

Insomnia and sleep apnea in midlife women: prevalence and consequences to health and functioning

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Abstract

Sleep disturbance is common during the menopausal transition, with numerous downstream consequences to health and functioning, including reduced quality of life, impaired mental health, and increased physical health morbidity. Insomnia affects approximately 50% of midlife women and is characterized by nocturnal symptoms of difficulties initiating or maintaining sleep (or both) and daytime symptoms that impair occupational, social, or other components of functioning. In addition, approximately 20% of midlife women develop sleep-disordered breathing during the menopausal transition. This commentary summarizes the prevalence, risk factors, and treatment options for each of these sleep disorders in midlife women, with specific focus on first-line treatments for insomnia (cognitive behavioral therapy for insomnia) and sleep-disordered breathing (continuous positive airway pressure) and unique considerations for treating sleep disorders in midlife women. Future directions are also discussed.

Introduction

Midlife women are at increased risk for insomnia and sleep-disordered breathing (SDB). In fact, disturbed sleep is such a hallmark of the menopausal transition that it was recognized as a core symptom of menopause in the 2005 National Institutes of Health (NIH) State-of-the-Science Conference panel report on menopause-related symptoms [1]. Menopause is defined as the cessation of menstruation because of degeneration of ovaries and follicles accompanied by changing levels of ovarian hormone (estrogen and progesterone). The World Health Organization [2] further defines menopause as the permanent cessation of menstrual periods that occurs naturally or is induced by surgery, chemotherapy, or radiation. Menopause may also be characterized by the transition from pre- to peri- to post-menopausal status, as defined by standardized criteria [3].

Menopause-related sleep disturbances are a significant public health problem because of their potential negative impact on quality of life, mental health, workplace productivity, health-care utilization, and disease morbidity

[4–7]. This commentary provides a brief summary of the prevalence, risk factors, and treatment options for insomnia and sleep-disordered breathing, the two most common sleep disorders in midlife women. We close with a call for additional research to advance our understanding of the pathophysiology of sleep disturbances in midlife women and for the development and testing of interventions to ameliorate these common and consequential sleep disorders. Each disorder is uniquely described, given differences in present knowledge and empirical support for insomnia and SDB with respect to the menopausal transition. Our discussion of insomnia focuses on treatment, which can be multifactorial and complex, and our discussion of SDB includes more detail regarding risk factors and consequences in midlife women.

Insomnia disorder

Prevalence, risk factors, and consequences

The prevalence of insomnia, defined as nocturnal symptoms of difficulties initiating or maintaining sleep (or both) 3 times per week for a period of at least 3 months

and daytime symptoms that impair occupational, social, or other areas of functioning, is estimated at 39-60% in peri- and post-menopausal women [1,8,9]. The health and functional consequences of insomnia in midlife women include reduced quality of life, increased health-care utilization and costs [4], disability [4], and risk for psychiatric and medical conditions (for example, depression and cardiovascular disease, or CVD) [10,11]. It remains unclear whether insomnia that occurs during the menopausal transition differs from insomnia during other stages of life. However, there are many factors that may complicate the development and maintenance of insomnia during menopause, including the effects of aging on sleep (for example, diminished sleep need and changes in sleep continuity and architecture) [12-14] as well as changes in the hormonal milieu, hot flashes, depression, anxiety, or comorbid medical conditions (for example, chronic pain) or a combination of these. For example, hot flashes occur in 60-80% of women during the menopausal transition [15] and persist for 4-5 years on average [16,17]. When hot flashes occur during the night, they frequently but not invariably awaken women from sleep [18,19]. Indeed, insomnia can occur during menopause independently of nocturnal hot flashes [20]. Although the precipitants of insomnia during menopause remain unclear, behavioral conditioning and certain behaviors (that is, sleep habits) may prolong insomnia, as described by Spielman's three-factor model of insomnia [21]. Among midlife women, distress about nocturnal hot flashes and their impact on sleep can lead to sleep habits that perpetuate insomnia, including spending too much time in bed, 'sleeping in' in the morning, and napping during the day [22].

Treatment

Psychotherapeutic and pharmacologic approaches may be used to treat insomnia in midlife women, as described below. The most widely used non-pharmacologic approach is cognitive behavioral therapy for insomnia (CBTI), which is a structured, skill-focused psychotherapy that includes components of cognitive therapy (challenging unhelpful beliefs about sleep), behavioral techniques (sleep restriction, stimulus control therapy, and relaxation techniques), and education about sleep. Therapeutic techniques that may benefit other menopausal symptoms (for example, hot flashes and depression) may also be used to augment CBTI in midlife women [23-26]. Below, we review individual components of CBTI, including specific strategies that may be appropriate to insomnia in midlife women.

Sleep restriction

Sleep restriction is used to consolidate sleep in patients with insomnia. Although it may seem paradoxical to

reduce the time a patient with insomnia stays in bed, sleep restriction addresses a mismatch between the amount of time spent in bed and the amount of time spent asleep; effectively, restricting insomnia patients' time in bed improves their sleep efficiency (time spent asleep/time in bed \times 100) [27]. At a physiological level, sleep restriction improves sleep efficiency by increasing the patient's homeostatic drive for sleep.

Sleep restriction therapy in CBTI is accomplished over a number of weeks. The clinician first must assess the patient's current sleep habits, including the timing of sleep (clock time at which the patient gets into and out of bed), the total amount of time spent in bed (hours between getting into and out of bed), and sleep duration (time spent asleep). These data are usually collected by using daily sleep diaries over a 1- to 2-week period. In the second step of sleep restriction therapy, the clinician prescribes the timing and duration of time in bed on the basis of the patient's average sleep duration. For example, sleep restriction in an insomnia patient with an average time in bed of 8.5 hours and average sleep duration of 7 hours would entail a new time in bed of 7 hours. Sleep restriction generally entails changing a patient's bed time, as rise time is often dictated by circumstances such as work schedule and family responsibilities. Patients continue to complete daily sleep diaries during sleep restriction so that they and their clinician can monitor sleep efficiency and adjust sleep duration accordingly. As the patient's sleep efficiency increases, time in bed is lengthened in 15- to 30-minute increments over subsequent weeks until an optimal quantity of sleep is achieved without decreasing average sleep efficiency to below 85%. More detailed information on the delivery of sleep restriction therapy is available in published guidelines (for example, *Treatment Plans and Interventions for Insomnia* by Manber and Carney [28], *Overcoming Insomnia: A Cognitive-Behavioral Therapy Approach Workbook* by Edinger and Carney [29], and *Cognitive Behavioral Treatment of Insomnia: A Session-by-Session Guide* by Perlis and colleagues [30]).

Increased daytime sleepiness is a common side effect at the start of sleep restriction therapy. It is, thus, important that patients be made aware of and monitored for the risk of increased daytime sleepiness. Prescribed increases in time in bed over the course of sleep restriction therapy attenuate daytime sleepiness. Sleep restriction therapy is inadvisable for individuals whose jobs require heightened vigilance to avoid accidents (for example, professional drivers, pilots, air traffic controllers, and machine operators). Other contraindications include conditions that can be exacerbated by sleepiness or deep sleep (for example, epilepsy, parasomnias, and SDB). Risk for

sleep apnea should be evaluated (for example, reports of loud snoring, pauses in breathing, gasping for breath, daytime sleepiness, and obesity), and referrals for formal assessment and treatment should be made prior to initiating sleep restriction therapy; this caution is especially important in midlife women given the increased prevalence in sleep apnea during the menopausal transition (see the following section).

Stimulus control

In insomnia, the bed and bedroom can become associated with frustration, intrusive thoughts, anxiety and distress, and elevated physiological arousal, which, in turn, perpetuate the patient's inability to sleep [31]. Using principles of classic conditioning theory [32,33], Bootzin [32,34] designed stimulus control therapy for insomnia, which strengthens conditioned associations between the bed and bedroom as cues for sleep and extinguishes the conditioned arousal response to the bed and bedroom. Stimulus control therapy prescribes that the patient go to bed when sleepy, get out of bed when they are unable to sleep, and engage in quiet activities away from the bed and bedroom until they are sleepy, at which time they return to bed. The bed is limited to sleep and sexual activity. Participants are also instructed to maintain a consistent wake time and avoid napping during the day. Modifications to the stimulus control instructions may be necessary in midlife women for whom leaving the bed during the night is contraindicated, as in individuals at risk for falls, or in women who are disabled and cannot leave the bed without assistance.

Cognitive therapy

Principles of cognitive therapy for insomnia are designed to challenge maladaptive beliefs and attitudes that serve to maintain insomnia. Worrying, faulty attributions, or unrealistic expectations of sleep may lead to increased emotional distress, feeding a vicious cycle that maintains and may exacerbate disturbed sleep in midlife women (for example, *"If I don't get my 8 hours of sleep, I'm useless."*). Challenging unhelpful beliefs about sleep will decrease an individual's anxiety and arousal [35,36]. The first step is to make the patient aware of her unhelpful sleep beliefs. Once these beliefs are identified, the individual is taught to challenge their unhelpful beliefs through guided discovery. The patient is encouraged to view her thoughts as one of the many possible interpretations instead of the absolute truth (for example, *"I don't even know whether I'll get a good sleep tonight."*). The final step is to replace dysfunctional cognitions with alternative interpretations that are more adaptive and realistic and that are based on past evidence (for example, *"Despite feeling bad at work, I do a good job*

99.9% of the time."). Menopausal women experiencing hot flashes may also have maladaptive thoughts related to hot flashes (for example, *"It seems as if I'll never feel like myself again."*). Cognitive therapy techniques can also teach women to apply effective cognitive reframing skills to unhelpful thoughts about hot flashes. Women who cope with hot flashes by using disclosure to others or self-talk (*"Letting the flash pass without being hooked by the feelings."*) and by staying calm (*"I can just relax and accept it."*) report less distress about hot flashes [37–39].

Relaxation training

Relaxation techniques can be effective in reducing physiological hyperarousal and are especially effective in helping with sleep initiation [40–42]. Relaxation techniques commonly used to treat insomnia include progressive muscle relaxation, body scanning (a form of mindfulness meditation focusing attention on particular body parts (for example, Jon Kabat-Zinn's *Mindfulness for Beginners* [43]), autogenic training (that is, visualizing a calming scene), and diaphragmatic breathing. Because there is little evidence to suggest differential effectiveness for insomnia across these relaxation techniques [44], patients may select the technique that feels most appropriate to them. These techniques may be practiced in bed before going to sleep or during awakenings from sleep. Relaxation techniques may be especially helpful to midlife women who experience hot flashes [45,46]. Although the exact mechanism of hot flashes is not clear, they appear to be mediated by increased sympathetic nervous system activity [47]. This knowledge has generated considerable interest in the idea that reducing stress may reduce hot flashes by reducing central sympathetic activation. In this context, paced respiration may be an effective tool to reduce stress, hot flashes, and their impact on symptoms of insomnia [48,49].

Sleep hygiene

Sleep hygiene therapy seeks to identify and correct behaviors and environmental factors that may interfere with or enhance sleep in insomnia. Sleep hygiene therapy is most effective when used in conjunction with other components of CBTI [41,50]. Examples of sleep-interfering factors are use of caffeine throughout the day, use of alcohol to induce sleep, and a bedroom environment that is bright, hot, and noisy. Sleep hygiene recommendations in midlife women with insomnia might include wearing lighter pajamas to bed and keeping a second pair near the bed, using lighter bedding and layering, keeping the ambient room temperature cool, keeping a fan nearby and a cool beverage near the bed, limiting caffeine products throughout the day, and avoiding alcohol and smoking.

Pharmacologic therapy

Sedative hypnotics, including zaleplon (Sonata; King Pharmaceuticals, Bristol, TN, USA), zolpidem (Ambien; Sanofi, Paris, France) [51], and eszopiclone (Lunesta; Sunovion Pharmaceuticals Inc., Marlborough, MA, USA), are effective for the treatment of acute insomnia [52]. However, tolerance, withdrawal, dependence, and rebound insomnia at discontinuation may occur when sedative hypnotics are used for more than 2 weeks [53]. Sex differences in their pharmacokinetics and side effect profiles, including increased risk of cognitive impairment in the morning and motor vehicle accidents, led the US Food and Drug Administration to require the manufacturers of Ambien and Lunesta to lower recommended starting doses in women. The recommended starting dose of zolpidem for women was lowered from 10 to 5 mg for immediate-release products and from 12.5 to 6.25 mg for extended-release products. The recommended starting dose of eszopiclone for women was lowered from 2 to 1 mg. Although dosing differences have been identified for zolpidem and eszopiclone, other sedative hypnotics may also differ with respect to their pharmacokinetics, including rates of absorption, metabolism, and excretion. Ramelteon, a selective melatonin receptor agonist, shows promise for the treatment of insomnia without the side effect profile associated with sedative hypnotics [54].

Summary and future directions

The weight of evidence supporting CBTI, summarized in several meta-analyses [42,55,56], led to its recognition as a first-line treatment for insomnia by the NIH Consensus Statement [1] and the British Association of Psychopharmacology [57]. Improvements following CBTI are equivalent to those achieved during acute treatment with hypnotic medications [58,59], and its effects are more durable after treatment discontinuation [58]. CBTI has also been shown to be efficacious for the treatment of chronic insomnia in older adults, including mid- and late-life women [58,60]. CBTI can be readily adapted to the sleep disturbances often reported during the menopausal transition [8,19]. However, to date, no randomized clinical trials have been conducted to examine the efficacy of CBTI in menopausal women or identify special considerations for tailoring CBTI to midlife. We are aware of only one study that has evaluated CBTI in women who reported that *"my sleep is affected by menopause"* [61]. Preliminary data from this open trial revealed a significant reduction in symptoms of insomnia and depression from pre- to post-CBTI [61]. Although these data are promising, randomized clinical trials are needed to quantify the efficacy of CBTI or modified CBTI (or both) for insomnia during the

menopausal transition. Based on its efficacy and durability in other populations, CBTI holds promise for treating the increased incidence of insomnia in midlife women during the menopausal transition and beyond. Studies that evaluate the extent to which CBTI ameliorates medical risk associated with menopause, such as CVD and diabetes [62–64], are also needed.

The most significant barrier to dissemination of CBTI in midlife women with insomnia is the number of health-care providers trained to deliver this efficacious and durable treatment. There are too few behavioral sleep medicine specialists certified by the American Board of Sleep Medicine to diagnose and treat insomnia in the community. A recent national Veterans Affairs training initiative [65,66] has been instituted to train a broader range of health-care providers in the delivery of CBTI, including primary care clinicians, nurse practitioners, and licensed social workers. Health-care providers without expertise in the diagnosis and management of insomnia may also seek referrals for board-certified behavioral sleep medicine specialists through the Society for Behavioral Sleep Medicine website (www.behavioralsleep.org/findspecialist.aspx). Also available to health-care providers and the public are a variety of commercially available self-help books (for example, Carney and Manber's *Quiet Your Mind and Get to Sleep* [67]), internet-based CBTI programs (for example, www.sleepio.com and www.shuti.me), and mobile applications (for example, CBT-i Coach).

Obstructive sleep apnea

SDB is an umbrella term that encompasses a variety of sleep disorders defined by abnormal respiration during sleep. As the most common form of SDB, obstructive sleep apnea (OSA) is characterized by recurrent episodes of significant airflow reduction (hypopnea) or cessation (apnea) due to upper airway narrowing or collapse, respectively, despite continued respiratory effort. A brief arousal is often required to reestablish airway patency. This repeated pattern of breathing pauses and arousals results in recurring bouts of intermittent blood oxyhemoglobin desaturation and increased sympathetic activity, respectively, throughout the night. SDB severity is derived from overnight polysomnography and calculated as the number of apneas and hypopneas per hour of sleep (apnea-hypopnea index, or AHI). AHI values of 5 to less than 15, 15 to less than 30, and at least 30 represent mild, moderate, and severe disease categories, respectively [68].

Across multiple races and ethnicities and without regard to age and obesity status, recent estimates indicate that approximately 20% of women have at least mild OSA (AHI of at least 5) and that 6% have moderate to severe

OSA (AHI of at least 15) [69,70]. This represents a significant increase in OSA prevalence over the last 20 years and is largely attributed to an aging society and increased obesity [69]. Nevertheless, these statistics mask the dramatic increase in OSA risk for midlife women: in one study, the prevalence of moderate to severe OSA progressed from less than 3% in women who are 30-49 years old to 9% for women who are at least 50 years old [69]; in another study, OSA prevalence estimates were 4, 17, and 43% among women who are 20-44, 45-54, and 55-70 years old, respectively [71]. Indeed, a recent study from a community-based sample of midlife women reported that 20% of the sample had moderate to severe OSA [72].

Signs and symptoms of obstructive sleep apnea and diagnosis

Standard signs and symptoms of OSA include snoring, witnessed apneas, and daytime sleepiness. However, women with OSA often have a different clinical presentation, commonly reporting insomnia-like complaints such as fatigue or poor sleep quality along with mood disturbance [73,74]. These atypical OSA symptoms may divert clinicians from suspecting OSA; however, clinical studies have found that the majority of postmenopausal women who present with insomnia symptoms actually have significant OSA.

The standard method of OSA diagnosis is laboratory polysomnography that includes assessment of breathing, respiratory effort, and oxyhemoglobin saturation, although home-based testing using limited-channel devices is gaining popularity and acceptance in sleep medicine [75]. The vast majority of women with OSA have not been clinically diagnosed [76,77], and this is likely owing to the different manifestation of OSA symptoms and lower likelihood of being prompted by their partner to seek treatment [78].

Risk factors for obstructive sleep apnea

Midlife seems to be a time of increased OSA prevalence for women because of three interrelated factors: the menopausal transition, weight gain, and aging [79]. Although OSA is relatively rare among premenopausal women, its prevalence dramatically increases with menopause [80–82]. Postmenopausal women are 3.5 times more likely than premenopausal women to have moderate or severe OSA, even after adjustment for age and body mass index (BMI) [80]. It is commonly believed that estrogen and progesterone confer protection from OSA, likely by enhancing upper airway dilator function and respiratory control during sleep [83–85], but this has yet to be comprehensively examined in large

well-controlled studies. Moreover, some observational [79,80,86] and treatment [87–89] studies have found that hormone replacement therapy (HRT) is associated with reduced OSA risk and severity among postmenopausal women, whereas others have failed to demonstrate any effect of HRT on OSA risk [90–92]. Thus, the diminished production of these reproductive hormones with menopause may increase OSA risk among midlife women, although the available evidence is not entirely consistent.

Obesity is the strongest risk factor for OSA among adults [93] and undoubtedly plays a key role in the development and progression of OSA among midlife women, as the menopausal transition is associated with significant weight gain and greater central fat deposition [94]. However, the association between weight and OSA may be less important compared with males, as females have a higher BMI at each category of OSA severity [95] and the longitudinal association between changes in BMI and AHI is weaker among women compared with men [96,97]. This difference may be due to the distribution of excess weight, since the central fat distribution often seen in males is more likely to impact OSA risk compared with the peripheral fat distribution commonly observed in females [98].

Finally, age and poor sleep quality are important risk factors for OSA in midlife women. The risk of OSA increases steadily with age across adulthood until reaching a plateau at approximately 70 years [70,99]. In addition to weight gain that accompanies aging [94], upper airway collapsibility increases with age [100,101]. Poor sleep also predisposes to OSA: fragmented sleep increases OSA frequency, whereas slow-wave sleep is protective against OSA [102,103]. Midlife women experience decreased subjective, though not necessarily objective, sleep quality [19], and the age-related decline in sleep efficiency is greater among women compared with men [13].

Health consequences

Untreated OSA of at least moderate severity is independently associated with numerous health consequences, including cognitive impairment [104], mood disturbance [105], metabolic dysfunction [106], CVD [107], and early mortality [108]. Most studies on the health consequences of OSA have consisted primarily of male samples or have not examined whether the health risk of OSA differs by sex. The few studies that have examined sex differences in the health consequences of OSA have focused on CVD risk but have had equivocal findings [109–112]. Similarly, only a handful of studies have

exclusively focused on the health consequences of OSA in women. Each of these studies has focused on metabolic or CVD risk, and OSA was significantly associated with higher CVD surrogates [113] and greater risk for the metabolic syndrome [114], coronary heart disease and stroke [115], and CVD mortality [116]. As a prominent example, Theorell-Haglöw and colleagues [114] found that 57% of women with severe OSA had the metabolic syndrome compared with only 11% of women without OSA. Likewise, studies that focused exclusively on midlife women have found OSA to be associated with greater metabolic syndrome prevalence and higher levels of inflammatory and coagulation biomarkers that are prognostic for CVD and type 2 diabetes (for example, C-reactive protein, fibrinogen, and plasminogen activator inhibitor-1) [117,118]. It is important to note, however, that this literature is dependent on observational studies and cannot directly address causality; future studies that are specifically designed and powered to address causation are needed.

Treatment

Continuous positive airway pressure (CPAP) is the conventional treatment for OSA. With this therapy, a machine delivers a constant flow of air to the patient's airway via a nasal, facial, or oral interface, effectively providing a pneumatic splint to maintain airway patency during sleep. Although CPAP is highly efficacious when used, numerous studies have demonstrated that adherence is a notable problem as, on average, less than one half of adults prescribed CPAP use the device at least 4 hours per night [119]. However, research examining whether CPAP adherence differs by sex has provided inconsistent findings, with studies indicating greater [120], lower [121,122], or similar [123–125] CPAP compliance in women compared with men. Similarly, whether treatment response differs between men and women is unclear—the only study to examine this found similar improvements between middle-aged men and women in daytime functioning following CPAP therapy [125]. Two observational studies, using the same cohort of women with suspected OSA, found CPAP treatment to be associated with a reversal of the CVD morbidity and mortality risk observed for severe OSA [115,116]. Unfortunately, no studies have focused on the predictors of CPAP adherence or treatment outcomes associated with CPAP use in midlife women.

Oral appliances and weight loss represent the most common treatment alternatives to CPAP. As devices that reposition the lower jaw and soft tissue structures of the mouth to increase upper airway size during sleep, oral appliances are a primary treatment option for adults with mild to moderate OSA and for those who cannot

tolerate CPAP. Studies have generally found that oral appliances have a rate of treatment success (defined as an AHI of less than 10) of approximately 50% [126]. The only study to examine sex differences in oral appliance treatment response found that women were more than twice as likely to experience treatment success compared with men [127]. Alternatively, because excess weight is such a strong determinant of OSA risk [93], lifestyle interventions that focus on weight loss are commonly recommended in the management of OSA [128]. However, weight loss is associated with a smaller AHI reduction in females compared with males [97], and one randomized trial found that a lifestyle intervention was less effective at reducing AHI in women compared with men at 1 year [129] but not at 4 years [130]. Again, similar to CPAP research, no studies have specifically examined the efficacy, predictors, or outcomes associated with oral appliance or weight loss therapies for midlife women.

Finally, some experimental trials have found HRT to reduce OSA severity in postmenopausal women [87–89], although multiple studies have failed to observe such an effect [90–92]. Given the inconsistent findings of HRT on treatment efficacy and its known health risks (for example, breast cancer and venous thromboembolic disease), HRT is not recommended for treating OSA in postmenopausal women [131]. Thus, treatment considerations for midlife women with OSA do not appreciably differ from those recommended for the general adult population with OSA [132–134].

Important future directions

Much of the research involving the health consequences of OSA, adherence to OSA treatment options, and responses to OSA treatment has focused on males [135]. However, because women differ from men in the underlying pathophysiology and clinical presentation of OSA, these issues need to be explored in women. A focus on midlife women—who experience the greatest increase in OSA prevalence and, as a result, may benefit the most from early identification and intervention—seems especially warranted. In particular, efforts to attenuate the development, progression, and health consequences of OSA among midlife women should be explored.

Conclusions

Insomnia and SDB are common in midlife women and this is due, in part, to both direct and indirect consequences of menopause and aging. Although research has not specifically linked menopause-related sleep disturbances to morbidity and mortality, mounting evidence suggests that insomnia and SDB are significant risk factors for cardiometabolic disease and mortality [64,108,136].

Fortunately, there are effective treatment options for both disorders, although interventions may benefit from being tailored to midlife women, including the impact of nocturnal vasomotor symptoms on insomnia and apnea and motivational interviewing strategies to enhance compliance and effectiveness. Treatment of sleep disturbances in midlife women may have direct effects on quality of life as well as more downstream effects on mental and physical health, including both health span and life span.

Abbreviations

AHI, apnea-hypopnea index; BMI, body mass index; CBTI, cognitive behavioral therapy for insomnia; CPAP, continuous positive airway pressure; CVD, cardiovascular disease; HRT, hormone replacement therapy; NIH, National Institutes of Health; OSA, obstructive sleep apnea; SDB, sleep-disordered breathing.



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