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CHAPTER 22

POOR SLEEP QUALITY, CHRONIC PAIN, AND MELATONIN

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ABSTRACT

Objective: Considering that inflammatory responses affect the nocturnal peak of melatonin and that sleep interruption activates inflammatory mechanisms that trigger changes in the effector systems that regulate the immune system, increasing the inflammatory response and pain, this study investigates the efficacy of melatonin as a treatment for the symptoms of the poor sleep quality and pain in the endometriosis. **Methods:** Endometriosis was diagnosed by medical history and imaging tests (ultrasound or magnetic resonance imaging). Pain intensity was assessed using a visual analogue scale (VAS). Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI) questionnaire. Patients were treated with exogenous melatonin and signs of inflammation were assessed before and after treatment. **Results:** There was an improvement in sleep quality with melatonin compared with the placebo group, with no evidence of side effects. The dose of 3g exogenous melatonin was not effective for the symptom of pain. **Conclusion:** The poor sleep quality associated with the inflammatory state of endometriosis was controlled by the exogenous use of melatonin, reinforcing the role of sleep induction in conditions associated with chronic inflammation. However, melatonin was not effective in the pain state during treatment. The mechanisms involved in the modulation of pain in relation to the functional mechanisms of melatonin should be further investigated.

Keywords: Circadian rhythms. Pain. Melatonin. Sleep. Endometriosis.

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INTRODUCTION

The relationship between pain and sleep symptoms in chronic conditions has been described as bidirectional. Pain symptoms can disrupt sleep patterns, which in turn modulate pain thresholds (Afolalu et al., 2018). Hyperalgesia and increased spontaneous pain symptoms, such as muscle pain and headache, have also been associated with episodes of short or disturbed sleep (Finan et al., 2013). Despite this, little is known about the neurochemical mechanisms involved in this reciprocal relationship (Afolalu et al., 2018).

The neurobiological mechanisms of pain are thought to involve neuronal and non-neuronal components from a variety of systems, including opioids, monoaminergic, immunological, melatonin and endocannabinoids; the hypothalamic-pituitary-adrenal axis; and adenosine and nitric oxide signalling, among others (Woolf, 2004).

In chronic conditions, such as the inflammatory disease endometriosis, a variety of symptoms are observed, including chronic pelvic pain, poor sleep quality, dysmenorrhoea, dyspareunia and infertility (Florentino et al., 2019).

Several inflammatory molecules are responsible for both the onset of endometriosis and associated symptoms such as pain and infertility (Ishikura et al, 2020; Ribeiro et al, 2021). The presence of macrophages, interleukins IL-1, IL-2, IL-6, IL-8, tumour necrosis factor (TNF-α) and other immune cells such as B lymphocytes have identified endometriosis as an immune-mediated inflammatory disease (Arreola-Espino et al., 2007; El-Shenawy et al., 2002).

Melatonin, a sleep-inducing neurohormone with anti-inflammatory properties, is an important temporal and immunological marker for the body, capable of modulating several rhythmic effects (Simonneaux and Ribelayga, 2003). It also has many actions associated with anti-inflammatory, analgesic and sleep-promoting effects (Hardeland et al, 2011).

The mechanism of action of melatonin has been studied and investigated in several processes such as the regulation of sleep, mood, anxiety, thermogenesis, appetite, metabolism, immune responses, cardiovascular functions and other endocrine functions (Arendt and Skene, 2005; Chai et al., 2013; Scheer et al., 2009; Xia et al., 2008).

The mechanisms involved in the analgesic properties of melatonin are not fully understood, but appear to involve endorphins, the GABA receptor, opioid receptors and the nitric oxide-arginine pathway (Chen et al, 2016).

In conditions where levels of inflammatory mediators are elevated, such as interleukin-1 (IL-1) and tumour necrosis factor alpha (TNF-alpha), the properties of endogenous melatonin are affected by blockade of a number of biochemical processes

(Simonneaux and Ribelayga, 2013; 2003). Thus, melatonin production by the pineal gland is inhibited during the acute phase of an inflammatory response (Pontes et al., 2006).

Endometriosis, being an immune-mediated inflammatory disease, may possibly alter the nature of melatonin, leading to the onset of sleep disorders as seen in these patients (Ishikura et al., 2020).

In sleep disorders such as insomnia and circadian rhythm sleep disorder, exogenous melatonin appears to have a beneficial effect. Sleep improvement can be observed by reducing sleep onset latency or regulating sleep-wake times (Auld et al., 2017; Reiter, 1991).

In chronic pain conditions such as fibromyalgia and irritable bowel syndrome, exogenous melatonin administration has shown positive results in reducing subjective pain and improving endogenous pain prevention in fibromyalgia (de Zanette et al., 2014).

As the beneficial effects of exogenous melatonin are well documented in the literature (Reiter, 1991), this study investigated the use of exogenous melatonin to improve sleep quality and pain in patients with endometriosis.

MATERIAL AND METHODS

SETTING AND SAMPLE

This project is a randomized, double-blind, placebo-controlled clinical trial investigation involving 16 women of reproductive age, aged between 18 and 45 years, diagnosed with endometriosis. Inclusion criteria were with characteristic signs of endometriosis based on clinical condition and changes on imaging tests such as transvaginal ultrasound or pelvic magnetic resonance imaging. Women without a complete diagnosis or using beta-blockers, medications that interfere with melatonin production, or sedative-hypnotics were excluded. The recommendations of the National Health Council Resolution (CNS 466/2012) on guidelines and regulatory standards for research involving human subjects were followed, and the study was approved by the Research Ethics Committee (CEP 5.729.149). The study was carried out at the Center for Medical Specialties. The participants underwent a clinical evaluation and were informed about the development and participation in the research.

THE VISUAL ANALOGUE SCALE (VAS) AND SLEEP QUALITY

The VAS scale was used to measure the intensity of pain in each patient, with values ranging from 0 (no pain) to 10 (pain). Parameters characterising the quality of sleep were obtained by applying a sleep questionnaire - the Pittsburgh Sleep Quality Index (PSQI)

(Buysse et al., 1989). The PSQI consists of seven questions: sleep quality, time to sleep onset, sleep efficiency, sleep disturbances, hypnotic use and daytime dysfunction. Each sub-item is worth 3 points, and a score > 7 can be considered to indicate the presence of a sleep disorder. The higher the score, the more severe the sleep disorder.

MELATONIN TREATMENT

Exogenous melatonin at a dose of 3 mg or placebo was added to the treatment of endometriosis, given regularly as a single dose one hour before bedtime for one month. Melatonin was given in tablet form. The participants were divided into two analysis groups, a sample group treated with exogenous melatonin 3 mg and a comparison group treated with placebo.

ANALYSIS OF RESULTS

Results were expressed as mean ± standard deviation (SD) and analysed using appropriate statistical methods. Comparison of means was performed using Student's t-test.

RESULTS

ANALYSIS OF VAS AND SLEEP QUALITY – PSQI

The VAS was used before and after treatment with melatonin. The results highlighted patients with pain complaints between levels 7 and 10, considered high by the VAS. At the end of treatment, there were no significant differences between melatonin and placebo. This suggests ineffectiveness in the use of melatonin (dose of 3 mg) for pain control (Table 1 - Melatonin and placebo - VAS; Graph 1).

Patients were given the PSQI sleep questionnaire before and after melatonin treatment. Initial results prior to melatonin treatment showed recurrent complaints of quality of sleep, with a global score greater than 7, which is considered an indicator of poor sleep quality by the sleep questionnaire used. Comparative data are presented below (Table 1 – Melatonin and Placebo – PSQI). The data suggest a beneficial effect of using melatonin in the improve sleep quality in endometriosis.

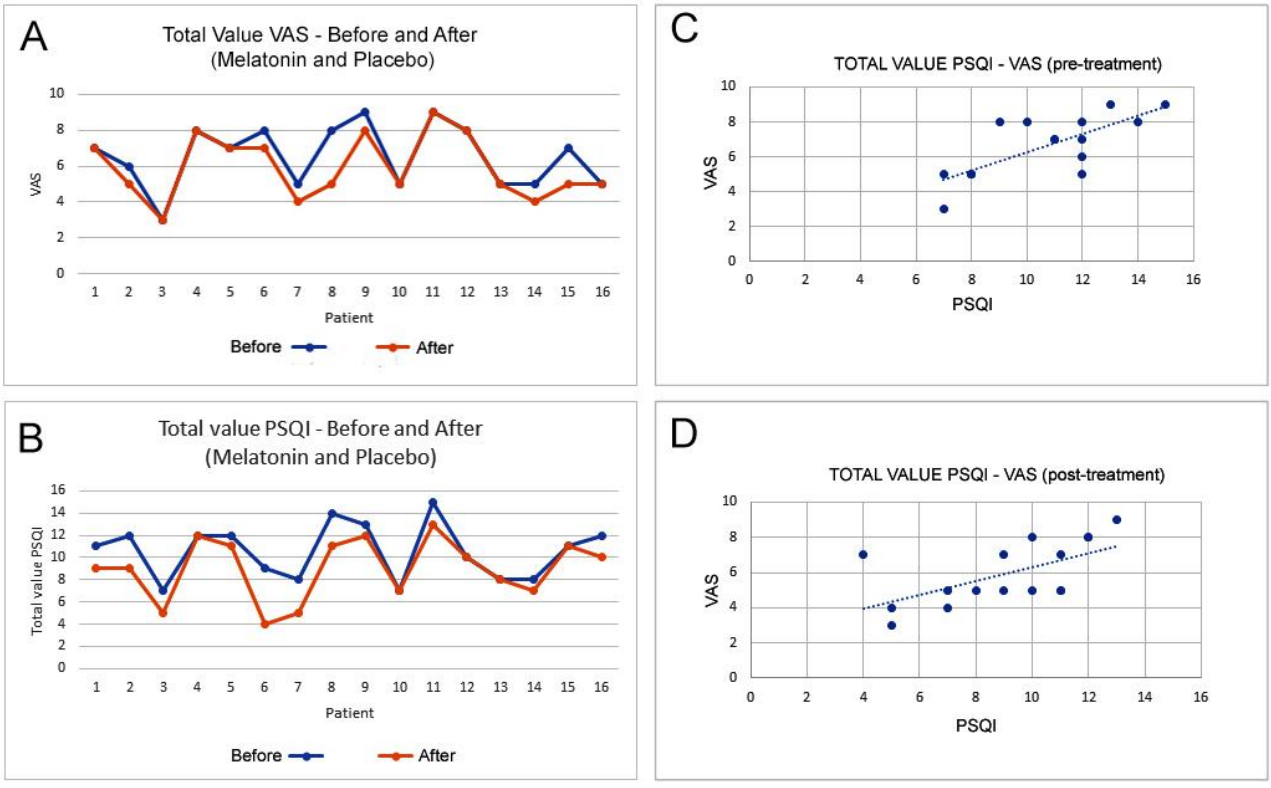
Table 1. PSQI and VAS - before and after melatonin treatment

	VISUAL ANALOGUE SCALE				PITTSBURGH QUALITY INDEX			
	MELATONIN (VAS)		PLACEBO (VAS)		MELATONIN (PSQI)		PLACEBO (PSQI)	
PATIENT	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER
1	7	7	9	8	11	9	13	12
2	6	5	5	5	12	9	7	7
3	3	3	9	9	7	5	15	13
4	8	8	8	8	12	12	10	10
5	7	7	5	5	12	11	8	8
6	8	7	5	4	9	4	8	7
7	5	4	7	5	8	5	11	11
8	8	5	5	5	14	11	12	10
Mean ± dp	6,50 ± 1,77	5,75 ± 1,75	6,63 ± 1,85	6,13 ± 1,89	10,63 ± 2,39	8,25 ± 3,15	10,50 ± 2,78	9,75 ± 2,25

Comparison between the melatonin and placebo groups highlighting the differences in VAS scores before and after melatonin treatment. In the VAS analysis, according to Student's T-test at 5% a significance level, there was no significant difference in any of the comparisons, namely: before and after melatonin use (p=0.080), before and after placebo use (p=0.104), between melatonin and placebo use before treatment (p=0.912), and between melatonin and placebo use after treatment (p=0.703). When analyzing the total PSQI score, there was a significant difference between the pre- and post-treatment PSQI scores according to Student's T-test at 5% significance level (p=0.003). There was also a significant difference between the pre- and post-treatment scores (p=0.047), but a smaller difference. However, there were no significant differences between the use of melatonin and placebo before treatment (p=0.936) and after treatment (p=0.336).

When comparing the VAS and sleep questionnaires of the selected patients, there was a greater spread after treatment due to the improvement in sleep quality with the use of melatonin (Figures 1 – A, B, C, D). The data are presented below in a line graph for better visualization of before and after the use of melatonin and placebo for each patient.

Figure 1. PSQI and VAS - before and after melatonin treatment



Comparison of total VAS and PSQI between the melatonin and placebo groups. In graph A, the horizontal bar shows the patients (1 to 8 who took melatonin and 9 to 16 who took placebo) and the vertical bar shows the VAS, where it can be seen that in most patients there was no or little difference in VAS between before and after treatment with either melatonin or placebo. In graph B, the horizontal bar shows the patients (1 to 8 who used melatonin and 9 to 16 who used placebo) and the vertical bar shows the total PSQI score, where

it can be seen that there were reductions in PSQI scores mainly in patients treated with melatonin, while those treated with placebo showed a smaller reduction. Graph C shows the dispersion of the data on the relationship between the total PSQI score and the pre-treatment VAS. Graph D shows the dispersion of the data for the relationship between the total PSQI score and the post-treatment VAS.

CONCLUSIONS

This study evaluated the pathological condition of endometriosis in patients treated with exogenous melatonin for 30 days. We observed an improvement in sleep quality without side effects after the use of 3 mg of melatonin per day compared to the placebo group. These data may confirm the importance of melatonin in inflammatory conditions and promote its sleep-inducing role (Simonneaux and Ribelayga, 2003).

As for the symptom of pain associated with endometriosis, no significant improvement was observed. We suspect that this is due to the timing and dosage of melatonin used, which may need to be higher.

Classically, sleep disruption activates inflammatory mechanisms that trigger changes in the effector systems that regulate the immune system, increasing the inflammatory response and leading to increased pain (Ishikura et al, 2020).

In chronic inflammatory conditions such as fibromyalgia (Citera et al., 2000), patients who received melatonin during treatment showed an improvement in symptoms compared with the placebo group. Possibly, because melatonin exerts its antioxidant and immunomodulatory effects, and its results can be seen in different physiological and pathological situations (Reiter, 1998).

In neurodegenerative conditions, such as those seen in patients with moderate and severe Alzheimer's disease, the use of melatonin up to 10 mg has not shown improvement in sleep disturbances (McCleery et al, 2016).

Patients with endometriosis treated with 10 mg melatonin for 8 weeks showed an improvement in the inflammatory state as well as an improvement in sleep quality. In terms of pain symptoms, a 39.80% reduction in daily pain scores was observed. Regardless of the dose used, this supplement does not appear to have any adverse effects or toxicity. (Schwertner et al, 2013).

However, this change in timing and dose does not appear to be crucial, as the use of 10 mg for 3 months and 20 mg for 2 consecutive months in other groups of women with pain associated with endometriosis and dysmenorrhoea did not control the presence of pain (Soderman et al 2022).

Studies investigating chronic inflammation have observed that melatonin administration in animals attenuated the development of neuropathic pain after nerve injury, demonstrating that the melatonin system represents another potential mechanism for pain

in the absence of poor sleep (Citera et al., 2000; Mozaffari et al., 2010; de Zanette et al., 2014).

Although several studies have demonstrated the effects of melatonin on inflammatory processes, little is known about the mechanisms involved (Cuzzocrea and Reiter, 2002; Haack et al., 2020; Reiter, 1991; Reiter, 1998).

Since inflammatory responses affect the nocturnal melatonin peak, and sleep disturbance activates inflammatory mechanisms (Greco et al., 2024), exogenous melatonin administration may have affected circulating melatonin levels and consequently induced improvements in overall sleep patterns. However, the mechanisms involved in pain modulation and the pathways associated with the functional mechanisms of melatonin deserve further investigation.

PUBLIC SIGNIFICANCE STATEMENT

This research demonstrates the use of melatonin as a treatment for signs of poor sleep quality and chronic pain in the inflammatory state of endometriosis. The role of melatonin as a sleep inducer was reinforced and the patients sleep quality was restored. Melatonin was not effective for pain relief. The functional mechanisms of melatonin for pain control should be further investigated.

ETHICS STATEMENT

The recommendations of the National Health Council Resolution (CNS 466/2012) on guidelines and regulatory standards for research involving human subjects were followed, and the study was approved by the Research Ethics Committee (CEP 5.729.149).

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

CONTRIBUTION OF EACH AUTHOR NAMED IN THE ARTICLE SUBMITTED FOR PUBLICATION

- LMGC; SLM: Data collection, formal analysis, preparation of the original draft, writing – review and editing (equal).
- VCEA; dEVBS; GHAKG; APNG; CMA: methodology, formal analysis.
- LMGC: conceptualization, project administration, resources, supervision (lead), writing – review and editing (equal).

DATA AVAILABILITY STATEMENT

The data and all supplementary materials associated with this article are available on request from can be obtained from the corresponding author on request.

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REFERENCES

1. Afolalu, E. F., Ramlee, F., & Tang, N. K. Y. (2018). Effects of sleep changes on pain-related health outcomes in the general population: A systematic review of longitudinal studies with exploratory meta-analysis. Sleep Medicine Reviews, 39, 82–97. https://doi.org/10.1016/j.smrv.2017.08.001

2. Arendt, J., & Skene, D. J. (2005). Melatonin as a chronobiotic. Sleep Medicine Reviews, 9(1), 25–39. https://doi.org/10.1016/j.smrv.2004.05.002

3. Arreola-Espino, R., Urquiza-Marin, H., Ambriz-Tututi, M., Araiza-Saldana, C. I., Caram-Salas, N. L., Rocha-Gonzalez, H. I., Mixcoatl-Zecuatl, T., & Granados-Soto, V. (2007). Melatonin reduces formalin-induced nociception and tactile allodynia in diabetic rats. European Journal of Pharmacology, 577(1–3), 203–210. https://doi.org/10.1016/j.ejphar.2007.09.006

4. Auld, F., Maschauer, E. L., Morrison, I., Skene, D. J., & Riha, R. L. (2017). Evidence for the efficacy of melatonin in the treatment of primary adult sleep disorders. Sleep Medicine Reviews, 34, 10–22. https://doi.org/10.1016/j.smrv.2016.06.005

5. Buysse, D. J., Reynolds, C. F., Monk, T. H., Berman, S. R., & Kupfer, D. J. (1989). The Pittsburgh Sleep Quality Index: A new instrument for psychiatric practice and research. Psychiatry Research, 28(2), 193–213. https://doi.org/10.1016/0165-1781(89)90047-4

6. Chai, K., Liu, X., Zhang, Y., & Lin, H. (2013). Day-night and reproductive cycle profiles of melatonin receptor, kiss, and gnrh expression in orange-spotted grouper (Epinephelus coioides). Molecular Reproduction & Development, 80(7), 535–548. https://doi.org/10.1002/mrd.22191

7. Chen, W. W., Zhang, X., & Huang, W. J. (2016). Pain control by melatonin: Physiological and pharmacological effects. Experimental and Therapeutic Medicine, 12(4), 1963–1968. https://doi.org/10.3892/etm.2016.3565

8. Citera, G., Arias, M. A., & Maldonado-Cocco, J. A. (2000). The effect of melatonin in patients with fibromyalgia: A pilot study. Clinical Rheumatology, 19(1), 9–13. https://doi.org/10.1007/s100670050003

9. Cuzzocrea, S., & Reiter, R. J. (2002). Pharmacological actions of melatonin in acute and chronic inflammation. Current Topics in Medicinal Chemistry, 2(2), 153–165. https://doi.org/10.2174/1568026023394425

10. de Zanette, S. A., Vercelino, R., Laste, G., Rozisky, J. R., Schwertner, A., Machado, C. B., et al. (2014). Melatonin analgesia is associated with improvement of the descending endogenous pain-modulating system in fibromyalgia: A phase II, randomized, double-dummy, controlled trial. BMC Pharmacology & Toxicology, 15, Article 40. https://doi.org/10.1186/2050-6511-15-40

11. El-Shenawy, S. M., Abdel-Salam, O. M., Baiuomy, A. R., El-Batran, S., & Arbid, M. S. (2002). Studies on the anti-inflammatory and anti-nociceptive effects of melatonin in the rat. Pharmacological Research, 46(3), 235–243. https://doi.org/10.1016/s1043-6618(02)00094-4

12. Finan, P. H., Goodin, B. R., & Smith, M. T. (2013). The association of sleep and pain: An update and a path forward. The Journal of Pain, 14(12), 1539–1552. https://doi.org/10.1016/j.jpain.2013.08.007

13. Florentino, A. V. A., Pereira, A. M. G., Martins, J. A., Lopes, R. G. C., & Arruda, R. M. (2019). Quality of life assessment by the Endometriosis Health Profile (EHP-30) questionnaire prior to treatment for ovarian endometriosis in Brazilian women. Revista Brasileira de Ginecologia e Obstetrícia, 41(9), 548–554. https://doi.org/10.1055/s-0039-1693057

14. Greco, G., Di Lorenzo, R., Ricci, L., Di Serio, T., Vardaro, E., & Laneri, S. (2024). Clinical studies using topical melatonin. International Journal of Molecular Sciences, 25(10), 5167. https://doi.org/10.3390/ijms25105167

15. Hardeland, R., Cardinali, D. P., Srinivasan, V., Spence, D. W., Brown, G. M., & Pandi-Perumal, S. R. (2011). Melatonin: A pleiotropic, orchestrating regulator molecule. Progress in Neurobiology, 93(3), 350–384. https://doi.org/10.1016/j.pneurobio.2010.12.004

16. Haack, M., Simpson, N., Sethna, N., Kaur, S., & Mullington, J. (2020). Sleep deficiency and chronic pain: Potential underlying mechanisms and clinical implications. Neuropsychopharmacology, 45(1), 205–216. https://doi.org/10.1038/s41386-019-0439-z

17. Ishikura, I. A., Hachul, H., Pires, G. N., Tufik, S., & Andersen, M. L. (2020). The relationship between insomnia and endometriosis. Journal of Clinical Sleep Medicine, 16(8), 1387–1388. https://doi.org/10.5664/jcsm.8464

18. McCleery, J., Cohen, D. A., & Sharpley, A. L. (2016). Pharmacotherapies for sleep disturbances in dementia. Cochrane Database of Systematic Reviews, 11, CD009178. https://doi.org/10.1002/14651858.CD009178.pub3

19. Mozaffari, S., Rahimi, R., & Abdollahi, M. (2010). Implications of melatonin therapy in irritable bowel syndrome: A systematic review. Current Pharmaceutical Design, 16(33), 3646–3655. https://doi.org/10.2174/138161210794079254

20.

21. Reiter, R. J. (1991). Pineal melatonin: Cell biology of its synthesis and of its physiological interactions. Endocrine Reviews, 12(2), 151–180. https://doi.org/10.1210/edrv-12-2-151

22. Reiter, R. J. (1998). Oxidative damage in the central nervous system: Protection by melatonin. Progress in Neurobiology, 56(3), 359–384.

23. Ribeiro, H. S. A. A. et al. (2021). Psychological problems experienced by patients with bowel endometriosis awaiting surgery. Revista Brasileira de Ginecologia e Obstetrícia, 43(9), 676–681. https://doi.org/10.1055/s-0041-1735938

24. Scheer, F.A., Hilton, M.F., Mantzoros, C.S., Shea, S.A. (2009). Adverse metabolic and cardiovascular consequences of circadian misalignment. Proceedings of the National Academy of the Sciences. U S A. 106(11), 4453-4458. doi: 10.1073/pnas.0808180106.

25. Simonneaux, V., Ribelayga, C. (2003). Generation of the melatonin endocrine message in mammals: a review of the complex regulation of melatonin synthesis by norepinephrine, peptides, and other pineal transmitters. Pharmacological Reviews. 55 (2), 325-395. https://doi.org/ 10.1124/pr.55.2.2.

26. Schwertner, A. et al. (2013). Efficacy of melatonin in the treatment of endometriosis: a phase II, randomized, double-blind, placebo-controlled trial. Pain. 154(6), 874-881. https://doi.org/ 10.1016/j.pain.2013.02.025.

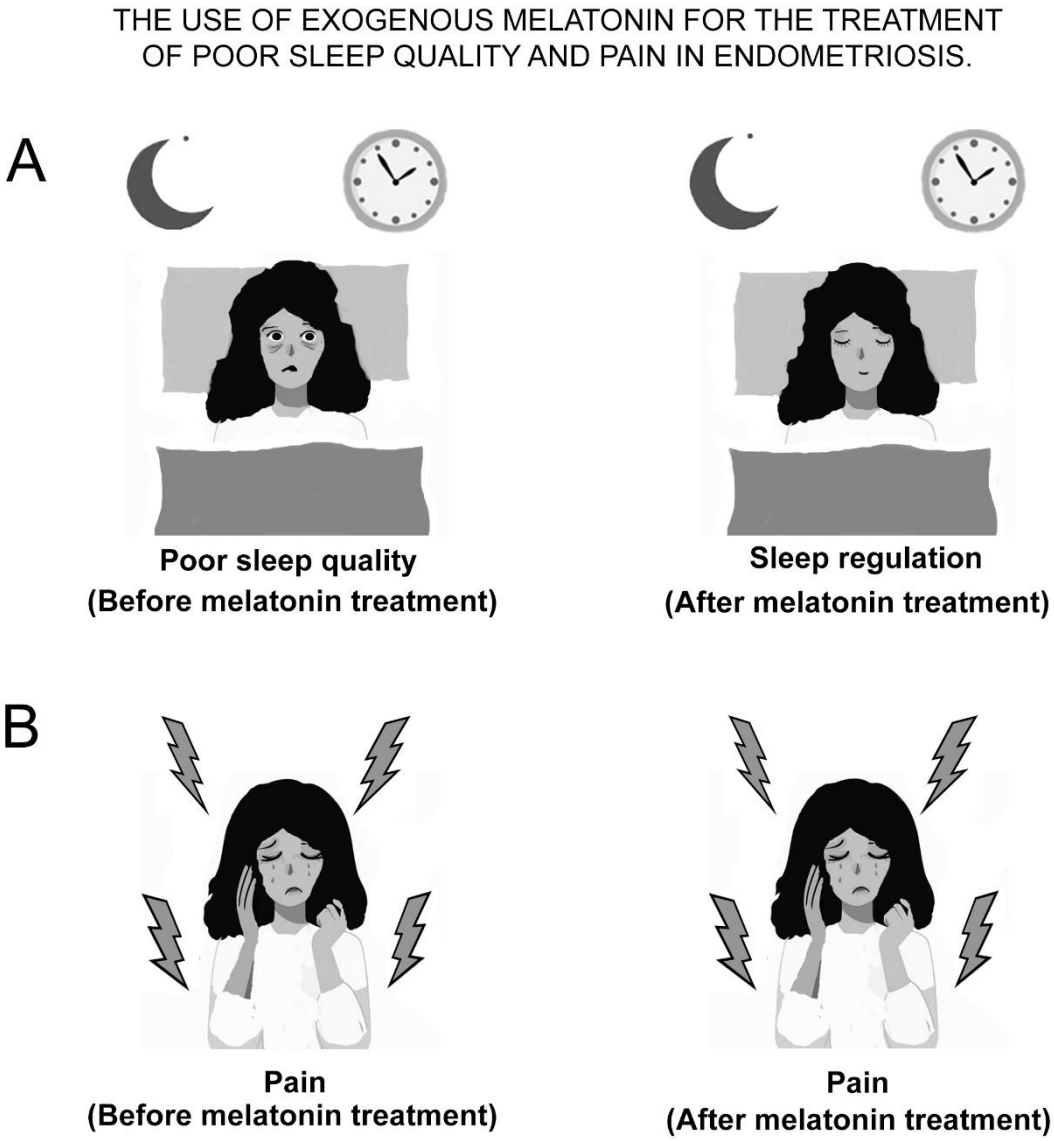
27. Soderman, L., Böttiger, Y., Edlund, M., Järnbert-Pettersson, H., Marions, L. (2022). Adjuvant use of melatonina for pain management in dysmenorrhea – a randomized double-blinded, placebo-controlled trial. European journal of clinical pharmacology. 78(6), 191-196. https://doi.org/ 10.1371/journal.pone.0286182.

28. Woolf, C.J. (2004). Pain: Moving from symptom control toward mechanism-specific pharmacologic management. Annals of Internal Medicine. 140(6), 441–451. https:// doi: 10.7326/0003-4819-140-8-200404200-00010.

29. Xia, C.M., Shao, C.H., Xin, L., Wang, Y.R., Ding, C.N., Wang, J. (2008). Effects of melatonin on blood pressure in stress-induced hypertension in rats. Clinical and Experimental Pharmacology & Physiology. 35(10), 1258-1264.

ATTACHMENTS

GRAPHICAL ABSTRACT



Graphical abstract: A and B are illustrative drawings of patients with endometriosis. In A it shows the quality of sleep before and after treatment with melatonin, indicating an effective result after treatment. In B, it shows the presence of pain before and after treatment with melatonin. Melatonin was not effective in treating the pain.