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REVIEW ARTICLES

Menopause Related Sleep Disorders

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Abstract: Sleep difficulty is one of the hallmarks of menopause. Following recent studies showing no cardiac benefit and increased breast cancer, the question of indications for hormonal therapy has become even more pertinent. Three sets of sleep disorders are associated with menopause: insomnia/depression, sleep disordered breathing and fibromyalgia. The primary predictor of disturbed sleep architecture is the presence of vasomotor symptoms. This subset of women has lower sleep efficiency and more sleep complaints. The same group is at higher risk of insomnia and depression. The "domino theory" of sleep disruption leading to insomnia followed by depression has the most scientific support. Estrogen itself may also have an antidepressant as well as a direct sleep effect. Treatment of insomnia in responsive individuals may be a major remaining indication for hormone therapy. Sleep disordered breathing (SDB) increases markedly at menopause for reasons that include both weight gain and unclear hormonal mechanisms. Due to the general under-recognition of SDB, health care providers should not assume sleep complaints are due to vasomotor related insomnia/depression without considering SDB. Fibromyalgia has gender, age and probably hormonal associations. Sleep complaints are almost universal in FM. There are associated polysomnogram (PSG) findings. FM patients have increased central nervous system levels of the nociceptive neuropeptide substance P (SP) and lower serotonin levels resulting in a lower pain threshold to normal stimuli. High SP and low serotonin have significant potential to affect sleep and mood. Treatment of sleep itself seems to improve, if not resolve FM. Menopausal sleep disruption can exacerbate other pre-existing sleep disorders including RLS and circadian disorders.

Keywords: Menopause,sleep, insomnia, depression, sleep disordered breathing, fibromyalgia, poysomnography, estrogen, progesterone, testosterone, melatonin, growth hormone, hot flashes, substance P, sodium oxybate, gamma hydroxybutyrate

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As members of the baby boom generation move into their 50's, an unprecedented number of women are experiencing menopause and its attendant medical concerns. This is a time of increased cardiovascular, cancer and osteoporosis risk. For many it marks a significant onset of new menopause related symptoms that is a challenge for both patients and the physicians caring for them.

Sleep physicians see many patients at menopause time because sleep difficulty is one of the hallmarks of menopause. One fourth to one half of all women will note some sleep complaint during menopause as compared to approximately 15% of the general population.[1,2,3,4] In a British study, menopausal women were 3.4 times more likely to report trouble sleeping than premenopausal women.[1] Insomnia, fibromyalgia and sleep disordered breathing are all more prevalent after menopause and sorting out appropriate treatment often involves sleep assessment and treatment. Additionally mood disorders, particularly depression, are more common in the menopausal age group and have been attributed to the associated hormone changes. The correlation between menopause, insomnia and depression has been debated over the years and is particularly pertinent at this time.

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HORMONE THERAPY RISKS/BENEFITS

Complicating the treatment of menopausal symptoms is the changing understanding of the risks and benefits of menopausal hormone replacement therapy (HRT). The Women's Health Initiative[5,6] and other recent studies such as the Heart and Estrogen/Progestin Replacement Study (HERS)[7] have effectively eliminated what had been perceived to be a major benefit of HRT. Until these studies, HRT had been presumed to have cardiovascular benefit on the basis of both epidemiologic and basic science evidence.[8] The WHI showed no long-term cardiovascular benefit and confirmed prior studies showing increased breast cancer risk. Notably, despite the increased risk of incident cancer, there was not an associated increase in breast cancer mortality. While it showed decreased osteoporotic fractures, the absence of cardiovascular benefit, the increase in thromboembolic phenomena and the increased likelihood of incident cancer clearly change the risk/benefit equation for most women.

The current understanding of the indications for HRT involves informed, individualized treatment of symptoms associated with menopause. The most common symptom is the vasomotor "hot flash" which can be quite disruptive to the quality of life either day or night. Of course nocturnal hot flashes or "night sweats" are associated with sleep disturbances. The only patients showing improved quality of life with HRT in the HERS trial were those patients with vasomotor symptoms. Currently the North American Menopause Society position is to use as low a dose as possible for a short period of time following menopause. Usually 5 years is the "safe" time frame cited.[9] Of course these recommen-

dations continue to shift as new information evolves. Sleep disturbances may be among the main indications for hormone therapy and certainly need to be evaluated for specific treatment in this age group.

Conversely, HRT should not be considered to be the first line of therapy for all or, even most of the sleep disorders that follow menopause. A casual "It's just hormones" should not end the search for causes and treatment of sleep complaints in menopausal women.

MENOPAUSE CHANGES IN SLEEP ARCHITECTURE

Menopause is associated with an increased amount of sleep related complaints but there have been few documented polysomnographic changes associated with menopause, despite widespread symptoms. In the Wisconsin cohort of individuals followed with polysomnograms over time, there were no significant polysomnographic changes associated with transition to menopause but there was documented an increase in obstructive apnea.[10,11] The polysomnograms of young women and men are similar but women tend to maintain delta sleep longer than do men with aging. In spectral analysis of quantitative EEG measures, women have higher power density than men in delta, theta, lower alpha and higher spindle frequency range, however the effect of aging was the same for men and women with attenuation of slower frequencies and increased power in the beta range, implying advancing age has a bigger impact rather than gender on the sleep EEG.[12]

A study of younger ovulatory cycling women vs older women (either cycling or menopausal) showed worsening sleep efficiency with age, but not with estrogen level, implying that loss of sleep efficiency was an age related effect.[13] Hollander, on the other hand, in a study of 436 healthy women reported independent associations between poor sleep and both hot flashes (OR 1.52) and estradiol levels (OR 0.53) in ages 45-49 years.[14]

Vasomotor symptoms have been associated with arousals and disruption of sleep architecture.[15] It may be that the primary menopausal problem is vasomotor instability in a subset of women followed by consequences of disturbed sleep. Not all women experience sleep problems with menopause, nor do all women experience hot flashes. In Hollander's study of healthy women,[14] only 17% reported poor sleep which is similar to a recent national survey.[16] Those with poor sleep, however, were the subset with vasomotor symptoms and low estrogen.[14]

EFFECT OF HORMONAL CHANGES ON SLEEP

Progesterone

While estrogen is a common focus of menopause discussions, progesterone has very profound effects on sleep and is somewhat more straightforward in its effects on sleep than estrogen. Progesterone, when given intravenously, has direct sedative qualities, stimulating benzodiazepine receptors that in turn stimulate the production of the NREM associated gamma-aminobutyric acid (GABA) receptors.[17] As a GABA agonist, progesterone is anxiolytic, although the exact mechanism is unclear, as it as it seems not to be helpful in attempts to taper patients off benzodiazepenes.[18] During a normal menstrual cycle, there is a rapid peak during the mid-luteal phase and a drop off premenstrually, which are associated with sleep difficulties and increased arousals.

A second impact of progesterone is its effect on breathing. Progesterone is a respiratory stimulant and has been used to treat mild obstructive sleep apnea.[19] During pregnancy, there is remarkably little obstructive sleep apnea, given the amount of weight gain that typically occurs, and it is felt that the high progesterone levels characteristic of pregnancy function as a respiratory stimulant. Similarly, prior to menopause, when there are naturally occurring higher progesterone levels, less sleep apnea is seen.

Estrogen

The effect of estrogen on sleep is more complicated than that of progesterone. In animals, estrogen suppresses REM sleep, but in humans it increases REM cycles. Estrogen is involved in norepinephrine (NE), serotonin (5 HT) and acetylcholine metabolism.[20] Estrogen has been shown to decrease sleep latency, decrease the number of awakenings after sleep occurs, increase total sleep time and decrease the number of cyclic spontaneous arousals.[21] During the luteal (low estrogen) phase in premenopausal women, a two-fold increase in the number of arousals occurs, particularly when both estrogen and progesterone levels are low.[17]

Estrogen is also related to temperature regulation in the body. An obvious effect of low estrogen levels is the classic hot flash characterized by increases in both peripheral and central temperature. Hot flashes also are characterized by bursts of catecholamines and surges in luteinizing hormone (LH).[22] A wide range in the severity of vasomotor symptoms is seen clinically at menopause. Obviously, hot flashes can be associated with increased arousals.

Estrogen replacement is associated with increasing the amount of both slow wave sleep and REM.[23,24] These changes would be associated with better quality sleep.

In addition to its obvious prevention of hot flashes, estrogen has a significant effect on core body temperature during sleep. Estrogen in mammals is a thermoregulatory hormone that helps regulate the time of lowest body temperature during the night. Stopping estrogen shifts this time forward and changes the depth of the temperature drop.[22] Both of these changes result in more arousability and lighter sleep. It is hypothesized that one of the reasons for deeper sleep during the follicular phase in premenopause is the temperature regulating effect of high estrogen during this time.

Estrogen may have a direct impact on mood through its central nervous system (CNS) receptors in the modulation of neurotransmitters. It is involved in both 5 HT and NE regulation centrally. Estrogen increases 5 HT postsynaptic responsivity as well as increasing both the number of 5 HT receptors and their uptake. Estrogen tends to be a 5 HT agonist. It also selectively increases NE activity in the brain, due to decreasing monoamine oxidase activity. It has other mixed effects on NE. It may also have dopaminergic effects as well. Finally it is a GABA agonist. All these effects imply that it would have an antidepressant effect centrally.[25]

Cortisol

Estrogen also affects sleep via its effect on cortisol. Menopause is associated with higher levels occurring earlier in the sleep period than the usual morning cortisol spike.[26] Menopausal women are more susceptible to nocturnal rises in cortisol associated with mild stressors.[27] Estrogen helps regulate the normal a.m.cortisol peak and therefore helps stabilize nighttime sleep. The same effect could be postulated to underlie the improvement of depression with estrogen replacement therapy.[28]

Melatonin

Melatonin and estrogen are somewhat inversely related and have a very complicated interaction. Melatonin is a reproductive hormone in animals with seasonal reproductive habits, and it functions to suppress estrus in these animals. In very high pharmacologic doses, melatonin can be used as a birth control pill. In males it can cause regression of testicular tissue. Melatonin is linked to LH production, such that disruption of melatonin will disturb LH surges and therefore cause fertility difficulties. It seems that the predominant direction in which melatonin and estrogen are related is melatonin driving reproductive hormones rather than vice versa. This may be related to mammalian estrus cycles that are less pronounced in humans.[29,30]

Melatonin primarily has a well-known circadian effect at sleep onset and may also be involved in sleep maintenance by blocking arousal mechanisms, thereby tending to keep humans asleep in the dark at night. In general, melatonin levels decrease with the aging process, but paradoxically, decreases in total melatonin levels are not necessarily associated with menopause. Prior to menopause, there is an age related drop in melatonin but immediately afterward melatonin increases for several years.[29] Estrogen deficiency at menopause may stimulate production of melatonin or menopause marks the loss of a pineal and pituitary control of ovarian cyclicity.[31] Post-menopausal women with insomnia generally have been shown to have lower melatonin levels than their cohorts.[29]

Additionally, estrogen may have a reciprocal melatonin-supportive function. Both tamoxifen, an anti-estrogen, and oophorectomy cause decreases in melatonin.[17]

Testosterone

Testosterone has been less well studied than the other sex hormones in relation to sleep. Testosterone tends to decrease REM sleep in animals, and significant gender differences have been seen in REM sleep in animals studies.[17] Testosterone seems to have a minor effect on sleep in humans except testosterone is related to developing or worsening obstructive sleep apnea (OSA). Higher testosterone levels seem to be associated with increased apnea. It has been shown that exogenous testosterone replacement can and does worsen obstructive sleep apnea.[32,33,34] The reason for this is unclear. This has implications regarding testosterone replacement therapy for both men and women and may be one of the reasons for the gender difference in OSA.

INSOMNIA AND DEPRESSION

Mood disorders, specifically depression and anxiety, are associated with menopause.[35,36] The reason for this is unclear and may be multifactorial. Several large longitudinal studies have documented this as recently reviewed by Soares.[37] There is an associated increase in the incidence of insomnia following menopause. Separate, however, from the effect of menopause, there is a "chicken and egg" discussion regarding insomnia and depression in general. In longitudinal studies insomnia appears to precede depression in cyclic mood disorders.[38] Sleep disruption has been associated with depression.[39] Whether simple sleep deprivation can produce depression in susceptible individuals is unclear, but insomnia is closely intertwined with depression.

Presumably multiple arousals permit the development of intrusive anxious thoughts at multiple times during the night. Obviously, pre-existing anxiety or depression will exacerbate these intrusive thoughts that prevent re-initiation of sleep. Insomnia has a performance anxiety quality to it as well. Thus, waking up repeatedly gives the mind the "opportunity" to be anxious during the night. If the anxious thoughts are about the inability to sleep, a self-perpetuating process of insomnia has been created. Increased wake after sleep onset (WASO) is created and sleep efficiency drops.

Thus, the "domino" theory of sleep disruption has long been thought to be at least one explanation for menopausal depression. It proposes that sleep is disturbed by hot flashes or other menopause related reasons. Insomnia follows sleep disruption and depression follows insomnia.[40]

Insomnia has been associated with depression in women with a 4.1 odds ratio.[41] The odds ratio of developing depression in patients with unremitting insomnia for one year was 39.8 in one study vs. an odds ratio of only 1.6 if insomnia resolves.[42] This would imply that treating or preventing insomnia is a major method for preventing the onset of depression. Since depression has multiple well-documented increased health risks associated with it, treatment of insomnia would be expected to have major long-term health benefits.

Soares points out the difficulty in studying menopause related depression.[37] There are problems with the variety of settings in which it has been studied and the lack of consistent definitions of menopause and depression in the various studies. This is pertinent because there have been a wide variety of responses to hormone therapy. If estrogen treats or prevents depression, it becomes an appropriate and perhaps major indication for HRT.

The connection between menopause and depression may be mediated through vasomotor changes. In one study of 476 women, the perimenopausal women with vasomotor symptoms were 4.39 times more likely to have depression. This did not change with adjustment for prior depression history.[43] A longitudinal study of mood and menopause has also recently reported the same association.[35]

Another study of 309 women, using a standard depression scale and estradiol levels, reported hot flashes with disturbed sleep. There was no direct correlation between estrogen levels and depression, but there was between hot flashes and disturbed sleep, and depression. This data supports the "domino" theory of disturbed sleep in menopause which proposes that vasomotor symptoms caused by fluctuations in estrogen levels results in depression rather than low estrogen levels directly leading to depression.[44]

Sleep disruption may be related to estrogen deficiency in ways other than simple hot flashes. Moe performed a stress challenge study in which estrogen replacement (ERT) and non ERT patients were stressed by having blood drawn during the night.[27] Although there was no difference at baseline between the 2 groups in polysomnography (PSG) parameters, following a stress challenge, the non ERT patients had more total wake time, less slow wave sleep and less REM than the ERT group. This might imply a direct estrogen effect on sleep quality and maintenance. Thus other disturbances such as personal stress factors or adverse environment would have less of a negative impact on the sleep of ERT patients. This perhaps expands the group of patients at-risk for depression from those with only hot flashes to those with other factors that could cause sleep disruptions.

Sleep disturbances have been correlated with nocturnal vasomotor symptoms.[3] Treatment with estrogen generally has been shown to improve sleep continuity.[45-48] Treatment has been shown to decrease both PSG arousals associated with hot flashes but also reduce Cyclic Alternating Pattern (CAP) of arousals in treated patients.[49]

Freedman, a major contributor to our understanding of thermoregulation and hot flashes, disputes the concept that hot flashes alone cause disturbed sleep.[50] He measured for the presence of hot flashes while monitoring patients with a polysomnogram. He studied symptomatic and asymptomatic subjects and found no significant differences in overall arousals between the groups. The symptomatic group only averaged 5 hot flashes in the night while experiencing 111 total arousals. It may be that estrogen deficiency, as proposed in Moe's stress challenge study, makes individuals more susceptible to arousals. These same patients are likely to be more sensitive to thermal changes as well.

Shaver reported that the majority of midlife female insomnia patients they studied had normal PSG patterns.[51] The insomnia subset that had abnormal PSGs showed hot flash related arousals. They noted that the hot flash group had fewer psychological stressors than the other insomnia patients. This implies a more physiologic cause of insomnia in this group. Sleep disruption has been associated with mood changes.[39] Thus, sleep disruption from either psychological or physiologic stressors has the potential to produce depression.

In summary, sleep disruption could be a result of hot flashes themselves, an increased sensitivity to disrupting events or a loss of some other sleep maintaining quality of estrogen. The disruptions then can create insomnia.

Treatment with estrogen for depression has had mixed clinical results. As reviewed by Soares, several studies have shown the effectiveness of ERT in reducing depression while others have not.[37,40,54-56] The negative studies have used conjugated estrogen and both peri- and post-menopausal women. Estrogen has been shown to help sub populations of women with depression. It has been generally more effective in the perimenopausal patients than postmenopausal. Soares speculates that hormonal fluctuation is more important in the development of hormone related depression than the absolute levels of hormones themselves. Thus HRT would be more likely to help the fluctuating hormones of perimenopause. This would also fit with the current model of using HRT transitionally for the first few menopausal years.

As mentioned above, estrogen may have a direct effect on central neurotransmitter mechanisms involved in the development of depression. It should not be assumed that the only mechanism is the "domino theory".

The above data point to an individualized approach to selection of patients that might respond favorably to HRT. This would include patients with hot flashes, perimenopausal patients and patients who have stressors that might affect sleep continuity.

TREATMENT OF MENOPAUSAL SYMPTOMS

Estrogen/Progesterone

Following the WHI and HERS studies there has been a major reduction in the use of HRT. Many patients are seeking out other alternative therapies or seeking advice on safe use of hormones to alleviate symptoms. The current recommendations are to use low doses and to use for not much longer than the first 5 years following menopause.[5] Low dose protocols have been effective in reducing vasomotor symptoms.[57]

It is possible that the lack of cardiac benefit and the increased incidence of breast cancer are related to the type of HRT used in these studies. Some would argue that conjugated estrogen and medroxyprogesterone (MPA) are not the optimal HRT regimen. There is no direct clinical evidence that this is the case and it is not likely that additional data will be available in the near future given the cost and scope of these studies. If electing to use HRT, it might be reasonable to use low dose estradiol rather than conjugated estrogen. There is also a suggestion that the transdermal route might be better for treatment of depression because of the lack of fluctuation in hormone levels.[52]

There has been a reported difference in the effect of different progesterone preparations. MPA is the most commonly used preparation but micronized progesterone has also been studied in the Post Menopausal Estrogen Progestin Intervention (PEPI) trial with the same protective effect on the endometrium.[58] Micronized progesterone is closer to human progesterone and may have fewer negative vascular effects. In a study of 21 women, the micronized preparation showed improved sleep efficiency of 8% with improvement in WASO vs. MPA.[59] The micronized progesterone preparation therefore may be a reasonable alternative to MPA. It might be an option alone without the estrogen. In the past, progesterone alone (megestrol) has been used successfully in treatment of hot flashes.[60]

OTHER THERAPIES

Herbals

The herbal therapy that has had the best data behind it is black cohosh. It has been shown to have a moderate effect on hot flashes in several European and US trials.[61] Soy isoflavones have had mixed studies with mild improvement. These have phytoestrogens and might be expected to have an effect on selected individuals. Other herbals have not been shown to be effective. These include: red clover, dong quai and vitamin E.[62,63,64]

Clonidine

This has been used for a number of years and is limited by its toxicity of dry mouth, fatigue and hypotensive effect. It had 34% and 44% reductions in symptoms.[65,66]

Gabapentin

In doses of 300 -900 mg which are relatively large and likely to be sedating, gabapentin has been shown to reduce symptoms by 66%.[67]

SSRIs and Other Antidepressants

The most popular prescriptive treatments for hot flashes other than HRT have been the antidepressants. Fluoxetine had a 50% reduction in symptoms.[68] Venlafaxine in higher doses (75 and 115mg) had 60% reduction in symptoms.[69] Others may be effective but haven't been studied. These obviously may be appropriate for patients with vasomotor symptoms who are already depressed. The side effect/benefit discussion might be different if only treating hot flashes however. Since fluoxetine is also alerting in general, it may improve depression and hot flashes but may

not improve sleep quality. Other antidepressants that are being studied would have the same pro and con discussion.

Behavioral and medical treatments are both indicated to address insomnia, being the substance of much of the practice of sleep medicine, but are beyond the scope of this review.

SLEEP DISORDERED BREATHING AND MENOPAUSE

Prior to menopause, women have approximately 1/3 the frequency of sleep disordered breathing than men. Shortly after menopause this disparity drops for unclear reasons.[70-74] In the Wisconsin Cohort, the odds ratios compared to premenopause for >15 apnea hypopnea index (AHI) goes from 1.1 at perimenopause to 3.5 postmenopause.[11] In a Canadian study the prevalence of apnea in a relatively heavy (BMI=30) population of 1315 women went from 21% to 47% after menopause. Differences persisted despite adjustments for body mass index.[73]

Weight gain associated with menopause with concomitant increase in neck circumference potentially adds to the total development of postmenopausal OSA. Weight gain is common during menopause. There have been recent studies emphasizing the interaction between sleep duration and weight gain.[75,76] Sleep deprivation due to decreasing sleep efficiency might be expected to create more hunger, causing more weight gain and SDB. Thus a cycle of hunger, gain and worsening SDB could be postulated.

The gender difference does not seem to be biased by the fact that men may be more likely to come to a sleep clinic, but rather a true reflection of a biologic change. The reasons are unclear and may have to do with gender differences in upper airway anatomy, distribution of fat tissue, sex hormone effects and gender differences in leptin. Leptin, a hunger suppressing adipokine stimulates breathing. Women with higher leptin levels are more resistant to airway collapse.[32] Loss of leptin with development of abdominal obesity, insulin resistance and leptin resistance may partially explain the association between diabetes and disordered breathing.

Men have higher testosterone levels than women and testosterone increases disordered breathing. Presumably, this is due to its effect on oropharyngeal muscle mass. Exogenous testosterone has been shown to increase sleep disordered breathing.[31,32] This might explain the gender difference, but does not completely explain why women develop more disordered breathing after menopause. However, loss of progesterone and a change in hypercapneic drive may also explain some of the change.[34]

Estrogen, testosterone and progesterone all have been reported to affect sleep disordered breathing. Some small studies have been reported in which ERT has improved sleep disordered breathing. In one study of 5 patients the AHI was reduced from 30 to 25 1 month after initiating estrogen and to 17 after 10 days of estrogen/progesterone.[77] In another study of 4 patients the AHI was reduced by 75%.[78] A third study of 6 patients showed a reduction of AHI from 22 to 12 with estrogen alone.[79] A larger crossover study of 62 healthy patients showed a reduction in AHI but not in upper airway partial obstruction.[80] In another treatment group of 51 insomnia patients treated with estrogen, the AHIs decreased with treatment with corresponding cognitive and subjective improvements.[81] Finally, women with sleep apnea have had lower measured estrogen levels. In this study of 53 consecutive women of all ages, there was a significant correlation between low estrogen and progesterone levels and OSA (AHI>10).[82]

The significance of these observations relates to the consistent under-assessment of sleep apnea in the general population. In the Wisconsin prevalence study 93% of women and 92% of men with moderate to severe sleep apnea were not clinically diagnosed.[70] It is a challenge to the sleep medicine community to alert the primary providers of post menopausal patients to the possibility of disordered breathing. A primary physician may note a change in sleep complaints and attribute it to menopausal insomnia. Given that OSA can develop during menopause without any significant change in the BMI, it would be easy to not think of disordered breathing.

It is also significant since menopause marks a change in cardiovascular risk in general. Thus, OSA is another cardiac risk to add to the lipid, blood pressure and other risk factors occurring at that same time.[83,84]

FIBROMYALGIA, PAIN DISORDERS AND MENOPAUSE

Fibromyalgia (FM) is a musculoskeletal pain disorder with widespread pain and hypersensitivity to normal painful stimuli, characterized by typical trigger point pain locations.[85,86] It is likely due to increased central pain sensitivity mechanisms that are beyond the scope of this discussion. However, it also is characterized by poor quality sleep, and has a typical onset at menopause with a female:male predominance of approximately 7:1.[87] Sleep disruption is so pervasive with this disorder that it is commonly thought that treatment of the sleep disorder corrects or improves the FM.

The majority of pain patients report poor sleep.[87] Indeed, sleep deprivation in general makes pain syndromes worse, presumably through the same mechanisms as FM.[88] Simple sleep deprivation will create a transient FM like increase in trigger point pain in a large proportion of normal individuals. This is thought to be modulated by a reduction in Substance P centrally, which in turn makes FM patients hyperaesthetic to normal stimuli.[89] The majority of arthritis patients presenting in a rheumatology practice have sleep complaints.[90] Whether this is due to pain causing sleep disturbances or a more central mechanism such as FM is unclear. Sleep disorders are also common in collagen/inflammatory disorders such as Sjogren,s syndrome and Lupus.[91]

POLYSOMNOGRAMS IN FM

The characteristic PSG finding in FM patients is the presence of alpha activity throughout NREM. Most common is the so-called "alpha delta" phenomenon first described by Moldofsky.[92] This is characterized by persistence of alpha activity throughout the delta rhythm, with alpha waves riding on top of the delta waves.

Moldofsky has described 3 distinct patterns of alpha intrusions in FM patients, phasic (simultaneous with delta) in 50%, tonic (present throughout NREM) in 20% and low alpha in the remaining 30%. He reports that the phasic pattern is most closely associated with long duration of pain and the worst self-rated sleep. It has been assumed that alpha intrusion is a marker for poor quality sleep.[93]

Fibromyalgia patients have other PSG abnormalities. Decreased spindle activity was noted in one study.[94] Other studies have noted an increase in the cyclic alternating pattern of arousals characterizing FM patients.[95] Both of these findings likely point to more arousability in FM patients.

SUBSTANCE P AND FM

Substance P (SP) is a central nociceptive neuropeptide related to pain control that is co-localized with 5 HT and dopamine. SP is involved in afferent pain reception (nociception). It is a proposed central mediator, along with reduced 5 HT, of pain in FM and other disorders.[96]

FM patients have increased levels of SP centrally.[96] SP mediates pain reception from the periphery into the CNS and works by modulating opioid and possibly NMDA receptors. Thus an increase in SP would imply hyperalgesia, or increased pain perception from normal stimuli.[97] It is regulated by both 5HT and dopamine (DA). FM patients have downregulated 5HT and DA along with high SP.[98] SP thus has a potential depression promoting effect. It could be a biochemical link between depression and FM. In fact, SP antagonists are being studied for antidepressant qualities.[99]

The relationship of SP and sleep is somewhat confusing at this time since it has a sleep promoting effect on the ventrolateral preoptic area that is the primary GABAergic area for sleep promotion.[100] It also stimulates cholinergic receptors and therefore should increase REM and delta sleep. However, direct infusion peripherally of SP to male subjects caused reduction in total sleep and delta sleep, and increased REM latency.[97]

Some of these observations are counterintuitive to findings in FM patients who have disturbed delta sleep. It may well be that increased SP and decreased 5HT are a regulatory response to interrupted sleep and stress in general. Thus, disturbed sleep causes the increased tonic pain perception of FM.[98]

A gender difference in central SP quantity or receptor status may help explain the gender difference in FM. While there are no direct studies of SP gender differences and FM, gender differences in SP occur in other settings. There is a gender based genetic variability in angiotensin response which controls SP degradation.[101] There also is an estrogen effect on the SP receptors in the gut.[102] In a study of vasodilation in response to beta NE agonists, there was a significant gender difference in sensitivity to SP.[103] Thus variability in SP response could be an explanation for why women develop FM more often than men, as well as a mechanism for inter-individual variation. Finally, progesterone has been shown to reduce SP and improve sleep.[104] The significance of this is unclear, but may point to gender specific relationships with SP and FM.

ESTROGEN AND FM

Why menopause seems to induce fibromyalgia or why there is a gender difference is unclear. It is possible that, since menopause is associated with worsening of sleep, and a reduction of sleep efficiency, FM develops by the same mechanisms as simple sleep deprivation. Gender differences thus may be explained by the increased sleep instability post-menopause. There also may be gender differences in pain perception that are related to changes in estrogen. Luteal phase pre-menopause and post menopause women both have lower pain thresholds that have been reported to be estrogen dependent.[105,106]

Depression also is very common in FM (80% or more) and, as discussed above, depression is common in menopause, presumably for mixed reasons. Estrogen is a mediator of the metabolism of the serotonin (5HT) precursor tryptophan. There is reduced 5 HT transcription activity in FM patients. Decreased estrogen levels thus result in reduced 5 HT (serotonin), which may contribute to the etiology of both depression and fibromyalgia.[107,108] Antidepressants have classically been used to treat FM. Estrogen in combination with antidepressants may therefore be synergistic.

TREATMENT OF FM BY SLEEP PHYSICIANS

Sleep physicians commonly see FM patients as part of a treatment program for FM. It has been assumed that treating sleep will improve FM. Treating other sleep disorders such as sleep disordered breathing and restless legs may be a necessary precursor to being able to adequately treat FM. The three most predictably effective treatments for FM are antidepressants, aerobic exercise and improved sleep. There have been multiple other proposed treatments, including complementary and behavioral therapies but the scope of these is beyond this review.

In support of the sleep connection to improvement in FM is the report by Scharf of treatment with sodium oxybate.[109] Sodium oxybate is a GABA agonist that quite effectively induces slow wave sleep. It recently has been introduced as a drug to consolidate sleep in narcoleptics, thereby producing a reduction in both cataplexy and daytime hypersomnolence. Scharf used it to treat a group of fibromyalgia patients and noted marked improvements in the clinical symptoms with reduction in tender points and in 6 of 7 pain fatigue scores. The reduction of alpha intrusions was notable with this treatment.

Delta sleep is characterized by production of growth hormone (GH). Sodium oxybate produces a large surge in GH in treated patients. It is possible this mediates some of its beneficial effects. The FM literature has reported both low and high GH in FM patients. Thus GH is likely involved but it is unclear in what way.[110,111,112]

Other treatments that may increase total sleep time, specifically benzodiazepines, do not show similar improvements in alpha delta activity. This could correlate with the general lack of improvement with benzodiazepines in fibromyalgia as compared to these reported for sodium oxybate. A larger study of fibromyalgia and sodium oxybate is currently in progress.

Fibromyalgia, like menopause, is a condition that crosses several medical disciplines. The sleep physician's role in treatment of FM is to support adequate sleep as an essential part of the treatment program. This involves treating all sleep disorders that may coexist such as restless legs, circadian disorders and disordered breathing. It also involves indirect support of sleep by treatment of menopause and associated insomnia and depression. Depression and insomnia need close interdisciplinary coordination among the sleep physician, the psychiatrist and the sleep behavioral therapist.

Pain management in these patients is commonly coordinated by the rheumatologist or a pain specialist and, of course, has significant impact on sleep. Narcotic medications may induce or exacerbate sleep disordered breathing. Some antidepressants have sleep effects and may exacerbate restless legs symptoms. If sodium oxybate were to be used, it would make a significant change in the mix of pain medications as well. It is likely that the sleep physician will be prescribing it rather than the rheumatologist.

OTHER SLEEP DISORDERS AND MENOPAUSE

Insomnia, depression, sleep disordered breathing and fibromyalgia are the most significant sleep related disorders that are di-

rectly associated with menopause. There are, however, other sleep disorders that may be affected secondarily.

Restless legs syndrome (RLS) is not directly correlated with menopause, although the frequency of this disorder increases with age.[113] It is very common and often is under-recognized by the patient and physician for many years. With the onset of menopause associated sleep disruption, a preexisting disorder may become more evident. Thus, the patient comes to a sleep physician to address menopausal onset sleep problems but relates long-term RLS symptoms. Prior to having hot flashes, the RLS may not have been severe enough to cause significant sleep disruption, but it now complicates the treatment of a menopause related sleep disorder. RLS may need to be treated first before one can expect adequate response to other sleep interventions. RLS and periodic leg movements (PLMs) do not respond to estrogen therapy.[114] Theoretically, menopause should improve RLS since iron deficiency becomes less likely. On the other hand, initiating a cyclic HRT program could induce worsening of RLS.

Similarly, circadian rhythm disorders are not particularly related to menopause. There is an age related phase advance that has been well documented, but this is not affected by transition into menopause.[115] Menopause also is not associated with circadian temperature shifts, despite the disruption in thermoregulation that is associated with estrogen deficiency.[116, 117]

Phase delay may in general be associated with inadequate sleep, due to social or work requirements. The onset of menopause related insomnia and loss of sleep efficiency would likely exacerbate any preexisting sleep inadequacies. Thus, patients suddenly need more time in bed to attain restorative sleep. Phase delay or inadequate sleep syndrome patients may therefore suddenly seek out treatment or evaluation as part of the menopause transition. When taking a sleep history, a common question is "Why do you seek help now, if you have had these sleep problems for years?" Menopause may be one answer to this question.

SUMMARY

Sleep physicians are routinely assessing sleep disorders in perimenopausal and menopausal patients. There is a tendency on the part of both patients and their physicians to attribute sleep concerns to hormonal changes and to subsequently normalize them. It is the responsibility of the sleep physician to sort out the benign from the not so benign aspects of sleep changes in this population. In the post Women's Health Initiative era, there is less of a tendency to prescribe HRT and to do so one needs a clear understanding of the risk/benefit ratios for the individual patient.

There are three major ways in which menopause affects sleep. All can be ameliorated or at least identified to give the most specific and effective therapy.

The first, and clearly most complicated and contended, is the concept of a menopausal mood disorder and the development of menopause related insomnia. Sleep efficiency drops with both aging and menopause. Presumably, the menopausal change in sleep efficiency is primarily due to vasomotor symptoms but may also result from a more complicated effect of estrogen on sleep maintenance. Sleep deprivation and multiple arousals provide a setting in which insomnia is likely to develop. Insomnia is closely linked, probably etiologically, to depression. Thus the "domino theory" of arousals causing insomnia that cause depression is a plausible explanation for the development of menopausal mood changes. There are likely other reasons for estrogen deficiency to cause sleep and mood instability given the ubiquitous nature of estrogen receptors in the brain. Clearly there is great individual variation in the response to estrogen loss. HRT has a variable track record in correcting menopausal depression, but insomnia may be one of the remaining appropriate indications for its use.

The second very common result of menopause is an increase in the prevalence of sleep-disordered breathing. Estrogen seems to have a protective effect in this regard. Why this is the case is not clear, but all evidence shows this to be the case. It is not just due to a menopause related weight gain. The significance of this is the necessity for all physicians, but especially sleep physicians, to be aware that, even without weight change, benign snoring can become disordered breathing over a fairly short period of time. Given the cardiovascular significance of SDB, assessment and treatment are an important part of menopausal evaluation. Even in the presence of insomnia, WASO may be increased because of SDB. There is a tendency to compartmentalize insomnia and SDB in the practice of sleep medicine. This is important because we tend not to do sleep studies on insomnia patients. We may need to maintain a lower threshold for polysomnographic evaluation in this population that is prone towards both entities.

The third result of menopause is an increase in the development of fibromyalgia. FM is a very disabling condition in many people and if there is a way to either avert or better treat it we need to do so. There is clearly a large sleep component to FM so the sleep physician is an integral part of the FM interdisciplinary treatment group that includes rheumatologists, pain specialists, psychiatrists, behavioral sleep practitioners and primary physicians. The initial response to sodium oxybate treatment implies that if sleep is normalized, FM is improved. This puts the sleep physician in the center of the treatment team for this entity.

Finally, sleep disorders often are multiple. The same patient could have had RLS and phase disordered sleep problems that previously had been managed well but menopause tipped the scales making these other disorders less bearable. The sleep physician is in a position to identify and treat a new array of problems that present with the onset of menopause.

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