Melatonin Research Paper

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Melatonin

Melatonin has long been known to aid in sleep; however, a myriad of other benefits has been discovered in the last decade of research. During this time, the therapeutic and physiological dose of melatonin for various uses has been explored, as has the form used in supplements. Melatonin, as a dietary supplement, comes in a variety of dosages from as low as 0.3mg to as high as 20mg. Historically, it was extracted from the pineal glands of animals, most often from cow or pig sources. Presently, however, it is almost exclusively synthetically produced. Plants naturally contain melatonin but at extremely low levels, (nanograms per milligram) making it very difficult to extract sufficient melatonin for therapeutic doses.

However, more recently there has been one plant-based melatonin product developed which is now commercially available with levels of 1mg of melatonin per 100mg of herbal biomass.

Melatonin comes in an immediate-release form or sustained-release, also referred to as slow-, controlled-, or time-release. Sustained-release appears to have less hypnotic or drowsiness effects than the immediate release and the benefits appear to be equal to or greater than the immediate-release form relative to primary insomnia; sleeplessness not attributed to a medical condition or medication.

Melatonin is a naturally occurring hormone produced in the human body by the pineal gland and secreted into the bloodstream. On average, the pineal gland produces between 0.1mg and 0.8mg of melatonin per day. Children typically produce double the amount of melatonin (0.5mg - 0.8mg) compared to adults. Production gradually declines as people age, starting in the late twenties through to the fifties, with production leveling out at approximately 0.3mg. However, production can drop even further due to diet and other lifestyle factors [1].

People of all ages dealing with jet lag, shift work, or challenges to their circadian rhythm due to environmental or seasonal changes may also be affected by low melatonin levels.

Melatonin is produced in response to darkness, as perceived by the retina of the eye. It is reduced by exposure to light and artificial light may also contribute to the reduction of a person's melatonin production and increased risk of disease. Some conditions and medications

have been shown to depress melatonin levels in the blood: Prostate cancer, breast cancer, autism, epilepsy, antidepressants, non-steroidal anti-inflammatory drugs (NSAIDs), beta- blockers, and calcium channel blockers for high blood pressure, caffeine, tobacco, and alcohol use have all been associated with low melatonin levels.

Melatonin has been found in many tissues beyond the pineal gland, including the brain, retina, lens, cochlea, trachea, skin, GI tract, liver, kidney, thyroid, pancreas, thymus, spleen, white blood cells, reproductive tissues, and beyond. Melatonin is present in nearly all bodily fluids including cerebrospinal fluid, saliva, bile, synovial fluid, amniotic fluid, urine, feces, and breast milk.

Beyond sleep, melatonin has been associated with cellular protection from oxidative stress- specifically linked to the redox status of cells and tissues, mitochondrial homeostasis, genomic effects, and its modulating effects of inflammatory and immune cytokines directly impacting both systemic and acute anti-inflammatory properties.

Sleep

Melatonin and sleep studies have looked at how shift work, particularly night work, may increase the risk of cancer and may aggravate both gastrointestinal and cardiovascular disease, complicate pregnancy, and interfere with drug therapy [2]. Multiple studies, opinions, and guidelines have suggested melatonin as primary therapy for improved health and sleep of shift workers [3,4,5].

A meta-analysis of melatonin for the treatment of primary sleep disorders looked at 19 studies involving 1683 individuals. Melatonin had a statistically significant effect on reducing sleep latency and increasing total sleep time. Trials that used higher doses of melatonin and conducted over a longer duration demonstrated even greater effects on these two sleep issues, and overall sleep quality was also significantly improved in melatonin users [6].

A 2017 systematic review found 5,030 studies on melatonin and sleep, but only 12 were included as they were randomized, controlled, and single or double-blind.

The summary concluded that melatonin is indicated for the following [7]

- Insomnia: Immediate release 1-3mg, <30 mins before bed; Slow-release can be used for sleep maintenance problems
- Regulating sleep in blind individuals
- Replicated normal endogenous pattern
- Delayed Sleep Phase

A delayed sleep phase is a persistent shift in sleep-wake times later than social norms, causing insomnia-like symptoms, difficulty waking in the morning, and excessive daytime sleepiness. This is best treated with melatonin at select times and a select amount of time before the desired bedtime and wake time. There are specific phase advancing protocols to support the sleep phase if current sleep times are less than three hours later than target time, and a different protocol if the need is to advance the phase when it is less than three hours. These protocols are best known by sleep specialists.

Brain Health

Endogenous melatonin is produced from tryptophan by way of 5-HTP and serotonin. The bi-directional neural processes from the gut and the brain rely on specific metabolic reactions. These metabolic reactions are reliant on the conversion of tryptophan into serotonin. In many ways, serotonin lays the foundation for the connection between the gut- brain axis, as it directly affects and influences neurological response and central nervous system transmission. The metabolism of tryptophan is directly influenced by inflammatory and immune responses, which trigger the throughput in the kynurenine pathway.

In addition to the importance of tryptophan's metabolism, an investigation into gut microbiota has identified microbial influences on the serotonergic and melatonergic systems [8]. The established serotonergic and melatonergic systems may be vulnerable before establishing a stable global biota in infancy. Elderly individuals may also be more susceptible to serotonergic and melatonergic system errors due to known lower amounts of biota diversity. Both serotonergic and melatonergic systems are also prone to immune and inflammatory responses, adding to the complexities of the gut-brain axis [9,10].

Melatonin is an antioxidant, combating free radicals, which can cause oxidative damage to our cells. Melatonin is both water and lipid-soluble, allowing it to freely flow among all bodily tissues.

Melatonin can also cross the blood-brain barrier, making it one of the most potent antioxidants in the brain [11]. Most substances, including antioxidants that we consume, do not cross this barrier. Yet, the wisdom of nature has provided us the ability to manufacture this defense mechanism and may in part explain its benefit in cognitive diseases.

In a small pilot study of elderly patients with a mild cognitive deficit, the ability to remember previously learned items improved, along with a reduction in depression, with the use of melatonin [12]. A larger longer-term study found patients with mild cognitive impairment scored better on the Mini-Mental Status Exam and the Sleep Disorders Index when taking melatonin [13]. Oxidative stress is a leading cause of age-related brain dysfunction by impairing neurogenesis and researchers are diving into potential influences on monoamine synthesis which is a common target for diseases of the aging brain [14,15]. Additionally, research into melatonin and its anti-beta-amyloid aggregation effects is being studied [16]. Beta-amyloid plaque is found in the brains of patients with Alzheimer's disease and these mechanisms along with the symptomatic relief of cognitive impairment found in other studies make melatonin a contributing factor in treatment.

Neurodegenerative conditions share mitochondrial dysfunction in their pathogenesis. Mitochondria, being the cellular source of energy, are also the target of oxidative damage. The sensitive nature of mitochondrial membranes, which can be damaged by a plethora of factors, may find protection with oral administration of melatonin [17]. Melatonin is selectively taken up by mitochondrial membranes, a function not shared by other antioxidants [18].

Kynurenine Pathway

Melatonin is derived from serotonin by way of 5-HTP and tryptophan [19]. Tryptophan is involved primarily in two pathways: The melatonin-serotonin pathway and the kynurenic pathway. The melatonin-serotonin pathway is thought to account for approximately 5% of dietary tryptophan degradation, while the kynurenic pathway accounts for approximately 95% of dietary tryptophan degradation. The kynurenic pathway is an essential process needed to convert tryptophan into nicotinamide adenine dinucleotide (NAD+) for cellular energy.

Although the bisecting pathways of tryptophan are involved in separate processes, one pathway is thought to impact the other. Exercise has been found to increase the throughput in the serotonin-melatonin pathway, eventually increasing both serotonin and melatonin levels impacting mood and cognition [19].

Conversely, acute or chronic inflammation and stress have been found to increase the throughput of the kynurenic pathway, leading to an increase of tryptophan's conversion to kynurenine. Kynurenine is a byproduct or metabolite that is kicked off when tryptophan is converted to niacin. High concentration levels of kynurenine in the brain are present in instances of depression. Kynurenine is then converted to either kynurenic acid or quinolinic acid. Quinolinic acid is known to be a neurotoxin, while kynurenic acid is known to have neuroprotective properties [19,20].

The broader picture of mental health, specifically depression, has been correlated to melatonin levels recently. While low levels of serotonin are known to be consistent with clinical depression, low levels of melatonin also appear to have a significant connection. Low levels of melatonin may trigger an upregulation in the kynurenine pathway, kynurenine production, and as well as trigger aryl hydrocarbon receptor (AhR) located on the outer membrane of the mitochondria. The aryl hydrocarbon receptor (AhR) is responsible for modulating mitochondrial metabolism, melatonergic pathways, acetyl-coenzyme A, and cyclooxygenase-2 (COX-2) prostaglandin. When AhR is triggered, overall endogenous pineal melatonin production is suppressed [19,23,24].

Downregulation of endogenous pineal melatonin has further been observed with increases of proinflammatory cytokines in the gut due to increased permeability and dysbiosis. One study observed postpartum melatonin levels in mothers that had a Caesarean delivery. Investigators found that postpartum depression was higher in mothers with lower melatonin levels. These researchers surmised that various single nucleotide polymorphisms could be a major contributor to postpartum melatonin levels of mothers and subsequent depression [8]. Delivery by Caesarean may also be associated with higher levels of pro-inflammatory cytokines when compared to vaginal births, thereby shunting the production of pineal gland melatonin synthesis, and upregulating the tryptophan conversion into the kynurenic pathway, offsetting the serotonin-melatonin pathway [25].

Cardiovascular Health

Improvements in LDL cholesterol and blood pressure have been shown in as few as two months of melatonin use in patients with documented metabolic syndrome who had not responded to a three-month intervention of therapeutic lifestyle modifications[26]. Further, it has been shown to decrease nocturnal hypertension, improve systolic and diastolic blood pressure, reduce the pulsality index in the internal carotid artery, decrease platelet aggregation, and reduce serum catecholamine levels [27,28,29].

More recent studies have shown melatonin improving outcomes in patients with heart failure and it is being considered as a preventive and adjunctive curative measure in these patients [29].

Pregnancy and Fertility

A review of the available literature by obstetric researchers found that because pregnancy has increased oxygen demands on the body and thus more free radical damage, melatonin may be a critical consideration for both complicated and normal pregnancies, counter to the traditional stance of avoiding it during pregnancy. The use of melatonin during pregnancy, which has been found safe in both mother and fetus according to some research, could prove to help limit complications during the critical periods before and shortly after delivery [30,31]. A recent study suggested that preeclampsia has a seasonal variation since it was observed that reduced melatonin levels were associated with the development of preeclampsia [32]. Therefore, it has been suggested that melatonin may help support a successful pregnancy.

Pregnancy is a critical time for fetal programming of hypertension. Melatonin, as an antioxidant therapy, can prevent hypertension in offspring of patients with a family history of hypertension [33]. It is hypothesized that oxidative stress harms fertility. Since melatonin is a strong scavenger of oxidative factors it could improve both male and female fertility [34,35]. A review of the literature also suggests that melatonin improves sperm quality and oocyte quality, resulting in increased fertilization. Melatonin shows promise for advanced age infertility and improving IVF outcomes [36,37,38].

Endometriosis

The antioxidant effects of melatonin also appear to alleviate the chronic pelvic pain of endometriosis. In this condition, endometrial tissue implants at various sites inside the body and causes inflammation. The pelvic pain experienced with endometriosis can be severe and surgical removal of the abnormally placed tissue can lead to problems of its own, such as adhesions that affect digestion and fertility. In a randomized double-blind placebo-controlled trial, Schwertner, et. al. found that melatonin at a higher dose of 10 mg nightly reduced endometriosis pain by about 40% and reduced the use of pain-relieving medications by 80% over 2 months [39]. This nutrient alone is not enough to manage endometriosis [40], but when it comes to pain relief, it's a safer starting point than pharmaceutical analgesics which may have significant side effects.

Digestive Health

Two types of cells are responsible for the production of melatonin: pinealocytes and enterochromaffin cells. Pinealocytes are located in the pineal gland, within the brain. Enterochromaffin cells are located on the surface of the entire GI tract (highly concentrated in the mucosal lining of the GI tract). Pinealocytes are affected by light and dark; exposure to light suppresses melatonin production and release from the pinealocytes, while darkness (when registered by the retina) increases melatonin production and release into the bloodstream starting with vessels in the brain. From the blood vessels in the brain, melatonin is carried to other body tissues. It is estimated that the enterochromaffin cells within the gut contain upwards of four- hundred-times the amount of melatonin than what is produced by pinealocytes. In addition, levels of gut melatonin can be anywhere from 10-100 times greater than melatonin found in blood serum levels [41].

Unlike pinealocytes, enterochromaffin cells are not regulated by light and dark, but rather appear to be affected by food intake and digestion. Melatonin from enterochromaffin cells has an antagonistic relationship with serotonin. Some of the melatonin from enterochromaffin cells stay in the GI tract, while some are released into portal circulation entering the liver first. If melatonin levels are high after a particularly larger meal, some melatonin may be released into the bloodstream from the liver and could cause drowsiness. Some of the enterochromaffin-produced melatonin is held in the gut. The release of melatonin in the gut increases activity and circulation in the gastric mucosa and enhances GI motility. In addition, melatonin reduces gastric acid production and increases gastrin and bicarbonate production.

With the increased production of gastrin, melatonin has also been attributed to increasing the tone of the lower esophageal sphincter. Further, melatonin has anti-excitatory properties in the gut and can stimulate the regeneration of epithelial cells. In addition, melatonin has been shown to have protective antioxidant effects on the lining of the GI tract.

- People suffering from heartburn and GERD have lowered GI melatonin levels
- Melatonin can be more effective than proton pump inhibitors in treating GERD
- Melatonin accelerates the healing of gastric ulcers in rats

Melatonin can improve symptoms of pain, bloating, and constipation in individuals with IBS-C and IBS-D. Dosing melatonin at 0.3mg daily for IBS-C, and 3.0mg daily for IBS- D may prove to be beneficial for patients with IBS [42].

Broad therapeutic benefits also exist for melatonin's role in oral care and digestive function, periodontal inflammation, post-dental surgery, and as antioxidant protection against dental materials [43,44]. Studies have investigated its use in Helicobacter pylori infections, gastric and duodenal ulcers, gastroesophageal reflux disease (GERD), and inflammatory bowel disease [45,46,47]. Melatonin and its precursor tryptophan have protective effects on mucosal tissue. Of interest is a study in which H. pylori-infected individuals were given melatonin, placebo, or tryptophan with omeprazole. Each of the three groups had seven subjects with gastric ulcers and seven with duodenal ulcers. At the 21-day mark, those treated with either tryptophan (250mg twice daily) or melatonin (5mg twice daily) had no ulcers, whereas the placebo group had three gastric ulcers and three duodenal ulcers. Also of note, is that in one study on GERD, melatonin given at 3mg daily over 8 weeks showed similar improvement in symptoms as omeprazole [47].

An additional study indicated that gut bacteria have their circadian clock and respond to melatonin, allowing the bacteria to synchronize with the human circadian rhythm [48]. Additionally, the gastrointestinal tract produces its melatonin, which in turn supports normal gut motility, mucosal integrity via its antioxidant activity, and support of the microbiome.

Oxidative Stress, and Inflammation

In a study of oxidative stress markers in those who ran a 50 km (31 mile) course, those who took melatonin had reduced levels of stress markers [49], underscoring not only the mechanism of antioxidant protection, but also a practical use in athletes who are exposed to oxidative stress and inflammation that may increase their risk for vascular incidents. Because melatonin has been shown to inhibit NF-kappa B, an important cellular signaling agent which is induced by reactive oxygen species, chemical stressors, and radiation, additional trials looking at anti-inflammatory conditions which may be helped by this mechanism may be seen [50,51].

Migraines and Headaches

Migraines are chronic and debilitating, affecting 12-20% of the world's population, more commonly women. Women account for about 75% of the 28 million Americans who experience migraine headaches. A randomized, multi- center, parallel-group design was conducted in which melatonin was compared with amitriptyline and placebo for 12 weeks. A 3mg dose of melatonin reduced migraine frequency demonstrating the same effectiveness as amitriptyline in the primary endpoint of the frequency of migraine headaches per month [52]. Melatonin was superior to amitriptyline in the percentage of patients with a greater than 50% reduction in migraine frequency and melatonin was better tolerated than amitriptyline. It has also been reported as an effective treatment for primary headache disorders [53].

An additional surveillance study observed 61 patients diagnosed with chronic tension headaches [54]. Patients were given 3 mg of melatonin for 30 days following a baseline period and then followed up with after 60 days. Quality scores were obtained using VAS pain intensity, Hamilton Anxiety Rating Scale (HAM-A), and Hamilton Depression Rating Scale (HAM-D) at the inception of the study, post 30 days of treatment, and post 60 days of treatments. Overall, significant decreases in pain and tension headache- associated symptoms were observed after melatonin use. Sleep quality was also significantly improved throughout and after the study.

Tinnitus

Melatonin has been used for the treatment of chronic tinnitus in adults. A significantly greater decrease in tinnitus scores on an audiometric test and self- rated tinnitus was observed after treatment with melatonin compared to placebo in one study [55]. Hormonal influences such as puberty, the menstrual cycle, pregnancy, hormonal birth control, hormone replacement therapy, and menopause are possible explanations why women may experience tinnitus. Other changes that could influence and worsen tinnitus during these times could be lack of sleep, fatigue, and stress. Whatever the cause, the use of melatonin 3mg in the evening is a reasonable and safe supplement to consider in tinnitus.

ADHD and Autism

The profound effects of melatonin may be far-reaching. Research groups have evaluated the genes that encode melatonin metabolism in patients with attention deficit hyperactivity disorder compared to controls. Genetic results suggest a melatonin-signaling deficiency in ADHD [56].

Sleep disorders are present as a comorbidity in those with ADHD, affecting cognitive, behavioral, and physical development. In most individuals with ADHD, there is a delayed circadian phase (evening preference) and subsequent issues with daytime function. In these individuals, endogenous pineal melatonin during the evening hours (triggered by dim light) is significantly dampened.

Evidence suggests somewhat variable responses to supplemental melatonin in clinical ADHD. This may be due to the fact that ADHD could be a manifestation of genetic SNPs related to sleep disturbance and circadian rhythm dysfunction, while other cases of ADHD could be attributed to the melatonin-signaling deficiency. More research is needed to determine appropriate dosage protocols specific to the pathophysiology of ADHD, and melatonin supplementation should be recommended when surveilled by a healthcare provider [57,58,59].

Sleep disturbances in autism have led researchers to investigate melatonin's role in this spectrum of disorders as well. Considered to have a genetic component, it was found that autistic patients have low melatonin levels, caused by a primary deficit in ASMT gene activity [60]. In a double-blind, placebo-controlled study, investigators tested children diagnosed with autism spectrum disorder (ASD) (n=103) and healthy children (n=73) for serum melatonin (antioxidant), the oxidants of nitric oxide, and malondialdehyde levels. Overall, children diagnosed with ASD and positive family history had higher serum melatonin and nitric oxide levels, with significantly lower malondialdehyde/melatonin ratios, suggesting greater impaired oxidant-antioxidant metabolism and balance in children with ASD [61]. A review article found that patients with autism had improved sleep parameters, better daytime behavior, and minimal side effects with melatonin use [62].

Overall, research has suggested that melatonin is effective as a sleep inductor, doses between 1-5 mg can be used 30 minutes before bedtime. For delayed sleep phase syndrome doses between 0.2-0.5 mg have been most effective when given 6 to 8 hours before desired sleep.

Immune Function

Melatonin has effects on the immune system, including some anti-carcinogenic properties [63]. In 1991, Dr. Paolo Lissoni conducted a study on patients with metastatic solid tumors and demonstrated that high doses of melatonin were effective in arresting tumor growth and improving quality of life markers [64]. His group, considered pioneers in this field, have provided several reports on this dose throughout the 1990s with subsequent studies confirming his findings.

A study reported that melatonin is linked to the seasonal relapse rate in MS patients. The same research team also found that melatonin reduced immune- cell production of inflammatory immune messengers and increases anti- inflammatory messengers [65].

Eye Health

Glaucoma may be the next therapeutic target for melatonin. Ophthalmic researchers are developing an understanding of how the potent antioxidant potential of melatonin may reduce intraocular pressure and the recognized comorbidities of depression, anxiety, and sleep disturbances [66]. Age-related macular degeneration is another serious ophthalmic condition that could benefit from melatonin administration [67].

Jet Lag

As our world gets smaller, more individuals need to recover from jet lag sooner and faster. There are many studies supporting melatonin's use in reducing the ill effects of jet lag and speeding up the normalization of circadian rhythms [68]. In a Cochrane review, 9 out of 10 trials found melatonin was effective in reducing jet lag symptoms in travelers, especially if traveling eastward or over greater than 5 time zones [69].

Bone Health

Melatonin may also hold promise as a modulator of anabolic bone formation and metabolism, especially if used in combination with other bone nutrients such as Vitamins D and K. According to the MOTS trial, melatonin may be able to reverse bone loss [70]. Melatonin is a hormone and nutritional supplement that has demonstrated efficacy to renormalize bone marker turnover in peri- menopausal women [71] and increase bone density in postmenopausal women with osteopenia [72].

Investigators reviewed melatonin's efficacy in age-related skeletal muscle disorders [73]. Overall, melatonin supplementation is considered to be a safe dietary supplement that may mitigate skeletal muscle frailty and lengthen physical performance in aging individuals [74].

Oncology

Melatonin may further help to re-establish altered circadian rhythm in oncology. Oncology patients with breast and colorectal cancers were observed to have altered circadian rhythm associated with flattened cortisol levels throughout the day [75]. Mortality was positively associated with erratic circadian rhythm and poor sleep. Normally, cortisol levels are lowest in the evening hours and start to rise in the morning. Cortisol and melatonin work inversely, so as cortisol rises, melatonin decreases and vice versa [76].

Under states of stress, tryptophan's conversion to serotonin and melatonin is shunted. Often, oncology patients experience chronic fatigue, anemia, depression, and overall decreased quality of life. Researchers recognized that oncology patients with solid tumors have an initial immune response involving pro-inflammatory cytokines as the body recognizes self from non-self [77]. In this process, the kynurenic pathway is sped up, causing inflammation-mediated tryptophan catabolism, fatigue, anemia, and depression [78]. In such cases, supplementation with melatonin may be an effective way to augment the standard of care and mitigate the inflammatory cascade that ultimately leads to decreased quality of life.

In night-shift workers, circadian disruption is prevalent due to light exposure at night [79]. Upon review of animal and human clinical trials specific to breast cancer risk in night-shift workers, researchers reported melatonin's ability to suppress the aerobic metabolism of tumors (known as the Warburg effect), while also suppressing the tumor cells' proliferation, tumor cells' survival, metastasis and potential drug resistance [80]. In both animal and human models, circadian rhythm disruption due to light exposure at night significantly increased breast cancer risk [80]. A meta-analysis examined the role of melatonin in 46 different microRNAs found in breast, oral, gastric, colorectal, prostate, and glioblastoma cancers. The microRNAs associated with breast, gastric and oral cancers were most responsive to melatonin treatments. Researchers identified the mechanical actions of melatonin to upregulate genes correlated to immune and apoptotic responses, where melatonin downregulated tumor cell survival involved in metastasis and angiogenesis [81].

Dosing

Over the last decade, we have learned that using the lowest effective dose of any hormone is the most appropriate course, and that larger doses do not always infer more benefits. Too much melatonin has been documented to produce side effects such as amnesia or a "melatonin hangover" the next day, finding it harder to fall asleep, or sleeping well for 3-4 hours and then waking up and not being able to go back to sleep. Some doctors also believe that high doses over the long-term can negatively impact the body's production of melatonin, with patients often becoming dependent over time. Doctors are also aware of patients reporting vivid dreams or even nightmares. Since the body produces between 0.1mg and 0.8mg of melatonin daily, doses in this range are known as physiologic doses. Amounts above this range are known as pharmacologic doses. Much has been written about melatonin's therapeutic value, but the doses used in studies appear to be chosen haphazardly or based on previous studies that did not have an explicit purpose for choosing the amount. Therefore, some dogma about dosing melatonin has developed in both the scientific research community and in clinical medicine.

Researchers from the Massachusetts Institute of Technology in 2001 compared physiologic doses to pharmacologic doses and very low (below physiologic) doses and found the best objective data at 0.3mg of melatonin. Sleep data were obtained by polysomnography. The physiologic dose (0.3mg) restored sleep efficiency and elevated plasma melatonin levels to normal. The pharmacologic dose (3.0mg), like the lowest dose (0.1 mg), also improved sleep; however, it induced hypothermia and caused plasma melatonin to remain elevated into the daylight hours. Interestingly, the control group (not insomniacs) also had low melatonin levels but melatonin did not improve sleep. The low dose in the study did not raise melatonin levels into the normal range. It is fascinating that we need to lower our body temperature to sleep well but doing so excessively can disrupt sleep. Melatonin's action of lowering body temperature is important to monitor and may give significant clues to the appropriate dosage. Symptoms like needing more blankets, or excessive movement, may suggest too much melatonin at night [82].

This same group evaluated the 0.3mg dose in children who suffer from Angelman Syndrome, a rare genetic condition in which sleep maintenance is difficult, among other developmental issues [83]. Parents were asked to log sleep habits and 0.3mg was administered 30-60 minutes before bedtime. Subjects wore an actigraph that measured movements per minute during the night. Serum levels of melatonin were measured hourly over two different 21-hour periods. The 0.3mg dose effectively elevated blood levels, decreased nocturnal motor function, and increased sleep onset. This before and after trial studied 13 children and compared their information to a 5-day baseline. The administration of melatonin lasted seven days. What is profoundly interesting is that many of these children were taking GABAergic medications, which are known to deplete melatonin, and AS children are thought to produce less melatonin than developmentally normal children, likely due to poorly formed pineal glands. That being said, these subjects likely have the most need for melatonin from an insufficiency perspective yet only 0.3mg was sufficient to see clinically relevant improvements [83].

Dr. Paolo Lissoni's cancer research demonstrated that 20mg was effective in arresting tumor growth and improving quality of life markers [64]. Studies since have all mirrored this dose; however, it is important to note that 20mg was a calculated dose. Little research to date has been conducted on lower doses to determine if they are as effective in cancer patients or if the physiological dose of 0.3mg can be used for prevention.

Hopefully, future studies will delve into these questions. In 2002 researcher Alfred J. Lewy and colleagues found that physiologic doses (0.5mg) may offer benefits that pharmacologic doses (20mg) do not [84]. They observed the effects of dosage of melatonin in blind humans who often have disrupted circadian rhythms due to the pineal gland not receiving appropriate stimulation from the retina. They concluded that "too much melatonin may spill over onto the wrong zone of the melatonin phase-response curve". The phase-response curve is the standard measure of biological rhythms. This supports the concept that too much melatonin may not be good for a person. It also begs

the question, “How much is too much?” It will be difficult to answer this for the masses as hormone production and timing of secretion has so many variables. In addition, the bioavailability of the form or product used can play a part. Many practitioners swear by doses of 1-3 mg; however, they find that when they switch brands, lower doses are just as effective. Melatonin is quickly broken down by the body and should be dosed at the appropriate, personalized level for each patient. Because of this fast metabolism, melatonin must be used daily and not every second or third day. If a person feels best on 1mg of melatonin, 3mg of melatonin every third day is not appropriate. Products containing 3-5mg are often chosen because they are perceived as a good value but getting more medicine for your dollar is not always better if the dose is incorrect. For this reason, starting at the physiological dose of 0.3mg and increasing if necessary is often recommended except for specific conditions where higher doses are needed short-term such as jet lag, shift work, or cancer.

There are some general opinions on dosing melatonin from a timing perspective. Historically all research related to sleep administered melatonin 30-60 minutes before bed; however, some studies have shown that it can be taken up to 4 hours prior and be effective. Lewy suggests that dosing for sleep requires a minimum of twelve hours of wakefulness. Dosing for jet lag from eastbound travel includes a preflight early evening treatment of melatonin for 1-3 days leading up to travel, followed by treatment at bedtime for 4 days after arrival, most studies are on 3-5mg nightly. For westbound travel, melatonin can be used for 4 days at bedtime when in the new time zone. For difficulty falling asleep, melatonin can be taken 3-4 hours before an imposed sleep period over four weeks. However, as it is always recommended to take melatonin in conjunction with being in darkness versus light stimulation from television and computers, it is often more practical to adhere to the 30-60 minutes before bed.

For difficulty maintaining sleep, a short-term, high dose, repeated low doses, or a controlled- release formulation may be required depending on the cause of disrupted sleep maintenance. Some authorities suggest limiting melatonin to 0.3mg in children. The use of melatonin in children is now widely accepted for various disorders but since the studies range so widely in dosing, a critical analysis is required for each patient. Dysomnia, attention-deficit disorder, and autism spectrum disorder have been studied and reviewed, all confirming effectiveness and safety of melatonin. It should be noted that studies were of various lengths with some as short as two weeks and the longest-lasting six months. Only one questionnaire-based study has looked at long-term melatonin use in children and by its design, was based on subjective symptom reports. In an average of 3.7 years of follow-up from previous clinical trial participation of pharmacologic doses of melatonin, 65% of children were still using melatonin as prescribed in the study but only 9% were able to discontinue use [85]. Implications of this information are two-fold for the practicing clinician. 1) Most of the time, parents need to be prepared for lifelong melatonin use when giving pharmacologic doses, and 2) because melatonin is over the counter, the dose initially recommended is what any given patient was on. Neither the parents nor children were being monitored in their melatonin use, but rather relied on the initial study proposal so dosing varied widely. Yet compliance nearly four years later was 65% due presumably to satisfaction of use.

Uses in seizure activity, idiopathic scoliosis, and anesthesia have been studied as well with positive outcomes. Where science has yet to meet clinical practice is dosing parameters may vary according to multiple factors such as the child’s medical problems, the severity, and type of sleep problems, or the associated neurological pathology. Indiscriminate dosing may lead to unnecessary dependence. Finally, to underscore the discussion of dosing in both pediatrics and adults, it is important to understand that melatonin is metabolized via the liver almost exclusively by CYP1A2. The slow metabolism of this enzyme has clinical application. A melatonin clearance test is reasonable yet difficult to practically implement. Therefore, loss of response after several weeks may suggest a patient’s tolerance of melatonin and dose reduction. In one report, clinicians noted that “the initial good response to melatonin disappeared within a few weeks after starting treatment, while the good response returned only after considerable dose reduction” [86]. What is optimal dosing of melatonin with the current understanding? Perhaps it is best stated as advised in a review of the literature “use of the lowest possible dose of immediate-release formulation melatonin to best mimic the normal physiological circadian rhythm of melatonin and to avoid prolonged, supra-physiological blood levels” [87].

Medications

Melatonin should not be combined with certain medications such as blood pressure medications like methoxamine (Vasoxyl) and clonidine (Catapres), blood-thinning medications such as warfarin (Coumadin), MAO inhibitor drugs, steroids, and immunosuppressive medications. Additionally, women who are pregnant or nursing should not take melatonin without medical approval and/or supervision, and people with autoimmune conditions, diabetes, thyroid conditions, epilepsy, leukemia, lymphoproliferative disorders, or mood disorders should only take it under medical supervision.

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