Complementary and Alternative Medicine for the Treatment of Depressive Disorders in Women

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KEYWORDS

• Complementary/alternative treatment • *S*-Adenosylmethionine
• Omega-3 fatty acids • St John's wort • Acupuncture
• Depression • Women

Complementary and alternative medicine (CAM) therapies are commonly practiced in the United States and are used more frequently among women than men. This article reviews several CAM treatments for depressive disorders in women, with a focus on major depressive disorder (MDD) across the reproductive life cycle. An emphasis on CAM treatments for MDD was selected because of the large evidence base compared with other psychiatric disorders. The CAM treatments selected for review are those with high clinical importance resulting from available data and prevalence of use. In

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women, omega-3 fatty acids, exercise, and folate are interventions that may be attractive to incorporate with standard treatments for MDD, because of low risk, benefits for general health, and evidence suggesting an adjunctive role in the treatment of MDD. *S*-Adenosylmethionine (SAMe) and bright light therapy may be reasonable therapeutic options for some individuals, as there is evidence to support monotherapy in MDD. St John's wort (*Hypericum perforatum)* has the most consistent evidence of efficacy in mild to moderate depression, but carries a risk of potential drug-drug interactions. As with standard antidepressants, SAMe, bright light therapy, and St John's wort have been associated with emergent hypomania or mania after treatment initiation, and this may be especially important in women who have bipolar disorder. Further studies are necessary before acupuncture can be recommended in the treatment of MDD. In general, although some treatments seem promising, well-powered rigorous studies are necessary to elucidate the role of CAM in the treatment of psychiatric disorders in women.

MOOD DISORDERS ACROSS THE REPRODUCTIVE LIFE CYCLE: MENSTRUAL CYCLE, ANTEPARTUM AND POSTPARTUM PERIODS, AND THE MENOPAUSAL TRANSITION

Menstrual Cycle

Women commonly experience mood, behavioral, and somatic symptoms in the luteal phase of the menstrual cycle. Symptoms can vary in intensity and duration, and may include depressed mood or dysphoria, anxiety, irritability, loss of energy, change in appetite or sleep, breast tenderness, or bloating. For most women, premenstrual syndrome (PMS) symptom severity is mild and functioning is not impaired. However, about 4.6% to 6.4% of women have more severe signs and symptoms accompanied by impaired social, occupational, or personal functioning and meet diagnostic criteria for premenstrual dysphoric disorder (PMDD).[1–3] Subthreshold PMDD has been reported in 18.6% to 20.7% of women.[4,5] The earliest PMS studies in CAM, including several with omega-3 fatty acids, bright light, and exercise, predate the new term PMDD, such that it is necessary to extrapolate findings from the older literature. Despite lack of rigorous clinical data, women often use CAM treatments, including vitamin and mineral supplements, exercise, and diet changes rather than standard antidepressants or oral contraceptives.[6] Thus, the rigorous investigation of CAM therapies in the treatment of severe PMS and PMDD is warranted.

Antepartum and Postpartum Periods

Women have greater 1-year and lifetime prevalence rates of MDD compared with men.[7,8] Hormonal fluctuations associated with reproductive events are believed to contribute to the higher prevalence of depression observed in women.[9,10] Estimates of prevalence for minor and major depression in the periods during pregnancy and the postpartum period vary widely, from 14% to 25%, depending on the different diagnostic criteria, time points, and specifics regarding the population studied, and overall study design.[9,11–18] Antenatal depression is associated with an increased risk of underutilization of prenatal care,[19] increased somatic symptoms and physician visits during pregnancy,[20,21] obstetric complications,[22] preterm birth,[23,24] negative childbirth experience,[20] and postpartum depression (PPD).[25]

Annually in the United States, it is estimated that 1 in 8 women develop depression after birth.[11,26–28] Untreated PPD is associated with consequences for the infant that include prolonged infant crying, infant colic,[29] insecure attachment between mother and child,[30] increased infant cortisol levels,[31] decreased general intelligence quotient and language skills,[32] and abnormal infant socioemotional development.[33,34]

For decades, the safety and efficacy of antidepressant treatment during pregnancy and lactation were not adequately studied. Only recently were treatment guidelines published by representatives from the American Psychiatric Association and the American College of Obstetrics and Gynecology regarding treatment algorithms for antenatal management of depression.[35] Women may be particularly motivated to seek treatment other than standard medications during pregnancy or while breastfeeding. Therefore, although CAM therapies have been less rigorously studied than standard antidepressants, many women may seek CAM treatments because they may believe they are a safer alternative to prescribed antidepressant treatment.

Menopausal Transition

The perimenopause refers to the transition characterized by hormonal fluctuation and changes in menstrual patterns, and this lasts typically for several years before menopause.[36] Women have higher prevalence rates of MDD during the perimenopausal transition compared with rates found in premenopausal women.[37] Recently, in 2 large prospective epidemiological studies, investigators reported an increased risk of new onset of MDD during the perimenopause.[38,39] Although estrogen may have antidepressant effects,[40,41] many women seek nonhormonal interventions for mood and somatic symptoms associated with the menopausal transition. Since the results of the Women's Health Initiative were published in 2002, the use of replacement hormones has become less common as the risks and benefits are reevaluated.[42] Associated with the decrease in prescriptions for hormonal therapies for perimenopausal symptoms was a corresponding increase in antidepressant prescriptions for perimenopausal women.[43,44] Antidepressants, particularly those with mechanisms of action on serotonergic neurotransmission, and other psychotropic medications are frequently used to treat the mood, insomnia, and vasomotor symptoms in menopausal and perimenopausal women.[45] Because the use of hormonal therapies has become more controversial, CAM therapies may be attractive to women for the potential treatment of mood and vasomotor symptoms.

WHAT IS CAM? DEFINITIONS, BELIEFS AND CHALLENGES

CAM refers to treatments that are not considered standard or established practices in Western medicine. Complementary approaches specifically refer to those that are consistent with the Western biomedical concepts, whereas the term alternative applies to those more philosophically separate from traditional Western medical practices. The term integrative medicine is perhaps a more constructive term, as it refers to an approach to medical care that incorporates standard Western medicine and CAM. As defined by the National Institutes of Health's National Center for Complementary and Alternative Medicine (NCCAM), CAM is ''a group of diverse medical and health care systems, practices, and products that are not presently considered to be part of conventional medicine'' (NCCAM, 2002). Because the NCCAM definition refers to what CAM treatments are not, rather than what they are, it is essentially impossible for the scientific community to make broad conclusions about CAM therapies.

Differing beliefs about CAM can create challenges for patients and clinicians alike. Some individuals perceive CAM treatments as safer because they are deemed natural, even when evidence is lacking or suggests otherwise. Clinicians might not prescribe CAM if they lack education about these treatments or perceive these treatments as ineffective.[46] Clinicians may in addition find it difficult to translate research findings into evidence-based practice because of the limited evidence base for some CAM treatments.

A limited evidence base may arise from several specific methodological challenges inherent to research in CAM. For example, few CAM treatments have been adequately studied in treatment trials with validated diagnoses as inclusion criteria and with validated assessment tools used to measure outcomes. The randomized controlled trial (RCT), considered essential for determination of efficacy, is sometimes extremely challenging when adequate control conditions are difficult to design. For example, control conditions are challenging to create in exercise and acupuncture interventions. When studies are not controlled, the high rate of placebo response in MDD makes trial results difficult to interpret. In addition, some alternative medical practices are enmeshed in a broader cultural context and belief system that makes them difficult to evaluate in controlled trials. These challenges must be overcome so that clinicians and patients may discuss the risks and benefits of CAM treatment so that safety and efficacy are optimized for each individualized treatment plan.

PREVALENCE OF USE

CAM treatments are commonly used. In the past couple of decades, CAM use has incrementally increased. Currently 40% of adult Americans use at least 1 CAM treatment annually.[47–49] In general, women use CAM treatments more frequently than men and are more likely to have disorders such as MDD and anxiety disorders for which CAM treatments are commonly sought.[50–54] In addition, when women use CAM therapies for psychiatric indications, they may do so in the context of reproductive life events (eg, menstrual cycle, pregnancy, lactation, and menopausal transition). Therefore, particular study is warranted regarding the safety and efficacy of commonly used CAM treatments among women of all ages. Despite the growing prevalence of CAM use, psychiatry generally lacks adequately powered, well-designed studies of CAM treatments in which diagnoses are verified at study entry and outcomes are clearly defined and assessed before and after treatment.

DEPRESSIVE DISORDERS AND SPECIFIC CAM TREATMENTS OF FOCUS

Because CAM therapies include a large number of diverse modalities that have varying amounts of study, the authors have selected treatments to review based on prevalence of use and the availability of randomized, placebo-controlled data. This review focuses on specific CAM treatments and considerations for their use in women, with selected treatments, including SAMe, omega-3 fatty acids, St John's wort, bright light therapy, acupuncture, and exercise. Although not an exhaustive review of all CAM treatments, the use of these treatments is widespread, and it is compelling to know about these to inform clinical practice.

SAMe

SAMe is a naturally occurring molecule in the body. It is produced from the amino acid L-methionine through the 1-carbon cycle, a metabolic pathway that requires adequate concentrations of folate and vitamin B_{12}.[55,56] SAMe is involved in the methylation of entities with important biological roles in psychiatric disorders, including neurotransmitters, phospholipids, and cellular receptors and channels.[55]

A systematic review has found that SAMe, studied in doses of 200 to 1600 mg per day, is efficacious in the treatment of MDD.[57] In addition, Mischoulon and Fava's 2002 review[55] of placebo-controlled RCTs found SAMe significantly more efficacious than placebo in 6 of 8 studies, and equivalent to placebo in 2 others. When compared with tricyclic antidepressants (TCAs), SAMe was at least equivalent in efficacy to TCAs in most RCTs and performed better than imipramine in 1. Two meta-analyses have

similarly found that SAMe seems superior to placebo and equivalent to TCAs, although adequate studies comparing it with newer antidepressants are lacking.[58–60]

Studies to evaluate the efficacy of SAMe have generally been of short duration (6 weeks or shorter), but meet rigorous standards for evidence for efficacy as monotherapy in MDD.[61] Fewer studies have evaluated SAMe as an augmentation strategy in MDD. Alpert and colleagues[62] assessed SAMe (maximum daily dose of 1600 mg) in a 6-week open trial as an adjunctive treatment in partial and nonresponders to selective serotonin reuptake inhibitors (SSRIs) or venlafaxine (N = 30). The response and remission rates were 50% and 43%, respectively, using the Hamilton Depression Rating Scale (HAM-D).

SAMe has been reported to be generally well tolerated, with infrequently reported side effects that include mild gastrointestinal symptoms, sweating, dizziness, irritability, and anxiety. In the treatment of bipolar depression, however, mania has been reported.[55,56,63,64]

SAMe in the treatment of antepartum and postpartum depression

No data are available regarding the efficacy of SAMe in antepartum depression. Although not specifically studied for MDD during pregnancy, SAMe had been used in treatment studies in pregnant women with liver disease. As it may have a protective role in liver function and the treatment of liver diseases, SAMe has been assessed as a treatment of cholestasis in pregnancy. In a review by the Agency for Healthcare Research and Quality,[57] 8 trials were identified in which SAMe was assessed for cholestasis in pregnancy. Five systematically assessed tolerability and side effects, with no evidence of adverse events or side effects for mothers or for their infants.

In a placebo-controlled study of women with postpartum depressive symptoms, Cerutti and colleagues[65] observed significant decreases in depressive symptoms with SAMe compared with the placebo group. A quick onset of response was noted after 10 days of treatment, with significantly greater improvement in the SAMe group compared with the placebo group. One limitation of this study was that investigators did not report the validation of the diagnosis of MDD.

Considerations in breastfeeding

There have not been systematic studies that address the safety of SAMe in the context of breastfeeding. There have been no reports of side effects or adverse events when breastfeeding mothers have been treated with SAMe. SAMe given in large doses to nursing rats has not been shown to cause neonatal adverse effects.[66]

SAMe in the treatment of depressive disorders during the menopausal transition

Salmaggi and colleagues[67] randomized 80 women with MDD or dysthymia who were within 6 and 36 months of natural or surgical menopause to SAMe or placebo after a 1-week single-blind placebo lead-in. Participants received either SAMe (1600 mg) or placebo daily for 30 days. There was a significantly greater improvement in depressive symptoms with SAMe by day 10 compared with placebo. SAMe was well tolerated, with side effects noted as minimal and transient.

Folate

Folate is necessary for homocysteine and 5-methyltetrahydrofolate (5-MTHF) formation, also known as methylfolate. Methylfolate is the immediate precursor of SAMe. An adequate supply of vitamin B_{12} is required to convert methionine from 5-MTHF.[68] Some patients with depression may be folate deficient, and experience impaired methylation and monoamine neurotransmitter metabolism.[69] The C677T polymorphism of the methylenetetrahydrofolate reductase gene is associated with

MDD and with poor conversion of folate into 5-methylfolate.[70,71] For those patients who do not efficiently metabolize folate, methylfolate is available and may be an important option. Low folate blood levels have been associated with a poorer response to treatment with antidepressants in MDD[68,72] and higher folate levels at baseline seem associated with a better response.[73] Current data are inadequate to suggest the efficacy of folate or methylfolate as a monotherapy for MDD.

Folate has been studied in a placebo-controlled trial as an adjunctive treatment to fluoxetine, with significantly greater improvement in the folate group, a difference most pronounced in women.[74] 94% of women who received fluoxetine with the addition of folate (500 μg per day) were treatment responders, compared with 61% of those who received fluoxetine and placebo. Those who received folate were less likely to experience side effects.

Folate in the treatment of antepartum and postpartum depression

There have been no studies published on the efficacy of folate monotherapy or augmentation therapy for antepartum or postpartum depression. One epidemiological study of 865 women who completed nutritional questionnaires during pregnancy and who recorded an Edinburgh Postnatal Depression Score (EPDS) between 2 and 9 months post partum did not report that higher folate intake during pregnancy resulted in lower rates of PPD.[75] However, folate in doses typical in multivitamins and prenatal vitamins is considered low risk, and known to protect against birth defects in early pregnancy. For the prevention of birth defects, 0.4 to 1 mg per day is recommended for women of reproductive age. High rates of unplanned pregnancy make folate supplementation important in women of reproductive age, regardless of plans to conceive. Considering the modest evidence that supports folate as an augmentation strategy and the attractive risk/benefit profile, folate can be represented as a reasonable adjunctive strategy for MDD that carries little risk and may decrease birth defects in the case of pregnancies.

Folate in the treatment of depressive disorders during the menopausal transition

No studies to date have evaluated the efficacy and tolerability of folate monotherapy or augmentation therapy in the treatment of MDD during the menopausal transition.

Omega-3 Fatty Acids

According to a recent national epidemiological survey of CAM use in the United States, omega-3 fatty acids are among the most commonly used CAM treatments.[47] Omega-3 fatty acids have received the most rigorous study to date in RCTs for the adjunctive treatment of MDD. Few controlled monotherapy studies have been completed. The preponderance of the current evidence suggests a role for omega-3 fatty acids as an adjunctive treatment of MDD[76,77] rather than monotherapy,[78,79] and some data support use in bipolar depression.[80] In general, the evidence base is limited by underpowered studies and inconsistent findings. The well-established health benefits of omega-3 fatty acids make them an important consideration from a public health standpoint. For example, the American Heart Association has issued specific recommendations for intake of omega-3 fatty acids based on the cardiovascular benefits of adequate consumption and supplementation.[81]

Omega-3 fatty acids are nutritional compounds with well-established benefits for human health and particular benefits for fetal and infant development.[81–83] Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are 2 crucial omega-3 fatty acids found in fish. Meta-analyses of RCTs report a statistically significant antidepressant benefit of omega-3 fatty acids in mood disorders overall, but there has been noted heterogeneity in study designs and results, and they are best studied as an

augmentation treatment.[80,84] In 2006, the Omega-3 Fatty Acids Subcommittee, assembled by the Committee on Research on Psychiatric Treatments of the American Psychiatric Association, recommended that patients with a mood disorder should consume 1 g EPA + DHA daily. Current evidence may support the use of 1 to 9 g supplement of EPA + DHA daily for patients with mood disorders, although use of greater than 3 g daily should be monitored by a physician.[85]

Omega-3 fatty acids in the treatment of premenstrual mood exacerbation and PMDD

The literature is sparse concerning the use of omega-3 fatty acids in PMS or PMDD. An early epidemiological study found that lower dietary intake of essential polyunsaturated omega-3 fatty acids was associated with menstrual pain.[86] A subsequent study found that 1080 mg EPA + 720 mg DHA + 1.5 mg vitamin E taken daily for 2 months resulted in a marked reduction in menstrual symptoms from baseline in adolescents with dysmenorrhea, including mood symptoms.[87] Three of 4 RCTs found no benefit of 3 to 6 g evening primrose oil, which contains the omega-6 fatty acid γ-linolenic acid,[88–91] in the reduction of menstrual symptoms versus placebo. One study found a small additional benefit of 3 g of omega-6 fatty acid taken for 4 menstrual cycles in reducing menstrual and depressive symptoms compared with that observed with placebo, but that study did not confirm PMS diagnoses and was not double-blinded.[88] Overall, there is insufficient evidence to support the efficacy of omega-3 or omega-6 fatty acid treatment of PMS or PMDD.

Omega-3 fatty acids in the treatment of antepartum and postpartum depression

Maternal omega-3 fatty acid intake has well-documented obstetrical and infant outcome benefits.[83,92,93] In rats, maternal brain DHA levels decrease when omega-3 fatty acid intake is deficient during pregnancy.[94] Despite increased demand for omega-3 fatty acids during pregnancy, dietary intake by pregnant and postpartum women in the United States has been noted as deficient, with dietary intake during pregnancy even more diminished after issuances from the US Food and Drug Administration of mercury advisories regarding fish intake during pregnancy.[95,96]

In a cross-national epidemiological study, Hibbeln[97] reported that per capita seafood intake was significantly inversely associated with depressive symptoms in postpartum women. In addition, in a large cohort study, Golding and colleagues[98] recently reported that higher levels of omega-3 fatty acid consumption during pregnancy are associated with lower rates of depressive symptoms during pregnancy and throughout the postpartum year. The association remained after adjustment for socioeconomic and demographic variables.

However, Browne and colleagues[99] did not find an association between prenatal fish consumption and PPD in a group that was not at risk for PPD. It is possible that the inclusion of subjects who eat white and oily fish in the fish-eating group of that study lessened the ability to detect a between-group difference because white fish contain significantly less omega-3 fatty acids than oily fish. Similarly, Miyake and colleagues[100] did not detect an inverse relationship between fish intake and later risk of PPD, although these investigators noted that their study population had a high overall intake of oily fish and that the protective effect of omega-3 fatty acids may be demonstrable only in populations with low oily fish intake.

Recently, in a large Danish prospective cohort study of more than 54,000 women, subjects who self-reported the lowest fish intake during pregnancy were at increased risk of being treated for depression with an antidepressant up to 1 year post partum.[101] Although lowest omega-3 fatty acid consumption was associated with higher

rates of treatment with an antidepressant, the investigators found that fish intake was strongly associated with sociodemographic characteristics. Therefore, in studies of fish consumption and risk of depression, it is important to assess covariates that may influence omega-3 fatty acid intake.

A small case-controlled study reported that women with lower third-trimester omega-3 fatty acid levels were approximately 6 times more likely to suffer from antenatal depression than those with higher levels.[102] Women at greater risk for depression had lower omega-3 polyunsaturated fatty acid levels, including DHA but not EPA.

Our group conducted an open-label study of omega-3 fatty acids in depression during pregnancy, and a randomized dose-finding study of omega-3 fatty acids in postpartum women.[85,103] Both provided promising preliminary data regarding feasibility, tolerability, and efficacy. However, 3 small randomized placebo-controlled trials have been conducted in which investigators assessed omega-3 fatty acids versus placebo for perinatal depression, and these have produced inconsistent findings. In 2, investigators did not detect a difference between omega-3 fatty acids and placebo.[104,105] However, Su and colleagues[106] reported a significant benefit of omega-3 fatty acids compared with placebo in antenatal depression. The RCTs conducted to date have several limitations. All included small numbers of subjects and were of short duration (up to 8 weeks). In the 2 studies that failed to find a difference between placebo, omega-3 fatty acid and placebo groups improved significantly from study entry, suggesting that other factors related to study participation were associated with improvement.[104,105] Dose may be especially important for further study, as the positive 2008 study by Su and colleagues used the highest dose. Omega-3 fatty acid supplements have been well tolerated by perinatal women[107] and seem free of significant levels of mercury or other contaminants.[108]

Omega-3 fatty acids in the treatment of depressive disorders during the menopausal transition

Although CAM treatments are often sought for hot flashes and other perimenopausal symptoms, few have evidence of benefit from RCTs. For example, Newton and colleagues[109] did not find an advantage of black cohosh (*Cimicifuga racemosa*), a multibotanical plus black cohosh, or a multibotanical with soy over placebo for the treatment of hot flashes. However, in a recent 8-week placebo-controlled RCT, omega-3 fatty acids were found efficacious in the treatment of hot flashes in women 40 to 55 years old who were experiencing psychological distress.[110] Women received 1200 mg per day of omega-3 fatty acids (1050 mg EPA and 150 mg DHA per day). Both groups experienced improved quality of life scores throughout the study.

Bright Light Therapy

Bright light therapy was first assessed as a treatment of seasonal MDD, and has subsequently been shown to be effective for nonseasonal unipolar depression.[111–115] Hypomania has been reported as an adverse event in the treatment of seasonal affective disorder, and switches to mixed state have been associated with light therapy used in patients with bipolar disorder.[115–117] Chronobiological interventions have been investigated in women at times of reproductive hormonal flux because estrogen and progesterone modulate circadian rhythmicity. Gonadal hormones affect the phase and amplitude of the circadian system: perturbation of this rhythmicity has been implicated in the development of mood disorders in women, and interventions such as bright light therapy have beneficial treatment effects in MDD.[118]

Bright light therapy in the treatment of premenstrual mood exacerbation and PMDD

A few studies support the efficacy of bright white light therapy during the symptomatic luteal phase of the menstrual cycle in women with PMDD. Women who received 1 week's treatment of either morning bright light (42%), evening bright light (21%), or evening dim light (26%) had a 50% or greater reduction in HAM-D ratings to a value less than 8.[119] Irritability and physical symptoms were significantly reduced after each of the light treatments compared with baseline. In a separate study, women treated with half an hour of evening light box therapy had fewer depression and premenstrual tension scores compared with women who received placebo (red light).[120]

Bright light therapy in the treatment of antepartum and postpartum depression

Two small studies that assessed bright light therapy in antepartum depression suggest potential efficacy. In a small open pilot trial, pregnant women received 60 minutes of bright light therapy in the morning.[121] Of 16 participants who received at least 3 weeks of bright light therapy, depression scores improved by a mean of 49%, and among the 7 subjects who completed at least 5 weeks, scores improved by 59%. Two patients reported treatment-related nausea but no other significant side effects were reported. In a small double-blind study, pregnant women (N = 10) were randomized to bright light therapy or a dim light placebo condition for 10 weeks.[122] One participant who received bright light therapy experienced the onset of hypomania. Bright light therapy produced a significantly greater antidepressant response rate than placebo, with significant differences after 5 weeks. In a small study of women with PPD (N = 15), participants were assigned randomly to bright light or a placebo dim light condition.[123] Both groups experienced significant improvement from baseline, without differences in response. Larger, controlled studies are needed to better evaluate the efficacy of bright light therapy in antepartum MDD and PPD, and patients should be monitored carefully for emergent symptoms of mania when bright light therapy is initiated.

Bright light therapy in the treatment of depressive disorders during the menopausal transition

No studies have specifically evaluated the efficacy and tolerability of bright light therapy in the treatment of MDD during the menopausal transition.

Exercise

Exercise is well known for its contribution to optimal health. Studies specifically looking at the effect of exercise on mood generally agree that regular exercise is associated with mood-enhancing and antidepressant effects. Several trials reported that aerobic exercise has antidepressant effects,[124,125] and epidemiological data suggest that regular exercise is associated with decreased risk of depressive symptoms.[126,127] Treatment research is difficult with exercise, as adequate study control conditions and maintenance to treatment assignment pose challenges in study design. Dose and adherence to exercise protocols are important considerations of study.[128]

Exercise in the treatment of premenstrual mood exacerbation and PMDD

Two small nonrandomized controlled studies and 2 small randomized studies have evaluated the effects of exercise on PMS signs and symptoms; all reported positive findings. Decreases in breast tenderness and fluid retention,[129–131] personal stress, anxiety,[130] depression,[130,131] muscle stiffness, cramps, anxiety, tension, and

restlessness[132] have been associated with either conditioning or aerobic exercise interventions.

Exercise in the treatment of antepartum and postpartum depression

Regular exercise is recommended for most pregnant women. According to recommendations from the American College of Obstetricians and Gynecologists, pregnant women without medical contraindications should engage in 30 minutes of moderate intensity exercise most days.[133]

Studies in pregnancy have mainly focused on women without depression rather than those with validated mood disorders. In 1 prospective study of pregnant women without MDD, those who engaged in regular exercise reported significantly fewer depressive symptoms in the first and second trimesters than those who did not exercise, a difference not observed later in the third trimester.[134] In a Taiwanese study of 80 women at 6 weeks post partum with EPDS scores of 10 or greater (considered at risk for PPD), women were randomized to 3 exercise sessions weekly or treatment as usual.[135] Women assigned to the exercise arm had significantly more improvement on their EPDS scores at 5 months post partum than controls.

St John's Wort

Hypericum perforatum, commonly referred to as St John's wort or goat weed, has been used for its medicinal properties since the times of ancient Greece. Over the past decade there has been increasing interest in its study as a treatment of MDD, and a considerable evidence base has developed backing its efficacy in the treatment of minor depression and mild to moderate MDD. Evidence has been less consistent for moderate to severe MDD. Its study is of particular interest in the study of depressive disorders given several of its bioactive substances, including hypericin, hyperforin, and flavinoids,[136] have affinity for neurotransmitter systems important to the pathophysiology and pharmacotherapy for MDD. In vitro receptor assays indicate that individual bioactive components of St John's wort have activity at γ-aminobutyric acid A ($GABA_A$), $GABA_B$, *N*-methyl-D-aspartic acid (NMDA), μ-, κ- and δ-opioid and 5-hydroxytryptamine ($5\text{-}HT_6$ and $5\text{-}HT_7$) receptors.[137–140]

Two large meta-analyses in 2004 and 2005 compared the efficacy of St John's wort versus placebo or standard antidepressants in the treatment of depressive symptoms or MDD.[141,142] Results from the individual studies were mixed with a more robust effect seen in patients with mild to moderate depressive symptoms. St John's wort, at daily dosage 300 to 1200 mg, had a significant advantage compared with placebo in these smaller studies, but in larger placebo-controlled studies in which patients met criteria for MDD, the effect size was smaller. St John's wort had similar efficacy to TCAs or SSRI antidepressants, and better efficacy than the standard antidepressant in a subgroup of patients with MDD of mild to moderate severity.[142] There is less of a consensus that St John's wort is efficacious in severe MDD.

The phase I metabolism and adenosine triphosphate (ATP)-binding cassette (ABC) membrane transport of St John's wort have been studied in regards to drug metabolism and drug-herb interactions. St John's wort, which contains high concentrations of the bioactive component hyperforin, induces the cytochrome P450 system (CYP3A4) and inhibits ABCB1, a membrane-bound transporter that facilitates transport across the intestinal lumen and the blood-brain barrier.[143,144] St John's wort may interact with medications such as SSRIs, oral contraceptives, and hormone replacement,[145,146] resulting in a diminished level of the 3A4 substrate. Reduced levels of oral contraceptives could result in ovulation; unplanned pregnancies have been reported, as a result of suspected drug-herb interactions.[147]

St John's wort in the treatment of antepartum and postpartum depression

Few studies have evaluated the safety of St John's wort during pregnancy, and no RCTs have been published that have evaluated the efficacy or safety of St John's wort for antepartum or postpartum depression. There are no data on animal or human placental transfer of the bioactive components of St John's wort. There is a limited body of animal data, most of which has reported a lack of adverse effects on the progress of gestation during organogenesis,[148–152] although a small number of animal studies have raised concerns regarding exposure to the key St John's wort metabolites hypericum and hypercin.[149,153,154] Limited data in 54 human pregnancies indicated no increased risk of major malformations or prematurity rate for infants born to women taking St John's wort during pregnancy and matched controls.[155]

Considerations in breastfeeding

St John's wort is excreted into breast milk at undetectable to low levels, comparable with other antidepressants, and its bioactive components are either undetectable or at the limit of quantification in infant plasma.[156,157] In 1 small prospective observational cohort study of nursing women (N = 33) treated with hypericum, increased rates of adverse events including colic, drowsiness, and lethargy were reported in breastfed newborns compared with infants of matched depressed and nondepressed controls.[96] None of the reported events required medical intervention.[158] Between groups, there was no difference in either maternal reports of decreased milk volume or infant weight as recorded by medical records over the first year.

St John's wort in the treatment of depressive disorders during the menopausal transition

No studies have evaluated St John's wort as a monotherapy for depression occurring during the menopausal transition; however, a couple of studies have evaluated the efficacy of a combination of St John's wort and other phytotherapies for menopausal and psychological complaints. In a double-blind RCT of late-perimenopausal and postmenopausal women, the combination of St John's wort and chaste tree/berry (*Vitex agnus-castus*) therapy was found no more effective in the management of hot flashes and other menopausal symptoms than placebo.[159] However, a double-blind RCT of a fixed combination of St John's wort and black cohosh was found superior to placebo in reducing menopausal and depressive symptoms as measured by the Menopause Rating Scale (MRS) and the HAM-D. Active treatment effects were seen at 8 (34.8% reduction in MRS score, 30% reduction in HAM-D score) and 16 (50% reduction in MRS score, 41.8% reduction in HAM-D score) week study time points.[160] The combined herbal treatment was well tolerated.

Acupuncture

According to traditional Chinese medicine, the body is seen as a balance of 2 forces: yin and yang; maintenance of this balance is associated with health and imbalance is associated with a blockage of vital energy (qi). Acupuncture stimulates anatomical points on the body, often with thin metallic needles (manual acupuncture), which serves to restore qi flow that has been blocked by trauma. Controlled trials evaluating acupuncture as a treatment of MDD have been mixed.[161–164] A recent meta-analysis of 8 RCTs evaluated the efficacy of manual, electro-, or laser acupuncture versus sham treatment in patients with MDD or depressive neurosis.[165] Acupuncture was found to significantly reduce HAM-D or Beck Depression Inventory scores but there was no significant effect of acupuncture on either the response or remission rate.

Assessment of the evidence base for acupuncture is challenging for clinicians practicing primarily Western medicine, as many studies are published in Asian languages,

diagnostic and symptom assessments may not be standardized across studies, and acupuncture techniques may vary across studies.[166] In addition, establishing an effective placebo for acupuncture research is challenging. Three types of placebo have been traditionally used: nonspecific acupuncture, sham acupuncture, and placebo needles.[167]

Acupuncture in the treatment of antepartum and postpartum depression

There are few data on the safety or efficacy of acupuncture during pregnancy or in the postpartum period. Some acupuncture points have been reported to enhance cervical ripening at term and advance labor and delivery.[168–170]

In 1 small RTC, 61 pregnant women with MDD were randomized to receive 8 weeks of treatment with either active acupuncture, active control acupuncture, or massage.[171] Response rates were higher for active acupuncture (69%) compared with the control acupuncture (47%) or massage groups (32%), and responders to the acute treatment during pregnancy had lower depression scores in the postpartum period than nonresponders. Tolerability of the different treatment modalities was not reported.

Acupuncture in the treatment of depressive disorders during the menopausal transition

Several RCTs, and a couple of systematic reviews, have investigated whether acupuncture therapy reduces vasomotor symptoms associated with natural menopause, with divergent results. The recent Cho and Whang systematic review[172] evaluated 11 RCTs of varying methodological quality, 6 of which compared active with sham or placebo acupuncture. Only 1 of those 6 RCTs reported a significant reduction in vasomotor symptoms between active and placebo groups. In several trials active and placebo or sham acupuncture reduced vasomotor symptoms, without significant between-group differences.

The effectiveness of acupuncture plus self-care versus self-care alone on hot flashes was studied in postmenopausal women in an RCT conducted in Norway.[173] Women who received 10 acupuncture treatment sessions plus education on self-care experienced a statistically significant reduction in mean hot flash frequency (5.8 per 24 hours) compared with women receiving only education on self-care (3.7 per 24 hours). Women who received the combined therapy also had significant improvements in somatic and sleep symptoms as measured by the Women's Health Questionnaire. There was no sham or placebo acupuncture control group in this study.

A few RCTs that used nonspecific, sham, or placebo acupuncture as a control reported reduction of menopausal vasomotor symptoms between active and control groups,[174–177] but other studies have not been able to show a significant difference between active and placebo or sham acupuncture.[178,179] In addition, some studies that reported a positive benefit of acupuncture treatment of vasomotor symptoms did not include a placebo or sham control.[173] Currently there is not enough evidence to support recommendation of acupuncture in the treatment of vasomotor symptoms related to natural menopause.

SUMMARY

As many patients will not experience remission from psychiatric disorders with standard treatments, and CAM use is growing in prevalence, it is important to consider the potential role of CAM treatments when use is supported by an evidence base of efficacy and safety. Pursuing CAM treatments in lieu of standard evaluation and treatments carries the risk of delaying other possibly efficacious treatment. The popularity

of many CAM treatments necessitates that health care providers actively and respectfully inquire about CAM use and understand their risks and benefits.

However, with appropriate consideration of benefit and harm evidence, some of the better-studied CAM treatments can expand the list of treatment options available to patients. Almost 40% of the adult US population currently uses some form of CAM treatment, with anxiety, depression, and insomnia among the top 10 health conditions for which CAM is most frequently used.[180,181] Given the acceptability of CAM, inclusion of evidence-based CAM therapies in clinical practice may help to engage some individuals who may be wary of standard treatments. In addition, CAM therapies may increase treatment strategies for patients who have not remitted with standard treatments or have had difficulty tolerating them.

Further study is necessary to delineate the role of specific CAM therapies in PMS, PMDD, antepartum and postpartum depression, lactation, and the menopausal transition. Further well-designed, adequately powered studies are warranted to assess CAM therapies not only in MDD, which has the largest evidence base, but also in anxiety and psychotic disorders, which have received much less investigation. Future research should evaluate these treatments with large enough sample sizes in men and women to discern any gender-based differences in efficacy or tolerability, as has been shown for synthetic antidepressants.

REFERENCES

1. Cohen LS, Soares CN, Otto MW, et al. Prevalence and predictors of premenstrual dysphoric disorder (PMDD) in older premenopausal women. The Harvard Study of Moods and Cycles. J Affect Disord 2002;70(2):125–32.
2. Rivera-Tovar AD, Frank E. Late luteal phase dysphoric disorder in young women. Am J Psychiatry 1990;147(12):1634–6.
3. Sternfeld B, Swindle R, Chawla A, et al. Severity of premenstrual symptoms in a health maintenance organization population. Obstet Gynecol 2002;99(6):1014–24.
4. Steiner M, Macdougall M, Brown E. The premenstrual symptoms screening tool (PSST) for clinicians. Arch Womens Ment Health 2003;6(3):203–9.
5. Wittchen HU, Becker E, Lieb R, et al. Prevalence, incidence and stability of premenstrual dysphoric disorder in the community. Psychol Med 2002;32(1):119–32.
6. Kraemer GR, Kraemer RR. Premenstrual syndrome: diagnosis and treatment experiences. J Womens Health 1998;7(7):893–907.
7. Regier DA, Boyd JH, Burke JD Jr, et al. One-month prevalence of mental disorders in the United States. Based on five epidemiologic catchment area sites. Arch Gen Psychiatry 1988;45(11):977–86.
8. Blazer DG, Kessler RC, McGonagle KA, et al. The prevalence and distribution of major depression in a national community sample: the National Comorbidity Survey. Am J Psychiatry 1994;151(7):979–86.
9. Llewellyn AM, Stowe ZN, Nemeroff CB. Depression during pregnancy and the puerperium. J Clin Psychiatry 1997;58(Suppl 15):26–32.
10. Warner R, Appleby L, Whitton A, et al. Demographic and obstetric risk factors for postnatal psychiatric morbidity. Br J Psychiatry 1996;168(5):607–11.
11. 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.

12. O'Hara MW, Gorman LL, Wright EJ. Description and evaluation of the Iowa Depression Awareness, Recognition, and Treatment Program. Am J Psychiatry 1996;153(5):645–9.
13. Bennett HA, Einarson A, Taddio A, et al. Prevalence of depression during pregnancy: systematic review. Obstet Gynecol 2004;103(4):698–709.
14. Dietz PM, Williams SB, Callaghan WM, et al. Clinically identified maternal depression before, during, and after pregnancies ending in live births. Am J Psychiatry 2007;164(10):1515–20.
15. Reck C, Stehle E, Reinig K, et al. Maternity blues as a predictor of DSM-IV depression and anxiety disorders in the first three months postpartum. J Affect Disord 2009;113(1–2):77–87.
16. Vesga-Lopez O, Blanco C, Keyes K, et al. Psychiatric disorders in pregnant and postpartum women in the United States. Arch Gen Psychiatry 2008;65(7): 805–15.
17. Forman DN, Videbech P, Hedegaard M, et al. Postpartum depression: identification of women at risk. BJOG 2000;107(10):1210–7.
18. Gaynes BN, Gavin N, Meltzer-Brody S, et al. Perinatal depression: prevalence, screening accuracy, and screening outcomes. Evid Rep Technol Assess (Summ) 2005;119:1–8.
19. Marcus SM. Depression during pregnancy: rates, risks and consequences–Motherisk Update 2008. Can J Clin Pharmacol 2009;16(1):e15–22.
20. Andersson L, Sundstrom-Poromaa I, Bixo M, et al. Point prevalence of psychiatric disorders during the second trimester of pregnancy: a population-based study. Am J Obstet Gynecol 2003;189(1):148–54.
21. Larsson C, Sydsjo G, Josefsson A. Health, sociodemographic data, and pregnancy outcome in women with antepartum depressive symptoms. Obstet Gynecol 2004;104(3):459–66.
22. Chung TK, Lau TK, Yip AS, et al. Antepartum depressive symptomatology is associated with adverse obstetric and neonatal outcomes. Psychosom Med 2001;63(5):830–4.
23. Wisner KL, Sit DK, Hanusa BH, et al. Major depression and antidepressant treatment: impact on pregnancy and neonatal outcomes. Am J Psychiatry 2009; 166(5):557–66.
24. Dayan J, Creveuil C, Herlicoviez M, et al. Role of anxiety and depression in the onset of spontaneous preterm labor. Am J Epidemiol 2002;155(4): 293–301.
25. Robertson E, Grace S, Wallington T, et al. Antenatal risk factors for postpartum depression: a synthesis of recent literature. Gen Hosp Psychiatry 2004;26(4): 289–95.
26. Kumar R, Robson KM. A prospective study of emotional disorders in childbearing women. Br J Psychiatry 1984;144:35–47.
27. Kendell RE, McGuire RJ, Connor Y, et al. Mood changes in the first three weeks after childbirth. J Affect Disord 1981;3(4):317–26.
28. Wisner KL, Peindl K, Hanusa BH. Relationship of psychiatric illness to childbearing status: a hospital-based epidemiologic study. J Affect Disord 1993; 28(1):39–50.
29. Vik T, Grote V, Escribano J, et al. Infantile colic, prolonged crying and maternal postnatal depression. Acta Paediatr 2009;98(8):1344–8.
30. McMahon CA, Barnett B, Kowalenko NM, et al. Maternal attachment state of mind moderates the impact of postnatal depression on infant attachment. J Child Psychol Psychiatry 2006;47(7):660–9.

31. Brennan PA, Pargas R, Walker EF, et al. Maternal depression and infant cortisol: influences of timing, comorbidity and treatment. J Child Psychol Psychiatry 2008;49(10):1099–107.
32. Laplante DP, Barr RG, Brunet A, et al. Stress during pregnancy affects general intellectual and language functioning in human toddlers. Pediatr Res 2004; 56(3):400–10.
33. Murray L, Cooper P. Effects of postnatal depression on infant development. Arch Dis Child 1997;77(2):99–101.
34. Dawson GAS. On the origins of a vulnerability to depression: the influence of the early social environment on the development of psychobiological systems related to risk of affective disorder. In: Nelson CA, editor. Minnesota Symposia on Child Psychology: the effects of early adversity on neurobehavioral development, vol. 31. Mahwah (NJ): Lawrence Erlbaum Associates; 2000. p. 245–79.
35. Yonkers KA, Wisner KL, Stewart DE, et al. The management of depression during pregnancy: a report from the American Psychiatric Association and the American College of Obstetricians and Gynecologists. Gen Hosp Psychiatry 2009;31:403–13.
36. Soares CN, Cohen LS. The perimenopause, depressive disorders, and hormonal variability. Sao Paulo Med J 2001;119(2):78–83.
37. Bromberger JT, Assmann SF, Avis NE, et al. Persistent mood symptoms in a multiethnic community cohort of pre- and perimenopausal women. Am J Epidemiol 2003;158(4):347–56.
38. Cohen LS, Soares CN, Vitonis AF, et al. Risk for new onset of depression during the menopausal transition: the Harvard study of moods and cycles. Arch Gen Psychiatry 2006;63(4):385–90.
39. Freeman EW, Sammel MD, Lin H, et al. Associations of hormones and menopausal status with depressed mood in women with no history of depression. Arch Gen Psychiatry 2006;63(4):375–82.
40. Schmidt PJ, Nieman L, Danaceau MA, et al. Estrogen replacement in perimenopause-related depression: a preliminary report. Am J Obstet Gynecol 2000; 183(2):414–20.
41. Carranza-Lira S, Valentino-Figueroa ML. Estrogen therapy for depression in postmenopausal women. Int J Gynaecol Obstet 1999;65(1):35–8.
42. Rossouw JE, Anderson GL, Prentice RL, et al. 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(3): 321–33.
43. Hersh AL, Stefanick ML, Stafford RS. National use of postmenopausal hormone therapy: annual trends and response to recent evidence. JAMA 2004;291(1): 47–53.
44. McIntyre RS, Konarski JZ, Grigoriadis S, et al. Hormone replacement therapy and antidepressant prescription patterns: a reciprocal relationship. CMAJ 2005;172(1):57–9.
45. Soares CN. Practical strategies for diagnosing and treating depression in women: menopausal transition. J Clin Psychiatry 2008;69(10):e30.
46. Pirotta MV, Cohen MM, Kotsirilos V, et al. Complementary therapies: have they become accepted in general practice? Med J Aust 2000;172(3):105–9.
47. Barnes PM, Bloom B, Nahin RL. Complementary and alternative medicine use among adults and children: United States, 2007. Natl Health Stat Report 2009;12:1–23.

48. Eisenberg DM, Davis RB, Ettner SL, et al. Trends in alternative medicine use in the United States, 1990–1997: results of a follow-up national survey. JAMA 1998; 280(18):1569–75.
49. Tindle HA, Davis RB, Phillips RS, et al. Trends in use of complementary and alternative medicine by US adults: 1997–2002. Altern Ther Health Med 2005; 11(1):42–9.
50. Mackenzie ER, Taylor L, Bloom BS, et al. Ethnic minority use of complementary and alternative medicine (CAM): a national probability survey of CAM utilizers. Altern Ther Health Med 2003;9(4):50–6.
51. Weissman MM, Leaf PJ, Holzer CE 3rd, et al. The epidemiology of depression. An update on sex differences in rates. J Affect Disord 1984;7(3–4):179–88.
52. Wu P, Fuller C, Liu X, et al. Use of complementary and alternative medicine among women with depression: results of a national survey. Psychiatr Serv 2007;58(3):349–56.
53. Elkins G, Rajab MH, Marcus J. Complementary and alternative medicine use by psychiatric inpatients. Psychol Rep 2005;96(1):163–6.
54. Unutzer J, Klap R, Sturm R, et al. Mental disorders and the use of alternative medicine: results from a national survey. Am J Psychiatry 2000;157(11):1851–7.
55. Mischoulon D, Fava M. Role of S-adenosyl-L-methionine in the treatment of depression: a review of the evidence. Am J Clin Nutr 2002;76(5):1158S–61S.
56. Spillmann M, Fava M. S-adenosyl-methione (ademthionine) in psychiatric disorders. CNS Drugs 1996;6:416–25.
57. Hardy M, Coulter I, Morton SC, et al. S-Adenosyl-L-methionine (SAMe) for depression, osteoarthritis and liver disease. Rockville (MD): Agency for Healthcare Research and Quality; 2002.
58. Delle Chiaie R, Pancheri P, Scapicchio P. Efficacy and tolerability of oral and intramuscular S-adenosyl-L-methionine 1,4-butanedisulfonate (SAMe) in the treatment of major depression: comparison with imipramine in 2 multicenter studies. Am J Clin Nutr 2002;76(5):1172S–6S.
59. Bressa GM. S-Adenosyl-l-methionine (SAMe) as antidepressant: meta-analysis of clinical studies. Acta Neurol Scand Suppl 1994;154:7–14.
60. Pancheri P, Scapicchio P, Chiaie RD. A double-blind, randomized parallel-group, efficacy and safety study of intramuscular S-adenosyl-L-methionine 1,4-butanedisulphonate (SAMe) versus imipramine in patients with major depressive disorder. Int J Neuropsychopharmacol 2002;5(4):287–94.
61. Thachil AF, Mohan R, Bhugra D. The evidence base of complementary and alternative therapies in depression. J Affect Disord 2007;97(1–3):23–35.
62. Alpert JE, Papakostas G, Mischoulon D, et al. S-adenosyl-L-methionine (SAMe) as an adjunct for resistant major depressive disorder: an open trial following partial or nonresponse to selective serotonin reuptake inhibitors or venlafaxine. J Clin Psychopharmacol 2004;24(6):661–4.
63. Goren JL, Stoll AL, Damico KE, et al. Bioavailability and lack of toxicity of S-adenosyl-L-methionine (SAMe) in humans. Pharmacotherapy 2004;24(11): 1501–7.
64. Carney MW, Chary TK, Bottiglieri T, et al. Switch mechanism in affective illness and oral S-adenosylmethionine (SAM). Br J Psychiatry 1987;150:724–5.
65. Cerutti R, Sichel MP, Perin M, et al. Psychological distress during the puerperium: a novel therapeutic approach using S-adenosylmethionine. Curr Ther Res 1993;53(6):701–16.
66. Cozens DO, Barton SJ, Clark R, et al. Reproductive toxicity studies of ademetionine. Arzneimittelforschung 1988;38:1625–9.

67. Salmaggi P, Bressa GM, Nicchia G, et al. Double-blind, placebo-controlled study of S-adenosyl-L-methionine in depressed postmenopausal women. Psychother Psychosom 1993;59(1):34–40.
68. Papakostas GI, Petersen T, Mischoulon D, et al. Serum folate, vitamin B12, and homocysteine in major depressive disorder, Part 1: predictors of clinical response in fluoxetine-resistant depression. J Clin Psychiatry 2004;65(8): 1090–5.
69. Bottiglieri T, Laundy M, Crellin R, et al. Homocysteine, folate, methylation, and monoamine metabolism in depression. J Neurol Neurosurg Psychiatry 2000; 69(2):228–32.
70. Gilbody S, Lewis S, Lightfoot T. Methylenetetrahydrofolate reductase (MTHFR) genetic polymorphisms and psychiatric disorders: a HuGE review. Am J Epidemiol 2007;165(1):1–13.
71. Lopez-Leon S, Janssens AC, Gonzalez-Zuloeta Ladd AM, et al. Meta-analyses of genetic studies on major depressive disorder. Mol Psychiatry 2008;13(8):772–85.
72. Papakostas GI, Petersen T, Mischoulon D, et al. Serum folate, vitamin B12, and homocysteine in major depressive disorder, Part 2: predictors of relapse during the continuation phase of pharmacotherapy. J Clin Psychiatry 2004;65(8): 1096–8.
73. Alpert M, Silva RR, Pouget ER. Prediction of treatment response in geriatric depression from baseline folate level: interaction with an SSRI or a tricyclic antidepressant. J Clin Psychopharmacol 2003;23(3):309–13.
74. Coppen A, Bailey J. Enhancement of the antidepressant action of fluoxetine by folic acid: a randomised, placebo controlled trial. J Affect Disord 2000;60(2): 121–30.
75. Miyake Y, Sasaki S, Tanaka K, et al. Dietary folate and vitamins B12, B6, and B2 intake and the risk of postpartum depression in Japan: the Osaka Maternal and Child Health Study. J Affect Disord 2006;96(1–2):133–8.
76. Su KP, Huang SY, Chiu CC, et al. Omega-3 fatty acids in major depressive disorder. A preliminary double-blind, placebo-controlled trial. Eur Neuropsychopharmacol 2003;13(4):267–71.
77. Nemets B, Stahl Z, Belmaker RH. Addition of omega-3 fatty acid to maintenance medication treatment for recurrent unipolar depressive disorder. Am J Psychiatry 2002;159(3):477–9.
78. Marangell LB, Martinez JM, Zboyan HA, et al. A double-blind, placebo-controlled study of the omega-3 fatty acid docosahexaenoic acid in the treatment of major depression. Am J Psychiatry 2003;160(5):996–8.
79. Mischoulon D, Papakostas G, Dording CM, et al. A double-blind randomized controlled trial of ethyl-eicosapentaenoate for major depressive disorder. J Clin Psychiatry 2009;70(12):1636–44.
80. Parker G, Gibson NA, Brotchie H, et al. Omega-3 fatty acids and mood disorders. Am J Psychiatry 2006;163(6):969–78.
81. Kris-Etherton PM, Harris WS, Appel LJ. Omega-3 fatty acids and cardiovascular disease: new recommendations from the American Heart Association. Arterioscler Thromb Vasc Biol 2003;23(2):151–2.
82. Freeman MP, Hibbeln JR, Wisner KL, et al. Randomized dose-ranging pilot trial of omega-3 fatty acids for postpartum depression. Acta Psychiatr Scand 2006; 113(1):31–5.
83. McGregor JA, Allen KG, Harris MA, et al. The omega-3 story: nutritional prevention of preterm birth and other adverse pregnancy outcomes. Obstet Gynecol Surv 2001;56(5 Suppl 1):S1–13.

84. Freeman MP. Omega-3 fatty acids and perinatal depression: a review of the literature and recommendations for future research. Prostaglandins Leukot Essent Fatty Acids 2006;75(4–5):291–7.
85. Freeman MP, Hibbeln JR, Wisner KL, et al. Omega-3 fatty acids: evidence basis for treatment and future research in psychiatry. J Clin Psychiatry 2006;67(12): 1954–67.
86. Deutch B. Menstrual pain in Danish women correlated with low n-3 polyunsaturated fatty acid intake. Eur J Clin Nutr 1995;49(7):508–16.
87. Harel Z, Biro FM, Kottenhahn RK, et al. Supplementation with omega-3 polyunsaturated fatty acids in the management of dysmenorrhea in adolescents. Am J Obstet Gynecol 1996;174(4):1335–8.
88. Puolakka J, Makarainen L, Viinikka L, et al. Biochemical and clinical effects of treating the premenstrual syndrome with prostaglandin synthesis precursors. J Reprod Med 1985;30(3):149–53.
89. Callender K, Thomas CS. Treating the premenstrual syndrome. BMJ 1988; 297(6649):684.
90. Collins A, Cerin A, Coleman G, et al. Essential fatty acids in the treatment of premenstrual syndrome. Obstet Gynecol 1993;81(1):93–8.
91. Khoo SK, Munro C, Battistutta D. Evening primrose oil and treatment of premenstrual syndrome. Med J Aust 1990;153(4):189–92.
92. Dunstan JA, Simmer K, Dixon G, et al. Cognitive assessment of children at age 2(1/2) years after maternal fish oil supplementation in pregnancy: a randomised controlled trial. Arch Dis Child Fetal Neonatal Ed 2008;93(1):F45–50.
93. Hibbeln JR, Davis JM, Steer C, et al. Maternal seafood consumption in pregnancy and neurodevelopmental outcomes in childhood (ALSPAC study): an observational cohort study. Lancet 2007;369(9561):578–85.
94. Levant B, Radel JD, Carlson SE. Reduced brain DHA content after a single reproductive cycle in female rats fed a diet deficient in N-3 polyunsaturated fatty acids. Biol Psychiatry 2006;60(9):987–90.
95. Oken E, Kleinman KP, Berland WE, et al. Decline in fish consumption among pregnant women after a national mercury advisory. Obstet Gynecol 2003; 102(2):346–51.
96. Benisek D, Shabert J, Skornick R. Dietary intake of polyunsaturated fatty acids by pregnant or lactating women in the United States. Obstet Gynecol 2000;95: 7778.
97. Hibbeln JR. Seafood consumption, the DHA content of mothers' milk and prevalence rates of postpartum depression: a cross-national, ecological analysis. J Affect Disord 2002;69(1–3):15–29.
98. Golding J, Steer C, Emmett P, et al. High levels of depressive symptoms in pregnancy with low omega-3 fatty acid intake from fish. Epidemiology 2009;20(4): 598–603.
99. Browne JC, Scott KM, Silvers KM. Fish consumption in pregnancy and omega-3 status after birth are not associated with postnatal depression. J Affect Disord 2006;90(2–3):131–9.
100. Miyake Y, Sasaki S, Yokoyama T, et al. Risk of postpartum depression in relation to dietary fish and fat intake in Japan: the Osaka Maternal and Child Health Study. Psychol Med 2006;36(12):1727–35.
101. Strom M, Mortensen EL, Halldorsson TI, et al. Fish and long-chain n-3 polyunsaturated fatty acid intakes during pregnancy and risk of postpartum depression: a prospective study based on a large national birth cohort. Am J Clin Nutr 2009; 90(1):149–55.

102. Rees AM, Austin MP, Owen C, et al. Omega-3 deficiency associated with perinatal depression: case control study. Psychiatry Res 2009;166(2–3): 254–9.
103. Freeman MP, Hibbeln JR, Wisner KL, et al. An open trial of omega-3 fatty acids for depression in pregnancy. Acta Neuropsychiatr 2006;18:21–4.
104. Rees AM, Austin MP, Parker GB. Omega-3 fatty acids as a treatment for perinatal depression: randomized double-blind placebo-controlled trial. Aust N Z J Psychiatry 2008;42(3):199–205.
105. Freeman MP, Davis M, Sinha P, et al. Omega-3 fatty acids and supportive psychotherapy for perinatal depression: a randomized placebo-controlled study. J Affect Disord 2008;110(1–2):142–8.
106. Su KP, Huang SY, Chiu TH, et al. Omega-3 fatty acids for major depressive disorder during pregnancy: results from a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry 2008;69(4):644–51.
107. Freeman MP, Sinha P. Tolerability of omega-3 fatty acid supplements in perinatal women. Prostaglandins Leukot Essent Fatty Acids 2007;77(3–4):203–8.
108. Foran SE, Flood JG, Lewandrowski KB. Measurement of mercury levels in concentrated over-the-counter fish oil preparations: is fish oil healthier than fish? Arch Pathol Lab Med 2003;127(12):1603–5.
109. Newton KM, Reed SD, LaCroix AZ, et al. Treatment of vasomotor symptoms of menopause with black cohosh, multibotanicals, soy, hormone therapy, or placebo: a randomized trial. Ann Intern Med 2006;145(12):869–79.
110. Lucas M, Asselin G, Merette C, et al. Effects of ethyl-eicosapentaenoic acid omega-3 fatty acid supplementation on hot flashes and quality of life among middle-aged women: a double-blind, placebo-controlled, randomized clinical trial. Menopause 2009;16(2):357–66.
111. Terman M, Terman JS, Quitkin FM, et al. Light therapy for seasonal affective disorder. A review of efficacy. Neuropsychopharmacology 1989;2(1):1–22.
112. Eastman CI, Young MA, Fogg LF, et al. Bright light treatment of winter depression: a placebo-controlled trial. Arch Gen Psychiatry 1998;55(10):883–9.
113. Kripke DF, Mullaney DJ, Klauber MR, et al. Controlled trial of bright light for nonseasonal major depressive disorders. Biol Psychiatry 1992;31(2):119–34.
114. Sumaya IC, Rienzi BM, Deegan JF 2nd, et al. Bright light treatment decreases depression in institutionalized older adults: a placebo-controlled crossover study. J Gerontol A Biol Sci Med Sci 2001;56(6):M356–60.
115. Golden RN, Gaynes BN, Ekstrom RD, et al. The efficacy of light therapy in the treatment of mood disorders: a review and meta-analysis of the evidence. Am J Psychiatry 2005;162(4):656–62.
116. Sit D, Wisner KL, Hanusa BH, et al. Light therapy for bipolar disorder: a case series in women. Bipolar Disord 2007;9(8):918–27.
117. Chan PK, Lam RW, Perry KF. Mania precipitated by light therapy for patients with SAD. J Clin Psychiatry 1994;55(10):454.
118. Parry BL, Newton RP. Chronobiological basis of female-specific mood disorders. Neuropsychopharmacology 2001;25(Suppl 5):S102–8.
119. Parry BL, Mahan AM, Mostofi N, et al. Light therapy of late luteal phase dysphoric disorder: an extended study. Am J Psychiatry 1993;150(9):1417–9.
120. Lam RW, Carter D, Misri S, et al. A controlled study of light therapy in women with late luteal phase dysphoric disorder. Psychiatry Res 1999; 86(3):185–92.
121. Oren DA, Wisner KL, Spinelli M, et al. An open trial of morning light therapy for treatment of antepartum depression. Am J Psychiatry 2002;159(4):666–9.

122. Epperson CN, Terman M, Terman JS, et al. Randomized clinical trial of bright light therapy for antepartum depression: preliminary findings. J Clin Psychiatry 2004;65(3):421–5.
123. Corral M, Wardrop AA, Zhang H, et al. Morning light therapy for postpartum depression. Arch Womens Ment Health 2007;10(5):221–4.
124. Trivedi MH, Greer TL, Grannemann BD, et al. Exercise as an augmentation strategy for treatment of major depression. J Psychiatr Pract 2006;12(4): 205–13.
125. Otto MW, Church TS, Craft LL, et al. Exercise for mood and anxiety disorders. J Clin Psychiatry 2007;68(5):669–76.
126. Strawbridge WJ, Deleger S, Roberts RE, et al. Physical activity reduces the risk of subsequent depression for older adults. Am J Epidemiol 2002; 156(4):328–34.
127. Penninx BW, Rejeski WJ, Pandya J, et al. Exercise and depressive symptoms: a comparison of aerobic and resistance exercise effects on emotional and physical function in older persons with high and low depressive symptomatology. J Gerontol B Psychol Sci Soc Sci 2002;57(2):P124–32.
128. Dunn AL, Trivedi MH, Kampert JB, et al. Exercise treatment for depression: efficacy and dose response. Am J Prev Med 2005;28(1):1–8.
129. Prior JC, Vigna Y, Alojada N. Conditioning exercise decreases premenstrual symptoms. A prospective controlled three month trial. Eur J Appl Physiol Occup Physiol 1986;55(4):349–55.
130. Prior JC, Vigna Y, Sciarretta D, et al. Conditioning exercise decreases premenstrual symptoms: a prospective, controlled 6-month trial. Fertil Steril 1987;47(3): 402–8.
131. Steege JF, Blumenthal JA. The effects of aerobic exercise on premenstrual symptoms in middle-aged women: a preliminary study. J Psychosom Res 1993;37(2):127–33.
132. Stoddard JL, Dent CW, Shames L, et al. Exercise training effects on premenstrual distress and ovarian steroid hormones. Eur J Appl Physiol 2007;99(1):27–37.
133. Artal R, O'Toole M. Guidelines of the American College of Obstetricians and Gynecologists for exercise during pregnancy and the postpartum period. Br J Sports Med 2003;37(1):6–12 [discussion: 12].
134. Da Costa D, Rippen N, Dritsa M, et al. Self-reported leisure-time physical activity during pregnancy and relationship to psychological well-being. J Psychosom Obstet Gynaecol 2003;24(2):111–9.
135. Heh SS, Huang LH, Ho SM, et al. Effectiveness of an exercise support program in reducing the severity of postnatal depression in Taiwanese women. Birth 2008;35(1):60–5.
136. Butterweck V. Mechanism of action of St John's wort in depression: what is known? CNS Drugs 2003;17(8):539–62.
137. Simmen U, Burkard W, Berger K, et al. Extracts and constituents of *Hypericum perforatum* inhibit the binding of various ligands to recombinant receptors expressed with the Semliki Forest virus system. J Recept Signal Transduct Res 1999;19(1–4):59–74.
138. Simmen U, Higelin J, Berger-Buter K, et al. Neurochemical studies with St. John's wort in vitro. Pharmacopsychiatry 2001;34(Suppl 1):S137–42.
139. Gobbi M, Moia M, Pirona L, et al. In vitro binding studies with two *Hypericum perforatum* extracts–hyperforin, hypericin and biapigenin–on 5-HT6, 5-HT7, GABA(A)/benzodiazepine, sigma, NPY-Y1/Y2 receptors and dopamine transporters. Pharmacopsychiatry 2001;34(Suppl 1):S45–8.

140. Cott JM. In vitro receptor binding and enzyme inhibition by *Hypericum perforatum* extract. Pharmacopsychiatry 1997;30(Suppl 2):108–12.
141. Linde K, Mulrow CD, Berner M, et al. St John's wort for depression. Cochrane Database Syst Rev 2005;(2):CD000448.
142. Roder C, Schaefer M, Leucht S. [Meta-analysis of effectiveness and tolerability of treatment of mild to moderate depression with St. John's Wort]. Fortschr Neurol Psychiatr 2004;72(6):330–43 [in German].
143. Hennessy M, Kelleher D, Spiers JP, et al. St Johns wort increases expression of P-glycoprotein: implications for drug interactions. Br J Clin Pharmacol 2002; 53(1):75–82.
144. Gutmann H, Poller B, Buter KB, et al. *Hypericum perforatum*: which constituents may induce intestinal MDR1 and CYP3A4 mRNA expression? Planta Med 2006; 72(8):685–90.
145. Roby CA, Anderson GD, Kantor E, et al. St John's Wort: effect on CYP3A4 activity. Clin Pharmacol Ther 2000;67(5):451–7.
146. Murphy PA, Kern SE, Stanczyk FZ, et al. Interaction of St. John's Wort with oral contraceptives: effects on the pharmacokinetics of norethindrone and ethinyl estradiol, ovarian activity and breakthrough bleeding. Contraception 2005; 71(6):402–8.
147. Schwarz UI, Buschel B, Kirch W. Unwanted pregnancy on self-medication with St John's wort despite hormonal contraception. Br J Clin Pharmacol 2003;55(1): 112–3.
148. Borges LV, do Carmo Cancino JC, Peters VM, et al. Development of pregnancy in rats treated with *Hypericum perforatum*. Phytother Res 2005;19(10):885–7.
149. Rayburn WF, Christensen HD, Gonzalez CL. Effect of antenatal exposure to Saint John's wort (*Hypericum*) on neurobehavior of developing mice. Am J Obstet Gynecol 2000;183(5):1225–31.
150. Rayburn WF, Gonzalez CL, Christensen HD, et al. Impact of hypericum (St.-John's-wort) given prenatally on cognition of mice offspring. Neurotoxicol Teratol 2001;23(6):629–37.
151. Rayburn WF, Gonzalez CL, Christensen HD, et al. Effect of prenatally administered hypericum (St John's wort) on growth and physical maturation of mouse offspring. Am J Obstet Gynecol 2001;184(2):191–5.
152. Dugoua JJ, Mills E, Perri D, et al. Safety and efficacy of St. John's wort (hypericum) during pregnancy and lactation. Can J Clin Pharmacol 2006;13(3):e268–76.
153. Chan LY, Chiu PY, Lau TK. A study of hypericin-induced teratogenicity during organogenesis using a whole rat embryo culture model. Fertil Steril 2001; 76(5):1073–4.
154. Gregoretti B, Stebel M, Candussio L, et al. Toxicity of *Hypericum perforatum* (St. John's wort) administered during pregnancy and lactation in rats. Toxicol Appl Pharmacol 2004;200(3):201–5.
155. Moretti ME, Maxson A, Hanna F, et al. Evaluating the safety of St. John's Wort in human pregnancy. Reprod Toxicol 2009;28(1):96–9.
156. Klier CM, Schafer MR, Schmid-Siegel B, et al. St. John's wort (*Hypericum perforatum*)–is it safe during breastfeeding? Pharmacopsychiatry 2002; 35(1):29–30.
157. Klier CM, Schmid-Siegel B, Schafer MR, et al. St. John's wort (*Hypericum perforatum*) and breastfeeding: plasma and breast milk concentrations of hyperforin for 5 mothers and 2 infants. J Clin Psychiatry 2006;67(2):305–9.
158. Lee A, Minhas R, Matsuda N, et al. The safety of St. John's wort (*Hypericum perforatum*) during breastfeeding. J Clin Psychiatry 2003;64(8):966–8.

159. van Die MD, Burger HG, Bone KM, et al. *Hypericum perforatum* with *Vitex agnus-castus* in menopausal symptoms: a randomized, controlled trial. Menopause 2009;16(1):156–63.
160. Uebelhack R, Blohmer JU, Graubaum HJ, et al. Black cohosh and St. John's wort for climacteric complaints: a randomized trial. Obstet Gynecol 2006; 107(2 Pt 1):247–55.
161. Allen JJ, Schnyer RN, Chambers AS, et al. Acupuncture for depression: a randomized controlled trial. J Clin Psychiatry 2006;67(11):1665–73.
162. Luo H, Meng F, Jia Y, et al. Clinical research on the therapeutic effect of the electro-acupuncture treatment in patients with depression. Psychiatry Clin Neurosci 1998;52(Suppl):S338–40.
163. Gallagher SM, Allen JJ, Hitt SK, et al. Six-month depression relapse rates among women treated with acupuncture. Complement Ther Med 2001;9(4):216–8.
164. Zhang WJ, Yang XB, Zhong BL. Combination of acupuncture and fluoxetine for depression: a randomized, double-blind, sham-controlled trial. J Altern Complement Med 2009;15(8):837–44.
165. Wang H, Qi H, Wang BS, et al. Is acupuncture beneficial in depression: a meta-analysis of 8 randomized controlled trials? J Affect Disord 2008;111(2–3):125–34.
166. Halbreich U. Systematic reviews of clinical trials of acupuncture as treatment for depression: how systematic and accurate are they? CNS Spectr 2008;13(4): 293–4, 299–300.
167. Streitberger K, Kleinhenz J. Introducing a placebo needle into acupuncture research. Lancet 1998;352(9125):364–5.
168. Rabl M, Ahner R, Bitschnau M, et al. Acupuncture for cervical ripening and induction of labor at term–a randomized controlled trial. Wien Klin Wochenschr 2001;113(23–24):942–6.
169. Motl JM. Acupuncture. In: Shannon S, editor. Handbook of complementary and alternative therapies in mental health. San Francisco (CA): Academic Press; 2002. p. 443–52.
170. Gaudet LM, Dyzak R, Aung SK, et al. Effectiveness of acupuncture for the initiation of labour at term: a pilot randomized controlled trial. J Obstet Gynaecol Can 2008;30(12):1118–23.
171. Manber R, Schnyer RN, Allen JJ, et al. Acupuncture: a promising treatment for depression during pregnancy. J Affect Disord 2004;83(1):89–95.
172. Cho SH, Whang WW. Acupuncture for vasomotor menopausal symptoms: a systematic review. Menopause 2009;16(5):1065–73.
173. Borud EK, Alraek T, White A, et al. The Acupuncture on Hot Flushes Among Menopausal Women (ACUFLASH) study, a randomized controlled trial. Menopause 2009;16(3):484–93.
174. Avis NE, Legault C, Coeytaux RR, et al. A randomized, controlled pilot study of acupuncture treatment for menopausal hot flashes. Menopause 2008;15(6): 1070–8.
175. Nir Y, Huang MI, Schnyer R, et al. Acupuncture for postmenopausal hot flashes. Maturitas 2007;56(4):383–95.
176. Cohen SM, Rousseau ME, Carey BL. Can acupuncture ease the symptoms of menopause? Holist Nurs Pract 2003;17(6):295–9.
177. Huang MI, Nir Y, Chen B, et al. A randomized controlled pilot study of acupuncture for postmenopausal hot flashes: effect on nocturnal hot flashes and sleep quality. Fertil Steril 2006;86(3):700–10.
178. Vincent A, Barton DL, Mandrekar JN, et al. Acupuncture for hot flashes: a randomized, sham-controlled clinical study. Menopause 2007;14(1):45–52.

179. Sandberg M, Wijma K, Wyon Y, et al. Effects of electro-acupuncture on psychological distress in postmenopausal women. Complement Ther Med 2002;10(3): 161–9.
180. Barnes P, Powell-Griner E, McFann K, et al. CDC advance data report #343. Complementary and alternative medicine use among adults: United States, 2002; 2004.
181. Barnes PM, Bloom B, Nahin R. CDC national health statistics report #12. Complementary and alternative medicine use among adults and children: United States, 2007; 2008.