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Melatonin

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Continuing Education Activity

Endogenous melatonin is a naturally produced hormone primarily synthesized and secreted in the pineal gland. Melatonin regulates the body's sleep-wake cycles by interacting with the suprachiasmatic nucleus of the hypothalamus and the retina. The best-known purpose of melatonin is its role in promoting sleep and inhibiting wake-promoting signals through interactions with its MT1 and MT2 receptors. Although melatonin is not officially approved for any indication by the US Food and Drug Administration (FDA) in the United States, exogenously supplied melatonin, which is available as a synthetic dietary supplement, mimics the regulatory functions of endogenous melatonin.

The American Academy of Family Physicians (AAFP) recognizes melatonin as the first-line pharmacological therapy for insomnia, emphasizing its crucial role in managing sleep-related concerns. Melatonin is also used for the management of posttraumatic brain injury, jet lag, neurodegenerative disorders, and migraine prophylaxis. This activity explores the safety profile of melatonin supplementation, highlighting its relatively low risk of adverse effects. This activity further elucidates the mechanism of action, pharmacology, adverse event profile, monitoring strategies, and pertinent interactions of melatonin. The interprofessional healthcare team can use melatonin as an adjunct to offer essential insights for collaborative patient care in sleep disorders.

Objectives:

- Identify appropriate indications for melatonin supplementation in managing sleep disorders and insomnia.
- Implement evidence-based dosing and timing strategies for melatonin administration tailored to individual patient needs.
- Assess patient response to melatonin therapy through regular follow-up evaluations and monitoring for efficacy and adverse effects.
- Coordinate comprehensive patient care plans, integrating melatonin supplementation as an adjunctive therapy to manage sleep disorders.

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Indications

Endogenous melatonin is a naturally produced hormone primarily synthesized and secreted in the pineal gland. Melatonin regulates the body's sleep-wake cycles by interacting with the suprachiasmatic nucleus (SCN) of the hypothalamus and the retina. The best-known purpose of melatonin is its role in promoting sleep and inhibiting wake-promoting signals through interactions with its MT1 and MT2 receptors.

FDA-Approved Indications

Although not officially approved for any indication by the US Food and Drug Administration (FDA) in the United States, exogenously supplied melatonin, available as a synthetic dietary supplement, mimics the regulatory functions of endogenous melatonin. However, melatonin

receptor agonists, such as ramelteon and tasimelteon, are available on the market and are FDA-approved for the treatment of insomnia.[1][2]

Off-Label Uses

Insomnia: Despite the lack of FDA approval, the American Academy of Family Physicians (AAFP) recognizes melatonin as the first-line pharmacological therapy for insomnia, emphasizing its crucial role in managing sleep-related concerns. This drug is relatively safe with a low risk of adverse effects. Research on the efficacy of melatonin supplementation for treating insomnia has shown varied results. However, a meta-analysis conducted by Ferracioli-Oda et al concluded that individuals who used melatonin experienced an average reduction in sleep onset latency by approximately 7 minutes, an increase in total sleep duration by approximately 8 minutes, and subjectively reported an improvement in the quality of their sleep, as compared to those who were given a placebo. Nevertheless, there was considerable variability in doses, study outcomes, and overall study quality.[3]

Melatonin is endorsed by the American Academy of Sleep Medicine (AASM) for treating rapid eye movement (REM) sleep behavior disorder and circadian rhythm disorders.[4][5] In addition, melatonin has been studied and recommended primarily for the treatment of [6][7] primary insomnia (insomnia not due to secondary cause), posttraumatic brain injury,[8] age-related insomnia, jet lag disorder,[9] shift work sleep disorder, neurodegenerative disorders, and migraine prophylaxis.[10]

Research-based: Although no formal recommendations are recognized, ongoing clinical research is investigating the potential role of melatonin in the treatment of various conditions, including cancer,[11] pain syndromes, metabolic disorders, cardiovascular disorders, [12] gastrointestinal conditions, neurodegenerative disorders,[13] mental disorders, and reproductive dysfunctions.[14]

Mechanism of Action

Synthesis of Endogenous Melatonin

Endogenous melatonin is a hormone produced naturally, synthesized, and primarily secreted in the pineal gland. Melatonin production starts with tryptophan, which is converted into serotonin in other parts of the brain through a pathway. Some of this serotonin reaches the pineal gland, where it undergoes a cyclic, light-dependent process to be converted into melatonin.[15]

The conversion of serotonin to melatonin is regulated by the SCN of the hypothalamus, which coordinates the body's circadian rhythms. Information about varying light conditions, ranging from low light to darkness, is transmitted from the retina through the retinohypothalamic tract to the SCN. The SCN then communicates signals via the sympathetic nervous system to the superior cervical ganglion, which innervates the pineal gland.

Sympathetic stimulation of the pineal gland upregulates the production of the enzyme arylalkylamine *N*-acetyltransferase (AA-NAT). AA-NAT converts serotonin to *N*-acetyl-serotonin, representing the rate-limiting step in melatonin formation. Subsequently, this intermediate is converted to melatonin. Studies in rats have demonstrated that bilateral surgical removal of the superior cervical ganglia or SCN halts AA-NAT activation and abolishes the rhythmic pattern of melatonin secretion, leading to disruptions in the sleep-wake cycle.[16][17][18]

Functions of Endogenous Melatonin

The primary role of melatonin is best known for its involvement in promoting sleep. Melatonin is released by the pineal gland into the third ventricle and the circulation. The drug regulates the body's sleep-wake cycles through interactions with the SCN of the hypothalamus and the retina,

promoting sleep and inhibiting wake-promoting signals via interactions with its MT1 and MT2 receptors.[19]

Biological Mechanism of Melatonin

Cancer suppression: Activating tumor suppressor genes such as *p53*, exerting oncostatic activity, modulating estrogen and androgens, immunomodulation, and increasing cytokine production, collectively contributing to cancer suppression.

Bone deposition: MT2 receptors found on osteoblasts suggest melatonin's involvement in regulating their function.

Metabolic disorders: Melatonin exhibits antioxidative and anti-inflammatory effects and regulates lipid and glucose metabolism.

Cardiovascular diseases: Melatonin demonstrates anti-hypertensive effects.

Gastrointestinal conditions: Melatonin displays antioxidative and anti-inflammatory effects.

Neurodegenerative disorders: Melatonin may activate mitochondrial cell survival pathways, potentially safeguarding against neurodegeneration induced by mitochondrial dysfunction. In addition, the drug regulates apoptosis and helps prevent vasoconstriction of cerebral arteries.

Mental disorders: Agomelatine, the melatonin receptor agonist, is recognized as an anxiolytic drug and is approved for treating depression in Europe.

Pain syndromes: Melatonin exhibits anti-nociceptive, anti-inflammatory, and analgesic effects.

Reproductive functions: Melatonin is involved in several pathways that reduce the risk of complications, enhance gonadotropic secretion, and contribute to higher rates of mature oocytes and quality embryos.[20][21][22]

Pharmacokinetics

Absorption: The bioavailability of melatonin varies significantly, ranging from 1% to 74%, with likely dependence on the formulation and dosage.

Metabolism: Ninety percent of melatonin is metabolized in the liver, primarily mediated by the CYP1A2 enzyme, with a minor contribution from the CYP2C19 enzyme. Melatonin metabolism involves hydroxylation, converting it to 6-hydroxymelatonin. Subsequently, it undergoes conjugation with sulfuric or glucuronic acid before excretion in the urine. A smaller portion is excreted in feces.[23]

Distribution: Approximately 61% to 78% of melatonin binds to albumin, significantly influencing its distribution.[24]

Elimination: The elimination half-life of melatonin is relatively short, typically ranging from 1 to 2 hours, varying with the formulation used. In critically ill patients, medication absorption is accelerated while elimination is compromised, potentially resulting in altered pharmacokinetics and drug effects. Premature neonates often exhibit a prolonged half-life of melatonin compared to adults.[25]

Administration

Melatonin Content of Supplements

The FDA does not regulate supplements as rigorously as pharmaceutical drugs, as they are generally considered safe. However, this lack of oversight can raise concerns regarding the actual concentrations of supplements, including melatonin. A study examining 31 melatonin supplements discovered that the actual melatonin content varied widely, ranging from −83% to +478% of the labeled content.[26]

Variable tablet content can make accurate dosing challenging and might contribute to the wide range of efficacy reported in various trials. One approach to ensure precise dosing is to seek supplements approved by the United States Pharmacopeia (USP)—an independent nonprofit organization. Choosing supplements labeled as "USP verified" can guarantee the quality and dosing accuracy of the supplements.

Melatonin Administration Routes [27] [28]

Routes of melatonin administration include oral tablets, oral liquids, rectal suppositories, and transdermal patches.

Melatonin Formulations [29]

Melatonin formulations include immediate-release, extended-release, and combined immediate and extended-release options.

Adult Dosage

- Effective dosing for melatonin is not well-defined as the FDA does not regulate it as a drug. Melatonin dosages used in studies have ranged from 0.1 mg to 10 mg, typically administered up to 2 hours before bedtime. The maximum dosage has not been defined in trials.
- AASM provides recommendations regarding using melatonin for intrinsic circadian rhythm sleep-wake disorders. Specifically, for adults with delayed sleep-wake phase disorder (DSWPD), the AASM supports treatment with melatonin. Furthermore, for blind adults with non-24-hour sleep-wake rhythm disorder (N24SWD), the AASM suggests strategically timed melatonin administration. This can involve administering melatonin 1 hour before the patient's preferred bedtime or at a fixed time (for instance, 9 PM).[4]

Specific Patient Populations

Hepatic impairment: Clinicians should exercise caution when prescribing melatonin to patients with impaired liver functioning, as their ability to metabolize the medication may be reduced. However, based on several clinical trials, researchers have concluded that melatonin does not induce hepatotoxicity. The likelihood score of hepatotoxicity is rated as E, indicating an unlikely cause of clinically apparent liver injury.[30]

Renal impairment: Clinicians should exercise caution when prescribing melatonin to patients undergoing dialysis due to the increased risk of adverse effects resulting from impaired elimination of the medication.[31]

Pregnancy and breastfeeding considerations: Clinicians should advise pregnant and breastfeeding women to avoid using melatonin due to insufficient evidence of its safety in this population.[22][32]

Pediatric patients: Melatonin production usually starts around 3 months of age, with peak concentrations at 0.2 ng/mL during darkness. Supplementing infants with melatonin can result in higher levels than naturally produced by the body, and assumptions about safety based on its endogenous nature may be misleading. Therefore, the presence of elevated exogenous melatonin levels in postmortem pediatric cases warrants attention.[33]

Older patients: Although melatonin is generally considered safer than benzodiazepines, certain reports indicate a potential risk of falls and fractures in this population.[34]

Adverse Effects

Melatonin is relatively nontoxic, although some mild adverse effects have been reported with higher doses and extended-release formulations, including [35][36] drowsiness, daytime

sedation, nausea, and headaches. No evidence suggests that patients develop tolerance to melatonin. However, impaired glucose tolerance has been reported in some cases.

Drug-Drug Interactions

CYP1A2 inhibitors: As melatonin is metabolized by CYP1A2, caution should be exercised when using it concurrently with potent CYP1A2 inhibitors such as fluvoxamine.[37]

Sedatives or hypnotics: Melatonin should not be combined with other drugs, including benzodiazepines, zolpidem, or eszopiclone, as this combination may result in excessive sedation.[38]

Contraindications

Despite being generally well-tolerated, melatonin supplements are rarely associated with angioedema. As melatonin is a naturally produced hormone, allergic reactions can also be caused by unregulated excipients in some formulations.[39][40] Clinicians should exercise caution when considering melatonin supplementation for patients with autoimmune diseases, such as rheumatoid arthritis or post-organ transplant. Melatonin stimulates the function of the immune system via the production of interleukins (ILs), including IL-1, IL-2, IL-6, and IL-12, interferon-gamma, helper T cells, cytotoxic T cells, and B- and T-cell precursors. However, the clinical significance of this effect remains undefined.[41]

Monitoring

Clinicians should monitor for improvements in insomnia in individuals and watch for adverse drug reactions, such as daytime sleepiness and headaches, associated with melatonin therapy when prescribing melatonin.[42]

Toxicity

Toxicity due to melatonin might present as follows:

- Melatonin demonstrates remarkably low acute toxicity according to findings from animal and human studies. At supraphysiological doses, it may result in minor adverse drug reactions such as headaches, rashes, gastritis, nightmares, and insomnia. Notably, researchers have not established an LD50 in animals even at high doses of up to 800 mg/kg, and melatonin does not cause fatalities in animal studies.
- Preliminary observations in humans suggest that long-term melatonin administration may be associated with reduced semen quality in healthy men, probably due to aromatase inhibition at the testicular level.[43]
- A recent analysis published in the morbidity and mortality report raises concerns, indicating a significant increase in annual pediatric melatonin overdose cases from 8000 in 2012 to more than 52,000 in 2021, with 15% of children requiring hospitalization due to overdoses.[44]

Enhancing Healthcare Team Outcomes

Insomnia is a common complaint observed in both outpatient and inpatient settings. Melatonin serves as a safe first-line sleep aid, potentially aiding in promoting a regular sleep cycle. Furthermore, melatonin is one of the few over-the-counter supplements that healthcare professionals can recommend for insomnia. Despite lacking FDA approval, melatonin is widely used for insomnia and jet lag disorders. Therefore, all pertinent healthcare providers must be knowledgeable about the mechanism, off-label indications, and adverse effects of melatonin.

Individuals often take melatonin as an over-the-counter supplement. However, healthcare providers can recommend melatonin for insomnia and jet lag disorders. Pharmacists should offer patient counseling regarding the potential adverse effects of melatonin and advise against its concurrent use with other central nervous system depressants, such as benzodiazepines or alcohol. In addition, it is crucial to inform patients that the FDA does not regulate supplements, and melatonin currently lacks FDA approval. Nursing staff can monitor the patient's response to melatonin therapy. Melatonin has shown efficacy in circadian rhythm sleep-wake disorders, and consultation with sleep medicine specialists is recommended for appropriate diagnosis and treatment.[4][45]

If insomnia persists despite melatonin therapy, the clinician should consider consulting a psychiatrist to explore potential underlying disorders. Furthermore, if primary sleep disorders are suspected, the patient may benefit from consultation with a sleep medicine specialist. The interprofessional collaboration of various healthcare providers, including clinicians, pharmacists, nurses, and specialists, is crucial for optimizing patient outcomes.

Review Questions

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