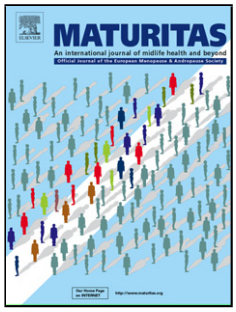

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Insomnia and depressive symptoms during the menopausal transition: the theoretical and therapeutic implications of a self-reinforcing feedback loop

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Highlights

- Insomnia and depressive symptoms recur frequently during the peri-menopause, with negative consequences for health.
- Insomnia and depressive symptoms can form a self-reinforcing feedback loop in the peri-menopause.
- By treating insomnia we may interrupt the self-reinforcing feedback loop with depressive symptoms.
- The treatment of insomnia during the peri-menopause may therefore also improve any symptoms of depression.

Abstract

Insomnia is a common and recurring condition during the menopausal transition that negatively affects both quality of life and health. Peri-menopausal insomnia has a multifactorial etiology; previous depression, hormonal changes and age/hormone-related irregularity in circadian rhythms can contribute to menopausal insomnia. Age-related poor health, pain and stress may favor the development of insomnia, while vasomotor symptoms, in particular hot flashes, may contribute to chronic forms of insomnia by activating a vicious

cycle. Insomnia increases two- to threefold the risk of developing depressive symptoms during the peri-menopause. In fact, the menopausal transition is a window of vulnerability for the development of depressive symptoms, in which the risk of a major depressive disorder is 2 to 4 times greater than in the premenopausal period. Depression naturally has a negative impact on daily functioning, quality of life and health. Since the relationship between insomnia and depressive symptoms has been shown to be bidirectional, the aim of this review is to provide a brief overview of their association in the context of the menopausal transition. By exploring the potential pathways of their bidirectional relationship, this overview should be useful for preventive and therapeutic purposes. By treating insomnia we may be able to interrupt the self-reinforcing feedback loop with depressive symptoms, and thereby improve affective symptoms and women's wellbeing in this period of their life.

Keywords: mood, depression, sleep disorders, insomnia, menopause

Introduction

The menopausal transition is associated with fluctuating hormone levels and the emergence of physiological and psychological symptoms, including hot flashes, sleep disturbances and mood changes, that may vary among women in terms of frequency, severity, and duration [1,2]. Midlife women transitioning menopause are more likely than younger women to report sleep difficulties; the prevalence of symptoms of insomnia may range from 39% to 60%, with 26% of peri-menopausal women experiencing a chronic form and a negative impact on daytime functioning, quality of life and health [1-4]. A better understanding of the mechanisms involved in the development and maintenance of insomnia during the menopausal transition should help to improve treatment strategies.

Several longitudinal studies have found that the menopausal transition is associated with affective changes, ranging from an increase in depressive symptoms to a diagnosed

major depressive episode [5]. During this period, women are 2 to 4 times more likely to develop a major depressive disorder [5,6]. Across the peri-menopause, affective changes may have significant negative implications for daily functioning, quality of life and health [5,6]. Similarly to insomnia, greater understanding of the mechanisms underlying these affective changes during the peri-menopause should improve preventive and treatment strategies. It has been shown that, among other factors, insomnia and disturbed sleep may contribute to depressive disorders during the menopausal transition [1,2]. Since the relationship between insomnia and depressive disorders has been shown to be bidirectional [7,8], the aim of this review is to provide a brief overview of insomnia and its association with depressive symptoms in the context of the menopausal transition. In this framework, the adaptation of the psychobiological model of insomnia [9] in the context of menopausal transition should be useful to understand insomnia and its consequences during this period of a woman's life. By exploring the potential pathways of the bidirectional relationship between insomnia and depressive symptoms during the peri-menopause, this overview should be useful for preventive and therapeutic purposes. Hence, in this review we first discuss the psychobiological model of insomnia in the framework of the menopausal transition before examining the role of insomnia in depressive symptoms and the therapeutic implications of their relationship during the peri-menopause.

Methods

The PubMed, PsycINFO and Embase electronic databases were searched for literature published up to November 2018 on insomnia, depressive symptoms and menopause. Several combinations of search terms were used such as "insomnia" or "insomnia symptoms" and "menopause" and "depressive symptoms" or "depression". Studies were included if they: (1) involved human adults; (2) were longitudinal, observational, case–control, cross-sectional

studies, or reviews; (3) were published before November 2018. Studies were excluded if: (1) they were not available in full text; or (2) they were not available in English. The data were integrated in a narrative review.

Psychobiological model of insomnia in the context of the menopausal transition

Around 25-30% of the general population experience symptoms of insomnia, compared with 39-60% of peri-menopausal women. In this context, they are one of the most disturbing types of symptom, and, together with vasomotor manifestations, they have a negative impact on everyday functioning, quality of life and health [for a comprehensive review see 1,2,10,11].

According to one of the most influential models of insomnia, the 3P model [9], predisposing, precipitating and perpetuating factors play important roles in its initiation and maintenance (Figure 1). Predisposing factors are present before insomnia is manifested and are hypothesized to interact with precipitating factors to increase the risk of insomnia in vulnerable individuals. Stressful life events are a common precipitating factor of insomnia: life stressors are associated with the development of new-onset insomnia. On this basis, a diathesis–stress model of insomnia has been developed: predisposed individuals may develop insomnia in response to acute stressors. Subjects with insomnia show elevated cognitive, somatic and physiological hyperarousal in response to stressful events, which is the key factor in insomnia and is present over 24 hours [12-14]. Stressful events may interact with cognitive and emotional factors to perpetuate the insomnia by creating a vicious cycle that sustains insomnia in the long term [12-14].

[Figure 1 near here]

According to this model, we reviewed the available data on vulnerability to insomnia during the menopausal transition and we have seen that it can be considered multifactorial [1,2]. Among the psychological/psychopathological factors, personality traits such as obsessive–compulsive traits and neuroticism (the general tendency to experience negative affect such as fear, sadness, anxiety) may predispose to the development of insomnia. In addition, a history of severe premenstrual symptoms may increase a woman's vulnerability to insomnia during the menopausal transition, as may a history of depression or insomnia. Endocrine and hormonal changes are also predisposing factors for insomnia during the peri-menopause; for instance, the decrease in estradiol levels is associated with worse sleep quality [2]. In addition, since estrogen and progesterone regulate and stabilize the circadian system, a decreased sensitivity to estrogens in the hypothalamus during menopause has been related to circadian rhythm disturbances. These circadian rhythm alterations, together with age-related sleep changes, may contribute to the development of sleep difficulties during the peri-menopause [15]. All these factors may interact with precipitating factors, providing a complex basis for the development of insomnia in midlife women. Among the factors precipitating insomnia, age-related stress, poor health, sleep-related breathing and movement disorders and chronic pain may play a role during the menopause [1,2]. In addition, as estrogen levels decline, vasomotor symptoms, which are a hallmark of the menopausal transition, tend to emerge, and the presence of hot flashes is consistently associated with insomnia and may contribute to its precipitation [2].

Factor perpetuating insomnia include the persistence of hot flashes, which, during the peri-menopause, tend to occur in the early hours of the night and, by interrupting sleep, perpetuate insomnia with a self-reinforcing feedback loop. In addition, physiological hyperarousal has been described in the peri-menopause and may contribute to the

maintenance of insomnia by also favoring dysfunctional cognitions such as worry and rumination about sleep and misattribution of the cause of sleep problems. It may also trigger maladaptive sleep habits (excessive time in bed, irregular sleep schedule), and alterations in mood and quality life. Therefore, the physiological hyperarousal seen in the peri-menopause may contribute to the vicious cycle of insomnia during this period of a woman's life [1,2,10,11,16,17].

Depressive symptoms and menopausal transition: what is the role of insomnia?

Menopausal transition is a window of vulnerability for the development of depressive symptoms, which are the psychiatric symptoms most commonly reported by peri-menopausal women [6,18]. Women in the menopausal transition are 2 to 4 times more likely to suffer from a major depressive disorder than are pre-menopausal women [6]. These mood changes may impact on daily functioning, quality of life and health during the peri-menopause [5,6]. Among the factors that may lead to depressive symptoms, hormonal fluctuations represent the endocrine triggers [18]. A history of depressive episodes, recent exposure to stressful events and the presence of vasomotor symptoms have also been shown to play a role [18]. In addition, sleep disturbances play a key role in depressive symptoms during the peri-menopause. In particular, insomnia has been shown to increase the risk of developing depressive symptoms two- to threefold during this period of a woman's life. In addition, a longitudinal investigation found that insomnia may also contribute to the persistence and recurrence of major depressive disorders during the menopause [19]. Furthermore, symptoms of insomnia in menopausal women worsen their vasomotor symptoms and have been related to a higher frequency of hot flashes, to tiredness and pain, and to anxiety and depressive symptoms [1,2,10,11,19].

Different pathways may underlie the strong relationship between insomnia and depressive symptoms during the peri-menopause (Figure 2). Besides the neurobiological mechanisms which generally contribute to both depression and insomnia, hormonal changes during the menopause may contribute to both sleep and depressive disorders [1,2, 11,19]. Some studies have shown that peri- and postmenopausal depression may be due to climacteric vasomotor symptoms, which compromise not only quality of sleep but also quality of life, reducing psychological well-being [20-24]. In addition, a "domino effect" has been postulated among hot flashes, insomnia and depressive symptoms and may contribute to the perpetuation of both insomnia and depressive symptoms. Age-related irregularity in circadian rhythms has also been indicated as a mechanism which may predispose to both sleep and mood disorders [1,2, 11,19]. Insomnia-related cognitive factors may also represent a vulnerability to depressive symptoms and vice versa [1,2].

Please insert Figure 2 here

Although further research is needed, preliminary data have shown that by targeting insomnia there is an improvement not only in insomnia symptoms and in vasomotor symptoms but also in depressive symptoms [25]. According to recent guidelines, the first-choice treatment for insomnia is cognitive behavioral therapy for insomnia,CBT-I [26]. CBT-I is multimodal intervention and consists of a combination of cognitive therapy, such as cognitive restructuring for dysfunctional beliefs about sleep, and behavioral interventions, such as sleep restriction, stimulus control, and sleep hygiene for maladaptive sleep habits [26], and it has been adapted for menopausal women [27-30]. Insomnia should be evaluated and subsequently treated in the context of menopause in order to improve any coexisting depressive symptoms, as suggested by current guidelines [30].

Conclusion

The existence of a bidirectional relationship between mood and sleep disturbances during the menopausal transition might be considered in order to improve women's wellbeing across this period of their life. By treating insomnia we may interrupt the self-reinforcing feedback loop with depressive symptoms and thereby improve depressive symptoms and clinical outcomes.

Practice points

- Insomnia and depressive symptoms recur frequently during the peri-menopause.
- They have negative consequences for women's mental and physical health.
- Insomnia may contribute to depressive symptoms and vice versa during the peri-menopause.
- By assessing and treating insomnia during the peri-menopause, we may interrupt its self-reinforcing feedback loop with depressive symptoms.
- By treating insomnia, we may be able to improve preventive and therapeutic approaches to depressive symptoms during the peri-menopause.

Research agenda

- Longitudinal studies are needed to track trajectories in women who approach the menopausal transition and develop insomnia, and to investigate whether treatment effectively corrects the symptoms of insomnia in the long term in these women.
- Longitudinal studies are needed to track trajectories in women who approach the menopausal transition and develop symptoms of both depression and insomnia, to investigate whether treating the insomnia effectively corrects both sets of symptoms in these women.

Contributors

Danila Caruso contributed to the writing and preparation of the paper.
Isabella Masci contributed to the writing and preparation of the paper.
Giada Cipollone contributed to the writing and preparation of the paper.
Laura Palagini contributed to the writing and preparation of the paper and supervision of the review.

Conflict of interest
The authors declare that they have no conflict of interest.

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Figure 1

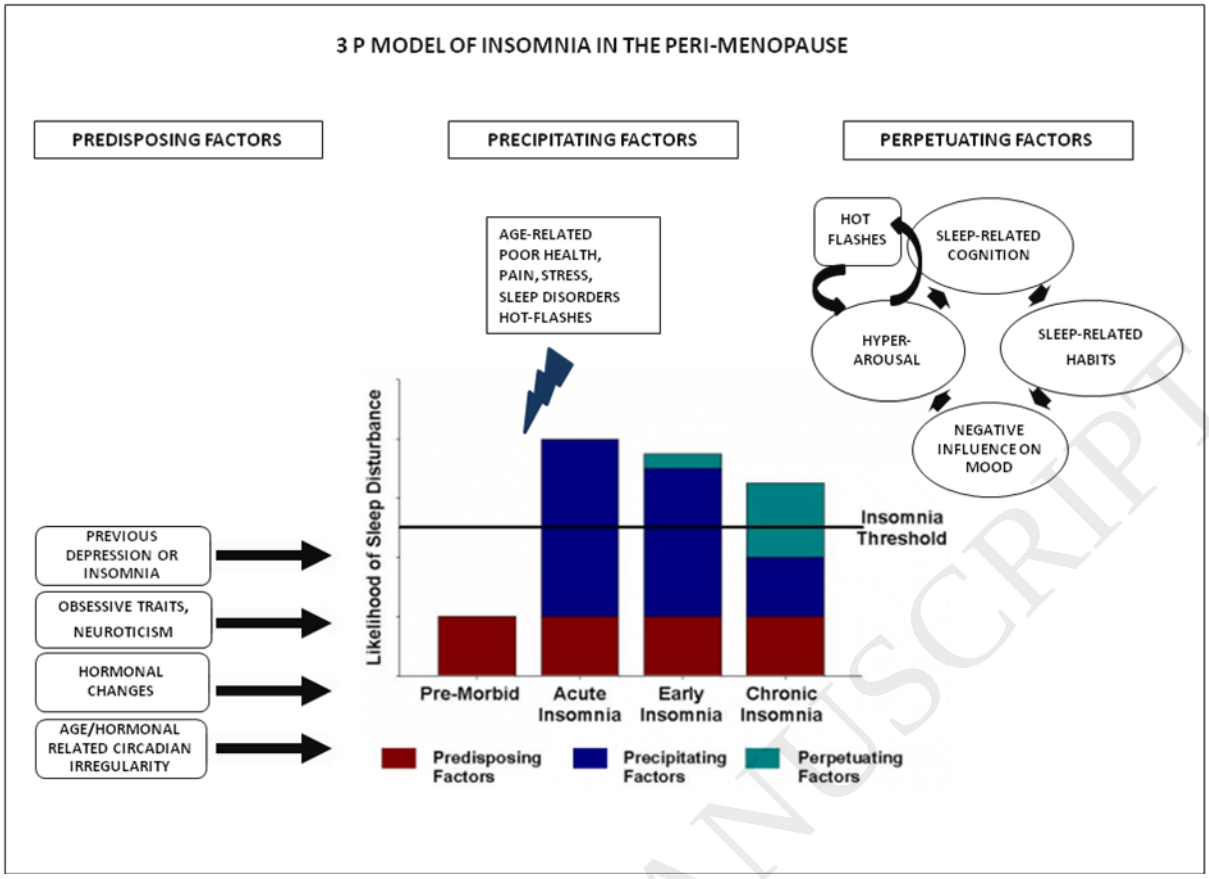

Figure 1. Psychobiological model of insomnia: the 3P model in the framework of the menopausal transition

According the 3P model of insomnia, predisposing, precipitating, and perpetuating factors contribute to insomnia. **Predisposing factors** during the peri-menopause include: 1) psychological/psychopathological factors (personality traits such as obsessive–compulsive traits and neuroticism, severe premenstrual symptoms, previous depression and/or insomnia), 2) endocrine and hormonal changes, 3) - disturbances of circadian rhythm related to hormonal changes, 4) age-related sleep changes. **Precipitating factors** during the peri-menopause include: 1) age-related stress, poor health, sleep-related breathing and movement disorders, 2) hot flashes. **Perpetuating factors** for insomnia during the peri-menopause include: 1) hot flashes, 2) physiological hyperarousal, 3) dysfunctional cognitions (worry over sleep loss, rumination over its consequences, misattribution of sleep

problems), maladaptive sleep habits (excessive time in bed, irregular sleep schedule, daytime napping), mood alterations which contribute to the vicious cycle of insomnia.

Figure 2

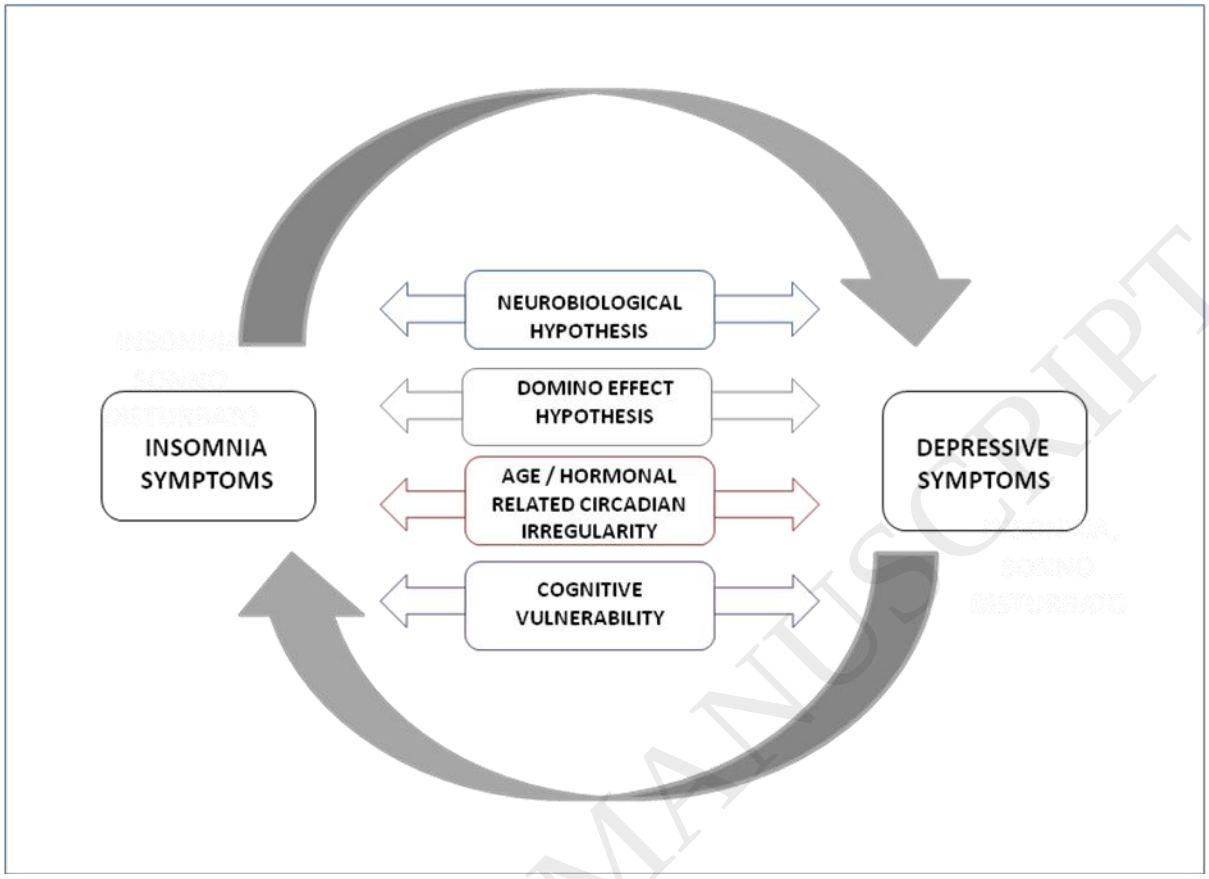

Figure 2. Association between insomnia and depressive symptoms in the peri-menopausal period: theoretical hypotheses of a self-reinforcing feedback loop.
There is a self-reinforcing feedback loop between insomnia symptoms and depressive symptoms. Different pathways may underlie this strong relationship during the peri-menopause. Besides the neurobiological mechanisms which generally contribute to both depression and insomnia, hormonal changes in the menopause may contribute to both sleep and depressive disorders. A "domino effect" has been postulated among hot flashes, insomnia and depressive symptoms which may contribute to the perpetuation of both insomnia and depressive symptoms. Age-related irregularity in circadian rhythms may predispose to both sleep and mood disorders. Insomnia-related cognitive factors may also represent a cognitive vulnerability to depressive symptoms and vice versa.