

Melatonin: Adjunctive, non-opioid for chronic musculoskeletal pain?

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Chronic musculoskeletal pain affects millions across Europe, often leading to significant disability and a reliance on analgesics with considerable side effect profiles. Current management strategies frequently fall short, leaving many patients with persistent discomfort and impaired quality of life. The search for effective, well-tolerated alternatives continues to drive research.

New evidence indicates melatonin, a hormone primarily associated with circadian rhythm regulation, may offer a novel approach to managing chronic muscle and joint pain. This finding presents a potential non-opioid therapeutic avenue for a patient population in desperate need of better options.

KEY TAKEAWAYS

- ° The Pivot: Melatonin, traditionally viewed as a sleep aid, demonstrates analgesic properties for chronic musculoskeletal pain.
- ° The Data: Patients receiving melatonin reported a mean reduction in pain scores of 2.5 points on a 0-10 VAS scale, compared to 0.8 points for placebo.
- ° The Action: Clinicians might consider melatonin as an adjunctive therapy for chronic musculoskeletal pain, particularly in patients with comorbid sleep disturbances.

Chronic musculoskeletal pain represents a pervasive and debilitating condition, impacting an estimated 20% of the adult population in Europe. This persistent discomfort, often stemming from conditions like osteoarthritis, fibromyalgia, or chronic low back pain, exacts a heavy toll on individuals and healthcare systems. Existing pharmacological interventions, ranging from non-steroidal anti-inflammatory drugs (NSAIDs) to opioids, frequently carry substantial risks, including gastrointestinal bleeding, cardiovascular events, and the well-documented dangers of addiction and overdose. The clinical community has long sought therapies that can effectively reduce pain without introducing these severe liabilities, particularly for long-term management.

Melatonin, an endogenous neurohormone produced primarily by the pineal gland, plays a central role in regulating sleep-wake cycles. Its secretion increases in the evening, signalling the body's preparation for sleep. Beyond its chronobiotic effects, melatonin also exhibits potent antioxidant, anti-inflammatory, and immunomodulatory properties. These broader biological actions have led investigators to explore its potential in various conditions, including pain management. The hypothesis driving this line of inquiry posits that melatonin's anti-inflammatory and analgesic effects, possibly mediated through its interaction with specific receptors (MT1 and MT2) and its free radical scavenging

capabilities, could mitigate chronic pain pathways. This mechanism differs significantly from conventional analgesics, offering a distinct therapeutic angle.

What the trial actually measured

A recent meta-analysis, synthesizing data from multiple randomised controlled trials, examined the efficacy and safety of melatonin in patients with chronic musculoskeletal pain. The patient populations across these trials included individuals diagnosed with fibromyalgia, osteoarthritis, chronic low back pain, and temporomandibular joint disorders. Most studies enrolled adults over 18 years of age, with a mean age ranging from 45 to 68 years, reflecting the typical demographic affected by these chronic conditions. The primary endpoint across the included trials was a reduction in pain intensity, typically measured using a Visual Analogue Scale (VAS) or Numeric Rating Scale (NRS) over a follow-up period ranging from 4 to 24 weeks. Secondary endpoints often included improvements in sleep quality, functional status, and quality of life, alongside an assessment of adverse events.

The pooled analysis revealed that melatonin significantly reduced pain intensity compared with placebo. Patients receiving melatonin reported a mean reduction in pain scores of 2.5 points (95% CI, 1.8-3.2; $P<.001$) on a 0-10 VAS scale, compared to a mean reduction of 0.8 points (95% CI, 0.4-1.2; $P=.003$) for those on placebo. This difference translates to a clinically meaningful improvement for many patients, particularly given the often refractory nature of chronic musculoskeletal pain. The effect size, while modest, is comparable to or exceeds that seen with some non-opioid pharmacological interventions currently in use. The number needed to treat (NNT) for a 30% pain reduction was approximately 5, indicating that for every five patients treated with melatonin, one additional patient achieved a clinically relevant pain reduction compared to placebo.

Melatonin's impact extended beyond pain reduction. The analysis also showed improvements in sleep quality, a common comorbidity in chronic pain patients. Participants on melatonin reported a mean improvement of 1.2 points (95% CI, 0.7-1.7; $P<.001$) on a 0-10 sleep quality scale, whereas placebo recipients showed only a 0.3-point improvement (95% CI, -0.1-0.7; $P=.15$). This dual benefit, addressing both pain and sleep, is particularly relevant given the bidirectional relationship between these two symptoms; poor sleep often exacerbates pain, and vice versa. The doses of melatonin used in the trials varied, typically ranging from 3 mg to 10 mg taken orally at bedtime. No significant dose-response relationship was definitively established across the included studies, suggesting that even lower doses may confer benefit.

Safety data from the meta-analysis indicated melatonin was generally well-tolerated. The incidence of adverse events was comparable between the melatonin and placebo groups. The most commonly reported side effects were mild and transient, including drowsiness, dizziness, and headache. These events occurred in 12% of melatonin-treated patients (95% CI, 9-15%) compared to 10% of placebo-treated patients (95% CI, 7-13%), with no statistically significant difference ($P=.21$). No serious adverse events were attributed to melatonin in any of the included trials. This favourable safety profile stands in stark contrast to many conventional pain medications, which often carry a higher burden of severe or dose-limiting side effects, making melatonin an attractive option for long-term use.

The individual trials contributing to this meta-analysis employed various methodologies, including double-blind, placebo-controlled designs, which strengthen the overall evidence. However, heterogeneity existed in patient populations, specific pain conditions studied, and duration of treatment. For example, some trials focused exclusively on fibromyalgia, a condition known for its widespread pain and sleep disturbances, while others included patients with

more localised joint pain. This variability, while reflecting real-world clinical diversity, also introduces some complexity in interpreting the generalisability of the findings. The duration of follow-up, ranging from 4 to 24 weeks, means that long-term efficacy and safety beyond six months remain less thoroughly investigated. While the NNT of 5 for a 30% pain reduction is encouraging, it also means that a substantial proportion of patients may not achieve this threshold of improvement. Clinicians must manage patient expectations accordingly.

The mechanism by which melatonin exerts its analgesic effects is likely multifactorial. Beyond its direct anti-inflammatory and antioxidant actions, melatonin may modulate pain perception through its influence on central nervous system pathways. It interacts with opioid receptors, albeit indirectly, and can influence neurotransmitter systems involved in pain processing, such as gamma-aminobutyric acid (GABA) and serotonin. Its role in regulating circadian rhythms also cannot be overlooked; by improving sleep, melatonin may indirectly reduce pain sensitivity and improve coping mechanisms. This complex interplay of effects suggests melatonin is not merely a sedative but a pleiotropic agent with broad physiological impacts relevant to chronic pain states. Further research is needed to fully elucidate these intricate mechanisms and identify specific patient phenotypes most likely to respond to melatonin therapy.

The open-label design of some smaller trials included in the meta-analysis is an obvious caveat. While the larger, double-blind studies provide robust data, the inclusion of less rigorously designed trials could introduce bias. The meta-analysis did attempt to account for this by conducting sensitivity analyses, which generally confirmed the overall findings. Still, the lack of standardisation in melatonin formulations and delivery methods across studies also presents a limitation. Melatonin is available in various forms, including immediate-release and extended-release preparations, which may have different pharmacokinetic profiles and, consequently, different clinical effects. Future research should aim for greater uniformity in these aspects to allow for more direct comparisons and clearer guidance on optimal dosing strategies.

The trial was not powered to detect differences in specific pain etiologies, and that gap matters. While the overall effect on musculoskeletal pain was positive, it is unclear whether melatonin is equally effective for neuropathic pain, inflammatory arthritis, or mechanical back pain. Subgroup analyses, where performed, were often underpowered, preventing definitive conclusions about differential efficacy. This means clinicians currently lack precise guidance on which specific chronic pain populations might benefit most. Future, larger trials should focus on specific pain conditions to provide more granular data. Furthermore, the interaction of melatonin with other pain medications was not a primary focus, leaving questions about its role as an add-on therapy versus a monotherapy in complex pain regimens. The potential for drug-drug interactions, particularly with central nervous system depressants, warrants careful consideration in clinical practice.

CLINICAL IMPLICATIONS

The data on melatonin for chronic musculoskeletal pain offers a compelling argument for its inclusion in the therapeutic armamentarium, particularly given the current opioid crisis and the limitations of existing non-opioid options. Clinicians should view this not as a standalone cure, but as a valuable adjunctive therapy. Its favourable safety profile and potential to improve comorbid sleep disturbances make it an attractive option for patients who have exhausted other avenues or are seeking to reduce reliance on more problematic medications.

The modest effect size, while clinically meaningful, means melatonin will not be a panacea. It is unlikely to

replace primary analgesics for severe pain, but it could significantly contribute to overall pain management, especially in patients with moderate chronic pain or those with a strong sleep component to their discomfort. The low risk of adverse events makes a trial of melatonin a reasonable step before escalating to therapies with greater side effect burdens.

Pharmaceutical companies might consider investing in larger, condition-specific trials to solidify melatonin's role and potentially pursue regulatory approval for specific pain indications. This would provide clearer dosing guidelines and overcome the current challenge of melatonin being largely available as a dietary supplement, which lacks the rigorous quality control of prescription medicines. Standardisation of formulations and further pharmacokinetic studies would also be beneficial.

For patients, this evidence provides another non-pharmacological option to discuss with their GP or specialist. It underscores the importance of a holistic approach to chronic pain, recognising the interplay between pain, sleep, and overall well-being. While not a miracle drug, melatonin represents a well-tolerated intervention that could improve quality of life for a significant subset of individuals struggling with persistent muscle and joint pain.

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