

# Depression and Insomnia in Women

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Depression and insomnia are both significantly more prevalent in women than in men. Risks appear linked to fluctuations and transitions in gonadal hormones during various phases of women's lives, with the risk of depression greatest during the period from menarche to menopause. Increased risks of both insomnia and depression also coincide with the late luteal phase of the menstrual cycle, during and after pregnancy, and during the peri-/postmenopausal period. Gonadal hormones exert significant effects on the neurohumoral systems most intimately associated with depression and insomnia, with corresponding implications for treatment. Medications related to the serotonin system—the selective serotonin reuptake inhibitors, or SSRIs—appear to be uniquely effective in the treatment of insomnia and depression experienced by women. SSRIs and the nonbenzodiazepine receptor agonists are generally useful as first-line treatments in a number of circumstances; hormone replacement therapies can also be considered. Behavioral therapies for insomnia may be particularly relevant for postpartum patients because of safety concerns and to prevent the development of autonomous chronic insomnia, which may also increase the risk of depression. In light of the high risk of relapse and high likelihood of comorbidity, it is crucial to effectively treat both insomnia and depression in women. However, few data exist for many key areas related to the treatment of these disorders in women, and research is greatly needed. (*Clinical Cornerstone*®. 2004;6[Suppl 1B]:S19–S28). Copyright © 2004 Excerpta Medica, Inc.

The treatment of depression and insomnia in women is a common challenge for primary care physicians. Although both disorders are widespread in the general population, both occur significantly more frequently in women. Depression is estimated to affect 10% to 25% of women during their lifetime, a risk double that of men.<sup>1</sup> This increased risk of depression carries with it an increased prevalence of insomnia, occurring in ~75% of those with major depression.<sup>2</sup> However, depression is just 1 factor leading women to have a 1.3- to 1.8-fold greater risk of insomnia.<sup>3,4</sup> Women represent the majority of the 10% to 14% of the general population who suffer from insomnia and an even higher percentage of primary care patients.<sup>5,6</sup>

## KEY POINT

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Why women are more likely to suffer from depression and insomnia remains unclear. Multiple factors predispose women to experience both disorders, with various psychologic, social, and

neurobiologic factors proposed to explain these differences. Psychosocial hypotheses include low societal value placed on women's traditional roles, and the social isolation and stresses associated with child-rearing. In addition, there is a tendency, perhaps culturally fostered or mediated, for women to internalize their response to adversity, in contrast to externalizing their behaviors, eg, through substance abuse or aggressive behavior.<sup>7</sup> The neurobiologic challenge has been to understand how observed differences in insomnia and depression are accounted for by genetic differences, and how these unfold phenotypically over the female life span. What distinguishes women who develop depression and insomnia from other women and men?

The hypothalamic-pituitary-gonadal (HPG) system is the most clearly gender-divergent system, playing a fundamental role in the formation of structural, physiologic, and behavioral dimorphisms that characterize men and women.<sup>8</sup> Furthermore, the HPG system is hypothesized to contribute to the risk of depression and insomnia in women. Increased risks of both disorders tend to coincide with particular points in women's lives where significant transitions in this system occur, corresponding to fluctuations in gonadal hormones such as estrogen and progesterone.<sup>9,10</sup> However, it is only during the period from menarche to menopause that women are at greater risk of suffering from depression than men.<sup>7,11</sup> Insomnia and depression symptoms are linked to the late luteal phase of the menstrual cycle, during and after pregnancy, and in the peri-/postmenopausal transition.<sup>4,9</sup>

Substantial evidence links the HPG system and key systems believed to underlie the neurobiologic pathophysiology of insomnia and depression, providing explanations by which differences in HPG function in men and women could confer differential risk of these disorders.<sup>10</sup> The key systems include the serotonin (5-HT),  $\gamma$ -aminobutyric acid (GABA), melatonin, and hypothalamic-pituitary-adrenal (HPA) system, among others. The HPG system has complex interrelationships with the insomnia- and depression-associated pathophysiologic systems, such that different mechanisms may mediate insomnia and depression at different times in women's lives.

## THE HPG SYSTEM AND INSOMNIA AND DEPRESSION IN WOMEN

### From Menarche to Menopause

An increase in the prevalence of depression and insomnia in women during the period of menarche to menopause may be related to HPG system involvement.<sup>11</sup> Although the overall prevalence of depression is 2-fold greater in women than in men, in prepubertal children and adults aged >55 years the rates are equal, or even slightly higher, in males.<sup>7</sup> A direct link between depression and elevated circulating estrogen levels is based on observations that gender-based disparity in rates of depression begins between Tanner stages II and III, when girls begin to have higher levels of estrogen, and ceases during menopause when estrogen levels diminish.<sup>7</sup> However, the implied hypothesis—that relatively high estrogen levels that accompany a woman's reproductive years confer an increased risk of insomnia and depression—is complicated by additional factors.

Like estrogen, a number of HPG system hormones, such as progesterone, allopregnanolone, androgens, follicle-stimulating hormone (FSH), and luteinizing hormone (LH), have important elevations and fluctuations during the reproductive years.<sup>10</sup> The key points at which the increased risks for depression and insomnia occur coincide not with the highest estrogen levels, but with periods of most rapid decline in estrogen, such as the late luteal phase of the menstrual cycle, pregnancy, and during the menopausal transition.<sup>9</sup> This observation has led to the hypothesis that fluctuations in gonadal hormones trigger episodes of insomnia and depression.<sup>9,10</sup>

### KEY POINT

**The key points at which the increased risks for depression and insomnia occur coincide not with the highest estrogen levels, but with periods of most rapid decline in estrogen.**

### The Premenstrual (Late Luteal) Phase of the Menstrual Cycle

In some women, mood symptoms are regularly associated with the late luteal phase of the menstrual cycle.<sup>11</sup> Typically, depressive symptoms begin after ovulation occurs (the onset of the luteal phase), and subside as menses begin.<sup>12</sup> Mild symptoms reportedly affect 20% to 40% of women in the United States, with symptoms associated with significant impairment in 2% to 10%.<sup>12</sup> Episodes of disturbed sleep repeatedly occurring in the premenstrual phase are sometimes reported, but their prevalence is difficult to estimate.<sup>4</sup> Several small studies suggest a greater incidence of sleep disturbance based on self-reported and polysomnographic awakenings in the luteal phase of the menstrual cycle.<sup>11</sup> In fact, sleep difficulties represent 1 of 11 symptoms that currently comprise the *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)* criteria for premenstrual dysphoric disorder.<sup>1</sup> However, uncertainty remains as to whether premenstrual mood symptoms and sleep disturbances constitute formal disorders.<sup>4</sup> Both have provisional status in the major psychiatric and sleep diagnostic systems, identified as needing further study because of insufficient information in the *DSM-IV*, and designated as a proposed disorder when symptoms occur together in the *International Classification of Sleep Disorders*.<sup>1,2</sup>

The symptoms occur at a period in the menstrual cycle after a surge in LH, during which there is an initial rise in both estrogen and progesterone, followed by a substantial decline in both hormones in the last several days before menses.<sup>13</sup> The belief that fluctuations in HPG steroids are responsible for premenstrual symptoms is supported by findings that the symptoms are absent during anovulatory cycles, and that they can be relieved by ovariectomy or administration of a gonadotropin-releasing hormone antagonist.<sup>13</sup> On this basis and the timing of symptoms, some have proposed that the symptoms derive from the decline in estrogen and/or progesterone that occurs premenstrually; however, this theory is controversial. Many studies have been conducted comparing estrogen and progesterone levels during the menstrual cycle in women with and without significant premenstrual difficulties and generally have not found a difference.<sup>13</sup>

### Pregnancy and Postpartum

Overall rates of depression are similar in pregnant and nonpregnant women. However, complaints of difficulty with sleeping are frequent in the third trimester, primarily due to overall discomfort, back pain, urinary frequency, fetal activity, periodic movements of sleep, and restless legs syndrome.<sup>4,9</sup> Coincident with reductions in estrogen and progesterone following delivery is a significant increase in the risk of depression.<sup>9</sup> Although the vast majority of women may experience only mild dysphoria, 5% to 20% experience depression that begins postpartum.<sup>14</sup> The incidence of depression in the first 5 weeks after delivery increases by a factor of 3, whereas the rate of psychiatric hospitalization increases 7-fold.<sup>9</sup> A small subset of women will also experience symptoms of hypothyroidism following delivery. The predisposition to postpartum depression may be related to the precipitous declines in estrogen and progesterone or substantial changes in other HPG system hormones after delivery. However, studies to date do not support this view,<sup>14</sup> and the causes of postpartum depression remain unclear.

Postpartum maternal sleep disturbance is a significant factor affecting mood. Sleep disruption is inevitable beginning immediately postpartum until the baby is able to sleep through the night. Maternal sleep disruption—which is extremely common and likely to be sustained for considerable periods—and infant sleep disturbance are both associated with maternal depressive symptoms.<sup>15</sup> In 1 study, 36% to 46% of parents reported that their infants had sleep problems in the second 6 months of life and that interventions designed to improve their infant's sleep improved maternal mood ratings.<sup>16</sup> Although evidence exists for a relationship between disrupted maternal sleep and mood, there are no data on its relationship with postpartum depression. It has not been determined to what extent postpartum sleep disruption contributes to postpartum depression.

Nevertheless, maternal sleep disruption is not synonymous with insomnia. Generally, women would not have difficulty sleeping were it not for the disruption caused by their baby's demands and the associated environmental disturbances. As these effects diminish, it would be expected, and it appears to be the case, that the sleep of affected women tends

to improve.<sup>15</sup> An appropriate model for postpartum sleep disturbance is exogenous sleep disruption/deprivation in normal individuals, which tends to produce daytime sleepiness, cognitive deficits, fatigue, and irritability, the latter consistent with mood symptoms reported in the postpartum literature.<sup>17</sup> At the same time, no consistent data link such sleep deprivation to major depression.

In contrast, those with insomnia take longer to fall asleep than normal controls when given the opportunity to sleep day or night, and, in fact, appear to have associated physiologic evidence of hyperarousal.<sup>17</sup> One feature that distinguishes many individuals with insomnia from those with sleep deprivation is that their sleep difficulty becomes autonomous, ie, if there is a precipitating factor (in this case the disruption associated with the infant), the sleep difficulties may persist independently of, or following cessation of, that precipitant.<sup>2,18</sup> This occurs in some women following the normalization of their baby's sleep.<sup>2</sup> Many cases are encountered in clinical practice of women with chronic insomnia who report that their sleep difficulties began following the birth of their child, even though that may have occurred a number of years earlier and their sleep environment has long since normalized.

Numerous mechanisms have been proposed to explain how autonomous insomnia develops in such a setting. Individuals may respond to sleep disruption with behaviors intended to help with coping but which actually perpetuate sleep difficulties, eg, consuming caffeine, napping, and spending more time in bed. They may experience conditioning caused by repeated experiences of frustration, arousal, worry, stress, and anxiety occurring in the bedroom or in association with attempts to sleep that, once conditioning occurs, become elicited each time they enter the bedroom, carry out presleep behaviors, and/or attempt to sleep.<sup>18</sup> Some individuals may have a physiologic response to sleep deprivation that disrupts their sleep, eg, an elevation in evening cortisol following sleep disturbance, which can itself disrupt sleep.<sup>19</sup> The extent to which these mechanisms and the development of chronic insomnia postpartum contribute to the elevated incidence of chronic insomnia in women compared with men remains unknown.<sup>4</sup>

## KEY POINT

**One feature that distinguishes many individuals with insomnia from those with sleep deprivation is that their sleep difficulty may become autonomous, eventually persisting independently of, or following cessation of, a precipitating factor, should one have been present.**

### Peri-/Postmenopausal Period

An accurate determination of the effects of the peri-/postmenopausal transition on the risks of insomnia and depression is also hindered by a lack of data.<sup>4,20</sup> Very high percentages of women report depressive symptoms and sleep disturbance during peri-/postmenopause; however, there is controversy about whether these difficulties are directly related to peri-/postmenopausal changes or whether they reflect the high frequency of such problems in this age group, independent of hormonal status. Accordingly, peri-/postmenopausal depression and insomnia are not included as entities in the psychiatric or sleep diagnostic systems but have provisional status.<sup>1,2</sup>

One factor complicating the understanding of peri-/postmenopausal mood and sleep difficulties is that the 2 problems appear to be interrelated. Some studies suggest a clear increase in risk of depression, although longitudinal epidemiologic data do not suggest an increased risk of new-onset major depression in the peri-/postmenopausal period.<sup>11,21</sup> Comparable contradictions exist for insomnia studies; however, an association is consistently found between insomnia and night sweats during this transition.<sup>20</sup> When an analysis was conducted that accounted for both problems, the symptoms of depression present during this period appeared to only occur as a result of night sweats and sleep disruption.<sup>22</sup> Accordingly, peri-/postmenopausal depressive symptoms may be similar to postpartum depressive symptoms, where a source of sleep disruption may lead to the development of depressive symptoms. In the former case, they are neonatal-related disruptions; in the latter, they are nocturnal vasomotor events.

The association with night sweats suggests that peri-/postmenopausal sleep disruption might be related to the changes in HPG hormones that occur during this transition, including a fall in estradiol and rise in LH and FSH.<sup>15</sup> This hypothesis is undermined by the lack of a clear association between hormone levels and insomnia or depressive symptoms, and the inconsistent response of sleep disruption to hormone replacement therapy.<sup>20</sup> The observation that vasomotor symptoms improve more consistently following hormone replacement therapy than sleep difficulties suggests that either the sleep disruption was caused by factors other than night sweats (eg, chronic pain, ongoing sleep disorders, etc) or that the sleep disruption, caused by the night sweats, precipitated an autonomous insomnia that continued after resolution of the vasomotor symptoms, analogous to persistent postpartum insomnia.<sup>4,20</sup>

### **FLUCTUATIONS IN HPG HORMONES, INSOMNIA, AND DEPRESSION**

Fluctuating HPG hormone levels are clearly associated with insomnia and depression in women. Despite limited data, current thinking is that when HPG fluctuations occur, the HPG axis affects the function of the neurohumoral systems believed to mediate insomnia and depression.<sup>10,13</sup> However, it is unresolved why only a subset of women experience these problems, and why it has not been possible to establish that affected women have greater fluctuations and/or differences in HPG hormone levels compared with asymptomatic women.<sup>13,14</sup> This has led to investigations of whether activation of the HPG system and the corresponding increases in hormones at menarche sensitize neurohumoral systems such as 5-HT, GABA, and the HPA axis—all of which are intimately tied to depression and insomnia as related to fluctuations in gonadal hormones.<sup>10</sup> Assuming this were true, affected women either have differences in their HPG axis activity before the development of symptoms that might explain why they are uniquely sensitized, or they are predisposed to have sensitivity to HPG axis fluctuations for another reason. Evidence exists of a genetic component to the risks experienced in these settings.<sup>9,14</sup> This suggests a model in which a subset of women inherit sensitivities to fluctuations in HPG hormones in  $\geq 1$  of the key neurohumoral systems, such that when HPG fluctuations occur

following menarche, these women develop symptoms of insomnia or depression.<sup>13</sup>

### **THE HPG AXIS AND THE NEUROHUMORAL SYSTEMS**

Gonadal hormones have diverse effects on a wide range of central nervous system (CNS) psychopharmacologic systems. Apart from their neuronal function through binding to traditional membrane-bound receptors, these lipid-soluble molecules are able to pass through neuronal membranes and appear to exert most of their effects at intracellular receptors.<sup>23</sup> Complexes formed by these steroids diffuse to the nucleus, where they bind to response elements in the genome and modulate the transcription of various proteins. As a result, they are able to affect many aspects of neuronal function including the synthesis, degradation, and regulation of the effects of numerous neurotransmitters and other hormonal systems.<sup>23</sup> The affected systems and neurotransmitters include those most closely associated with both depression and insomnia, in particular, the HPA axis, 5-HT, and GABA.

#### **The HPA Axis**

A link between elevated HPA-axis activity and both insomnia and depression is supported by observations that Cushing's syndrome, Cushing's disease, and exogenous administration of corticosteroids are all associated with a high frequency of depression and insomnia, which at times occur independently.<sup>24,25</sup> Similarly, individuals suffering from major depression and primary insomnia have been found to have elevated serum and 24-hour urine levels of cortisol.<sup>19,26–28</sup> It is tempting to speculate that a common defect in these disorders, leading to elevated HPA activity and cortisol levels, might predispose individuals to both depression and insomnia.<sup>19</sup>

Nevertheless, only a subset of individuals with insomnia and ~50% of individuals with depression have significant hypercortisolemia.<sup>29,30</sup> The serum levels of cortisol and the sequelae that typify Cushing's disease, Cushing's syndrome, or iatrogenic Cushing's are generally not characteristic features of individuals with either depression or chronic insomnia.<sup>30</sup> Furthermore, cortisol elevation may be a nonspecific response to sleep disruption that

may, in some individuals, further disrupt sleep, leading to chronic insomnia.<sup>19,31</sup> A parallel hypothesis of self-perpetuating hypercortisolemia and depression is based partly on evidence that normalization of elevated HPA-axis activity generally precedes antidepressant response and that sustained hypercortisolemia predicts a greater risk of depressive relapse.<sup>25</sup> Although the direction of causality remains undetermined, an association clearly exists between elevated glucocorticoid levels and both depression and insomnia.

The influence of gonadal hormones on the HPA system may be important to understanding depression and insomnia, given the observed gender differences in both disorders. Studies in animals indicate that preferential binding of estrogen to intracellular estrogen beta receptors in the paraventricular nucleus of the hypothalamus increases HPA activity including serum cortisol levels.<sup>32</sup> There is also evidence that the relationship between estrogen and HPA function is affected by the state of menstrual cyclicity. It has been demonstrated in rodents, non-human primates, and humans that surgical, pharmacologic, or natural menopause enhances the response of the HPA axis to stress or pharmacologic stimulation.<sup>33</sup> In several studies, institution of estrogen replacement attenuated the response of the HPA axis.

### Serotonin

Serotonin (5-HT) is the neurotransmitter most closely identified with major depression. Effective antidepressants include selective serotonin reuptake inhibitors (SSRIs); tricyclic antidepressants, many of which also inhibit 5-HT reuptake; serotonin-type 2 and 3 receptor antagonists; and monoamine oxidase inhibitors (MAOIs), which impede the degradation of 5-HT and other monoamines. Gonadal hormones also exert diverse effects on serotonergic function. Both spontaneous and surgical menopause decrease serum 5-HT levels, which are normalized by estrogen and/or progesterone replacement.<sup>34</sup> Hormone replacement has also been reported to enhance serotonergic neurotransmission and serum and urinary levels of a primary 5-HT metabolite. Lower serum estrogen is associated with upregulation of central 5-HT<sub>2A</sub> receptors and the 5-HT reuptake process.<sup>35</sup> In animals, estrogen modulates 5-HT synthesis, turnover, uptake, and binding sites.

It also amplifies the response to 5-HT<sub>1A</sub> agonists.<sup>11</sup> Estrogen also inhibits MAO activity in the hypothalamus and limbic system of the rat, an effect that is reversed by progesterone.<sup>11</sup> Some studies suggest changes in serotonergic function in the late luteal phase of the menstrual cycle.<sup>23</sup> It is hypothesized that the 5-HT<sub>2A</sub> receptor, which is regulated by estrogen and progesterone, plays an important role in the vasomotor symptoms that occur in peri-/postmenopausal women.<sup>34</sup> On this basis, 1 aspect of the serotonin system is implicated in the development of peri-/postmenopausal sleep disruption, which may in turn lead to depression symptoms and/or chronic insomnia. It is difficult to draw conclusions about the pathophysiologic or therapeutic mechanisms based on this literature because of the complexities of the 5-HT system. Nonetheless, these observations suggest that the HPG system has strong and diverse effects on the 5-HT system, which is believed to be most intimately involved with major depression.<sup>23</sup>

### γ-Aminobutyric Acid

GABA, the major inhibitory neurotransmitter that figures significantly in the initiation and maintenance of sleep, is also affected by gonadal hormones. First-line insomnia treatments enhance the effect of GABA on the GABA(A) receptor. Estrogen appears to diminish the number of CNS GABA(A) receptors, an effect reversed by progesterone.<sup>36</sup> Metabolites of progesterone appear to enhance GABA's effect on the GABA(A) receptor. Whether fluctuations in estrogen and/or progesterone lead to changes in GABA function, and whether this mechanism plays a role in menstrual

### KEY POINT

**It is widely recognized that insomnia and depression are often comorbid. The view has long been that insomnia is always secondary to the depression; this viewpoint is changing based on new evidence that suggests that insomnia is also a risk factor for depression.**

cycle, postpartum, or peri-/postmenopausal sleep disturbances, has not been determined.

### **THE RECIPROCAL RELATIONSHIP BETWEEN INSOMNIA AND DEPRESSION**

Insomnia and depression are often comorbid.<sup>37</sup> The unidirectional view that insomnia is always secondary to depression is changing, based on substantial evidence from epidemiologic studies that have found insomnia to be a risk factor for depression.<sup>37-42</sup> These collective observations raise the possibility that any mechanism, including those associated with fluctuations in gonadal hormones, that leads to depression will increase the risk of insomnia, and circumstances that lead to insomnia will increase the risk of depression. The extent that this occurs in women during their lives will lead to a prevalence of both insomnia and depression that exceeds what would be expected on the basis of the identifiable gender-divergent mechanisms.

### **TREATMENT IMPLICATIONS FOR WOMEN WITH INSOMNIA AND DEPRESSION**

Clinicians need to be aware of the complex relationships between insomnia and depression that may appear in women during periods of fluctuating levels of gonadal hormones, and recognize that the optimal treatment regimen for insomnia and depression may differ for men and women. Given the bidirectional relationship between insomnia and depression, the occurrence of 1 disorder may predispose affected individuals to the other. Comorbid insomnia and depression are more likely to be seen in women in practice, and the risk of recurrence of both conditions is heightened. More aggressive treatment of both conditions, as well as prophylaxis against relapse, is indicated.

Appropriate choices of pharmacologic treatment include sedating antidepressants, or the combination of an antidepressant and a sedative/hypnotic agent. The most commonly prescribed antidepressant agents are the SSRIs. Although their side-effect profiles are preferable to other available options for many individuals, SSRIs provide relatively little therapy for the associated insomnia and can, in fact, disrupt sleep in some individuals.<sup>43,44</sup> Institution of effective adjunctive therapy for insomnia is often indicated. The current first-line pharmacologic

agents for therapy for insomnia are the nonbenzodiazepine receptor agonists (non-BZRAs), which include zolpidem and zaleplon. In a double-blind, placebo-controlled study of 190 patients with persistent insomnia despite effective and stable therapy with an SSRI, treatment for 4 weeks with zolpidem was associated with improved quantity and quality of sleep, no development of tolerance, and no worsening of depressive symptoms.<sup>44</sup>

The sedating antidepressant trazodone is commonly prescribed in this setting to address insomnia; however, it has a number of disadvantages compared with the BZRAs. The major problems of this group of medications are the associated side effects, duration of action, and risk of overdose, which is a particular concern with the tricyclic antidepressants. Not only are depressed patients at high risk for attempted suicide, there is evidence that insomnia is an independent risk factor for suicide attempts.<sup>45</sup> In addition, empirical support for the efficacy and safety in the treatment of insomnia is minimal for the sedating antidepressants, including trazodone, compared with the BZRAs.<sup>46,47</sup> In fact, in the only study undertaken of the treatment of primary insomnia with trazodone, its efficacy appeared to be modest.<sup>46</sup>

Cognitive-behavioral therapy for insomnia is another option. This form of treatment should be considered in all cases to prevent the development of autonomous chronic insomnia, which may be particularly more likely to occur postpartum and in the peri-/postmenopausal period.<sup>4</sup> Attention should be directed toward correcting maladaptive behaviors, such as napping and excessive caffeine use, and, to reverse the conditioning process, minimizing worrying in bed and time awake in bed.

### **CHOOSING TREATMENT OPTIONS FOR WOMEN WITH INSOMNIA AND DEPRESSION**

As previously mentioned, drugs that target serotonin are particularly effective in the treatment of depression and insomnia in women.<sup>48</sup> In general, evidence suggests that for women, SSRIs are more effective for the treatment of depression and better tolerated than the tricyclic antidepressants or MAOIs.<sup>48</sup> When using these agents in the treatment of depression, however, adjunctive therapy for insomnia may be necessary.

In terms of depression occurring at particular points in women's lives, a series of studies have indicated a preferential response of premenstrual dysphoria to the SSRIs, which appear to be just as effective when used only during the late-luteal phase of the menstrual cycle.<sup>4</sup> For those with relatively isolated recurrent premenstrual insomnia, a short course of a non-BZRA during this period has been helpful in some cases, although no prospective data exist regarding this practice.<sup>4</sup>

With respect to sleep disruption, insomnia, and depression emerging postpartum, it is important to institute effective therapy<sup>14</sup> to prevent impairment in responsiveness and caretaking capacity, which could adversely affect the infant. Various studies suggest the efficacy of SSRIs, venlafaxine, interpersonal therapy, and estrogen administration.<sup>14</sup> Because of the risks associated with the presence of medications in breast milk, consideration of nonpharmacologic therapies is important in mothers who are breastfeeding. Although there are more data for SSRI use in lactating mothers than for any other class of medication, no systematic data are available to allow comparison with other treatments or provide definitive capacity to estimate risks.<sup>14</sup> Awareness of the emergence of maladaptive behaviors when disruption of sleep is occurring can be very helpful. The longer such behaviors persist, the harder they are to eliminate. Furthermore, it is important to assess whether the infant may be having sleep difficulties and to take steps to address this, given the apparent effects on the mother.<sup>16</sup>

In the peri-/postmenopausal period, SSRIs also appear to be effective in ameliorating vasomotor symptoms that may lead to insomnia and dysphoria.<sup>34</sup> Hormone replacement therapy should also be considered, although its risks should be taken into account.<sup>4</sup> The fact that insomnia sometimes persists despite eliminating vasomotor symptoms points to the need to consider cognitive behavioral therapy to address maladaptive behaviors and conditioning that may have taken place.<sup>4,20</sup> Despite few data on the pharmacologic management of insomnia in this setting, a small open-label trial of 75 mg of trazodone and preliminary data from a large placebo-controlled trial of zolpidem 10 mg suggest that pharmacotherapy of insomnia in this setting can be safely and effectively instituted.<sup>4</sup>

## SUMMARY

Insomnia and depression are highly interrelated, and both are more prevalent in women. Strong evidence demonstrates links between the HPG system and the key neuropharmacologic systems that are most related to depression and insomnia; however, the mechanisms by which these disorders occur in women remain unclear. Because of the high risk of relapse and high likelihood of comorbidity, effective and expeditious treatment of both insomnia and depression in women is required. The serotonin system is strongly influenced by gonadal hormones, and medications related to this system, eg, the SSRIs, appear to be uniquely effective in treating insomnia and depression in women. For some, hormone replacement therapies may be effective. Behavioral therapies may be particularly important for women because of safety concerns postpartum and to prevent development of autonomous chronic insomnia, which may in turn increase the risk of depression. Of crucial concern is the need for research in many key areas related to the treatment of insomnia and depression in women.

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