

# MELATONIN RESEARCH REFERENCES

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## **Melatonin and Health: An Umbrella Review of Health Outcomes and Biological Mechanisms of Action**

**Pawel P. Posadzki et al. (2018 - BMC Medicine)**

### **Study Intention:**

The primary goal of the study was to review the scientific literature on the effects of melatonin—both endogenous (naturally occurring) and exogenous (supplemented)—on various health outcomes. The researchers also sought to understand the biological mechanisms by which melatonin exerts its effects. This comprehensive review included 195 studies and utilized both qualitative and quantitative approaches to assess the strength of evidence for different health outcomes.

### **Main Results:**

The review found significant evidence supporting melatonin's role in improving several health outcomes:

1. **Sleep Improvement:** Melatonin reduced sleep latency (the time it takes to fall asleep) and improved overall sleep quality.
2. **Preoperative Anxiety:** Melatonin showed a significant reduction in anxiety levels before surgery.
3. **Cancer Prevention:** Evidence suggested that melatonin might lower the risk of breast cancer, though more high-quality trials are needed.

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4. Prevention of Agitation: The supplement also showed benefits in reducing agitation, particularly in certain clinical settings.

However, many of the included studies were of low methodological quality, and only a subset of meta-analyses showed statistically significant results. The authors emphasized the need for more rigorous clinical trials to confirm melatonin's efficacy for various conditions.

### **Implications:**

Melatonin appears to have potential in addressing a variety of health concerns, particularly related to sleep, anxiety, and potentially cancer risk. However, given the mixed quality of available studies, healthcare providers should exercise caution when recommending melatonin for uses beyond sleep regulation. Further research is essential to clarify its benefits and mechanisms, especially for long-term and off-label use [OBJ] [OBJ].

This review adds weight to melatonin's growing reputation in integrative medicine but underscores the necessity of high-quality evidence to solidify its broader health applications.

## **Efficacy of Melatonin for Sleep Disturbance Following a Traumatic Brain Injury: A Randomized Controlled Trial**

**Nicole A. Grima et al. (2018 - BMC Medicine)**

### **Study Intentions:**

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The study aimed to evaluate the efficacy of melatonin in treating sleep disturbances in individuals who had suffered a traumatic brain injury (TBI). Sleep disturbances are common after TBI, often exacerbating cognitive, psychological, and physical recovery. The authors sought to determine if melatonin, known for its role in regulating sleep-wake cycles, could improve sleep quality, quantity, and overall well-being in TBI patients.

**Main Results:**

1. **Sleep Quality and Quantity:** The study found that melatonin did not significantly improve objective measures of sleep quantity (total sleep time) or sleep efficiency (percentage of time spent asleep while in bed).
2. **Subjective Sleep Reports:** Patients taking melatonin reported improved sleep quality and reduced daytime sleepiness. However, these subjective improvements were not strongly supported by objective sleep measurements.
3. **Safety:** Melatonin was well-tolerated by participants, with no significant adverse effects reported during the trial.

**Implications:**

1. **Subjective vs. Objective Sleep Improvements:** While melatonin may help individuals feel as though their sleep has improved (subjectively), it may not necessarily translate into measurable changes in actual sleep patterns (objectively). This discrepancy highlights the complexity of treating sleep disturbances following TBI.
2. **Potential Role of Melatonin:** Melatonin could still play a role in sleep management for TBI patients, especially for those who prioritize the perception of improved rest or need a low-risk treatment option. Further research with larger sample sizes and longer treatment durations may help clarify its role.
3. **Future Directions:** The study suggests that other treatments may need to be explored in conjunction with melatonin to provide more comprehensive support for post-TBI sleep disturbances.

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This study adds valuable insight into the ongoing exploration of non-pharmacological treatments for sleep issues in TBI patients but indicates that more robust solutions may be needed to address these challenges effectively.

## **Melatonin: Shedding Light on Infertility? - A Review of the Recent Literature**

**Shavi Fernando and Luk Rambauts (2014 - Journal of Ovarian Research)**

### **Study Intention:**

The primary intention of the study is to review recent literature on the role of melatonin in the context of infertility. Melatonin, a hormone traditionally known for regulating sleep-wake cycles, is also recognized for its potent antioxidant properties. The review aims to investigate melatonin's impact on reproductive function, particularly in relation to improving fertility outcomes, protecting against oxidative stress in the reproductive system, and supporting assisted reproductive technologies (ART).

### **Main Results:**

1. **Melatonin and Oocyte Quality:** Studies reviewed suggest that melatonin can improve oocyte quality by reducing oxidative stress, particularly during in vitro fertilization (IVF) treatments. Melatonin's antioxidant role is key in reducing oxidative damage to ovarian follicles, which can lead to better oocyte maturation and embryo development.
2. **Endometrial Function:** Melatonin appears to play a role in improving endometrial receptivity, which is crucial for successful embryo implantation. Its regulatory effects

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on the reproductive cycle and hormonal balance are thought to enhance implantation rates in ART.

3. **Male Infertility:** The review also highlights melatonin's potential benefits in improving sperm quality. Its antioxidant properties help mitigate oxidative damage to sperm DNA, which can otherwise lead to decreased fertility in men.
4. **Clinical Applications in ART:** Preliminary studies suggest that melatonin supplementation in ART may improve pregnancy rates, though the evidence is still emerging. The authors stress that more research is needed to standardize dosages and protocols for melatonin use in infertility treatments.

### **Implications:**

1. **Promising Therapeutic Role:** The findings suggest that melatonin has potential as an adjunctive therapy for improving fertility outcomes, particularly in women undergoing ART. Its ability to reduce oxidative stress may play a key role in enhancing both oocyte and sperm quality.
2. **Need for Further Research:** Although early results are promising, the authors highlight that the clinical application of melatonin in infertility is still in its infancy. Larger, more robust clinical trials are necessary to confirm optimal dosing, timing, and the overall efficacy of melatonin in fertility treatments.

In conclusion, the review points to melatonin as a potential therapeutic agent for infertility due to its antioxidative properties, but calls for more research to fully validate its use in clinical settings.

## **Mechanics of Melatonin in Alleviating Alzheimer's Disease**

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## **Mayuri Shukla et al. (2017 - Current Neuropharmacology)**

### **Study Intention:**

The study explores the role of melatonin in alleviating the symptoms and progression of Alzheimer's Disease (AD), a neurodegenerative disorder characterized by cognitive decline and memory loss. The authors aim to investigate how melatonin, a hormone with antioxidant and anti-inflammatory properties, influences the molecular mechanisms contributing to AD, focusing on pathways related to oxidative stress, beta-amyloid accumulation, and tau protein hyperphosphorylation.

### **Main Results:**

- **Antioxidant Effects:** Melatonin has potent antioxidant properties that help reduce oxidative stress, a major contributing factor in AD. This is crucial as oxidative damage accelerates the progression of neurodegeneration in AD.
- **Reduction of Beta-Amyloid Accumulation:** Melatonin helps in reducing the buildup of beta-amyloid plaques, which are toxic to neurons and a hallmark of Alzheimer's pathology.
- **Inhibition of Tau Protein Hyperphosphorylation:** The hormone also affects the tau protein, preventing its abnormal phosphorylation, which leads to the formation of neurofibrillary tangles—another key feature in AD progression.
- **Anti-inflammatory Properties:** Melatonin suppresses neuroinflammation, which is increasingly recognized as a critical factor in AD. It helps modulate inflammatory responses, protecting brain cells from damage.

### **Implications:**

The study suggests that melatonin has significant potential as a therapeutic agent for Alzheimer's Disease. Its ability to target multiple AD-related pathways—oxidative stress, amyloid deposition, tau phosphorylation, and inflammation—positions melatonin as a promising multifaceted treatment. These findings imply that early intervention with

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melatonin supplementation might help delay the onset or progression of AD, though more clinical studies are needed to confirm its efficacy in human subjects.

This research underscores the need for further investigation into melatonin's therapeutic benefits and its potential integration into treatment plans for Alzheimer's patients.

## **Meta-Analysis: Melatonin for the Treatment of Primary Sleep Disorders**

**Eduardo Ferracioli-Oda, Ahmad Qawasmi, and Michael H. Bloch**

**(2013 - PLOS ONE)**

### **Study Intentions:**

The meta-analysis by Eduardo Ferracioli-Oda, Ahmad Qawasmi, and Michael H. Bloch aimed to evaluate the effectiveness of melatonin for the treatment of primary sleep disorders. Primary sleep disorders are conditions not directly caused by another medical issue or external factor, such as insomnia, delayed sleep phase disorder (DSPD), or other circadian rhythm disturbances. The researchers sought to synthesize evidence from multiple randomized controlled trials (RCTs) to determine how melatonin supplementation impacts sleep onset latency, total sleep time, and sleep quality in patients with these disorders.

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**Main Results:**

The meta-analysis pooled data from various studies and found that melatonin significantly reduced sleep onset latency (time it takes to fall asleep), shortened by an average of 7.06 minutes compared to placebo. Additionally, melatonin modestly increased total sleep time by 8.25 minutes and improved overall sleep quality as assessed by the studies included in the analysis. However, the magnitude of these effects varied depending on the type of sleep disorder, with some showing more benefit than others.

**Implications:**

The results suggest that melatonin can be a useful treatment option for patients with primary sleep disorders, particularly for reducing the time it takes to fall asleep. While the improvements in total sleep time and sleep quality were modest, the consistency of melatonin's impact on sleep onset suggests it could be helpful for individuals who struggle to fall asleep. The findings support the potential use of melatonin in clinical settings, but they also highlight the need for further research to better understand its long-term efficacy, appropriate dosing, and the subpopulations that may benefit the most. Given the modest improvements in sleep duration and quality, melatonin might be most effective as part of a broader sleep management plan.

## **Acute Melatonin Administration in Humans Impairs Glucose Tolerance in Both the Morning and Evening**

**Patricia Rubio-Sastre et al. (2014 - Sleep)**



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## **Study Intentions:**

The primary aim of this study was to investigate how acute administration of melatonin impacts glucose tolerance in humans during different times of the day—both morning and evening. Melatonin is a hormone commonly associated with the regulation of sleep-wake cycles, but it also interacts with insulin secretion and glucose metabolism. The researchers sought to determine whether melatonin intake, especially around meals, could impair the body's ability to manage blood sugar levels.

## **Main Results:**

The study found that acute melatonin administration significantly impaired glucose tolerance in humans, regardless of the time of day (both in the morning and evening). Key observations included:

- After melatonin administration, participants exhibited elevated blood glucose levels following a glucose tolerance test, indicating that melatonin reduced the efficiency of insulin in lowering blood sugar.
- The impairments were seen consistently in both morning and evening sessions, suggesting that the time of melatonin intake may not mitigate its adverse effects on glucose metabolism.

## **Implications:**

These findings suggest that melatonin supplementation could potentially interfere with glucose regulation, raising concerns for individuals at risk of diabetes or insulin resistance, particularly if melatonin is consumed around meal times. The results indicate a need for further investigation into how melatonin impacts glucose metabolism in different populations, including those with metabolic disorders. For those using melatonin supplements, particularly for sleep, caution may be advised, especially regarding timing in relation to food intake. This study also highlights the complexity of melatonin's role in the

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body beyond sleep regulation and opens the door for more research on its metabolic effects.

## **Should Melatonin Be Used as a Sleeping Aid for Elderly People?**

**Pawel P. Posadzki et al. (2019 - CJHP)**

### **Study Intention:**

The study aimed to evaluate the efficacy and safety of melatonin as a sleeping aid specifically for elderly individuals. As sleep disturbances are common in this population, and the use of medications like benzodiazepines carries risks, melatonin—being a natural hormone—has been explored as a potentially safer alternative for sleep management in elderly people.

### **Main Results:**

This Point-Counterpoint article suggests that melatonin can have modest benefits in improving sleep onset latency (how quickly a person falls asleep) and sleep duration in elderly individuals. The results of studies have shown variability in efficacy, with some elderly patients responding better than others. Importantly, melatonin was generally well-tolerated, with minimal side effects, particularly compared to prescription sleep medications, which carry higher risks of dependency and cognitive impairment.

### **Implications:**

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Overall, this article suggests that melatonin may be a suitable first-line intervention for elderly individuals experiencing mild to moderate sleep disturbances, particularly in cases where avoiding stronger sedative medications is a priority. However, there should be more personalized approaches, as not all elderly patients may respond equally well to melatonin. Physicians should carefully consider the overall health profile and sleep needs of each patient when recommending melatonin, with close monitoring for efficacy and tolerability.

In conclusion, melatonin presents as a low-risk, modestly effective option for elderly individuals with sleep disturbances, though more research is needed to fully understand its long-term efficacy in this population.

## **Effects of Melatonin on Cardiovascular Diseases: Progress in the Past Year**

**Hang Suna, Aaron M. Gusdonb, and Shen Qua (2016 - Current Opinions Lipidology)**

### **Study Intention:**

The paper aimed to review the recent progress in understanding the effects of melatonin on cardiovascular diseases (CVDs). The authors sought to consolidate findings from studies conducted in the past year, focusing on melatonin's mechanisms and its potential therapeutic roles in managing various cardiovascular conditions.

### **Main Results:**

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1. **Antioxidant and Anti-inflammatory Properties:** The review highlighted that melatonin acts as a powerful antioxidant and anti-inflammatory agent, which is crucial in preventing oxidative stress and inflammation, both of which are significant contributors to the development and progression of CVDs.
  2. **Cardioprotective Effects:** Several studies cited in the review showed that melatonin protects the heart against ischemia-reperfusion injury (damage caused when blood supply returns to the heart after a period of ischemia or lack of oxygen). It was also found to reduce myocardial infarction (heart attack) size and improve cardiac function after injury.
  3. **Blood Pressure Regulation:** Melatonin supplementation was found to have a modest effect on lowering blood pressure in hypertensive patients. It helped regulate blood pressure through its influence on the circadian rhythm and vasodilation effects.
  4. **Lipid Profile Improvement:** Melatonin demonstrated potential benefits in improving lipid profiles by reducing low-density lipoprotein (LDL) levels and increasing high-density lipoprotein (HDL) levels, which are key factors in managing atherosclerosis, a major contributor to CVDs.
  5. **Heart Failure Management:** Emerging studies suggested that melatonin could reduce cardiac remodeling and fibrosis in heart failure patients, improving overall cardiac function.

### **Implications:**

The review underscores the growing evidence that melatonin could play a significant therapeutic role in managing cardiovascular diseases, particularly through its antioxidant, anti-inflammatory, and blood pressure-lowering properties. The authors suggest that melatonin could be used as an adjunct treatment alongside conventional therapies for patients with CVDs. However, they also note the need for more large-scale, randomized controlled trials to establish appropriate dosing and long-term safety in cardiovascular patients.

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The study encourages further exploration into how melatonin could be integrated into treatment plans, particularly for its protective effects on the heart and its ability to mitigate CVD risk factors.

## **A Review of Melatonin, It's Receptors and Drugs**

### **Mucahit Emet et al. (2016 - EAJM)**

This study outlines melatonin as a critical hormone produced mainly by the pineal gland, with its primary function in regulating circadian rhythms. Beyond its role in sleep, melatonin has been shown to have antioxidant, anti-inflammatory, and immunomodulatory effects, making it a potential candidate for a range of therapeutic applications.

#### **Study Intent:**

The intention of the review is to provide a comprehensive overview of melatonin's physiological role, its receptor mechanisms, and the various drugs or supplements derived from or influenced by melatonin. The authors aim to clarify the molecular pathways involved and discuss how this knowledge is applied in clinical treatments.

#### **Main Results:**

1. Melatonin Receptors: The paper describes two major melatonin receptors, MT1 and MT2, which are G-protein-coupled receptors involved in the regulation of circadian rhythms and sleep-wake cycles. These receptors are found in various tissues, not limited to the brain, indicating a broad range of potential effects.

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2. **Therapeutic Uses:** Melatonin has been researched for its use in treating sleep disorders (such as insomnia and jet lag), and neurodegenerative diseases, and it may have benefits in cardiovascular conditions, cancer treatment, and immune function modulation.
  3. **Drug Development:** Several melatonin-based drugs have been developed, including synthetic analogs. These aim to enhance the bioavailability of melatonin or target specific receptor subtypes for more precise therapeutic effects.

**Implications:**

The review underscores the potential for melatonin to be used beyond its conventional role as a sleep aid. Given its antioxidant and anti-inflammatory properties, the paper suggests melatonin could be considered in therapies for oxidative stress-related diseases, including neurodegenerative and cardiovascular disorders. Additionally, targeting melatonin receptors with novel drugs could lead to more effective treatments for circadian rhythm disorders and other conditions.

Overall, the study highlights the growing body of research supporting the diverse therapeutic uses of melatonin and its receptor-targeting drugs, suggesting that further investigation could reveal even broader applications in medicine.

## **International Expert Opinions and Recommendations on the Use of Melatonin in the Treatment of Insomnia and**

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# Circadian Sleep Disturbances in Adult Neuropsychiatric Disorders

**Laura Palagini et al. (2021 - Frontiers in Psychiatry)**

The research paper titled “International Expert Opinions and Recommendations on the Use of Melatonin in the Treatment of Insomnia and Circadian Sleep Disturbances in Adult Neuropsychiatric Disorders” offers an extensive review of melatonin’s therapeutic use in treating insomnia and circadian sleep disorders, particularly in adults with neuropsychiatric conditions.

## **Study Intentions:**

The authors aimed to gather and present expert opinions and consensus on the use of melatonin for sleep disturbances, specifically targeting insomnia and circadian rhythm disorders within adult neuropsychiatric populations. These populations include individuals with depression, anxiety, bipolar disorder, and neurodegenerative diseases, as they often experience sleep disruptions. The research aimed to synthesize evidence-based recommendations and clinical insights for healthcare providers to better understand melatonin’s role and practical use in these conditions.

## **Main Results:**

1. Efficacy of Melatonin:
  - a. Melatonin is found to be effective in managing insomnia and circadian rhythm disturbances, especially in neuropsychiatric conditions like major depressive disorder and bipolar disorder. Melatonin’s role in regulating the sleep-wake cycle makes it a suitable treatment option.
  - b. In patients with neurodegenerative disorders, such as Alzheimer’s or Parkinson’s, melatonin has shown benefits in improving sleep quality and reducing nighttime awakenings.

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2. Safety and Tolerability:

- a. Melatonin is generally well-tolerated and has a favorable safety profile, even for long-term use. Unlike many pharmacological sleep aids, melatonin doesn't induce dependence or significant side effects, making it a good option for chronic sleep disturbances.

3. Timing and Dosage:

- a. The paper emphasizes the importance of proper timing (chronotherapy) and individualized dosing for melatonin's success in treating circadian rhythm disorders. Evening doses are particularly effective in advancing sleep onset and regulating disrupted sleep patterns.
- b. Doses between 1–5 mg are commonly recommended, but lower doses may also be effective, depending on the individual and specific disorder.

4. Use in Specific Neuropsychiatric Disorders:

5. For depression, bipolar disorder, and anxiety, melatonin has potential benefits, particularly by regulating sleep disruptions that may exacerbate these conditions.
6. In neurodegenerative diseases, melatonin's antioxidant and neuroprotective properties may also provide secondary benefits beyond sleep regulation.

**Implications:**

1. Clinical Recommendations:

- a. The paper strongly recommends melatonin as a first-line treatment for circadian rhythm disorders and as an adjunct therapy for insomnia in neuropsychiatric populations. Healthcare providers should consider melatonin for patients experiencing sleep-wake disturbances due to its safety, efficacy, and low side-effect profile.

2. Personalized Medicine:



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- a. The research emphasizes the need for personalized treatment strategies, considering individual patient characteristics, underlying conditions, and specific sleep disturbance patterns.
3. Further Research:
    - a. While melatonin has shown promising results, the paper calls for more randomized controlled trials to refine dosage and treatment protocols, particularly in varying neuropsychiatric populations.

### **Conclusion:**

This paper underscores melatonin's role as a safe and effective treatment option for insomnia and circadian rhythm disturbances in adults with neuropsychiatric disorders. The recommendations provided offer a solid foundation for clinicians to adopt melatonin in managing sleep issues while tailoring treatment to individual patient needs.

## **Melatonin: Buffering the Immune System**

### **Antonio Carrillo-Vico et al. (2013 - International Journal of Molecular Sciences)**

The paper "Melatonin: Buffering the Immune System" by Antonio Carrillo-Vico and colleagues explores the effects of melatonin on the immune system, emphasizing its role in maintaining immune homeostasis and modulating immune responses.

### **Study Intentions:**

The primary aim of the study is to understand how melatonin interacts with the immune system, particularly its role as an immune buffer. The researchers focus on melatonin's anti-inflammatory and immunomodulatory properties, investigating how it influences both innate and adaptive immune responses. They also explore how melatonin could help balance overactive immune reactions and provide therapeutic potential for immune-related diseases.

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**Main Results:**

1. **Melatonin as an Immune Modulator:** Melatonin was found to modulate immune responses by interacting with various immune cells, such as lymphocytes, macrophages, and neutrophils. It regulates cytokine production, which helps reduce inflammation and immune overactivity.
2. **Antioxidant Effects:** The study highlighted melatonin's role as an antioxidant, protecting immune cells from oxidative stress. This is particularly important in preventing damage from excessive immune reactions or chronic inflammation.
3. **Circadian Regulation:** Melatonin's influence on immune function is closely tied to its role in regulating circadian rhythms, suggesting that immune responses fluctuate based on melatonin's natural daily cycle.
4. **Therapeutic Potential:** The authors suggest melatonin could be useful in treating autoimmune diseases, sepsis, and chronic inflammation by dampening excessive immune responses while boosting overall immune efficiency.

**Implications:**

The study concludes that melatonin acts as a crucial buffer for the immune system, balancing pro- and anti-inflammatory responses. This makes it a potential therapeutic agent for various immune-related conditions. Its ability to modulate immune activity, along with its antioxidant properties, highlights melatonin's promise for conditions involving immune dysfunction, such as autoimmune diseases and chronic inflammatory states. The findings support further exploration of melatonin in clinical applications, particularly for its potential in reducing inflammation and managing immune disorders.

This research broadens our understanding of melatonin beyond its traditional role in sleep regulation, positioning it as an important player in immune health.

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# Management of REM Sleep Behavior Disorder: An American Academy of Sleep Medicine Clinical Practice Guideline

**Michael Howell, MD et al. (2033 - Journal of Clinical Sleep Medicine)**

## **Study Intentions:**

This clinical practice guideline, developed by the American Academy of Sleep Medicine, provides evidence-based recommendations for the management of REM Sleep Behavior Disorder (RBD). The main goals are to improve patient care by standardizing the treatment approaches for RBD, a parasomnia characterized by dream-enactment behaviors and loss of normal muscle atonia during REM sleep. RBD can lead to injury for patients and bed partners and is often associated with neurodegenerative disorders, such as Parkinson's disease and dementia.

## **Main Results:**

The guideline reviews a range of treatment options, including pharmacologic and non-pharmacologic interventions. Key findings include:

1. Pharmacologic Treatments:
  - a. Clonazepam and melatonin are recommended as the first-line treatments for RBD, based on moderate- to high-quality evidence.
  - b. Clonazepam has been found effective in reducing violent behaviors during sleep, though it may cause side effects like daytime sedation.
  - c. Melatonin is noted for having fewer side effects and has comparable efficacy to clonazepam in some cases, making it a safer option for certain populations, such as older adults.

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2. Non-pharmacologic Treatments:

- a. Environmental modifications, such as removing dangerous objects from the bedroom and protecting the sleeper and bed partner, are strongly recommended to prevent injury.
- b. There is less evidence supporting cognitive or behavioral therapies, but they may be considered for some patients.

3. Additional Considerations:

- a. The guideline discusses the importance of long-term management, given the association between RBD and neurodegenerative diseases, and emphasizes monitoring patients for progression to these conditions.
- b. It also highlights the need for personalized treatment plans, considering individual patient needs, comorbidities, and potential drug side effects.

**Implications:**

This guideline underscores the critical need for early diagnosis and appropriate management of RBD to reduce injury risk and improve quality of life for patients and their bed partners. It also provides a framework for clinicians to balance the benefits and risks of pharmacologic treatments like clonazepam and melatonin. Additionally, the recognition of RBD as an early indicator of neurodegenerative disease reinforces the importance of ongoing patient evaluation and monitoring.

The recommendations help standardize care and provide guidance for healthcare professionals in treating a condition that can significantly impact safety and well-being during sleep.

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# **Melatonin Natural Health Products and Supplements: Presence of Serotonin and Significant Variability of Melatonin Content**

**Lauren A.E. Erland, MSc and Praveen K. Saxena, PhD (2017 - Journal of  
Clinical Sleep Medicine)**

## **Study Intentions:**

The primary goal of this study was to investigate the quality and consistency of melatonin supplements available on the market. Specifically, the researchers aimed to:

1. Measure the actual melatonin content in these products compared to what is listed on their labels.
2. Determine if serotonin, a related compound that could have unintended health effects, was present in these supplements.

## **Main Results:**

1. Significant Variability in Melatonin Content:

The study found that melatonin content varied widely across products. Some supplements contained as little as 83% less melatonin than advertised, while others had up to 478% more than the labeled amount. The variability was observed between brands, batches, and even between different lots from the same manufacturer.

2. Presence of Serotonin:

Serotonin, a neurotransmitter not expected in melatonin supplements, was detected in 8 of the 30 products tested. While the detected levels were small, the presence of serotonin in products marketed as melatonin supplements raises concerns about purity and

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potential health risks, especially considering serotonin's effects on mood, sleep, and overall brain chemistry.

**Implications:**

1. **Consumer Safety Concerns:** The variability in melatonin content means that consumers might be taking far more or less melatonin than they intend, which could lead to unpredictable effects on sleep and other health outcomes. This inconsistency is especially concerning for children and those sensitive to melatonin, as dosing accuracy is critical for safe use.
2. **Regulation and Standardization Needs:** The presence of serotonin and the variability in melatonin content indicate that better regulation and standardization of melatonin supplements are needed to ensure product safety and effectiveness. This study calls for stricter oversight of the manufacturing process and labeling accuracy for melatonin products.
3. **Clinical Implications:** For healthcare providers recommending melatonin, this study highlights the importance of advising patients to be cautious about product selection. It also suggests the need for further research to assess the long-term effects of taking melatonin supplements with unpredictable content and potential contaminants like serotonin.

This study underscores the need for better quality control and transparency in the melatonin supplement industry.

## **Poor Quality Control of Over-the-Counter Melatonin: What They Say Is Often Not What You Get**

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**Madeleine M. Grigg-Damberger, MD and Dessislava Ianakieva, MD (2017  
- Journal of Clinical Sleep Medicine)**

**Study Intentions:**

This commentary discusses the research conducted by Erland and Saxena, which focused on the variability in melatonin content and the presence of serotonin in over-the-counter (OTC) melatonin supplements. The study aimed to investigate whether the actual melatonin content in these supplements matched the labeled dosage and to assess the presence of any contaminants, specifically serotonin.

**Main Results:**

Erland and Saxena's findings revealed significant inconsistencies in the melatonin content across different brands and formulations. Some products contained as little as 83% less melatonin than labeled, while others had up to 478% more. Moreover, 71% of the products tested had different amounts of melatonin from what was claimed on their labels. Additionally, the study found serotonin contamination in a number of these supplements, which is a serious concern due to its potential health risks, especially for people taking serotonin-influencing medications or those with serotonin syndrome risk.

**Implications:**

This study raises critical concerns about the quality control of OTC melatonin supplements. The unpredictable dosing could lead to ineffective treatment or potential overdosing, particularly in sensitive populations like children or individuals using melatonin for sleep disorders. The presence of serotonin is alarming and could cause harmful interactions. This underscores the need for stricter regulation of melatonin supplements, ensuring that what consumers purchase aligns with what is claimed on the label to avoid unintended health consequences.

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# **Pediatric Melatonin Ingestions - United States 2012-2021**

## **Karima Lelak, MD et al. (2022 - CDC Morbidity and Mortality Weekly Report)**

### **Study Intentions:**

The study aimed to analyze trends in pediatric melatonin ingestions reported to the U.S. Poison Control Centers over a 10-year period (2012–2021). Given the increasing popularity of melatonin as a sleep aid and supplement, the study sought to assess potential risks, particularly among children, due to accidental or intentional ingestion of melatonin.

### **Main Results:**

1. From 2012 to 2021, the number of pediatric melatonin ingestions increased significantly, by 530%. In 2012, there were about 8,300 cases, which grew to over 52,000 in 2021.
2. 94.3% of the reported ingestions occurred in children aged 5 years and younger, highlighting a vulnerability in younger age groups.
3. Most ingestions were unintentional, and the majority (83%) resulted in minimal or no significant health effects.
4. However, there was an increase in more severe outcomes, with 4,097 hospitalizations and five reported deaths during the study period.
5. The COVID-19 pandemic contributed to the rising trend, with more exposures occurring at home due to increased melatonin use, especially as routines shifted during the pandemic.

### **Implications:**

1. The dramatic rise in pediatric melatonin ingestions suggests a need for increased public health measures to prevent accidental exposures in children, such as better packaging (e.g., child-resistant containers) and parental education.



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2. Healthcare providers should inform families about the potential risks of keeping melatonin supplements within reach of young children.
  3. Further regulatory consideration might be necessary as melatonin is widely available over-the-counter but not regulated as stringently as prescription medications.

This study underscores the importance of being vigilant about supplement safety and storage, particularly in households with young children.

## **The Role of Melatonin in the Treatment of Primary Headache Disorders**

**Amy A. Gelfand, MD and Peter J. Goadsby, MD, PhD (2016 - Headache)**

### **Study Intentions:**

The study aimed to explore the potential therapeutic role of melatonin in managing primary headache disorders, such as migraines and cluster headaches. It focused on reviewing the existing literature and understanding the biological mechanisms that could link melatonin to headache pathophysiology. The researchers were particularly interested in melatonin's involvement in regulating circadian rhythms, its anti-inflammatory effects, and its influence on the central nervous system.

### **Main Results:**

1. Melatonin Levels and Headaches: Several studies showed an association between disrupted melatonin levels and certain headache disorders, particularly migraines

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and cluster headaches. For instance, patients with cluster headaches often exhibited lower nocturnal melatonin levels.

2. Melatonin as a Treatment: Clinical trials indicated that melatonin supplementation could be beneficial for some headache sufferers. In particular, melatonin showed promise for reducing the frequency and intensity of cluster headaches and migraines. A 3 mg dose taken nightly was often effective, particularly for cluster headache patients.
3. Comparative Effectiveness: Melatonin appeared to be comparable to some existing treatments for headaches, like amitriptyline for migraines, with fewer side effects. However, melatonin did not consistently work for all patients, and its efficacy varied based on the type of headache disorder and individual patient characteristics.

### **Implications:**

The findings suggest that melatonin could be a useful, well-tolerated treatment option for certain individuals suffering from primary headache disorders, particularly for those with circadian rhythm disturbances. Further research is needed to determine optimal dosing, timing, and patient selection to maximize its benefits. Melatonin's relatively benign side effect profile makes it an attractive option compared to traditional medications, but more large-scale, controlled trials are necessary to solidify its place in headache management protocols.

This study highlights melatonin's potential role in non-drug approaches to headache management, especially in patients who prefer alternative or adjunct therapies to conventional treatments.

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# Melatonin for the Prevention and Treatment of Cancer

Ya Li et al. (2017 - Impact Journals - Oncotarget)

## Study Intentions:

The primary goal of this paper is to explore how melatonin, a hormone commonly known for regulating sleep-wake cycles, can play a role in cancer therapy. The study reviews existing literature and evidence to understand melatonin's anti-cancer properties, mechanisms, and how it can be used both as a preventative and treatment option in various types of cancers. The authors also examine melatonin's influence on cancer cell growth, apoptosis (programmed cell death), metastasis, and the immune system's response to tumors.

## Main Results:

1. **Antioxidant Activity:** Melatonin has strong antioxidant properties, which help reduce oxidative stress, a contributing factor in cancer development. It scavenges free radicals, protecting cells from DNA damage that can lead to cancerous changes.
2. **Regulation of Apoptosis:** Melatonin promotes apoptosis in cancer cells by regulating various molecular pathways. It helps in the activation of pro-apoptotic factors and the suppression of anti-apoptotic mechanisms in tumor cells.
3. **Inhibition of Tumor Growth and Metastasis:** The hormone has been found to inhibit the growth of several cancer cell types and prevent the spread of tumors by affecting cell signaling pathways related to cancer progression.
4. **Synergistic Effects with Chemotherapy and Radiotherapy:** The paper discusses how melatonin can improve the efficacy of conventional cancer therapies, such as chemotherapy and radiotherapy, by enhancing the sensitivity of cancer cells to these treatments while protecting healthy cells from damage.

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5. Immune System Modulation: Melatonin enhances the body's immune response against tumors by activating immune cells like T lymphocytes and natural killer cells, which are essential for detecting and destroying cancer cells.

**Implications:**

The findings from the study suggest that melatonin holds significant promise as a supplementary treatment in cancer therapy. It has the potential to:

1. Reduce the side effects of traditional cancer treatments,
2. Act as a preventive agent against cancer development,
3. Enhance the overall effectiveness of cancer treatments by sensitizing cancer cells to therapy while protecting healthy tissue.

The authors propose that melatonin's multifaceted roles in antioxidant defense, immune modulation, and tumor inhibition make it a valuable therapeutic option in cancer prevention and treatment. They advocate for further clinical trials to assess its efficacy and potential as a standard part of cancer care regimens.