Effects of melatonin and estradiol on chronic pain during postmenopause

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ABSTRACT

Chronic pain is a major public health problem that affects approximately 40% of the adult population worldwide. Several epidemiological studies have shown a higher prevalence of chronic pain in women, with variations within the menstrual cycle and an increase in pain after menopause. Clinical and experimental studies have shown differences in pain perception between genders, but the underlying mechanisms of this inequality are complex and far from being understood. Estrogens play an important role in pain modulation and seem to account at least partially for these differences. Melatonin is a neurohormone synthesized mainly by the pineal gland that regulates circadian rhythms and has anti-inflammatory, antioxidant, sedative, antidepressant, anxiolytic, and analgesic effects. After menopause, melatonin levels decrease, which may be the cause of the sleep disorders that usually affect women during this period of life. Some studies have demonstrated an interaction between melatonin and estrogens in terms of antioxidant effects. The present study seeks to provide a review on melatonin, estradiol, and chronic pain in women.

Keywords: *Chronic pain; melatonin; menopause; estradiol*

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Chronic pain constitutes a major challenge in the healthcare field due to the difficulties and limitations of current treatments, and is considered a disease entity in its own right. In 2010, the American Society of Anesthesiologists defined chronic pain as "pain of any etiology not directly related to neoplastic involvement, associated with a chronic medical condition or extending in duration beyond the expected temporal boundary of tissue injury and normal healing, and adversely affecting the function or well-being of the individual"[1]. Global statistics show that 75–80% of people seek medical attention for pain and that 40% of adults suffer with some form of chronic pain[2–5]. Several studies have demonstrated an increased prevalence of chronic pain in women[3–9]. Pain perception also seems to differ between males and females, and in female mice, appears to vary during the estrous cycle[10].

Regarding treatment, chronic pain is difficult to manage, as it responds poorly to the conventional pharmacological armamentarium (NSAIDs and opioids) and thus requires a variety of alternative therapy strategies. This has led to countless investigations into nonpharmacological therapies and novel substances that can address this challenge. Among the substances researched for this purpose, melatonin has emerged as an interesting option for conditions that include disruption of the endogenous clock system associated with pain, inflammation, and changes in the sleep-wake cycle[11].

Gender differences in a variety of pain-related aspects have been an object of substantial research, both in humans[12–14] and in animals[15,16].

Epidemiological studies have shown that women have a greater prevalence of disorders with a chronic pain component, such as migraine, temporomandibular joint dysfunction, arthritis, fibromyalgia, and interstitial cystitis; increased susceptibility to nociceptive stimuli; and more frequent analgesic use[2–9,17]. Clinical studies have shown an increased prevalence of pain disorders in women than in men, and experimental research has demonstrated gender differences in the functional and structural characteristics of pain pathways[18]. For instance, female rats are more susceptible to inflammatory pain and to development of neuropathic pain than males[19–22].

However, the effects of gender on pain processing and response and the mechanisms underlying these differences are complex and far from being understood[23]. Although genetic, environmental, social, and cultural factors must be taken into account, sex hormones unquestionably play a major role. Among them, estrogens, as the main female hormones, have received the most research attention[15,24,25], but with contradictory results; some studies have reported pronociceptive action, while others found antinociceptive effects[16,18,23,26,27].

Menopause is known to affect pain, depending on its type and characteristics[28]. Estradiol has been shown to alter the pain system at various levels, such as inflammatory response, dorsal root ganglia, opioidergic and serotonergic systems, limbic circuits and stress responses[14]. Studies have demonstrated low melatonin levels in many diseases associated with chronic pain[29,30]. Furthermore, melatonin administration has been shown to improve chronic pain conditions in humans[31–33]. As chronic pain syndromes are known to change after menopause[28] and both melatonin and estradiol levels decrease in postmenopausal years, it is important to study how these hormones can affect pain, although many others substances may be involved too[34,35]. Within this context, this review article seeks to address the effects of estradiol and melatonin on chronic pain during the postmenopausal period.

LITERATURE REVIEW

This review seeks to address the main aspects of postmenopausal chronic pain and elucidate its pathogenesis and the role of estradiol and melatonin. The MEDLINE (PubMed), LILACS, and SciELO databases were searched. Combining the search term “chronic pain” with “menopause”, “melatonin”, and “estradiol” yielded 58, 155, and 108 articles, respectively. The search string “chronic pain” and “menopause” plus “melatonin” yielded only three articles, whereas a combination of all four search terms yielded none. Of the 421 articles identified in our initial search, 28 were duplicates. Of the 393 remaining articles, 68 were selected and included after a review of abstracts, and their references were hand-searched in an attempt to locate additional relevant studies not identified by our original search strategy.

CHRONIC PAIN

The International Association for the Study of Pain (IASP) defines pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage”[36]. From a temporal perspective, there are two types of pain: acute and chronic. Acute pain lasts seconds, days or weeks and usually occurs as a signal of tissue damage, while chronic pain can last for months or years and not be associated with concomitant injury[37]. Chronic pain may be due to disorders of the systems responsible for both pain perception and pain inhibition. Basically, chronic pain is the result of long-lasting nociceptive stimuli or changes in the peripheral or central nervous system[36].

Depending on its pathogenesis, chronic pain may be classified as nociceptive or neuropathic. Nociceptive pain is the result of direct activation of nociceptors in response to tissue injury with concomitant inflammation, whereas neuropathic or neurogenic pain is the result of peripheral or central nerve injury[37–39]. Namely, chronic nociceptive pain occurs for long-lasting activation of nociceptors, as in chronic inflammatory diseases; while chronic neuropathic pain is characterized by spontaneous pain without any apparent stimulus[38].

In addition to neurophysiological phenomena, psychological, cognitive, behavioral, social, and cultural aspects modulate the experience of pain[37,39]. Several predisposing factors for chronic pain are known, including gender, age, psychosocial issues, underlying disease, type of nerve injury, and severity of inflammatory response. Factors specific to surgical cases include the use and type of preoperative analgesia, type and duration of surgery, and the intensity of acute postoperative pain[40,41].

Pain perception depends on specialized receptors (nociceptors) that are activated only when a stimulus reaches a noxious threshold and

that respond progressively in accordance with the intensity of the stimulus[38]. Continued stimulation may decrease the response threshold of nociceptors, in a process known as sensitization[42–44].

Myelinated A delta (Aδ) fibers respond to intense mechanical and thermal stimuli and are responsible for sharp, highly localized "first pain", whereas unmyelinated C fibers respond to mechanical, thermal, and chemical stimuli and mediate the so-called "second pain", which is poorly localized and diffuse. These fibers are axons of primary afferent neurons known as first-order neurons[42–44].

When a nociceptor is activated, the neurotransmitters glutamate, substance P, and calcitonin gene-related peptide (CGRP) are released at the synapse with the second-order neuron, in the spinal cord, and peripherally at the site of injury. Peripherally, neurotransmitters stimulate nociceptors to induce peripheral sensitization and produce the cardinal signs of inflammation: erythema, edema, pain, and loss of function[38,43].

Substance P and CGRP stimulate histamine and bradykinin release by mast cells at the site of injury. CGRP also induces vasodilation, which increases the release of inflammatory molecules such as prostaglandins. These processes reduce the nociceptor activation threshold, producing hyperalgesia (an augmented response to a painful stimulus) and allodynia (perception of a non-noxious stimulus as painful)[38,42,44] (figure 1).

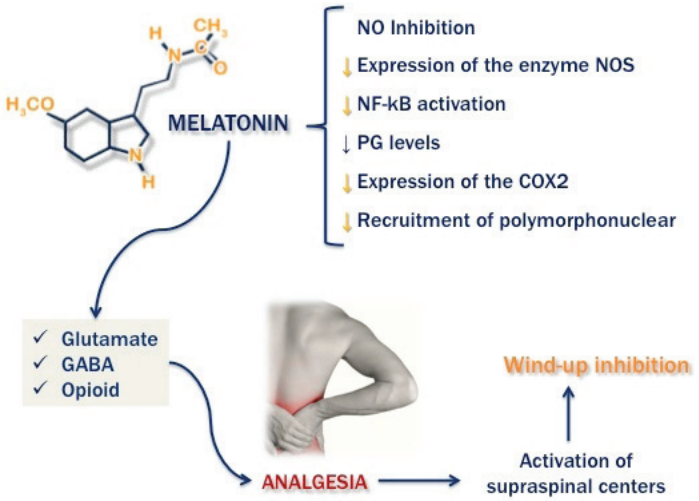

Figure 1: Neurophysiological mechanisms of chronic pain: central sensitization, peripheral responses, hyperalgesia, and allodynia. CGPR: calcitonin gene-related peptide.

A delta and C fibers synapse at the posterior horn of the spinal cord, thus initiating the pain modulation process through descending pathways. The second-order neurons may be nociceptive-specific (NS) neurons, which only synapse with A delta and C fibers, or wide dynamic range (WDR) neurons, which receive data from all sensory fiber types[37,38].

After its integration at the spinal cord, nociceptive information is conveyed to the thalamus and thence to the somatosensory cortex. Each level of the central nervous system (CNS) contains pain-modulating mechanisms. N-methyl-D-aspartate (NMDA) and opioid receptors, which are the two most important systems for modulation of nociception and antinociception respectively, are distributed across nearly all regions of the CNS[37,38].

Modulatory mechanisms sensitize or suppress nociception at each of the "way stations" where it is processed. At the various stages of each pain pathway, different control systems constantly modulate both ascending and descending transmission of nociceptive information[37–39].

In the setting of severe or persistent injury, C fibers fire repeatedly, and the response of dorsal horn neurons increases gradually, leading to central sensitization by the so-called "wind-up" phenomenon, which results from repetitive

excitatory stimulation of WDR neurons by glutamate[37,38,42].

Peripheral and central sensitizations are mechanisms that amplify the noxious stimulus so as to evoke a protective behavioral response. However, when these mechanisms become maladjusted, they may induce permanent changes in the communication of pain pathways and, consequently, to the development of chronic pain[38,44,45].

In addition to maladaptive peripheral and central sensitization, the loss of descending inhibition from the brainstem centers and periaqueductal gray (PAG), astrocyte and microglial activation, and direct signaling from neurons to glial cells may be responsible for the persistence of pain[44,45].

MELATONIN

Melatonin is a neurohormone synthesized and released by the pineal gland that plays an important role in the regulation of circadian rhythms [46,47]. This hormone is derived from L-tryptophan and, in addition to a major chronobiological role in the regulation of neuroendocrine and physiologic functions, has several pharmacologic properties, including sedative, anxiolytic, antidepressant, antioxidant, anti-inflammatory, and analgesic actions[48–54].

Melatonin is released during the dark period, and signals the start and end of this period. Therefore, it signals the alternating light-dark cycle and seasons of the year. The melatonin release profile provides a good measure of circadian phase. Its production begins to increase in the evening, peaks at 60–100 times its baseline level in the early morning hours, and decreases gradually thereafter; this cycle is considered the hormonal expression of the biological clock[55,56].

The mechanisms of action of melatonin involve two transmembrane receptors (MT1 and MT2). A third cytosolic binding site (MT3) has been purified and characterized as the enzyme quinone reductase 2 (QR2)[57]. Inhibition of QR2 by melatonin may explain a protective effect which has been reported in several animal models and is associated with its antioxidant properties[57].

MELATONIN AND ANTINOCICEPTION

The antinociceptive effect of melatonin is uniquely important. Several possible mechanisms have been proposed for the actions of melatonin on inflammatory and algogenic processes, including inhibition of nitric oxide production and reduced expression of the enzyme nitric oxide synthase, activation of the transcription factor NF-κB (nuclear factor kappa B), a reduction in prostaglandin levels and cyclooxygenase-2 expression, and decreased recruitment of polymorphonuclear leukocytes to the site of inflammation[50] (figure 2).

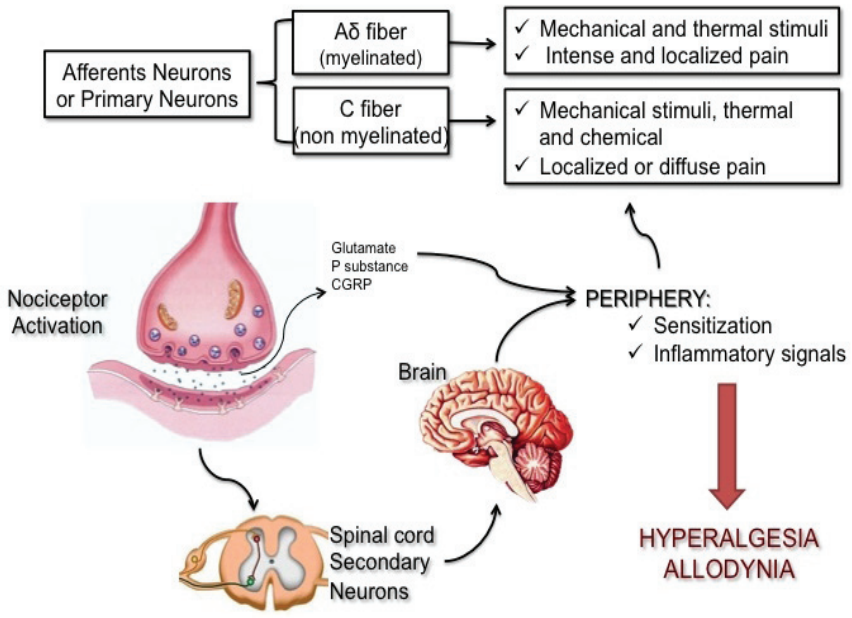

Figure 2: Melatonin and antinociception: mechanisms involved. NO: nitric oxide. NOS: nitric oxide synthase. NF-kB: nuclear factor kappa B. PG: prostaglandin. COX2: cyclooxygenase-2.

Glutamate, gamma-amino butyric acid (GABA), and, particularly, opioid neurotransmission appear to play a role in the analgesic effect of melatonin[58]. Studies using melatonin receptor antagonist support a role for its receptors in analgesia[58,59]. Investigators suggested that the antinociceptive effect of melatonin may involve activation of supraspinal centers and inhibition of the wind-up phenomenon[60,61]. This hypothesis is corroborated by data from experimental studies of acute and chronic pain, including inflammatory acute pain, in which melatonin was administered orally and intrathecally to rodents, and a dose-dependent antinociceptive effect was observed[50,61,62].

In addition to its analgesic effect, melatonin has effects on mood modulation and on the sleep-wake cycle[63]. These multifaceted effects make melatonin an appealing therapy for conditions that involve disruption of the endogenous clock system and pain, inflammation, or changes in sleep-wake rhythms[31]. These effects were first observed in acute pain in humans[54] and in experimental models of pain[53].

1. Experimental works on melatonin's antinociceptive effect

Several researchers have demonstrated the antinociceptive effect of melatonin. The most frequently used animals for these studies are rats and mice.

Yu et al. (2000) evaluated the analgesic effects of intraperitoneal (i.p.) and intracerebroventricular (i.c.v.) administration of melatonin and found that on i.p. administration, melatonin (30, 60 and 120 mg/kg) produced the antinociceptive effect in a dose-dependent manner, and when administered i.c.v., melatonin (0.25, 0.5 and 1 mg/kg) also resulted in dose-dependent antinociception. Moreover, 10 µg of naloxone injected i.c.v. to rats antagonized significantly the antinociceptive effect induced by i.p. melatonin. These authors concluded that melatonin has an analgesic effect in rats and the central nervous system (CNS) may be the primary site for melatonin to elicit the response, and the effect of melatonin is related to the central opioid system[61].

Models of chronic inflammatory pain induced by carrageen, latex or complete Freund's adjuvant (CFA) injection have been used to test melatonin's effect. Laste et al. (2012) assessed the effect of exogenous melatonin in a model of chronic inflammation induced by CFA in rats and found that melatonin had strong chronobiotic and antinociceptive effects[11]. In a model of chronic neuropathic pain, melatonin produced a blockade of thermal hyperalgesia, but not mechanical allodynia in mice[64].

2. Clinical studies on melatonin's analgesic effect

Korszun et al. (1999), in a case-control study, found significantly increased plasma melatonin levels in patients with fibromyalgia[65]. Their findings contradicted those of Wikner et al. (1998), who found that fibromyalgic patients had a melatonin secretion 31% lower than that of healthy subjects during the hours of darkness[29]. Corroborating the hypothesis of melatonin involvement on fibromyalgia, Citera et al. (2010) reported improvements in pain, fatigue, and sleep quality in patients with fibromyalgia when a dose of 3 mg/day of melatonin was administered[66].

Recently, Zanette et al. performed a phase II, randomized, double-dummy, controlled trial to evaluate melatonin alone or in combination with amitriptyline for the management of fibromyalgia. Sixty-three female patients were randomized to receive only amitriptyline (25 mg), only melatonin (10 mg) or amitriptyline (25 mg) + melatonin (10 mg) for a period of six weeks. Treatment with melatonin alone or in combination with amitriptyline significantly reduced pain on the Visual Analogue Scale when compared with amitriptyline alone. Moreover, melatonin's ability to improve the function of the inhibitory endogenous pain-modulating system was demonstrated[33].

Two clinical trials also demonstrated the analgesic effect of melatonin on other chronic pain conditions such as temporomandibular disorders[31] and endometriosis[32].

These findings raise the possibility that melatonin be used as an adjuvant in the treatment of pain.

MELATONIN IN POSTMENOPAUSAL WOMEN

There is ample evidence of the interaction of melatonin with other hormones, including sex hormones. Decreased melatonin secretion has been well documented in aging patients[67,68]. Recent studies revealed an association between sleep disorders and a decreased level of melatonin only in women in perimenopause[69]. Okatani, Morioka & Wakatsuki (2000) found a significant negative correlation between peak serum melatonin and estradiol levels in women aged 40 to 50 years, and found that daily administration of conjugated estrogens suppressed nighttime melatonin secretion in postmenopausal women[70]. Toffol et al. (2014), in a randomized, placebo-controlled trial of

the effects of hormone replacement therapy (HRT) on serum melatonin levels, found a mean delay of 2 h 21 min in peak melatonin time (acrophase) among postmenopausal women after 6 months of HRT, but mean melatonin levels and mean duration of melatonin secretion did not differ between patients and controls[71].

Blaicher et al. (2000), in a case-control study, investigated the interaction between melatonin, sex steroids, and the neuroendocrine system in postmenopausal women and found significantly lower melatonin levels in women with insomnia and those with obesity when compared with controls[72]. In 1997, Cagnacci et al. demonstrated that administration of melatonin increases cortisol levels in postmenopausal women, and that estradiol reverses this effect[73]. Melatonin supplementation in the postmenopausal period was suggested by Baxi et al. (2013) as a safe and powerful alternative to mitigate the increased oxidative stress caused by decreased estrogen levels[74].

ESTRADIOL

Estrogens are female sex steroid hormones. In humans, the most potent estrogen hormone is 17-beta-estradiol (E2). The biological effects of estrogens are based on genomic mechanisms, mediated by their interactions with the nuclear receptors alpha (ER-α) and beta (ER-ß), but also by rapid, nongenomic mechanisms involving G-protein coupled receptors (GPCRs), which can activate intracellular signaling cascades. Nuclear and transmembrane estrogen receptors are biochemically identical and can work in tandem[75–77].

Estradiol can effect all four known types of hormonal action: intracrine (regulation of vital activities within its cell of origin), autocrine (regulation of vital activity within cells involved in its formation, secretion, and reuptake), paracrine (regulation of vital activities in neighboring cells in the same tissue), and endocrine (influencing cells at remote organ)[75].

Estrogens regulate a wide range of cell functions. Originally identified as regulators of reproduction and sexual behavior alone, they are now known to affect the somatosensory system, and a possible action on pain processing at the spinal level has been suggested[78].

Estradiol is produced not only in the ovaries and adrenal glands, but also in non-endocrine tissues such as the CNS and bone, where it plays important roles[75]. For instance, in experimental studies, estradiol has been shown to induce proliferation of hematopoietic stem cells[79], protect against brain injury, neurodegeneration, and cognitive decline[80].

It is well established that many of the actions of estrogens on the CNS are mediated by their nuclear receptor ER-ß, which interacts with response elements in steroid target genes (genomic action – slow). However, there is convincing evidence of the presence of transmembrane estrogen receptors (GPCRs) in hypothalamic neurons and other areas of the CNS (nongenomic action – rapid). Indeed, estrogens are able to rapidly alter neuronal activity (within seconds). Furthermore, estrogens can affect second-messenger systems involving calcium mobilization and kinase activation to alter cell signaling and contribute to homeostasis[81–83].

ESTRADIOL AND ANTINOCICEPTION

1 . Experimental works on estradiol and antinociception

Various studies on sex differences in basal nociceptive sensitivity have been performed on animals, most of them rodents. Craft et al. (2008) showed that estradiol administration dose- and time-dependently alters sensitivity to the antinociceptive effects of morphine in female rats[15]. In an inflammatory pain model using complete Freund's adjuvant (CFA), female rats developed inflammation more quickly and with greater peak hyperalgesia than males, with the lowest nociceptive thresholds seen in estrous and proestrous[22].

Many authors have studied the effect of estradiol on pain modulation. Zhang et al. (2012), using electrophysiological, morphological, and biochemical methods, demonstrated that estradiol can directly modulate spinal cord synaptic transmission by enhancing NMDA receptors in dorsal horn neurons, increasing glutamate release from primary afferent terminals, and increasing dendritic density in cultured spinal cord neurons[24]. The presence of estrogen receptors in the PAG suggests that estrogen hormones can influence descending pain modulation pathways – a hypothesis supported by studies showing that female rats in estrous are less sensitive than those in diestrus to antinociception induced by intra-PAG morphine injection; furthermore, female rats are more susceptible than males to the reduction in antinociception induced by irreversible blockade of μ-opioid receptors in the PAG[84].

2. Human studies on estradiol and chronic pain

The main sex difference with respect to pain is the greater prevalence of chronic pain syndromes in women as compared to men[6]. Irritable bowel syndrome (IBS), fibromyalgia, temporomandibular disorder (TMD), and chronic headaches are more frequent in females than in males[5,6]. In addition, the incidence of less well-defined chronic pain conditions such as fibromyalgia peaks around menopause[85]. Postmenopausal women are twice more likely to experience joint pain or stiffness than premenopausal women[86].

The discovery of gender differences in nociceptive response implies that sex steroids modulate sensitivity to analgesic drugs and to environmental stimuli involving the neurobiological systems that play a role in the pain perception process. As estrogens can influence the function of several body systems, including the nervous, immune, musculoskeletal, and cardiovascular systems, estrogenic pain modulation is exceedingly complex, alternating between pro-nociceptive and antinociceptive effects, depending on the extent to which each of these systems is involved and on the type of pain.

INTERACTION BETWEEN MELATONIN AND ESTRADIOL

Several studies have shown that both melatonin and estradiol have antioxidant effects, and some of these studies have confirmed the analgesic and anti-inflammatory actions of melatonin[50,52,53,87]. Regarding estradiol, however, studies are still conflicting.

In addition to Cagnacci et al., who demonstrated that melatonin administration increases cortisol levels in postmenopausal women and that this effect is reversed by estradiol[73], Kerdelhué et al. (2006) also studied the interaction among melatonin, estradiol, and cortisol. These authors found a rapid, significant decline in serum cortisol levels after intramuscular administration of estradiol valerate at 8:00 a.m. in postmenopausal women. However, they found only a nonsignificant decrease in serum melatonin levels[88].

In 2012, Karadayian et al. studied the interaction between estradiol and melatonin in mice subjected to a behavioral model of ethanol-induced hangover and found that estrogen interferes by blocking the protective action on motor performance conferred by melatonin during a hangover[89]. Another experimental study found an increase in the antioxidant effect of estradiol when combined with melatonin[90].

CONCLUSION

The transition from reproductive to menopausal status induces several physiological adjustments involving all body organs and their functions. These modifications are believed to relate mostly to hormonal changes, mainly to the decrease of estradiol, the leading hormonal alteration in postmenopausal women. Melatonin secretion was also shown to change in perimenopausal and postmenopausal years and to affect and be affected by estradiol levels. Another condition that is known to change with menopause is chronic pain. Most of the painful disorders where the analgesic properties of melatonin have been investigated are known to be more prevalent in women, and to be affected by menopause, such as fibromyalgia, chronic arthritis, IBS and TMD. Studies have demonstrated a close interaction between estradiol and melatonin. Therefore, further research into the involvement of these two hormones on nociceptive processes is required to advance our understanding of the pathways involved in pain modulation and to establish sex-tailored therapies to chronic painful disorders.

REFERENCES

1. American Society of Anesthesiologists Task Force on Chronic Pain Management, American Society of Regional Anesthesia and Pain Medicine. Practice guidelines for chronic pain management: an updated report by the American Society of Anesthesiologists Task Force on Chronic Pain Management and the American Society of Regional Anesthesia and Pain Medicine. Anesthesiology. 2010;112:810-33.
2. Vaegter HB, Andersen PG, Madsen MF, Handberg G, Enggaard TP. Prevalence of neuropathic pain according to the IASP grading system in patients with chronic non-malignant pain. Pain Med. 2014;15:120-7.
3. Vieira EB, Garcia JB, Silva AA, Araujo RL, Jansen RC, Bertrand AL. Chronic pain, associated factors, and impact on daily life: are there differences between the sexes? Cad Saude Publica. 2012;28:1459-67.
4. Sa K, Baptista AF, Matos MA, Lessa I. Prevalence of chronic pain and associated factors in the population of

Salvador, Bahia. Rev Saude Publica. 2009;43:622-30.

5. Tsang A, Von Korff M, Lee S, Alonso J, Karam E, Angermeyer MC, et al. Common chronic pain conditions in developed and developing countries: gender and age differences and comorbidity with depression-anxiety disorders. J Pain. 2008;9:883-91.

6. Unruh AM. Gender variations in clinical pain experience. Pain. 1996;65:123-67.

7. Blyth FM, March LM, Brnabic AJ, Jorm LR, Williamson M, Cousins MJ. Chronic pain in Australia: a prevalence study. Pain. 2001;89:127-34.

8. Sjogren P, Ekholm O, Peuckmann V, Gronbaek M. Epidemiology of chronic pain in Denmark: an update. Eur J Pain. 2009;13:287-92.

9. Harker J, Reid KJ, Bekkering GE, Kellen E, Bala MM, Riemsma R, et al. Epidemiology of chronic pain in denmark and sweden. Pain Res Treat. 2012:371248.

10. Vacca V, Marinelli S, Pieroni L, Urbani A, Luvisetto S, Pavone F. Higher pain perception and lack of recovery from neuropathic pain in females: a behavioural, immunohistochemical, and proteomic investigation on sex-related differences in mice. Pain. 2014;155:388-402.

11. Laste G, Vidor L, de Macedo IC, Rozisky JR, Medeiros L, de Souza A, et al. Melatonin treatment entrains the rest-activity circadian rhythm in rats with chronic inflammation. Chronobiol Int. 2013;30:1077-88.

12. Hashmi JA, Davis KD. Women experience greater heat pain adaptation and habituation than men. Pain. 2009;145:350-7.

13. Greenspan JD, Craft RM, LeResche L, Arendt-Nielsen L, Berkley KJ, Fillingim RB, et al. Studying sex and gender differences in pain and analgesia: a consensus report. Pain. 2007;132 Suppl 1:S26-45.

14. Craft RM, Mogil JS, Aloisi AM. Sex differences in pain and analgesia: the role of gonadal hormones. Eur J Pain. 2004;8:397-411.

15. Craft RM, Ulibarri C, Leitl MD, Sumner JE. Dose- and time-dependent estradiol modulation of morphine antinociception in adult female rats. Eur J Pain. 2008;12:472-9.

16. Fillingim RB, King CD, Ribeiro-Dasilva MC, Rahim-Williams B, Riley JL, 3rd. Sex, gender, and pain: a review of recent clinical and experimental findings. J Pain. 2009;10:447-85.

17. Badley EM, Kasman NM. The Impact of Arthritis on Canadian Women. BMC Womens Health. 2004;4 Suppl 1:S18.

18. Tall JM, Stuesse SL, Cruce WL, Crisp T. Gender and the behavioral manifestations of neuropathic pain. Pharmacol Biochem Behav. 2001;68:99-104.

19. Coyle DE, Sehlhorst CS, Mascari C. Female rats are more susceptible to the development of neuropathic pain using the partial sciatic nerve ligation (PSNL) model. Neurosci Lett. 1995;186:135-8.

20. Coyle DE, Sehlhorst CS, Behbehani MM. Intact female rats are more susceptible to the development of tactile allodynia than ovariectomized female rats following partial sciatic nerve ligation (PSNL). Neurosci Lett. 1996;203:37-40.

21. Aloisi AM, Affaitati G, Ceccarelli I, Fiorenzani P, Lerza R, Rossi C, et al. Estradiol and testosterone differently affect visceral pain-related behavioural responses in male and female rats. Eur J Pain. 2010;14:602-7.

22. Cook CD, Nickerson MD. Nociceptive sensitivity and opioid antinociception and antihyperalgesia in Freund's adjuvant-induced arthritic male and female rats. J Pharmacol Exp Ther. 2005;313:449-59.

23. Racine M, Tousignant-Laflamme Y, Kloda LA, Dion D, Dupuis G, Choiniere M. A systematic literature review of 10 years of research on sex/gender and pain perception - part 2: do biopsychosocial factors alter pain sensitivity differently in women and men? Pain. 2012;153:619-35.

24. Zhang Y, Xiao X, Zhang XM, Zhao ZQ, Zhang YQ. Estrogen facilitates spinal cord synaptic transmission via membrane-bound estrogen receptors: implications for pain hypersensitivity. J Biol Chem. 2012;287:33268-81.

25. Small KM, Nag S, Mokha SS. Activation of membrane estrogen receptors attenuates opioid receptor-like1 receptor-mediated antinociception via an ERK-dependent non-genomic mechanism. Neuroscience. 2013;255:177-90.

26. Coulombe MA, Spooner MF, Gaumond I, Carrier JC, Marchand S. Estrogen receptors beta and alpha have specific pro- and anti-nociceptive actions. Neuroscience. 2011;184:172-82.

27. Blackburn-Munro G, Blackburn-Munro R. Pain in the brain: are hormones to blame? Trends Endocrinol Metab. 2003;14:20-7.

28. 28. Meriggiola MC, Nanni M, Bachiocco V, Vodo S, Aloisi AM. Menopause affects pain depending on pain type and characteristics. Menopause. 2012;19:517-23.

29. Wikner J, Hirsch U, Wetterberg L, Rojdmark S. Fibromyalgia--a syndrome associated with decreased nocturnal melatonin secretion. Clin Endocrinol (Oxf). 1998;49:179-83.

30. Almay BG, von Knorring L, Wetterberg L. Melatonin in serum and urine in patients with idiopathic pain syndromes. Psychiatry Res. 1987;22:179-91.

31. Vidor LP, Torres IL, Custodio de Souza IC, Fregni F, Caumo W. Analgesic and sedative effects of melatonin in temporomandibular

disorders: a double-blind, randomized, parallel-group, placebo-controlled study. J Pain Symptom Manage. 2013;46:422-32.

32. Schwertner A, Conceicao Dos Santos CC, Costa GD, Deitos A, de Souza A, de Souza IC, et al. Efficacy of melatonin in the treatment of endometriosis: a phase II, randomized, double-blind, placebo-controlled trial. Pain. 2013;154:874-81.

33. de Zanette SA, Vercelino R, Laste G, Rozisky JR, Schwertner A, Machado CB, et al. Melatonin analgesia is associated with improvement of the descending endogenous pain-modulating system in fibromyalgia: a phase II, randomized, double-dummy, controlled trial. BMC Pharmacol Toxicol. 2014;15:40.

34. Toffol E, Kalleinen N, Haukka J, Vakkuri O, Partonen T, Polo-Kantola P. Melatonin in perimenopausal and postmenopausal women: associations with mood, sleep, climacteric symptoms, and quality of life. Menopause. 2014;21:493-500.

35. Vakkuri O, Kivela A, Leppaluoto J, Valtonen M, Kauppila A. Decrease in melatonin precedes follicle-stimulating hormone increase during perimenopause. Eur J Endocrinol. 1996;135:188-92.

36. IASP. IASP Taxonomy 2012 [1 September 2014]. Available from: http://www.iasp-pain.org/Education/Content.aspx?ItemNumber=1698.

37. Schaible HG. [Pathophysiology of pain]. Orthopade. 2007;36:8, 10-2, 4-6.

38. Millan MJ. The induction of pain: an integrative review. Prog Neurobiol. 1999;57:1-164.

39. Loeser JD, Melzack R. Pain: an overview. Lancet. 1999;353:1607-9.

40. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. Lancet. 2006;367:1618-25.

41. Peters ML, Sommer M, de Rijke JM, Kessels F, Heineman E, Patijn J, et al. Somatic and psychologic predictors of long-term unfavorable outcome after surgical intervention. Ann Surg. 2007;245:487-94.

42. Riedel W, Neeck G. Nociception, pain, and antinociception: current concepts. Z Rheumatol. 2001;60:404-15.

43. Besson JM. [The complexity of physiopharmacologic aspects of pain]. Drugs. 1997;53 Suppl 2:1-9.

44. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. Pain. 2011;152:S2-15.

45. Mifflin KA, Kerr BJ. The transition from acute to chronic pain: understanding how different biological systems interact. Can J Anaesth. 2014;61:112-22.

46. Arendt J, Skene DJ. Melatonin as a chronobiotic. Sleep Med Rev. 2005;9:25-39.

47. Arendt J. Melatonin and human rhythms. Chronobiol Int. 2006;23:21-37.

48. Ferracioli-Oda E, Qawasmi A, Bloch MH. Meta-analysis: melatonin for the treatment of primary sleep disorders. PLoS One. 2013;8:e63773.

49. Mantovani M, Pertile R, Calixto JB, Santos AR, Rodrigues AL. Melatonin exerts an antidepressant-like effect in the tail suspension test in mice: evidence for involvement of N-methyl-D-aspartate receptors and the L-arginine-nitric oxide pathway. Neurosci Lett. 2003;343:1-4.

50. Cuzzocrea S, Zingarelli B, Gilad E, Hake P, Salzman AL, Szabo C. Protective effect of melatonin in carrageenan-induced models of local inflammation: relationship to its inhibitory effect on nitric oxide production and its peroxynitrite scavenging activity. J Pineal Res. 1997;23:106-16.

51. Wilhelmsen M, Amirian I, Reiter RJ, Rosenberg J, Gogenur I. Analgesic effects of melatonin: a review of current evidence from experimental and clinical studies. J Pineal Res. 2011;51:270-7.

52. Reiter RJ, Calvo JR, Karbownik M, Qi W, Tan DX. Melatonin and its relation to the immune system and inflammation. Ann N Y Acad Sci. 2000;917:376-86.

53. El-Shenawy SM, Abdel-Salam OM, Baiuomy AR, El-Batran S, Arbid MS. Studies on the anti-inflammatory and anti-nociceptive effects of melatonin in the rat. Pharmacol Res. 2002;46:235-43.

54. Caumo W, Torres F, Moreira NL, Jr., Auzani JA, Monteiro CA, Londero G, et al. The clinical impact of preoperative melatonin on postoperative outcomes in patients undergoing abdominal hysterectomy. Anesth Analg. 2007;105:1263-71, table of contents.

55. Claustrat B, Brun J, Chazot G. The basic physiology and pathophysiology of melatonin. Sleep Med Rev. 2005;9:11-24.

56. Macchi MM, Bruce JN. Human pineal physiology and functional significance of melatonin. Front Neuroendocrinol. 2004;25:177-95.

57. Jockers R, Maurice P, Boutin JA, Delagrange P. Melatonin receptors, heterodimerization, signal transduction and binding sites: what's new? Br J Pharmacol. 2008;154:1182-95.

58. Zurowski D, Nowak L, Machowska A, Wordliczek J, Thor PJ. Exogenous melatonin abolishes mechanical allodynia but not thermal hyperalgesia in neuropathic pain. The role of the opioid system and benzodiazepine-gabaergic mechanism. J Physiol Pharmacol. 2012;63:641-7.

59. Srinivasan V, Pandi-Perumal SR, Spence DW, Moscovitch A, Trakht I, Brown GM, et al. Potential use of melatonergic drugs in analgesia:

mechanisms of action. Brain Res Bull. 2010;81:362-71.

60. Esposito E, Paterniti I, Mazzon E, Bramanti P, Cuzzocrea S. Melatonin reduces hyperalgesia associated with inflammation. J Pineal Res. 2010;49:321-31

61. Yu CX, Zhu B, Xu SF, Cao XD, Wu GC. The analgesic effects of peripheral and central administration of melatonin in rats. Eur J Pharmacol. 2000;403:49-53.

62. Raghavendra V, Agrewala JN, Kulkarni SK. Melatonin reversal of lipopolysacharides-induced thermal and behavioral hyperalgesia in mice. Eur J Pharmacol. 2000;395:15-21.

63. Chen WY, Giobbie-Hurder A, Gantman K, Savoie J, Scheib R, Parker LM, et al. A randomized, placebo-controlled trial of melatonin on breast cancer survivors: impact on sleep, mood, and hot flashes. Breast Cancer Res Treat. 2014;145:381-8.

64. Ulugol A, Dokmeci D, Guray G, Sapolyo N, Ozyigit F, Tamer M. Antihyperalgesic, but not antiallodynic, effect of melatonin in nerve-injured neuropathic mice: Possible involvements of the L-arginine-NO pathway and opioid system. Life Sci. 2006;78:1592-7.

65. Korszun A, Sackett-Lundeen L, Papadopoulos E, Brucksch C, Masterson L, Engelberg NC, et al. Melatonin levels in women with fibromyalgia and chronic fatigue syndrome. J Rheumatol. 1999;26:2675-80.

66. 66. Citera G, Arias MA, Maldonado-Cocco JA, Lazaro MA, Rosemffet MG, Brusco LI, et al. The effect of melatonin in patients with fibromyalgia: a pilot study. Clin Rheumatol. 2000;19:9-13.

67. Reiter RJ. Pineal function during aging: attenuation of the melatonin rhythm and its neurobiological consequences. Acta Neurobiol Exp (Wars). 1994;54 Suppl:31-9.

68. Hardeland R. Neurobiology, pathophysiology, and treatment of melatonin deficiency and dysfunction. ScientificWorldJournal. 2012;2012:640389.

69. Kolesnikova LI, Madaeva IM, Semenova NV, Suturina LV, Berdina ON, Sholohov LF, et al. Pathogenic role of melatonin in sleep disorders in menopausal women. Bull Exp Biol Med. 2013;156:104-6.

70. Okatani Y, Morioka N, Wakatsuki A. Changes in nocturnal melatonin secretion in perimenopausal women: correlation with endogenous estrogen concentrations. J Pineal Res. 2000;28:111-8.

71. Toffol E, Kalleinen N, Haukka J, Vakkuri O, Partonen T, Polo-Kantola P. The effect of hormone therapy on serum melatonin concentrations in premenopausal and postmenopausal women: a randomized, double-blind, placebo-controlled study. Maturitas. 2014;77:361-9.

72. Blaicher W, Speck E, Imhof MH, Gruber DM, Schneeberger C, Sator MO, et al. Melatonin in postmenopausal females. Arch Gynecol Obstet. 2000;263:116-8.

73. Cagnacci A, Soldani R, Yen SS. Melatonin enhances cortisol levels in aged women: reversible by estrogens. J Pineal Res. 1997;22:81-5.

74. Baxi DB, Singh PK, Vachhrajani KD, Ramachandran AV. Melatonin supplementation in rat ameliorates ovariectomy-induced oxidative stress. Climacteric. 2013;16:274-83.

75. Halbe HW. Conceitos e aspectos bioquímicos dos estrógenos. Rev Clinica Ter. 2005;31:68-76.

76. Kuhl H. Pharmacology of estrogens and progestogens: influence of different routes of administration. Climacteric. 2005;8 Suppl 1:3-63.

77. Prossnitz ER, Oprea TI, Sklar LA, Arterburn JB. The ins and outs of GPR30: a transmembrane estrogen receptor. J Steroid Biochem Mol Biol. 2008;109:350-3.

78. Evrard HC. Estrogen synthesis in the spinal dorsal horn: a new central mechanism for the hormonal regulation of pain. Am J Physiol Regul Integr Comp Physiol. 2006;291:R291-9.

79. Qiu X, Jin X, Shao Z, Zhao X. 17beta-estradiol induces the proliferation of hematopoietic stem cells by promoting the osteogenic differentiation of mesenchymal stem cells. Tohoku J Exp Med. 2014;233:141-8.

80. Hoffman GE, Merchenthaler I, Zup SL. Neuroprotection by ovarian hormones in animal models of neurological disease. Endocrine. 2006;29:217-31.

81. Hall JM, Couse JF, Korach KS. The multifaceted mechanisms of estradiol and estrogen receptor signaling. J Biol Chem. 2001;276:36869-72.

82. Malyala A, Kelly MJ, Ronnekleiv OK. Estrogen modulation of hypothalamic neurons: activation of multiple signaling pathways and gene expression changes. Steroids. 2005;70:397-406.

83. Ronnekleiv OK, Malyala A, Kelly MJ. Membrane-initiated signaling of estrogen in the brain. Semin Reprod Med. 2007;25:165-77.

84. Bernal SA, Morgan MM, Craft RM. PAG mu opioid receptor activation underlies sex differences in morphine antinociception. Behav Brain Res. 2007;177:126-33.

85. Pamuk ON, Cakir N. The variation in chronic widespread pain and other symptoms in fibromyalgia patients. The effects of menses and menopause. Clin Exp Rheumatol. 2005;23:778-82.

86. Szoeke CE, Cicuttini FM, Guthrie JR, Dennerstein L. The relationship of reports of aches and joint pains to the menopausal transition: a longitudinal study. Climacteric. 2008;11:55-62.

87. Hardeland R, Madrid JA, Tan DX, Reiter RJ. Melatonin, the circadian multioscillator system and health: the need for detailed analyses of peripheral melatonin signaling. J Pineal Res. 2012;52:139-66.

88. Kerdelhue B, Andrews MC, Zhao Y, Scholler R, Jones HW, Jr. Short term changes in melatonin and cortisol serum levels after a single administration of estrogen to menopausal women. Neuro Endocrinol Lett. 2006;27:659-64.

89. Karadayian AG, Mac Laughlin MA, Cutrera RA. Estrogen blocks the protective action of melatonin in a behavioral model of ethanol-induced hangover in mice. Physiol Behav. 2012;107:181-6.

90. Turgut O, Ay AA, Turgut H, Ay A, Kafkas S, Dost T. Effects of melatonin and dexpanthenol on antioxidant parameters when combined with estrogen treatment in ovariectomized rats. Age (Dordr). 2013;35:2229-35.

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