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Nonpharmacologic Treatments for Depression Related to Reproductive Events

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Abstract There is a growing body of evidence suggesting that nonpharmacological interventions have an appropriate place in the treatment of major depressive disorders (MDDs) as both stand-alone and supplemental treatments. Because women may be reluctant to use psychotropic medications due to strong values or treatment preferences during specific reproductive events, clinicians need to be able to offer empirically based alternatives to medication. In this review, we present recent findings from studies of acupuncture, bright light therapy, electroconvulsive therapy, omega fatty acid supplementation, physical activity, and psychosocial intervention for women experiencing depressive symptoms in the contexts of menstruation, pregnancy, postpartum, and menopause.

Keywords Major depressive disorder · Depression · Reproductive events · Premenstrual syndrome · Premenstrual dysphoric disorder · Antenatal · Perinatal · Postnatal · Postpartum · Perimenopausal · Menopausal · Menstrually related mood disorders

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Introduction

Consistently, women experience higher lifetime rates of major depressive disorder (MDD) than men, peaking during the reproductive years [1]. Nonpharmacologic interventions are particularly important for women desiring to avoid medications (i.e., adverse side effects, concern for fetus, potential interactions with other necessary medications). Here, we summarize recent research reporting the effects of such treatments, organized first by approach and second by the reproductive context of the study samples. Of note, because of the ethical dilemmas posed by including pregnant or lactating women in randomized controlled trials, there are few robust studies upon which to confidently base treatment decision-making for this group of women [2].

Acupuncture

For over 2000 years acupuncture has been used in traditional Chinese medicine for physical and psychological ailments. While empirical evidence supports its use for physical ailments [3], research investigating potential antidepressant effects is limited [4]. Preclinical research suggests acupuncture administered prior to a laboratory stressor decreases stress-induced ACTH and cortisol release [5]; acupuncture may therefore benefit mood by downregulating stress-responsive pathways.

Menstrually Related Mood Disorders

Menstrually related mood disorders (MRMDs) include premenstrual dysphoric disorder (PMDD), the most severe form of a MRMD. Characterized by the cyclic recurrence of affective and somatic symptoms in the luteal phase of the menstrual cycle, PMDD afflicts 5–8 % of reproductive-aged [6] women

and causes impairment equivalent to that of major depression, panic disorder, and PTSD [6, 7]. There may be an under-identification of women suffering from PMDD due to the restrictive criteria listed in the Diagnostic and Statistical Manual of Mental Disorders (5th ed.; DSM-5) [8] requiring five rather arbitrarily chosen symptoms. With that in mind, the prevalence of women experiencing clinically significant premenstrual symptoms characterized by impairment, treatment seeking, and suicide risk but not meeting the five symptom criterion is estimated to be 13–19 % [9–11]. Premenstrual syndrome (PMS) refers to the presence of premenstrual symptoms with minimal impairment or distress (the presence of a mood symptom is not required for the PMS diagnosis). Because of inconsistent classification of PMS, studies described in this review that included women with PMS may or may not have included women with significant mood symptomatology [12, 7].

A systematic review identified eight randomized controlled trials (RCTs) assessing the efficacy of acupuncture for PMS. Pooled results suggest acupuncture is more effective in treating PMS compared to control conditions (daily progestin taken alone or combined with an anxiolytic, sham acupuncture, and acupuncture at points unrelated to PMS) [13]. Methodological weaknesses such as random sequence generation, allocation concealment, and blinding suggest cautious interpretation of findings. The studies reviewed also varied considerably in the rigor with which PMS was diagnosed (i.e., self-report vs. prospective daily ratings).

However, a recent single-blind RCT published after the above-cited review thoroughly addressed the abovementioned limitations in study design [14••]. Thirty participants, aged 20–45 and meeting the DSM-IV criteria for PMDD based on prospective daily symptom ratings over two or more consecutive menstrual cycles, were randomized to receive either twice-weekly acupuncture or sham acupuncture for 8 weeks. Study investigators protected participant blinding by inducing a "prick" sensation in both conditions whether or not the needle penetrated the skin. Symptom response was evaluated using the clinician-administered Hamilton Rating Scale for Depression (HAM-D) and parallel scale for anxiety (HAM-A), administered on the first day of the menstrual cycle, inquiring about the previous 2 weeks. While both groups improved compared to baseline, participants receiving traditional acupuncture exhibited a statistically significant reduction in symptoms compared to those receiving sham acupuncture (59 vs. 21 % reduction in depression and 52 vs. 19 % reduction in anxiety). Despite the small sample size and single-blind study design, thorough assessment of PMDD and careful concealment of treatment arm from participants addressed the biases found in previous research.

Antepartum Depression

Antepartum depression (APD), depression occurring during pregnancy, is estimated to affect between 10 and 20 % of women [15]. Treatment of APD considers the health of both woman and fetus.

Manber et al. [16] examined the efficacy of electroacupuncture, a variation of traditional acupuncture involving the administration of low-voltage electrical pulses through the acupuncture needles, in a sample of 150 pregnant women between 12 and 30 weeks gestation and meeting the DSM-IV criteria for MDD. The women were randomized to one of three treatments: (1) acupuncture specifically targeting depression, (2) general acupuncture not intended for the treatment of depression, and (3) massage. All three groups received 12 sessions over 8 weeks. Although response rates (defined as a ≥50 % symptom decrease as reported on the HAM-D) reached statistical significance in the depression-specific acupuncture group (63 %) compared to the combined controls (44 %) or the general acupuncture group (38 %), remission rates in the general acupuncture and massage (50 %) groups did not significantly differ. Furthermore, between-group remission rates, defined as a HAM-D score <7, after 8 weeks of treatment were not significantly different (35 % for depression-specific acupuncture, 28 % for general acupuncture, and 31 % for massage). Overall, the results of this study therefore do not support acupuncture as a targeted treatment for APD.

Postpartum Depression

The DSM-V MDD specifier "with peripartum onset" describes an onset of symptoms during pregnancy or within 4 weeks of delivery. Because a majority of studies include women experiencing symptoms up to 12 months postpartum, study results may not be specific to the DSM-V time frame [17].

A double-blind (patient and assessor) RCT conducted by Chung et al. [18] examining electroacupuncture for postpartum depression (PPD) assigned 20 women meeting the DSM-IV criteria for MDD with postpartum onset (mild severity) to receive twice-weekly sessions of either traditional or sham electroacupuncture for 4 weeks [18]. Although both groups significantly improved, with remission rates of 50 and 44 % for sham and treatment conditions, respectively, the groups did not differ significantly from each other. A small RCT testing the use of traditional versus sham acupuncture for anxious symptoms in 30 lactating mothers of premature infants supported the previous findings [19]. Participants in both treatment arms experienced a significant reduction in anxiety over 12 weeks, but final results lacked statistical significance.

Summary

Recent literature suggests that acupuncture may be effective in the treatment of both PMS and the more severe diagnosis of PMDD. Since significant differences between traditional and sham acupuncture for APD or PPD are elusive, potent non-specific effects (e.g., the relaxing environment in which acupuncture is administered, a therapeutic relationship established with an acupuncturist, scheduling of a structured activity) may contribute to elevated placebo response rates. However, currently, there is insufficient evidence to support the use of acupuncture as monotherapy in the treatment of severe APD or PPD. There have been no studies of acupuncture to treat depression related to the menopause transition (DMT), a major depressive episode whose onset coincides with the onset of menstrual irregularity (and its accompanying hormonal changes) in midlife [20].

Bright Light Therapy

The efficacy of bright light therapy (BLT) for depressive disorders has been well established, particularly for seasonal affective disorder (SAD) [21–24]. The mechanisms of action have yet to be established, but may involve improvements in sleep [25], decreased daytime fatigue [26, 27], or correction of circadian misalignment and/or neuroendocrine dysregulation [28].

Menstrually Related Mood Disorders

Parry and colleagues [29] randomized 17 women with PMDD and 14 healthy control women to either six hours BLT treatment (3000 lx) or 3-h BLT treatment (6000 lx) during the second morning or evening during a 3-day cycle in both follicular and luteal menstrual cycle phases. Morning BLT advanced the melatonin offset significantly less in women with PMDD than in healthy controls, but only when administered during the luteal phase of the menstrual cycle. These findings suggest that women with PMDD may experience a blunted responsiveness to environmental cues (including morning light), perhaps playing a role in circadian rhythm malsynchonization [29]. Considering the potential pathophysiological role of circadian malsynchronization in affective disorders [30, 31], physiological findings from this study lend support to the biological plausibility of BLT for PMDD. However, there were no significant changes from baseline in the clinician-rated Structured Interview Guide for the Hamilton Rating Scale for Depression–Seasonal Affective Disorder Version (SIGH-SAD) or self-report Beck Depression Inventory (BDI) measures of mood following BLT exposure (1 day, morning or evening). To date, further trials are needed to investigate BLT as a treatment for women with PMDD.

Antepartum Depression

When a woman desires to minimize medication exposures to the fetus/baby during pregnancy and/or during breastfeeding, BLT may be a promising option given the low side effect profile [32, 21] and the rapid onset of therapeutic effect (averaging 3 to 7 days) [21]. Three recent studies examined BLT for APD, only one of which utilized an RCT design with a sufficient sample size for analysis of group differences [33••]. Wirz-Justice and colleagues [34] randomized 27 women with antepartum depression to 5 weeks of either active treatment (7000 lx bright light, $n=16$) or placebo (70 lx dim red light, $n=11$), administered for 60 min daily and initiated within 10 min of awakening. The symptom response rate (established by a clinician-administered HAM-D ≥50 % improvement from baseline to week 5) was significantly greater for bright light (81.3 %) than for placebo (45.5 %). No significant differences between groups were found in self-reported ratings of depression on the Montgomery-Asberg Depression Rating Scale (MADRS) and the BDI.

Postpartum Depression

Two studies examined BLT as a treatment for PPD, an open trial ($n=2$), and a small RCT of BLT for PPD ($n=15$) [33••]. In both studies, women showed substantial clinical improvement (49–75 % reduction in HAM-D scores) following 4 to 6 weeks of morning BLT (10,000 lx) administered for 30 min daily. In the RCT trial, no significant differences were observed between the BLT group ($n=10$) and the placebo (600 lx dim red light) group ($n=5$), although both groups significantly improved from baseline (average 49 % reduction in SIGH-SAD scores).

Summary

The precise mechanisms underlying BLT's antidepressant effects are not yet clear, but may involve circadian resynchronization [35, 36], increased daytime alertness [36, 26], improvements in sleep [37, 36, 38], and/or positive effects on dysregulated neurotransmitters and/or steroid hormones [33••, 39–41].

The potential for BLT to impact both neuroendocrine and sleep-wake parameters may be particularly meaningful, as evidence suggests that women with reproductive-related mood disorders report substantially poorer sleep than matched controls [42–44].

Bright light therapy can be associated with minor side effects including headache, eye strain, nausea, and agitation but these have rarely led to treatment discontinuation [21, 32].

It should also be noted that increased mania has been reported in some individuals following BLT, though this remains understudied [45••]. Evidence for the use of BLT as a treatment for women experiencing depression during reproductive-related events is, to date, inconclusive, and is limited by methodological inconsistencies and small sample sizes. Considering that antidepressant effects of BLT have been established for nonreproductive-related depressive disorders [45••], further investigations of BLT for reproductive-related depressions are warranted.

Electroconvulsive Therapy

In the general population, electroconvulsive therapy (ECT) is a well-established effective treatment for both severe unipolar and bipolar depression, with remission rates of about 50 % [46]. However, it has not been well researched for depression specifically in the context of reproductive events.

Antepartum Depression

Because the electric current used in ECT does not pass through the uterus, ECT is a treatment option for pregnant women suffering from severe MDD and/or other mental illness who wish to minimize fetal exposure to psychotropic medication. In a retrospective observational study of 33 pregnant inpatients (19 with MDD), ECT was administered three times weekly for an average of 11 sessions [47]. Eighty-four percent of women with MDD achieved remission with treatment. The incidence of adverse fetal outcomes was low, including one stillbirth, one case of congenital hip dysplasia, and one temporary heart failure (neither hip dysplasia nor heart failure were believed to be related to the ECT). An autopsy could not be performed to determine the cause of the stillbirth. The authors concluded that ECT was a safe and effective treatment for severe mental illness in the pregnant patient [48, 49••].

Summary

There is little research on the use of ECT specifically during reproductive events. A small literature exists on the use of ECT during pregnancy with treatment adaptations recommended (for a comprehensive list of these guidelines, see [49••]). Also of potential clinical utility is a scale developed for the general population to assist clinicians in determining the indications for ECT by assessing the severity, chronicity, and heritability of the patient's depression [50].

Omega Fatty Acids

Complementary and alternative (CAM) approaches to depression have growing bodies of evidence, primarily in the general population. A thorough review of all nutraceuticals or food supplements is beyond the scope of this review; here, we focus upon omega-3 fatty acids (OFAs; also known as omega-3 polyunsaturated fatty acids [PUFA]), as this supplement is one of the most commonly used nutritional supplements [51••]. Active ingredients in OFA are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) naturally found in fish. Because in animal and human studies, deficiencies of OFA have been associated with neuronal function, particularly in the serotoninergic and dopaminergic systems, it is speculated that these acids influence or regulate receptor function [52, 53••].

Menstrually Related Mood Disorders

A randomized double-blind controlled pilot trial with 184 women who met the criteria for PMS both by clinical interview and retrospective self-report questionnaires was conducted with university students in Tehran [54]. Outcomes of interest were both psychiatric (depression, nervousness, jitteriness, anxiety, dizziness, poor concentration, reduced social activity) and somatic (breast tenderness, bloating, headache, edema), and were collected at 45 and 90 days after beginning treatment. The treatment group was prescribed 2 g of OFA (two 1 g pearls), and the control group received placebo (two identical pearls manufactured by the same facility as the OFA). Analyses were significant, both at 45 and 90 days, with the OFA group reporting lower severities of premenstrual symptoms of depression, anxiety, impaired concentration, and bloating. In addition to reduced severities, at 90 days, there were also significant reductions in the duration of symptoms of depression, nervousness, anxiety, headache, impaired concentration, bloating, headache, and breast tenderness.

Antepartum Depression

Current recommendations for perinatal patients are supplementation of 1 g EPA+DHA daily [51••]. Although omega-3 fatty acids are naturally found in fish, dietary intake of fish by perinatal women in the USA and UK is insufficient, perhaps partly due to the FDA mercury advisories [51••].

Depression Related to the Menopause Transition

Freeman et al. [55] gathered preliminary data on the use of OFA in an open trial with 20 women who received 8 weeks of

treatment with OFA capsules (2 g per day). They reported a response rate (depressive symptoms) of 70 % as rated on the MADRS, and 95 % of the women completed the trial. None reported any adverse effects, and a side benefit was a significant decrease (p=0.02) in the number of hot flashes per day from baseline.

Summary

Across all populations, epidemiological studies do not strongly support associations between OFA intake and mood improvement. Even in experimental research, findings are inconclusive because the literature is limited by publication bias, variability/lack of standardization in assessments of depression or the OFA regimens tested, and durations of trials insufficient for illuminating slower mechanisms of action [53••]. Although OFA may not be appropriate as a first-line intervention in the treatment of MDD in women, inclusion in treatment regimens may optimize health outcomes in general.

Physical Activity

Regular participation in physical activity (PA) may protect against the development of adverse mental health outcomes, including depression [56–59]. Though dose-response effects have not been fully elucidated, the psychological benefits of regular physical exercise appear to be most highly associated with regular participation in moderate to vigorous intensity PA (intensity maintained at 55–90 % of maximal heart rate; MVPA) [60, 61]. The exact neurobiological mechanisms underlying the antidepressant effects of PA are currently unknown. However, it is thought that the antidepressant effects of regular exercise training may be mediated through neurobiological adaptations (e.g., increased availability of neurotransmitters including serotonin and dopamine, attenuated HPA axis reactivity to stressors) [62], and/or psychosocial adaptations (e.g. increased self-efficacy/mastery, increased self-esteem) [63]. Other PA modalities such as resistance exercise and yoga-based activities may also have antidepressant effects through similar physiological and psychosocial mechanisms [64]. Yoga-based practices traditionally promote mindfulness, also associated with antidepressant effects [64, 65].

Menstrually Related Mood Disorders

Samadi et al. randomized 40 sedentary young women with PMS (diagnosis established by self-report questionnaire and prospective daily ratings during two menstrual cycles) to either 8 weeks of 1-hour supervised aerobic exercise three times a week or to a sedentary control condition [66]. Women in the exercise group experienced a 65 and 52 % reduction in physical and psychological symptoms of PMS, respectively. In contrast, the control group reported reductions of only 10 and 7 % in physical and psychological symptoms. In a second RCT, 90 women with PMS were randomized to one of three conditions: moderate-intensity aerobic exercise, high-intensity aerobic exercise, or no exercise [67]. Both exercise conditions included 50-min sessions of supervised aerobic exercise three times a week; the moderate intensity group aimed to reach 60–65 % of their maximum heart rate, while the high intensity group aimed for 80–85 %. Compared to the sedentary control group, women in both exercise groups experienced greater improvements in negative mood, discomfort, and edema, but no significant differences were found between the two intensities of exercise.

Antepartum Depression

Current American College of Obstetricians and Gynecologists (ACOG) recommendations suggest that, in the absence of medical or obstetric complications, perinatal women follow the current Centers for Disease Control and Prevention and American College of Sports Medicine recommendations for participation in MVPA for 30 min or more on most, if not all, days of the week [68]. Regular participation in PA has been shown to improve maternal cardiovascular fitness [69, 70], reduce adverse maternal obstetric complications and fetal/infant health outcomes [71, 72], reduce postpartum weight retention [71], and improve maternal mood in euthymic women [73, 74]. Results from another systematic review and meta-analysis of six available studies indicate a low to moderate effect size for PA as a treatment for APD (SMD=−0.46 [−0.87, −0.05]) [75]. The authors conclude interpretations of these data warrant caution because of methodological limitations, significant heterogeneity between studies, and the large variability in outcome measures.

Although ACOG guidelines provide general best practices for healthy perinatal women, little is known regarding the modality, intensity, or appropriate duration of exercise/PA interventions for the treatment of APD or PPD. Considering that exercise is also a physiologic and psychological stressor, examination of the safety and efficacy of PA interventions for women with APD may be particularly important [84]. For example, the timing of exercise initiation (e.g., prior to pregnancy or during certain gestational stages) may be an important consideration for women with APD, as research suggests that women exhibit different physiologic and psychological responses to stress across gestation [76].

Postpartum Depression

The majority of studies investigating associations between PA and PPD have reported an inverse association between regular

participation in PA (either prepregnancy, during pregnancy, or postpartum) and the presence of postpartum depressive symptoms [77]. However, none of these studies have investigated this association in perinatal women with depression at study baseline, and many studies failed to report key components of PA interventions including intensity, modality, and/or duration of sessions [77].

Depression Related to the Menopause Transition

Studies examining exercise as a treatment for depression in midlife associated with menstrual cycle irregularity or somatic symptoms of the menopausal transition (D-MT) are absent in the literature, but two RCTs tested the efficacy of aerobic exercise in improving mental health and quality of life in euthymic peri and postmenopausal women [78–81]. Luoto et al. randomized 176 peri and early postmenopausal women to a control condition or to aerobic exercise training (four 50-min sessions of unsupervised exercise training per week). The aerobic exercise training group experienced modest improvements in mood swings, irritability, and depressed mood as well as a decrease in vasomotor symptoms [78] and improvements in sleep [79], and improvement was linked to the number of sessions attended. In a second RCT, 390 euthymic women reporting significant vasomotor symptoms were randomized to one of the following 12-week programs: (1) once-weekly 90-min yoga classes with daily at-home practice, (2) three-weekly supervised 40–60-min sessions of individualized aerobic exercise, or (3) usual activity [80, 81]. Compared to those in the usual activity group, women assigned to yoga reported modest improvements in sexual functioning and vasomotor symptoms [80], while those in the aerobic exercise group modestly improved depressive symptoms, insomnia symptoms, subjective sleep quality, and physical functioning [81]. However, neither group experienced improved psychosocial functioning or overall menopause-related quality of life when compared to the control group.

Summary

The evidence available suggests that regular aerobic exercise training may improve the physical and psychological symptoms of PMS. Though further research is needed, available evidence suggests that these benefits of PA may be obtained with regular participation in moderate-intensity exercise. There are few systematic investigations of treatment outcomes regarding PA dose, modality, or timing, in women with APD or PPD. Finally, there is evidence that regular participation in aerobic exercise can induce modest improvements in mood among euthymic sedentary peri and postmenopausal women. While the efficacy of PA as monotherapy for D-MT remains to be seen, the cardiovascular and weight-control benefits of regular exercise participation recommend that PA may be of benefit for women in midlife.

Psychosocial Approaches

Because environmental stressors such as increased caregiving burden, socioeconomic instability, interpersonal violence, and gender discrimination may trigger MDD, psychosocial interventions (psychoeducation, social support, psychotherapy) play an important role in treatment [82]. These modalities have the ability to target specific cognitive or affective characteristics, adverse events, or social contexts in which depressive symptoms appear and are perpetuated. Psychotherapy, in particular, is one of the earliest treatments for depression, with thousands of studies to date providing acceptability, accessibility, safety, efficacy, and feasibility data across most populations [83, 84]. For women of reproductive age, acceptability, safety, and efficacy are generally well supported, but accessibility and feasibility remain challenging for populations with scarce resources (e.g., time, money, transportation, child care) and those living in communities with few providers.

Menstrually Related Mood Disorders

Research on psychosocial interventions in MRMDs is sparse, with only three randomized trials more than a decade old. Each used prospective ratings to confirm either moderate to severe PMS in women seeking treatment [85, 86] or PMDD [87]. While the three trials did document benefit of cognitive behavior therapy or coping skills training in this population [85–87], they suffered from substantial attrition rates [86, 87], small samples [85], lack of structural equivalence between treatment groups [86], or lack of an active control condition [85]. Given that nonresponse rates to pharmacologic interventions in women with MRMDs is 40 % or greater [88], additional research on psychosocial interventions in women with MRMDs designed to address the limitations of this early work is clearly warranted.

Antepartum Depression

A recent Cochrane review of psychosocial interventions for treating perinatal depression located only 13 trials meeting the criteria for comparison, most of which were conducted with either mixed samples or postpartum women [89]. However, over the last 20 years, interpersonal psychotherapy (IPT) has been the most studied approach [90••]. The most rigorous study to date randomized 142 socially disadvantaged pregnant women meeting the DSM-IV criteria for MDD to 12 weeks of

either IPT or psychoeducation (parenting education) across three sites in New York City. Both groups improved significantly from baseline, leading to several potential interpretations. Findings may suggest that both increased social support (a primary target of IPT) and psychoeducation were equally beneficial, or the psychoeducation groups themselves provided increased social support, or perhaps neither intervention contained a mechanism of action outside nonspecific effects (e.g., social interactions in the group setting, regular positive activity outside the home, benefits of study incentives).

Postpartum Depression

Interpersonal psychotherapy (IPT) continues to be the most broadly studied model in both individual and group frameworks for treatment, but CBT has been tested for the prevention of PPD [90••, 91, 92]. Other valuable approaches such as mindfulness have been proposed or undergone preliminary investigation in pilot trials, but small sample sizes, inconsistent diagnostic processes, and multiple ways of measuring outcomes prevent robust endorsement of a singular therapy [84]. Of particular interest in the future will be RCTs of novel administrations of psychological approaches through the telephone, the internet, smart phone applications, and home visits, as these circumvent the above-discussed barriers to most psychosocial treatments [90••, 93].

Depression Related to the Menopause Transition

We located no studies specific to the menopausal transition, but one secondary analysis found no significant differences in the response to cognitive therapy between pre, peri, or postmenopausal women, suggesting psychotherapy research findings are generalizable to this population [94]. In view of identified risk factors for MDD in the menopausal transition such as adverse life events, negative attitudes toward aging, and simultaneous obligations to aging parents and adolescent/young adult offspring, treatment recommendations that include a psychosocial approach could be of short-term and long-term benefit [95].

Summary

Psychosocial treatment has a long track record of efficacy across populations. Specific study has been conducted with pregnancy and postpartum women, with IPT heavily represented in both individual and group treatment. Current ACOG guidelines suggest it is appropriate as a first-line treatment in mild to moderate depression during pregnancy [96].

Conclusions

In conclusion, there is evidence that nonpharmacological approaches to MDD across the female reproductive lifecycle are valuable for both stand-alone and supplemental treatment. Since research specific to reproductive contexts is limited, treatment discussions could be based upon findings from general populations until there is a larger body of efficacy research.

Compliance with Ethics Guidelines

Conflict of Interest Anna R. Brandon and Susan S. Girdler declare that they have no conflict of interest.

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