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REVIEW ARTICLE

Analgesic effects of melatonin: a review of current evidence from experimental and clinical studies

Abstract: Melatonin is an endogenous indoleamine, produced mainly by the pineal gland. Melatonin has been proven to have chronobiotic, antioxidant, antihypertensive, anxiolytic and sedative properties. There are also experimental and clinical data supporting an analgesic role of melatonin. In experimental studies, melatonin shows potent analgesic effects in a dose-dependent manner. In clinical studies, melatonin has been shown to have analgesic benefits in patients with chronic pain (fibromyalgia, irritable bowel syndrome, migraine). The physiologic mechanism underlying the analgesic actions of melatonin has not been clarified. The effects may be linked to G_i-coupled melatonin receptors, to G_i-coupled opioid μ-receptors or GABA-B receptors with unknown downstream changes with a consequential reduction in anxiety and pain. Also, the repeated administration of melatonin improves sleep and thereby may reduce anxiety, which leads to lower levels of pain. In this paper, we review the current evidence regarding the analgesic properties of melatonin in animals and humans with chronic pain.

Michael Wilhelmsen[1], Ilda Amirian[1], Russel J. Reiter[2], Jacob Rosenberg[1] and Ismail Gögenur[1]

[1]Department of Surgical Gastroenterology, Herlev Hospital, University of Copenhagen, Herlev, Denmark; [2]Department of Cellular and Structural Biology, The University of Texas Health Science Center, San Antonio, TX, USA

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Address reprint requests to Ilda Amirian, Department of Surgical Gastroenterology, Herlev Hospital, University of Copenhagen, Herlev Ringvej 75, 2730 Herlev, Denmark.
E-mail: iamirian@gmail.com

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Introduction

Pain is an almost ubiquitous phenomenon in all medical conditions, and its management has great clinical importance. Morphine, its analogues, nonsteroid anti-inflammatory drugs (NSAID) and acetaminophen are among the most commonly used and efficient drugs for treating pain. The side effects of most of these analgesics are, however, substantial. The NSAIDs are known to cause gastrointestinal damage particularly in the stomach and duodenum, which clinically is seen as ulceration and inflammation [1], and preliminary studies have shown that the use of NSAIDs also may increase the risk of anastomotic leakage in patients having a colorectal anastomosis [2, 3]. The side effects of morphine are well known and include constipation, confusion, sedation, sleep disturbances and respiratory depression [4]. Morphine also has the potential for creating drug addiction and the therapeutic index narrows if used for a long time [4, 5]. Because of these substantial side effects, it is important to find the methods of reducing the use of analgesics, identifying alternative analgesics with reduced side effects or developing drugs that antagonize the side effects (e.g., peripheral morphine receptor antagonists [6–8]).

Melatonin, an endogenous chronobiotic [9–11] with potent antioxidant effects [12–14], has been shown to have analgesic effects in both experimental and clinical studies. Thus, melatonin is effective in reducing pain in conditions with chronic pain such as fibromyalgia (FM), inflammatory bowel syndrome (IBS) and migraine [15–29]. In preliminary studies, it has also been suggested that melatonin may have potent analgesic and anxiolytic effects in the perioperative period. This was recently reviewed in detail [30], where it was concluded that melatonin has a significant preoperative anxiolytic effect. Compared with midazolam, melatonin had a similar anxiolytic efficacy yet with less psychomotor impairment and fewer side effects. The analgesic effect of melatonin, however, remained controversial as there were opioid-sparing effects or reduced pain scores in five studies, while three studies remained contradictory [31].

In this report, we review the literature regarding the analgesic effects of melatonin in experimental studies. We also summarize the results of clinical studies where melatonin has been used for the treatment of chronic pain syndromes.

Experimental studies

In animals, the analgesic effect of melatonin has been extensively studied. The most frequently used species for these investigations are rats [32–36] and mice [5, 37–45].

Electrically induced pain

Two models using electrically induced pain have been used to evaluate the analgesic effect of melatonin [34, 46].

Antinociceptive threshold is the smallest amount of current capable of eliciting a vocal response [34, 46]. Intraperitoneally (i.p.) injected melatonin significantly modified the antinociceptive effect up to 210 min after administration [46], and after intrathecal (i.t.) administration, a similar effect, in a dose dependant manner, was found on the spinal wind-up activity even though this effect only lasted for 30 min [34] (Table 1) .

Thermally induced pain

Thermal stimulation is often used experimentally. The behavioural endpoints used with this test are either the withdrawal/tail flick time after placement on a hotplate [38, 39, 41, 45, 47] or the tail flick latency to hot water [39, 41, 45]. With the tail flick latency test, both i.p. and intracerebroventricular (icv.) administration of melatonin were

Table 1. Models of pain in animals

Author	Species	N	Quality of pain	Administration form of melatonin	Dose melatonin	Significant analgesic effect	Analgesic duration
Noseda et al. [31]	Male Wistar rats	Not specified	Withdrawal reflex following electric stimulation of the sural nerve	IT	10, 30 or 90 μg	+, dd	30 min
El-shewany et al. [15]	Male Sprague-Dawley rats	18	Vocalization following electric tail stimulation	IP	0.5 and 1 mg/kg	+	210 min
Wang et al. [13]	Male Kunming mice	80	Tail flick test following nociceptin induced hyperalgesia	IP or ICV	i.p: 5, 10, 50 mg/kg i.c.v: 5, 10, 50 μg/mouse	+	70 min
Raghavendra et al. [41]	Male Balb/c mice	15	Behavioural assessment, tailflick and hotplate test following LPS induced hyperalgesia	SC	5 or 10 mg/kg	+	600 min
Li et al. [35]	Male Kunming mice	80	Tail flick latency following warm water test	IP or ICV	i.p.: 1, 5, 25 mg/kg i.c.v.: 0.25, 0.5, 1 mg/kg	+	90 min
Yu et al. [53]	Male Sprague-Dawley rats	16	Tail flick latency following warm water test	IP or ICV	i.p.: 30, 60, 120 mg/kg i.c.v.: 0.25, 0.5, 1 mg/kg	+	IP: 100 min ICV: 80 min
Zahn et al. [43]	Male Sprague-Dawley rats	72	Withdrawal response to mechanical and thermal stimulus following paw incision	IT	10, 30, 100 nmol	–	–
Ulugol et al. [35]	Male Balb-c albino mice	48	Withdrawal response to mechanical and thermal stimulus following partial ligation of the sciatic nerve	IP and ICV	i.p.: 30, 60, 120 mg/kg i.c.v.: 0.001, 0.01, 0.1 nmol	+, dd	60 min
Naguib et al. [32]	Male Sprague-Dawley rats	12	Righting reflex within 15 s and paw withdrawal threshold/vocalization following pinch of hind paw	IV	3 doses of 70 mg/kg	+, dd	NR
Naguib et al. [33]	Male Sprague-Dawley rats	12	Righting reflex within 15 s and tail clamp response following application of rubber clamp across tail	IV	15, 30 and 45 mg/kg	+, dd	40 min
Ray et al. [39]	Male Swiss mice	32	Paw licking response following injection of formalin in hind paw	IP	25, 50 or 100 mg/kg	+, dd	40 min
Pang et al. [40]	Male ICR mice	52–60	Paw licking response following injection of formalin in hind paw	IP	0.1, 5 and 20 mg/kg	NS	NS
Padhy et al. [44]	Male Wistar rats	6	Stair climbing ability test, motility test and dorsal flexion pain test following subplantar injection of DL or carrageenan	SC	5 and 50 mg/kg	+	600 min

–, nonsignificant; +, significant; dd, dose dependent; DL, dried latex; ICV, intra cerebroventricularly; IP, intraperitoneal; IPL, intraplantaril; IT, intrathecal; IV, intravenous; LPS, lipopolysaccharide; NR, not reported; NS, not significant; SC, subcutaneous.

examined. Melatonin given i.p. produced a significant analgesic response at all examined doses (up to 120 mg/kg) [39, 41, 47]. Up to 50 μg melatonin/mouse given icv. produced a significant analgesic effect [39, 41, 47]. The effects of melatonin lasted a minimum of 70 min when melatonin was given ip. or icv.

Paw withdrawal latency has been used to examine the analgesic effect of melatonin. In these tests, melatonin has been given i.p. or icv. [38]. For one test, the sciatic nerve was partially cut and ligated as a model of chronic neuropathic pain. After 2–3 wk, the authors performed analgesic tests with paw withdrawal latency after heat stimulation. Melatonin caused a dose-dependent analgesic response, which lasted for 1 hr with the indoleamine being administered via either route. No side effects were found [38].

The response to both mechanical and thermal stimuli was used by Zahn et al. [48] as a model of postoperative acute pain in rats. On the day of surgery and on the first postoperative day, the investigators measured the mechanical withdrawal response to application of 15–247 mN and thermal withdrawal latencies as behavioural endpoints of pain. Melatonin was given via a lumbar spine catheter to investigate what role spinal melatonin receptors play in antinociceptive response. Thermal and mechanical withdrawal responses were tested up to 5 hr after surgery and on the postoperative day. The researchers reported no analgesic effect of melatonin on incisional pain when it was given alone. When the indoleamine was combined with opioids, an analgesic response was observed that lasted for a maximum of 60 min [48] (Table 1).

Mechanical induction of pain

Tail-clamping is an experimental pain model where pain is induced at the proximal third of the tail and a change in righting reflex is measured and compared with baseline values [35, 36]. In the two studies where this model was used, the analgesic effect of either intravenous melatonin [35] or 2-bromomelatonin [36] was measured. 2-Bromomelatonin was found to dose dependently induce an analgesic effect, but only in doses higher than 30 mg/kg. Injection of three boluses of melatonin was also found to produce analgesia [35] (Table 1).

Chemical induction of pain

This pain model is probably the closest resembling acute pain in humans because it tests the combined effect of a first and second phase in which an inflammatory response is induced [43, 44]. Inflammation was induced by the injection of either lipopolysaccharide (LPS) [45], glutamate [40], capsaicin [40], latex [49] or formalin [43, 44].

Subcutaneous (sc.) injection of melatonin has been used to attenuate pain associated with thermal injury and after LPS injection. Melatonin had a significant antihyperalgesic effect compared to a control injection but no isolated analgesic effect. The authors presumed that the preventive action of melatonin was because of the immune regulatory effects of the indoleamine [45].

When glutamate or capsaicin was used to induce pain, melatonin administered via different routes, prior to the pain-provoking agents, resulted in a significant antinociceptive effect. The response to melatonin was dose dependent [40] (Table 1). As in many previous studies, these workers reported no side effects of melatonin [40].

Injection of latex causes inflammatory hyperalgesia. *Calotropis procera* (*C. procera*) and *carrageena* are commonly used as inflammatory agents. Melatonin, when given s.c. after the inflammatory mediators, was found to effectively reduce the associated pain. This effect lasted up to 10 hr, depending on the mediator used [49].

The formalin test has been used in two studies [43, 44]. Results varied according to the melatonin doses used. Thus, with i.p. administration of melatonin, no significant analgesic effect was found when doses of 0.1–20 mg/kg were administered [44]. A significant benefit, however, was reported when either 25, 50 or 100 mg melatonin/kg were administered [43]. The time of melatonin administration differed in the two studies possibly explaining the differences in outcomes, although the different responses may have been exclusively related to the doses of melatonin injected.

Human studies

In humans, the analgesic effect of melatonin on chronic pain has not been studied extensively. In chronic pain models, melatonin has been examined as a potential therapy in patients with FM, IBS or migraine.

Fibromyalgia

FM is a syndrome characterized and diagnosed according to the American College of Rheumatologists (ACR) criteria. The features of FM include tenderness, altered sleep pattern and a number of painful trigger points. In all studies conducted with melatonin as a therapeutic agent, the patients have been diagnosed based on these criteria [15, 18, 20, 22, 24]. The patient group suffering from FM is predominantly women (90%) with a prevalence of 2–5% in the Western world [18, 20, 23]. Depressive disorders are often also observed in these patients [24].

Disturbances in melatonin secretion have been proposed to be part of the pathophysiology leading to FM. However, the experimental findings are conflicting. The circadian rhythm [18] and secretion of melatonin have been examined in patients with FM [19, 22, 24]. No significant differences were observed in the 24-hr plasma melatonin, cortisol cycle or core body temperature between ten subjects and ten controls [18]. In another study including eight patients with FM and eight controls, the concentration of melatonin in plasma and urine between 23.00 and 07.00 hr was found to be significantly lower in patients with FM [24]. Korszun et al. [19], however, reported that the melatonin concentration in urine was elevated in patients with FM when compared to controls. Press et al. [22] did not find that the melatonin level was different in patients compared to controls in the largest study with 39 female patients and 39 controls. The observations on whether an abnormality in the melatonin secretion contributes to FM are clearly inconclusive [18–20, 22, 24].

Treatment of FM with melatonin was performed in an open-label, randomized-study including 21 female patients. No side effects of the treatment were observed. Melatonin, when given in doses of 3 mg orally for 4 wk 30 min before sleeping time, significantly improved sleep quality and resulted in significantly fewer painful trigger points than before treatment. The investigations also claimed improvements with regard to pain, fatigue and depressive symptoms, although these changes were not statistically significant [15].

Hussein et al. [50] performed a double-blinded and placebo-controlled study in 101 patients to evaluate different doses of melatonin alone or in combination with fluoxetine for the management of FM. The patients were randomized into four groups: group A was treated with 20 mg/day fluoxetine, group B was treated with 5 mg melatonin, group C was treated with 20 mg fluoxetine plus 3 mg melatonin and group D was treated with 20 mg fluoxetine plus 5 mg melatonin. The patients were evaluated by interviews using the Fibromyalgia Impact Questionnaire. Treatment with fluoxetine alone improved symptoms of fatigue, morning stiffness, anxiety and depression but it had no influence on the rest/sleep score. While the effects of treatment with melatonin alone were less than treatment with fluoxetine alone, there were still significant improvements in pain, fatigue, rest/sleep, stiffness and depression. A combination of melatonin and fluoxetine showed a significant reduction in the anxiety score and fatigue and highly significant reduction in depressive symptoms. All treatment approaches significantly reduced the pain score compared to the pretreatment values (Table 2). In conclusion, adjuvant use of melatonin with fluoxetine improves the clinical picture of patients with FM.

The pathophysiological relationship between circadian disturbances and FM has not been entirely clarified, but several studies indicate benefits of treatment with melatonin alone and melatonin combined with fluoxetine in FM patients. The significant improvement of melatonin treatment combined with a selective serotonin reuptake inhibitor should be investigated in future larger-scaled clinical trials.

Irritable bowel syndrome

IBS is a painful condition of the gastrointestinal system. This syndrome is diagnosed according to the Rome 2 criteria including abdominal pain, flatulence, constipation or diarrhoea and sleep disturbances. In the clinical studies that have been published, patients were diagnosed based on these criteria [26, 27]. IBS is estimated to affect 11–20% of the adult population [26]. The amount of melatonin in the gastro intestinal (GI) tract is estimated to be 400 times greater than that in the pineal gland, suggesting it has relevance to gastrointestinal physiology and pathology [51, 52]. Its production and secretion by the enterochromaffin cells of the gut is not circadian in nature. The detailed mechanisms governing melatonin synthesis and discharge in the GI tract are still unknown, but it does appear to be influenced by food intake. Melatonin also enhances the immune system through inhibition of the macrophages by reducing inflammatory mediators, which prevents ulceration of the GI mucosa and colon injury [53]. Significantly lower levels of saliva melatonin ($P < 0.001$) have been

Table 2. Experimental findings with melatonin treatment in humans suffering from chronic pain

Study	Design	Condition	Duration treatment (wk)	Treatment and dose	N	Pain	Anxiety	Sleep	Depression	Other effects
Citera et al. [16]	Open pilot study	FM	4	Melatonin 3 mg	19	↓, NS	↑	↑	→	Improvement of global assessment and tender point count
Hussein et al. [45]	Randomized, double-blinded, placebo-controlled	FM	4	Melatonin 5 mg	101	↓	→	↑	↓	Improvement in fatigue and stiffness
Song et al. [12]	Randomized, double-blinded, placebo-controlled	IBS	2	Melatonin 3 mg	40	↓	→	→	→	No significant improvement in QOL score and overall IBS score
Lu et al. [11]	Randomized, placebo-controlled	IBS	8	Melatonin 3 mg	42	↓	→	→	→	Improvement in overall IBS score
Saha et al. [48]	Randomized, double-blinded, placebo-controlled,	IBS	8	Melatonin 3 mg	18	↓	NC	NC	NC	Improvement of overall IBS and QOL score
Alstadhaug et al. [51]	Randomized, double-blinded, placebo-controlled crossover study	Migraine	8	Circadian 2 mg	46	→	NC	→	NC	No other effect
Peres et al. [50]	Open labelled trial	Migraine	12	Melatonin 3 mg	32	↓	NC	NC	NC	Decrease of headache frequency and intensity

↓, reduced; ↑, increased; → , unchanged; FM, fibromyalgia; IBS, irritable bowel syndrome; N, number of patients completing the study; NC, not considered; NS, not significant; QOL, quality of life.

observed in patients suffering from IBS compared to healthy volunteers [26].

Several clinical trials summarized by Mozaffari et al. [53] conclude that melatonin reduced abdominal pain and aided defecation without having an effect on sleep and anxiety. Saha et al. [54] found positive effects of melatonin over placebo in improving extracolonic symptoms in IBS through either sedative/anxiolytic or direct effects on the GI tract. The possible central nervous system action of melatonin in relieving IBS suggests that these mechanisms remain to be clarified as patients with IBS also have a high response to placebo [53].

Two randomized placebo-controlled clinical trials have been carried out by the same group to examine the analgesic actions of melatonin in patients with IBS [26, 27]. In both studies, 3 mg of oral melatonin was used (Table 2). One study investigated 40 patients randomized to melatonin or placebo for 2 wk [27]. In the other investigation, 24 patients were included in a randomized crossover trial where patients received melatonin or placebo for 8 wk followed by a 4-wk washout period [26]. There were no differences in patient characteristics. A reduction in abdominal and rectal pain sensitivity after 2 wk of treatment was found [27]. The patients, all of whom were women, also experienced an improvement in the IBS symptom scores after 8 wk of treatment [26]. No side effects of the treatment were observed in either study. Although the results of some clinical trials point to an effect of melatonin in IBS, further randomized controlled trials with larger sample sizes are required.

Migraine

Migraine is a common condition characterized by attacks of severe headache, neurologic dysfunction, sleep disturbances and pain-free intervals. People suffering from this condition are often women in the age group between 10 and 40 yr. The relationship between nocturnal melatonin secretion and migraine has been studied in three studies [28, 29, 55].

One study consisted of ten patients suffering from migraine and nine healthy matched controls. Patients and controls were otherwise comparable [28]. Urine was collected throughout the menstrual cycle, and the urinary melatonin concentration was found to be significantly lower in subjects suffering from migraine compared to controls. In another study by the same group, three of six patients were shown to have a clear disturbance in melatonin secretion with either a phase delay or phase advance of the nocturnal melatonin peak compared to healthy matched controls. The altered secretion pattern was not influenced by three nights of a 5-hr infusion of 4 μg melatonin/hr [29]. Four of six patients experienced relief of headache in the morning after the first infusion and the remaining two experienced this relief after the third infusion. Three patients also claimed a reduction in the reported pulsatility of pain. No side effects of melatonin were observed [29]. The largest migraine study included 220 patients of which 146 were migraine sufferers and 74 were controls. Among the patients suffering from migraine with pain, a significantly lower urinary concentration of 6-sulphatoxymelatonin (the major melatonin metabolite) was found than in the controls or migraine sufferers without pain; this suggests a pathophysiological relationship between pain and lowered melatonin secretion [55].

Peres et al. [56] performed an open-labelled trial including 34 patients, to assess the effect of melatonin in migraine prevention. The patients received 3 mg melatonin as prophylaxis 30 min before bedtime. Of the 32 patients who completed the study, melatonin reduced headache frequency, headache intensity and duration in all of them. Significant clinical improvement was already achieved at 1 month. Overall analgesic consumption was also reduced, and even migraines during the menstrual period were less frequent [56]. Alstadshaug et al. [57] found that prolonged-release melatonin (2 mg 1 hr before bedtime) provided no significantly better effect over placebo as a migraine prophylaxis. This may relate to the fact that melatonin's benefits in migraine sufferers may be dose dependent.

In general, the findings suggest a pathophysiological relationship between disturbances in melatonin secretion and migraine [28, 55] and also indicate that melatonin may have a therapeutic benefit in this severe condition [29, 56].

Discussion

Generally, there seems to be a dose-dependent analgesic effect of melatonin in experimental studies. The evidence supporting melatonin's analgesic actions in clinical reports are preliminary and indicate a possible effect on chronic pain related to IBS, migraine and FM.

An analgesic action of melatonin treatment has been observed in essentially all experimental studies. Regardless of the manner of pain induction, i.e., electrical [34, 46], mechanical [35, 36], thermal [38, 39, 41, 45, 47] or chemical [32, 40, 43–45, 49], a significant analgesic action of melatonin was noted. The route of administration of melatonin is irrelevant in reference to its analgesic actions. Melatonin has been found effective after i.t. [33, 34, 48] i.p. [38–41, 43, 46, 47], icv. [5, 38–41, 47], sc. [45, 49] or iv. [35, 36] administration. Melatonin exhibits a clear dose-dependent analgesic action in animals. This effect occurs irrespective of route of administration in several of the pain models used [5, 32–47, 49, 58–61].

The exact mechanistic pathway by which melatonin exerts its analgesic actions remains to be clarified. A variety of mechanisms have been proposed: via GABA receptors [62], β-endorphins [39], opioid μ-receptors [5, 41] and the NO-arginine pathway [38]. Both GABA-B receptors, opiate receptors and melatonin membrane receptors are G_i-protein coupled and reduce the concentration of the second messenger cAMP upon stimulation [63–65]. GABA-B receptor agonists have been shown to have analgesic properties [66, 67]. This is interesting because melatonin exhibits significant anxiolytic and analgesic effects in humans as well as in experimental studies. Thus, it could be that at the molecular/cellular level, melatonin functions in the modulation of opioids and GABA-B receptors via presently unknown intracellular changes downstream of the common second messenger, cAMP.

The majority of conditions where the analgesic properties of melatonin have been investigated in patients with chronic

pain are well-known clinical syndromes. These syndromes are characterized by the presence of a variety of different symptoms, which may have very different underlying mechanisms in their development. Thus, it is often impossible to outline a plausible pathophysiologic connection between symptoms and effectors.

Most studies have shown a significant analgesic effect of melatonin when used to treat chronic pain. Two studies in FM [15, 50] and two studies regarding IBS [26, 27] have been published. The shortest duration of treatment in which melatonin was shown to be beneficial was 2 wk [27]. Pain was reported to be significantly inhibited in all studies [26, 27, 54, 68] except one [15]; in the latter, there was only a slight (nonsignificant) reduction in pain. The tender points and severity of pain, however, were reduced in FM with melatonin treatment alone and when combined with flouxetine [15, 50]. Anxiety levels remained unchanged [26, 27] except in one study where they increased [15]. Sleep improved in two studies [15, 68] and did not change significantly in the remaining two [26, 27]. The degree to which patients felt depressed was unchanged [26, 27] or improved insignificantly [15, 50]. In conclusion, these reports document that patients suffering from FM or IBS may experience an analgesic effect and overall improvement with melatonin therapy. It is hypothesized that this benefit, at least in part, may be a result of the hypnotic and anxiolytic effects of melatonin, although one study in IBS patients showed that the alleviation of abdominal pain was without effect on sleep and anxiety [53]. While the general tendency in these clinical trials points towards benefits of melatonin therapy, further randomized controlled trials are necessary. This is especially true for IBS where larger sample sizes are required.

Patients who suffer from migraine have similarly experienced a positive effect of melatonin therapy [29, 56], although there only is one controlled clinical trial to support this. An open-labelled trial claimed that melatonin was useful as prophylaxis in patients suffering from migraine headaches [56]. A larger controlled clinical trial should be performed to establish whether melatonin has analgesic and prophylactic effects in migraine. An analgesic action of melatonin in status migrainosus can also be obtained. Thus, an early study found that one infusion relieved the pain in four of six patients participating in the trial, two infusions also relieved four of six patients while three infusions reduced the pain in all [29].

Sugden [69] reported a potential for motor-incoordination when using melatonin in high doses in experimental studies. This is a possible confounder of the results in studies where motor responses to analgesia have been studied. This potential side effect has been noted in several of the studies reported, but not found to play a role, which supports the safe use of melatonin [38, 40, 43, 44, 70]. In clinical studies, no side effects have been observed [26, 27, 31] and melatonin is reported to have an excellent safety profile [31, 71]. A randomized, double-blind, placebo-controlled study assessed the toxicology of chronic melatonin treatment [71]. Thirty male volunteers were given 10 mg melatonin once a day for 28 days and ten were given placebo. The volunteers were monitored by laboratory examinations, Epworth Somnolence Scale, sleep diary, polysomnography (PSG) and serum melatonin levels. A six-fold rise in serum melatonin concentrations of the melatonin group was seen throughout the study compared to the placebo group. The laboratory examinations remained within the normal range for both groups during the entire study. The melatonin reported side effects including somnolence and headache, yet these symptoms were also reported in the placebo group, and no significant difference was calculated. The PSG revealed that the volunteers of the melatonin group had a more consolidated sleep and that the sleep latency was decreased compared to the placebo group. In conclusion, the study did not find any toxicological effect that might compromise the use of melatonin [71].

Although the available data are encouraging, there are several issues that require further clarification before melatonin can be recommended as an analgesic for routine use in chronic pain syndromes in adults such as FM, IBS and migraine. The mechanisms should be investigated in humans, and more information relating to the effective doses is required. It is important that further studies clarify these issues because melatonin, with its high safety profile, represents an interesting analgesic alternative or add-on to existing analgesic regimens.

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