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. 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. Women have higher prevalence rates of MDD during the perimenopausal transition compared with rates found in premenopausal women. Recently, in 2 large prospective epidemiological studies, investigators reported an increased risk of new onset of MDD during the perimenopause. Although estrogen may have antidepressant effects, 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. Associated with the decrease in prescriptions for hormonal therapies for perimenopausal symptoms was a corresponding increase in antidepressant prescriptions for perimenopausal women. 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. 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. 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 B12.55,56 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 review55 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 colleagues62 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 colleagues65 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 colleagues67 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 B12 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. 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 and higher folate levels at baseline seem associated with a better response. 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. 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. 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. 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 rather than monotherapy, and some data support use in bipolar depression. 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. Omega-3 fatty acids are nutritional compounds with well-established benefits for human health and particular benefits for fetal and infant development. 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. 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.

**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. 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. Three of 4 RCTs found no benefit of 3 to 6 g evening primrose oil, which contains the omega-6 fatty acid \(\gamma\)-linolenic acid, 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. 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. In rats, maternal brain DHA levels decrease when omega-3 fatty acid intake is deficient during pregnancy. 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. In a cross-national epidemiological study, Hibbeln 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 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 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 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 postpartum. 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. 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. 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. However, Su and colleagues 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. 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 and seem free of significant levels of mercury or other contaminants.

**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 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. 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. 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. 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.
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 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.

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. 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. 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, 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-HT_6 and 5-HT_7) receptors.

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. 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. 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. St John’s wort may interact with medications such as SSRI, oral contraceptives, and hormone replacement, 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.
**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,⁴⁴⁻⁵² although a small number of animal studies have raised concerns regarding exposure to the key St John’s wort metabolites hypericum and hypercin.⁴⁹,¹⁵³,¹⁵⁴ 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 chastetree/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. 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.

**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.

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. 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 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. 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, but other studies have not been able to show a significant difference between active and placebo or sham acupuncture. In addition, some studies that reported a positive benefit of acupuncture treatment of vasomotor symptoms did not include a placebo or sham control. 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.\textsuperscript{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.

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