SA: 12%, ns	—
TCA's			
Simon and others (72) <i>n</i> = ?	ns	ns	ns
McElhatton and others (73) <i>n</i> = 330	3.3	Premature: 5.8 SA: 11.5	4.5%
SSRIs			
Simon and others (72)	ns	0.9-week decrease	175 g decrease birth weight; 0.29 decrease in Apgar score at 5 minutes
Ericson and others (64) ^b Total <i>n</i> = 531, CIT <i>n</i> = 375, PRX <i>n</i> = 118	3.9	7.9	5.3% < 2500 g
Kulin and others (70) ^c Total <i>n</i> = 267, PRX <i>n</i> = 97, SER <i>n</i> = 147, FLV <i>n</i> = 26 SSRI vs control subjects	4.1 vs 3.8 in control subjects	ns	Birth weight ns

^ans = not significant (*P* > 0.05); ^bThe remaining 38 patients were using other SSRIs; ^cThree patients were taking 2 SSRIs, and the remaining 264 patients were being treated with 1 drug.

BSP = buspirone; CBT = cognitive-behavioural therapy; CGI-S = Clinical Global Impression Severity; CGI-I = CGI Improvement; CIT = citalopram; COPE = Calendar of Premenstrual Experiences; DRSP = Daily Record of Severity of Problems; DSR = Daily Symptom Report; FLV = fluvoxamine; FLX = fluoxetine; NEF = nefazodone; PBO = placebo; PRX = paroxetine; SA = spontaneous abortion; SER = sertraline; SSRI = selective serotonin reuptake inhibitor; VEN = venlafaxine

Table 4 Edinburgh Postnatal Depression Scale (EPDS)

Instructions: How are you feeling? Because you have recently had a baby, we would like to know how you are feeling now. Please underline the answer that comes closest to how you have felt in the past 7 days, not just how you feel today.

1. I have been able to laugh and see the funny side of things.
2. I have looked forward to enjoyment in things.
3. I have blamed myself unnecessarily when things went wrong.
4. I have felt worried and anxious for no very good reason.
5. I have felt scared or panicky for no very good reason.
6. Things have been getting on top of me.
7. I have been so unhappy that I have had difficulty sleeping.
8. I have felt sad or miserable.
9. I have been so unhappy that I have been crying.
10. The thought of harming myself has occurred to me.

Modified from Cox and others (93).

inadequate support, lower socioeconomic status, high levels of interpersonal sensitivity and neuroticism, and wanting to stay in hospital longer are also risk factors for postpartum depression (46,86,99–106); however, the practical utility of these factors in predicting who is at risk for postpartum depression is low, and the factor with the greatest clinical utility remains a history of depression, whether related or unrelated to a previous delivery.

Reducing the Risk of Postpartum Depression

Postpartum depression lends itself to prophylactic intervention because its onset is predicted by a clear marker, giving birth; its period of risk for illness is well defined; and women at high risk can be identified (107). Antidepressant therapy, psychotherapy, and support or educational programs have been assessed as primary and secondary prevention strategies.

Recent studies of varying levels of support in the postpartum period have not shown any benefits with more intensive interventions, compared with less intensive interventions, in reducing the occurrence of postpartum depression (108–110). Escobar and colleagues found no differences in maternal depressive symptoms among women who received home visits, compared with a control intervention of hospital-based group follow-up visits, among 1014 mother–infant pairs (108). Similarly, Morrell and colleagues found no health benefit of additional home visits by community postnatal support workers, compared with traditional community midwifery visits, at 6 months follow-up among 623 postnatal women (109). In a large study ($n = 1004$), no significant differences were reported between women randomized to a weekly support group or a mailed support manual (110). In contrast, a pilot study in 42 women found that telephone-based peer support was effective in reducing the frequency of depression as measured on the EPDS, compared with a control group, at both 4 weeks (10% vs 41%) and 8 weeks (52.4% vs 15%) (111).

One open study of 23 women with histories of postpartum depression showed that starting antidepressants (mainly fluoxetine and clomipramine) within 24 hours of delivery was associated with a marked reduction of depression recurrence, compared with the group receiving no antidepressant treatment (112). More recently, immediate postpartum nortriptyline had no additional efficacy over placebo in preventing recurrence of postpartum depression in a double-blind trial in 51 women with histories of at least 1 prior episode. No difference was found in the rate of recurrence between the treatment groups (23% vs 24%) (107). In contrast, Chabrol and colleagues found that a cognitive-behavioural prevention session resulted in significantly lower rates of depression at 4 to 6 weeks postpartum, compared with a control group (30% vs 48%), in 258 women at risk (113).

Antenatal psychosocial or educational programs have yielded conflicting results. A program designed to increase social support and problem-solving skills did not significantly impact depression rates at 12 weeks postpartum, compared with routine care, in 190 primiparous women (114). Similarly, a randomized comparison of an antenatal educational intervention found no differences in symptoms of depression, compared with a control group, in primiparous women (115). Conversely, another study showed that women at higher risk who were randomized to a psychosocial support intervention had significantly more positive mood at 12 weeks postpartum, compared with those who received routine care (EPDS scores 3 and 8, respectively) (116). Rates of depression (borderline or diagnosed) were also lower at 19%, compared with 39% with routine care. Benefits were statistically significant among first-time but not second-time mothers.

Management of Postpartum Depression

The use of pharmacotherapy for the treatment of postpartum depression has not been extensively documented; in fact, a recent Cochrane database review included only 1 evaluable

Table 5 Drugs and secretion in lactation

Drug and study	% Maternal dose	Milk and plasma	Tolerability	Detectable (% of infants)
Venlafaxine				
Ilett and others (132) <i>n</i> = 7	6.4	2.5 (2.7 ODV)	Good	Yes (14), 57 ODV
Sertraline				
Stowe and others (133) <i>n</i> = 2	—	2.3 (1.4 NDS)	Good	Yes (50)
Kristensen and others (134) <i>n</i> = 8	0.2 (0.3 NDS)	1.9 (1.6 NDS)	Good	No (—)
Wisner and others (135) <i>n</i> = 9	—	—	Good	Yes (22)
Hendrick and others (136) <i>n</i> = 30	—	—	Good	Yes (24)
Dodd and others (137) <i>n</i> = 10	< 2	1.8	Good	— (—)
Stowe and others (8) <i>n</i> = 26	0.5 (0.5 NDS)	0.4–4.8	Good	Yes (18), 50 NDS
Paroxetine				
Begg (139) <i>n</i> = 10]	1.3	0.39	Good	Yes (14)
Ohman and others (140) <i>n</i> = 7	0.7–2.9	0.69	Good	na (na)
Stowe and others (141) <i>n</i> = 16	—	0.056–1.3	Good	No (—)
Misri and others (142) <i>n</i> = 24	1.1	0.53	Good	No (—)
Hendrick and others (136) <i>n</i> = 16	—	—	Good	No (—)
Fluoxetine				
Taddio and others (143) <i>n</i> = 11	10.8	0.88 (0.82 NF)	Good	— (—)
Bimbaum and others (144) <i>n</i> = 35	—	—	Good	Yes (26)
Kristensen and others (145) <i>n</i> = 14	6.8	0.68 (0.56 NF)	Good	Yes (56), 78 NF
Hendrick and others (146) <i>n</i> = 19	—	—	Good	Yes (30), 85 NF
Suri and others (147) <i>n</i> = 10	—	0.01–3.92 (0.05–1.4 NF)	—	Yes (40), 80 NF
Citalopram				
Rampono and others (8) <i>n</i> = 7	4.4–5.1	1.8 (1.8 DMC)	Good	Yes (43) DMC 29
Heikkinen and others (149) <i>n</i> = 11	0.2–0.3	2–3	Good	— (—)

DMC = demethylcitalopram; na = not applicable; NDS = N-desmethylsertraline; NF = norfluoxetine; ODV = O-desmethylvenlafaxine

randomized controlled trial (RCT) (117). In that study, fluoxetine was significantly more effective than placebo and, after an initial session of counselling, was as effective as a full course of cognitive-behavioural counselling for short-term treatment (118). Many new mothers are unwilling to take psychotropic medication because of the desire to breastfeed newborns. In this fluoxetine study, over one-half of the women who were eligible for the trial (101/188) refused to enter, most commonly because of a reluctance to take medication (118).

In an 8-week, open-label study, venlafaxine was found to be effective in the treatment of 15 women with postpartum major depression (119). Statistically significant improvements from baseline to endpoint were noted by week 2 in the 17-item Hamilton Depression Rating Scale (HDRS₁₇), and the Kellner Anxiety Subscale. At endpoint, 80% of patients had achieved remission (HDRS₁₇ score ≤ 7 or Clinical Global Impression Scale (CGI) score ≤ 2). In open-label reports, sertraline (120) and fluvoxamine (121) have also demonstrated beneficial effects in the treatment of postpartum depression.

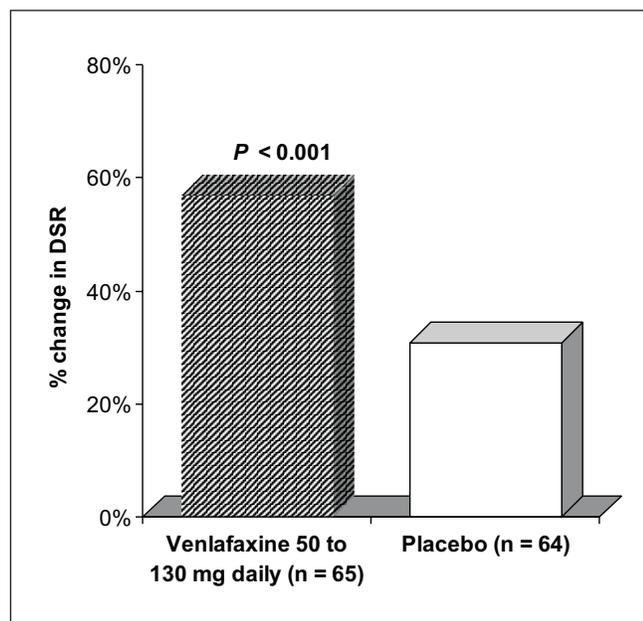
Psychotherapy has demonstrated some benefits for the prevention and treatment of postpartum depression. O'Hara and colleagues randomized 120 women with MDD in the

postpartum period to interpersonal psychotherapy (IPT) or a control group (122). IPT was associated with significantly greater improvements in HDRS scores, compared with the control (–11.1 vs –3.0). Remission rates (HDRS₁₇ score ≤ 6) were significantly higher with IPT, compared with control (37.5% and 13.7%, respectively).

Although most studies of psychosocial interventions involve prevention of postpartum depression, one study demonstrated that partner support had measurable effects on women experiencing postpartum depression (123). Women with postpartum depression (*n* = 29) randomized to a support group with their partners had a significant decrease in depressive symptoms and other psychiatric conditions, compared with a control group of women who participated without their partners (123).

Fluctuating levels of estrogen and progesterone are implicated in the development of postpartum depression, and women with a history of postpartum depression appear differentially sensitive to mood-destabilizing effects of gonadal steroids (124). Estrogen augmentation therapy may improve outcome. In a placebo-controlled trial, Gregoire and colleagues demonstrated significantly greater improvement during the first month of therapy with estradiol used as

Figure 1 Venlafaxine compared with placebo therapy for PMDD. Data are from Freeman and others (38)



monotherapy or add-on to antidepressant therapy in women with postpartum depression (125). A small open study reported that estradiol might have benefits in preventing recurrence of postpartum depression (126). A Cochrane database review included the Gregoire trial and 1 other trial of estrogens and progestogens in the prevention and treatment of postnatal depression; it concluded that synthetic progestogens have no role in postpartum depression, while estrogen may be of modest value at a late stage in severe cases (127). The data do not currently support the use of estrogens as a first-line therapy for postpartum depression, and although the data are sparse, treatment with an antidepressant is the first-line choice for moderate-to-severe postpartum depression. There are no comparative studies to suggest that one antidepressant is more likely to be effective than another in the postpartum period, and therefore the clinical decision must rely on the usual factors that determine clinician choice of antidepressant treatment.

Antidepressants and Breastfeeding

Most antidepressants pass into breast milk, and these data have been reviewed in detail in several recent articles (128–131). In Table 5, we have reviewed only those case series that included 5 or more mother–infant pairs (132–149). The estimated infant daily dosage ranges from 0.1% to 6.2% of the maternal dosage, and there are very few reports of adverse effects on nursing infants exposed to psychotropic medications in breast milk (19,150). A review of 36 reports of antidepressant use during breastfeeding revealed no adverse events among the infants in most cases (131). Adverse events were reported in only 7/253 infants and included uneasy sleep,

crying, emesis, diarrhea, and hyperactivity. In our review, no adverse effects were reported in the infants in any of these studies (Table 5); when choosing medications that are not listed, it is important to evaluate the evidence for safety during lactation, as some commonly used antidepressants have not been well studied in mother–infant dyads.

The advantages of breastfeeding will likely outweigh the very low risk of an adverse event from drug exposure to the infant (128,150). However, an individualized risk–benefit assessment with the goal of minimizing infant exposure while maintaining maternal emotional health is the ideal approach (19,150).

Some data suggest that discarding hind milk can substantially reduce the antidepressant dose to the infant, but this has not been well studied. A significant gradient effect has been observed for sertraline and paroxetine, with the highest concentrations in the hind milk (133,138,140,141). In one study, the mean paroxetine concentration in hind milk was 78% higher than in fore milk (140). For sertraline, mathematical modelling determined that discarding breast milk 9 hours after maternal dosage decreased the infant dosage by a mean of 17% (138).

Effects of Depression on Parenting and Child Development

Several factors describe why parental depression may have an effect on child development (151). Mother and child share a mutual regulation, with infants responding to maternal depressed behaviour as early as 3 months (152). Women with a history of depression or anxiety disorders, even those who report few or no current symptoms, show interactive and emotional difficulties with their children (151). Maternal habits such as smoking and alcohol use can also compromise infant outcome in women with depression (153).

In a nationally representative sample of 7537 mothers of toddlers, 24% had elevated depressive symptoms when the mean age of their child was 17 months and 17% when the mean age of their child was 35 months (154). Depression was persistent from the first to the second survey in 36% of women. Not having breast-fed, an ill-timed or unwanted pregnancy, and poor child health status were related to elevated depressive symptoms.

Depression was associated with a negative impact on maternal behaviour and disengagement from the child in a metaanalysis of 46 observational studies (153). Negative effects were greatest with current depression, but residual effects of prior depression were also seen. In addition, less optimal mother–infant interactions and insecure infant attachment were more marked when mothers had comorbid diagnoses, compared with either mothers with depression only or those with no

psychopathology (155). An examination of maternal depression and its influence on maternal behaviours indicates an association with an increased likelihood of smoking, not administering vitamins to a child, and not restraining children in appropriate car seats (156).

Exposure to maternal MDD during infancy and young childhood has been shown to have varying effects on the emotional, cognitive, and psychological development of children (157–162). A metaanalysis of 9 studies indicated that postpartum depression had a detectable effect on cognitive and emotional development of children older than the age of 1 year (163). Nulman and colleagues found that exposure to TCAs or fluoxetine throughout pregnancy was associated with little risk of adverse effects on cognition, language development, or the temperament of the children, but exposure to the mothers' depression was associated with impairments in cognitive and language achievements (164). The severity and chronicity of maternal depressive symptoms were related to more behaviour problems and lower vocabulary scores in a cohort of 4953 children (161). Antenatal anxiety has also been identified as a separate risk and additive risk in addition to postnatal depression for behavioural or emotional problems in children (165). It is therefore important for all clinicians who interact with mothers and their infants to understand that there are consequences to failing to find or treat depression in mothers that may extend beyond the distress experienced by the mother into long-term sequelae for her child. This fact cannot be ignored in the risk–benefit analysis of the decision to treat the depression.

Menopause

The median age for menopause is 51 years, with the perimenopause occurring in the 5 to 7 years prior to complete cessation of ovulation (166). Some studies have not found an increased risk of new-onset MDD in association with perimenopause (167–169); however, there is an increased risk of recurrence among women with a history of mood disorders (1). A recent 3.5-year survey of over 2000 women found that the transition from pre- to perimenopause and peri- to postmenopause was independently related to a significant increase in depression scores (odds ratio 1.8 for both) (170). Depression in the perimenopausal period is associated with risk factors such as a history of depressive disorders, particularly PMDD; poor physical health; and environmental stressors, rather than with hormonal changes (167–169,171).

Managing Depression During the Perimenopausal Period

Treatment of depressive disorders in menopausal women has focused on 2 strategies: estrogen replacement therapy (ERT) and antidepressant therapy. Estrogen has been reported to reduce somatic and mild depressive symptoms among

menopausal women (172–175). A RCT in 50 perimenopausal women with major and minor depression found a significantly higher rate of remission among those who received ERT (17-beta-estradiol transdermal patch), compared with placebo (68% and 20%; $P = 0.001$) (172).

ERT may enhance the effects of antidepressant medications in peri- or postmenopausal women. In a study of elderly women with depression receiving fluoxetine, a significant interaction between ERT and treatment effect was found (176). Similarly, in an open study in which peri- and postmenopausal women were treated with citalopram alone ($n = 22$) or as adjunct to ERT ($n = 13$), remission rates were higher among patients receiving the combination, compared with those treated with citalopram alone (84.6% vs. 59%) (177). Anxiety and somatic complaints improved significantly. ERT augmented the antidepressant response to sertraline in an analysis of data from 127 women over age 60 years treated in 2 multicentre trials (178). Women treated with sertraline who were taking ERT had significantly greater global improvement and quality of life than those not receiving ERT, and modest improvements in anxiety and cognition were also reported.

In contrast, a retrospective analysis of women taking fluoxetine for 8 weeks found no difference in efficacy rates in those taking fluoxetine alone, compared with estrogen therapy (179), and there was a trend toward higher relapse rates in women taking the combination. In a pooled analysis of data from RCTs of venlafaxine, remission rates in women age 50 years or over receiving venlafaxine were similar in those who were taking ERT and those who were not (50% and 44%, respectively) (16). The debate over whether estrogen has value in augmenting antidepressant treatment has not yet been settled, and in a recent review, the authors noted shortcomings of the current literature, “including combining women of various ages, failure to confirm life stage, the use of different types of estrogens, the inclusion of women with a range of mood disturbances, and the enrollment of women with concurrent psychiatric illness” (180).

Hot flashes are common during menopause and affect up to 75% of women (181,182). Antidepressants may improve hot flashes, and may be helpful in women for whom hormonal therapy is contraindicated (183–185). Venlafaxine demonstrated significant reductions in hot flash score, compared with placebo, during 4 weeks of therapy (61% vs 27%) (186,187), and improvements were maintained during continuation therapy (188). In a small pilot trial, paroxetine reduced the frequency (67%) and severity (75%) of hot flashes, as well as improving depression, sleep, anxiety, and quality of life scores (189). Antidepressants may therefore represent a

reasonable alternative to the treatment of hot flashes when hormone therapy is either contraindicated or unacceptable to the patient. Of the currently available antidepressants, the data to date support the use of venlafaxine and paroxetine.

Summary

Depression in women is more prevalent than in men, and biological, hormonal, and psychosocial factors have been considered to explain the differences in the nature of depression in women. In addition to increased frequency, and perhaps intensity, of depression, there are several aspects of mood disorders that are relevant only to women. The cyclical nature of premenstrual depression has led to the investigation of novel dosing strategies for antidepressants and to the provocative finding that antidepressants work very quickly in PMDD and can be used in a targeted manner during the late luteal phase. Depression during pregnancy and breastfeeding elicits special consideration, as many women are reluctant to take medications despite substantial evidence that now points to both the safety of antidepressants during these periods and the consequences of untreated depression on both mother and child. It is critical that physicians, women, and their families understand the risks and benefits of treating depression during these times, so that optimally informed decisions regarding pharmacotherapy and other therapeutic interventions can be made and the best outcome assured.

References

- Kessler R, McGonagle K, Swartz M, Blazer D, Nelson C. Sex and depression in the National Comorbidity Survey. I: Lifetime prevalence, chronicity and recurrence. *J Affect Disord* 1993;29:85–96.
- Weissman M, Bland R, Joyce P, Newman S, Wells J, Wittchen H. Sex differences in rates of depression: cross-national perspectives. *J Affect Disord* 1993;29:77–84.
- Kornstein S. The evaluation and management of depression in women across the life span. *J Clin Psychiatry* 2001;62(Suppl 24):11–7.
- Kornstein S, Schatzberg A, Thase M, Yonkers K, McCullough J, Keitner G, and others. Gender differences in chronic major and double depression. *J Affect Disord* 2000;60:1–11.
- Ernst C, Angst J. The Zurich Study. XII. Sex differences in depression. Evidence from longitudinal epidemiological data. *Eur Arch Psychiatry Clin Neurosci* 1992;241:222–30.
- Sargeant J, Bruce M, Florio L, Weissman M. Factors associated with 1-year outcome of major depression in the community. *Arch Gen Psychiatry* 1990;47:519–26.
- Keitner G, Ryan C, Miller I, Kohn R, Epstein N. 12-month outcome of patients with major depression and comorbid psychiatric or medical illness (compound depression). *Am J Psychiatry* 1991;148:345–50.
- Winokur G, Coryell W, Keller M, Endicott J, Akiskal H. A prospective follow-up of patients with bipolar and primary unipolar affective disorder. *Arch Gen Psychiatry* 1993;50:457–65.
- Elliott M. Gender differences in causes of depression. *Women Health* 2001;33:163–77.
- Kockler M, Heun R. Gender differences of depressive symptoms in depressed and nondepressed elderly persons. *Int J Geriatr Psychiatry* 2002;17:65–72.
- Kornstein S, Schatzberg A, Thase M, Yonkers K, McCullough J, Keitner G, and others. Gender differences in treatment response to sertraline versus imipramine in chronic depression. *Am J Psychiatry* 2000;157:1445–52.
- Joyce P, Mulder R, Luty S, Sullivan P, McKenzie J, Abbott R, and others. Patterns and predictors of remission, response and recovery in major depression treated with fluoxetine or nortriptyline. *Aust N Z J Psychiatry* 2002;36:384–91.
- Martenyi F, Dossenbach M, Mraz K, Metcalfe S. Gender differences in the efficacy of fluoxetine and maprotiline in depressed patients: a double-blind trial of antidepressants with serotonergic or norepinephrinergic reuptake inhibition profile. *Eur Neuropsychopharmacol* 2001;11:227–32.
- Quitkin F, Stewart J, McGrath P, Taylor B, Tisminetzky M, Petkova E, and others. Are there differences between women's and men's antidepressant responses? *Am J Psychiatry* 2002;159:1848–54.
- Entsuaeh A, Huang H, Thase M. Response and remission rates in different subpopulations with major depressive disorder administered venlafaxine, selective serotonin reuptake inhibitors, or placebo. *J Clin Psychiatry* 2001;62:869–77.
- Entsuaeh A, and others. Poster presented at First World Congress on Women's Mental Health; March 2001; Berlin (Germany).
- Ouslander J. Drug therapy in the elderly. *Ann Intern Med* 1981;95:711–22.
- Hamilton J. Sex and gender as critical variables in psychotropic drug research. In: Willie C, Reicker P, Kramer B, Brown B, editors. *Mental health, racism and sexism*. Pittsburgh (PA): Taylor & Francis, Inc; 1995. p 297–350.
- Altschuler L, Cohen L, Moline M, Kahn D, Carpenter D, Docherty J. The Expert Consensus Guideline Series. Treatment of depression in women. *Postgrad Med* 2001;1:1–107.
- Endicott J. History, evolution, and diagnosis of premenstrual dysphoric disorder. *J Clin Psychiatry* 2000;61(Suppl 12):5–8.
- Ross L, Steiner M. A biopsychosocial approach to premenstrual dysphoric disorder. *Psychiatr Clin North Am* 2003;26:529–46.
- Wittchen H, Becker E, Lieb R, Krause P. Prevalence, incidence and stability of premenstrual dysphoric disorder in the community. *Psychol Med* 2002;32:119–32.
- Yonkers K. The association between premenstrual dysphoric disorder and other mood disorders. *J Clin Psychiatry* 1997;58(Suppl 15):19–25.
- Cohen L, Soares C, Otto M, Sweeney B, Liberman R, Harlow B. Prevalence and predictors of premenstrual dysphoric disorder (PMDD) in older premenopausal women. The Harvard Study of Moods and Cycles. *J Affect Disord* 2002;70:125–32.
- Pearlstein T, Frank E, Rivera-Tovar A, Thoft J, Jacobs E, Mieczkowski T. Prevalence of axis I and axis II disorders in women with late luteal phase dysphoric disorder. *J Affect Disord* 1990;20:129–34.
- American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. 4th ed. Washington (DC): American Psychiatric Association; 1994.
- Endicott J, Harrison W. Daily rating of severity of problems form. New York: Department of Research and Training, NY State Psychiatric Institute; 1990.
- Mortola J, Girton L, Beck L, Yen S. Diagnosis of premenstrual syndrome by a simple, prospective, and reliable instrument: the calendar of premenstrual experiences. *Obstet Gynecol* 1990;76:302–7.
- Freeman E, De RR, Rickels K. Reliability and validity of a daily diary for premenstrual syndrome. *Psychiatry Res* 1996;65:97–106.
- Steiner M, Macdougall M, Brown E. The premenstrual symptoms screening tool (PSS) for clinicians. *Arch Women Ment Health* 2003;6:203–9.
- Pariser S, Nasrallah H, Gardner D. Postpartum mood disorders: clinical perspectives. *J Womens Health* 1997;6:421–34.
- Graze K, Nee J, Endicott J. Premenstrual depression predicts future major depressive disorder. *Acta Psychiatr Scand* 1990;81:201–5.
- Rojansky N, Halbreich U, Zander K, and others. Imipramine receptor binding and serotonin uptake in platelets of women with premenstrual changes. *Gynecol Obstet Invest* 1991;31:146–52.
- Dimmock P, Wyatt K, Jones P, O'Brien P. Efficacy of selective serotonin-reuptake inhibitors in premenstrual syndrome: a systematic review. *Lancet* 2000;356:1131–6.
- Halbreich U, Bergeron R, Yonkers K, Freeman E, Stout A, Cohen L. Efficacy of intermittent, luteal phase sertraline treatment of premenstrual dysphoric disorder. *Obstet Gynecol* 2002;100:1219–29.
- Cohen L, Miner C, Brown E, Freeman E, Halbreich U, Sundell K, and others. Premenstrual daily fluoxetine for premenstrual dysphoric disorder: a placebo-controlled, clinical trial using computerized diaries. *Obstet Gynecol* 2002;100:435–44.
- Miner C, Brown E, McCray S, Gonzales J, Wohlreich M. Weekly luteal-phase dosing with enteric-coated fluoxetine 90 mg in premenstrual dysphoric disorder: a randomized, double-blind, placebo-controlled clinical trial. *Clin Ther* 2002;24:417–33.
- Freeman E, Rickels K, Yonkers K, Kunz N, McPherson M, Upton G. Venlafaxine in the treatment of premenstrual dysphoric disorder. *Obstet Gynecol* 2001;98:737–44.
- Landen M, Eriksson O, Sundblad C, Andersch B, Naessen T, Eriksson E. Compounds with affinity for serotonergic receptors in the treatment of premenstrual dysphoria: a comparison of buspirone, nefazodone and placebo. *Psychopharmacology* 2001;155:292–8.
- Hunter M, Ussher J, Browne S, Cariss M, Jolley 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.
- Macdougall M, Steiner M. Treatment of premenstrual dysphoria with selective serotonin re-uptake inhibitors: focus on safety. *Expert Opin Drug Saf* 2003;2:161–6.

42. Steiner M, Romano S, Babcock S, Dillon J, Shuler C, Berger C, and others. The efficacy of fluoxetine in improving physical symptoms associated with premenstrual dysphoric disorder. *Br J Obstet Gynaecol* 2001;108:462–8.
43. Bolton H, Hughes P, Turton P, Sedgwick P. Incidence and demographic correlates of depressive symptoms during pregnancy in an inner London population. *J Psychosom Obstet Gynaecol* 1998;19:202–9.
44. O'Hara M, Zekoski E, Philipps L, Wright E. Controlled prospective study of postpartum mood disorders: comparison of childbearing and nonchildbearing women. *J Abnorm Psychol* 1990;99:3–15.
45. Josefsson A, Berg G, Nordin C, Sydsjo G. Prevalence of depressive symptoms in late pregnancy and postpartum. *Acta Obstet Gynecol Scand* 2001;80:251–5.
46. O'Hara M. Social support, life events, and depression during pregnancy and the puerperium. *Arch Gen Psychiatry* 1986;43:569–73.
47. O'Hara M. Depression during pregnancy. Postpartum depression: causes and consequences. New York: Springer-Verlag; 1994. p 110–20.
48. Gotlib I, Whiffen V, Mount J, Milne K, Cordy N. Prevalence rates and demographic characteristics associated with depression in pregnancy and the postpartum. *J Consult Clin Psychol* 1989;57:269–74.
49. Henshaw S. Unintended pregnancy in the United States. *Fam Plann Perspect* 1998;30:24–9, 46.
50. Cohen L. Course and treatment of mood disorders during pregnancy and the postpartum period. *Women's Mental Health: A Decade of Progress*. American Psychiatric Association Annual Meeting; 2000; Chicago (IL).
51. Steer R, Scholl T, Hediger M, Fischer R. Self-reported depression and negative pregnancy outcomes. *J Clin Epidemiol* 1992;45:1093–9.
52. Orr S, Miller C. Maternal depressive symptoms and the risk of poor pregnancy outcome. Review of the literature and preliminary findings. *Epidemiol Rev* 1995;17:165–71.
53. Zuckerman B, Bresnahan K. Developmental and behavioral consequences of prenatal drug and alcohol exposure. *Pediatr Clin North Am* 1991;38:1387–406.
54. Pritchard C. Depression and smoking in pregnancy in Scotland. *J Epidemiol Community Health* 1994;48:377–82.
55. Ikard F, Tomkins S. The experience of affect as a determinant of smoking behavior: a series of validity studies. *J Abnorm Psychol* 1973;81:172–81.
56. Paton S, Kessler R, Kandel D. Depressive mood and adolescent illicit drug use: a longitudinal analysis. *J Genet Psychol* 1977;131:267–89.
57. Beckman L. Perceived antecedents and effects of alcohol consumption in women. *J Stud Alcohol* 1980;41:518–30.
58. Kielholz P. Alcohol and depression. *Br J Addict Alcohol Other Drugs* 1970;65:187–93.
59. Zuckerman B, Amaro H, Bauchner H, Cabral H. Depressive symptoms during pregnancy: relationship to poor health behaviors. *Am J Obstet Gynecol* 1989;160:1107–11.
60. Sadler T, Langman J. *Langman's medical embryology*. Philadelphia: Lippincott Williams & Wilkins Publishers; 2000.
61. Dicke J. *Teratology: principles and practice*. *Med Clin North Am* 1989;73:567–82.
62. Koren G, Pastuszak A, Ito S. Drugs in pregnancy. *N Engl J Med* 1998;338:1128–37.
63. *Physician's Desk Reference*. Montvale (NJ): Medical Economics Company; 2000.
64. Ericson A, Kallen B, Wiholm B. Delivery outcome after the use of antidepressants in early pregnancy. *Eur J Clin Pharmacol* 1999;55:503–8.
65. Goldstein D, Corbin L, Sundell K. Effects of first-trimester fluoxetine exposure on the newborn. *Obstet Gynecol* 1997;89:713–8.
66. Chambers C, Johnson K, Dick L, Felix R, Jones K. Birth outcomes in pregnant women taking fluoxetine. *N Engl J Med* 1996;335:1010–5.
67. Loebstein R, Koren G. Pregnancy outcome and neurodevelopment of children exposed in utero to psychoactive drugs: the Motherisk experience. *J Psychiatry Neurosci* 1997;22:192–6.
68. Cohen L, Heller V, Bailey J, Grush L, Ablon J, Bouffard S. Birth outcomes following prenatal exposure to fluoxetine. *Biol Psychiatry* 2000;48:996–1000.
69. Addis A, Koren G. Safety of fluoxetine during the first trimester of pregnancy: a meta-analytical review of epidemiological studies. *Psychol Med* 2000;30:89–94.
70. Kulin N, Pastuszak A, Sage S, Schick-Boschetto B, Spivey G, Feldkamp M, and others. Pregnancy outcome following maternal use of the new selective serotonin reuptake inhibitors: a prospective controlled multicenter study. *JAMA* 1998;279:609–10.
71. Einarson A, Fatoye B, Sarkar M, Lavigne S, Brochu J, Chambers C, and others. Pregnancy outcome following gestational exposure to venlafaxine: a multicenter prospective controlled study. *Am J Psychiatry* 2001;158:1728–30.
72. Simon G, Cunningham M, Davis R. Outcomes of prenatal antidepressant exposure. *Am J Psychiatry* 2002;159:2055–61.
73. McElhatton P, Garbis H, Elefant E, Vial T, Bellemin B, Mastroiacovo P, and others. The outcome of pregnancy in 689 women exposed to therapeutic doses of antidepressants. A collaborative study of the European Network of Teratology Information Services (ENTIS). *Reprod Toxicol* 1996;10:285–94.
74. Costei A, Kozer E, Ho T, Ito S, Koren G. Perinatal outcome following third trimester exposure to paroxetine. *Arch Pediatr Adolesc Med* 2002;156:1129–32.
75. Altshuler L. The use of SSRIs in depressive disorders specific to women. *J Clin Psychiatry* 2002;63(Suppl 7):3–8.
76. Einarson A, Bonari L, Voyer-Lavigne S, Addis A, Matsui D, Johnson Y, and others. A multicentre prospective controlled study to determine the safety of trazodone and nefazodone use during pregnancy. *Can J Psychiatry* 2003;48:106–10.
77. Kesim M, Yaris F, Kadioglu M, Yaris E, Kalyoncu N, Ulku C. Mirtazapine use in two pregnant women: is it safe? *Teratology* 2002;66:204.
78. Reiff-Eldridge R, Heffner C, Ephross S, Tennis P, White A, Andrews E. Monitoring pregnancy outcomes after prenatal drug exposure through prospective pregnancy registries: a pharmaceutical company commitment. *Am J Obstet Gynecol* 2000;182:159–63.
79. Nulman I, Rovet J, Stewart D, Wolpin J, Gardner H, Theis J, and others. Neurodevelopment of children exposed in utero to antidepressant drugs. *N Engl J Med* 1997;336:258–62.
80. Stiskal J, Kulin N, Koren G, Ho T, Ito S. Neonatal paroxetine withdrawal syndrome. *Arch Dis Child Fetal Neonatal Educ* 2001;84:F134–F135.
81. Nordeng H, Lindemann R, Perminov K, Reikvam A. Neonatal withdrawal syndrome after in utero exposure to selective serotonin reuptake inhibitors. *Acta Paediatr* 2001;90:288–91.
82. Laine K, Heikkinen T, Ekblad U, Kero P. Effects of exposure to selective serotonin reuptake inhibitors during pregnancy on serotonergic symptoms in newborns and cord blood monoamine and prolactin concentrations. *Arch Gen Psychiatry* 2003;60:720–6.
83. Brockington I. The maternity blues. In: Brockington I, editor. *Motherhood and mental health*. Oxford (UK): Oxford University Press; 1996. p 147–53.
84. Stocky A, Lynch J. Acute psychiatric disturbance in pregnancy and the puerperium. *Baillieres Clin Obstet Gynaecol* 2000;14:73–87.
85. Kendal R, Chalmers J, Platz C. Epidemiology and perinatal psychoses. *Br J Psychiatry* 1987;150:662–73.
86. Watt S, Sword W, Krueger P, Sheehan D. A cross-sectional study of early identification of postpartum depression: Implications for primary care providers from The Ontario Mother & Infant Survey. *BMC Fam Pract* 2002;3:5.
87. Georgiopoulos A, Bryan T, Yawn B, Houston M, Rummans T, Therneau T. Population-based screening for postpartum depression. *Obstet Gynecol* 1999;93:653–7.
88. Stein A, Guth D, Bucher J, Bond A, Day A, Cooper P. The relationship between post-natal depression and mother-child interaction. *Br J Psychiatry* 1991;158:46–52.
89. Campbell S, Cohn J. Prevalence and correlates of postpartum depression in first-time mothers. *J Abnorm Psychol* 1991;100:594–9.
90. Sameroff A, Seifer R, Zax M. Early development of children at risk for emotional disorder. *Monographs of the Society for Research in Child Development* number 47, Serial number 199. Ann Arbor (MI): Society for Research in Child Development; 1982.
91. Field T, Healy B, Goldstein S. Behavior-state matching and synchrony in mother-infant interactions of nondepressed vs. depressed dyads. *Developmental Psychology* 1990;7:14.
92. Field T. Infants of depressed mothers. *Infant Behavior and Development* 1995;1:1–13.
93. Cox J, Holden J, Sagovsky R. Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. *Br J Psychiatry* 1987;150:782–6.
94. Evins G, Theofrastous J, Galvin S. Postpartum depression: a comparison of screening and routine clinical evaluation. *Am J Obstet Gynecol* 2000;182:1080–2.
95. Lee D, Yip A, Chiu H, Chung T. Screening for postnatal depression using the double-test strategy. *Psychosom Med* 2000;62:258–63.
96. Garvey M, Tuason V, Lumry A, Hoffmann N. Occurrence of depression in the postpartum state. *J Affect Disord* 1983;5:97–101.
97. O'Hara M. *Postpartum depression: causes and consequences*. New York: Springer-Verlag; 1995. p 168–94.
98. Wisner K, Peindl K, Hanusa B. Relationship of psychiatric illness to childbearing status: a hospital-based epidemiologic study. *J Affect Disord* 1993;28:39–50.
99. O'Hara M, Neunaber D, Zekoski E. Prospective study of postpartum depression: prevalence, course, and predictive factors. *J Abnorm Psychol* 1984;93:158–71.
100. O'Hara M, Swain A. Rates and risk of postpartum depression—a meta-analysis. *Int Rev Psychiatry* 1996;37–54.
101. Gotlib I, Whiffen V, Wallace P, Mount J. Prospective investigation of postpartum depression: factors involved in onset and recovery. *J Abnorm Psychol* 1991;100:122–32.
102. Beck C. A meta-analysis of predictors of postpartum depression. *Nurs Res* 1996;45:297–303.
103. Kumar R, Robson K. A prospective study of emotional disorders in childbearing women. *Br J Psychiatry* 1984;144:35–47.
104. Zekoski P, Milet T. Postpartum psychiatric disorders: their relationship to psychological adjustment and marital satisfaction in the spouses. *J Abnorm Psychol* 1996;105:281–5.
105. Marks M, Wieck A, Checkley S, Kumar R. Contribution of psychological and social factors to psychotic and non-psychotic relapse after childbirth in women with previous histories of affective disorder. *J Affect Disord* 1992;24:253–63.
106. Matthey S, Barnett B, Ungerer J, Waters B. Paternal and maternal depressed mood during the transition to parenthood. *J Affect Disord* 2000;60:75–85.

107. Wisner K, Perel J, Peindl K, Hanusa B, Findling R, Rapport D. Prevention of recurrent postpartum depression: a randomized clinical trial. *J Clin Psychiatry* 2001;62:82–6.
108. Escobar G, Braveman P, Ackerson L, Odouli R, Coleman-Phox K, Capra A, and others. A randomized comparison of home visits and hospital-based group follow-up visits after early postpartum discharge. *Pediatrics* 2001;108:719–27.
109. Morrell C, Spiby H, Stewart P, Walters S, Morgan A. Costs and effectiveness of community postnatal support workers: randomised controlled trial. *BMJ* 2000;321:593–8.
110. Reid M, Glazener C, Murray G, Taylor G. A two-centred pragmatic randomised controlled trial of two interventions of postnatal support. *Br J Obstet Gynecol* 2002;109:1164–70.
111. Dennis C. The effect of peer support on postpartum depression: a pilot randomized controlled trial. *Can J Psychiatry* 2003;48:115–24.
112. Wisner K, Wheeler S. Prevention of recurrent postpartum major depression. *Hosp Community Psychiatry* 1994;45:1191–6.
113. Chabrol H, Teissedre F, Saint-Jean M, Teissyre N, Roge B, Mullet E. Prevention and treatment of post-partum depression: a controlled randomized study on women at risk. *Psychol Med* 2002;32:1039–47.
114. Brughla T, Wheatley S, Taub N, Culverwell A, Friedman T, Kirwan P, and others. Pragmatic randomized trial of antenatal intervention to prevent post-natal depression by reducing psychosocial risk factors. *Psychol Med* 2000;30:1273–81.
115. Hayes B, Muller R, Bradley B. Perinatal depression: a randomized controlled trial of an antenatal education intervention for primiparas. *Birth* 2001;28:28–35.
116. Elliott S, Leverton T, Sanjack M, Turner H, Cowmeadow P, Hopkins J, and others. Promoting mental health after childbirth: a controlled trial of primary prevention of postnatal depression. *Br J Clin Psychol* 2000;39:223–41.
117. Hoffbrand S, Howard L, Crawley H. Antidepressant drug treatment for postnatal depression. *Cochrane Database Syst Rev* 2001:CD002018. Oxford (UK): Update Software Ltd; 2001.
118. Appleby L, Warner R, Whitton A, Faragher B. A controlled study of fluoxetine and cognitive-behavioural counselling in the treatment of postnatal depression. *BMJ* 1997;314:932–6.
119. Cohen L, Viguera A, Bouffard S, Nonacs R, Morabito C, Collins M, and others. Venlafaxine in the treatment of postpartum depression. *J Clin Psychiatry* 2001;62:592–6.
120. Stowe Z, Casarella J, Landry J. Sertraline in the treatment of women with postpartum major depression. *Depression* 1995:49–55.
121. Suri R, Burt V, Altshuler L, Zuckerbrow-Miller J, Fairbanks L. Fluvoxamine for postpartum depression. *Am J Psychiatry* 2001;158:1739–40.
122. O'Hara M, Stuart S, Gorman L, Wenzel A. Efficacy of interpersonal psychotherapy for postpartum depression. *Arch Gen Psychiatry* 2000;57:1039–45.
123. Misri S, Kostaras X, Fox D, Kostaras D. The impact of partner support in the treatment of postpartum depression. *Can J Psychiatry* 2000;45:54–8.
124. Bloch M, Schmidt P, Danaceau M, Murphy J, Nieman L, Rubinow D. Effects of gonadal steroids in women with a history of postpartum depression. *Am J Psychiatry* 2000;157:924–30.
125. Gregoire A, Kumar R, Everitt B, Henderson A, Studd J. Transdermal oestrogen for treatment of severe postnatal depression. *Lancet* 1996;347:930–3.
126. Sichel D, Cohen L, Robertson L, Ruttenberg A, Rosenbaum J. Prophylactic estrogen in recurrent postpartum affective disorder. *Biol Psychiatry* 1995;38:814–8.
127. Lawrie T, Herxheimer A, Dalton K. Oestrogens and progestogens for preventing and treating postnatal depression. *Cochrane Database Syst Rev* 2000:CD001690. Oxford (UK): Update Software Ltd; 2000.
128. Dodd S, Buist A, Norman T. Antidepressants and breast-feeding: a review of the literature. *Paediatr Drugs* 2000;2:183–92.
129. Wisner K, Perel J, Findling R. Antidepressant treatment during breast-feeding. *Am J Psychiatry* 1996;153:1132–7.
130. Newport D, Wilcox M, Stowe Z. Antidepressants during pregnancy and lactation: defining exposure and treatment issues. *Semin Perinatol* 2001;25:177–90.
131. Newport D, Hostetter A, Arnold A, Stowe Z. The treatment of postpartum depression: minimizing infant exposures. *J Clin Psychiatry* 2002;63(Suppl 7):31–44.
132. Ilett K, Kristensen J, Hackett L, Paech M, Kohan R, Rampono J. Distribution of venlafaxine and its O-desmethyl metabolite in human milk and their effects in breastfed infants. *Br J Clin Pharmacol* 2002;53:17–22.
133. Stowe Z, Owens M, Landry J, Kilts C, Ely T, Llewellyn A, and others. Sertraline and desmethylsertraline in human breast milk and nursing infants. *Am J Psychiatry* 1997;154:1255–60.
134. Kristensen J, Ilett K, Dusci L, Hackett L, Yapp P, Wojnar-Horton R, and others. Distribution and excretion of sertraline and N-desmethylsertraline in human milk. *Br J Clin Pharmacol* 1998;45:453–7.
135. Wisner K, Perel J, Blumer J. Serum sertraline and N-desmethylsertraline levels in breast-feeding mother-infant pairs. *Am J Psychiatry* 1998;155:690–2.
136. Hendrick V, Fukuchi A, Altshuler L, Widawski M, Wertheimer A, Brunhuber M. Use of sertraline, paroxetine and fluvoxamine by nursing women. *Br J Psychiatry* 2001;179:163–6.
137. Dodd S, Stocky A, Buist A, Burrows G, Maguire K, Norman T. Sertraline in paired blood plasma and breast-milk samples from nursing mothers. *Hum Psychopharmacol* 2000;15:161–264.
138. Stowe Z, Hostetter A, Owens M, Ritchie J, Sternberg K, Cohen L, and others. The pharmacokinetics of sertraline excretion into human breast milk: determinants of infant serum concentrations. *J Clin Psychiatry* 2003;64:73–80.
139. Begg E, Duffull S, Saunders D, Buttimore R, Ilett K, Hackett L, and others. Paroxetine in human milk. *Br J Clin Pharmacol* 1999;48:142–7.
140. Ohman R, Hagg S, Carleborg L, Spigset O. Excretion of paroxetine into breast milk. *J Clin Psychiatry* 1999;60:519–23.
141. Stowe Z, Cohen L, Hostetter A, Ritchie J, Owens M, Nemeroff C. Paroxetine in human breast milk and nursing infants. *Am J Psychiatry* 2000;157:185–9.
142. Misri S, Kim J, Riggs K, Kostaras X. Paroxetine levels in postpartum depressed women, breast milk, and infant serum. *J Clin Psychiatry* 2000;61:828–32.
143. Taddio A, Ito S, Koren G. Excretion of fluoxetine and its metabolite, norfluoxetine, in human breast milk. *J Clin Pharmacol* 1996;36:42–7.
144. Birnbaum C, Cohen L, Bailey J, Grush L, Robertson L, Stowe Z. Serum concentrations of antidepressants and benzodiazepines in nursing infants: a case series. *Pediatrics* 1999;104:e11.
145. Kristensen J, Ilett K, Hackett L, Yapp P, Paech M, Begg E. Distribution and excretion of fluoxetine and norfluoxetine in human milk. *Br J Clin Pharmacol* 1999;48:521–7.
146. Hendrick V, Stowe Z, Altshuler L, Mintz J, Hwang S, Hostetter A, and others. Fluoxetine and norfluoxetine concentrations in nursing infants and breast milk. *Biol Psychiatry* 2001;50:775–82.
147. Suri R, Stowe Z, Hendrick V, Hostetter A, Widawski M, Altshuler L. Estimates of nursing infant daily dose of fluoxetine through breast milk. *Biol Psychiatry* 2002;52:446–51.
148. Rampono J, Kristensen J, Hackett L, Paech M, Kohan R, Ilett K. Citalopram and demethylcitalopram in human milk: distribution, excretion and effects in breast fed infants. *Br J Clin Pharmacol* 2000;50:263–8.
149. Heikkinen T, Ekblad U, Kero P, Ekblad S, Laine K. Citalopram in pregnancy and lactation. *Clin Pharmacol Ther* 2002;72:184–91.
150. Llewellyn A, Stowe Z. Psychotropic medications in lactation. *J Clin Psychiatry* 1998;59(Suppl 2):41–52.
151. Weinberg M, Tronick E. The impact of maternal psychiatric illness on infant development. *J Clin Psychiatry* 1998;59(Suppl 2):53–61.
152. Cohn J, Tronick E. Three-month-old infants' reaction times to simulated maternal depression. *Child Dev* 1983;54.
153. Lovejoy M, Graczyk P, O'Hare E, Neuman G. Maternal depression and parenting behavior: a meta-analytic review. *Clin Psychol Rev* 2000;20:561–92.
154. McLennan J, Kotelchuck M, Cho H. Prevalence, persistence, and correlates of depressive symptoms in a national sample of mothers of toddlers. *J Am Acad Child Adolesc Psychiatry* 2001;40:1316–23.
155. Carter A, Garrity-Rokous F, Chazan-Cohen R, Little C, Briggs-Gowan M. Maternal depression and comorbidity: predicting early parenting, attachment security, and toddler social-emotional problems and competencies. *J Am Acad Child Adolesc Psychiatry* 2001;40:18–26.
156. Leiferman J. The effect of maternal depressive symptomatology on maternal behaviors associated with child health. *Health Educ Behav* 2002;29:596–607.
157. Essex M, Klein M, Miech R, Smider N. Timing of initial exposure to maternal major depression and children's mental health symptoms in kindergarten. *Br J Psychiatry* 2001;179:151–6.
158. Petterson S, Albers A. Effects of poverty and maternal depression on early child development. *Child Dev* 2001;72:1794–813.
159. Kurstjens S, Wolke D. Effects of maternal depression on cognitive development of children over the first 7 years of life. *J Child Psychol Psychiatry* 2001;42:623–36.
160. Galler J, Harrison R, Ramsey F, Forde V, Butler S. Maternal depressive symptoms affect infant cognitive development in Barbados. *J Child Psychol Psychiatry* 2000;41:747–57.
161. Brennan P, Hammen C, Andersen M, Bor W, Najman J, Williams G. Chronicity, severity, and timing of maternal depressive symptoms: relationships with child outcomes at age 5. *Dev Psychol* 2000;36:759–66.
162. Murray L, Sinclair D, Cooper P, Ducourneau P, Turner P, Stein A. The socioemotional development of 5-year-old children of postnatally depressed mothers. *J Child Psychol Psychiatry* 1999;40:1259–71.
163. Beck C. The effects of postpartum depression on child development: a meta-analysis. *Arch Psychiatr Nurs* 1998;12:12–20.
164. Nulman I, Rovet J, Stewart D, Wolpin J, Pace-Asciak P, Shuhaiber S, and others. Child development following exposure to tricyclic antidepressants or fluoxetine throughout fetal life: a prospective, controlled study. *Am J Psychiatry* 2002;159:1889–95.
165. O'Connor T, Heron J, Glover V. Antenatal anxiety predicts child behavioral/emotional problems independently of postnatal depression. *J Am Acad Child Adolesc Psychiatry* 2002;41:1470–7.
166. Burt V, Stein K. Epidemiology of depression throughout the female life cycle. *J Clin Psychiatry* 2002;63(Suppl 7):9–15.
167. Kaufert P, Gilbert P, Tate R. The Manitoba Project: a re-examination of the link between menopause and depression. *Maturitas* 1992;14:143–55.
168. Kessler R. Epidemiology of women and depression. *J Affect Disord* 2003;74:5–13.

169. Collins A, Landgren B. Reproductive health, use of estrogen and experience of symptoms in perimenopausal women: a population-based study. *Maturitas* 1994;20:101–11.
170. Maartens L, Knottnerus J, Pop V. Menopausal transition and increased depressive symptomatology. A community based prospective study. *Maturitas* 2002;42:195.
171. Robinson G. Psychotic and mood disorders associated with the perimenopausal period: epidemiology, aetiology and management. *CNS Drugs* 2001;15:175–84.
172. Soares C, Almeida O, Joffe H, Cohen L. 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.
173. Gambacciani M, Ciaponi M, Cappagli B, Monteleone P, Benussi C, Bevilacqua G, and others. Effects of low-dose, continuous combined estradiol and noretisterone acetate on menopausal quality of life in early postmenopausal women. *Maturitas* 2003;44:157–63.
174. Rasgon N, Altshuler L, Fairbanks L, Dunkin J, Davtayan C, Elman S, and others. Estrogen replacement therapy in the treatment of major depressive disorder in perimenopausal women. *J Clin Psychiatry* 2002;63(Suppl 7):45–8.
175. Schmidt P, Nieman L, Danaceau M, Tobin M, Roca C, Murphy J, and others. Estrogen replacement in perimenopause-related depression: a preliminary report. *Am J Obstet Gynecol* 2000;183:414–20.
176. Schneider L, Small G, Hamilton S, Bystritsky A, Nemeroff C, Meyers B. Estrogen replacement and response to fluoxetine in a multicenter geriatric depression trial. Fluoxetine Collaborative Study Group. *Am J Geriatr Psychiatry* 1997;5:97–106.
177. Soares C, Poitras J, Prouty J, Alexander A, Shifren J, Cohen L. Efficacy of citalopram as a monotherapy or as an adjunctive treatment to estrogen therapy for perimenopausal and postmenopausal women with depression and vasomotor symptoms. *J Clin Psychiatry* 2003;64:473–9.
178. Schneider L, Small G, Clary C. Estrogen replacement therapy and antidepressant response to sertraline in older depressed women. *Am J Geriatr Psychiatry* 2001;9:393–9.
179. Amsterdam J, Garcia-Espana F, Fawcett J, Quitkin F, Reimherr F, Rosenbaum J, and others. Fluoxetine efficacy in menopausal women with and without estrogen replacement. *J Affect Disord* 1999;55:11–7.
180. Grigoriadis S, Kennedy S. Role of estrogen in the treatment of depression. *Am J Ther* 2002;9:503–9.
181. von Muhlen D, Kritz-Silverstein D, Barrett-Connor E. A community-based study of menopause symptoms and estrogen replacement in older women. *Maturitas* 1995;22:71–8.
182. Malacara J, Canto dCT, Bassol S, Gonzalez N, Cacique L, Vera-Ramirez M, and others. Symptoms at pre- and postmenopause in rural and urban women from three States of Mexico. *Maturitas* 2002;43:11–9.
183. Grady D, Herrington D, Bittner V, Blumenthal R, Davidson M, Hlatky M, and others. Cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/Progestin Replacement Study follow-up (HERS II). *JAMA* 2002;288:49–57.
184. Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B, and others. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/Progestin Replacement Study (HERS) Research Group. *JAMA* 1998;280:605–13.
185. Rossouw J, Anderson G, Prentice R, La Croix A, Kooperberg C, Stefanick M, and others. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *JAMA* 2002;288:321–33.
186. Loprinzi C, Kugler J, Sloan J, Mailliard J, La Vasseur B, Barton D, and others. Venlafaxine in management of hot flashes in survivors of breast cancer: a randomised controlled trial. *Lancet* 2000;356:2059–63.
187. Barton D, Loprinzi C, Wahner-Roedler D. Hot flashes: aetiology and management. *Drugs Aging* 2001;18:597–606.
188. Barton D, La Vasseur B, Loprinzi C, Novotny P, Wilwerding M, Sloan J. Venlafaxine for the control of hot flashes: results of a longitudinal continuation study. *Oncol Nurs Forum* 2002;29:33–40.
189. Stearns V, Isaacs C, Rowland J, Crawford J, Ellis M, Kramer R, and others. A pilot trial assessing the efficacy of paroxetine hydrochloride (Paxil) in controlling hot flashes in breast cancer survivors. *Ann Oncol* 2000;11:17–22.

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