Melatonin

While melatonin has long been known to aid in sleep, a myriad of other functions now have been realized over just the last decade of research. Additionally, the daily dose of melatonin and the form used in supplements has been questioned and explored.

Melatonin, as a dietary supplement, comes in a variety of dosages from as high as 20 mg to as low as 0.3 mg. It is often synthetically produced from petro-chemicals or extracted from animal glands most often from bovine or porcine source; however, a bio-identical, non-synthetic form from plants (vegetarian/vegan) now exists. Melatonin comes in 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 in relation to primary insomnia (that is 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 blood stream. On average, the pineal gland produces between 0.1mg – 0.8mg of melatonin per day. Children typically produce double the amount of melatonin (0.5mg – 0.8mg) as compared to adults. Production gradually declines from our twenties through to our fifties, with production leveling at approximately 0.3mg. However, production can drop even lower due to diet and other lifestyle factors.¹

People of all ages who are dealing with jet lag, shift work, and challenges to their circadian rhythm due to seasonal changes may also be affected by low melatonin levels. Research into the effects of melatonin on cancer, cognitive function and autism is now being conducted. Melatonin is produced in response to darkness, as perceived by the retina of the eye. It is reduced by exposure to light and it appears from research. Additionally, the daily dose of melatonin and the form used in supplements has been questioned and explored.

A number of conditions and medications have been shown to depress melatonin levels in the blood. Prostate cancer, breast cancer, autism, and epilepsy, anti-depressants, 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.

**Some Benefits of Melatonin**

**Melatonin and Sleep**

Studies have looked at how shift work, particularly that including night work, may increase the risk of cancer and may aggravate gastrointestinal and cardiovascular disease, complicate pregnancy, and interfere with drug therapy.² Multiple studies, opinions, and guidelines have suggested melatonin as a primary therapeutic 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 nineteen studies involving 1683 individuals. Melatonin was significantly effective in reducing the time it takes to fall asleep (sleep latency) as well as 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

**Melatonin and Brain Health**

Melatonin works as an antioxidant, combating free radicals, which can cause oxidative damage to our cells. Melatonin, uniquely, can also cross the blood-brain barrier, making it one of the most potent antioxidants in the brain.⁷ 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 mild cognitive deficit, the ability to remember previously learned items improved along with a reduction in depression. 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 given melatonin.

While avoiding mechanistic studies here, it is important to note that oxidative stress is a leading cause in age-related brain dysfunction by impairing neurogenesis and researchers are diving into potential influences to monoamine synthesis which is a common target for such diseases as schizophrenia and Parkinson’s disease. Additionally, research into melatonin and its anti-beta-amyloid aggregation effects are being illustrated. Beta-amyloid plaquing 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 an attractive solution.

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. Melatonin is selectively taken up by mitochondrial membranes, a function not shared by other antioxidants.

Melatonin and Cardiovascular Health

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

Melatonin and Pregnancy and Fertility

A review of the available evidence done by obstetric researchers has 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 which goes against the traditional stance of no use during pregnancy. In fact, the use of melatonin during pregnancy, which has been found safe in both mother and fetus according to some researchers, could prove to help limit complications during the critical periods prior to, and shortly after, delivery. A recent study has suggested that preeclampsia has a seasonal variation since it was observed that reduced melatonin levels were associated to the development of preeclampsia. Therefore, melatonin has been suggested to be involved in 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.

It is hypothesized that oxidative stress has an adverse effect on fertility. Since melatonin is a strong scavenger of oxidative factors it could improve fertility. A review of the literature also suggests that melatonin improves sperm quality and oocytes quality, resulting in increased fertilization. Melatonin shows promise for advanced age infertility and improving IVF outcomes.

Melatonin and 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 high dose of 10 mg nightly) reduced endometriosis pain by about 40% and reduced the use of pain-relieving medications by 80% over 2 months. This nutrient alone will not be enough to manage endometriosis, but when it comes to pain relief, it’s a safer starting point than pharmaceutical analgesics (which may have significant side effects).
Melatonin and Digestive Health

Broad therapeutic benefits also exist for oral care and digestive function such as oxidative stress and periodontal inflammation, post-dental surgery, and as an antioxidant against dental materials. Studies have investigated its use in Helicobacter pylori infections, gastric and duodenal ulcers, GERD, and irritable bowel syndrome.27,28,30,31

Melatonin and its precursor amino acid tryptophan have protective effects to mucosal tissue. Of interest is the 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 additionally with either tryptophan or melatonin had no ulcers whereas the placebo group had three gastric ulcers and three duodenal ulcers.

A recent study has indicated that gut bacteria have their own circadian clock and respond to melatonin, allowing the bacteria to synchronize with the human circadian rhythm.32

Melatonin and 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 markers33, 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, we will likely see additional trials into inflammatory conditions such as diabetes with and without neuropathy, weight gain, and obstructive pulmonary disease.34

Migraines and Headaches

Migraines are chronic and debilitating and affect 12-20% of the world’s population, and are more common in women. Women account for about three quarters 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 has been shown reduce migraine frequency demonstrating the same effectiveness as amitriptyline in the primary endpoint of frequency of migraine headaches per month. 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.35 It has also been reported as an effective treatment for primary headache disorders.36

Melatonin and Tinnitus

A recent study was published reporting on the results of using melatonin 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.37

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 3 mg in the evening, is a reasonable and safe supplement to try for the challenging problem of tinnitus.

Melatonin and Autism and ADHD

The profound effects of melatonin may be far reaching. Research groups have evaluated the genes that encode for melatonin metabolism in patients with attention deficit hyperactivity disorder compared to controls. Genetic results suggest melatonin-signaling deficiency in ADHD and the next step is a large-scale trial evaluating effectiveness in reducing symptoms.38
Sleep disturbances in autism have lead 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. A review article found that patients with autism had improved sleep parameters, better daytime behavior, and minimal side effects with melatonin use.

**Melatonin and Immune Function**

Melatonin has effects on the immune system, including some anti-carcinogenic properties. In 1991, Dr. Paolo Lissoni from Italy performed cancer research 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. His group is considered the pioneers in this work and provided several reports on this dose throughout the 1990’s with subsequent studies confirming his findings.

A recent 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.

**Melatonin and Eye Health**

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

**Dosing of Melatonin**

What we have learned, particularly over the last decade about using hormones is that the lowest effective dose is appropriate and that larger doses do not always infer more benefits. This is the paradox of dosing hormones.

Too much melatonin has been documented to produce side effects such as amnesia or having a “melatonin hang-over” 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 long term can negatively impact the body’s own production with patients often becoming dependent over extended high dose use. Doctors are also aware of patients reporting vivid dreams or even nightmares. This can be particularly alarming if the patient is a child.

Since the body produces between 0.1 mg and 0.8 mg 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 dose used in the studies appears 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 (MiT) in 2001 compared physiologic doses to pharmacologic doses and very low (below physiologic) doses and found the best objective data at the 0.3 mg doses of melatonin. Sleep data were obtained by polysomnography. The physiologic melatonin dose (0.3 mg) restored sleep efficiency and elevated plasma melatonin levels to normal. The pharmacologic dose (3.0 mg), 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 to lower body temperature is important to remember and monitor for patients and may give significant clues to the appropriate dosage. As an example, patients may notice a need for more covers or may get complaints from their partner regarding their ability to share the blankets. These clues as well as excessive movement may suggest too much melatonin at night.
This same group evaluated the 0.3 mg dose in children who suffer from Angelman’s Syndrome (AS), a rare genetic condition in which sleep maintenance is difficult in addition to a myriad of other symptoms up to and including severe mental retardation. Parents were asked to log sleep habits and 0.3 mg was administered 30-60 minutes before the habitual bedtime. Subjects wore an actigraph, which measured movements per minute during the night. Serum levels of melatonin were measured hourly over two different 21-hour periods. The actigraphic information, diary and serum data was collected and determined that the 0.3 mg dose effectively elevated blood levels, decreased nocturnal motor function, and parents’ reports indicated faster sleep onset. This before-and-after trial studied 13 children and compared their information to a 5-day baseline. Administration of melatonin lasted 7 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 0.3 mg was sufficient to see clinically relevant improvements.47

Dr. Paolo Lissoni’s cancer research demonstrated that 20 mg was effective in arresting tumor growth and improving quality of life markers.48 Dr. Tina Kaczor has written a review article summarizing the subsequent work on cancer and melatonin.49 Studies since have all mirrored this dose; however, it is important to note that 20 mg was a calculated dose. Little research to date has been conducted on lower dosages to determine if lower doses are as effective in cancer patients or if the physiological dose of 0.3 mg 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 (0.5 mg) may offer benefits that pharmacologic doses (20 mg) do not.50 They observed the effects of dose 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 “too much melatonin may spill over onto the wrong zone of the melatonin phase-response curve”. The phase-response curve (PRC) 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 even among populations. In addition, bioavailability of the form or product used can play a part. Many practitioners will swear by higher dosages of 1-3 mg; however, they find that when they switch brands, lower dosages are just as effective.

Melatonin is quickly broken down by the body and should be dosed daily at the appropriate level. Therefore, the dosing of melatonin is a very personalized question for each patient. Because of this fast metabolism, melatonin must be used daily and not every second or third day to accommodate a lower daily dosage from a larger dose capsule. For example, if a person feels best on 1 mg of melatonin, 3mg of melatonin every third day is not appropriate. Off-the-shelf products containing 3-5 mg are often chosen because they are perceived as a good value, but getting more medicine for your dollar is not always a better value if the dose is incorrect.

**For this reason, starting at the physiological dose of 0.3 mg 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, as it was related to sleep, administered melatonin 30-60 minutes prior to bed; however, some studies have shown that it can be taken up to 4 hours prior and be effective. Lewy suggests that dosing for purposes of sleep requires a minimum of twelve hours of wakefulness. Melatonin should be taken on an empty stomach. 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 four days after arrival. For westbound travel, melatonin can be used for four 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 such as television, computers and the like it is often more practical to adhere to the 30-60 minutes before bed. For difficulty maintaining sleep, a high dose in the short-term, repeated low doses, or a controlled-release formulation may be required depending upon the cause of disrupted sleep maintenance.

Some authorities suggest limiting melatonin to 0.3 mg 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 clinical practice. One dose-dependent study found that using a calculated dose of 0.05 mg/kg was as effective as higher doses.51 Unfortunately, this is the lowest dose studied in this
trial. In practical terms, this is 0.9 mg for a 40-pound child. Dysomnia, attention-deficit disorder, and autism spectrum disorder have been studied and reviewed, all confirming effectiveness and safety of melatonin.\textsuperscript{52} 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 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.\textsuperscript{53} 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 given pharmacologic doses and 2) the use of melatonin in children with sleep disturbance is a self-filling prescription at the dose initially recommended. Neither the parents nor children were being monitored in their melatonin use but rather relied on the initial study proposal. Yet compliance nearly four years later was 65\% due presumably to satisfaction of use.

Melatonin use has been studied in neonatal care with breast milk content of melatonin varying during the day which has implications for the lactating mother who is pumping and storing her production and even more important for non-breastfed infants.\textsuperscript{54} Uses in seizure activity, idiopathic scoliosis and anesthesia have been studied as well with positive outcomes. Where the science has yet to meet clinical practice is dosing parameters. “The dose of melatonin applicable to each patient must vary according to multiple factors such as the child’s medical problems, the severity and type of sleep problems, or the associated neurological pathology. This suggestion ought to be heeded. 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 cytochrome P450 enzyme CYP1A2. Slow metabolism at 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 reported “the initial good response to melatonin disappeared within a few weeks after starting treatment, while the good response returned only after considerable dose reduction.”\textsuperscript{55}

**Melatonin and Medications**

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